3rd edition

JGES Gastroenterological Endoscopy Handbook

Editor

JGES Postgraduate Education Committee



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Foreword

In December 1992, the Guidelines for Upper Gastrointerological Endoscopy (draft) were first published in the Japanese journal of Japan Gastroenterological Endoscopy Society (JGES) as one of the drafted versions of the Guidelines for Gastroenterological Endoscopy. We owe it to many of our senior colleagues for the subsequent publication of the Guidelines for Gastroenterological Endoscopy, whose first edition came out in May 1999, followed by the second edition in December 2002, and the third edition in October 2006. At that time, there were hardly any EBM (evidence-based medicine) guidelines, and although the publications had the word "guidelines" in the title, their content encompassed what would now be considered as both guidelines and a handbook. Subsequently, careful deliberations were conducted by the Guidelines Review Committee (currently referred to as Guidelines Committee) and the Postgraduate Education Committee regarding the positioning of the Guidelines for Gastroenterological Endoscopy. At a joint meeting held in May 2010, it was decided to have the Guidelines Committee prepare the guidelines in a revised format that applies EBM principles and have the Postgraduate Education Committee newly edit and publish the Gastroenterological Endoscopy Handbook.

While providing a set of standardized guidelines for gastroenterological endoscopy practice, the handbook is designed to aid members engaged in gastroenterological endoscopy in acquiring the knowledge and skills required in clinical settings. Its purpose is to contribute to the advancement, standardization, and medical safety in the field of endoscopy through its practical and instructive content. Gastroenterological Endoscopy Handbook (1st Edition) was published in May 2012 under the editorial guidance of the Postgraduate Education Committee (Supervising Director: Dr. Hiroyasu Makuuchi; Chairperson: Dr Shinji Tanaka) with the support of numerous doctors. The publication has been widely used and well received since its release, especially as a practical and educational reference for physicians and medical practitioners engaged in endoscopic care in their daily clinical work. The revised second edition was published in May 2017 (Supervising Director of Postgraduate Education Committee: Dr. Shinichi Takahashi → Dr. Shinji Tanaka; Chairperson: Dr. Shinji Tanaka → Dr. Kunio Kasugai). Seven years have passed since then, and the handbook has been newly planned and edited to incorporate the recent advances in endoscopic devices and equipment, diagnosis as well as treatment, and is being published as the of the Gastroenterological Endoscopy Handbook (Revised 3rd Edition) (Supervising Director of Postgraduate Education Committee: Dr. Akiko Shiotani; Chairperson: Dr. Kunio Kasugai → Dr. Ichiro Yasuda). In a concise manner, this volume covers a wide range of topics that are essential in endoscopic practice, including pathology, medical specialist system, risk management, informed consent, preparation and implementation of clinical pathways, infection control and safety measures, AI, endoscopic data management, and the Japan Endoscopic Database (JED). On a personal note, as someone who was deeply involved in the preparation of the first two versions, I acknowledge the significance and weight of this book, which has been produced through the collective efforts of the members of our academic society. We thought it would be a great loss to limit the use of the Gastroenterological Endoscopy Handbook to Japan alone and decided to produce an English version that would contribute to improving the standards of endoscopic practice worldwide. Used in conjunction with the various guidelines published by the JGES's Guidelines Committee, we sincerely hope that this Gastroenterological Endoscopy Handbook (Revised 3rd Edition) will serve as a valuable reference in your daily clinical practice and contribute to the advancement of gastroenterological endoscopic care.

Finally, I would like to extend my deepest gratitude toward everyone that oversaw the editing of the book,

including Dr. Akiko Shiotani; director in charge of the Postgraduate Education Committee, Dr. Kunio Kasugai; former chairperson, Dr. Ichiro Yasuda; current chairperson, and all the committee members, and to all the contributors and reviewers who participated in the preparation of this book.

December 2025

Shinji Tanaka
President
Japan Gastroenterological Endoscopy Society (JGES)

Preface

The Japan Gastroenterological Endoscopy Society (JGES) published the first edition of the Guidelines for Gastroenterological Endoscopy in 1999 and subsequently released the third edition in 2006. These early editions presented the standard knowledge and techniques of gastrointestinal endoscopic practice at the time and served as the foundation for JGES's specialist training curriculum.

The Gastroenterological Endoscopy Handbook was first published in May 2012 under the editorial supervision of the Postgraduate Education Committee. It represented a revised and expanded version of the Guidelines for Gastroenterological Endoscopy, with the aim of providing a more detailed explanation of endoscopic techniques and their practical applications. The contents consisted of a general section and specialized chapters organized by organ systems: pharynx and esophagus, stomach and duodenum, small intestine, colon, and biliary-pancreatic and ampullary regions. Each section offered detailed commentary on procedural techniques, key points, and precautions for young endoscopists performing gastrointestinal endoscopic examinations and treatments.

As stated in the preface to the first edition by Dr. Hiroyasu Makuuchi, who was the Supervising Director at the time of publication, the purpose of the handbook was to serve as a clinically useful manual for gastrointestinal endoscopic practice. It has since been widely utilized in clinical settings across Japan.

Five years after the first publication, the Gastroenterological Endoscopy Handbook (Revised 2nd Edition) was issued in May 2017. As noted in the preface written by former Supervising Director Dr. Shinichi Takahashi and current JGES President and former Supervising Director Dr. Shinji Tanaka, the revised edition incorporated the most up-to-date knowledge reflecting advances in endoscopic practice at the time. Newly added topics included data management in endoscopy and JED (Japan Endoscopy Database), the Kyoto classification of gastritis, colon capsule endoscopy, cold polypectomy, and drainage for walled-off pancreatic necrosis.

Seven years later, the third edition has been published in May 2024. Building upon the foundation of the first and second editions, this revision focuses particularly on endoscopic techniques, with detailed descriptions in three major areas:
(1) Practical methods and key techniques for basic procedures,
(2) Strategies and tips for managing difficult cases, and
(3) Post-procedural management and handling of complications.

Newly introduced topics in the third edition include underwater EMR and endoscopic papillectomy (EP). The rapid progress of endoscopic instruments and devices has been remarkable. Today's gastrointestinal endoscopists are expected not only to perform routine endoscopic procedures accurately and safely, but also to competently manage advanced and complex diagnostic and therapeutic interventions. It is our hope that this handbook will assist practitioners in mastering both fundamental skills and new knowledge in the ever-evolving field of gastrointestinal endoscopy.

Currently, the Postgraduate Education Committee is planning the development of a video library linked to the topics covered in this handbook, further enhancing its educational value. This edition has been authored primarily by members of the Postgraduate Education Committee and other contributing physicians, with editorial and review support from members of the JGES Board of Directors. We wish to extend our deepest appreciation to all the contributing authors, the members of the Postgraduate Education Committee who were responsible for editing this handbook, and the staff of the JGES Secretariat and Editorial Office for their dedicated efforts in the preparation of this publication.

December 2025

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I.General

I. General

1 Adverse Events and Their Management

Gastrointestinal endoscopy is indispensable for the diagnosis and treatment of gastrointestinal diseases, serving not only for observation but also as a means of performing procedures such as biopsies and various endoscopic operations. However, endoscopic examination itself is invasive to some extent, and even with the utmost care, adverse events (AEs) remain an unavoidable issue to be addressed. The occurrence of adverse events due to carelessness and excessive patient suffering must be absolutely avoided. Therefore endoscopists must always approach endoscopic examinations thoughtfully with a desire for improvement. It is important to provide clear and thorough explanations from the patient's perspective to ensure their understanding and build trust. Additionally, pretreatment and premedication should be tailored to each patient's needs. Practitioners should strive for proficiency in endoscopic techniques and be well-versed in adverse events and their treatments. It's also important to be aware of the risk of adverse events and to take proactive steps to prevent them, cooperative strategies which may involve working with other healthcare professionals.

1. Adverse Events Caused by Pretreatment

The Report on the Seventh National Survey on Gastrointestinal Endoscopy-related Adverse Events for Three Years (the 7th National Survey) by the Japan Gastroenterological Endoscopy Society (JGES) presents the results of a prospective survey on adverse event and its management associated with gastrointestinal endoscopy. This survey was conducted over a three-year period from 2019 to 2021, with each facility selecting one arbitrary week for data collection. Preparation-related adverse events occurred in 177 cases (0.072%), of which 4 cases (0.002%) resulted in death.[1)] The overall adverse event rate was 0.271% (668 cases). While adverse events from preparation were less common compared to overall occurrences, the presence of fatal cases highlights the need for attention. The adverse events happened to 119 cases (67.2%) used sedatives/analgesics, followed by 47 cases (26.6%) related to bowel cleansing agents. Among the deaths, 3 cases (75.0%) were attributed to sedatives/analgesics and 1 case (25.0%) to bowel cleansing agents (**Table 1**). Although adverse events related to sedatives/analgesics occur most commonly, the occurrence of adverse events related to bowel cleansing agents is also noticeable.

2. Managing Adverse Events Caused by Pretreatment

In order to prevent adverse events associated with pretreatment for endoscopic examinations, it is

Table 1 Preparation-related adverse events.

Pretreatment	Number of AEs	Fatal Cases
Pharyngeal anesthesia	2	0
Nasal anesthesia	0	0
Other local anesthesia	0	0
Antispasmodics	2	0
Sedatives/Analgesics	119	3
Bowel cleansing agents	47	1
Antithrombotics discontinued	1	0
Others	6	0
Total	177	4

[Cited from Literature 1]

extremely important for medical staff to **predict risks** based on prior understanding of patient information and **pharmacological knowledge** of premedication, pharyngeal anesthetics, sedatives and such. Regarding toxic symptoms and anaphylactic shock due to overdose of local anesthetics, shock due to premedication with butylscopolamine bromide or glucagon, and respiratory suppression due to sedatives and analgesics, it is necessary to fully understand that they can take a serious course. It is also important **to prepare for emergency treatment and conduct emergency training by endoscopic staff in case unexpected conditions** are observed.

Bowel cleansing agents, used for pretreatment in colonoscopy, can cause a rapid increase in intraluminal pressure. This pressure surge poses a risk, particularly in individuals with intestinal stenosis, and potentially leads to adverse events such as intestinal obstruction and perforation. In severe instances, these complications can be fatal. It is necessary to carefully confirm bowel movements through medical interviews and perform thorough abdominal examinations. **When suspecting intestinal stenosis lesions**, it is critical for endoscopists to assess the appropriateness of oral administration of bowel cleansing agents at the time of prior image diagnosis such as ultrasound or CT. Moreover, other adverse events associated with bowel cleansing agents include aspiration pneumonia and Mallory-Weiss syndrome. Therefore, particular attention is needed to the rate of administration for minimizing these risks, especially in elderly patients.

3. Adverse Events in Gastrointestinal Endoscopy

Table 2 shows procedure-related complications and the number of procedures for each examination method reported by the 7th National Survey. [1)]

(1) Upper gastrointestinal endoscopy

According to the results of the 7th National Survey,[1)] the number of peroral esophagogastroduodenoscopy (EGD) performed for observation (including biopsy) was 126,304, of which the number of adverse events was 56 (0.044%). Since the incidence of adverse events in

Table 2 Adverse events in observation-only gastrointestinal endoscopy (including biopsy).

Device	Procedures	AEs	(%)	Fatal Cases	(%)
Transnasal upper endoscopy	14,768	43	0.291	0	0
Peroral upper endoscopy	126,304	56	0.044	0	0
Balloon-assisted enteroscopy (Peroral)	272	1	0.368	0	0
Balloon-assisted enteroscopy (Transanal)	495	1	0.202	0	0
Other enteroscopy	266	0	0	0	0
Colonoscopy	61,083	28	0.046	0	0
Duodenoscopy (ERC)	7,048	11	0.156	0	0
Duodenoscopy (ERP)	628	2	0.318	0	0
Duodenoscopy (Non-ERCP)	69	0	0	0	0
Balloon-assisted enteroscopy (ERCP)	182	1	0.549	0	0
Dedicated EUS (Upper)	1,838	4	0.218	0	0
Dedicated EUS (Lower)	41	0	0	0	0
Dedicated EUS (Pancreatobiliary)	2,829	13	0.46	0	0
Biliary IDUS	247	0	0	0	0
Pancreatic IDUS	48	0	0	0	0
Dedicated EUS-FNA	845	4	0.473	0	0
EUS probe (Upper)	432	1	0.231	0	0
EUS probe (Lower)	73	0	0	0	0
Peroral cholangioscopy	66	0	0	0	0
Peroral pancreatoscopy	10	0	0	0	0
Percutaneous transhepatic cholangioscopy	68	0	0	0	0
Capsule endoscopy	564	0	0	0	0
Total	218,176	165	0.076	0	0

(Cited from Literature 1)

endoscopy for therapeutic purposes is reported to be 1.145%, the frequency of adverse events in peroral endoscopy for observation purposes is less likely than 1/20 of that of therapeutic endoscopy. Among 47 adverse events, the most common was tear, and endoscopic treatment was performed in 3 cases (**Table 3**). On the other hand, transnasal endoscopy has been increasing in recent years and its adverse events were 43 cases (0.291%). Although this rate is higher than that in peroral endoscopy, most of the adverse events were epistaxis, and all but one case were conservatively cured (**Table 4**).

(2) Colonoscopy

According to the 7th National Survey,[1] the number of colonoscopy completed for observation (including biopsy) was 61,083, of which the number of adverse events was 28 (0.046%). **Table 5**

Table 3 Adverse events in peroral esophagogastroduodenoscopy.

Adverse Event	Number of Cases	Treatment (Conservative/Endoscopic/Surgical)	Outcome (Recovered/Sequelae/Fatal)
Tear (Including Mallory-Weiss syndrome)	18	15/3/0	18/0/0
Respiratory suppression	7	7/0/0	7/0/0
Hemorrhage	4	2/2/0	4/0/0
Bradycardia	4	4/0/0	4/0/0
Aspiration	3	3/0/0	3/0/0
Teeth dislodgment	2	2/0/0	1/1/0
Perforation	1	0/0/1	0/1/0
Emphysema due to perforation	1	1/0/0	1/0/0
Hematoma (Hypopharynx)	1	1/0/0	1/0/0
Hyperventilation	1	1/0/0	1/0/0
Panic	1	1/0/0	1/0/0
Esophageal mucosal detachment	1	1/0/0	1/0/0
Hypertension	1	1/0/0	1/0/0
Discomfort	1	1/0/0	1/0/0
Vasovagal reflex	1	1/0/0	1/0/0
Total	47	41/5/1	45/2/0

(Cited from Literature 1)

Table 4 Adverse events in transnasal esophagogastroduodenoscopy.

Adverse Event	Number of Cases	Treatment (Conservative/Endoscopic/Surgical)	Outcome (Recovered/Sequelae/Fatal)
Hemorrhage/Epistaxis	40	39/1/0	40/0/0
Tear	1	1/0/0	1/0/0
Respiratory suppression	2	2/0/0	2/0/0
Total	43	42/1/0	43/0/0

(Cited from Literature 1)

indicates that perforation was one of the most frequently observed adverse event, with five cases in total. Surgical intervention was required in four of those cases, representing 80.0% of the incidents. Notably, sigmoid colon was the most common site of perforation, also accounting for 80.0% of the cases which is four out of the five.

Table 5 Adverse events in colonoscopy.

Adverse Event	Number of Cases	Treatment (Conservative/Endoscopic/Surgical)	Outcome ((Recovered/Sequelae/Fatal)
Perforation	5 (Sigmoid : 4 Unknown : 1)	0/1/4	4/1/0
Hemorrhage	5	0/5/0	5/0/0
Bradycardia	4	4/0/0	4/0/0
Vomiting	3	3/0/0	3/0/0
Thromboembolism	2	2/0/0	1/1/0
Hypotension	2	2/0/0	2/0/0
Panic	1	1/0/0	1/0/0
Tear	1	0/1/0	1/0/0
Total	23	12/7/4	21/2/0

(Cited from Literature 1)

Table 6 Adverse events in balloon-assisted enteroscopy.

Peroral

Adverse Event	Number of Cases	Treatment (Conservative/Endoscopic/Surgical)	Outcome (Recovered/Sequelae/Fatal)
Perforation/Peritonitis	1	0/0/1	1/0/0
Total	1	0/0/1	1/0/0

Transanal

Adverse Event	Number of Cases	Treatment (Conservative/Endoscopic/Surgical)	Outcome (Recovered/Sequelae/Fatal)
Respiratory suppression	1	1/0/0	1/0/0
Total	1	1/0/0	1/0/0

(Cited from Literature 1)

(3) Enteroscopy

According to the 7th National Survey, [1] the number of balloon-assisted enteroscopy for only observation including biopsy, was 272 via oral route and 495 via anal route, and adverse events occurred in 1 case perorally (0.368%) and 1 case transanally (0.202%). These were higher than the occurrence of other examinations. Among them, the case of perforation was cured by surgery (**Table 6**)

Table 7 Organ bleeding caused by antithrombotic use/non-use.

	No Use					Use					
	n	Hemorrhage	%	Severe bleeding	%	n	Hemorrhage	%	Severe bleeding	%	P-value
Upper digestive	8,593	22	0.26	18	0.21	6,894	52	0.75	42	0.61	P 0.001
Colon	3,985	11	0.28	10	0.25	3,567	32	0.90	27	0.76	P 0.001
Small intestine	30	0	0	0	0	21	0	0	0	0	–
Bile/Pancreas	348	1	0.29	0	0	392	12	3.06	6	1.53	P 0.005
Total	12,956	34	0.26	28	0.22	10,874	96	0.88	75	0.69	

(Cited from Literature 3)

Table 8 Bleeding caused by antithrombotic use/non-use for each procedure.

	No Use					Use					
	n	Hemorrhage	%	Severe bleeding	%	n	Hemorrhage	%	Severe bleeding	%	P-value
Observation	8,597	4	0.05	2	0.02	7,347	15	0.20	8	0.11	P 0.005
Biopsy	2,685	10	0.37	8	0.30	1,979	16	0.81	14	0.67	P 0.05
Low-risk procedure	309	1	0.32	0	0	299	5	1.67	0	0	P 0.09
High-risk procedure	1,365	19	1.39	18	1.32	1,249	60	4.80	53	4.24	P 0.001
Total	12,956	34	0.26	28	0.22	10,874	96	0.88	75	0.69	

(Cited from Literature 3)

4. Managing Adverse Events Associated with Gastrointestinal Endoscopy

(1) Hemorrhage

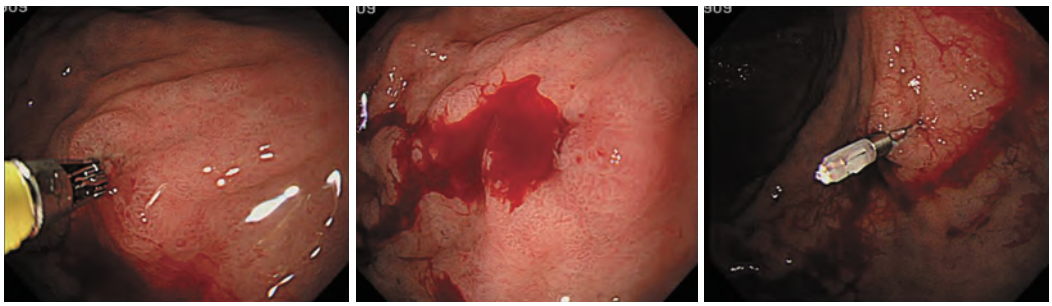
When endoscopic procedures are performed with insufficient skill or excessive force, complications may arise, especially in cases where smooth examination is difficult due to physiological factors such as gag reflex or hyperperistalsis. In such situations, the endoscope may cause damage to the gastrointestinal mucosa, and the damage leads to bleeding or hematoma formation. Contact with mucosa is more likely when a distal attachment (hood) is used. This often occurs during insertion of upper gastrointestinal endoscope from the pharynx to the esophageal entrance or from the bulbus to the anterior wall of the superior duodenal angle. In colonoscopy, excessive suctioning can contribute to bleeding. Generally, cases requiring hemostatic intervention are rare. In principle, endoscopists must **carefully understand local anatomy and advance scopes without contacting the gastrointestinal mucosa while confirming the direction of advancement** to avoid bleeding.

After completion of a biopsy, bleeding requiring hemostatic treatment is usually very rare. In practice, greater care should be taken with patients who have a systemic bleeding tendency due to liver diseases or blood disorders. For patients taking antithrombotic drugs, Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment published by JGES in 2012 began to

Table 9 Bleeding due to antithrombotic continuation/discontinuation.

	Continued					Discontinued					
	n	Bleeding	Incidence %	Severe	Frequency(%)	n	Bleeding	Incidence %	Severe	Frequency(%)	P-value
Observation	5,298	12	0.23	5	0.09	1,850	3	0.16	3	0.16	0.60
Biopsy	992	11	1.11	10	1.01	917	5	0.55	4	0.44	0.18
Low-risk procedure	141	4	2.84	0	0.00	115	1	0.87	0	0.00	0.26
High-risk procedure	228	7	3.07	7	3.07	935	53	5.67	46	4.92	0.11
Total	6,659	34	0.51	22	0.33	3,817	62	1.62	53	1.39	

(Cited from Literature 3)



a | b | c

Figure 1 Post-biopsy hemorrhage.

A biopsy was performed on a reddened lesion (a), and continuous bleeding was observed immediately after (b). Hemostasis was achieved by clipping (c).
(Cited from Literature 5)

highlight the prevention of thromboembolic events due to discontinuing anticoagulants over the risk of bleeding events due to continuing anticoagulants.[2] In biopsies, it is probable to continue antithrombotic therapy with one agent, and it is probable to carefully manage individual cases with two or more agents. After the implementation of these guidelines, a nationwide survey was conducted for adverse events related to gastrointestinal endoscopy in patients with use of antithrombotic agents.[3] Although bleeding was significantly higher in cases with antithrombotics than in cases without the agents (**Tables 7 & 8**), no significant difference in bleeding rates was observed with or without prior discontinuation of antithrombotics (**Table 9**). After the publication of these guidelines, several direct oral anticoagulants (DOACs) became available. As a result, in the 2017 Appended Guidelines, a statement was added to clarify that mucosal biopsy can be performed without discontinuing DOAC therapy.[4]

The risk of thromboembolism is related not only to drug discontinuation but also to dehydration due to endoscopic pretreatment, so **attention should also be paid to fluid replacement.** After biopsy, it is important for endoscopists to carefully observe the bleeding condition and complete the examination after confirmation of hemostasis. If hemostasis is not achieved, another methods are introduced including compression with forceps, application of agents like thrombin preparations, and hemostatic procedures like clipping or cauterizing (**Figure 1**).[5]

(2) Perforation

Perforation is a severe adverse event associated with gastrointestinal endoscopy.

1. Upper gastrointestinal endoscopy

It can occur when insertion is performed too much in the left piriform sinus or Zenker's diverticulum. The hypopharynx contains regions where longitudinal muscle is deficient, including Lannier-Hackerman gap (the site of Zenker's diverticulum, a pulsion diverticulum) and Laimer area. Due to the relative weakness of these areas, excessive pressure applied by an endoscope poses a significant risk of perforation. The symptoms of perforation vary depending on its severity, ranging from shock to being completely asymptomatic. If a tear occurs in the mucosal surface, air can escape into the soft tissues, and the damage leads to subcutaneous emphysema. This symptom is observed during or immediately after the examination, spreading from the neck area to the face and the anterior chest, and if infective organisms come in, it develops cellulitis. **CT is useful not only for diagnosing subcutaneous emphysema and mediastinal emphysema but also for depicting the spread of inflammation.** Early diagnosis is important, and in most cases, conservative treatment with fasting and antibiotics is definite. If mediastinitis develops, the condition becomes severe. In such cases, timely introduction of surgical treatment is essential to avoid missing the appropriate intervention window.

Gastric perforation develops typically from a mucosal tear, manifesting in minimal symptoms at the beginning. Over time, abdominal pain and distension develop gradually. If such a case is suspected, the course is often followed with continuous suction of gastric contents and antibiotic administration, but when the peritoneal irritation symptom appears, surgical intervention is required.

Duodenal perforation can occur when a scope is inserted forcibly into the descending part of duodenum. This causes a large perforation area in the anterior wall of the bulb, where the scope pushes out into the abdominal cavity. In principle, surgery is required for such conditions.

2. Colonoscopy

Perforation frequently occurs in sigmoid colon due to its complex anatomical course and its predisposition as a common site for diverticula formation.

During the endoscopy, it is essential for a practitioner to advance the scope while confirming the lumen in the direction of travel, and it is absolutely necessary to avoid pushing the distal tip while it is in contact with the mucosa. It is also important to thoroughly acquire safe insertion techniques without causing the patients' pain. **Warning signs of perforation** include sensation of scope insertion and its twisting, failure to see the lumen appearance even after insertion, and severe pain of patients by the scope manipulation. In such a situation, it is necessary to never advance the scope and withdraw it to a controllable point.

Since deep biopsy to muscularis propria is rarely conducted in gastrointestinal tract, perforation usually does not occur in this process. In fact, there have been reports of perforation caused by collecting samples from ulcer base or by puncturing the needle into a diverticulum.

(3) Tear

Physically, tearing can occur in the mucosa immediately below the cardia due to vomiting reflex, and this condition is known as **Mallory-Weiss tear.** The primary mechanism involves the protrusion of gastric mucosa into the esophageal lumen due to a violent vomiting reflex. This syndrome occurs spontaneously due to severe retching or vomiting, whereas the adverse event related to endoscopic procedures is iatrogenic. This incident causes a linear tear extending in the longitudinal direction from the gastroesophageal junction to just below the cardia, and its occurrence can be observed during endoscopy. Bleeding is common with this condition, but in most cases, it can be controlled with simple monitoring. In rare cases, massive bleeding may occur and require treatment to stop it. Even then, the area typically heals within one to two weeks.

(4) Others

During endoscopic examination, autonomic nervous system activity may fluctuate due to anxiety about the endoscopy, vomiting reflex during endoscopic passage, and vagal reflex associated with gastrointestinal distension. In severe electrocardiographic changes, fatal arrhythmias or myocardial infarction may be induced. It is known that blood pressure increases when endoscopy is performed without using sedatives. When increase in blood pressure is more pronounced in subjects with hypertension, cerebral hemorrhage or subarachnoid hemorrhage may develop. As the aging population grows, the frequency of endoscopic examinations has increased in patients with comorbid conditions, including cardiopulmonary diseases. This underscores the importance of thorough assessment on overall health condition prior to the procedure.

Temporomandibular joint dislocation frequently occurs in individuals with a history of recurrent dislocation. In some cases, the jaw may return to its normal position spontaneously with movement. However, in more difficult cases, manual reduction is warranted.

Salivary gland swelling may be observed after endoscopy. This symptom often improves within 2-3 hours, but a full explanation is necessary since patients may feel anxious.

5. Adverse Event Associated with ERCP and Its Management

(1) Outline of adverse events associated with ERCP

Endoscopic retrograde cholangiopancreatography (ERCP) and its related procedures are essential techniques established for diagnosing and treating biliary and pancreatic diseases. However, it is a high-risk endoscopic method that can sometimes lead to fatal outcomes, requiring careful attention. According to the 7th National Survey on adverse events related to gastrointestinal endoscopy, adverse events related to diagnostic endoscopic retrograde cholangiography (ERC) were 11 out of 7,048 cases (0.156%), and those related to diagnostic endoscopic retrograde pancreatography (ERP) were 2 out of 628 cases (0.318%). Adverse events related to therapeutic ERCP were 104 out of 6,424 cases (1.619%), with 2 deaths reported (0.031%).[1)], Endoscopic sphincterotomy (EST) and endoscopic papillary balloon dilation (EPBD) are papillary procedures that carry a risk for fatality or other adverse events. Therefore, meticulous technique during the procedure and careful postoperative management are essential to minimize these risks.

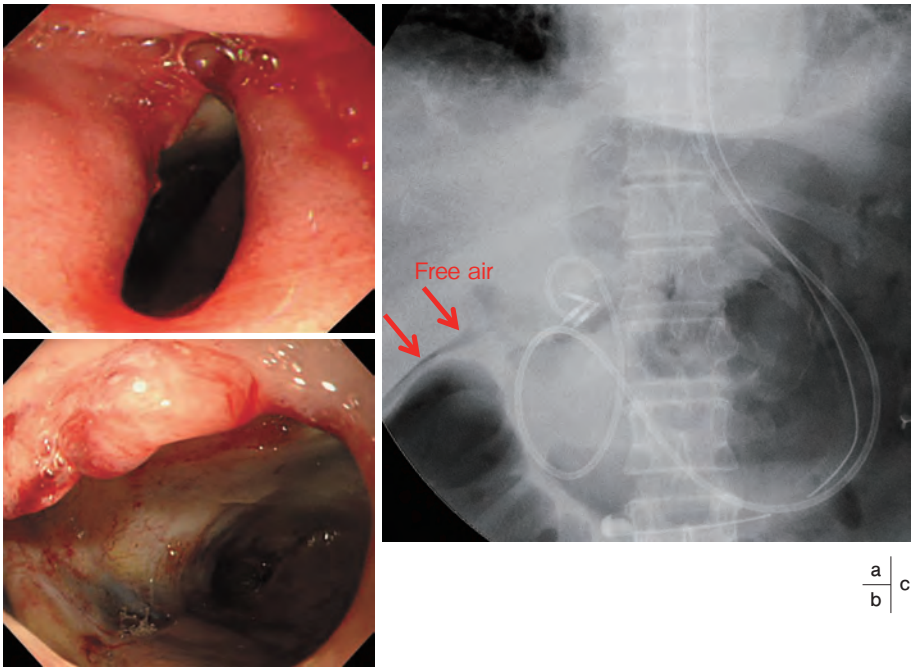


Figure 2 **Unresectable advanced carcinoma of the pancreatic head.**

Chemotherapy was being administered on an outpatient basis, but ERCP was implemented due to biliary stent occlusion. Upon insertion of the side-viewing endoscope into the duodenal bulb, perforation occurred (a). The endoscopic-observation confirmed a retroperitoneal exposure (b). Since closure with metal clips was deemed unfeasible, ENBD was placed, followed by surgical intervention (c). (Cited from Literature 5)

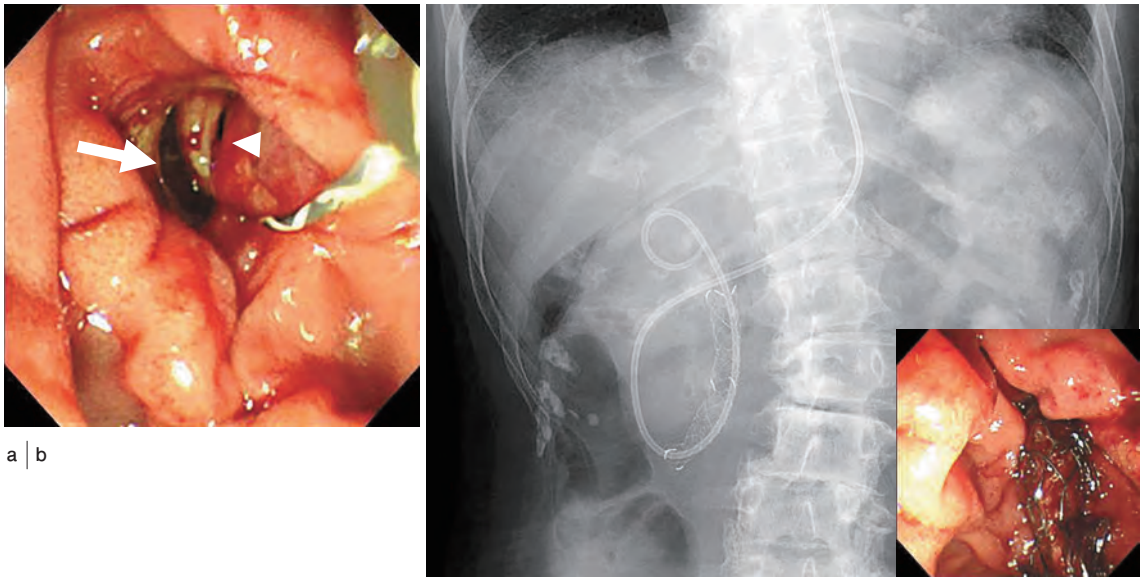
(2) Managing adverse events related to scope insertion

In scope insertion, blind passage areas require careful attention for avoiding mucosal injury and perforation, such as the esophageal entrance, esophagogastric junction, and duodenum. When the scope passes through the esophagogastric junction, it should be advanced gently, although tearing and bleeding may occur. Most cases stop bleeding spontaneously, but if bleeding persists, the scope should be changed to a forward-viewing one in order to endoscopically achieve hemostasis by clipping forceps.

When inserting a side-viewing scope into the duodenum, practitioners should pay attention to avoid duodenal perforation.[6] This accident usually occurs during scope insertion into the descending part or during stretching process. In cases of duodenal stenosis caused by carcinoma of the pancreas or gallbladder invading into the duodenum or by chronic pancreatitis, the duodenal adhesions can increase the risk of perforation. The affected area makes the duodenal wall more vulnerable, particularly during endoscopic retrograde cholangiopancreatography (ERCP) process. To reduce the risk of duodenal perforation, careful endoscopic techniques are essential. Rather than persistently attempting to stretch the duodenum forcefully, endoscopists shall take more cautious approaches. Awareness of these risks allows for safer ERCP procedures, thereby minimizing complications related to duodenal fragility.

If perforation is suspected, abdominal CT should be performed immediately to check for intra-abdominal free air.

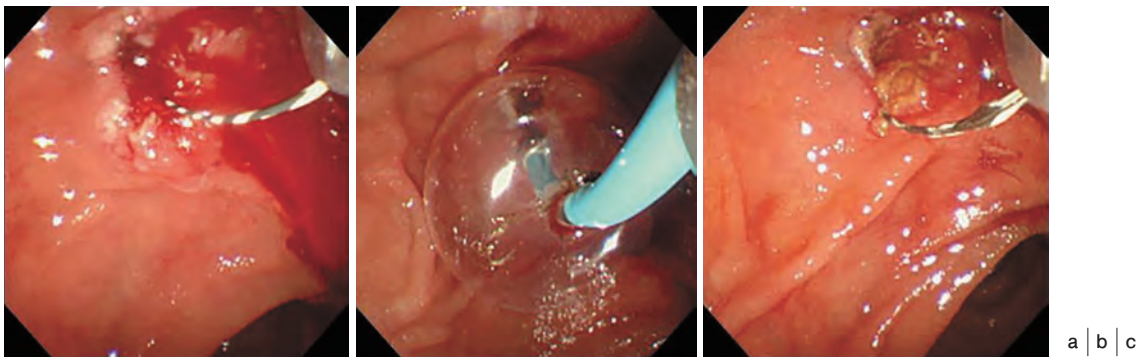
Duodenal perforation caused by scopes is generally due to direct intestinal wall injury and often has a



a | b

Figure 3 **Papilla perforation after EST.**

The bile duct opening (arrowhead) and the perforation site (arrow) were identified (a). A fully-covered self-expandable metal stent was placed, and ENBD was performed. This leads to improvement by conservative treatment (b).

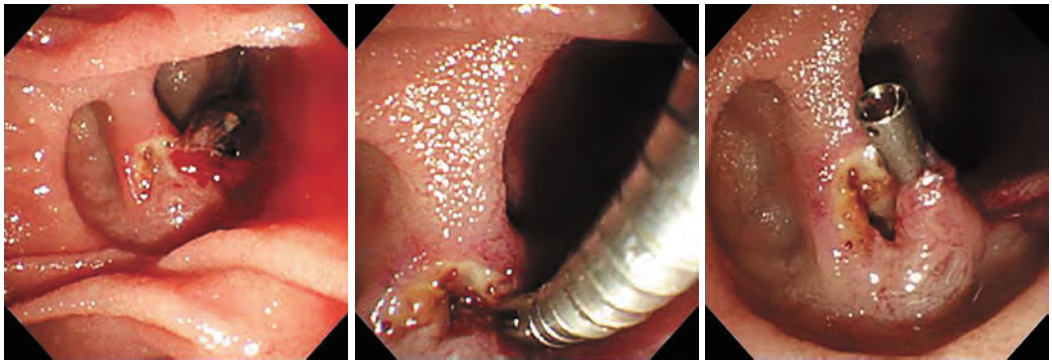


a | b | c

Figure 4 **Balloon compression for bleeding after EST.**

Gushing bleeding was observed after EST (a). Hemostasis was achieved through balloon catheter compression (b, c).

large perforation area. Thus surgical closure of the damaged area should be implemented. For this case, external biliary drainage by percutaneous transhepatic cholangial drainage (PTCD) or endoscopic naso-biliary drainage (ENBD) is effective in prevention of biliary leakage into the retroperitoneal space (**Figure 2**).[5] On the other hand, in cases of duodenal mucosal injury without obvious perforation findings (micro-perforations), the area is sutured with clipping forceps, and conservative treatment with gastric tube insertion and nil per os are performed. If the abdominal CT shows an increase in free air or ascites over time, or if peritoneal irritation or inflammation is severe, surgical intervention should be introduced.



a | b | c

Figure 5 **Hemostasis with metal clip after EST.**

Spurting hemorrhage was observed after EST (a). Hemostasis was successfully achieved by a metal clip (b, c).

(3) Managing adverse events related to procedures for duodenal papilla

In general, perforation rarely occurs even with ERCP cannulation of major papilla. However, perforation can occur when cannulation is performed together with a guidewire. The perforated siteis usually small and resolves with conservative treatment. However, perforation of duodenal papilla associated with EST, EPBD, and especially endoscopic papillary large balloon dilation (EPLBD), often results in a larger perforation In such cases, ENBD or biliary stents are placed (**Figure 3**), and closure of the hole is proceeded with clipping forceps. During ERCP, if perforation is suspected, it is important for practitioners to prevent excessive pressure buildup in the retroperitoneal space, or it can worsen the condition. One key measure to minimize this risk is the employment of carbon dioxide (CO_2) insufflation. The same procedure is performed when the papilla is perforated with basket forceps during common bile duct stone removal. Postoperatively, abdominal CT is implemented to check for intra-abdominal free air or ascites, and the patient is carefully monitored. Typically, perforation caused by instruments are small, so they often improve with biliary drainage, gastric tube placement, and administration of antibiotics with proton pump inhibitors (PPIs). Fever and elevated inflammatory markers are typically observed for several days following perforation. In most cases, these symptoms subside gradually, and recovery is generally achieved within one to two weeks.

Although rare in diagnostic ERCP, bleeding can occur after EST or endoscopic papillectomy. In such cases, practitioners can often achieve hemostasis by spraying epinephrine solution or absorbable local hemostatic agents, or by compression with a retrieval balloon catheter (**Figure 4**). In cases of massive bleeding or arterial bleeding, treatments are required by local injection with hypertonic saline epinephrine solution (HSE), high frequency coagulation hemostasis, argon plasma coagulation (APC) cauterization, or hemostasis with clips (Hemoclip) (**Figure 5**). These hemostatic procedures are possibly unsuitable for bleeding from the papilla into the bile duct. In such cases, fully-covered self-expandable metal stent is beneficial for hemostasis,7) but is not covered by insurance in Japan. If endoscopic hemostasis is difficult, interventional radiology (IVR) should be introduced. In this case, clipping at the bleeding site is useful for identifying the responsible vessel during angiography.

(4) Managing adverse events related to biliary and pancreatic procedures

Perforation of bile duct or cystic duct may occur during endoscopic lithotripsy or guidewire manipulation for bile duct stricture. Since most of these are small holes caused by an instrument or a guidewire, most of all can be treated conservatively with biliary drainage such as bile duct stenting or ENBD. Likewise, pancreatic duct perforation may occur during pancreatic stone removal or guidewire manipulation for pancreatic duct stricture. Since there is a high possibility of developing post-ERCP pancreatitis (PEP), endoscopic nasal pancreatic drainage (ENPD) or pancreatic duct stenting is performed for the purpose of preventing pancreatic juice leakage outside the pancreatic duct. In such cases, it is useful to place the tip of the tube beyond the pancreatic duct perforation site when feasible.

(5) Managing post-ERCP pancreatitis (PEP)

Careful attention is required for the management of PEP, because PEP sometimes leads to fatal outcomes. Patient-related risk factors include Oddi's sphincter dysfunction, female sex, history of pancreatitis, young age, absence of extrahepatic bile duct dilation, not-chronic pancreatitis, and normal serum bilirubin levels.

Procedure-related risk factors include precutting, pancreatography, more than 5 cannulation attempts, endoscopic pancreatic sphincterotomy (EPST), endoscopic papillary balloon dilation (EPBD), and endoscopic papillectomy.[8] Temporary pancreatic stent placement is helpful for preventing PEP caused by pancreatic juice stasis due to post-procedure papillary edema. Actually, pancreatic stent placement for PEP prevention is not covered by insurance in Japan, thus it should be implemented for high-risk groups. Suppositories of non-steroidal anti-inflammatory drug (NSAID) are beneficial in reducing the risk of PEP onset and can be applied when there are no contraindications. Although protease inhibitors are commonly used in daily practice for PEP prevention, recent meta-analyses have questioned their efficacy, and do not recommend the routine administration of protease inhibitors.[8]

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2 Basics and Principles of Image-enhanced Endoscopy

The history of gastrointestinal endoscopy in Japan began in 1949, when Uji and his colleagues developed the gastrocamera. This is a device with a small camera attached to the tip of a tube. The invention was followed by the introduction of fiberscopes, which used bundles of glass fibers to transmit light from the lens at the tip of the scope to the eyepiece, allowing for both visual observation and photography. Since the emergence of electronic endoscopes in 1984, nearly 40 years have passed. Whereas gastroparesis and fiberscopes directly observe and display light information irradiated onto mucosa, electronic endoscopes capture light information with charge-coupled devices (CCDs), convert it into electrical signals, and further convert and process it into image signals for display on a screen. The advancement allows for image enhancement processing by applying various transformations during the image creation process.

Early-stage tumors and inflammatory diseases often exhibit limited morphological and color changes compared to advanced cancers, making diagnosis difficult with conventional white light endoscopy alone. Image-enhanced observation modalities are designed to highlight subtle mucosal changes and variations. This emphasis aims to improve the detection of early cancers and clarify the underlying mechanisms of various gastrointestinal diseases that are challenging to diagnose with conventional endoscopy. Among image-enhanced observation methods, **chromoendoscopy (dye-based image-enhanced observation)** was developed in the 1960s and has been improved. It has greatly contributed to the advancement of Japanese gastrointestinal endoscopy and is still used in daily clinical practice. However, due to the complexity of preparing and applying dyes, it has not become widely used in clinical settings. On the other hand, **equipment-based image-enhanced observation** uses optical and electronic technologies to improve images by pushing a single button.[1-3] This method has become widely adopted and is now a standard feature in most general-purpose endoscopy. Basic knowledge of these technologies is necessary for their further effective utilization.

Magnifying endoscopes were developed to obtain detailed images during endoscopy, that is critical information similar to what is obtained through pathological diagnoses. The goal is to realize optical diagnoses, eliminating the need for biopsies. Such devices are now commercially available for general use in endoscopy, allowing treatment plans to be developed based on endoscopic findings alone, without the need for tissue sampling. Furthermore, super-magnifying endoscope systems have been developed to capture cell-level images inside the body. These systems aim to provide even more precise optical diagnoses that can approximate histological tissue images. To obtain cellular-level images, specialized microscopic endoscopy techniques are required. The techniques include endocytoscopy and confocal endomicroscopy. This section provides an overview of the basics and principles of these examination methods.

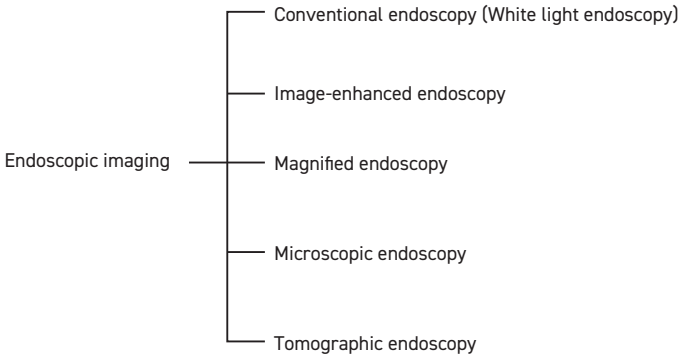


Figure 1 **Classification of endoscopic imaging methods for intended use (Hirofumi Niwa & Hisao Tajiri).**

(Cited from Literature 4)

1. Endoscopic Observation Methods

The types of observation methods in endoscopy are broadly categorized into five groups: (1) conventional endoscopy (white light); (2) image-enhanced endoscopy; (3) magnified endoscopy; (4) microscopic endoscopy; and (5) tomographic endoscopy (**Figure 1**).[4] Moreover, image-enhanced endoscopy is further classified according to the method of obtaining the image enhancement effect: (i) optical method, (ii) digital method, (iii) optical digital method, and (iv) chromoendoscopy (**Figure 2**).[4]

The optical method enhances images purely through optical effects by altering properties (mainly the wavelength) of the light emitted from endoscopes. This method is comparable to the previous modalities that used ultraviolet or infrared light for fiber scopes. The problem is that the optical method alone does not provide sufficient light intensity or enhancement effects for practical use in endoscopic examinations. Furthermore, since electronic endoscopy processes light information as electrical signals, all equipment-based image-enhanced observation methods utilized in clinical sites fall under either digital methods (FICE or i-scan) or optical-digital methods (AFI, NBI, BLI, LCI, i-scan OE, or RDI).

2. Conventional Endoscopy (White light endoscopy)

(1) Light color and three primary colors

To facilitate understanding of the mechanism of electronic endoscopy and the principle of image enhancement effects by optical and digital methods, the relationship between light wavelength and color should be explained. Among electromagnetic waves, those with wavelengths from 360 nm to 780 nm can be perceived by human eyes and are called light or visible light. Light appears in different hues depending on its wavelength, from long-wavelength red to short-wavelength violet (**Figure 3**). White light, like sunlight, is separated into the light of various colors when dispersed by a prism. When all the light of all wavelengths is combined, the human eye perceives the light as white. Different wavelengths of light produce different hues, but humans can perceive a wide range of hues by changing the proportion of three primary colors: red, blue, and green. For example, mixing green and blue light produces cyan, which can

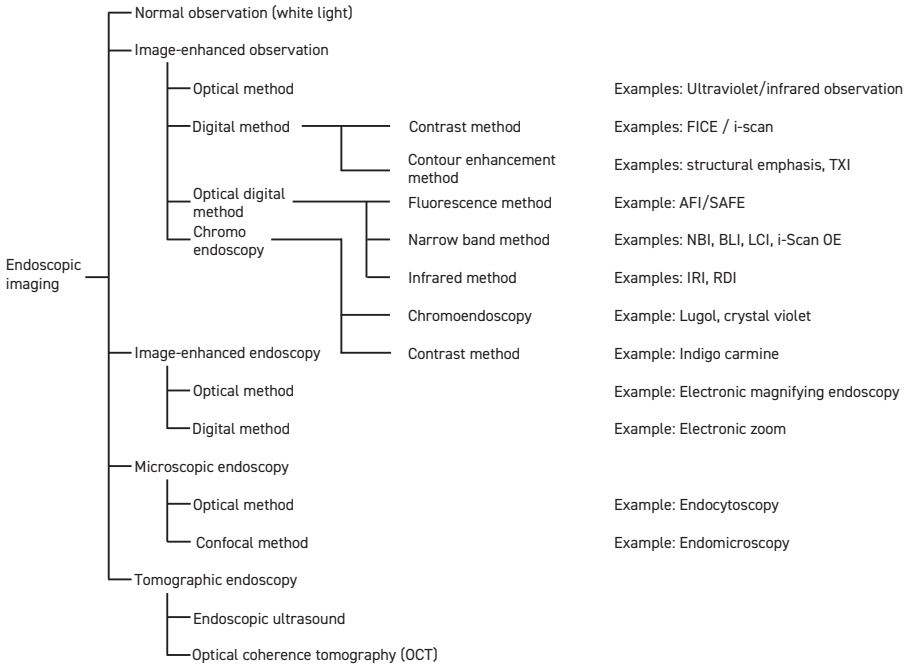


Figure 2 **Subclassification of endoscopic imaging methods by intended use (Hirofumi Niwa & Hisao Tajiri).**

(Cited from Literature 4)

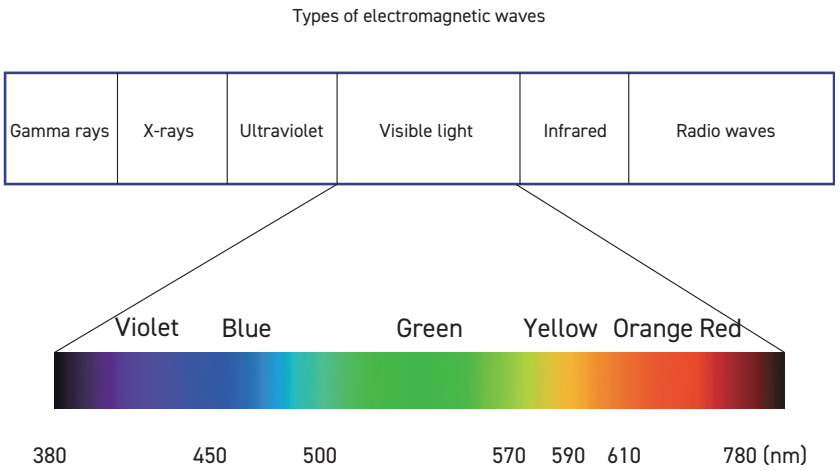


Figure 3 **Electromagnetic spectrum and hues by wavelength in visible light.**

also be created by attenuating red light from white. Likewise, magenta is a mixture of red and blue, which is created by attenuating green light from white (**Figure 4**).[5)]

(2) Mechanism of electronic endoscopy

Because the charge-coupled device (CCD) used in electronic endoscopes detects only the intensity of light, the original image it produces is in black and white. In electronic endoscopy, filters are induced to

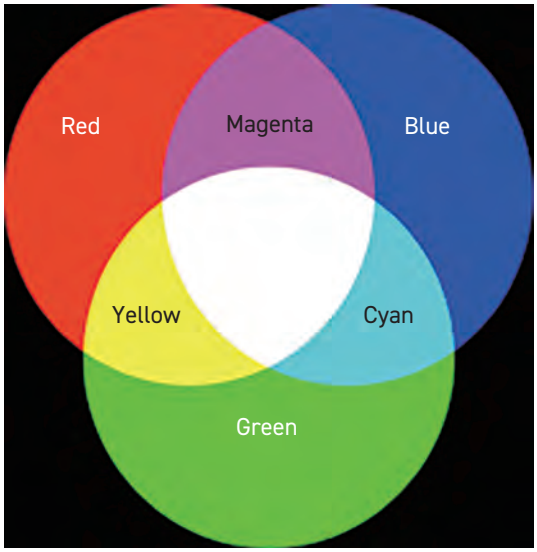


Figure 4 **Additive color mixing using three primary colors.**

(Cited from Literature 5)

reproduce colors in a manner similar to what is seen with the naked eye, and the images are displayed as color-added images. There are two main methods for creating color images: the color chip method and the sequential color illumination method.

1) Color chip method

Usually, a CCD sensor is incorporated as an aggregate of many small elements behind the lens to capture lights. In electronic endoscopy employing the color chip method, a red, green, or blue color filter is built into the light-receiving surface of each pixel and arranged in a mosaic pattern. Therefore, when white light from the light source reflects off tissue, each sensor element in the endoscope simultaneously captures the intensity of red, green, and blue components of that light. The endoscopes processor then uses this information to artificially give color and combine these individual color intensities, ultimately producing full-color endoscopic images (**Figure 5**). Electronic endoscopy employing the color chip method captures and combines all color channels at the same time. This prevents the color distortion that occurred with the previous sequential color illumination method, where rapid movement caused misalignment between separately captured color images. Olympus' EVIS-100 series is widely used in Latin American countries, Asian countries excluding Japan, Korea, and China, and Western countries excluding the UK. The EVIS X1 system uses the color chip for GIF-EZ1500 and CF-EZ1500 scopes. The latest models use light emitting diodes (LEDs) for the light source and complementary metal oxide semiconductor (CMOS) for the image sensor (**Figure 6**). Compared to CCDs, CMOS has a merit of rapid processing, which allows for high-speed and high-resolution image processing even with a large number of pixels. Olympus uses five colors of LEDs: bluish-purple, blue, green, amber, and red (**Figure 7**). Fujifilm uses four colors: bluish-purple, blue, green, and red. Electronic endoscopes from Fujifilm, Pentax, and other companies are all color chip type.

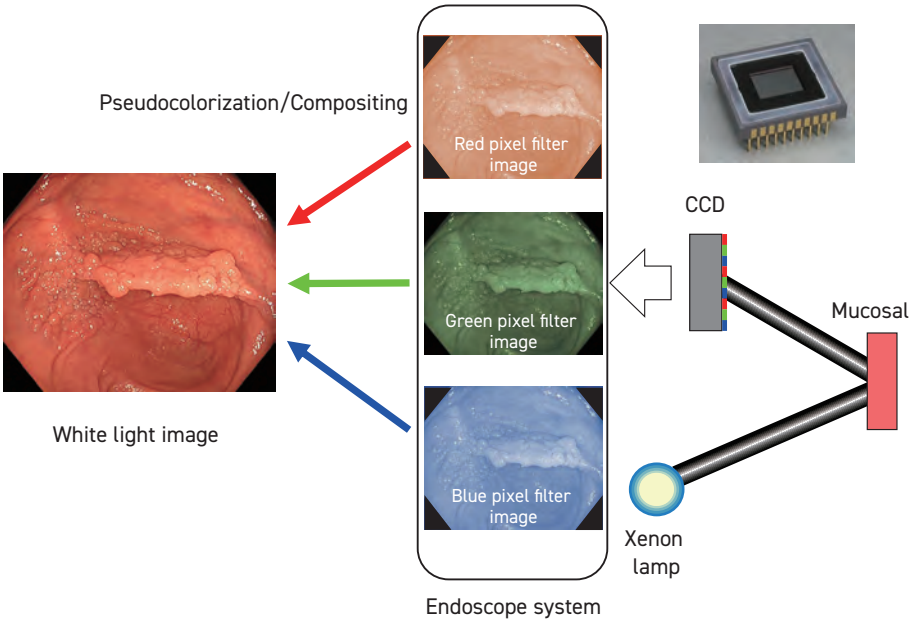


Figure 5 **Mechanism of electronic endoscopy employing the color chip method.**

(Provided by Olympus Marketing)

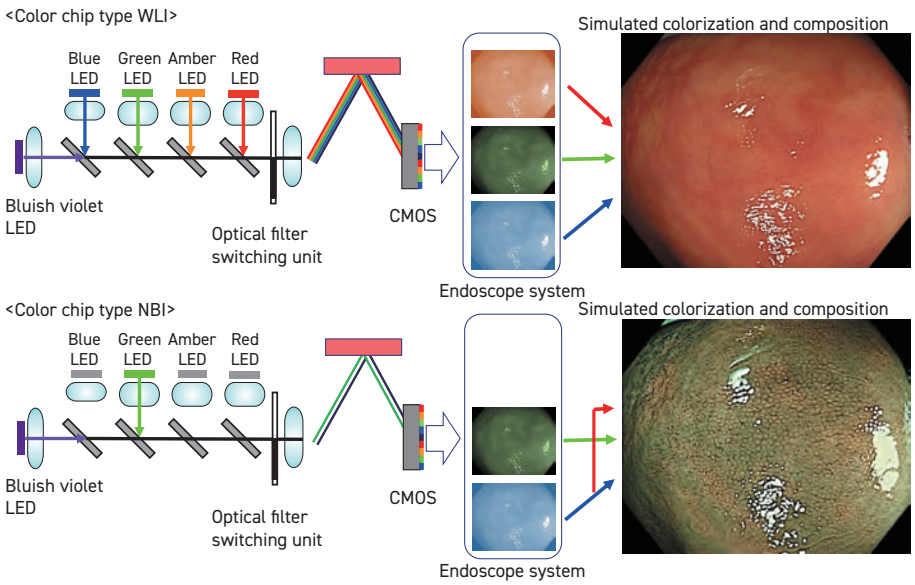


Figure 6 **Structure of color-chip-type electronic endoscope with LED light.**

(Provided by Olympus Marketing)

2) Sequential color illumination method

Each color of light is sequentially emitted through a rotating three-color filter (red, green, and blue) mounted in front of the white light lamp of the light source. The reflected light of each color from the mucosa is sequentially captured by a monochrome CCD, and these are reproduced and simulated by the processor to form a color image (**Figure 8**). In contrast to the color chip method, where the pixels of the

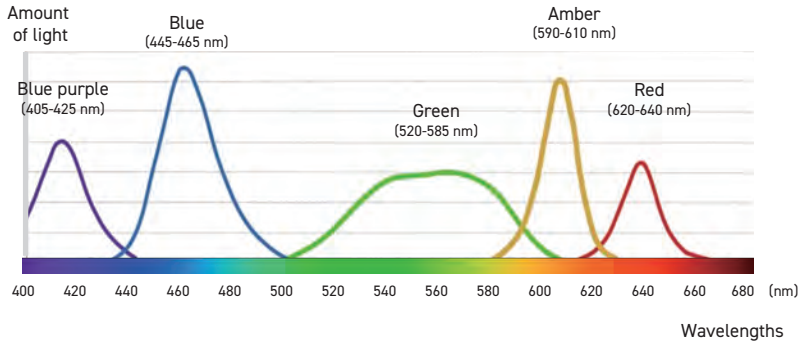


Figure 7 **Wavelength and hue of LED light.**

(Provided by Olympus Marketing)

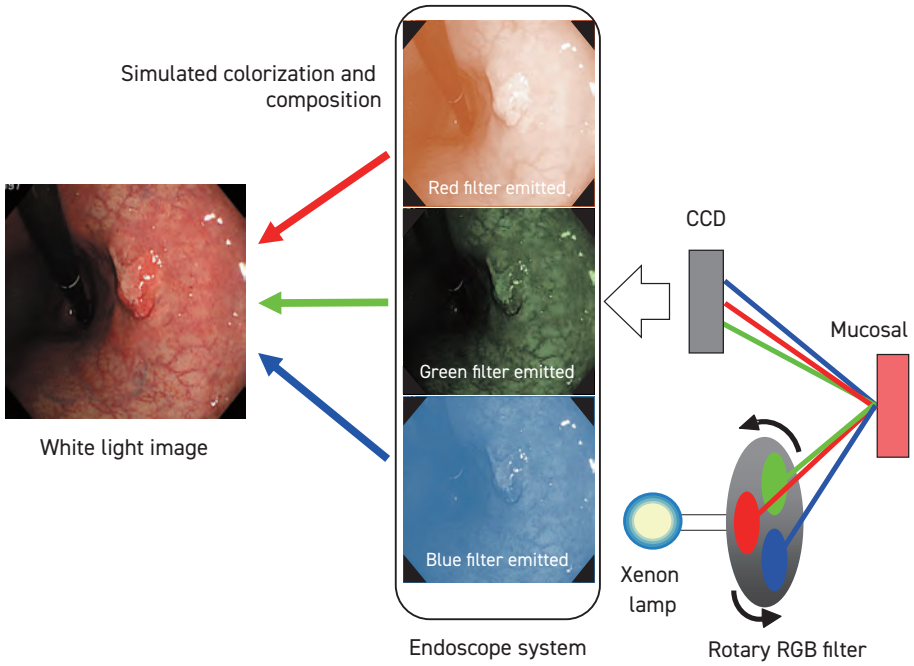


Figure 8 **Structure of sequential-type electronic endoscope.**

(Provided by Olympus Marketing)

CCD are allocated to each of the three colors (red, green, and blue), in the sequential color illumination method, all pixels can be used for each color. This technology has the advantage of higher resolution in principle. In addition, the sequential color illumination method allows switching of the filters built into the light source. This enables various physical changes to the illumination light and provides the advantage of achieving image enhancement effects through optical methods. Typical examples are Olympus' GIF-XZ1200 and EVIS-200 series, which are used in Japan, China, Korea, and the UK. The EVIS X1 system applies a sequential color illumination method for CF-XZ1200 scope. It creates white light by sequentially emitting three types of light using an LED source: green, a composite of bluish-purple/blue, and a composite of amber/red. These are processed as RGB signals and displayed on the monitor (**Figure 9**). In addition, the switching speed of the illumination light in this method is double that of the rotating filter method, thereby resulting in smoother image display.

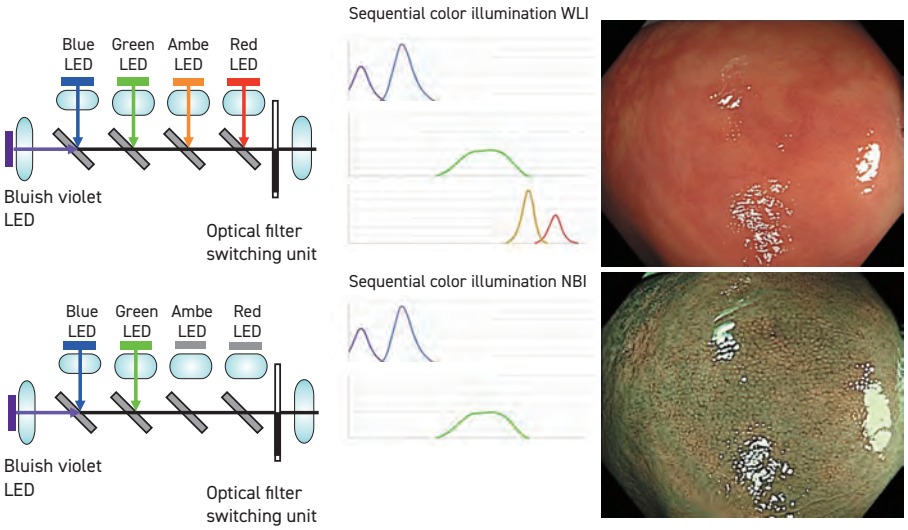


Figure 9 Structure of a sequential-type electronic endoscope with LED light.

(Provided by Olympus Marketing)

3. Image-enhanced Endoscopy

(1) Digital modality

This is a technique that obtains image enhancement effects by **electrically processing images captured, using the same white light as in conventional endoscopy.** Many image processing methods are used depending on the purpose and means, such as techniques to emphasize the contrast of light intensity and color (contrast method) and techniques to emphasize outlines and fine patterns (contour enhancement method). Because it is an electrical image processing, combinations of several different image processing methods are also available.

1) Adaptive structure enhancement (Olympus)

This image processing technique increases the sharpness of endoscopic images by electrically accentuating minute details in mucosal patterns with the structure and distribution of blood vessels. It works by employing band enhancement processing to emphasize specific frequency components of images that are particularly effective for improving the clarity of endoscopic visuals. There are two mode types: A and B modes. A mode emphasizes parts with large frequency components (rough changes in luminance and color tone), so band-like and even structures (vessel, crypt opening, intervening part, etc.) are thickened and emphasized (**Figure 10a**). It is effective for observing flat lesions and emphasizing pits. B mode emphasizes parts with small frequency components (fine changes in luminance and color tone), so edges of structures are sharpened and emphasized (**Figure 10b**). It is easier to observe fine structural changes in the mucosa (mucosal patterns, vascular formation, etc.). Similar structure enhancement functions are also incorporated into image processors of other endoscope manufacturers.

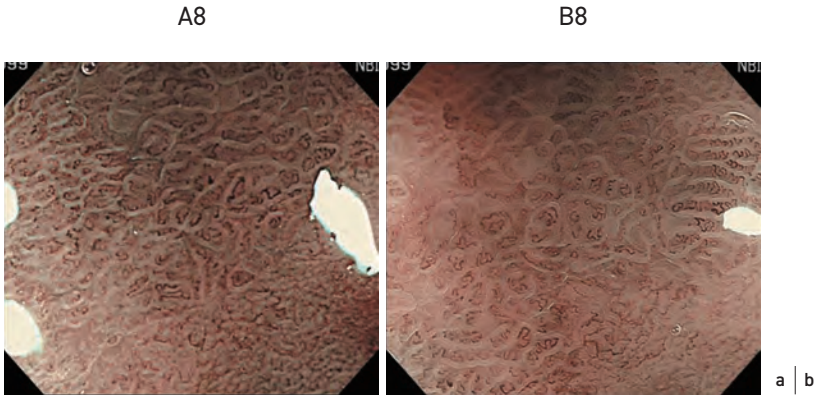


Figure 10 Comparison between adaptive structure enhancement A mode and B mode.

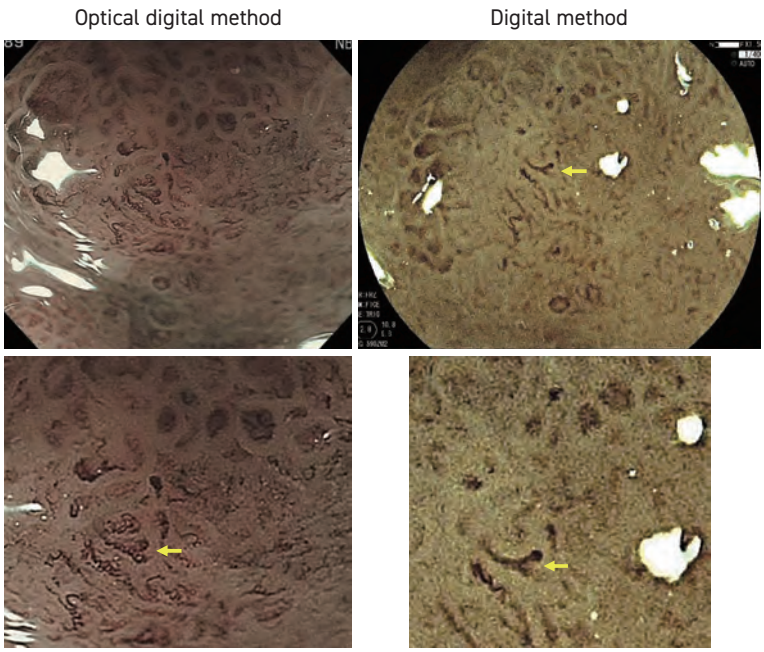


Figure 11 Comparison between the optical digital method and the digital method in endoscopic imaging.

(Cited from Literature 5)

2) Flexible spectral imaging color enhancement: FICE (Fujifilm)

Based on white light image information, it electronically calculates and estimates spectral images of arbitrary wavelengths and assigns them to RGB color channels for displaying reproduced color. Because images of all wavelengths can be depicted, there are a large number of combination patterns. Similarly, narrow band imaging (NBI) creates spectral images by optically using illumination light of specific wavelengths. In contrast, FICE generates spectral images through computerized electrical processing of images originally captured with normal white light. Therefore, optical effects such as image sharpening and improved visibility of vessel pattern due to narrow-band light irradiation, like NBI, cannot be obtained, and the disadvantage is that the image becomes unclear due to noise from image processing

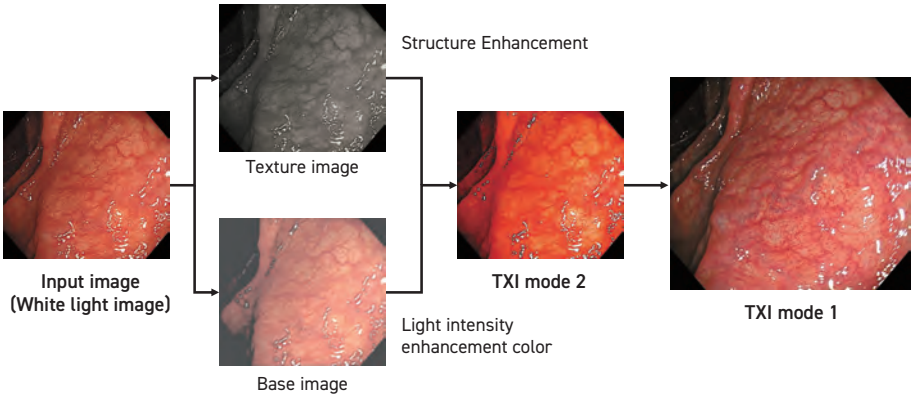


Figure 12 Mechanism of texture and color enhancement imaging (TXI).

(**Figure 11**).[5] However, on the other hand, the image is characterized by being generally bright because it is based on a normal white light image.

3) i-scan (Pentax)

Image enhancement by i-scan consists of three modes: (i) surface enhancement (SE), which recognizes and sharpens boundaries of objects on the image to perform structure enhancement; (ii) contrast enhancement (CE), which emphasizes depressions and structural differences by amplifying the blue component of the reproduced color of low-luminance parts based on pixel-by-pixel luminance information and coloring it in a bluish tone; and (iii) tone enhancement (TE), which independently converts and synthesizes color tones of images of each color information obtained from RGB pixels of the color chip type CCD along a tone curve. I-scan creates images in which color tone and structure are electrically emphasized by the image processor based on a white light image, and there is no emphasis effect on vascular images.

4) IHb color enhancement (Olympus)

Blood (hemoglobin: Hb) in microvessels within the mucosa is an important factor that determines the color tone of the mucosa, and color tone changes of lesions in various gastrointestinal diseases are related to the amount (increase/decrease) of blood vessels (Hb) within the mucosa. The IHb color enhancement image function uses normal endoscopic images to calculate the average value of hemoglobin index from two wavelengths (560 nm and 650 nm) strongly related to Hb, thereby displaying parts with higher values in red and parts with lower values in white for each pixel.

5) Texture and color enhancement imaging: TXI (Olympus)

Based on white light image information, this processor first separates white light images into two components: a texture image and a base image. Texture Enhancement is applied to the texture image to highlight surface irregularities, while Brightness Enhancement is applied to the base image to adjust and emphasize brightness. These processed images are then combined, and Color Tone Enhancement is added to highlight red areas, thereby resulting in a final image with enhanced visual clarity (**Figure 12**). Two modes are available: Mode 1 uses all three enhancements, and Mode 2 uses only texture enhancement and brightness enhancement/correction. The adaptive structure enhancement is unavailable when TXI is used.

(2) Optical-digital modality

This technology obtains image enhancement effects by **changing the characteristics of illumination light by applying optical filters and different light sources, and simultaneously performing processing with an image processor**.

1) Fluorescence

Fluorescence endoscopy includes a method of endoscopically observing differences in uptake and adhesion of exogenously administered fluorescent substances and a method of observing fluorescence (autofluorescence) from endogenous fluorescent substances in the living body.

(I) Autofluorescence imaging: AFI (Olympus)

AFI sequentially irradiates excitation light (395-475 nm) and green light (540-560 nm) from the light source of a sequential color illumination electronic endoscope through a rotating filter, captures autofluorescence images (detection wavelength 490-625 nm) and green reflected light images, and performs simulated colorization for display. In AFI images, normal mucosa is depicted in bright green, tumors are depicted in magenta with reduced green color reproduced by autofluorescence imaging, and blood vessels are depicted in dark green with reduced red/blue color reproduced by autofluorescence imaging.

2) Narrow band light

Narrow band light endoscopy is a technology that improves diagnostic ability by **limiting the wavelength of illumination light to a specific band** to obtain specific optical effects.

(I) Narrow band imaging: NBI (Olympus)

NBI emphasizes and depicts mucosal surface structure and vascular pattern by using narrow-band light rays of short wavelengths for illumination. It employs 400-430 nm blue and 525-555 nm green, limited in the Hb absorption curve (**Figure 13**).[5] In addition, narrowing the wavelength of illumination light to a short wavelength not only prevents blurring at the edges of objects but improves sharpness for depicting microvessels. Furthermore, in combination with magnified endoscopy, it becomes possible to observe fine surface structure and vascularity comparable to the histopathological profile. The color tone of NBI image assigns 400-430 nm images to blue/green color reproduction, and 525-555 nm images to red color reproduction. Therefore, vessels on the mucosal surface that absorb 400-430 nm are depicted in reddish tone (brown), which is the complementary color of cyan, and the slightly deeper blood vessels that absorb 525-555 nm are depicted in cyan tone (blue), which is the complementary color of red. The major impact of NBI technology on endoscopic diagnosis of the gastrointestinal tract is that it allows added evaluation of vascular images to conventional diagnostics based on color tone and morphology. This has also led to the development of Blue LASER Imaging (BLI) and i-scan Optical Enhancement (OE). The first-generation NBI systems produced dark images, which made it difficult to view the entire gastrointestinal tract. In contrast, the second-generation systems have been improved by increasing light intensity, using 415 nm light twice, and enhancing image processing for clearer visualization (**Figure 14**). The latest models irradiate bluish-purple and green LEDs, which have been narrowed in bandwidth and increased in light intensity among the five colors of LEDs. The reflected light passes through the blue and green pixel filters of the CMOS RGB sensor, and the resulting light information is sent to the monitor via the RGB channels. In NBI, part of the blue light information is also assigned to the R channel to help reproduce color more effectively (**Figure 6**).

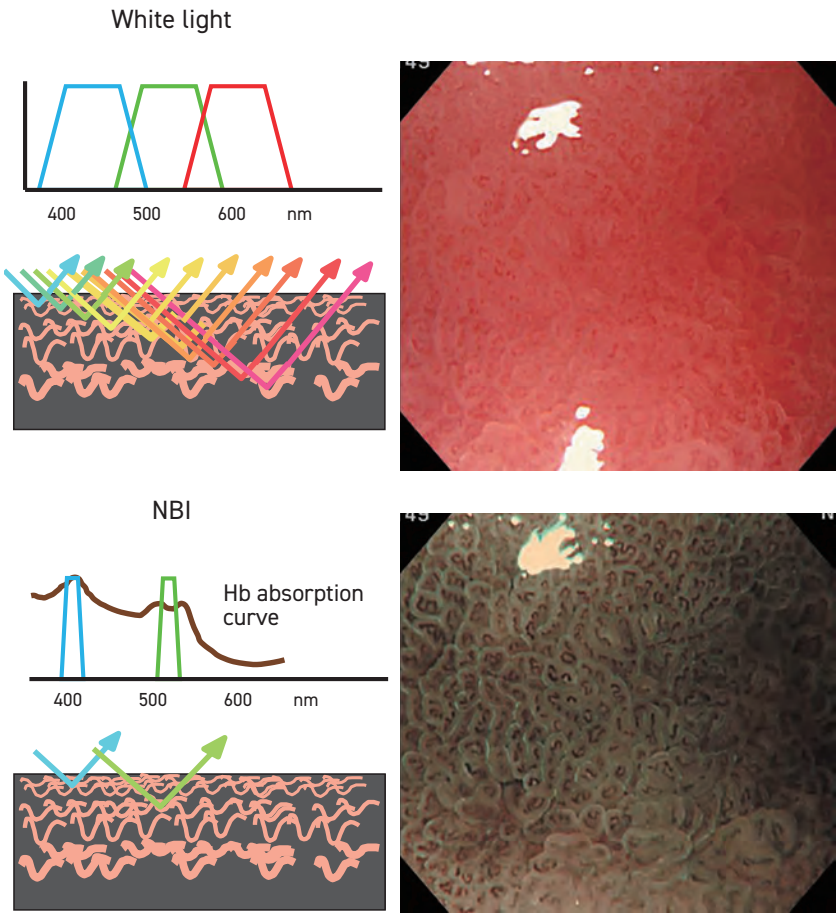


Figure 13 Mechanism of narrow band imaging (NBI).

(Modified from Literature 5)

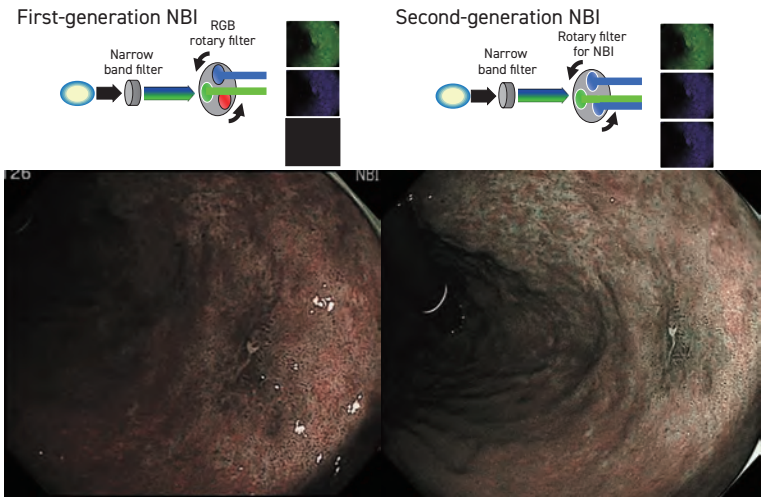


Figure 14 Mechanism of first- and second-generation NBI.

(Provided by Olympus Marketing)

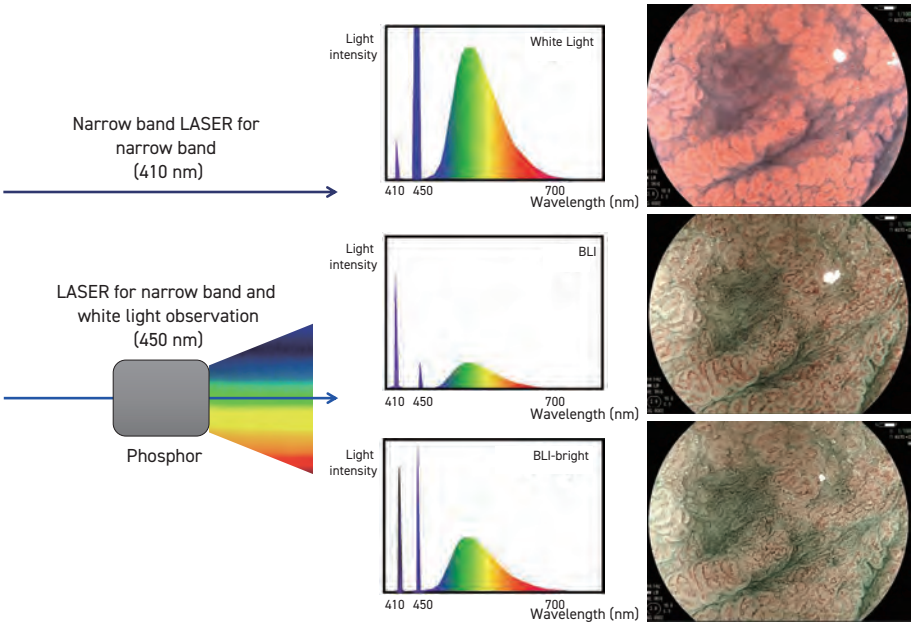


Figure 15 **Mechanism of blue LASER imaging (BLI).**

(Modified from Literature 5)

(II) Blue LASER imaging or blue light imaging: BLI (Fujifilm)

Blue LASER Imaging is an endoscope system that uses a laser as a light source for narrow-band light. The light source emits a laser of two wavelengths: 450±10 nm and 410±10 nm. Of these, a 450±10 nm laser is irradiated not only onto the mucosa for narrow-band observation but also causes phosphor to emit broad-band light for white light observation, whereas 410±10 nm is irradiated onto the mucosa for narrow-band observation. By changing the ratio of these light effects, it is possible to switch between white light observation and narrow-band light observation (**Figure 15**).[5] Because BLI uses narrow-band blue light laser in almost the same band as NBI, it is possible to emphasize and depict mucosal surface structure and vascular pattern same as with NBI. BLI stands for Blue LASER Imaging, because BLI uses a laser as a light source. This product is unavailable outside Japan. In the other countries, light sources using bluish-purple, blue, green, and red LEDs have been widely adopted, and they were also introduced in Japan starting in 2020. By controlling the light intensity of each of the four colors of LEDs and optically synthesizing them, illumination for white or narrow-band light endoscopy is possible. These LED type model is abbreviated as BLI same as Blue Light Imaging.

(III) Linked color imaging: LCI (Fujifilm)

LCI uses a laser light source of the BLI, irradiating narrow-band observation light laser capable of emphasizing blood vessels without compromising screen brightness by broad-band light for white light observation. It then applies image processing to enhance the separation of colors, especially in the red spectrum. LCI was developed for more specifically analyzing and emphasizing redness caused by inflammation (**Figure 16**).[5]

(IV) i-scan optical enhancement: i-scan OE (Pentax)

In addition to the conventional three image enhancement modes, i-scan is equipped with optical enhancement (OE) mode using band-limiting filters (OE filter). The OE mode has two modes. OE mode 1 irradiates band-limiting light of short wavelengths covering the peak of the Hb absorption curve,

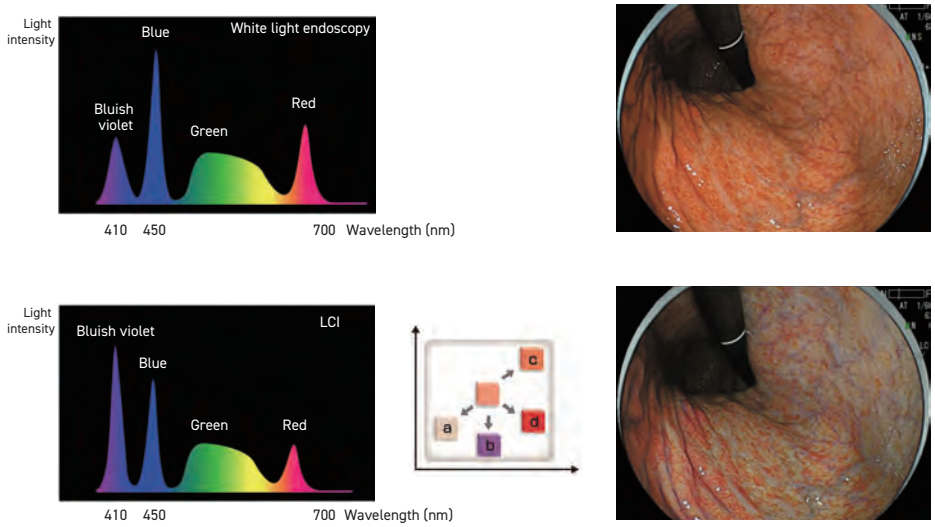


Figure 16 Mechanism of linked color imaging (LCI).

(Modified from Literature 5)

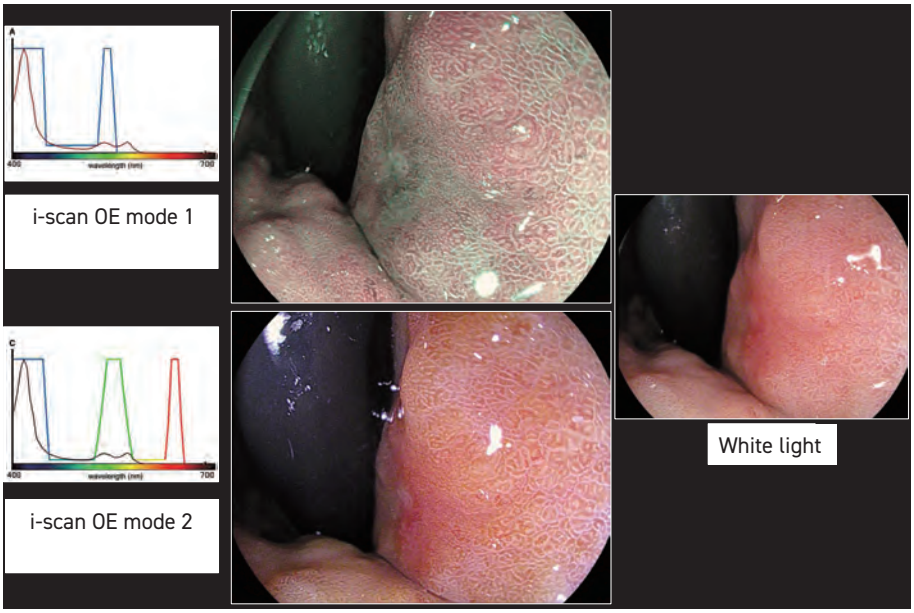


Figure 17 Mechanism of i-scan optical enhancement.

(Cited from Literature 6)

similar to NBI, and performs color simulation similar to NBI. OE mode 2 obtained images through band-limiting light, including long-wavelength light without color simulation (**Figure 17**).[6)]

(V) Red dichromatic imaging: RDI (Olympus)

RDI is a technology that uses illumination light combining narrow-band light of three wavelengths: red (630 nm), amber (600 nm), and green (540 nm). Amber is easily absorbed by human hemoglobin, whereas red is hardly absorbed. Furthermore, amber and red are long-wavelength light and therefore

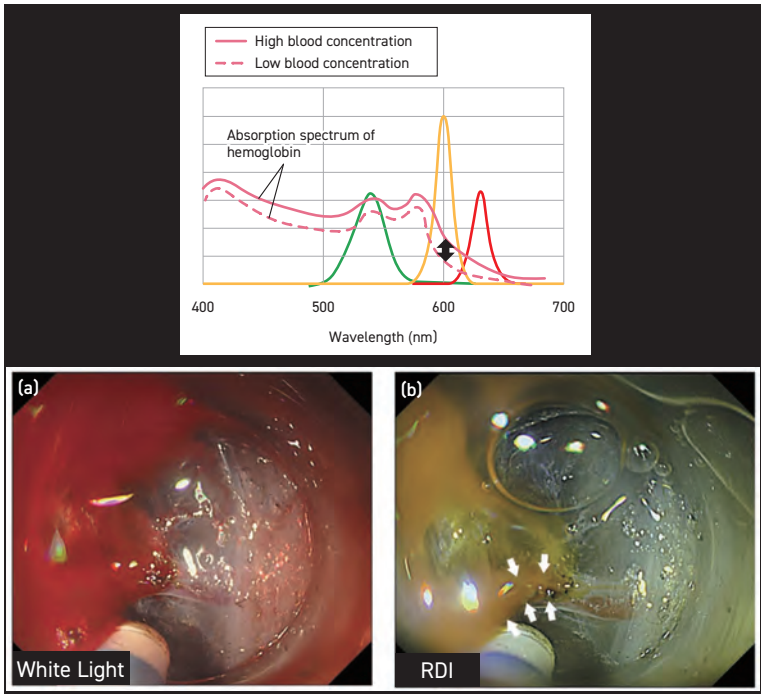


Figure 18 Mechanism of red dichromatic imaging (RDI).

(Cited from Literature 7)

penetrate deeply. Utilizing these characteristics, RDI is expected to be useful for improving the visibility of blood vessels and hemorrhagic sources during endoscopic treatment by improving the depiction of thick blood vessel images (**Figure 18**).[7)]

3) Infrared light method

(I) Infra red imaging: IRI (Olympus)

Infrared rays have long wavelengths and good permeability, so they reach deep into the mucosa. It is possible to depict blood vessels in the deep layer of mucosa more clearly by intravenous injection of indocyanine green (ICG) dye, because this dye has the maximum absorption wavelength in the infrared region (800-810 nm) in blood. IRI sequentially irradiates two types of infrared light with wavelengths of 790-820 nm and 905-970 nm from the light source of a sequential color illumination electronic endoscope using a rotating filter, thereby specifically depicting blood vessels in blue where only 790-820 nm infrared light is absorbed by ICG in blood.

4. Chromoscopy

The purpose of chromoendoscopy is to improve diagnostic ability and understand pathological conditions by applying various dye solutions to the mucosal surface of the gastrointestinal tract and performing endoscopic observation.[8)] In Japan, the application of dyes in the digestive field began in 1960s, and subsequently, research applying various dyes was reported in 1970s. In 1978, a unification of terminology for chromoendoscopy was suggested, and chromoendoscopy was broadly divided into (i) contrast method, (ii) staining method, (iii) dye reaction method, (iv) fluorescence method, and (v) others, based

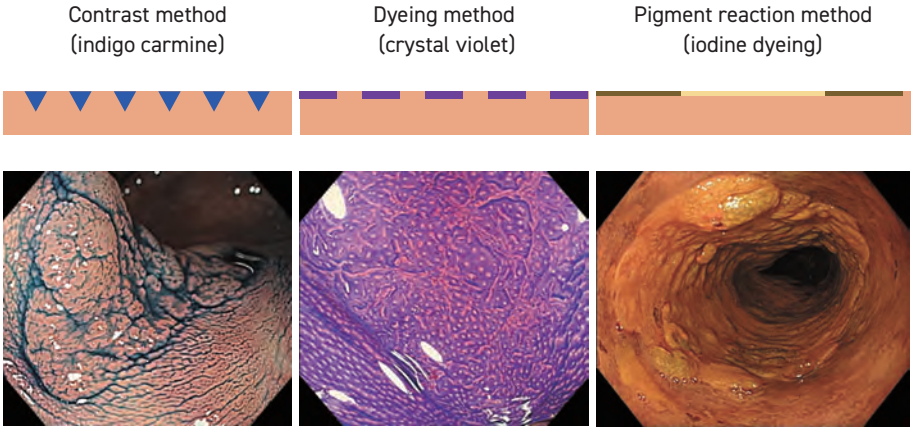


Figure 19 Classification of major chromoendoscopy techniques.

Table 1 Chromoendoscopy and its related dyes.

	Main Dyes and Their Concentrations				Indications
	Dye	Color	Toxicity	Concentration	
Contrast method	ndigo carmine	Blue to dark blue	LD50 = 93 mg/kg (rats, IV)	0.04 - 3.0%	Barrett's esophageal cancer Qualitative diagnosis of gastric cancer and its extent Detection and qualitative diagnosis of colorectal tumors, etc.
	Evans blue	Blue-green	(–)	0.1 - 0.2%	
	Brilliant blue	Blue	LD50 = 4.6 g/kg (mice, SC)	0.5 - 1.0%	
	Methylene blue	Blue	1,180 mg/kg (rats, oral)	0.05%	Diagnosis on extent of gastric cancer, etc.
Staining method	Methylene blue	Blue	1,180 mg/kg (rats, oral)	0.2 - 1.0%	Diagnosis of intestinal metaplasia, Diagnosis on extent of gastric cancer, etc.
	Crystal violet (pyoktanin solution)	Dark green, changes with pH	LD50 = 420 mg/kg (rats, oral) or 180 mg/kg (rats, oral)	0.05%	Qualitative diagnosis of colorectal tumors, etc.
	Toluidine blue	Bluish violet	LD50 28.93 mg/kg rats		Qualitative diagnosis of superficial esophageal cancer, etc.
Reactive method	Lugol's solution, Iodine solution	Reddish brown	Hypersensitivity	Adjusted to 1.2–3.0% iodine	Detection and extent diagnosis of esophageal cancer, etc.
	Congo red	pH 3: bluish violet, pH 5: red	LD50 = 15.2 g/kg (rats, oral)	0.3%	Diagnosis of acid secretion areas, etc.
	Phenol red	pH6 pH8	752 mg/kg (rats, IV)	0.05% (used with urea)	Diagnosis of H. pylori-infected mucosa spread, etc.
Fluorescence method	Acridine orange	Reddish orange	(–)	0.025% (direct) 500 mg (indirect)	Detection and extent diagnosis of gastric cancer, etc.
	Fluorescein	Yellow-red	LD50 = 6,721 mg/kg (rats, oral)	10%/5 mL ampoule	
Intravascular administration	Indocyanine green	Green	LD50 = 87.1 mg/kg (rats, IV)	2 mg/kg	Extent and invasion-depth diagnosis of gastric cancer (infrared endoscopy), etc.
	Fluorescein	Yellow-red	LD50 = 6,721 mg/kg (rats, oral)		Tissue diagnosis of GI cancers (confocal laser endoscopy), etc.

(Modified from Literature 5)

on its mechanism (**Figures 2 & 19**). **Table 1** lists the main dyes and their usage included in each method.[5] The fluorescence method is a process of administering fluorescently sensitive dyes such as acridine orange and fluorescein to the surface of the mucosa and observing the difference in affinity between normal tissue and lesions in endoscopic images. Please refer to Fluorescence in the section of Optical-digital modality.

(1) Contrast method

This is a method of applying dye to gastrointestinal mucosa and utilizing the accumulation of the dye solution in depressed areas to emphasize and observe morphological changes in lesions and surrounding mucosa, and differences in mucosal surface structure. Dyes with a different color tone from the mucosa are desirable, and blue dyes (indigo carmine and brilliant blue) are often selected.

(2) Staining method

This involves observation of the staining of living tissue due to the infiltration or absorption of dye into the mucosal epithelium. Methylene blue is often used for the diagnosis of small intestinal mucosa with absorptive capacity and intestinal metaplasia, and has recently also been applied to super-magnifying observation from staining of cell nuclei. Crystal violet is also used in combination with magnifying endoscopy to observe pit patterns from staining of the covering epithelium.

(3) Dye reaction method

This involves endoscopically observing various pathological conditions because the dye specifically reacts under certain conditions. For example, iodine is used for the diagnosis of esophageal cancer, Congo red for viewing gastric acid secretion areas, and phenol red for viewing the intragastric distribution of *Helicobacter pylori*.

5. Magnified Endoscopy

This technology was developed to get magnified images of the surface of the gastrointestinal lining. The goal was to improve diagnostic accuracy and understanding of diseases, making it comparable to a histopathological diagnosis, which is typically made by examining a tissue sample and is the standard for diagnosing gastrointestinal conditions. In Japan, its development began in the 1960s, and in 1977, a 30-fold magnified image of colonic mucosa was reported.[9] With the introduction of electronic mechanisms into scopes, endoscopy capable of magnifying from 40 to 100 times have become available. In combination with dye observation and narrow-band light observation, such endoscopy enables observation of fine surface structure and microvascular pattern of mucosa in detail. This modality is used for differential diagnosis of benignancy/malignancy and tumor/non-tumor, as well as depth of tumor invasion and lesion extent diagnoses. In the end, magnified endoscopy diagnostic classifications have been published for each organ including the esophagus, stomach, and colon. There are optical and digital methods for magnifying observation. During magnifying endoscopy, the depth of field becomes shallow, so this endoscopy is conducted with the target area positioned very close to the imaging lens, typically at a distance of about 1 to 2 millimeters.

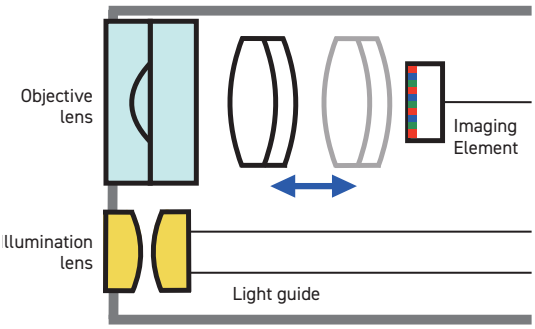


Figure 20 Mechanism of the magnifying endoscope.

(1) Optical method

This function uses a technique called the variable focus method, where an additional lens is placed inside the objective lens and shifted to change the focal length, that is, the distance to the image sensor. This adjustment allows the image to be enlarged without reducing resolution and enables observation from distant to close-up with a single endoscope (**Figure 20**).

(2) Digital method

This function stretches images acquired by the image sensor and projects them onto the monitor. Since the size of the original images does not change, the resolution decreases as magnification increases. Endoscopes from Olympus and Fujifilm are equipped with both optical zoom and digital zoom functions.

6. Microscopic Endoscopy

While magnified endoscopy has allowed practitioners to observe the vascularity and structure, microscopic endoscopy was developed for the purpose of observing structures at cellular resolution to more closely relate to pathological findings. The depth of field at maximum magnification is several tens of μm, and observation is performed with the objective lens in contact with the target object, so it is also called contact endoscopy. Since cells are optically transparent, staining is necessary.[10)]

(1) Optical method

Endocytoscopy was a probe type when it was first developed in 2004 and needed to be inserted through the instrument channel of mother scopes. Currently, these devices have an integrated single lens in which the microscopic observation lens and the normal observation lens are integrated. This technology enables continuous magnification from the normal level to 520 times by lever switching. By combining optical imaging with NBI, vascular structures are observed. Additionally, when a 1.0% methylene blue stain is applied, cell nuclei and glandular lumens become visible (**Figure 21**). In super-magnifying endoscopy, when the distal tip is in contact with the mucosa, the illumination light propagates through the mucosa cells, meanwhile repeatedly refracting and scattering at boundaries of the nucleus and cell membrane.

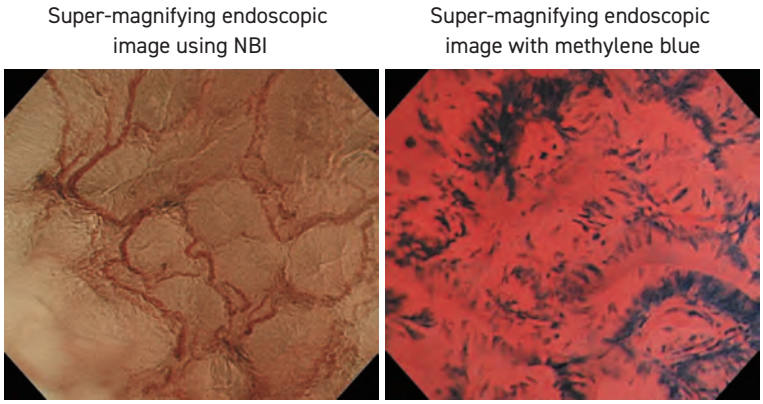


Figure 21 Super-magnifying endoscopic image using NBI and staining.

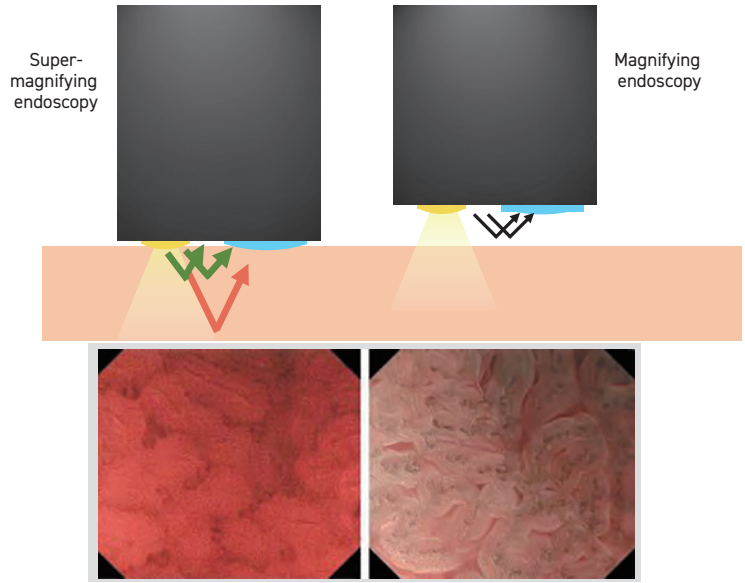


Figure 22 Comparison between super-magnifying and magnifying endoscopy.

(Cited from Literature 11)

When diffused light is applied to illuminate superficial cells targeted for observation, it acts like a backlight. This effect allows visibility of both stained and unstained areas with high contrast. In super-magnifying endoscopy, narrow-band light reflects off the mucosal surface. Because this reflection occurs close to the point of illumination, only a small amount of light reaches the objective lens. Therefore, in narrow-band light observation, the entire field turns dark, or the image becomes slightly reddish compared to the magnified observation image (**Figure 22**).[11)]

(2) Confocal method

Confocal laser endomicroscopy (CLE) makes images with fluorescent absorbed into cells by laser rays emitted from the tip of endoscopes. Currently, only probe types are commercially available. Fluorescein is administered as a fluorescent dye, and the probe goes through the instrument channel to contact the target. Tissues that absorb the fluorescent dye appear bright, while those that do not appear dark. This method can obtain magnified images approximately 1,000 times.

Conclusion

Image-enhanced endoscopy may not lead to an accurate diagnosis if enhancement modes or dyes are used without careful planning. It is essential for practitioners to gain basic knowledge on target diseases, principles of examination methods, and basic endoscopic operation techniques, regardless of which observation method is selected. It is also important to have a mind of performing systematic diagnosis while appropriately interpreting endoscopic findings and inferring underlying pathological conditions and tissue structure.

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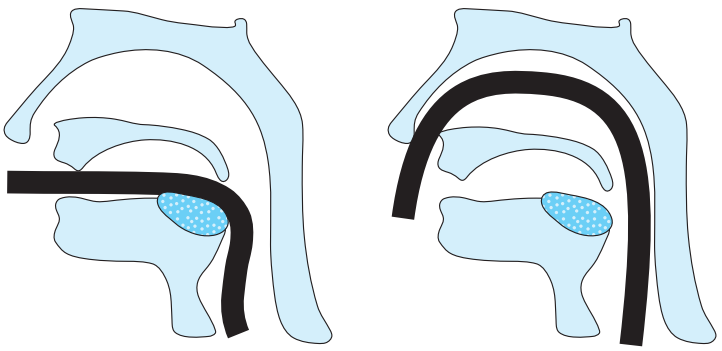
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Kenichiro Imai and Noriya Uedo

3 Transnasal Endoscopy

1. Outline

Regarding transnasal endoscopy (TNE), numerous reports have demonstrated its usefulness in reducing patient discomfort and its high acceptability. Because transnasal endoscopy avoids contact with the base of tongue and the posterior pharyngeal wall during insertion, **it can significantly reduce gag reflex** (Figure 1).[1] This is considered the most important characteristic and advantage of transnasal endoscopy. Furthermore, reduced gag reflex allows for detailed observation of laryngopharynx, the passage route. Conversation is also possible during the examination, which is useful for relieving patient anxiety. Transnasal endoscopy is less likely to induce cardiac burden due to sympathetic nerve stimulation caused by gag reflex, foreign body sensation, and breathlessness when the endoscope passes through pharynx and esophagus, as well as hypoxia caused by saliva accumulation during scope insertion.[2,3] It has also been reported that the procedure has **minimal impact on cardiopulmonary function**,[4] especially on respiratory function in elderly and high-risk patients, compared to peroral endoscopy. Furthermore, examinations can be performed with only nasal anesthesia without pharyngeal anesthesia, **thereby probably preventing aspiration during and after the procedure, especially in elderly patients**, compared to using peroral endoscopy. Transnasal endoscopy also tends to induce less peristalsis, so



(a) with peroral endoscope insertion
the endoscope sharply bends at the upper pharynx before advancing to pharyngoesophageal junction, pressing against and stimulating the base of tongue, thereby triggering gag reflex.

(b) with transnasal endoscope insertion
the endoscope does not pass through the oral cavity and thus does not press or stimulate the base of tongue.

Figure 1 Insertion routes of peroral endoscopy and transnasal endoscopy.
(Cited from Literature 1)

antispasmodics are not always necessary, and the use of sedatives and analgesics is also unnecessary, while the amount of topical anesthetic used can be reduced. These factors contribute to improved safety from the perspective of preventing adverse events due to drug use.

Following the recommendation of endoscopic examination as a strategy for gastric cancer screening in the *Japanese Guidelines for Gastric Cancer Screening* (2014 edition),[5] strategy-based endoscopic screening was started based on the revision of the *Guidelines for Priority Education of Cancer Prevention and the Implementation of Cancer Screening* in February 2016.[6] Furthermore, with the publication of the *Manual for Cancer Screening in the Workplaces* in 2018,[7] endoscopic screening is becoming more widespread in workplace screenings, and the number of local administration and healthcare centers introducing endoscopic screening is increasing throughout Japan. Transnasal endoscopy is thought to play a major role in endoscopic screening.

However, it is essential to acknowledge the performance limitations of transnasal endoscopy, such as **inferior image quality, reduced aspiration efficiency, and smaller instrument channel compared to peroral endoscopy due to the smaller diameter**. Although recent small-diameter endoscopes have improved image quality with increased image resolution,[8] they still have problems such as difficulty in removing dirt from the lens surface and weak air insufflation and aspiration. It is important for practitioners to fully understand the characteristics of transnasal endoscopy and to upskill and take care not to reduce diagnostic capability by simultaneously performing careful close-up observation, image-enhanced endoscopy (IEE), and dye spraying.

2. Indications and Contraindications

(1) Indications

The indications for transnasal endoscopy are generally the same as those for peroral endoscopy, including observation and diagnosis of pharynx, esophagus, stomach, and descending duodenum, as well as certain endoscopic procedures.[9] However, given the limitation on aspiration and lens cleaning capabilities and the lack of magnification it is generally considered unsuitable for precise examinations of lesions and **more appropriate for screening including check-ups**. Furthermore, it has been clarified that transnasal endoscopy has less impact on respiratory and circulatory dynamics, making it a good indication for **elderly with underlying diseases.**[4] Additionally, transnasal endoscopy is more suitable for cases with oral opening difficulties or esophageal stenosis due to malignant tumors of the head and neck, **where passage with a conventional endoscope is difficult.** In recent years, it has become more common to perform **ileostomy tube insertion and percutaneous endoscopic gastrostomy** under the assistance of transnasal endoscopy.

(2) Contraindications

Contraindications are also basically the same as those for peroral endoscopy, but since it is a route through nasal cavity, transnasal insertion is contraindicated **in cases with nasal cavity stenosis or severe deviated nasal septum**. Additionally, full attention is necessary in cases that easily cause **epistaxis**. There are currently no guidelines for transnasal endoscopy in patients undergoing antithrombotic therapy, and because most nasal bleeding during transnasal endoscopy occurs in the turbinate but not at the Kiesselbach's plexus, it has been reported that serious bleeding is rarely caused by careful insertion.[10]

3. Pretreatment

One of the advantages of transnasal endoscopy is that patients' discomfort could be reduced, and **sedation is generally unnecessary**. In order to improve the observation capability of thin endoscopes, it is desirable to perform thorough mucus removal and defoaming by oral administration of dimeticone syrup (Gascon® Drop Oral Solution 2%) and a proteolytic enzyme (Pronase® MS) solution before anesthesia. For the operation, it is easier to aspirate by diluting 80 mL of the solution to 160 mL. Administration of a local vasoconstrictor such as 0.05% naphazoline nitrate (Privina®) into nasal cavity not only improves nasal passage but is also useful in preventing epistaxis and pain. However, it is important to leave at least 15 minutes between spraying and the start of the process for sufficient efficacy. Since transnasal endoscopy uses a unique insertion route through nasal cavity, nasal anesthesia is naturally required. There are currently no guidelines for **nasal anesthesia** for transnasal endoscopy, and nasal anesthesia is broadly classified into spray methods[11] and stick methods,[12] and both methods are being used with some original modifications among medical facilities. In some cases, cotton swabs soaked in anesthetic are used instead of sticks. Although some facilities add pharyngeal anesthesia in addition to nasal anesthesia, it is possible to perform the examination without pharyngeal anesthesia because accidental stimulation of the base of tongue is reduced by nasal insertion. Thus, it is unlikely to induce the pharyngeal reflex. The basic techniques of both premedication methods are explained next.

(1) Spraying anesthetic

The basic method is to spray 4% lidocaine hydrochloride solution alone or its mixture with a local vasoconstrictor into nasal cavity. This is a simple technique and can shorten the anesthesia time. Although 8% lidocaine hydrochloride spray has the highest anesthetic effect because it contains ethanol, it is inappropriate for direct spraying into nasal cavity. Additionally, in cases where nasal cavity is narrow or nasal septum is deviated, anesthesia may be insufficient if the spraying substance alone does not sufficiently adhere to the deeper area, and it is necessary to use the stick method as needed.

(2) Sticking anesthetic

A typical method involves first injecting 2% lidocaine hydrochloride viscous solution into nasal cavity, then applying 2% lidocaine hydrochloride jelly or viscous to a stick and spraying it with 8% lidocaine hydrochloride spray (allowing the alcohol to evaporate after spraying), and finally inserting the stick (a Nelaton catheter or similar should be used as a substitute) into nasal cavity. In a two-step method, a slightly thinner stick (12-14 Fr) is inserted first, followed by a thicker stick (16-18 Fr) a while later, and in a one-step method, a thick stick (15-17 Fr) is inserted from the beginning. Although slightly more complicated than the spray method, this process achieves a certain anesthetic effect by allowing the anesthetic to reach deeply in nasal cavity. It also has a relaxing effect on examinees who have less experience with transnasal endoscopy as it provides a simulated experience of endoscope insertion.

4. Insertion and Manipulation Techniques

(1) Checking transnasal endoscope

Before performing the examination, endoscopists should check the endoscope equipment. They routinely check to ensure that insufflation, irrigation and aspiration devices and angulation function in the up/down and left/right directions operate smoothly. Small-caliber endoscopes could have less angulation capabilities than regular ones, so it is necessary to check them before each examination to avoid hindering the procedure.

(2) Passing through nasal cavity

In transnasal endoscopy, there are two possible routes for passing through the nasal cavity: one along the inferior margin of the middle turbinate and the other along the inferior margin of the inferior turbinate. Although both routes are used, if significant resistance is encountered during endoscope insertion due to anatomical or skeletal structure, the procedure should not be forced, and switching to peroral insertion becomes necessary.

(3) Operating procedures for transnasal endoscope insertion

After passing through nasal cavity, the process for the insertion method is the same as in regular peroral endoscopy, but the following points require attention. The endoscopes have low shaft rigidity (they are soft and flexible), which makes it harder to transmit force to the distal tip due to bending or flexing of the shaft along its length. Therefore, the scope is held close to the external nostril. In esophagus, it is necessary to manipulate the up/down and left/right angles so that the scope is centered in the lumen. Saliva influx and peristaltic movement tend to occur due to swallowing, making observation difficult during withdrawal. Therefore, observation during insertion is more important.

In esophagogastric junction, deep inspiration and gastric observation by retroflexion are important. The endoscope does not require sedation and is flexible, which is advantageous for observing this area.

In stomach, as with peroral endoscopy, special attention should be given to observing the posterior wall of angulus and posterior wall of body. Because of this angle, these areas tend to appear tangentially in the field of vision and the presence of lesions or subtle changes could be harder to detect. Furthermore, the lesser curvature of antrum and angulus, and the greater curvature of body need to be observed under adequate insufflation. If observation of the greater curvature of body is insufficient, it is easy to change the patient's position to supine in transnasal endoscopy.

In duodenum, insertion into the bulb may be hindered in cases of cascade stomach and gastric ptosis. After sufficiently aspirating air from the stomach, this process can be achieved. Furthermore, it is difficult to advance the scope into descending duodenum due to the characteristics of small-caliber scopes such as the low shaft rigidity.

(4) Biopsy

It has been pointed out that transnasal endoscopes become difficult to flex when a biopsy forceps is

inserted, which could hinder targeting. Also, the forceps cup is small, making it difficult to obtain sufficient tissue samples. Biopsy of the cardia area obtained by retroflexion is particularly difficult, and **skill is required in the selection of biopsy forceps and manipulation methods.**[13)]

(5) Troubleshooting and management

Among the troubles that occur with transnasal endoscopy, poor water clearing and lens dirt or fogging hinders observation.

1) Poor water clearing

Due to the position of aspiration port and lens, transnasal endoscopes have poor water clearing, and water easily adheres to the lens. As a practical measure, after blowing off the water with insufflation, operator should apply very slight aspiration to remove residual water.

2) Dirt or fogging of lens

Due to the tip structure of the scope, the lens easily becomes dirty and is difficult to clean. As a practical measure, it is important to prevent the lens from directly touching gastric mucosa during observation and mucus aspiration. For aspirating viscous mucus, it is useful to inject water to lower the viscosity before aspiration.

5. Observation

The fundamental principles of diagnosis using transnasal endoscopy include (i) **close-up observation**, (ii) **the combined use of image-enhanced endoscopy (IEE)**, and (iii) **taking sufficient time for the procedure**. As with peroral endoscopy, it is important to take pre-procedural measures such as the use of defoaming agent and proteolytic enzyme preparation, along with thorough cleaning of mucus and foam in the stomach.

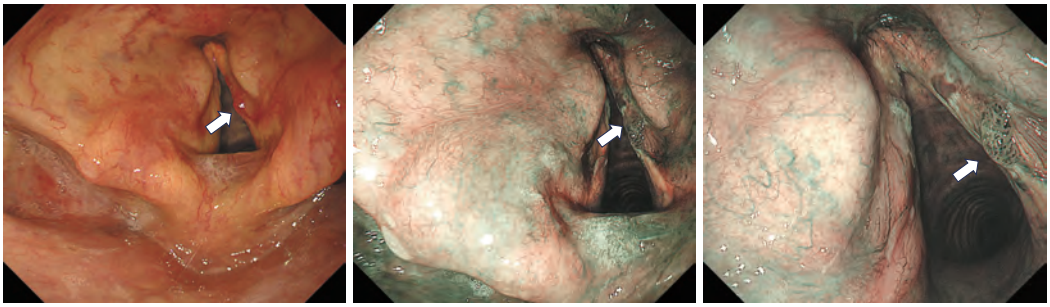
(1) Pharynx

Inflammatory changes such as reddening and erosive lesions are commonly observed. Differentiating between minor inflammatory and cancerous lesions by white light imaging alone is challenging. Recent advancements in resolution and observation depth of small-caliber endoscopes have enabled ultra-close observation of abnormal vessels in lesion areas, improving the capability to distinguish between benign and malignant conditions. Transnasal insertion minimizes reflex stimulation, **broadens the visual field in pharyngolaryngeal region**, and improves visibility using techniques like the Valsalva maneuver. These advantages highlight the utility of transnasal endoscopy, especially in high-risk patients for head and neck cancers.[14)]

[Case presentation (Vocal cord cancer, scope used: GIF-1200N)]

A man in his 70s underwent transnasal endoscopy as part of post-ESD surveillance for early gastric cancer. White light imaging revealed redness in the right vocal fold (**Figure 2a**, arrow).

Upon NBI (narrow band imaging) observation of the same area, a brownish area was noted (**Figure 2b**, arrow). Closer observation revealed abnormal dot-like vascular patterns (**Figure 2c**, arrow), suggestive



a | b | c

Figure 2 Diagnosis of vocal cord cancer.

(a) Conventional endoscopy using white light
(b) Narrow band imaging (NBI)
(c) Close-up view using NBI
The scope used is GIF-1200N, and EVIS XI System

of abnormal intra-epithelial papillary capillary loops (IPCL). A biopsy confirmed squamous cell carcinoma. Despite advancements in endoscopic capabilities, the pharynx and larynx are part of otolaryngological domain, necessitating collaboration with specialists in this field for diagnosis and treatment.

(2) Esophagus

With transnasal insertion, patients can swallow, thereby resulting in increased peristaltic movements compared to peroral endoscopy. These movements degrade image quality, so patients should be encouraged to expel saliva for observation of esophageal area after peristalsis subsides. The capability to observe vascular patterns in mucosa is slightly inferior to that of standard scopes, **necessitating the use of IEE modalities such as narrow-band imaging (NBI) or Blue Light/LASER Imaging (BLI)**. Abnormalities in vascular patterns may warrant the additional use of iodine staining. Typical endoscopic findings of early superficial esophageal carcinoma using magnified NBI include dilation, tortuosity, irregular caliber, and heterogeneous shape of IPCL in the basal layer.[15] These changes could also be identified as brownish areas in non-magnified endoscopy with NBI and BLI. These IPCL changes are recognized as a brownish area even in NBI non-magnified observation,[16] and similar observation is possible with BLI.

Transnasal endoscopy is advantageous for observing esophagogastric junction (EGJ) since it does not require sedation, enabling deep-inspiration observation. Its flexible scope allows for retroflexed observation from the gastric side, offering benefits over peroral endoscopy.

[Case presentation (Esophageal cancer, scope used: EG-L580NW7)]

A woman in her 60s underwent transnasal endoscopy for upper gastrointestinal screening. White light imaging revealed reddish mucosa with loss of vascular visibility on the anterior wall of middle esophagus extending to the left wall, with an indistinct border (**Figure 3a**).

Image-enhanced observation of the same area revealed enhancement of the clearly demarcated reddish mucosa with linked color imaging (LCI) (**Figure 3b**) and was recognized as a brownish area with BLI (**Figure 3c**). Endoscopic resection confirmed squamous cell carcinoma confined to the intraepithelial mucosa, measuring 25 x 21 mm.



a | b | c

Figure 3 Diagnosis of early esophageal cancer.

(a) White light endoscopy
(b) Linked color imaging (LCI)
(c) Blue light imaging (BLI)
The scope used is EG-L580NW7.

(3) Stomach

Recent advancements in transnasal endoscope imaging quality have achieved resolution comparable to high-resolution endoscopy (HRE). Reports suggest higher sensitivity and specificity with white light imaging in modern transnasal endoscopy, and close-up observation allows mucosal structural analysis equivalent to weak magnification in peroral scopes, enabling differentiation of benign and malignant lesions.

Regarding the diagnostic accuracy of small-caliber endoscope, while some reports indicate significant inferiority compared to high-resolution endoscopy (HRE),[17] others suggest **that the detection of tumorous lesions is equivalent to peroral endoscopy,**[18] **and that accuracy can be improved by the combined use of indigo carmine staining**[19] **and IEE.**[20] In recent years, the image quality of transnasal endoscopy has improved, and images comparable to HRE are now possible. There are reports that in white light observation, the improved transnasal endoscopy increases sensitivity and specificity, compared with conventional models.[21] Moreover, in close-up observation of mucosal structure, the improved transnasal endoscopy is comparable to peroral endoscopy with low-magnification, enabling differentiation between benign and malignant lesions.[22]

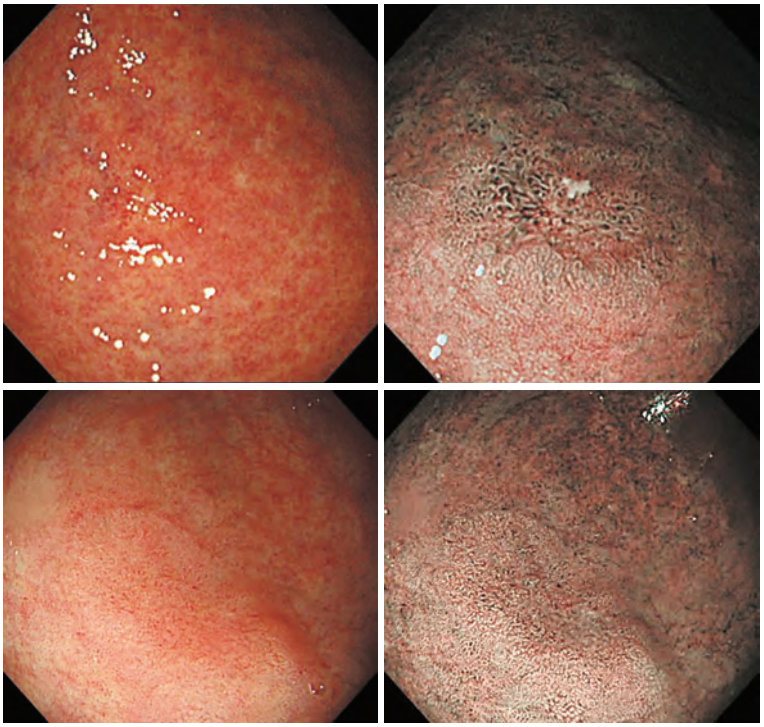
[Case presentation (Early gastric cancer, scope used: GIF-XP290N (**Figures 4a&b**), GIF-1200N (**Figures 4c&d**))[21]]

Figures 4a and 4b show a man in his 70s with early gastric cancer (0-IIc, tub2>1, pT1a (M), ly0, v0) near the greater curvature of anterior wall in lower body. In white light observation (**Figure 4a**), the lesion had some redness, but clear marginal irregularity and unevenness in depressed lesion could not be visually confirmed. In NBI close-up observation (**Figure 4b**), the lesion clearly showed a demarcation line (DL), and the depressed area showed an irregular surface pattern.

Figures 4c and 4d show a man in his 90s with early gastric cancer (tub1, 0-IIc, pT1a (M), UL(−), ly0, v0) near the anterior wall of greater curvature in antrum. In white light observation (**Figure 4c**), the lesion showed microsurface unevenness in the depressed area with patchy reddening. In NBI combined observation (**Figure 4d**), it was possible to observe a fine, irregular microsurface pattern throughout the depressed area.

[Case presentation (Early gastric cancer, scope used: EG-L580NW7)]

The patient was a man in his 70s. Transnasal endoscopy was performed for regular follow-up after successful eradication therapy. Within the atrophic mucosa of anterior wall of antrum, slight unevenness



a b
c d

Figure 4 Diagnosis of early gastric cancer.

(a) White light endoscopy
(b) NBI
(c) White light endoscopy
(d) NBI
Images (a) and (b) were taken using the GIF-XP290N with the EVIS LUCERA ELITE system, while images (c) and (d) were taken with the GIF-1200N and the EVIS LUCERA ELITE system.
(Cited from Literature 21)

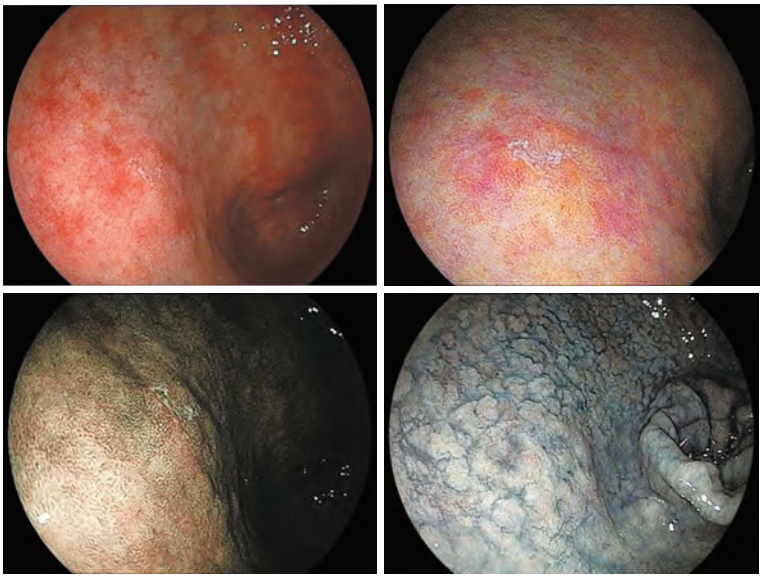
was suspected on white light observation, but no clear color change was evident (**Figure 5a**). LCI observation showed a lesion with a slight orange discoloration, which differed from the surrounding reddish-purple, but the lesion was unclear with BLI and indigo carmine observation. Endoscopic treatment was performed, and it was a well-differentiated adenocarcinoma confined to the 13 x 12 mm mucosa. In this case, visibility of lesion was best with LCI endoscopy.

(4) Duodenum

In recent years, the incidence of duodenal tumors, especially superficial carcinoma, has been increasing. The distribution of milk-white mucosa has been reported to be useful for differentiating tumorous lesions,[23] and IEE observation is also useful in transnasal endoscopy.

[Case presentation (Duodenal adenoma, scope used: EG-L580NW7)]

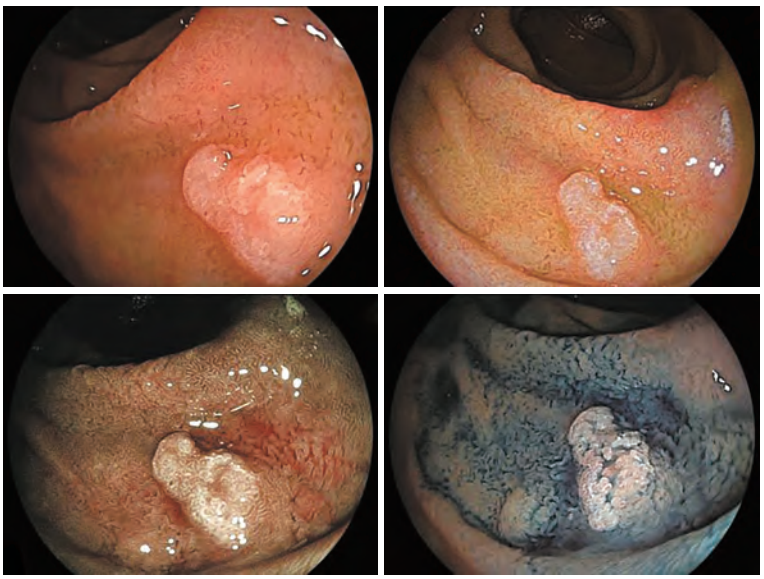
A woman in her 50s underwent transnasal endoscopy for upper gastrointestinal screening. A white, flat elevated lesion with slight redness and depression was observed in the descending duodenum opposite the papilla (6 x 3 mm, intestinal-type adenoma). Compared to white light imaging (**Figure 6a**), LCI (**Figure 6b**), and BLI (**Figure 6c**) enhanced lesion visibility, and indigo carmine staining provided the clearest visualization of the uneven surface of the lesion.



a b
c d

Figure 5 **Diagnosis of early gastric cancer.**

(a) White light endoscopy
(b) LCI
(c) BLI
(d) Chromoendoscopy using indigo carmine dye
The scope used is EG-L580NW7.



a b
c d

Figure 6 **Diagnosis of duodenal adenoma.**

(a) White light endoscopy;
(b) LCI;
(c) BLI;
(d) Chromoendoscopy using indigo carmine dye
The scope used is EG-L580NW7.

6. Adverse Events and Their Management

(1) Epistaxis

Epistaxis is a specific adverse event associated with transnasal endoscopy. However, because the usual insertion route avoids contact with Kiesselbach's area, there have been **no reports of severe epistaxis** requiring hemostatic treatment by otolaryngologists; **most cases are controlled with procedures such as nasal alar compression**. A report indicates that young people and females are at higher risk for epistaxis, and that antithrombotic therapy is not a significant risk factor.[24] As countermeasures, (i) performing the endoscopic procedure slowly where by checking for oozing from nasal cavity and accurately identifying the bleeding site, reliable hemostasis becomes possible (compression hemostasis using cotton balls or dental roller cotton soaked with a local vasoconstrictor); (ii) ensuring sufficient time for the local vasoconstrictor sprayed into nasal cavity to take effect; and (iii) avoiding forceful insertion when resistance is encountered and opting for an alternative route if necessary.

(2) Other adverse events

There have been reports of dizziness and headaches, although their incidence is low. Lidocaine should be administered cautiously, ensuring the total dose does not exceed 200 mg. Headaches may be associated with stimulation of the trigeminal nerve. In cases of severe pain, switching to oral insertion rather than continuing with forceful insertion should be considered.

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Rie Yoshimura and Takashi Kawai

4 High Frequency Electrosurgical Unit in Endoscopic Procedures

The use of high frequency electrosurgical unit has become more frequent in endoscopic treatments. To provide safer treatment, it is essential to not only master the technique but also acquire knowledge about high frequency electrosurgical unit. This section explains the basic knowledge needed to effectively use high frequency electrosurgical unit.

1. Fundamental Knowledge

(1) Basic principles of electricity

When considering settings for using a high frequency electrosurgical unit, it is necessary to understand Ohm's Law and Joule's Law.

$U\,[V] = R\,[\Omega] \times I\,[A]$

$P\,[W] = U \times I = R \times I^2$

$Q\,[J] = P \times \text{Time (t) [sec]} = U \times I \times t = R \times I^2 \times t$

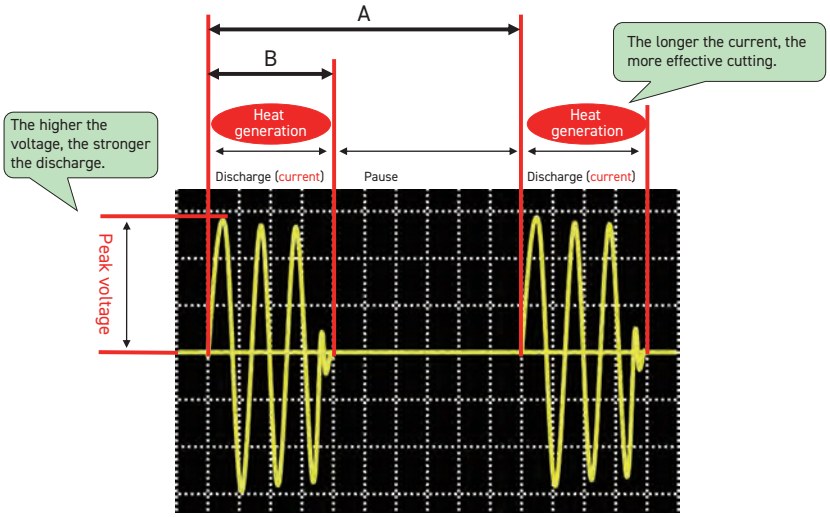
V: Voltage, Ω: Ohm, A: Ampere, W: Watt, J: Joule

U: Voltage, R: Resistance, P: Electric power, I: Electric current, Q: Heat quantity

(2) Basics of high frequency electrosurgical unit

Based on the presented Ohm's Law and Joule's Law, the effects of current and voltage will be explained in detail. High voltage results in stronger discharge, while low voltage leads to smaller discharge. If the voltage falls below 200V, no discharge occurs where this principle is used in soft coagulation. The amount of heat generated per unit area is proportional to the square of current density. Thus, higher current density results in more heat, and lower current density results in less heat. Each mode is defined by the combination of current/voltage with the duration of continuous waves (Duty cycle: DC*).

In general, there are two methods for using high frequency electrosurgical unit based on the path of current flow: monopolar and bipolar. In bipolar, current flows between two poles of the device, so no patientplate is needed. In monopolar treatment, the current is returned through the patientplate. Improper placement of the patientplate causes problems such as inadequate incision or burns at the placement site, so the correct setting is essential.



DC (%) = B ÷ A × 100

Figure 1 **Duty cycle (DC) / modulation rate.**

(Provided by AMCO Inc.))

<Patientplate placement>

- The plate is typically positioned on areas with few wrinkles or body hair, a smooth surface, and a thin layer of fat, such as the lower back or thighs.
- The plate should not be placed directly over bones or areas with skin wounds.
- The plate should be securely attached after placement.

*Duty cycle (DC)/ Modulation factor

Duty cycle (DC) represents the proportion of time within a given period during which continuous waves are output (%). A higher DC indicates a longer duration of continuous wave output (easier incision), while a lower DC reflects a longer inactive phase (less incision means more coagulation). Typically, modes with higher voltage are set with lower DC values (**Figure 1**).

(3) Incision and coagulation

Incision mode is characterized by low voltage and high current, with a high DC setting. Due to continuous current flow, the temperature rises rapidly in local tissues, causing an explosive vaporization effect that cuts through the tissue. Low voltage minimizes the discharge impact, resulting in a thin coagulation layer at tissue edges. The surrounding tissue damage is minimal, whereas bleeding control is limited.

Coagulation mode involves high voltage, low current, and low DC. Because the voltage is high, the discharge is strong, and blood vessels at the incision edges are cauterized in the incision process (**Figure 2**).

Incision capability depends not only on the settings of high frequency electrosurgical unit but also on the contact area of the device. A smaller contact area leads to higher current density which increases incision capability.

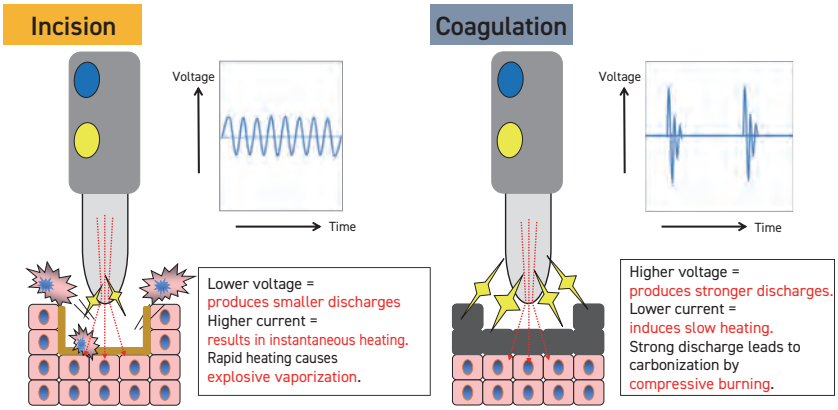


Figure 2 Incision and coagulation.

(Provided by AMCO Inc.)

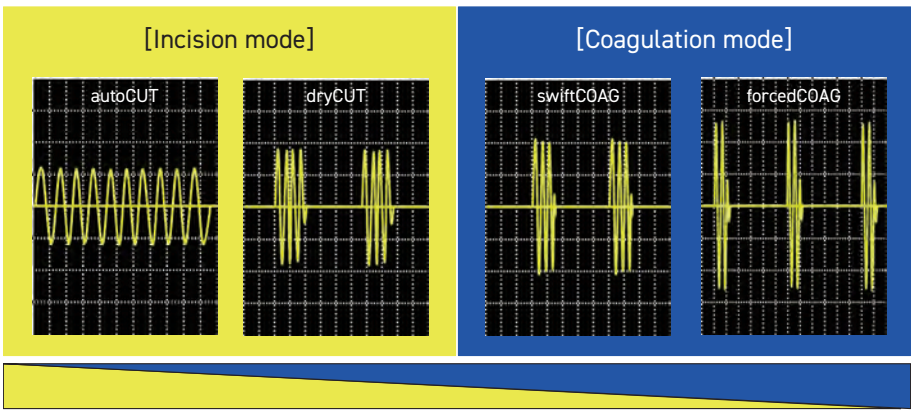


Figure 3 Output waveforms of key modes.

(Provided by AMCO Inc.)

2. System Mode

This section primarily explains VIO3 (by ERBE) and ESG300 (by Olympus) models. The output waveforms of representative modes are shown in **Figure 3**.

(1) VIO3

1) autoCUT

This is a complete incision mode (duty cycle: 100%) for continuous output while the foot switch is pressed. For endoscopic submucosal dissection (ESD), experienced practitioners can control incision time and device operation to minimize the impact of coagulation.

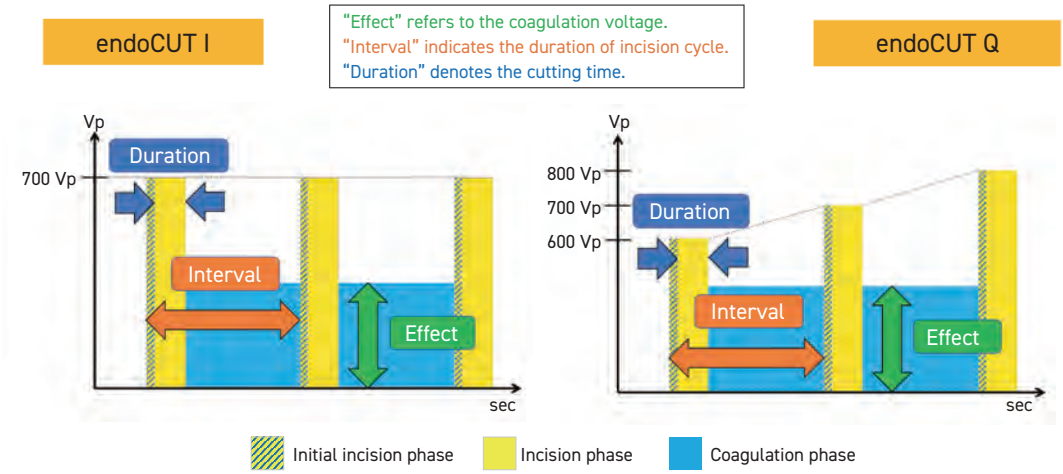


Figure 4 endoCUT settings.

2) endoCUT I (Figure 4)

This mode performs incisions intermittently with alternating between cutting and coagulation waveforms, operating at a fixed peak voltage of 700 Vp. This mode is often selected for mucosal incision in ESD and endoscopic sphincterotomy (EST).

<Effect>

The setting adjusts the amount of soft coagulation between incision cycles. At Effect 1, no coagulation occurs. As the Effect setting increases from 2 to 4, the coagulation strength also increases.

<Interval>

This determines the duration between incision cycles. As the setting number increases, the interval between each incision becomes longer, resulting in an extended duration of soft coagulation output during those intervals. Continuous foot switch operation allows practitioners to adjust the interval to their preference, while intermittent foot switch operation benefits from a longer Interval setting.

<Duration>

This controls the time for each incision wave output. It determines the incision distance per cycle. Adjusting the incision sharpness is controlled by the Duration setting, not by the Effect setting. For beginners, it is recommended to use the lowest possible setting and proceed with gradual incisions for greater safety.

3) endoCUT Q (Figure 4)

This setting works similarly to the endoCUT I mode, but the voltage gradually increases as continuous pressure is applied to the foot switch, progressing from 600 Vp to 700 Vp and then to 800 Vp. It is commonly used in endoscopic mucosal resection (EMR).

4) dryCUT

This is an incision mode with enhanced coagulation capability. Compared to autoCUT and endoCUT, this mode operates with a duty cycle of approximately 30%. Unlike endoCUT, it outputs continuously while the foot switch is pressed.

5) swiftCOAG

This is a high-incision-capability coagulation mode with a duty cycle of approximately 20%. Due to its relatively high voltage settings, it facilitates dissection even in highly fibrotic or fat-rich tissues during ESD.

6) forcedCOAG

This mode provides a balance between incision and coagulation, with a duty cycle of around 15%. Due to complete voltage control in VIO3, it offers more uniform coagulation depth during ESD.

7) sprayCOAG

This mode is designed to achieve broad and superficial coagulation through non-contact discharge. While the duty cycle is approximately 10%, the voltage is set exceptionally high at 4,300 Vp across all effect levels. As a result, applying electrocautery directly on the muscle layer carries a significant risk of perforation during endoscopic submucosal dissection (ESD).

8) preciseSECT

This mode was first introduced with VIO3. It automatically adjusts the duty cycle between almost 25% and 75% in response to tissue resistance, enabling stress-free dissection. It is recommended to use a lower voltage setting than that of swiftCOAG or forcedCOAG. Due to this considerable incision capability, it is particularly effective for fibrotic or fatty tissues in ESD. However, this requires precise knife control.

9) softCOAG

Although the DC is the same as for incision waves at 100%, the voltage is controlled to remain below 200V, preventing discharge. As a result, it is a purely coagulative mode with no incision effect and is primarily used for treating bleeding with hemostatic forceps.

VIO3 includes a quick-start function that briefly increases the voltage for 50 milliseconds at the start of activation, where users can turned this feature on or off if needed. This feature is particularly effective in low-resistance conditions, such as during procedures involving water immersion or active bleeding, where heat generation can otherwise take longer.

Modes 1) to 4) can be assigned to the yellow foot switch, while modes 5) to 9) can be assigned to the blue foot switch.

(2) ESG300

1) PureCut

This is a continuous incision mode with minimal coagulation process. It shares similar characteristics with autoCUT on VIO3.

2) PulseCut (Slow/Fast)

This mode performs incision and coagulation phases alternately. The interval from the start of incision phase to the start of the next incision phase is set to 800 msec for Slow and 550 msec for Fast. Slow is

generally used.

3) BlendCut

This is an incision mode with enhanced coagulation capability and a duty cycle of approximately 35%. It shares similar characteristics with dryCUT on VIO3.

4) PowerCoag

This is a coagulation mode with high incision capability and a duty cycle of approximately 20%. It shares similar characteristics with swiftCOAG on VIO3.

5) ForcedCoag

This is a coagulation mode with high hemostasis capability and a duty cycle of approximately 12.5%. It shares similar effects with forcedCOAG on VIO3.

6) SprayCoag

This is a mode that cauterizes tissue surface by non-contact discharge with a duty cycle of approximately 7.5%. It shares similar effects with sprayCOAG on VIO3.

7) SoftCoag

This is a coagulation mode that does not generate discharge and is mainly used for hemostasis with hemostatic forceps. It shares similar effects with softCOAG on VIO3.

Modes 1) to 3) can be assigned to the yellow foot switch, and modes 4 to 7 can be assigned to the blue foot switch.

3. Troubleshooting

If the expected output is not achieved, it is often due to issues with the correct patientplate placement. In such cases, replacement of the patientplate should be performed according to the Patientplate Placement. In cases of large lesions, devices are likely to degrade, causing reduced incision capability. If the trouble occurs, such a device should be changed.
If no output is observed, it is important to check for cable damage or improper patientplate attachment.

4. Argon Plasma Coagulation (APC)

APC is a non-contact high-frequency coagulation method that utilizes ionized argon gas. Compared to the sparks in contact coagulation methods, APC provides thermal effect over a broader area with a consistent depth of penetration, thereby making it suitable for conditions listed in **Table 1**. Typically, the gas emanation is set to 2 L/min or lower for stomach and 1 L/min or lower for the other parts of gastrointestinal tract. Gastrointestinal endoscopy APC probes are available with the axial, lateral, and radial apertures which are selected based on the application site to facilitate efficient cauterization (Figure 5). This section provides an explanation of the various modes of APC3 system (manufactured by ERBE).

Table 1 Indications for APC.

1	Vascular lesions such as GAVE (gastric antral vascular ectasia), DAVE (diffuse antral vascular ectasia), and radiation-induced proctitis
2	Ulcer bleeding, particularly in thin-walled organs at risk of perforation
3	Consolidation treatment for esophageal varices
4	Tumor ablation, including residual or recurrent lesions and tumor ingrowth or overgrowth after stent placement
5	Marking during EMR/ESD

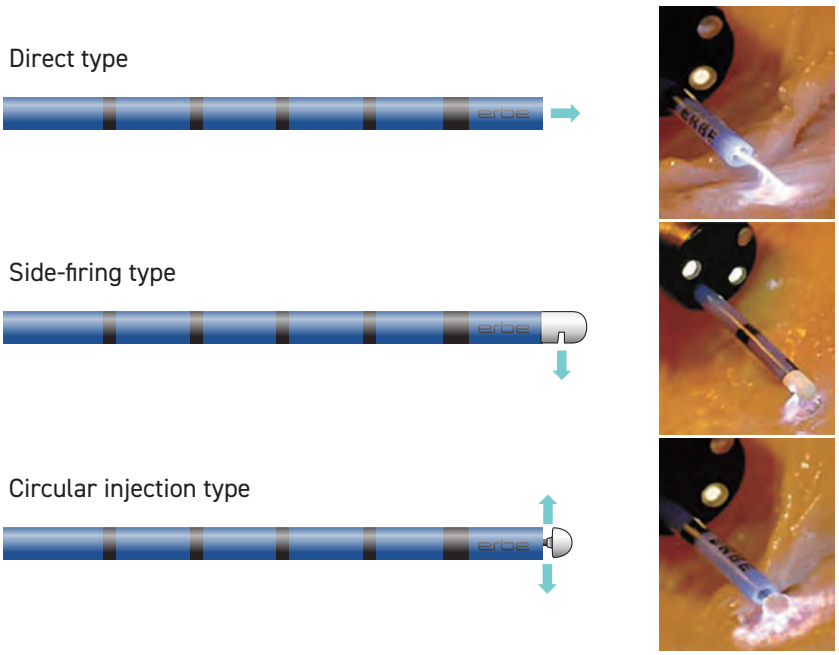


Figure 5 Types of APC probes.

(Provided by AMCO Inc.)

(1) forcedAPC

This mode is the standard for APC and offers the highest precision. It is frequently used for hemostasis in the gastrointestinal tract, additional cauterization of residual lesions after endoscopic resection, ESD marking, and the treatment for tumor ingrowth or overgrowth after stent placement.

(2) pulsedAPC

This mode allows selection between slow and fast settings. In the slow setting, discharge occurs once every 800 msec, while in the fast setting, discharge occurs once every 60 msec. The fast setting results in a wider coagulation range but with shallower penetration depth than the slow setting. Compared to forced APC, it easily provides the thermal effect on larger areas and is commonly used for conditions such as GAVE, DAVE, esophageal varices consolidation, and radiation-induced enteritis.

(3) preciseAPC

This is a unique mode that allows for consistent penetration depth regardless of the distance between probes and tissues. It enables the safe superficially coagulative propagation, even in thin-walled tissues or areas with significant respiratory movement. It is undesirable for large-area penetration but is useful for cauterizing duodenum and small intestine.

APC uses argon gas, which is likely to cause gastrointestinal duct dilation in prolonged procedures. Therefore, the output duration should be limited to approximately 1-3 seconds per application (1-2 seconds for thin-walled organs), and aspiration should be used as needed. Additionally, it is critical to pay careful attention to the risk of intestinal pneumatosis or gas embolism when the probe is in direct contact with gastrointestinal duct.

Reference

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Hiromitsu Ban and Takashi Toyonaga

II.Pharyngoesophageal

II. Pharyngoesophageal

1 Definition and Classification of Pharyngeal and Esophageal Regions

1. Anatomy and Subclassification of Oropharynx/Hypopharynx

In Japan, the subclassification of oropharynx/hypopharynx was defined based on the location of cartilages. Recently, however, the 6th Edition Supplement of the *General Rules for Clinical Studies on Head and Neck Cancer* incorporated a site-specific subclassification,[1] based on endoscopic findings for head and neck (**Figure 1**).

Pharynx lacks muscularis mucosae and is classified into the epithelium, subepithelium, and muscularis propria.

Superficial tumor is defined as a cancer where invasion of cancer cells is limited to the subepithelium and does not extend to the muscularis propria in pharynx and larynx, regardless of the presence or absence of lymph node metastasis.

The T factor for head and neck cancer excluding lip and oral cavity cancer, does not include depth of tumor invasion. Since pharynx and larynx lack muscularis mucosae, the depth of tumor invasion is replaced by and described as the tumor thickness at the site of deepest invasion. A multi-institutional study on superficial tumor that can be endoscopically resected revealed that the frequency of vascular invasion is high when the tumor thickness exceeds 1,000 μm.

2. Esophagus

(1) Division of esophagus

From the 12th Edition of the *Japanese Classification of Esophageal Cancer*, the area 2 cm above and below gastroesophageal junction is classified as gastroesophageal junction zone (Jz) as seen in **Figure 2.**[2]

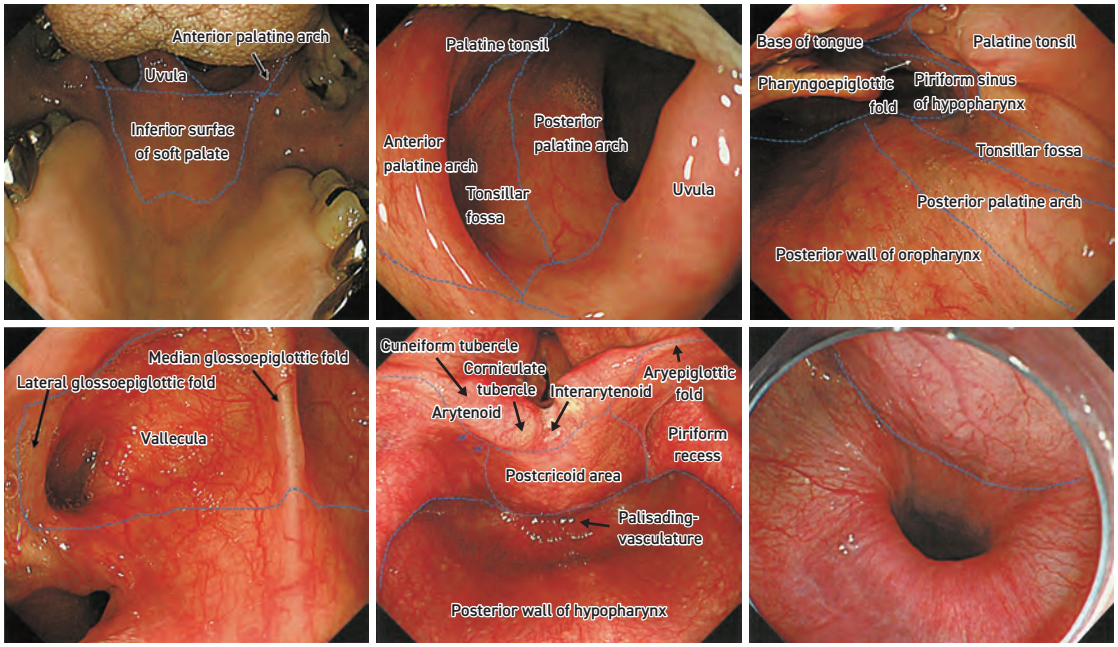


Figure 1 Anatomy of oropharynx/hypopharynx (Upper gastrointestinal endoscopy).

a: Superior and lateral walls of oropharynx
b: Lateral wall of oropharynx
c: Boundary between the posterior and lateral walls of oropharynx
d: Left epiglottic vallecula
e: Hypopharynx
f: Boundary between hypopharynx and esophagus
(Cited from Literature 1)

(2) Squamous cell carcinoma

1. Classification of depth of tumor invasion (Figure 3)[2)]

Tx: Depth of tumor invasion cannot be assessed
T0: No evidence of primary tumor
T1: Superficial cancer (primary tumor confined to mucosa or submucosa)
T1a: Tumor invades mucosa
T1a-EP: Carcinoma in situ
T1a-LPM: Tumor invades lamina propria mucosae
T1a-MM: Tumor invades muscularis mucosae (MM)
T1b: Tumor invades submucosa
T1b-SM1: Tumor invades the upper third of the submucosal layer
T1b-SM2: Tumor invades the middle third of the sub mucosal layer
T1b-SM3: Tumor invades the lower third of the sub mucosal layer
T2: Tumor invades muscularis propria (MP)
T3: Tumor invades adventitia (AD)
T4: Tumor invades adjacent structures (AI)

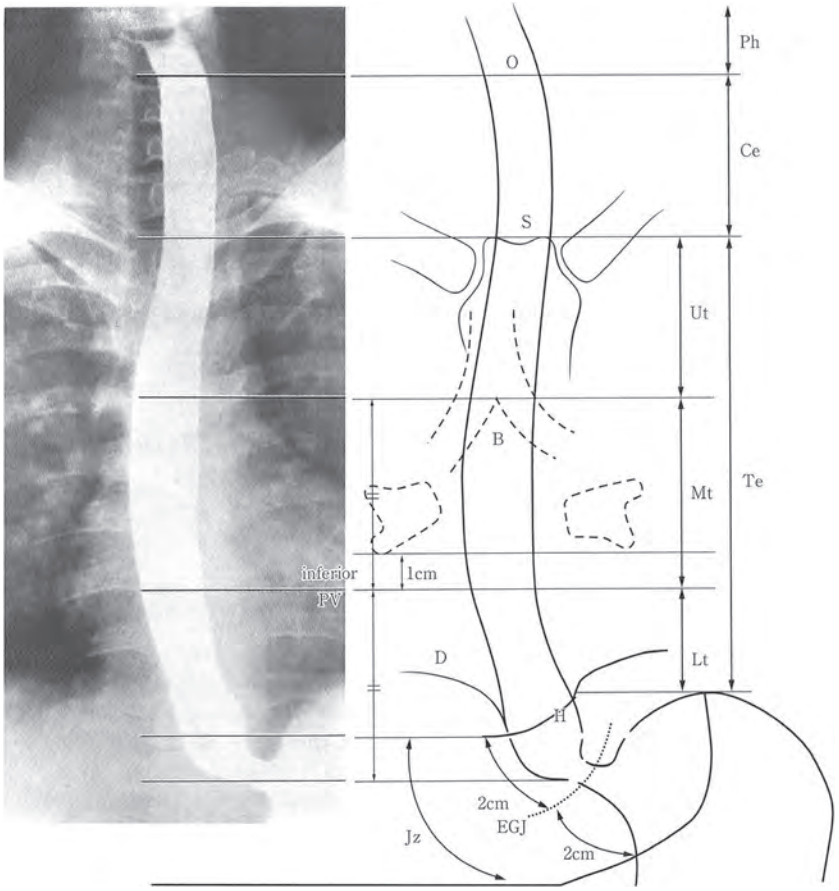


Figure 2 Location of esophagus.

O: Esophageal orifice
S: Superior margin of the sternum
B: Tracheal bifurcation
PV: Pulmonary vein
D: Diaphragm
EGJ: Esophagogastric junction
H: Esophageal hiatus
(Modified from Literature 2)

Ph: Hypopharynx
Ce: Cervical esophagus
Te: Thoracic esophagus
Ut: Upper thoracic esophagus
Mt: Middle thoracic esophagus
Lt: Lower thoracic esophagus
Jz: Esophagogastric junction zone

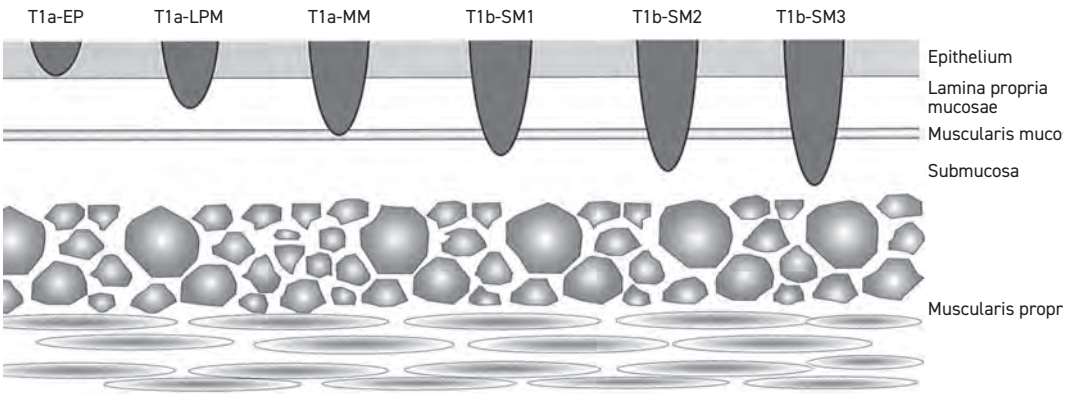


Figure 3 Subclassification based on depth of tumor invasion in esophageal cancer.

(Cited from Literature 2)

Superficial cancer is defined as a tumor with depth of its invasion confined to submucosa, regardless of the presence or absence of lymph node metastasis.

Early cancer is defined as an esophageal tumor with depth of its invasion confined to mucosa, regardless of the presence or absence of lymph node metastasis.

For lesions endoscopically resected, tumor confined to submucosa within 200 μm of muscularis mucosae is classified as T1b-SM1, and tumor invading from muscularis mucosae more than 200 μm into submucosa is classified as T1b-SM2 (SM3 is not defined).

2. Macroscopic criteria for assessing the depth of tumor invasion in esophagus

Type A: Microvessels without severe irregularities

Type B: Microvessels with severe irregularities

B1: Loop-like abnormal vessels showing all of dilatation, tortuosity, variation in caliber, and irregularity. These features correspond to EP to LPM.

B2: Vessels without a loop-like formations. This feature correspond to MM to SM1.

B3: Highly dilated vessels which have a greater vessel diameter. This feature correspond to SM2 or deeper.

Avascular area (AVA) is defined as a certain area without vessels or with sparse vessels surrounded by (any subtypes of) Type B microvessels**.**

AVA-small finds the size less than 0.5 mm in diameter. This feature correspond to EP to LPM

AVA-middle finds the size 0.5 mm or more but less than 3 mm in diameter. This feature correspond to MM to SM1.

AVA-large finds the size 3 mm or more in diameter. This feature correspond to SM2 or deeper.

(Cited from Literature 2)

(3) Adenocarcinoma

Definition of Barrett's esophagus: An esophagus with Barrett's mucosa (columnar epithelium extending from stomach into esophagus, regardless of the presence or absence of intestinal metaplasia) is called Barrett's esophagus. Long segment of Barrett's esophagus (LSBE) is defined as having Barrett's mucosa of 3 cm or more in any part.

Definition of Barrett's adenocarcinoma: Adenocarcinoma arising in Barrett's mucosa is called Barrett's adenocarcinoma. In Barrett's esophagus, in addition to original muscularis mucosae, a new one may form deep in columnar epithelium, resulting in a double muscularis mucosae.

The original one is called deep muscularis mucosae (DMM), and the new one superficial muscularis mucosae (SMM).

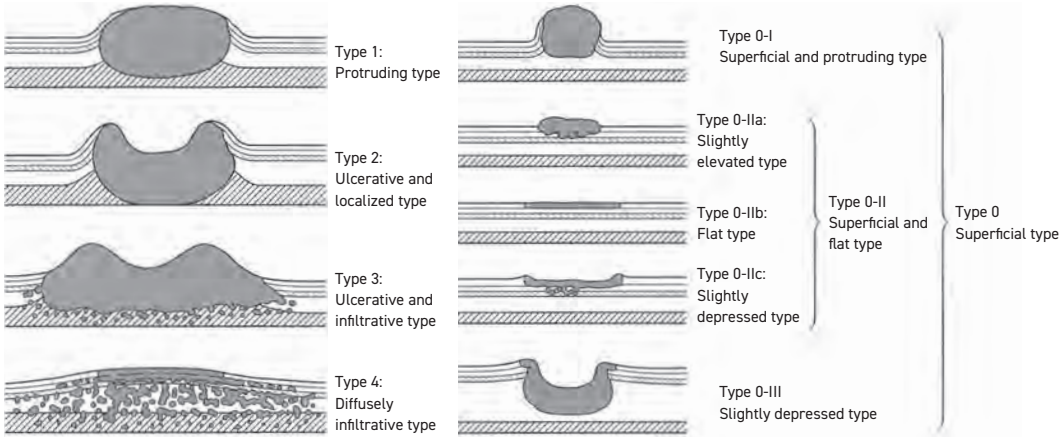


Figure 4 Macroscopic classification.

(Cited from Literature 2)

1. Depth of tumor invasion[2)]

TX: Depth of tumor unknown

T0: No evidence of primary tumor

T1: Tumor confined to the mucosa (M) or submucosa (SM)

T1a: Tumor confined to the mucosa (M)

T1a-SMM: Tumor invading the superficial muscularis mucosae (SMM).

T1a-LPM: Tumor invading the lamina propria mucosa.

T1a-DMM: Tumor invading the deep muscularis mucosae (DMM).

T1b: Tumor confined to the submucosa (SM)

T2: Tumor invading muscularis propria (MP)

T3: Tumor invading the subserosa (SS)

T4: Tumor invasion is contiguous to or exposed beyond the serosa, or the tumor invading adjacent structures.

T4a: Tumor invasion is contiguous with the serosa or penetrates the serosa and is exposed in the peritoneal cavity (SE)

T4b: Tumor invading adjacent structures (AI/SI)

(4) Macroscopic tumor type (Figure 4)[2)]

0Type 0: Superficial

Type 1: Protruding

Type 2: Ulcerative and localized

Type 3: Ulcerative and infiltrative

Type 4: Diffusely infiltrative

Type 5: Unclassifiable

Type 5a: Unclassifiable without treatment

Type 5b: Unclassifiable after treatment

(5) Subclassification of superficial type (Type 0)[2)]

Type 0-I: Superficial and protruding type
- 0-Ip: Pedunculated type
- 0-Is: Sessile (broad-based) type

Type 0-II: Superficial type
- 0-IIa: Slightly elevated type
- 0-IIb: Flat type
- 0-IIc: Slightly depressed type

Type 0-III: Superficial and excavated type

According to the Paris classification, type 0-III refers to depressed lesions caused by ulceration and is described as being applicable to Barrett's esophagus and gastric lesions. However, in Japan, type 0-III is regarded as lesions characterized by both tumor thickness and depression, and it indicates lesions in which the excavated area is presumed to extend beyond the muscularis mucosae.

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2 Observation Methods

1. Basics for Observing Pharynx and Esophagus

In endoscopic observation of pharynx and esophagus, it is crucial to keep in mind that early cancer detection is the primary goal. Head and neck cancers and esophageal cancer, not only have poor prognoses but also significantly impair quality of life, making early detection essential. This requires not only understanding the risk factors for these disease entities but also conducting efficient and effective observations during endoscopy, especially for high-risk groups.

(1) Risk factors for head and neck cancer and esophageal cancer

The International Agency for Research on Cancer (IARC), a part of the World Health Organization (WHO), classifies environmental factors related to cancer risk from Group 1 (carcinogenic to humans) to Group 4 (probably not carcinogenic to humans). In October 2009, IARC designated not only tobaccos and alcohols but acetaldehyde, a breakdown of alcoholic beverages, as a Group 1 carcinogen for squamous cell carcinoma of the head and neck or esophagus.[1)]

Ethanol in alcoholic drinks is absorbed in the stomach, duodenum, and small intestine, transported to the liver, and metabolized into acetaldehyde by alcohol dehydrogenase 1B (ADH1B) in the mitochondria of hepatocytes. Acetaldehyde is then metabolized into non-carcinogenic acetic acid by aldehyde dehydrogenase 2 (ALDH2), which is also located in the mitochondria.

ALDH2 has genetic polymorphisms. Approximately 50% of Japanese population have the wild-type (*1/*1), about 40% have the heterozygous deficient type (*1/*2), and less than 10% have the homozygous deficient type (*2/*2).[2)] The homozygous deficient type possesses almost no ALDH2 enzyme activity, whereas the heterozygous deficient type has about 17% of the wild-type activity. Many individuals with the *ALDH2* deficient type (defined here as both heterozygous and homozygous deficient) find flushers who experience facial redness even after small drinks such as a glass of beer, indicating alcohol intolerance, but they possibly become heavy drinkers with continued consumption.[3)] Ethanol administration to *ALDH2* knockout mice induces genetic damage by acetaldehyde and generates DNA adducts.[4)] Meta-analysis revealed that heavy drinkers with the *ALDH2* heterozygous deficient type have a high risk of developing esophageal cancer.[5)]

ADH1B also has genetic polymorphisms. 5-7% of Japanese have the homozygous low-activity form of the *1 allele (defined here as the *ADH1B* slow-metabolizing type). Because ethanol metabolism is slower in this type, these individuals are exposed to ethanol for longer periods upon drinking,

developing tolerance more easily. They also have weaker flushing reactions and are prone to heavy drinking. Notably, oral bacteria produce high concentrations of acetaldehyde from ethanol in saliva.[6] Since *ADH1B* slow-metabolizing types retain ethanol and acetaldehyde in saliva for longer periods after drinking, they are considered to have higher risks of esophageal squamous cell carcinoma even with the same alcohol consumption level.[7] Meta-analysis also indicates that heavy drinkers with the *ADH1B* slow-metabolizing type have a high risk of developing esophageal cancer.[8]

In addition to drinking, it has been shown that genetic mutations accumulate in seemingly normal esophageal mucosa with age, and these mutations are further affected with risk factors such as smoking.[9] Mutations in the tumor suppressor gene *TP53* are frequently observed in the background esophageal mucosa of the cancers and are considered a cause of the malignancy.[9,10]

(2) Field cancerization in head and neck or esophagus

The head and neck or esophagus are known for the frequent occurrence of atypical epithelium and squamous cell carcinoma, a pattern of carcinogenesis reported as field cancerization.[11] In a prospective cohort study (JEC study, n=330) that registered and followed cases of endoscopic resection of esophageal cancer in Japan, the 5-year cumulative incidence of second primary head and neck cancers was 6.6%, and the 5-year cumulative incidence of second primary multiple esophageal cancers was 25.5%.[12] In a national multicenter survey of superficial head and neck cancers (n=568), the 3-year cumulative incidence of metachronous cancers arising multiply in head and neck after transoral surgery was 16.7%, and the 3-year cumulative incidence of metachronous cancers arising in other organs was 14.7%. Of the 131 second primary cancers developed in other organs, 90 were esophageal cancers. [13] Therefore, in cases with a history of treatment for head and neck or esophageal cancers, it is necessary to conduct examinations for the possibility of new cancers developing metachronously in these regions.

(3) Lugol-voiding lesions of esophageal mucosa

Lugol chromoendoscopy is a test in which the solution of iodine together with potassium iodide is sprayed onto the esophageal mucosa, causing normal mucosa to stain brown. This technique for staining the esophageal mucosa brown utilizes the fact that normal esophageal mucosal cells contain glycogen, which reacts with the iodine and potassium iodide solution through iodine-starch reactions. Because the cancerous cells do not contain glycogen, they form the Lugol-voiding lesions (LVL).[14] Suspicion for a neoplastic lesion arises when a LVL is observed with the sharp demarcation and irregular margins. If the pink color sign appears several minutes after spraying, carcinoma should be suggested (**Figure 1**).[15]

Notably, Lugol chromoendoscopy could find multiple LVL in the esophageal mucosa. This phenomenon was named by Muto and colleagues, who investigated its association with alcohol consumption and *ALDH2* gene polymorphism.[16] LVL includes inflammation and esophageal dysplasia. In esophageal cancers, when the alcohol consumption habit was less than 100 grams of pure ethanol per day (one cup of sake, approximately 20 grams), *ALDH2* deficiency found to significantly increase the risk of developing multiple LVL compared to the cases with normal ALDH2 enzyme activity (Odds ratio [OR], 8.85; 95% confidence interval (CI), 1.68-46.69; p=0.01).[17]

In a prospective cohort study (JEC study) that registered and followed the cases of endoscopic resection of esophageal cancer, the severity of LVL observed in the background esophageal mucosa was



Figure 1 **Pink color sign.**

The arrow indicates a Lugol-voiding lesion that exhibits the pink color sign.

classified into three grades (Grade A: no lesions; Grade B: 1-9 lesions; Grade C: 10 or more lesions present in one endoscopic field). The 5-year cumulative incidence of second primary esophageal cancer was 6.0% for Grade A, 17.8% for Grade B, and 47.1% for Grade C (Grade A vs. B: p=0.022, A vs. C: p<0.0001) with the median follow-up period of 80.7 months (range: 1.3-142.3). The 5-year cumulative incidence of second primary head and neck cancer was 0.0% for Grade A, 4.3% for Grade B, and 13.3% for Grade C (Grade A vs. B: p=0.12, A vs. C: p=0.0007).[12] In multivariate analysis, Grade C was an independent risk factor for metachronously developing esophageal cancers (Hazard ratio [HR], 8.76; 95% CI, 3.02-25.5) and head and neck cancers (HR, 3.51; 95% CI, 1.34-9.20) (**Figure 2**).[10]

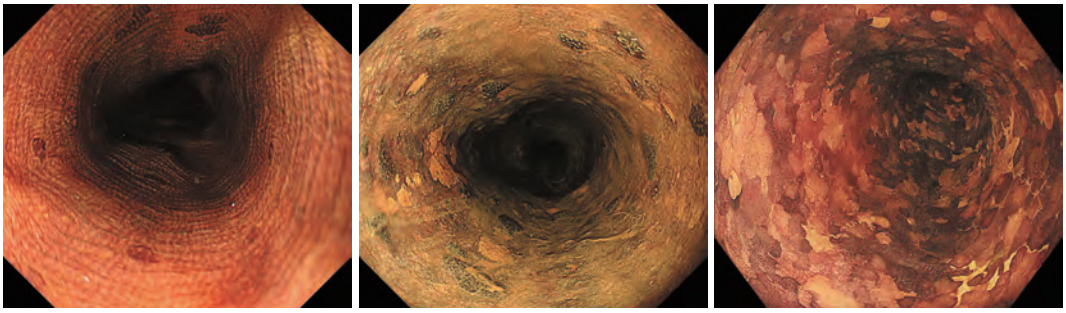
In a case-control study using multivariate analysis to identify factors for synchronous or metachronous development of superficial head and neck cancer in esophageal cancer patients, significant risk factors included multiple LVL (OR, 61.12; 95% CI, 5.4-691.64; p=0.001), *ALDH2* deficient type (OR, 16.19; 95% CI, 1.15-228.06; p=0.04), and smoking habit (OR, 8.02; 95% CI, 1.09-59.22; p=0.04).[18]

Therefore, the grade of LVL observed in the esophageal mucosa is a strong biomarker for predicting the development of synchronous or metachronous head and neck or esophageal cancers.

(4) Recommendation of abstinence from drinking and smoking for patients with head and neck or esophageal cancer and the high-risk groups

In a prospective cohort study (JEC study) of esophageal squamous cell carcinoma patients who underwent endoscopic resection, the follow-up cases consuming habitually 22 grams (equivalent to about one cup of sake) or more of pure ethanol per day were associated with a significant reduction in the cumulative incidence of metachronous esophageal cancer upon cessation of alcohol (HR, 0.47; 95% CI, 0.26-0.85; p=0.013). This tendency was particularly pronounced in Grade C LVL cases (HR, 0.30; 95% CI, 0.13-0.67; p=0.003).[12] In a study targeting males with an HRA-F score of 12 or higher, abstinence from alcohol also significantly reduced the cumulative incidence of metachronous esophageal cancer (HR, 0.37; 95% CI, 0.14-0.97; p=0.042).[19] Furthermore, the grade of LVL sometimes improved by abstinence or reduction of alcohol consumption, and this improvement involved a decreased incidence of metachronous esophageal cancer.[20]

When the Alcohol Use Disorders Identification Test (AUDIT), a screening test developed by the WHO



Grade A Grade B Grade C

Figure 2 **The grade of Lugol-voiding lesion of esophageal mucosa.**

Grade A: no lesions; Grade B: 1-9 lesions; Grade C: 10 or more lesions present in one endoscopic field

for problematic drinkers, was administered to cases registered in the JEC study, 25.4% were in the group suspected of alcohol dependence (AUDIT score of 15 or higher), and 36.7% were in the group with problematic drinking (AUDIT score of 8-14). These results indicate that a certain number of endoscopic resection of esophageal cancers require strong guidance to the patients for alcohol abstinence.[21] Smoking cessation has also been reported to significantly reduce the cumulative incidence of metachronous esophageal cancer (median follow-up period 80.7 months, HR, 0.49; 95% CI, 0.26-0.91; p=0.024).[12] For the purpose of preventing the development of metachronous esophageal cancer, guidance for abstinence from drinking and smoking is recommended for patients after endoscopic resection of esophageal cancers.

2. Endoscopic Diagnosis by Non-magnifying Endoscopy

Given that the pharynx and esophagus are both lined with squamous epithelium, many aspects of endoscopic diagnosis are similar for both regions. Under white light endoscopy, early carcinomas can be detected by the findings such as interrupted background vessels, regional changes in mucosal coloration, microgranular changes, white deposit (keratinization or white coat), irregular depressions or elevations, erosions, and minor bleeding points.[22]

In esophageal carcinomas, there is a correlation between the endoscopic macroscopic classification and the depth of tumor invasion (**Figure 3**). The esophageal mucosa (M) consists of the epithelium (EP), lamina propria mucosae (LPM), and muscularis mucosae (MM). In surgically resected specimens, cancer invading the submucosa (SM) is subclassified into three layers: SM1 for invasion up to the upper third of the submucosa, SM2 for invasion up to the middle third, and SM3 for invasion up to the lower third. In endoscopic resection specimens, lesions confined to the submucosa within 200 μm from the muscularis mucosae are subclassified as SM1, and those invading the submucosa more than 200 μm from the muscularis mucosae as SM2.

Type 0-IIb carcinomas are indistinct on white light imaging and can only be detected as EP by Lugol chromoendoscopy. Type 0-IIa finds the low elevation with granular changes, and is likely to invade LPM/MM layers, whereas type 0-I exhibits the coarse nodular elevation of 1 mm or more and type 0-III shows the deep depression, and both are likely to invade SM2/SM3 layers. Yoshida and colleagues reported that

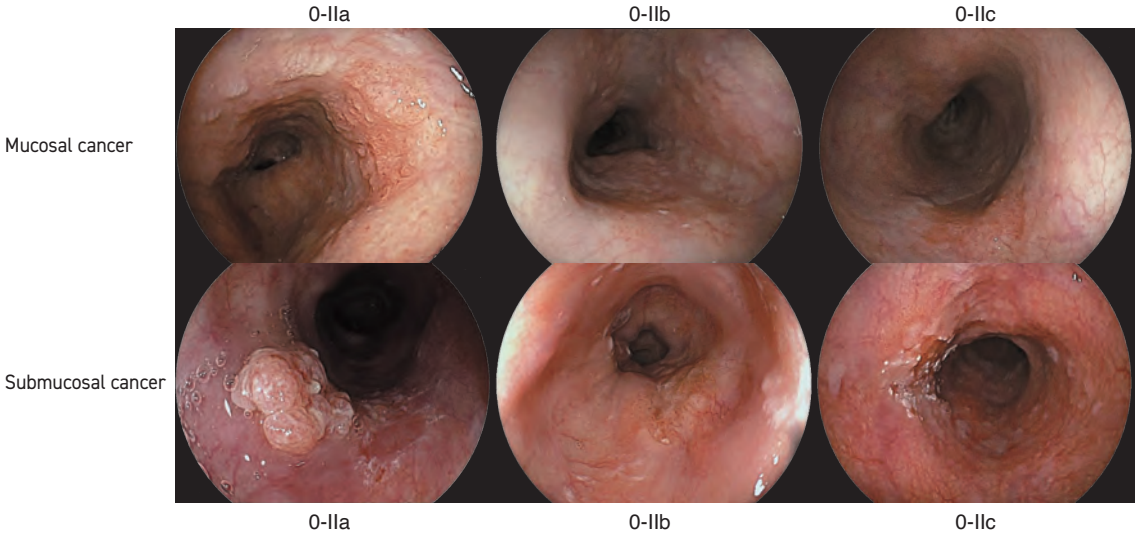


Figure 3 Endoscopic macroscopic classification of superficial esophageal cancer and the invasion depth.

86% of type 0-II cases were M cancers, and 90% of type 0-I cases and 96% of type 0-III cases were SM cancers.[23] Distinctly, type 0-IIc is most frequently observed. In addition, there are superficial lesions including mixed type in which multiple basic types coexist and 0-II superficial spreading type with a maximum diameter of 5 cm or more. These types vary in the invasion depth from M to SM. In superficial esophageal cancer, as the invasion depth increases, microgranular changes and irregularities within the depression become more prominent. When wall thickening or wall deformation remains during insufflation and expansion, tumor invasion deeper than MM should be suspected. According to the 6th edition supplementary edition of the *General Rules for Clinical Studies on Head and Neck Cancer* (edited by the Japan Society for Head and Neck Cancer, Kanehara), since the pharynx and larynx have almost no muscularis mucosae, the invasion depth of superficial cancer is described based on the thickness of the tumor at its deepest. In a study comparing the endoscopic classification and tumor thickness, the frequency of each type was 14.9% in 0-Is, 4.5% in 0-Ip, 68.6% in 0-IIa, 9.0% in 0-IIb, and 3.0% in 0-IIc, with the type 0-IIa being the most frequent. The tumor thickness was significantly correlated with 0-Is (3,575 ± 2,660 μm), 0-Ip (7,267 ± 3,288 μm), 0-IIa (848 ± 798 μm), 0-IIb (325 ± 220 μm), and 0-IIc (2,148 ± 2,169 μm) ($p < 0.0001$) (**Figure 4**).[24]

3. Image Enhanced Endoscopy

Image enhanced endoscopy (IEE) is a technique that enhances images obtained by endoscopy to facilitate the recognition of lesions. It can be classified into three categories: Digital method that processes images obtained with white light by computation; Optical digital method that uses light other than white light; and Chromoendoscopy that uses dyes. Digital method includes texture and color enhancement imaging (TXI), which improves the visibility of lesions by computer processing of images. Optical digital method includes narrow band imaging (NBI), blue LASER imaging (BLI) and linked color imaging (LCI), which uses non-white light to clearly visualize the microstructures of mucosal surface. Chromoendoscopy includes Lugol chromoendoscopy, a staining method for dyeing mucosae.

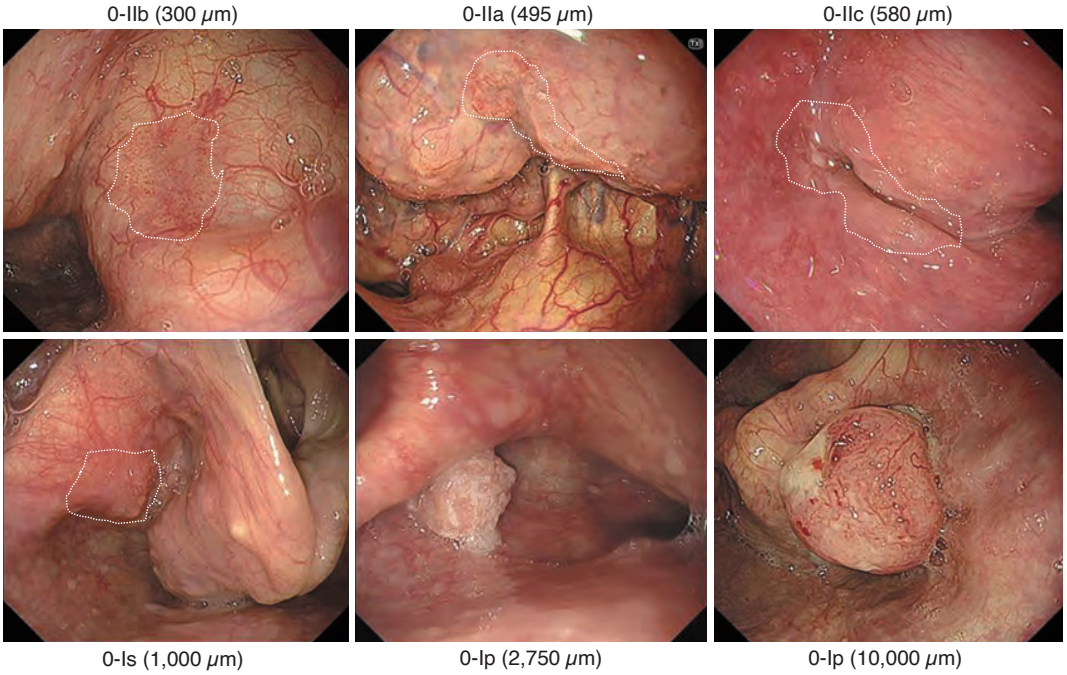


Figure 4 Endoscopic macroscopic classification of superficial head and neck cancer and the tumor thickness.

(1) Detection and differential diagnosis

NBI is an optical digital approach that emphasizes the fine vascular and surface structures of digestive tracts. It can be combined with magnifying endoscopy to visualize the changes in microvessels and microsurface pattern characteristic of tumors more easily. Muto and colleagues were the first in the world to report in 2004 that the NBI combined with magnifying endoscope findings of superficial head and neck cancer were well-demarcated brownish area and scattered foci of microvascular proliferation.[25] Furthermore, they conducted a multicenter randomized controlled trial for early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by NBI magnifying endoscopy in 320 cases with esophageal squamous cell carcinoma. In this study, the subjects were divided into a group that underwent an initial examination with white light magnifying endoscopy (n=162) and a group that underwent an initial examination with NBI magnifying endoscopy (n=158), for observation of their head and neck and esophagus. Compared with conventional endoscopy, NBI magnifying endoscopy significantly detected superficial head and neck cancer (NBI: 100% vs. white light: 8%, $p<0.001$) and esophageal superficial cancer (NBI: 97% vs. white light: 55%, $p<0.001$). Furthermore, sensitivity and diagnostic accuracy were significantly higher with NBI than with white light endoscopy. Therefore, NBI magnifying endoscopy has become the standard examination method for screening the head and neck or esophagus.[26]

Katada and colleagues conducted a prospective study (n=112) using NBI magnifying endoscopy to examine the head and neck region of patients with esophageal cancer, and reported that 16 superficial head and neck cancers were detected. Of these cases, 56.3% were hypopharyngeal cancer (9 lesions: 5



Figure 5 **Differential diagnosis of brownish area.**

pyriform sinus and 4 postcricoid area), 25.0% were oropharyngeal cancer (4 lesions: 3 superior wall and 1 posterior wall), and 18.8% were oral cancer (3 lesions: 2 tongue and 1 hard palate), and radical cure was obtained with minimally invasive treatment that preserved the organ.[27] Hosono and colleagues reported that in the differential diagnosis of cancerous and non-cancerous lesions using the presence or absence of abnormal microvessels observed by NBI magnifying endoscopy in laryngeal lesions. In the diagnosis, sensitivity, specificity, positive-negative predictive value, and diagnostic accuracy were 84.4%, 88.6%, 91.0%, 80.5% and 86.1%, respectively. Furthermore, multivariate analysis showed that abnormal microvessels (OR, 31.1; $p<0.0001$) were the most useful finding for differential diagnosis between cancerous and non-cancerous lesions.[22] Based on these results, NBI magnifying endoscopy is considered an effective examination method for the detection and differential diagnosis of head and neck and esophageal cancers.

Ono and colleagues conducted a randomized controlled trial on the capability to detect upper gastrointestinal neoplastic lesions using LCI in 1,502 cases with gastrointestinal cancer. In this study, the subjects were divided into a group that underwent an initial examination with white light imaging (n=752) and a group that underwent an initial examination with LCI (n=750), and the pharynx, esophagus, and stomach were observed. LCI endoscopy detected significantly neoplastic lesions compared with conventional endoscopy (LCI: 8.0% vs. white light: 4.8%, $p=0.011$).[28] Ogata and colleagues conducted a multicenter randomized controlled trial on the capability to detect esophageal squamous cell carcinoma in high-risk patients using IEE (BLI or LCI). There was no difference in the detection rate of esophageal squamous cell carcinoma between BLI endoscopy (n=351) and LCI endoscopy (n=348) (BLI: 4.0% vs. LCI: 4.9%, $p=0.565$).[29] Based on these results, endoscopic observation by LCI and BLI is considered a useful examination method for diagnosis.

Diseases that present brownish areas (BA) similar to squamous cell carcinoma on NBI and BLI endoscopy

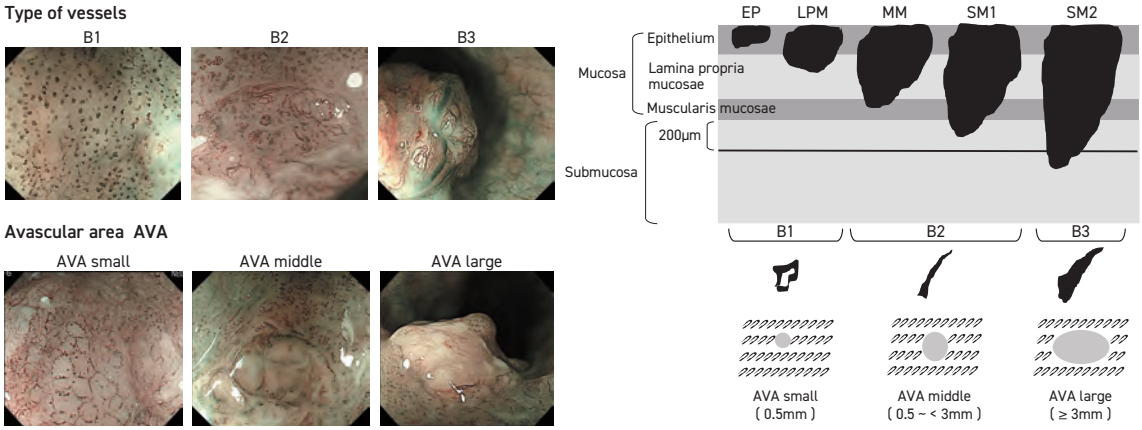


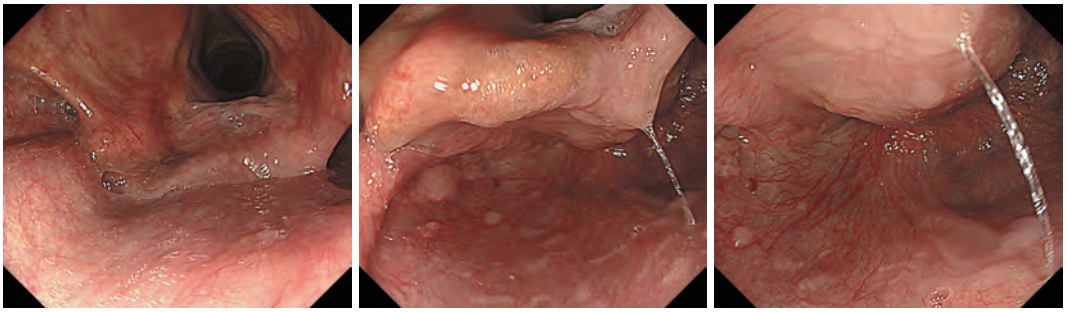
Figure 6 Magnifying endoscopic classification of the Japan Esophageal Society.

(Endoscopic images cited from Literature 30)

include esophagitis, dysplasia, ectopic gastric mucosa, melanosis, and squamous epithelial thinning. Lesions with clear margins and a dense inter-vascular background coloration (BC) are highly likely to be squamous cell carcinoma.[30] Esophagitis is often found at the gastroesophageal junction and is easily differentiated because it has feathery appearance of the esophageal lumen. Compared to squamous cell carcinoma, dysplasia finds reduced vascular proliferation, pale BC, and unclear demarcation. Ectopic gastric mucosa is common in the cervical esophagus with smooth margins and glandular structures, thereby facilitating its differentiation. If the background vessels pass through the BA without abnormal microvessels, this finding indicates thinning of the squamous epithelium (**Figure 5**).

(2) Diagnosis of invasion depth

To determine the treatment strategy for superficial esophageal cancer, the Japan Esophageal Society has established diagnostic criteria for the invasion depth using NBI magnifying endoscopy, based on the classifications of Inoue and Arima.[30-33] Type B vessels are abnormal microvessels with severe irregularity or highly dilated abnormal vessels and are categorized as follows: B1 includes a loop-like formation; B2 refers to Type B vessels without a loop-like formation; and B3 indicates highly dilated vessels which calibers appear to be more than three times that of the usual B2 vessels. These classifications generally correspond to invasion depths of EP/LPM for B1, MM/SM1 for B2, and SM2 or deeper for B3. Avascular area (AVA) is defined as a low or no vascularity area surrounded by Type B vessels, and are subclassified into AVA small (smaller than 0.5 mm in diameter), AVA middle (0.5 mm or between 0.5 and 3 mm), and AVA large (3 mm or larger). These classifications generally correspond to invasion depths of EP/LPM for AVA small, MM/SM1 for AVA middle, and SM2 or deeper for AVA large (**Figure 6**). In a study examining the accuracy of invasion depth diagnosis using NBI magnifying endoscopy in superficial esophageal squamous cell carcinoma (n=256), the positive predictive values of Type B vessel diagnosis were 93% for B1 vs. EP/LPM, 62% for B2 vs. MM/SM1, and 74% for B3 vs. SM2. Moreover, the positive predictive values of AVA diagnosis were 73% for small vs. EP/LPM, 89% for middle vs. MM/SM1, and 100% for large vs. SM2. Additionally, the



Before Valsalva maneuver | Hypopharynx after Valsalva maneuver | Esophageal inlet after Valsalva maneuver

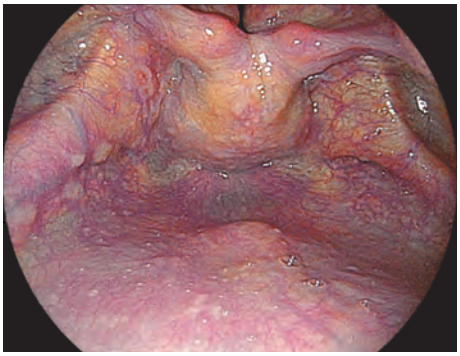
Figure 7 Valsalva maneuver using a specialized mouthpiece.

positive predictive values of white-light non-magnifying endoscopy for invasion depth diagnosis were 86% for EP/LPM, 53% for MM/SM1, and 74% for SM2, while the positive predictive values by the classification of the Japan Esophageal Society were 93% for EP/LPM, 65% for MM/SM1, and 77% for SM2. Consequently, these data suggest that NBI magnifying endoscopy could contribute to improving the accuracy of invasion depth diagnosis.[33]

Since the pharyngeal mucosa lacks the layer of muscularis mucosae, it is classified into epithelium and subepithelium. In a national multicenter survey of superficial head and neck cancers, Katada and colleagues showed that carcinomas in situ did not develop lymph node metastasis, and a tumor thickness of 1,000 μm or more was a risk factor for lymph node metastasis. The results indicated that tumor thickness can be used as a substitute for invasion depth.[34] In a study comparing NBI magnifying endoscopic findings with histopathological findings in patients with superficial pharyngeal cancer (n=67), 79.4% of cases diagnosed as B1 were intraepithelial cancers, indicating that it is difficult to apply Type B vessel diagnosis for predicting intraepithelial cancer. Compared with the classification of the Japan Esophageal Society with tumor thickness, Type B vessels showed significant correlations, with B1: 580±530 μm, B2: 1,264±1,238 μm, and B3: 4,583±3,079 μm (p<0.0001), and AVA showed significant correlations, with small (765±865 μ), middle (1,601±1,252 μm), and large (3,743±3,898 μm) (p=0.005).[24]

4. Preparation for Observation

Prior explanation and preparation are necessary when observing the pharynx and esophagus. According to the national multicenter survey of superficial head and neck cancers (n=568), the detection of superficial head and neck cancers was most frequently due to examinations conducted before or after esophageal cancer treatment (64.4%) and before or after head and neck cancer treatment (14.6%), as well as otolaryngological examinations (9.7%).[13] It is effective to conduct head and neck observations for individuals at high risk of carcinogenesis, such as those with a history of alcohol or tobacco use, or treatment for head and neck cancer or esophageal cancer.



Observation using LCI

Figure 8 **Valsalva maneuver by transnasal endoscopy.**

LCI: linked color imaging

(1) Preexamination explanation

For observation of the pharynx, endoscopists should explain the procedure to examinees beforehand for alleviating anxiety and reducing the gag reflex. It is also important to explain that the examinee is indicated to vocalize during the examination. When the endoscopist determines that a detailed examination is necessary, the Valsalva maneuver is effective. In this technique, the patient takes a deep breath, holds it, and inflates the cheeks to fill the air from the mouth to the pharynx. Practicing this maneuver before the procedure is recommended. If the examinee is allergic to iodine, Lugol chromoendoscopy is contraindicated. Thus, a prior medical interview is essential for the procedure.

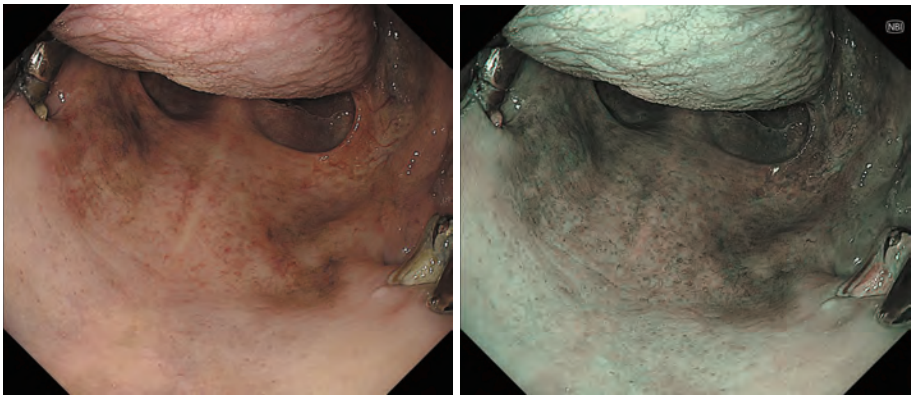
(2) Pretreatment

Since mucus such as saliva could adhere to pharynx, it is helpful for an examinee to drink a cup of water before pharyngeal anesthesia and remove mucus. For pharyngeal anesthesia, xylocaine viscous or xylocaine spray is used. If the gag reflex is inadequately controlled, additional xylocaine spray towards the base of tongue could be effective.

For transnasal endoscopy, nasal cavity anesthesia is performed with consideration for nasal pain and bleeding. The procedure starts after confirmation that sufficient dilation is obtained by using methods such as the stick method or spray method with naphazoline nitrate and either 4% xylocaine solution or xylocaine jelly. It should be noted that younger women have narrower nasal cavities with a higher risk of developing epistaxis.

(3) Premedication

Although sedation reduces gag reflex, this merit can also make it difficult for the examinee to follow instructions such as vocalization and the Valsalva maneuver, and the observation field tends to be limited due to sinking of the base of tongue. Therefore, deep sedation should be avoided for examinees with diminished gag reflex. Even when sedation is required due to strong reflex, it is easier to observe if



White light findings　　NBI findings

Figure 9 **Melanosis of soft palate.**

NBI: narrow band imaging

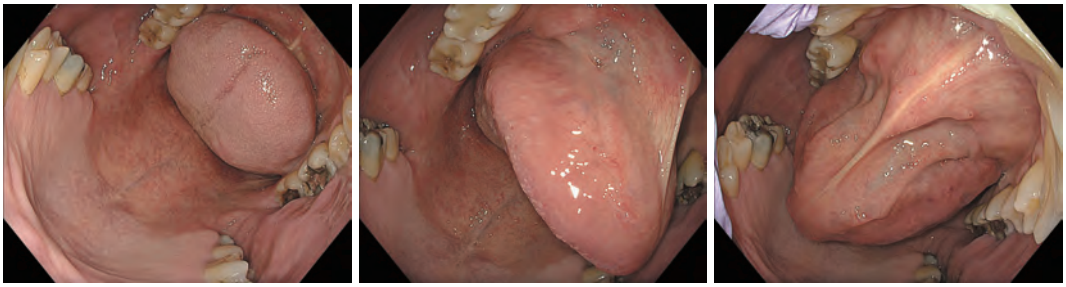
the examinee remains conscious. In such cases, conscious sedation using low-dose benzodiazepines or analgesics using opioids should be considered. Since transnasal endoscopy is less likely to trigger reflex, sedation is frequently unnecessary. Therefore, the choice of the insertion route should be considered according to the situation.

5. Practical Pharyngeal Examination Procedure

When examining the pharynx via oral insertion, there are blind spots and areas that are difficult to observe. The base of tongue becomes a blind spot due to its tangential orientation, and the posterior surface of the uvula also becomes a blind spot because the scope cannot be flipped. However, these areas are visualized by transnasal endoscopy. Just before the scope is inserted, the patient is instructed to bow deeply and then protrude the lower jaw forward. This sniffing position can help provide a clearer view of the hypopharynx. The midline region of the posterior wall and postcricoid area of the hypopharynx are often difficult to observe and probably become blind spots. To improve visualization, the operator should use a specialized mouthpiece for the Valsalva maneuver. In this maneuver, the patient takes a deep breath and then inflates both cheeks as much as possible while holding their breath. This action can elevate the larynx, making it easier to view the entire posterior wall and postcricoid area (**Figure 7**).[35] The Valsalva maneuver with a closed mouth under transnasal endoscopy also provides an effective field of vision (**Figure 8**).

(1) Timing of pharyngeal observation

The timing of pharyngeal examination is crucial. It is preferable to conduct the examination when the pharyngeal anesthesia is fully effective and there is minimal salivary accumulation. This provides a clearer field of vision. If the anxiety at the beginning of the examination exacerbates the gag reflex, it may be easier to examine the pharynx after observation of the esophagus, stomach, and duodenum. During scope withdrawal, pharyngeal anesthesia in the patient often wears off, and saliva tends to accumulate. As a result, the operator frequently fails to perform thorough observation.



Hard palate, soft palate, dorsum of the tongue | Lateral border of the tongue | Inferior surface of the tongue and floor of mouth

Figure 10 Oral cavity.

(2) Timing of image-enhanced endoscopy

In the observation of the pharynx and esophagus, the most clinically significant goal is to detect superficial cancers. Given that IEE has an improved detection rate for superficial cancers compared to white-light imaging, it is preferable to use IEE during insertion, when observation conditions are most favorable. However, since melanosis and varices might be difficult to visualize with NBI or BLI, conventional endoscopy should also be selected for the soft palate where melanosis is often observed, as well as the lower thoracic esophagus where varices are frequently seen (**Figure 9**). In NBI or BLI with a moderate insufflation, changes in color and vessels can be more easily visualized. TXI and LCI provide color information comparable to that of white light, rendering them highly suitable for observations conducted from standard viewing distances. IEE should be used according to the intention to use, and static images under white light should be saved when abnormal findings are identified.

(3) Oral cavity

If the examinee is at risk for head and neck or esophageal cancer, it is advisable for endoscopists to examine the oral cavity before attaching the mouthpiece or starting the transnasal insertion. Without the mouthpiece, the hard palate and buccal mucosa are easily observed. It becomes possible to examine the lateral borders of tongue, its inferior surface, and the floor of the mouth, when the examinee moves the tongue in the upward, downward, and lateral directions. (**Figure 10**). If oral examination is insufficient, otolaryngologist or oral surgeon should be introduced for the oral examination.

(4) Pharynx

To avoid triggering gag reflex or cough, it is advisable for endoscopists to insert the endoscope tip along the posterior wall during pharyngeal examination, minimizing contact with the mucosa of base of tongue or larynx. If excessive mucus like saliva is present, the endoscope tip should be brought close to the mucosa, and water is flushed with the water button to remove the mucus. It is crucial to use a minimal amount of water to prevent it from entering the airway.

When the upper wall of the oropharynx and the tongue are in close proximity, obstructing the

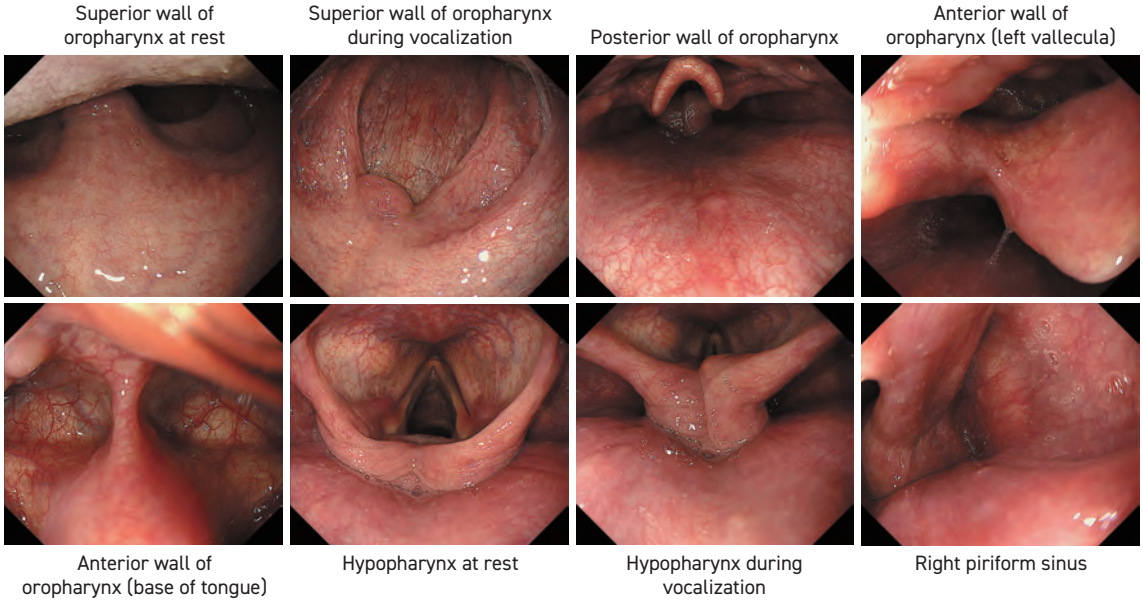


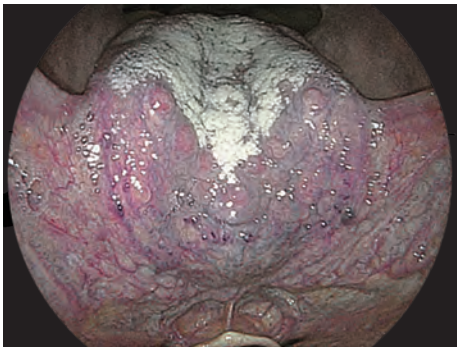
Figure 11 Pharynx by transoral endoscopy.

observation field, the operator instructs the patient to say "ah" to elevate the uvula, thereby securing the field of vision. In transoral insertion, it is difficult for endoscopists to secure a clear view of the anterior wall even with respiratory or vocalization maneuvers. The operator should insert the tip of the scope through the right epiglottis and gently touch the epiglottic surface. By lightly pressing the epiglottis toward the posterior wall with the tip of the scope, a clear field of vision is secured. To visualize the pyriform sinus in hypopharynx, the endoscopist instructs the patient to say "oo" to provide a clear view of the distal end. To examine the entire hypopharynx, the Valsalva maneuver should be performed (**Figure 11**).

In transnasal endoscopy, observation of the base of tongue is performed after the endoscope tip passes beyond the uvula. At this stage, the patient is typically asked to open the mouth and extend the tongue to facilitate visualization. While the patient says "ah," the endoscope tip should be gently bent towards the oral cavity within the oropharynx, allowing for a frontal view of the base of tongue (**Figure 12**).

(5) Larynx

When the examinee is at a risk for pharyngeal or esophageal cancer, it is advisable to examine the larynx as well. The laryngeal surface of the epiglottis could be overlooked if not examined intentionally. While findings are noted in the glottis during distant observation, advancing the endoscope tip to the arytenoids could provide differential diagnostic findings. A thin endoscope is able to provide even closer observation. As contact between the endoscope and the larynx tends to trigger reflexes, it is crucial to maintain a certain distance and observe with extreme care. In cases where a lesion is identified and further examination is necessary, endoscopists should consider consultation with an otolaryngologist for scheduling a subsequent detailed examination.



Endoscopy with LCI

Figure 12 **Base of tongue by transnasal endoscopy.**

LCI: linked color imaging

(6) Observation with transnasal endoscopy

Magnifying endoscopy is performed through transoral insertion, and it is often difficult to spend sufficient time on observation even with the use of sedatives, especially in examinees with severe gagging reflex. For such examinees, transnasal endoscopy reduces the pharyngeal reflex to perform a detailed examination over a sufficient period of time. In the close-up observation, superficial pharyngeal cancers are adequately visualized (Figure 13).

6. Practical Esophageal Examination Procedure

(1) Esophagus (Figure 14)

The segment from the esophageal inlet to the cervical esophagus (up to 18 cm from the incisors) is compressed anteriorly by the trachea and posteriorly by the vertebral bodies. Since this anatomy makes detailed observation difficult during insertion, it is often preferable to observe this area during scope withdrawal. For this reason, endoscopic observation typically begins at the upper thoracic esophagus, around 18 cm from the incisor. At this point, insertion is temporarily halted, and water is injected into the esophagus for completely removing mucus. Care must be given not to inject water quickly into the cervical esophagus, because such injection could cause reflux into the pharynx leading to choking.

The upper thoracic esophagus is compressed by the trachea on the right wall, the vertebral bodies on the posterior wall, and the aortic arch on the anterolateral wall. Beyond the aortic arch compression, the left main bronchus compresses the anterolateral wall and forms the second physiologic narrowing leading to the middle thoracic esophagus. Since there are shadowed areas, white light should be used appropriately. While the lumen of the lower thoracic esophagus can be easily expanded by insufflation, the anterior wall is difficult to closely observe due to cardiac pulsations. The anterior wall of the lower esophagus is not only easily overlooked but lesions are hardly detected. To mitigate this risk, it is advisable to rotate the endoscope and position it at the 6 o'clock position to enable frontal observation on the screen. Squamous cell carcinoma commonly develops in the middle and lower thoracic

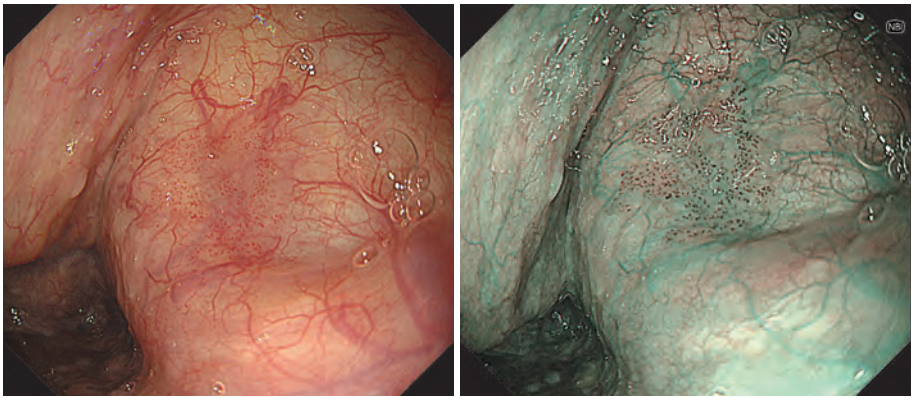


Figure 13 Superficial hypopharyngeal cancer in right piriform sinus by transnasal endoscopy.

esophagus. It is advisable to advance the scope slowly and carefully, or to observe it twice to ensure thorough examination in high-risk individuals.

The gastroesophageal junction is one of the areas that requires careful observation due to the high incidence of diseases such as reflux esophagitis, esophageal varices, Barrett's esophagus, and cancer. It is often closed by the lower esophageal sphincter, but it is easier for practitioners to observe by instructing the examinee to take a deep breath and hold it. In addition to the antegrade direction, the scope tip should always be flipped at the gastric cardia for retrograde observation.

The esophageal inlet and cervical esophagus are difficult to observe during endoscopic insertion. Thus, these areas should be observed during withdrawal with insufflating sufficiently and moving slowly. Ectopic gastric mucosa is commonly found in the cervical esophagus and should be distinguished from squamous cell carcinoma. IEE facilitates differentiation between squamous cell carcinoma and ectopic gastric mucosa. This is attributable to the fact that glandular structures characteristic of ectopic gastric mucosa can be clearly seen using this technique. This clear visualization helps avoid unnecessary biopsies. If the observation field of the cervical esophagus cannot be secured because of peristalsis, the observation should be paused tentatively until the movement passes over.

(2) Lugol chromoendoscopy

After observing the stomach, endoscopists aspirate the air or carbon dioxide filled in the gastric space, and return in the esophagus to perform iodine staining, if appropriate. Since esophageal cancer develops throughout the esophagus, iodine staining should be performed over the entire region from the upper thoracic esophagus to the lower thoracic esophagus. In screening process, an iodine concentration of 0.5 to 1.0% is considered sufficient from the standpoint of minimizing the impact on the esophageal mucosa and reducing discomfort for the examinee. Caution should be exercised since iodine staining tends to cause discomfort such as heartburn and chest pain, or allergic reactions. Iodine staining is contraindicated in examinees with a history of iodine allergy by contrast agents. Excessive iodine staining could exacerbate discomfort such as heartburn and chest pain, so care should be given to ensure that the entire esophagus is stained with a minimal amount of iodine. To alleviate the irritating effects of iodine, sodium thiosulfate is sprayed for neutralizing effect after observation.

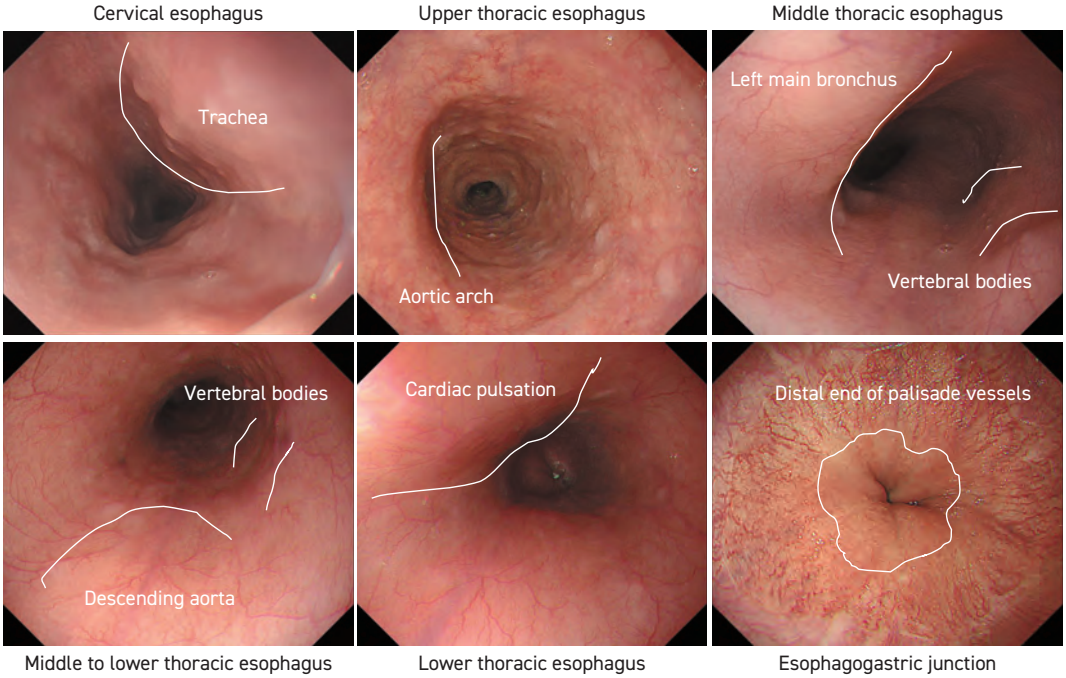


Figure 14 **Practical esophageal endoscopy.**

Since iodine staining has a tissue-destructive effect, the surface of the lesion could be sloughed off and covered by normal epithelium. Therefore, superficial cancer or atypical epithelium possibly becomes unclear due to the effects of iodine staining. If the extent of the lesion appears to be reduced at the time of endoscopic treatment, it is necessary to compare the affected area with the unstained region identified during initial iodine staining.

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Chikatoshi Katada, Kenro Kawada, and Manabu Muto

3 Endoscopic Ultrasonography

Endoscopic ultrasonography (EUS) is a modality that enables cross-sectional visualization of the gastrointestinal wall. It is broadly classified into two types: miniature probe EUS, in which a miniature probe is inserted through the instrument channel of a conventional endoscope, and the echoendoscope, in which the endoscope and ultrasound transducer are integrated. In the esophagus, EUS is primarily used for the qualitative diagnosis of submucosal tumors (SMTs) and subepithelial lesions (SELs), as well as for assessing the depth of invasion and lymph node metastasis.

1. Observation Methods by EUS

When performing EUS for esophageal lesions, it is necessary to fill the gastrointestinal lumen with a sonographic medium such as deaerated water or jelly.[1] While the water-filling method (deaerated water–filling method) is primarily used for the stomach, duodenum, and colon,[2] it is also commonly applied to the esophagus. However, the jelly-filling method[3] and the soft-balloon method[4] are also employed.

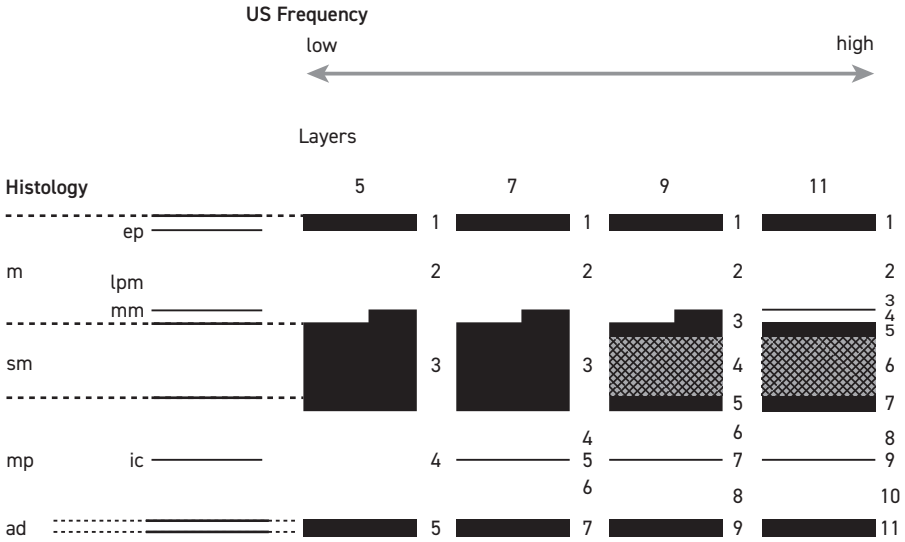
(1) Water-Filling Method

This method involves filling the esophagus with distilled or deaerated water for scanning. Because the esophagus exhibits peristaltic movement even with slight scope manipulation or water retention, maintaining water within the lumen is difficult. The use of an irrigator for water injection or an endoscope equipped with a water-supply function enables appropriate water supplementation, helps prevent aspiration, and facilitates examination.

Using a therapeutic endoscope with a large working channel allows efficient suction of bubbles, thereby improving visualization. In the deaerated-water filling method, distilled or deaerated water that has been boiled and left to stand for at least one night at room temperature is used. Because tap water contains numerous microbubbles, deaerated water should be used to obtain clearer images.

(2) Jelly-Filling Method

In this method, endoscopic jelly is injected into the esophageal lumen through the instrument channel of the endoscope. The jelly adheres well to the esophageal wall, providing stable scanning and reducing reflux, which is particularly advantageous for cervical esophageal lesions. This approach allows high-



ep: epithelium, 1pm: lamina propria mucosae, mm: muscularis mucosa,
ic: intermuscular connective tissue

Figure 1 **Endosonographic correlation with histology in a layered structure of the gastrointestinal wall.**

(Modified from Literature 7)

quality image acquisition with a lower risk of aspiration, even for lesions located in the cervical esophagus. Recently, the use of VISCOCLEAR® (Otsuka Pharmaceutical Factory), a novel gel designed to create space for endoscopic visualization, has also been reported.[5)]

(3) Soft-Balloon Method

The soft-balloon method involves inflating a balloon attached to the tip of the endoscope with water and performing scanning through the balloon. This technique is particularly useful for evaluating the esophagogastric junction and cervical esophagus, where fluid retention is difficult and the lumen tends to narrow. During scanning, the balloon gently compresses the lesion against the gastrointestinal wall, thereby altering its position to improve visualization. In practice, however, care must be taken to avoid overestimating the depth of invasion.[6)]

2. Esophageal Wall Layered Structure

The esophageal wall can be visualized as a nine- or seven-layered structure using high-frequency probes and as a seven- or five-layered structure with low-frequency probes. At the 60th Consensus Meeting of the Japan Gastroenterological Endoscopy Society, a consensus was reached regarding the interpretation of the esophageal wall's layered structure, as shown in **Figure 1**.[7)]

Using thin 20 MHz probes, the normal esophageal wall is typically depicted in nine distinct layers. The relatively hypoechoic fourth layer (the 4th of 9 layers) corresponds to the submucosa (SM), whereas the third layer (the 3rd of 9 layers) represents the muscularis mucosae. When the muscularis mucosae cannot be clearly identified, evaluation is performed based on a seven-layered structure.

3. Selecting Appropriate Miniature Probes or Echoendoscopes

One of the main advantages of miniature probes is their ability to be inserted through the instrument channel of a conventional endoscope, allowing real-time ultrasonographic assessment of lesions under direct endoscopic visualization. The frequency range of these probes typically lies between 12 and 20 MHz. Because ultrasound waves at such high frequencies are rapidly attenuated, miniature probes are primarily used for diagnosing SMTs or SELs measuring up to approximately 20 mm, as well as for evaluating the depth of invasion. In these situations, miniature probes can provide diagnostic accuracy comparable to that of echoendoscopes.[8,9)]

Echoendoscopes are classified into three types according to their scanning mechanism: radial, curved linear-array, and linear. The radial type provides 360-degree scanning in the short-axis direction and is particularly useful for evaluating larger SMTs or SELs exceeding 20 mm and for assessing lymph-node metastasis. The curved linear-array and linear types enable scanning in the long-axis direction and allow performance of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). The curved linear-array type, with an operating angle of 140–180 degrees, offers a wide fan-shaped scanning range. The linear type directs the ultrasound beam perpendicularly to the gastrointestinal wall, making it suitable for detailed visualization of areas adjacent to the esophageal wall, such as the gastroesophageal junction and cervicothoracic junction.

When performing long-axis scanning with an echoendoscope, the scope itself must be rotated to visualize the entire circumference—unlike the radial type, which provides a complete 360-degree view in a single scan. Standard echoendoscopes, including the electronic radial and curved linear-array models, are equipped with Doppler functions for assessing blood flow and elastography functions for evaluating tissue stiffness. In addition, some echoendoscopes allow the operator to select among a wide range of frequencies and perform tissue harmonic imaging, thereby enhancing overall image quality.

4. Advice for EUS Diagnosis Using Miniature Probes

The presence of small air bubbles around the ultrasound transducer of a miniature probe before use can cause dark or blurred images during examination. To remove these bubbles, the probe should be held approximately 5 cm from the tip with the distal end facing downward. Gently shaking or flicking the probe produces rapid motion and centrifugal force at the tip, which helps expel the bubbles.

After the endoscope is advanced into the esophagus or stomach, any residual fluid or air should be aspirated. Once the lumen is filled with water or jelly, insufflation should not be performed during scanning. The examination should be completed efficiently within the short period when esophageal peristalsis has subsided. Although anticholinergic agents can suppress esophageal peristalsis, they may increase heart rate and thereby make observation of lesions in the lower thoracic esophagus difficult. Their use should therefore be approached with caution.

When beginning the ultrasound examination, the proximal view should first be selected to obtain an image oriented similarly to the endoscopic view, facilitating recognition of the anatomical relationship. After orientation is confirmed, the image should be rotated so that the lesion appears at the 6 o'clock position, aligning the wall layers vertically from 12 to 6 o'clock. This orientation makes it easier to distinguish the individual layers. Because scope movement can induce gag reflexes or esophageal peristalsis, it is important to move the probe rather than the endoscope itself when shifting between the proximal and distal sides of the lesion. The probe should be advanced from normal tissue adjacent to the lesion into the

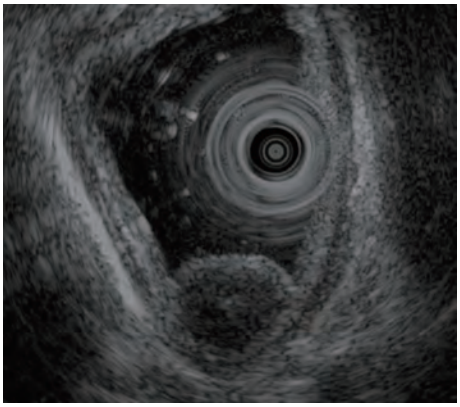


Figure 2 **Diagnosis of submucosal tumor in esophagus by a ultrasound probe.**

A homogeneously hypoechoic mass with continuity to the 2nd to 4th of nine wall layers was observed. It was diagnosed as leiomyoma.

lesion proper, enabling observation of progressive changes in the layered structure.

Reproducibility is crucial in EUS, and real-time evaluation is essential. However, it can be difficult for an endoscopist to simultaneously assess the lesion and capture still images. Therefore, performing the examination while recording continuous cine images, followed by selecting representative still frames from the video memory, allows for easier evaluation and ensures reproducibility.

When both EUS and biopsy are scheduled on the same day, the lesion should remain intact for EUS evaluation; thus, biopsy must always be performed after the EUS examination.

5. Diagnosis of SMTs/SELs Using Miniature Probes

Evaluation of SMTs and SELs by miniature probes focuses on identifying the layer of origin and assessing the internal echogenic characteristics of the lesion. Miniature probes are particularly suitable for diagnosing SMTs/SELs measuring less than 20 mm.

The most common benign esophageal tumor is leiomyoma. On EUS, leiomyomas typically appear as homogeneously hypoechoic lesions, exhibiting echogenicity similar to that of the muscularis propria. When the tumor arises from the muscularis mucosae, it usually appears as a uniformly hypoechoic area spanning the second to fourth of the nine layers (lamina propria to submucosa), with an intact layer remaining beneath the lesion (**Figure 2**).

Granular cell tumors, which present a characteristic yellowish-white, molar-like appearance under white-light endoscopy, are visualized on EUS as isoechoic to hypoechoic masses involving the second to fourth layers. A distinctive feature is thinning of the first (superficial mucosal) layer overlying the lesion.

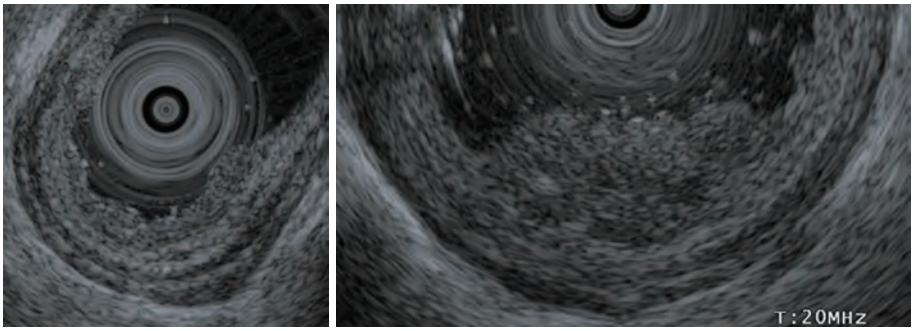


Figure 3 **Diagnosing invasion depth of superficial esophageal cancer by a ultrasound probe.**

a: T1a-MM/T1b-SM1. Tumor echoes were observed within the 2nd to 3rd of nine wall layers. No clear changes were noted in the 4th layer.

b: T1b-SM2. A hypoechoic tumor disrupted the 3rd layer and extended into the 4th layer, which corresponds to the submucosa.

6. Ultrasound Assessment of Invasion Depth in Early Esophageal Cancer

The invasion depth of early esophageal cancer is primarily assessed using miniature probes. When employing such probes, the nine-layered structure of the esophageal wall can often be visualized; however, if the muscularis mucosae cannot be clearly identified, evaluation is instead performed using a seven-layered structure.

In the nine-layered schema, the following criteria are used to assess invasion depth (**Figure 3**):

When the tumor echo extends to the third layer (representing the muscularis mucosae) but no distinct change is observed in the fourth layer (representing the submucosa), the lesion is diagnosed as cMM–SM1 cancer (**Figure 3a**).

When the tumor echo extends into the fourth layer, the lesion is diagnosed as cSM2/SM3 cancer (**Figure 3b**).

When the muscularis mucosae cannot be delineated, a diagnosis of cSM2 cancer is made based on thinning of the third of seven layers (3/7 layer) corresponding to the submucosa.

For extensive superficial cancers, it may be difficult to scan the entire lesion. In such cases, it is important to first identify the area most suggestive of deepest invasion by white-light and magnifying endoscopy, and then perform EUS scanning of that region.

The overall diagnostic accuracy of EUS using miniature probes for evaluating invasion depth in early esophageal cancer is approximately 80–90%. However, differentiating between cT1a-MM and cT1b-SM1 lesions remains particularly challenging.[10] Misdiagnoses often occur because very small foci of invasion may not be detectable, given the probe's spatial resolution of roughly 100 μm. Furthermore, distinguishing tumor invasion from inflammatory cell infiltration or fibrotic changes can be difficult, as can differentiating these findings from lymphoid hyperplasia, esophageal glands, or vascular structures.[11]

A multicenter prospective study (JCOG 1604) investigated the role of EUS in assessing the depth of invasion in esophageal squamous cell carcinoma exceeding cMM/SM1. In that study, EUS was performed on lesions suspected to be cMM/SM1 or deeper. However, when only white-light and magnifying endoscopy were used, the rate of over-diagnosis increased by 6.6%, and the addition of



Figure 4 **Diagnosing submucosal tumor of the esophagus by electronic radial echoendoscope.**

A homogeneously hypoechoic mass with continuity to the muscularis propria was identified. Leiomyoma was suspected. EUS-FNA was performed, and a diagnosis of leiomyoma was made.

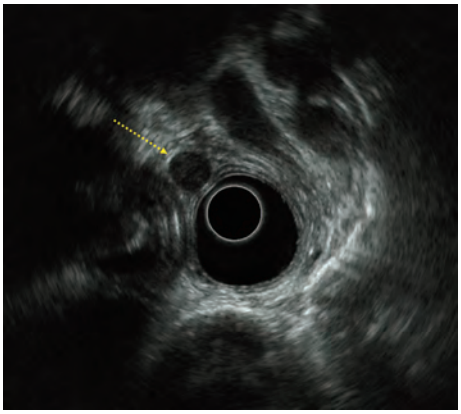


Figure 5 **Diagnosing lymph node metastasis by electronic radial echoendoscope.**

During follow-up after chemoradiotherapy for carcinoma of the esophagus, a round enlarged lymph node was observed at #106 recL (arrow) . The short axis measured 7.6 mm. Based on its morphology, lymph node metastasis was suspected, and lymph node dissection was performed.

EUS did not provide further diagnostic benefit.[12)]

According to the JGES Guidelines for Esophageal EMR/ESD,[13)] the preoperative diagnostic accuracy for cMM/SM1 cancer remains limited—27.4–55.2% of lesions pathologically diagnosed as pEP/LPM cancer and 15.5–27.9% as pSM2 cancer are incorrectly staged preoperatively. Therefore, endoscopic resection is recommended as a minimally invasive and safe therapeutic option, even when accurate depth assessment is difficult.

Consequently, when cMM/SM1 cancer is diagnosed by white-light endoscopy or magnifying endoscopy, the additional use of EUS to guide treatment decisions offers limited clinical benefit. In such cases, endoscopic resection should be considered as the appropriate therapeutic approach.

By contrast, EUS should be performed when lesions are suspected to be cSM2 or deeper. In the JCOG 1604 study, the rate of over-diagnosis was reduced by 6.8 % when EUS was selectively applied to lesions pre-diagnosed as cSM2 or deeper, and endoscopic resection was performed when the final diagnosis was cMM/SM1 cancer. This stepwise strategy is regarded as clinically appropriate.

In addition, for tumors that develop primarily within the submucosal layer, such as SMT/SEL-like esophageal cancers, EUS remains valuable for obtaining detailed submucosal information. In any case, clinicians should remain fully aware that EUS is a modality prone to over-diagnosis, and the results must always be interpreted with caution in the context of comprehensive endoscopic findings.

7. Diagnosis of Esophageal SMTs/SELs Using EUS by echoendoscopes

Because echoendoscopes operate at relatively low frequencies, they allow visualization of deeper structures, making them particularly suitable for diagnosing large SMTs or SELs measuring 20 mm or more (**Figure 4**). Although balloon methods are often employed for scanning, deaerated water can also be injected through the instrument channel when detailed observation of the layered structure is required.

8. Diagnosis of Lymph Node Metastasis in Esophageal Cancer by EUS Using Echoendoscopes

(1) Purpose of Lymph Node Metastasis Assessment

The stage of esophageal cancer is determined by two principal factors—depth of invasion and the presence of lymph node metastasis—and treatment strategies are planned accordingly. For advanced disease, neoadjuvant chemotherapy or chemoradiotherapy (CRT) is often administered prior to surgery, and salvage surgery may subsequently be performed after CRT.

Even in early-stage esophageal carcinoma, there remains a risk of lymph node recurrence after endoscopic resection, underscoring the need for early and accurate detection. Therefore, precise preoperative staging, evaluation of therapeutic response, and systematic follow-up are essential throughout all disease stages.

EUS plays an important role in each of these steps. Because lymph node metastases from esophageal cancer can occur in the cervical, mediastinal, and abdominal regions—even in superficial cases—a comprehensive, systematic lymph node evaluation across all three regions is required.[14)]

(2) Diagnostic Assessment of Lymph Node Metastasis

EUS diagnosis of lymph node metastasis is based on nodal morphology, long-axis diameter, internal echogenicity, and margin definition. Lymph nodes that are larger than 5 mm, round in shape, hypoechoic, and have well-defined margins are highly suggestive of metastasis (**Figure 5**). Among these features, shape is particularly important—even small, round nodes may represent metastatic involvement and warrant careful evaluation.

Compared with computed tomography (CT), EUS provides superior resolution for assessing small lymph nodes, allowing more detailed evaluation of shape and size. However, false-positive findings can occur, mainly due to reactive or inflammatory changes. To minimize misinterpretation, it is important to monitor changes in nodal morphology and size over time. In addition, EUS-FNA can be performed when necessary to obtain cytological confirmation and assist in treatment planning.

9. EUS-FNA Procedures

EUS-FNA is performed for SMTs, SELs, and lymph nodes that require histopathological diagnosis to determine an appropriate treatment strategy. The linear or curved linear-array echoendoscope is suitable for this procedure.

In Japan, 19–25-gauge (G) puncture needles are available, among which the 22 G needle is most commonly used. The procedure begins with identification of the lesion, assessment of its vascular relationships, and determination of the optimal puncture site and direction. Color Doppler imaging is utilized to confirm the absence of blood vessels along the intended needle path. To minimize the risk of tumor seeding, it is essential to select a puncture route that avoids passing through the gastrointestinal wall whenever possible.

Once the target is identified, the distance from the puncture entry site to the lesion is measured. The puncture needle is then inserted through and secured within the instrument channel. The needle is advanced slightly and extended from the sheath tip. After ensuring close contact between the gastrointestinal wall and the scope tip, the puncture is performed smoothly and without hesitation.

The diagnostic yield of EUS-FNA for gastrointestinal SMTs has been reported to range between 60% and 90%, which is relatively lower than that for pancreatic or lymph node lesions.

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4 Gastroesophageal Reflux Disease and Barrett's Esophagus

1. Gastroesophageal Reflux Disease (GERD)

(1) Endoscopic classification of GERD

In 1994, the Los Angeles classification was proposed as an endoscopic classification system for reflux esophagitis. This classification defines reflux esophagitis as the presence of a clear mucosal break. Furthermore, a mucosal break is defined as an area with sloughing or reddened mucosa that is distinctly demarcated from the more normal-appearing mucosa in the surrounding areas. The severity is categorized into Grades A, B, C, and D, with Grades A and B generally considered mild and Grades C and D considered severe. A modified Los Angeles classification has been presented, which includes Grade N (no endoscopic change) and Grade M (minimal change), and is widely used (**Figure 1**).[1,2] GERD is classified into reflux esophagitis with mucosal break and non-erosive reflux disease (NERD), which is diagnosed based solely on symptoms, without the presence of a mucosal break. Cases classified as Grade N or M are often diagnosed as NERD.

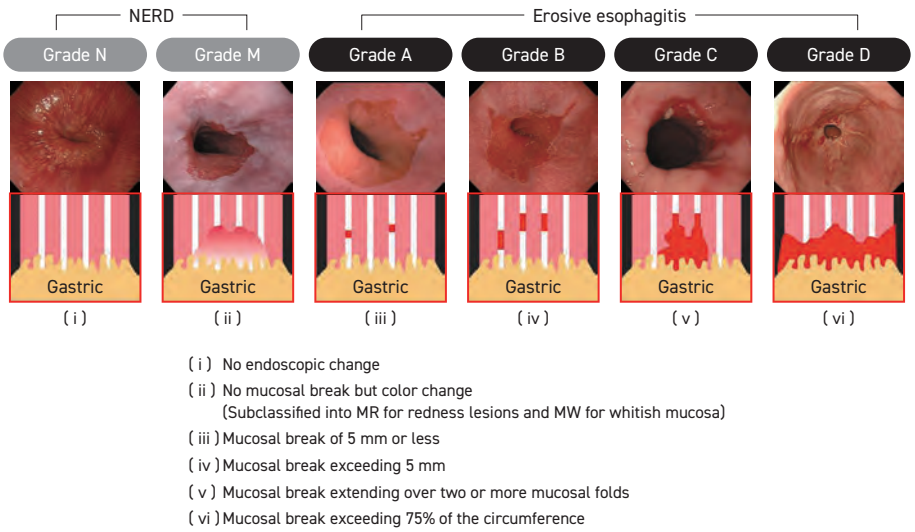


Figure 1 Practical application of the modified Los Angeles Classification.
(Modified from Literature 2)

(2) Diagnosis of reflux esophagitis by conventional endoscopy

Due to the contraction, peristalsis, and respiratory movement of the esophagogastric junction, meticulous endoscopic observation requires specific techniques. Specifically, it is crucial to deflate the stomach and instruct the patient to take a deep breath to maximally extend the lower esophagus. Therefore, it is necessary to be aware that the observation could be inadequate during conscious sedation. In addition, it is important to note that reflux esophagitis tends to have specific patterns of localization, with Grade A and B mild types often found on the anterior to right wall of the lower esophagus, while Grade C is more commonly seen on the posterior wall. Awareness of these patterns is essential for accurate endoscopic assessment.

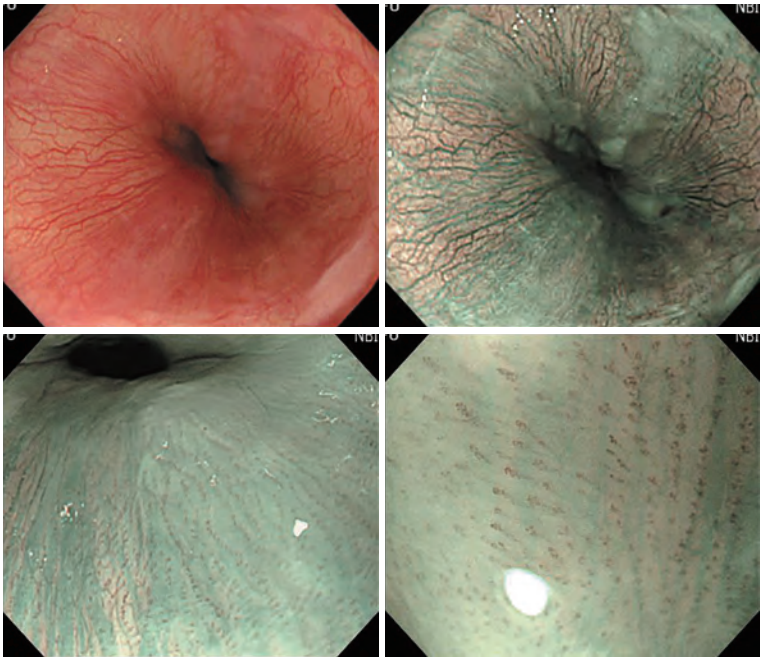
Subtle endoscopic findings of reflux esophagitis, such as erythema, whitish turbidity, friability, and mucosal edema, are classified as minimal changes. However, diagnostic agreement among endoscopists in training is particularly poor for these findings.[3] Several reports have assessed the diagnostic agreement of Grade N and M, but results have been unsatisfactory, and sufficient training is required to accurately recognize these conditions. Furthermore, the need for standardization of diagnostic criteria among institutions has been emphasized. [4,5] Although whitish turbidity and erythema in Grade M cases are considered to indicate esophageal acid exposure, studies involving 24-hour pH monitoring have found no significant difference between Grade N and M, and the clinical significance is unclear.[6] Future research, particularly using esophageal impedance-pH monitoring, is needed to clarify the endoscopic findings associated with NERD.

(3) Diagnosis of reflux esophagitis by image-enhanced endoscopy (IEE)

The endoscopic diagnosis of Grade M is based on mucosal color changes, such as erythema and whitish turbidity, but these findings can vary depending on the endoscopists' visual impression, compared to cases with definite mucosal break. Therefore, to establish more objective diagnostic criteria for NERD, including Grade M, image-enhanced endoscopy (IEE) has been employed. Various dye-based methods and optical digital methods have been investigated.

In a study of 39 patients with GERD showing no mucosal break on conventional endoscopy, 19 (49%) were found to have Lugol's unstained streaks, suggesting possible mucosal inflammation.[7] However, due to the risks of chest pain and allergic reaction associated with iodine staining, iodine staining endoscopy is not commonly used in clinical practice for diagnosing NERD.

A study using NBI magnifying endoscopy analyzed images of the esophagogastric junction in 20 patients with NERD and 30 control subjects. Multivariate analysis revealed that the most significant endoscopic predictor of NERD was either an increase in the number or dilation of intrapapillary capillary loops (IPCLs). This finding demonstrated high diagnostic yields, with a sensitivity of 80% and a specificity of 100%.[8] **Figure 2** illustrates the NBI endoscopic findings in a case with NERD.[9] While white-light endoscopy showed decreased visualization of the vascular pattern in the lower esophagus, particularly in the 1 o'clock, 4-8 o'clock, and 10 o'clock orientations, with subtle erythema and whitish turbidity (**Figure 2a**), NBI endoscopy clearly delineated the radial whitish turbidity areas (**Figure 2b**). Furthermore, NBI magnification revealed an increase in the number of IPCLs (hyperplasia) with a beaded appearance (**Figure 2c**), and further magnification showed mild elongation of the IPCLs in the whitish turbidity areas, with evident looped structures (**Figure 2d**). NBI magnifying endoscopy has been shown to be useful not only in diagnosing NERD but also in assessing the therapeutic response of acid



a | b
c | d

Figure 2 **White light imaging and narrow band imaging of Grade M reflux esophagitis.**

a: Conventional endoscopic image of Grade M reflux esophagitis. A decrease in the visibility of the palisade pattern is observed at the 1 o'clock, 4 to 8 o'clock, and 10 o'clock orientations of the lower esophagus. Mild erythema and whitish turbidity are also noted, though they are not clearly defined.
b: Narrow band imaging (NBI) endoscopic image. The radial whitish turbidity is clearly depicted compared to the conventional endoscopic image.
c: NBI with magnification (i). Upon magnified observation of the whitish turbidity area, an increase in intrapapillary capillary loops (IPCLs) is observed, forming a beaded appearance.
d: NBI with magnification (ii). Further magnification reveals mild elongation of the IPCLs in the whitish turbidity area, with the looped structure remaining intact.
(Cited from Literature 9)

suppressants.[10] Additionally, combined observation by linked color imaging (LCI) with white light has been reported to improve the diagnostic accuracy of Grade M compared to white light alone.[11]
While IEE and magnifying endoscopy are valuable tools in the endoscopic diagnosis of GERD, it is crucial to recognize that NERD may present differently from reflux esophagitis, potentially involving reflux of substances other than acid or increased esophageal sensitivity. Further investigation into the utility of IEE in diagnosing and assessing treatment outcomes in NERD is warranted, based on pathophysiological findings such as esophageal impedance-pH monitoring.

2. Barrett's Esophagus

(1) Definition of Barrett's esophagus

Barrett's esophagus is characterized by the continuous extension of columnar epithelium from the esophagogastric junction, which is defined as the upper end of the longitudinal folds of the stomach.

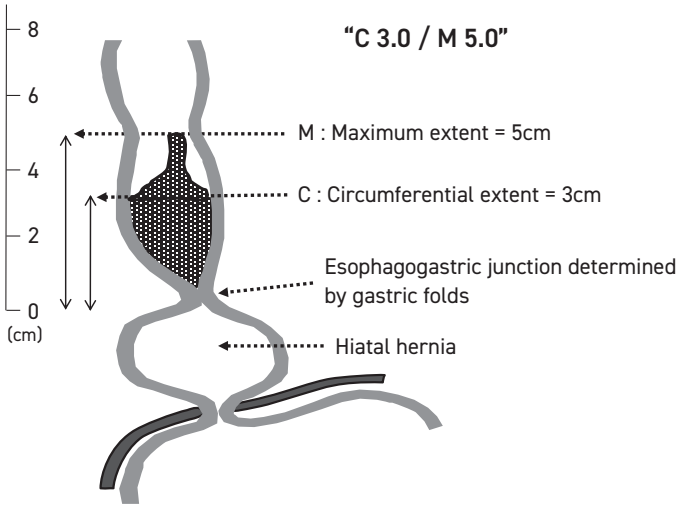


Figure 3 **Practical application of the C&M Classification for Barrett's esophagus.**

(Modified from Literatures 13 & 14)

According to the American College of Gastroenterology guidelines, the diagnosis of Barrett's esophagus requires confirmation of specialized intestinal metaplasia (SIM). In Japan and some other Asian countries, the esophagogastric junction is defined as the lower end of the palisade vessels in the esophagus. The histological diagnostic criteria for Barrett's esophagus in Japan require the presence of at least one of the following features within the columnar epithelium of esophagus: (i) esophageal proper glands, (ii) squamous island, (iii) a double-layered muscularis mucosae, or (iv) longitudinal vessels.[12] Barrett's esophagus is further categorized into long-segment Barrett's esophagus (LSBE) with a maximum length of 3 cm or more and short-segment Barrett's esophagus (SSBE) with a maximum length of less than 3 cm.[13] While the prevalence of LSBE in Western countries ranges from 2-7%, it is significantly lower in Japan, with an estimated prevalence of approximately 0.5%. Despite this difference, the annual cancer incidence rate is comparable across these regions.

(2) C&M criteria of Barrett's esophagus

In 2003, the circumferential (C) and maximum (M) criteria (Prague classification) were proposed as a standardized method for endoscopic description of Barrett's esophagus.[13,14] According to this classification, the esophagogastric junction (EGJ) is defined as the most proximal extent of the gastric folds. Since the vascular pattern can be obscured in Barrett's esophagus with reflux esophagitis due to mucosal inflammation and the presence of a double-layered muscularis mucosae, the Prague classification recommended not using the vascular pattern to determine the esophagogastric junction in the C & M criteria. Therefore, the C&M criteria describe Barrett's esophagus based on two parameters: C (circumferential extent) measures the length of the circumferential segment of the esophageal columnar epithelium, and M (maximum extent) measures the longest tongue of the esophageal columnar epithelium. Measurement of these lengths is recommended using the scale marked on the

endoscope shaft with the bite block set at the patient's mouth. For instance, in the case shown in **Figure 3**, the esophagogastric junction is identified at the most proximal margin of the gastric folds. The circumferential extent is measured as 3.0 cm (C), while the maximum extent is 5.0 cm (M), represented as C 3.0/M 5.0. For cases without the tongue projection, the notation is described as C 3.0/M 3.0, and for tongue-shaped Barrett's esophagus only, it is noted as C 0/M 3.0.

While the C&M criteria have shown high inter-observer and intra-observer agreement for rating long-segment Barrett's esophagus (LSBE), the agreement is lower for short-segment Barrett's esophagus (SSBE).[14] This discrepancy arises because the position of the upper end of the gastric folds (EGJ) can vary significantly based on the patient's inspiration and the endoscopist's insufflation during the examination. Additionally, in Japan, many patients have gastric mucosal atrophy, where the gastric folds on the gastric side are not visible, further complicating the diagnostic process.[15] Such discrepancies in endoscopic diagnosis make it difficult to elucidate the epidemiology and pathophysiology of Barrett's esophagus. In clinical practice, a thorough understanding and mastery of the appropriate diagnostic techniques are necessary to reliably apply the C&M criteria.

(3) Diagnosis of Barrett's esophagus by image-enhanced endoscopy

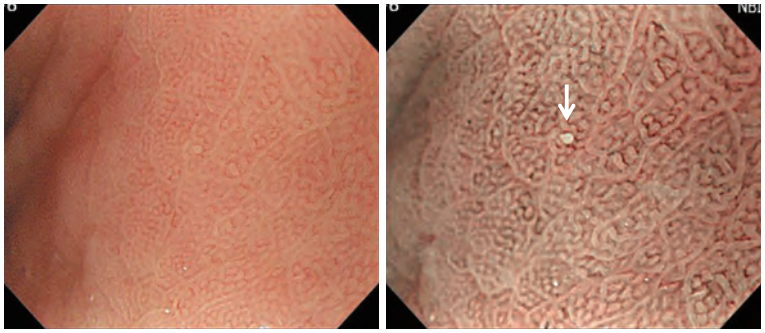
Numerous studies have investigated the utility of IEE for Barrett's esophagus. Various IEE techniques have been reported, including staining methods, contrast methods (indigo carmine), acetic acid chromoendoscopy, and digital methods/optical digital methods (NBI, BLI, LCI). For diagnosing SIM, techniques like methylene blue staining[16] and crystal violet chromoendoscopy[17] have also been utilized. Due to its ability to enhance visualization, IEE has become a valuable tool in the clinical practice of diagnosing Barrett's esophagus.

1) Diagnosis of Barrett's esophagus

While LSBE can be easily observed with conventional endoscopy, diagnosing short-segment Barrett's esophagus (with a length of less than 1 cm) can be challenging, especially when the palisade vessels and gastric longitudinal folds are obscured due to severe esophagitis or atrophic gastritis. In such cases, the presence of squamous islands within the columnar epithelium, a histological criterion for Barrett's esophagus in Japan, can serve as a valuable diagnostic clue. With magnified IEE, even very small squamous islands are clearly visualized as punctate white spots, providing useful information for accurate diagnosis (**Figures 4 & 5**).[9] Additionally, the use of LCI has been reported to improve the visibility of Barrett's esophagus.[18]

2) Diagnosis of specialized intestinal metaplasia (SIM)

Since 1994, it has been reported that many SIMs that are invisible on conventional endoscopy show a villous pattern under magnified endoscopic observation.[19] Similar findings have been reported using acetic acid chromoendoscopy, methylene blue staining, and contrast methods with indigo carmine.[20] However, magnified endoscopic examinations using these dyes or acetic acid are susceptible to staining and variations in color tone, and they require cumbersome techniques. Furthermore, methylene blue staining has raised concerns about DNA damage to Barrett epithelial cells. In recent years, there has been skepticism about the metaplasia-dysplasia-adenocarcinoma sequence, which traditionally viewed SIM as a precancerous field.[21] As a result, the diagnostic focus on SIM has diminished. However, in cases of LSBE, differentiating between dysplasia and SIM can be still challenging, making narrow band



a | b

Figure 4 **Magnified endoscopic images of Barrett's mucosa.**

a: Magnified endoscopic image of Barrett's mucosa showing fine mucosal patterns that are circular to ovoid in shape.
b: Narrow band imaging (NBI) magnified endoscopic image of Barrett's mucosa. Compared to white light magnification, fine mucosal patterns and surrounding vessels are more clearly visualized. Additionally, a minute squamous island, smaller than 1 mm (arrow) is clearly recognized, which is challenging to identify under white light endoscopy.
(Cited from Literature 9)

imaging with magnification an important tool for diagnosis.

3) Dysplasia/early cancer diagnosis

Recent studies have shown that magnified observation using IEE such as NBI, BLI, and LCI is more effective than conventional endoscopy in detecting dysplasia and Barrett's neoplasia.[22] Magnified endoscopy with NBI/BLI allows for detailed observation of not only mucosal patterns but also morphological changes in capillary patterns, making it highly useful for diagnosing early neoplastic changes. Numerous reports have shown that grouping both mucosal and capillary patterns helps efficiently identify SIM.[23,24] The Japan Esophageal Society has established a simplified and unified magnifying endoscopy classification using NBI, which is useful for detecting precancerous lesions, which are the primary targets of Barrett's esophageal surveillance. [24,25] This classification categorizes mucosal and vascular patterns into pit, non-pit, and net, non-net, respectively, and assesses their irregularity. The diagnostic method has shown high reliability and reproducibility, even among endoscopic trainees.[26] **Figure 4b** shows a normal Barrett mucosa with a typical regular pit-type mucosal pattern and a regular net-type vascular pattern. However, because this pattern is similar to that seen in fundic gland mucosa, the presence of a small squamous island in the image is a critical finding. **Figure 5c** shows narrow band imaging magnification of a lesion (arrow in **Figure 5b**) located at the 1 o'clock position in **Figures 5a** and **5b**. According to the Japan Esophageal Society's classification system, the mucosal pattern of the lesion is non-pit and irregular, and the vascular pattern is non-net and irregular, which allows it to be diagnosed as Barrett's esophagus-related neoplasia. Conversely, the mucosal pattern of the distal esophagus is pit pattern and regular, confirming it as benign Barrett's mucosa.

4) Basic techniques for magnification endoscopy of Barrett's esophagus

Diagnosis using manigfication endoscopy requires specialized knowledge, observational techniques, and skills. As magnification increases, the endoscope tip must be gradually brought closer to the mucosa. During high-magnification observations, maintaining a clear view can become challenging due

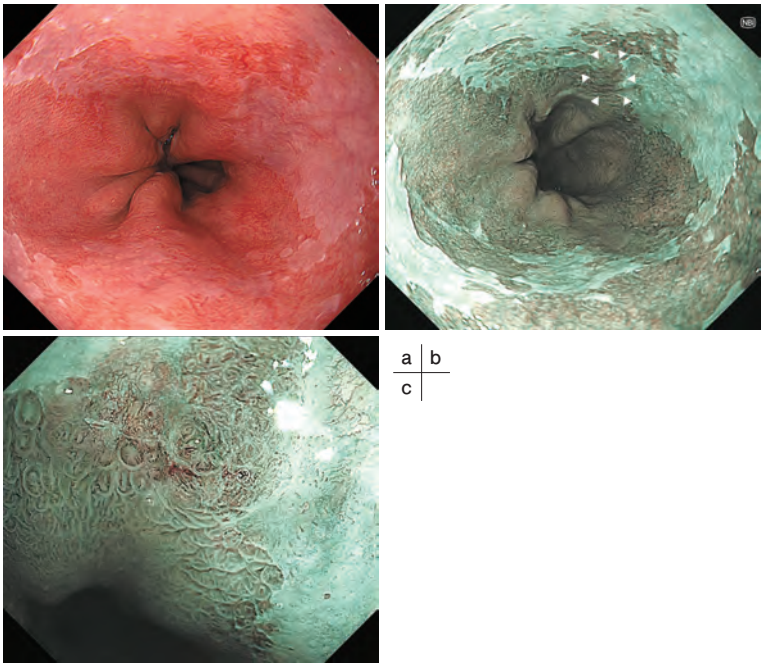


Figure 5 **NBI endoscopic diagnosis of LSBE with Barrett's cancer.**

a: Non-magnified conventional endoscopy of LSBE (C 0.5, M 4.0).
b: Non-magnified NBI endoscopic image. Compared to the conventional endoscopy, the palisade vessels are not as pronounced, but the squamous islands within Barrett's mucosa are more distinctly visualized.
c: Narrow band imaging with magnification of the lesion identified at the 1 o'clock orientation in a and b (arrowhead in b).
According to the Japan Esophageal Society classification, the mucosal pattern of the lesion is non-pit and irregular, and the vascular pattern is non-net and irregular, leading to a diagnosis of Barrett's adenocarcinoma. The mucosal pattern of the distal mucosa is a pit pattern and regular, indicative of normal Barrett's mucosa.

to contact between the endoscope tip and the mucosal surface. To maintain an optimal distance from the mucosa and ensure a stable view, a hood (distal attachment) is often used. However, using a distal hood can increase the risk of mucosal damage or bleeding, so a soft hood is recommended. This is especially beneficial for magnification endoscopy of the esophagus and esophagogastric junction, where peristalsis and cardiac pulsations may interfere. In terms of technique, the hood should be gently placed in contact with the mucosa slightly proximal to the target area during high-magnification examinations. This positioning helps maintain a stable, frontal view and allows for detailed evaluation without directly compressing the observation site. Additionally, slight deflation can facilitate better visualization by reducing tension on the mucosal surface, thus minimizing the risk of bleeding during magnification endoscopy.

Given the potential rise in cases of Barrett's esophagus and Barrett's adenocarcinoma in Japan, it is critically important to carefully observe esophagogastric junction. With conventional endoscopy, thorough irrigation and techniques such as breath-holding during deep inspiration are essential to avoid overlooking subtle mucosal changes, such as discoloration or unevenness. Active use of IEE techniques, chromoendoscopy, acetic acid staining, NBI/BLI, and LCI are critical, in addition to

magnification endoscopy. These measures are expected to improve early detection of Barrett's esophagus and Barrett's adenocarcinoma, facilitating timely intervention and appropriate treatment.

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Yuto Shimamura and Yuji Amano

5 Eosinophilic Esophagitis

Eosinophilic gastrointestinal disorders (EGIDs) are designated as rare diseases caused by pathological eosinophilic infiltration into the gastrointestinal tract. This allergic or immune-mediated process excludes other possible reasons as secondary factors. Allergies to dietary or airborne antigens play a significant role in the pathogenesis, and based on the affected site, it is broadly categorized into eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (non-EoE EGIDs).[1] EoE is characterized by the infiltration of a large number of eosinophils into the epithelium limited to the esophagus, leading to impaired esophageal motility and fibrosis-induced stricture, causing symptoms such as difficulty swallowing or dysphagia.[1]

EoE has been rapidly increasing in Western countries, and although it is still rare in Japan, there is a high possibility of an increase.[2] The incidence of EoE per endoscopy was approximately 0.02% in 2011 to 0.4% in 2016.[3]

For the diagnosis of EoE in Japan, there are both mandatory criteria and reference criteria (**Table 1**).[4] As with the mandatory criteria, a definitive diagnosis is obtained through endoscopic biopsy. In fact, upper gastrointestinal endoscopy is the most important examination. Typical endoscopic findings in EoE include (i) edema (decreased or absent vascular visibility), (ii) rings (concentric, trachea-like appearance), (iii) exudate (white exudate), (iv) furrows (longitudinal), and (v) stricture. The EoE endoscopic reference score (EREFS) has been devised to evaluate these findings and is becoming widespread, particularly in Western countries.[5] Edema appears in various conditions, including gastroesophageal reflux disease (GERD), and lacks specificity. Exudate is also known as white spot, and its differentiation from candidiasis is difficult, due to reflecting micro-abscesses caused by eosinophilic infiltration histologically. Among the endoscopic findings in EoE, longitudinal furrows are the most frequent and specific, followed by white spots or white exudates, and concentric rings (Figure 1: longitudinal furrows / white spots). Longitudinal furrows in the esophagus are attributed to inflammation and edema of the mucosa. Unlike the longitudinal erosions seen in reflux esophagitis, these furrows are characterized by 2-3 shallow, short creases that intersect with the furrows and form a wedge shape as the furrows run longitudinally. In Japan and the other Asian countries, such characteristic findings show similar trends as in Western countries, such characteristic findings show similar trends as in Western countries; however, clinically severe cases such as stricture and impaction due to advanced stnosis are clearly less frequent and lesser than in Western countries.[6]

It is also important to recognize that some cases of eosinophilic esophagitis (EoE) could present with no visible abnormalities on endoscopic examination. When a patient is clinically suspected for EoE but endoscopically normal, Western guidelines recommend 2-4 biopsies (in total 6 or more) from two or

Table 1 Diagnostic criteria for eosinophilic esophagitis (EoE).

Mandatory Criteria	1. Presence of symptoms related to esophageal dysfunction, such as dysphagia and difficulty swallowing 2. Biopsy of the esophageal mucosa revealing 15 or more eosinophils per high-power field (400x) in the epithelium (biopsies from multiple sites are recommended)
Supporting Criteria	1. Endoscopic findings such as white spot, longitudinal furrows, and trachea-like strictures in the esophagus 2. Poor response to proton pump inhibitors (PPIs) 3. Thickening of the esophageal wall on CT scan or endoscopic ultrasonography (EUS) 4. Increased eosinophils in peripheral blood 5. Male
Differential Diagnoses	Eosinophilic gastroenteritis with esophageal involvement (EGE or non-EoE EGID), gastroesophageal reflux disease (GERD), hypereosinophilic syndrome, celiac disease, Crohn's disease, infections (such as candidiasis), achalasia, drug allergies, graft-versus-host disease (GVHD), lymphocytic esophagitis.

(Cited from Literature 4)

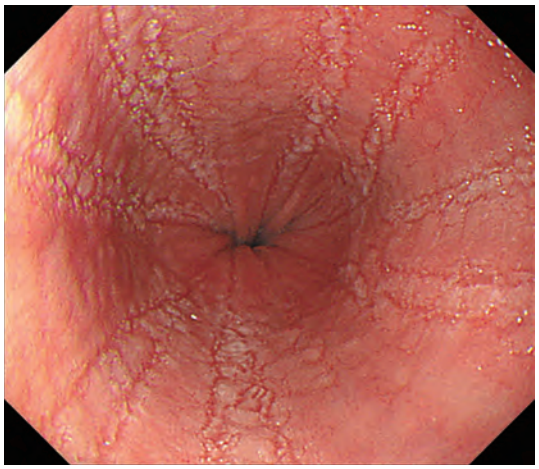


Figure 1 Longitudinal furrows and white spots (White light imaging).



Figure 2 Beige mucosa (Narrow band imaging).

more locations, such as the proximal and distal levels in the esophagus.[1] However, in a recent nationwide survey in Japan (2021), only 2% were endoscopically normal, and abnormal findings were detected in 98%.[2] This result suggests that if one is familiar with the characteristic endoscopic findings of EoE and observes carefully using the latest high-definition endoscopy, some abnormalities could be pointed out. However, it should also be recognized that there are cases with no symptoms (asymptomatic EoE) even if there are the endoscopic findings characteristic of EoE.

In order to accurately detect EoE lesions that show only localized or minute changes and have been possibly considered endoscopically normal, image enhancement techniques such as narrow band imaging (NBI) have been applied. One of the characteristic images of EoE by NBI is beige mucosa.[7] Okimoto and colleagues reported that biopsy of beige mucosa using non-magnified NBI (**Figure 2**) achieved a diagnostic accuracy of 98%,[8] suggesting its usefulness in screening and routine endoscopy.

The advantage of artificial intelligence (AI) in endoscopic diagnosis of EoE has also been reported.[9] Development of an ideal endoscopic method is warranted for the simple, quick, highly-accurate, and reproducible diagnosis.

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Kenichi Goda and Shunji Ishihara

6 Esophageal Motility Disorders

The diagnosis of esophageal motility disorders, such as achalasia, is made by gold-standard methods such as esophageal manometry and barium esophagography. On the other hand, for patients experiencing symptoms like dysphagia or chest pain which might indicate an esophageal motility disorder, esophagogastroduodenoscopy is frequently selected as the initial examination. In such cases, the primary role of this endoscopy is limited to ruling out structural (organic) diseases. However, new endoscopic findings related to achalasia have been reported in recent years, such as the esophageal rosette, gingko-leaf sign, champagne glass sign, and pinstripe pattern. These findings suggest that achalasia should now be strongly suspected based on endoscopic examination alone. Additionally, the presence of corkscrew appearance, multiple annular contractions and narrowing (poor distensibility) of the esophageal body suggests the possibility of motility disorders of esophageal body. To obtain these endoscopic findings, it is important to always consider the possibility of esophageal motility disorders when examining patients with dysphagia or chest pain. In the examination, practitioners should tell the patients to take a deep inspiration for extending the esophagus and observe the esophagogastric junction (EGJ). Simultaneously, they hold the scope in the middle of the esophagus for a while to confirm the movement of esophagus.

1. Classic Endoscopic Findings of Achalasia and Differential Diagnosis

The Japan Esophageal Society guidelines of *Descriptive Rules for Achalasia of the Esophagus* list the following endoscopic diagnostic criteria: dilatation of the esophageal lumen, abnormal retention of food and/or liquid remnants, whitish change and thickening of the esophageal mucosal surface, functional stenosis of the EGJ (winding of tissue around the scope or leafing of tissue on scope rotation), and the abnormal contraction waves of the esophagus (**Figure 1**).[1)] Such findings are generally not challenging for diagnosing achalasia. However, in patients with achalasia who do not have esophageal dilation and no food or fluid remnants in esophagus, the diagnosis could not be made by endoscopy alone.

While many cases of achalasia experience resistance when endoscopists pass the scope through the narrowed area of the EGJ, this insertion is usually possible. If there is significant resistance or the scope cannot go through, organic strictures should be suspected, for example, malignant tumors in the EGJ. This is important in the differential diagnosis of achalasia. Furthermore, since cases with achalasia have a high risk of developing esophageal cancer, regular endoscopic follow-ups are necessary both before and after the diagnosis and treatment of achalasia.

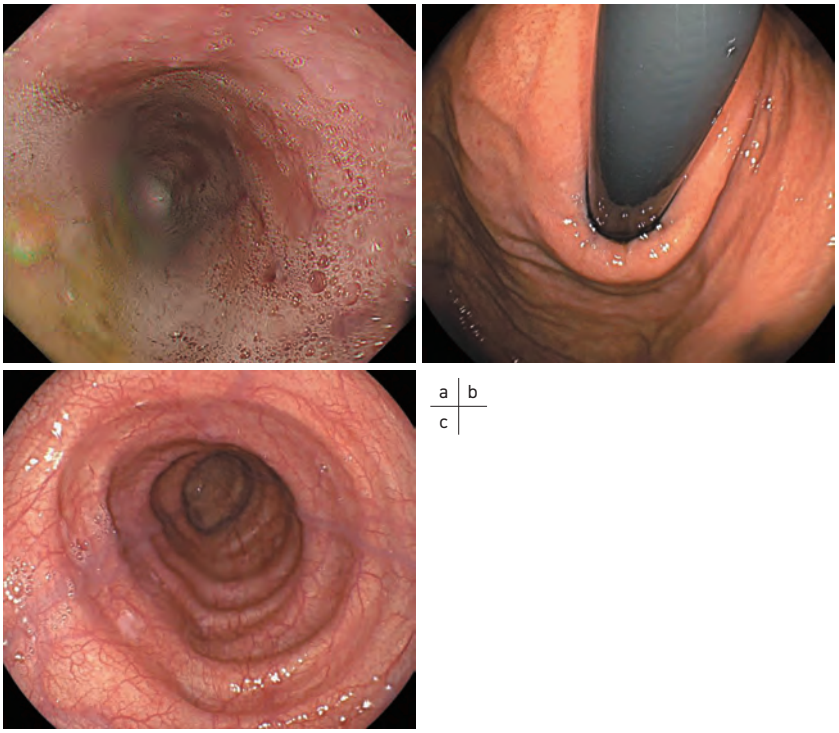


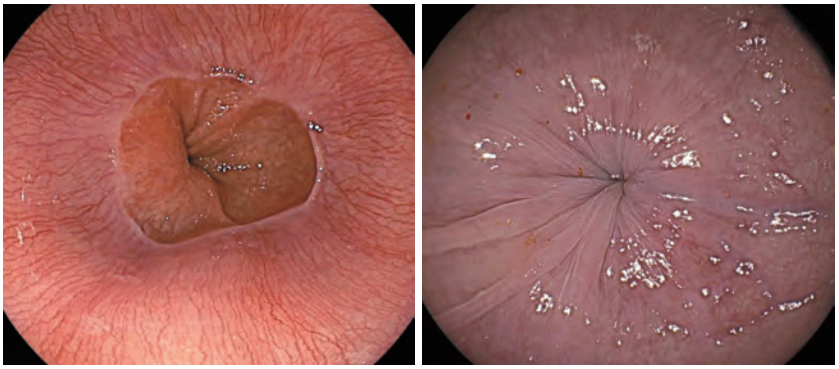
Figure 1 Classic endoscopic findings of achalasia.

a: Esophageal dilation, food residue, liquid retention, and frothy saliva remnant
b: Winding of tissue around the scope when the cardia is retroflex-viewed from the stomach
c: Abnormal contraction waves of the esophagus

2. Recent Endoscopic Findings Suggestive of Achalasia

(1) Esophageal rosette

When observing the lower esophagus of healthy individuals during their deep breath, the full extent of the esophageal palisade vessels is viewed and in some cases, some part of the gastric mucosa is also confirmed (**Figure 2**). In contrast, many patients with achalasia exhibit a characteristic finding upon their deep inspiration, which is an esophageal rosette. This profile is characterized by a circumferential fold pattern at the lower esophageal narrowing without the full extent of the esophageal palisade vessels (**Figure 2**).[2] Even in cases other than achalasia, circumferential folds exist in the esophagus when no air is insufflated into the esophagus, whereas the folds disappear while the esophagus is stretched on insufflation. In patients with achalasia, impaired relaxation of the lower esophageal sphincter (LES) is distinct. Due to this dysfunction, the area above the LES shows the loss of folds, whereas the LES itself remains contracted in high tone. In the transitional zone between the non-fold region and the LES site, the folds occur and continue into the LES, where it forms a circumferential, radiating pattern as seen on endoscopy. An esophageal rosette tends to be observed in cases where LES dysfunction extends over a wide area (**Figure 3**).[3]



Healthy Esophageal achalasia

Figure 2 **Endoscopic findings of achalasia in lower esophagus on a deep inspiration (esophageal rosette).**

In healthy individuals, on deep inspiration the full extent of the esophageal palisade vessels is apparent with some gastric mucosa. In achalasia, an esophageal rosette appears, characterized by a circumferential folds at the lower esophageal narrowing and an absence of the full extent of the esophageal palisade vessels on a deep inspiration.

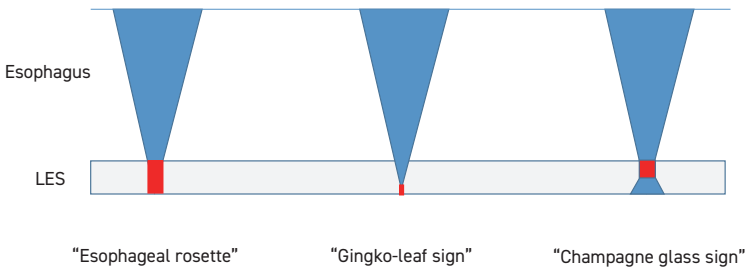


Figure 3 **Expected dysfunction sites (red) of lower esophageal sphincter (LES) in achalasia ("esophageal rosette," "gingko-leaf sign," and "champagne glass sign").**

The esophageal rosette suggests a broad area of LES dysfunction. The gingko-leaf sign indicates dysfunction at the lower end of the LES. The champagne glass sign suggests dysfunction in the middle to upper portion of the LES.
(Cited from Literature 3)

(2) Gingko-leaf sign

This endoscopic presentation is another feature in which the full extent of the esophageal palisade vessels is hardly observed together with a gingko leaf-shaped morphology of a longitudinal section of the EGJ on a deep inspiration (**Figure 4**).[4] These findings are likely attributable to dysfunction primarily affecting the lower end of the LES (**Figure 3**).[3] It is expected to be an early stage of achalasia, although it is infrequent.

(3) Champagne glass sign

This endoscopic presentation is confirmed in the retroflex view from the stomach, where the EGJ is observed. In the endoscopic imaging, the narrowing of contracted LES is positioned above the distal

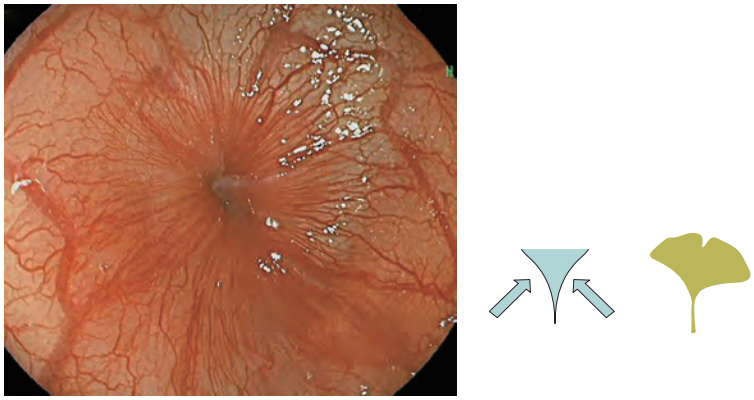


Figure 4 **Endoscopic findings of achalasia in lower esophagus on a deep inspiration ("gingko-leaf sign").**

The gingko-leaf sign refers to the absence of the full extent of the esophageal palisade vessels, resulting in a gingko leaf-shaped morphology of a longitudinal section of the esophagogastric junction.

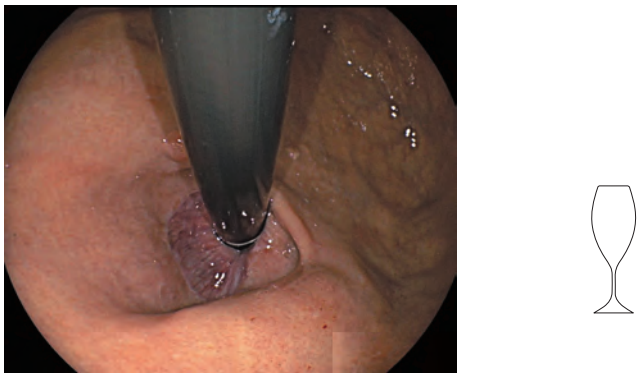


Figure 5 **Endoscopic findings of achalasia in esophagogastric junction (EGJ) on retroflex-view from the stomach ("champagne glass sign").**

The champagne glass sign refers to an endoscopic finding where the narrowing by the lower esophageal sphincter contraction is located proximally to the lower border of the palisade vessels when the EGJ is observed with retroflex-view from the stomach, suggesting relaxation of the EGJ. The lower esophagus is longitudinally assumed to take on a shape resembling a champagne glass.

palisade vessels, while the EGJ appears relaxed (**Figure 5**).[5] The longitudinal cross-section of the lower esophagus resembles the shape of a champagne glass, where the narrowing suggests dysfunction in the mid-to-upper portions of the LES (**Figure 3**).[3]

Based on these specific endoscopic findings in achalasia with the esophageal rosette, gingko-leaf sign, and champagne glass sign, the LES dysfunction is not always uniform in its presentation. Each sign offers a distinct visual cue reflecting the varying degrees and patterns of LES relaxation failure. These findings could reflect the differences in the LES involvement: the esophageal rosette is associated with widespread LES dysfunction, the gingko-leaf sign with localized dysfunction (primarily at the distal LES), and the champagne glass sign with dysfunction extending from the mid to upper LES (**Figure 3**).[3]

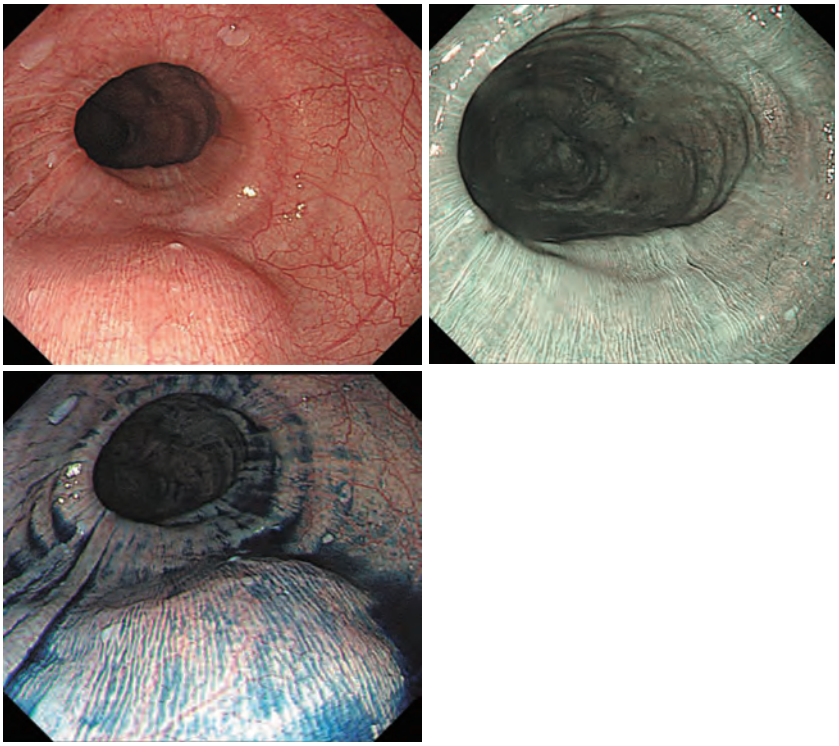


Figure 6 Longitudinal mucosal wrinkles in achalasia ("pinstripe pattern").

The pinstripe pattern refers to fine longitudinal superficial wrinkles of esophageal mucosa, which become more distinct with image enhancement or indigo carmine staining.

(4) Pinstripe pattern

This endoscopic presentation refers to the presence of the longitudinal superficial wrinkles of esophageal mucosa. This finding is seen in about 60% of patients with early-stage achalasia, including cases evaluated under sedation (**Figure 6**).[6] It typically resolves following peroral endoscopic myotomy (POEM). This disappearance suggests an involvement with the inner circular muscle contraction.

3. Endoscopic Findings Suggestive of Abnormal Motility of the Esophageal Body

In distal esophageal spasm (DES), hypercontractile esophagus (including jackhammer esophagus), and Type III achalasia accompanied by diffuse contractions of the esophageal body, endoscopic findings tends to reveal rosary beads appearance, corkscrew appearance, and esophageal narrowing (poor distensibility) in the esophageal body (**Figure 7**). When patients experience symptoms such as dysphagia or chest pain along with these clinical features, the possibility of an abnormal motility of the esophageal body should be considered. While Matsubara and colleagues examined the endoscopic findings of patients diagnosed with esophageal motility disorders using high-resolution manometry (HRM), they identified key endoscopic features, including resistance when passing through the EGJ, residue in the esophageal lumen, esophageal dilation, spastic contractions (corkscrew appearance or rosary beads appearance), and nonocclusive contractions within the esophageal lumen.[7]

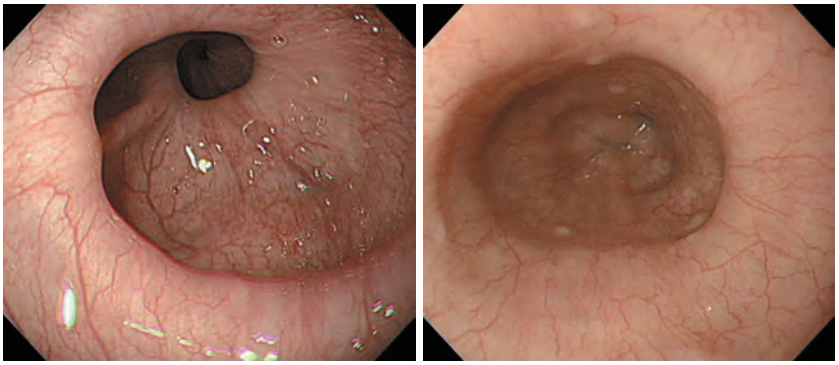


Figure 7 **Endoscopic findings of esophageal body in hypercontractile esophagus (jackhammer esophagus).**

In esophageal motility disorders characterized by diffuse and strong contractions in the esophageal body, endoscopic examination finds corkscrew appearance or narrowing of the esophagus (poor distensibility) in the esophageal body.

4. Endoscopic Treatment for Esophageal Motility Disorders

POEM is a minimally invasive treatment developed as an alternative to endoscopic balloon dilation and surgical myotomy for achalasia. This technique was introduced in 2016 under insurance coverage. In 2018, the Japan Gastroenterological Endoscopy Society published POEM guidelines, and the procedure is now the standard treatment for achalasia,[8] with reported efficacy rates exceeding 95%. One of POEM's distinct features is its ability to adjust the length and direction of the myotomy at operators' discretion, and its related-studies have shown no difference in treatment outcomes based on the subtype of achalasia identified via HRM. POEM is particularly recommended as the first-line treatment for Type III achalasia which requires longer myotomy of the diffuse contraction area. Symptomatic gastroesophageal reflux disease (GERD) occurs in approximately 15% of the cases following POEM, but these cases are generally mild and manageable with acid-suppressive medications. To minimize the risk of GERD, it has been reported that limiting the gastric side incision length to about 2 cm and preserving the oblique muscle layers is effective. Recently, POEM combined with endoscopic fundoplication (POEM+F) has also been performed, yielding favorable results.

For hypercontractile esophagus and DES, symptom control is often possible through medication or conservative treatment including observation. However, a multi-center study in Japan on hypercontractile esophagus found that patients experiencing impaired quality of life with greater maximal distal contractile integral (DCI) values, a measure of the strength of peristaltic contractions, underwent invasive treatments such as surgery or POEM.[9]

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Katsuhiko Iwakiri, Noriyuki Kawami, and Haruhiro Inoue

7 Treatment for Esophageal and Gastric Varices

Treatments for esophageal and gastric varices (referred collectively to as esophageal and gastric varices when appropriate) are classified into endoscopic procedure, endovascular catheter therapy, and surgical intervention. Among these, endoscopic procedure for esophageal varices includes endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL), whereas for gastric varices, endoscopic cyanoacrylate injection (ECI) is primarily used in cases of bleeding (Table 1).[1] The widespread use of these endoscopic treatments has brought benefit to many patients with varices. Therefore, endoscopic procedure for esophageal and gastric varices is one of the treatments that gastroenterologists should acquire. It is important to ensure safe and effective treatment with understanding thoroughly on the pathophysiology of underlying diseases such as cirrhosis and portal hemodynamics.

Table 1 Endoscopic treatments for esophageal and gastric varices.

Techniques
1. Endoscopic injection sclerotherapy (EIS) Intravariceal EIS (Intra EIS): ethanolamine oleate (EO) Paravariceal EIS (Para EIS): polidocanol
2. Endoscopic variceal ligation (EVL)
3. Endoscopic cyanoacrylate injection (ECI): n-butyl-2-cyanoacrylate
4. Others Snare placement technique, clipping, thermal coagulation (argon plasma coagulation, high-frequency coagulation), endoscopic ultrasound-guided puncture (coil embolization)
Combined Therapy
1. Esophageal varices Intra EIS+Para EIS, EIS+consolidation treatment, EIS+EVL, EVL + consolidation treatment
2. Isolated gastric varices ECI+EIS, ECI under shunt occlusion, EIS combined with snare placement

(Cited from Literature 1)

1. Endoscopic Criteria for Esophageal and Gastric Varices

The pathogenesis of esophageal and gastric varices involves abnormal collateral circulation due to portal hypertension. Upper gastrointestinal endoscopy is the most critical diagnostic method for identifying esophageal and gastric varices and determining treatment indications. According to the *General Rules for Study of Portal Hypertension*, 4th Edition (September 2022),[2] published by the Japan Society for Portal Hypertension, six parameters are defined for endoscopic examination: **location, form, color, red color sign, bleeding sign, and mucosal finding** (Table 2).

In gastric varices, treatment strategies are determined based on hemodynamic differences among the types of varices. Specifically, classification is made among cardiac varices in the lesser curvature near the esophagogastric junction (Lg-c), which are continuous with esophageal varices; cardiofundal varices (Lg-cf) involving both the cardia and fundus; and fundal varices (Lg-f) located in the gastric fundus and upper stomach. Typically, Lg-c is categorized as esophagogastric varices and grouped with esophageal varices, while Lg-cf and Lg-f are referred to as **isolated gastric varices**.

2. Indications and Contraindications

(1) Indications

In esophageal varices, treatment is indicated for varices exhibiting bleeding signs (Emergency case e.g., **active bleeding** or **fibrin plugs**). In addition, for patients with a history of bleeding, management focuses on preventing recurrence or addressing ongoing bleeding (Secondary prophylactic case after acute bleeding). Even in non-bleeding cases, varices with **F2 or larger size** or **positive red color signs (RC)** are considered at high risk of bleeding and require preventive treatment (Primary prophylactic case). For isolated gastric varices, treatment is also indicated for cases with bleeding or a history of bleeding, as well as for varices showing RC, erosion, ulcers, significantly distended F2 or F3 , or rapid growth within six months.[3]

(2) Contraindications

When performing endoscopic procedures, especially EIS, careful evaluation is necessary for patients who present with **significant jaundice (total bilirubin ≥ 4.0 mg/dL), hypoalbuminemia (albumin ≤ 2.5 g/dL), severe thrombocytopenia (≤ 20,000/μL), systemic bleeding tendencies, large-volume ascites, hepatic encephalopathy, or renal dysfunction.** For such cases, alternative endoscopic treatments should be considered. EVL could be appropriate for esophageal varices because it avoids the use of sclerosants or contrast agents. Endoscopic cyanoacrylate injection (ECI) is a potential option for gastric varices. In patients with advanced liver dysfunction like Child-Pugh Class C complicated with thrombocytopenia and reduced coagulation factors, even EVL could pose risks of persistent bleeding from ulceration after O-ring detachment. Therefore, determining whether treatment is appropriate requires careful consideration.

Table 2 Criteria for endoscopic findings on esophageal and gastric varices.

	Esophageal varices (EV)	Gastroesophageal varices (GV)
Location (L)	Ls: Extends to superior esophagus (cervical and upper thoracic esophagus). Lm: Extends to middle esophagus (middle thoracic esophagus). Li: Confined to inferior esophagus (lower thoracic esophagus and esophagogastric junction).	Lg-c: Confined to cardia. Lg-cf: Extends from cardia to fundus. Lg-f: Confined to fundus. (Note: Varices in gastric body are denoted as Lg-b, and those in pylorus as Lg-a.)
Form (F)	F0: Varices no longer visible after treatment (post-treatment finding) F1: Straight, small-caliber varices F2: Moderately enlarged, beady varices F3: Markedly enlarged, nodular or tumor-shaped varices	For gastric varices, the same criteria as for esophageal varices apply.
Color (C)	Cw: White varices Cb: Blue varices	For gastric varices, the same criteria as for esophageal varices apply.
	Note: i) If varices appear purple or purplish-red, "Violet" (V) can be added to the notation, such as Cbv. ii) Thrombosed varices are denoted as Cw-th and Cb-th.	
Red color sign (RC)	RC includes red wale marking (RWM), cherry red spot (CRS), and hematocystic spot (HCS).	
	RC0: No reddening sign RC1: Observed in only one varix. RC2: Between RC1 and RC3 RC3: Observed in all varices circumferentially	RC0: No reddening sign RC1: Either RWM or CRS or HCS
	Note: i) If telangiectasia is present, "Te" is added. ii) The characteristics of RC are added after RC, such as RWM, CRS, and HCS. iii) If RC is observed, it is expressed as RC1-3, even in case of F0.	
Bleeding sign (BS)	Active bleeding: Gushing bleeding, spurting bleeding, oozing bleeding Findings shortly after hemostasis: Red plug, white plug	For gastric varices, the same criteria as for esophageal varices apply.
Mucosal finding (MF)	Erosion (E): If present, "E" is added. Ulcer (Ul): If present, "U" is added. Scar (S): If present, "S" is added.	For gastric varices, the same criteria as for esophageal varices apply.

(Cited from Literature 2)

-In cases of bleeding, initial actions should focus on stabilizing the general condition. For patients with unstable hemodynamics or severe hepatic dysfunction, priority should be given on conservative therapy to improve overall condition, such as fluid replacement or blood transfusion. Unnecessary endoscopic interventions should be avoided because it could worsen the patient's status.

3. Informed Consent

Given that liver dysfunction is often an underlying condition, these procedures carry a risk of serious adverse events. Therefore, written informed consent should be obtained. If it is difficult to obtain informed consent from the patient, the attended family or the related parties should be informed. The necessity of the treatment (benefits and risks), the outline of procedure, and potential complications should be explained in simple and understandable terms.

4. Hemodynamics of Esophageal and Gastric Varices

(1) Basics of hemodynamics

Esophageal and gastric varices are collateral venous pathways that form naturally due to **portal hypertension**, acting as a compensatory mechanism to divert blood from the portal system to the systemic circulation.

Normally, blood from the upper and middle esophagus flows into the superior vena cava via the **azygos** and **hemiazygos veins**, while blood from the lower esophagus and upper stomach flows into portal vein via the **left gastric vein** and short gastric veins. However, as portal pressure increases, the inflow of blood into the portal vein via **the left gastric, posterior gastric, and short gastric veins** becomes impaired. This results in congestion and vasodilation of the upper stomach. Subsequently, the **palisade zone** at the esophagogastric junction dilates, and blood backflows. The problem leads to the dilated and tortuous veins located in the lamina propria mucosae (LPM) and submucosa of the esophagus, forming esophageal varices. Additionally, the development of a splenorenal shunt which directs blood to the left renal vein, could lead to the formation of gastric varices along its pathway.

(2) Imaging diagnosis

In ***The General Rules for Study of Portal Hypertension*, 4th Edition** (edited by the Japan Society for Portal Hypertension), the advantage of various imaging modalities is emphasized in diagnosing portal hypertension and assessing portal hemodynamics.[2] Particularly useful methods include endoscopic ultrasonography (EUS), multi-detector row CT (MDCT), angiography, and MRI. Proper treatment of esophageal and gastric varices requires the comprehension of the relationships between varices located within the esophageal and gastric walls and their **feeder, drainage, perforating, and paraesophageal veins**. Based on this understanding, strategies should be evaluated before treatment including the likelihood of endoscopic treatment, suitable treatment methods, and the necessity of consolidation therapy.

EUS is particularly suited for obtaining localized information about varices.[4,5] In addition to B-mode imaging, color Doppler functionality allows the assessment of blood flow direction. [6] CT is now an indispensable examination method for diagnosing liver diseases, including liver cancer. In particular, with the wide use of MDCT, three-dimensional image creation has become easy, enabling 3D-CT angiography.[6-8] Images created with volume rendering and maximum intensity projection (MIP) methods are as clear as those obtained from conventional percutaneous transhepatic portography (PTP). 3D-CT angiography is useful for comprehensively assessing the portal system, but it is difficult to distinguish between veins inside and outside the esophageal and gastric walls. Therefore, a more

accurate diagnosis can be made by combining EUS with 3D-CT angiography. In MRI, gadolinium-enhanced MRI and 3D-MR angiography enabling the creation of 3D images are useful for non-invasively analyzing portal hemodynamics.

5. Preoperative Preparations

- A standard forward-viewing endoscope should be used, preferably one with water-jet function.
- EIS for intravariceal injection is performed primarily in a fluoroscopy room.
- A procedure cart and an emergency cart should be prepared in the procedure area.
- A venous route should be secured, and blood pressure, pulse, and arterial oxygen saturation should be monitored. As sedation is generally required, the use of a capnometer is also recommended.
- Nasal cannula oxygen administration should also be considered, as deep sedation could occur.
- In addition to an assistant endoscopist, a physician in charge of sedation and a nurse responsible for monitoring should be attended.
- In cases of bleeding, the use of an overtube should be considered.

6. EIS for Esophageal Varices

EIS involves injecting a sclerosing agent into or around varices with an injection needle to induce thrombosis and occlusion of the varices. The procedure is divided into **intravariceal injection (Intra EIS)** and **paravariceal injection (Para EIS)**. For the former, **Ethanolamine oleate (EO)** is mainly used, whereas **polidocanol (aethoxysklerol: AS)** is primarily used for the latter method.

(1) Required items

- Injection needle: Variceal puncture needle
- Sclerosing agents: EO and AS
- Additional agents: Water-soluble contrast agents, absolute ethanol, haptoglobin
- Endoscope-attached balloon
- Tip attachment: Useful for ensuring a clear field of vision, identifying puncture sites, and providing compression hemostasis.

Type and effect of sclerosing agent

(i) Ethanolamine oleate (Trade name: Oldamine®)
EO is an anionic surfactant mixed with the equal amount of water-soluble contrast agent to a 5% concentration. It is primarily used for intravariceal injection. Once injected into varices (vessels), it damages endothelial cells, thereby inducing thrombosis. Due to its strong hemolytic effect, excessive systemic leakage of EO may lead to hemoglobinuria and renal failure.

(ii) Polidocanol (Trade name: Aethoxysklerol®)
AS is a non-ionic surfactant with less thrombogenic, tissue-damaging, and hemolytic than EO. It is mainly used for paravariceal injection.

(iii) Absolute ethanol (Not covered by insurance)
Absolute ethanol has a stronger endothelial cell-damaging effect than EO or AS and can

immediately obliterate veins. It is effective in cases with developed perforating veins or extramural shunts (escape routes). However, as the systemic circulation could lead to complications such as pulmonary embolism or myocardial infarction, its injections should be limited to 1 mL per shot, with a maximum of two shots. In addition to this limitation, care must be taken to avoid paravariceal injection.

(2) Basic techniques for intravariceal injection sclerotherapy [9,10]

The Intra EIS was first described by Takase group. This technique involves **puncturing the varices with an injection needle and retrogradely injecting EO solution (a sclerosing agent mixed with contrast medium) into the varices**. The mechanism of action is **the thrombosis and occlusion of the varices caused by vascular endothelial damage induced** by the EO solution. This method has demonstrated favorable treatment outcomes due to its ability to embolize both the endoscopically visible varices and their feeders. This endoscopic varicealography during injection sclerotherapy (EVIS) provides valuable information for hemodynamic assessment. Although it is possible to puncture F1 varices (those with a luminal diameter of approximately 2 mm or less on EUS), a thinner puncture needle should be selected. Thus the procedure should be performed by an experienced clinician.

- Prior to puncture, the needle is exposed in the gastric space, and EO is used to flush the inner lumen of the needle.
- The patient is positioned in a supine or left lateral decubitus position.
- The endoscopic balloon is inflated with air (approximately 15–30 mL) to prevent the retrograde flow of EO toward the proximal side (cranial direction).
- Puncture is performed within 5 cm of the esophagogastric junction in the inferior esophagus.
- After puncture, the assistant applies slight negative pressure to confirm the needle's position in the varix with observing blood reflux into the catheter.
- Under fluoroscopic guidance, EO is injected retrogradely up to the point just before it enters the portal vein (near the confluence of the left gastric vein and portal vein).
- In case of emergency bleeding, EO is injected directly into the bleeding varix. If bleeding is profuse, the endoscopic balloon is used for tamponade before puncture.
- When no blood reflux is observed or fluoroscopy shows EO pooling in the submucosa, the injection volume should be limited to 1 mL or less, preferably within 0.5 mL. If no EVIS findings could be confirmed, the injection should be immediately stopped due to the risk of the leakage into systemic circulation (e.g., via extramural shunts).
- To enhance the thrombogenic effect of EO, a stagnation time of at least 1 minute (preferably 5 minutes or more) is recommended.
- After deflating the balloon, the needle is withdrawn to minimize bleeding.
- Bleeding from the puncture site is controlled with applying pressure by the endoscopic balloon. During this process, the practitioner should guide the scope to the bleeding site after puncture, watching the endoscopic screen. The tip of the scope is then confirmed under X-ray fluoroscopy, and after the endoscopist temporarily removes air from the stomach, the bleeding site is compressed with the balloon for approximately 3 minutes. Holding the scope while touching the mouthpiece helps prevent slippage.
- The total EO dose is limited to 0.4 mL/kg or approximately 20 mL for a 50 kg patient. To prevent renal impairment from large-volume injections, haptoglobin (2,000–4,000 units) should be promptly administered intravenously, along with sufficient fluid infusion to ensure adequate urine output.

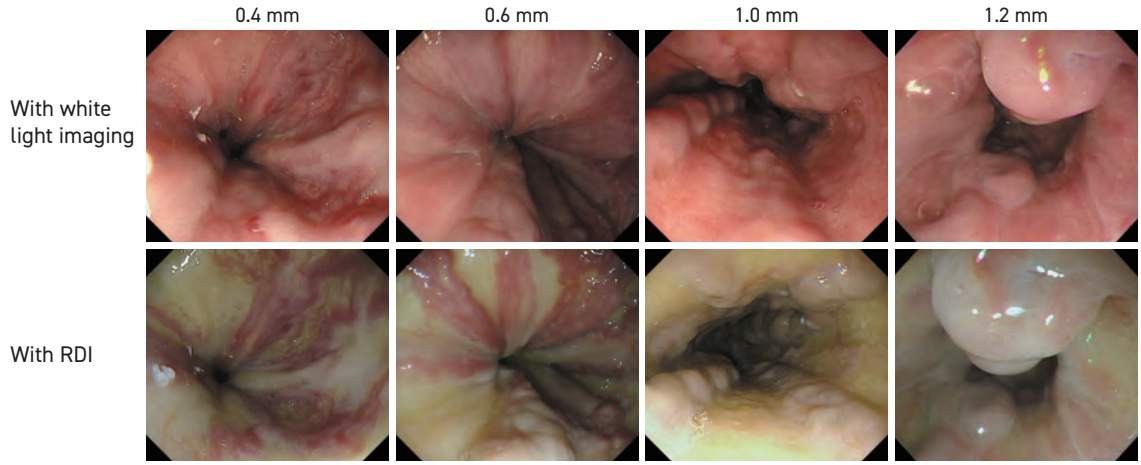


Figure 1 **Changes in visibility of esophageal varices by red dichromatic imaging (RDI).**

(Cited from Literature 12)

- Follow-up observation is conducted one week later, with additional treatment for any residual varices. If the varices are reduced to F1RC0 or less, consolidation therapy is initiated.

Recent advancements: Intravariceal EIS with red dichromatic imaging (RDI)

(i) RDI is an image-enhancement technology developed by Olympus, which improves the visibility of deep veins. Since esophageal varices are primarily located in the submucosa with some in the mucosa, RDI enhances visibility and helps predict the depth of varices based on the degree of change in imaging (**Figure 1**).[11,12]

(ii) RDI has also been reported to contribute to the success of intravariceal injection and a reduction in the recurrence rate of varices.[13] It is also effective in confirming the puncture site after the needle withdrawal and shortening the treatment time.[14-18] This technology makes coagulated blood clots more transparent to facilitate clearer visualization of the underlying mucosa and varices: transparency effect. This effect is particularly pronounced in clots with low hemoglobin concentrations after irrigation with water, as the amber and red wavelengths of RDI illumination are not absorbed, thereby allowing light to penetrate to the mucosa and varices beneath.

(3) Basic techniques for paravariceal EIS [19]

Para EIS involves injecting a 1% AS sclerosant into esophageal varices and the surrounding submucosa using an injection needle. The mechanism of action involves **creating superficial ulcers in the esophageal mucosa, and, during the healing process, they induce fibrosis, leading to the disappearance of varices and hardening of the mucosa.** Although AS has a milder thrombogenic effect than EO, it also contributes to thrombosis. Paral EIS is indicated for varices with smaller luminal diameters (F0–F1) that are unsuitable for intravariceal injection. It is typically used as an additional treatment following Intra EIS or EVL as well as treatment for small recurrent varices. Although EO is primarily used for Intra EIS, it is acceptable to switch to Para EIS if leakage occurs during the puncture

for intravariceal injection.

- Fluoroscopy or an endoscope-attached balloon is not generally required for Para EIS. However, when treating residual varices after switching from Intra EIS, a balloon could be used for hemostasis.
- After Intra EIS, injection is performed into the submucosa within 5 cm proximal to the esophagogastric junction near thrombosed varices or adjacent tissue. Care must be taken to avoid deep penetration into the muscularis, and the sclerosant should be injected to create submucosal bulging. When AS is used, each injection site typically receives 1–2 mL, with a total of up to 20 mL per session. When EO is used, individual injections should not exceed 0.5–1 mL, and the total volume should remain under 10 mL across multiple sites.
- If there is leakage from the puncture site, it often stops spontaneously due to the pressure of the sclerosing agent. If bleeding persists, additional sclerosing agent should be injected around the puncture site.
- Para EIS is a treatment for small varices and does not independently achieve embolization of feeding veins. Therefore, follow-up consolidation therapy is recommended with argon plasma coagulation (APC) to achieve F0RC0 status. If the ulcers caused by the sclerosing agent are extensive, the treatment session should be terminated, and an endoscopic examination should be performed a few weeks later to check for any remaining varices.

(4) Combined Intra-Para EIS technique and APC consolidation therapy [19,20]

- The combined Intra-Para EIS technique involves performing Intra EIS with 5% EO, followed by Para EIS with 1% AS after a one-week interval. Initially, Intra EIS is used to first obliterate esophageal varices and their feeders. At a later stage, when intravariceal injection becomes difficult, Para EIS is employed to eliminate any remaining small varices, aiming for complete obliteration.
- Although consolidation therapy is also possible with Para EIS, it has a higher rate of stricture. Therefore, it is recommended to perform 2-3 sessions of Intra EIS, one session of Para EIS, and then consolidation therapy with APC. APC is applied circumferentially to the lower esophagus within 5 cm proximally to the esophagogastric junction. While APC induces ulceration, the healing process replaces the mucosa and submucosa with fibrotic tissue, preventing the formation of new varices and reducing the risk of recurrence.

7. EVL for Esophageal Varices

(1) Preparations

- EVL devices: Devices such as Endoscopic Esophageal Varix Ligation Device® (SB-KAWASUMI LABORATORIES) and Speedband™ Superview Super7® (Boston Scientific) are used.
- Overtubes: Examples include Flexible Overtube® and hydrophilic-coated Top Overtube (SB-KAWASUMI LABORATORIES)
- In cases with a history of variceal treatment, it is advisable to proceed with EVL after preparing for balloon tamponade or EIS, because the aspiration process could be difficult resulting in unsuccessful EVL.

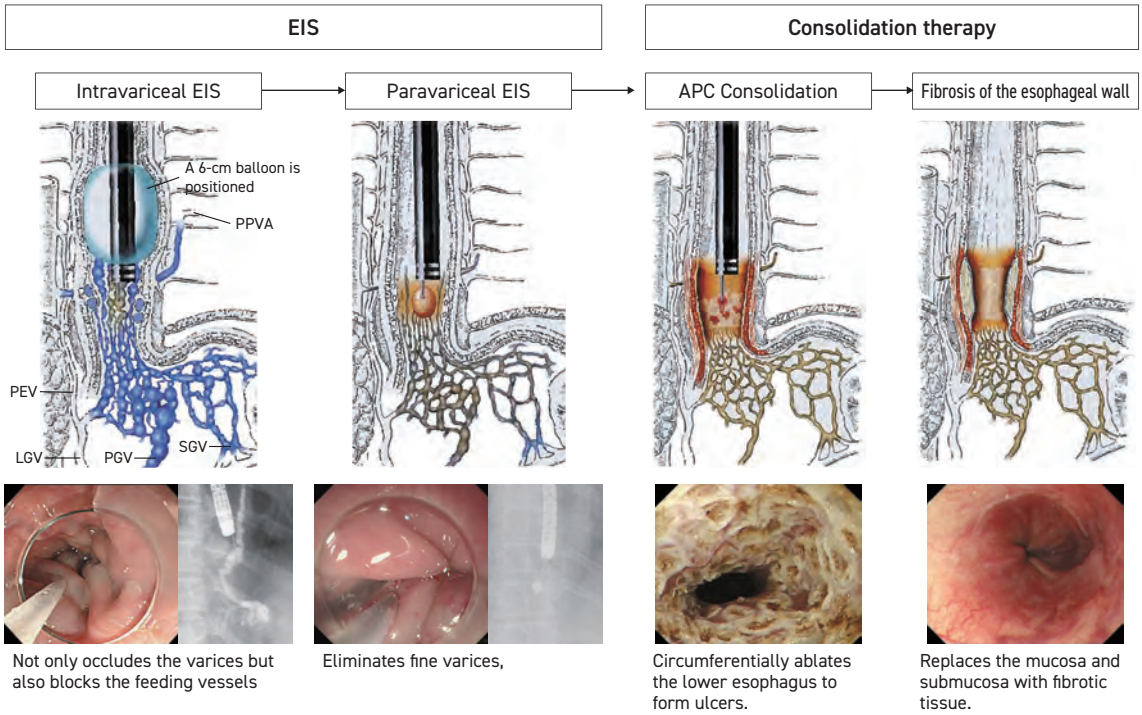


Figure 2 **Combined Intra EIS with Para EIS method, and consolidation therapy.**

(Modified from Literature 20)

Features and selection of EVL devices

There are single-use and multiple-use types. Single-use EVL requires the insertion and removal of the scope multiple times, necessitating the use of an overtube. Multiple-use devices allow for multiple ligations in a single scope insertion, eliminating the need for an overtube. However, since the instrument channel is not available and blood cannot be aspirated, it is better not to use it for the cases with bleeding.

(2) Basic techniques of EVL [21)]

EVL is **a procedure where an attachment is added to the tip of an endoscope to aspirate a varix into the attachment and ligate it with a rubber O-ring like snaring a polyp**. The mechanism of action involves **physical occlusion of blood flow to the varix by ligation, followed by thrombosis within the varix, ulcer formation at the ligation site, and disappearance of the varix due to fibrosis**. Since there is no bleeding due to variceal puncture or side effects from sclerosing agents (such as pleural effusion, hemoglobinuria, or impaired liver or kidney function), EVL is possibly performed even in patients with advanced liver dysfunction or kidney impairment, who are problematic with Intra EIS. However, since it is impossible to obliterate feeders, the recurrence rate is higher with EVL alone than Intra EIS, necessitating its combination with Para EIS or APC for better outcomes.

- For a single-band ligation system, an overtube is employed. Adequate lubrication should be applied on the overtube, and the device should be gently inserted into the patient in the left lateral decubitus

position to minimize risk during insertion rather than in supine position.

- After the overtube is inserted, the scope is withdrawn, and the device is attached to the tip of the scope.
- The procedure is generally performed from the slightly gastric side of the esophagogastric junction (the right anterior wall, or 2 o'clock orientation). Any contiguous Lg-c varices should also be ligated. However, larger varices in other directions may be addressed first if deemed appropriate.
- Ligation is performed progressively toward the proximal side, targeting the most prominent areas in view. Each varix is suctioned deeply into the device to create a ligated large polyp-like appearance, thereby ensuring a spacing of 1.5–2 cm between ligation sites. Keeping the distance helps ensure that the previously ligated area does not stretch or interfere with the next one, thereby enabling adequate suction.
- If the esophageal mucosa is pressed too firmly during suction, there won't be enough flexibility to pull the tissue into the device. On the other hand, if there is too much slack, the suction could extend to the muscularis so that it raises the risk of esophageal perforation. To make suction easier, a good technique is to pull in the mucosa from the 6 o'clock orientation (distal side) while using the 12 o'clock orientation (proximal side) on the endoscopic screen as a pivot point.
- Each treatment session should include 8 to 12 ligations, avoiding ligation of areas where varices are not present.
- When removing the scope, no damage to the pharynx or esophageal entrance should be confirmed. If an overtube is used, careful inspection should be made for the esophagus and pharynx after retraction of the overtube up to the control section of the scope.
- An endoscopic examination is performed one week later, and additional EVLs are conducted if residual varices remain. If there are no suitable varices like F1RC0 for suction, adjunctive treatments such as Para EIS or APC are recommended.
- In case of emergency bleeding, the bleeding site is ligated first for hemostasis. If direct ligation is difficult, the distal side of the bleeding site is ligated first to block blood flow, followed by ligation of the bleeding site. When the hemostasis is confirmed, unnecessary additional ligations should be avoided, but further treatment is planned after the assessment on the patient's overall condition.

Recent advancements: Fibrin plug color changes by narrow band imaging

Recent studies have highlighted the use of narrow-band imaging (NBI) to enhance the visibility of fibrin caps after spontaneous hemostasis, particularly white ones that are often overlooked when they blend with the background mucosa.22) NBI employs wavelengths absorbed by hemoglobin and improves detection by changing the fibrin cap's color to brownish, enhancing contrast against the background mucosa (**Figure 3**).

- Endoscopic injection sclerotherapy with ligation (EISL) is a treatment method in which EO is injected into the feeding veins, followed by EVL at the puncture site.[23)] Compared to EIS alone, EISL has been reported to shorten treatment time and improve treatment efficacy.

8. Other Endoscopic Treatments for Esophageal Varices

Other endoscopic treatments for esophageal varices include clipping with hemostatic clips as a ligation. However, EVL is generally simpler and more reliable. Therefore, clipping is recommended for cases

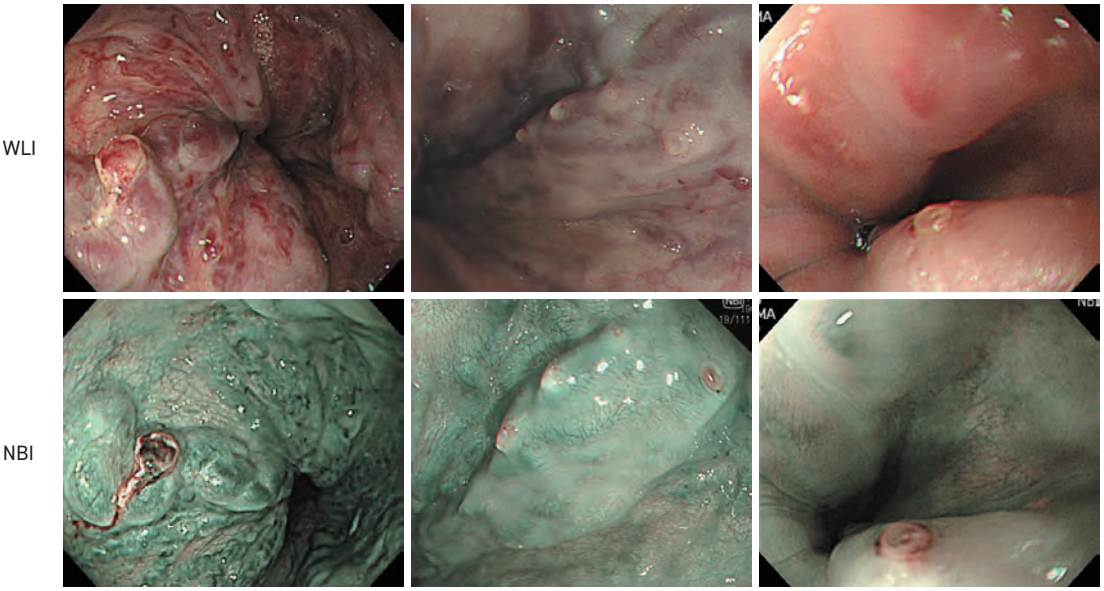


Figure 3 Color change of fibrin plugs by narrow band imaging (NBI) compared with white light imaging (WLI).

where an EVL setup is unavailable or when an experienced operator is absent. Additionally, cauterization using a high-frequency hemostatic forceps has been attempted as a consolidation method.

9. Endoscopic Cyanoacrylate Injection for Isolated Gastric Variceal Bleeding

(1) Preparation

- Puncture needle: Variceal puncture needle
- Medications: **n-butyl-2-cyanoacrylate (NBCA, trade name: Histoacryl®), oil-based ethiodized contrast medium (ethiodized oil, trade name: Lipiodol®)**
- Others (vary depending on the procedure): Water-soluble contrast medium, 5% glucose solution, EO solution

Precautions for using NBCA

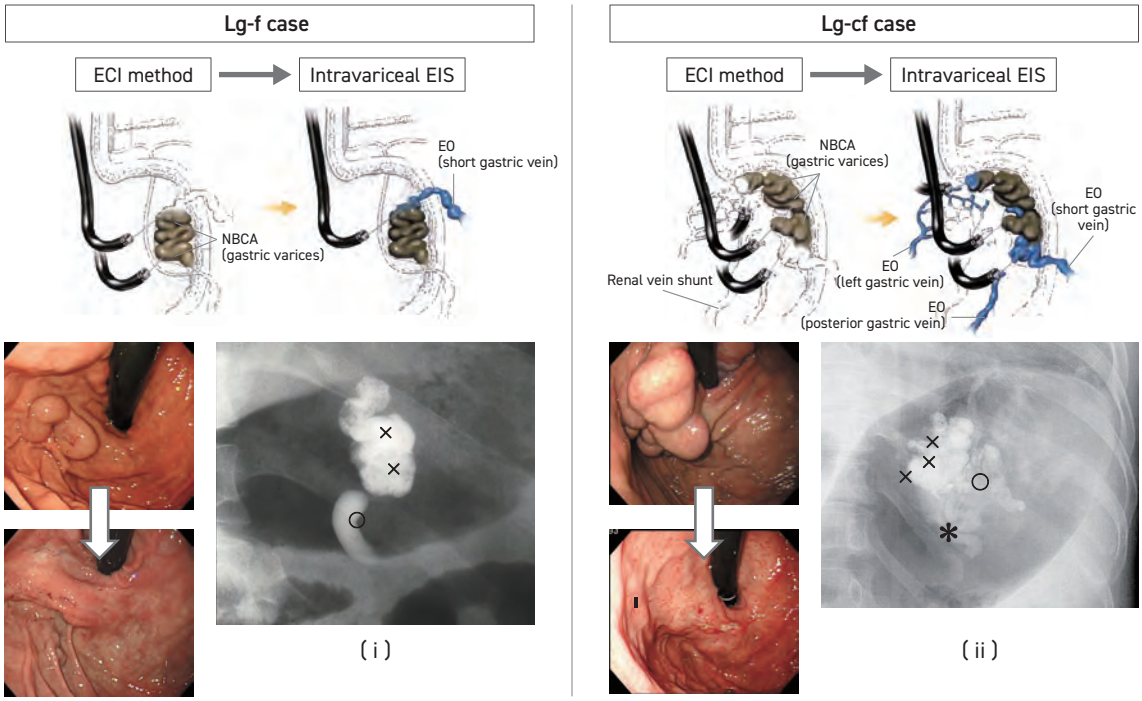
NBCA is a type of instant adhesive for tissues. It forms a polymer immediately upon contact with blood or tissue. Hemostasis is obtained relatively easily by injecting it into the vicinity of the bleeding point. It is the first-line drug for isolated gastric variceal bleeding. Although NBCA has been pharmaceutically approved for some time, the procedure of endoscopic cyanoacrylate injection (ECI) was also covered by insurance in the 2022 medical fee revision.

As a general rule, NBCA is used in combination with ethyl ester of iodinated poppy-seed oil fatty acid (Lipiodol®). Since NBCA alone does not have a contrast effect, it is impossible to evaluate the injection range. Therefore, the use of NBCA alone should be limited to emergency cases only when ethyl ester of iodinated poppy-seed oil fatty acid could not be prepared. In addition,

since there is a potential risk of pulmonary embolism or splenic embolism if NBCA flows into a large vein, NBCA injection should be performed by a highly skilled clinician.

(2) Basic technique of endoscopic cyanoacrylate injection [24-26)]

- Endoscope-attached balloon is not necessary. Except in emergency when transfer of the patient to an X-ray fluoroscopy room is not feasible, the procedure is generally performed under fluoroscopic guidance.
- The recommended concentration of NBCA mixture is between 60% and 90%. The specific concentration within this range should be determined based on the puncture needle used and the form of the target varices.
- **Example 1 for preparing** a 75% mixture: 0.5 mL of ethyl ester of iodinated poppy-seed oil fatty acid are applied into a 2.5 mL syringe, followed by 1.5 mL of NBCA, and mixed. At least two syringes of this mixture should be prepared.
- **Example 2 for preparing** a 75% mixture: 0.6 mL of ethyl ester of iodinated poppy-seed oil fatty acid are applied into a 2.5 mL syringe, followed by 1.8 mL of NBCA, and mixed to produce the NBCA mixture in total of 2.4 mL. For a 62.5% concentration, 0.9 mL of ethyl ester of iodinated poppy-seed oil fatty acid are applied into a 2.5 mL syringe, followed by 1.5 mL of NBCA, and mixed. Since multiple syringes of the NBCA mixture are often used during the procedure, it is advisable to prepare syringes pre-filled with ethyl ester of iodinated poppy-seed oil fatty acid.
- The concentration of the NBCA mixture is adjusted according to the diameter of the gastric varices as measured with EUS, a measurement which correlates with blood flow volume. In cases where the maximum transverse diameter exceeds 12 mm, blood flow volume is extremely high, and there is a risk of the NBCA mixture escaping into the systemic circulation via the renal shunt pathway. Therefore, embolization therapy under renal shunt occlusion should be considered.[20, 26)]
- **Injection Technique 1**: The endoscope system is connected to a puncture needle filled with 5% glucose solution. While 50% glucose solution is considered an alternative, normal saline is generally avoided due to the instantaneous polymerization of NBCA caused by sodium ions. In bleeding cases, puncture is performed near the bleeding point, with a position approximately 5 mm to the left being optimal. Following confirmation of blood backflow into the needle, approximately 1 mL of 5% glucose solution is injected to push the blood into the varix, after which 2.0 mL of the prepared NBCA mixture is delivered. A syringe containing 5 mL of 5% glucose solution is then used to inject 1.0–2.0 mL over 3–5 seconds to ensure complete delivery of the NBCA mixture. A waiting time of 10 seconds or so is taken before the needle is withdrawn. There is no need to worry about the needle becoming stuck. The use of a three-way stopcock to connect syringes containing the NBCA mixture and glucose solution is also an option.
- **Injection Technique 2**: The puncture needle filled with a water-soluble contrast agent is connected. After puncturing the varix, blood backflow is confirmed, after that contrast imaging is performed. The syringe containing 2.4 mL of the NBCA mixture is then used to inject the entire amount into the varix. The needle is gradually withdrawn. Unlike Technique 1, the residual NBCA in the needle is not flushed with glucose solution. Typically 1.4–1.5 mL of NBCA is delivered into the varix.
- For primary or secondary prophylactic treatments, the most prominent area is punctured first, and NBCA is injected. Then, surrounding areas are punctured sequentially, with a focus on regions showing backflow for NBCA injection. Special attention to feeding veins is especially effective during



(i) In Lg-f, NBCA was injected into two sites of the gastric varices (indicated by ×), followed by EO injection into the short gastric vein, the feeder (indicated by ○).

(ii) After NBCA was injected into three sites of the gastric varices (×), EO was administered into the short gastric vein (∗) and the posterior gastric vein (○), which are the feeders.

Figure 4 **Procedure of combined ECI with EIS method for isolated gastric varices.**

(Modified from Literature 20)

this process. Typically, the deepest protrusion in the fundus corresponds to the short gastric vein, while the posterior wall indicates the direction of the left gastric vein or posterior gastric vein.

- After injecting NBCA, it is important not to aspirate NBCA that leaks from the needle hole after withdrawal. Otherwise, the glue may clog the instrument channel of the endoscope. If NBCA sticks to the lens of endoscope, its repair is required. Therefore, it is crucial to ensure that NBCA does not come into contact with the endoscope inside the gastric lumen.
- Attachments are not typically used on the distal tip during this procedure, but the use of a hood can prevent NBCA from adhering to the lens.
- In bleeding cases, if hemostasis is not sufficient, it is necessary to repeat punctures into the soft, protruding areas of the varices.
- Oozing bleeding tends to occur after needle withdrawal but stops spontaneously.
- Once hemostasis is confirmed, the procedure is concluded promptly.
- In cases of bleeding, multiple injections of NBCA are allowed to obliterate the varices and some feeding veins with a solid, cast-like plug, while the patient's overall condition is stable and there is no renal failure.

- After replacing gastric varices with NBCA, feeding veins is also obliterated through the Intra EIS using EO method (ECI/EIS combination method) (**Figure 4**) .[20)]

10. Other Endoscopic Treatments for Isolated Gastric Varices

NBCA injection and coil placement with EUS-guided puncture have been reported for gastric varices. This method has the advantage of allowing puncture by confirming the variceal lumen on EUS images, but its indications and procedures have not been standardized, and the accumulation of treated cases by advanced facilities is warranted.[27)]

11. General Management After Treatment

- Fever and pain (chest pain, back pain) are the most important observations. Usually, fever is around 37.5℃, and if it exceeds 38℃, administration of antibiotics should be considered. Pain is managed with intravenous administration of acetaminophen or similar agents.
- Small amounts of oral fluids is allowed 4-6 hours later. Oral administration of gastric mucosal protective agents or intravenous/oral administration of acid suppressants is not essential, but should be considered in cases with severe acid reflux or mucosal break.
- On the following day, blood biochemical tests and chest/abdominal X-rays should be performed.
- In cases of emergency bleeding, sufficient fluid should be administered to stabilize circulation and protect renal function. In cases of severe hepatic dysfunction, temporary ascites or edema is likely to occur. It is important to pay attention to elevated ammonia levels and hepatic encephalopathy. When the general condition is stable, an endoscopic examination should be performed within 24-48 hours to confirm hemostasis. Once hemostasis is confirmed, resumption of feeding is considered.

12. Adverse Events and Their Management

(1) Main adverse events [28-30)]

Most common incidental injuries after variceal treatment are bleeding, spread of inflammation due to tissue damage (ulcer formation), infection, and multi-organ damage caused by the sclerosants. The main ones are listed in **Table 3**.[1)]

(2) Prevention, early detection, and management

- It is essential to avoid the excessive use of sclerosants in EIS. In Intra EIS of EO, it is important to monitor for hemolysis and hemoglobinuria.
- **Fever and pain (sore throat, chest pain, abdominal pain, back pain)** are important symptoms of complications after endoscopic treatment. Fever mainly suggests infection, and pain suggests the spread of inflammation or perforation.
- If symptoms are severe or if infection or perforation is suspected, the following examinations should be performed: blood biochemical tests, electrocardiogram, blood gas analysis, chest/abdominal X-rays, and chest/abdominal CT scans. While the general condition is stable, the treatment site is also

Table 3 Major treatment-related adverse events.

Occurrence	Organ	Adverse Event
Periprocedure	Respiratory/Circulatory	Hypertension, hypotension, arrhythmias, respiratory depression, hypoxemia
	Esophagus	Bleeding, pharyngeal and esophageal damage (perforation) due to overtube
	Stomach	Bleeding, portal vein thrombosis
	Others	Anaphylaxis
Postprocedure	Esophagus, Stomach	Erosion, ulcer, submucosal hematoma, postoperative bleeding, perforation
	Mediastinum	Mediastinitis, mediastinal emphysema (air in esophageal wall)
	Lung	Pleural effusion, pulmonary embolism, aspiration
	Heart	Heart failure
	Liver	Jaundice, ascites, hepatic encephalopathy, portal vein thrombosis, tissue adhesive portal vein outflow
	Kidney	Renal dysfunction, hemoglobinuria (hemolysis)
	Spleen	Splenic infarction
	Brain	Cerebral hemorrhage, cerebral infarction
	Blood	Sepsis, disseminated intravascular coagulation (DIC)
Late Stage	Esophagus	Esophageal stricture

(Modified from Literature 1)

be confirmed by endoscopy.

- After the treatment of esophageal varices, it is necessary not only to suspect adverse events in the cardiac and respiratory systems and the treated site, but to rule out embolism after NBCA treatment of gastric varices.
- If an overtube is used and there is severe sore throat or chest pain, damage or perforation of the hypopharynx or esophagus should be suspected, and a neck-to-chest CT scan should be conducted promptly.

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Yoshihiro Furuichi and Takuto Hikichi

8 Stenosis of esophagus

Esophagus stenosis (ES) is broadly categorized into benign and malignant types, with malignant stenosis frequently caused by esophageal cancer. Current treatment methods include dilation and stent placement. The primary goal in treating ES is to alleviate dysphagia, ensuring that the procedures are both effective and safe. This section focuses on the indications and procedural precautions for endoscopic balloon dilation (EBD), radial incision and cutting (RIC), and stent placement as treatments for ES.

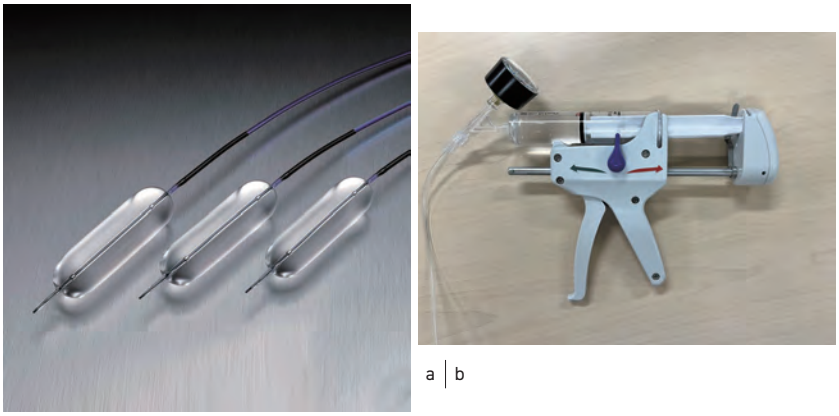
1. Balloon Dilation

(1) Indications

EBD is a minimally invasive, simple, and safe treatment method, particularly suited for benign stenosis regardless of their etiology. Common causes of benign ES include achalasia, cicatricial stenosis following endoscopic submucosal dissection (ESD) or chemoradiotherapy (CRT), and postoperative anastomotic stricture.[1)] Although EBD is widely used for various benign stenosis, it is contraindicated for long stenosis exceeding 5 cm, those with significant angulation, or stenosis associated with active inflammation or ulcerative lesions.[2)]

(2) Types of balloons

Dilation balloons are classified into two types: over-the-wire (OTW) balloon, which is inserted after the introduction of a guidewire, and through-the-scope (TTS) balloon, which is introduced through the endoscopic instrument channel and expanded. For the former, a guidewire is advanced to the distal side of the stenosis under fluoroscopic guidance, and then the balloon catheter is inserted over the guidewire. For the latter, a balloon catheter is inserted through the instrument channel, thereby enabling endoscopic observation of stenosis passage and expansion. Recently, TTS balloons with an integrated guidewire have become widely available. For achalasia of esophagus, the Rigiflex™ II Single-Use Achalasia Balloon Dilator is available from Boston Scientific. For postoperative anastomotic stenosis and cicatricial stenosis following ESD or CRT, the TTS-type ballon catheter, CRE™ Fixed Wire Balloon Dilators is available from Boston Scientific. This balloon product has six different types with different balloon expansion diameters (ranging from 6 to 20 mm) depending on the injection pressure. Therefore, a suitable device is selected and utilized according to the diameter of the stenosis (**Figure 1**).



a | b

Figure 1 **Through-the-scope (TTS) type CRE™ balloon catheters (Boston Scientific) and the inflator.**

a: These are TTS type CRE balloon catheters. There are six types with different balloon expansion diameters depending on the inflation pressure, covering a balloon expansion diameter range of 6 to 20 mm.
b: This is the inflation device for pressurization.

(3) Basic techniques of balloon dilation

The fundamental techniques for balloon dilation differ between OTW and TTS modalities, but this section focuses on the TTS balloon dilation technique.

(i) Initially, a narrowing area is observed with esophagogastroduodenoscopy, and that it is confirmed that the therapeutic scope cannot pass through the stenosis (**Figure 2a**).

(ii) Contrast medium (Gastrografin®) is injected via the instrument channel to evaluate the length and diameter of the stenosis under fluoroscopy.

(iii) Based on the stenosis condition, a balloon dilation catheter with the appropriate size is inserted while the endoscopist monitors the tip.

(iv) It should be ensured that the catheter passes through the stenosis without resistance. Any sensation of resistance should preclude forceful insertion.

(v) The position of the balloon is then adjusted so that its center aligns closely with the middle of the stenosis, and dilation is initiated. To prevent the balloon from being pulled toward the distal side of the stenosis, the scope is stabilized, while the catheter is pulled and stabilized with the left hand. Pressure is gradually and evenly applied to ensure uniform expansion across the stenosis (**Figure 2b**).

(vi) After each dilation session, the occurrence of mucosal tear is examined to ensure it has not extended into the muscularis propria. Although the pressure and duration of dilation vary depending on the situation, three rounds of dilation are preferable with 3 atm, 5 atm, and the maximum pressure for 30 seconds each (**Figure 2c**).

(vii) Following dilation, a repeat fluoroscopic examination with Gastrografin® is performed to verify the integrity of the stenosis and rule out any contrast leakage.

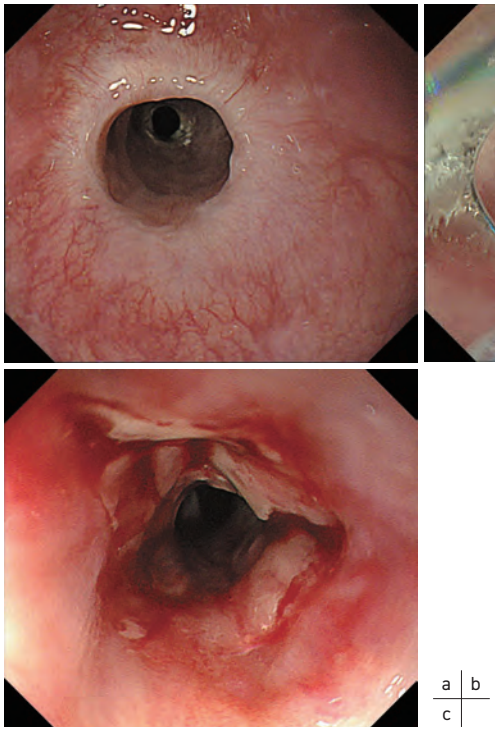


Figure 2 Actual procedure of endoscopic balloon dilation (EBD).

a: This is a case of post-ESD stenosis. GIF-Q260J (manufactured by Olympus) could not pass through the affected area.
b: Dilation of the narrowing area was performed using a through-the-scope (TTS) balloon.
c: The narrowing area after dilation shows development of tears, but the tearing hardly reaches deep into the muscle layer.

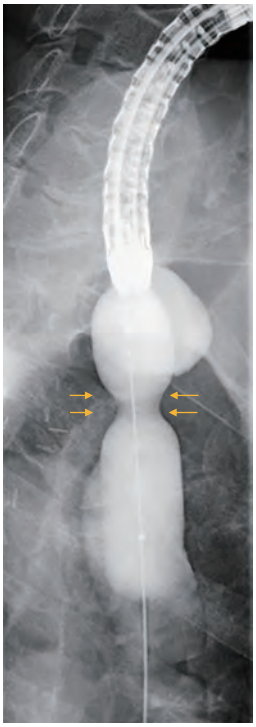


Figure 3 A difficult case for stenosis resolving by EBD .

The narrowing area is hard, and the deformation of the pressurized balloon is limited locally.

(4) Techniques and precautions for balloon dilation

The primary adverse events of EBD are bleeding and perforation. To prevent perforation, it is crucial to consider the condition of the proximal side of stenosis when performing EBD. When the balloon size exceeds the diameter of the stenosis, it could apply too much pressure to the narrowed area, thereby causing perforation. Therefore, it is helpful to use slightly smaller balloons and perform dilation in multiple steps with incremental pressure. The use of a diluted Gastrografin® solution in the inflator syringe enables fluoroscopic visualization of the balloon's position and ensures its proper expansion within the stenosis.[3)]

In cases where a stenosis is rigid and localized, as shown in **Figure 3**, EBD is ineffective in resolving the stenosis. Recent studies have reported the importance of injecting triamcinolone into tearing sites to prevent restenosis.[4,5)]

2. RIC Method

RIC is a novel technique developed by Muto and colleagues for treating refractory benign ES.[6)] This procedure involves excising the scarred tissue developed in the stenosis site with an ITknife. The method is expected to be effective for refractory stenosis that cannot be relieved by EBD.

(1) Indications

Indications for RIC are generally refractory benign ES that do not respond to EBD, regardless of the cause of the stenosis. The most suitable indication is postoperative stenosis of anastomotic sites following surgery, although the usefulness of RIC has also been reported in cases of radiation-induced stricture or stricture following endoscopic treatments.[7] However, the limitations of RIC method should be recognized in the following cases:

1) Cases with severe angulation

If an angulation is caused by the scar tissue, incision of the scar could alleviate the stenosis, but often could not improve the obstruction because the angulation does not improve.

2) Long strictur

Since RIC uses the blade of ITknife for incision, it is technically difficult for long stenosis. Some reports indicate that cases with strictures longer than 2 cm are not suitable.[8] Therefore it is important to confirm the length of the stenosis before starting the procedure.

(2) Equipment and devices for R

ITknife is generally used for RIC but many facilities do not maintain such devices. In fact, our facility has performed RIC using the ITknife nano but the ITknife 2 has been avoided due to the risk of making unexpectedly deep incisions. This occurs when the lower blade beneath the insulated tip catches on scar tissue and slides into the submucosal layer. Similarly, devices with tip knife are not commonly used, as they may causes excessively deep incisions in the vertical direction.[9] In cases where a scar is so hard that it cannot be cut into even with the cauterizing blade of ITknife, a needle knife is useful. Setting of the high-frequency device generally follow those used in ESD. Sedation is often provided according to ESD protocols. However, for strictures occurring after esophageal cancer surgery, treatment is performed near the cervical esophagus. Thus the use of analgesics such as pentazocine or pethidine is recommended to suppress the swallowing reflex.

(3) Basic techniques of RIC method

In **Figure 4**, schematic diagrams are shown regarding the basic procedure.

1) Confirmation of stricture length and shape (Figures 5a & 5b)

RIC is contraindicated for cases with severe angulation and long stenosis. Therefore, esophageal fluoroscopy is performed using Gastrografin® before the process to confirm the length and shape of stenosis.

2) Radial incision in stenosis (Figure 5c)

ITknife blade is placed parallel to the lumen and carefully inserted vertically to make an incision in the scar tissue. Notably, such incisions are made gently so that the heights of the mucosal surfaces on both proximal and distal sides of the stenosis are aligned. A deep incision raises the risk of perforation, so care

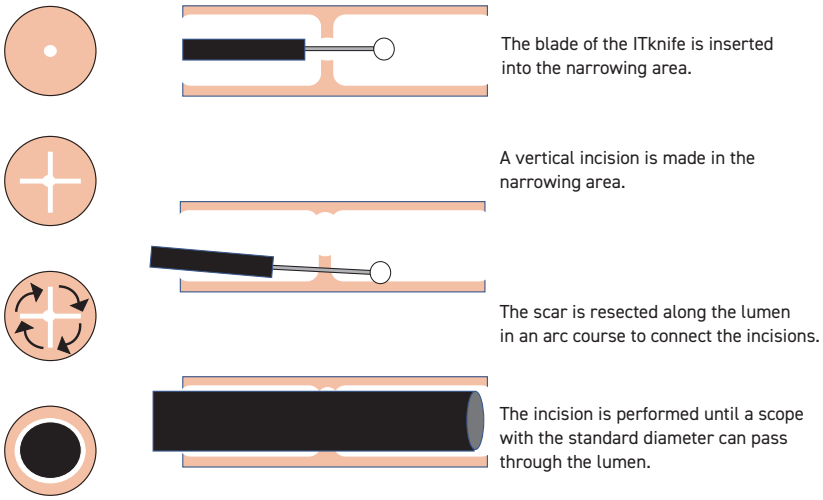


Figure 4 Schematic diagram of radial incision and cutting (RIC), method.

is taken to limit the cut to the level of the mucosal surface and not extend it beyond the distal end of the stenosis. This process is critical for severe stenosis because a longer incision easily leads to cutting too deep.

3) Dissection of scar tissue (Figures 5d & 5e)

ITknife should advance to the deepest point of the incision created in step 2. The scar tissue is then excised with the IT knife arcing along the lumen so that the deepest parts of each incision are connected. If the scar tissue cannot be completely removed with a single round of dissection, additional incisions and dissections are performed on the distal side as well. It is important not to cut deeper than the depth of the incision during this dissecting process. Cutting too deep could cause perforation. Cutting too shallow could leave some scar tissue. It is important to be constantly aware of the curve of lumen. The scar tissue might not be evenly thick depending on the shape of the stenosis. In some cases, the scar tissue is not thick evenly, and difficult or impossible to remove all of it. It is essential to focus on removing the scar tissue but not insisting on complete circumferential resection.

4) Confirmation of scope passage (Figures 5f & 5g)

Following the sequential completion of steps 2 and 3, the stenosis is regarded as relieved once a standard endoscope usually measuring 10 mm in diameter can pass through the affected site. Generally, the ulcer after RIC is extensive, leading to a higher risk of restenosis. To prevent this recurrence, steroid injections are performed into the ulcer base to reduce the risk of restenosis.

(4) Treatment outcomes and clinical applications of RIC

Reports on the treatment outcomes of RIC have primarily focused on refractory anastomotic stenosis after surgical resection for esophagogastric diseases. Muto and colleagues reported a 94% improvement in Dysphagia Score and a 6-month patency rate of 65.3% in 32 cases of postoperative ES resistant to EBD.[6] Currently, the standard treatment for postoperative ES is a combination therapy of EBD and

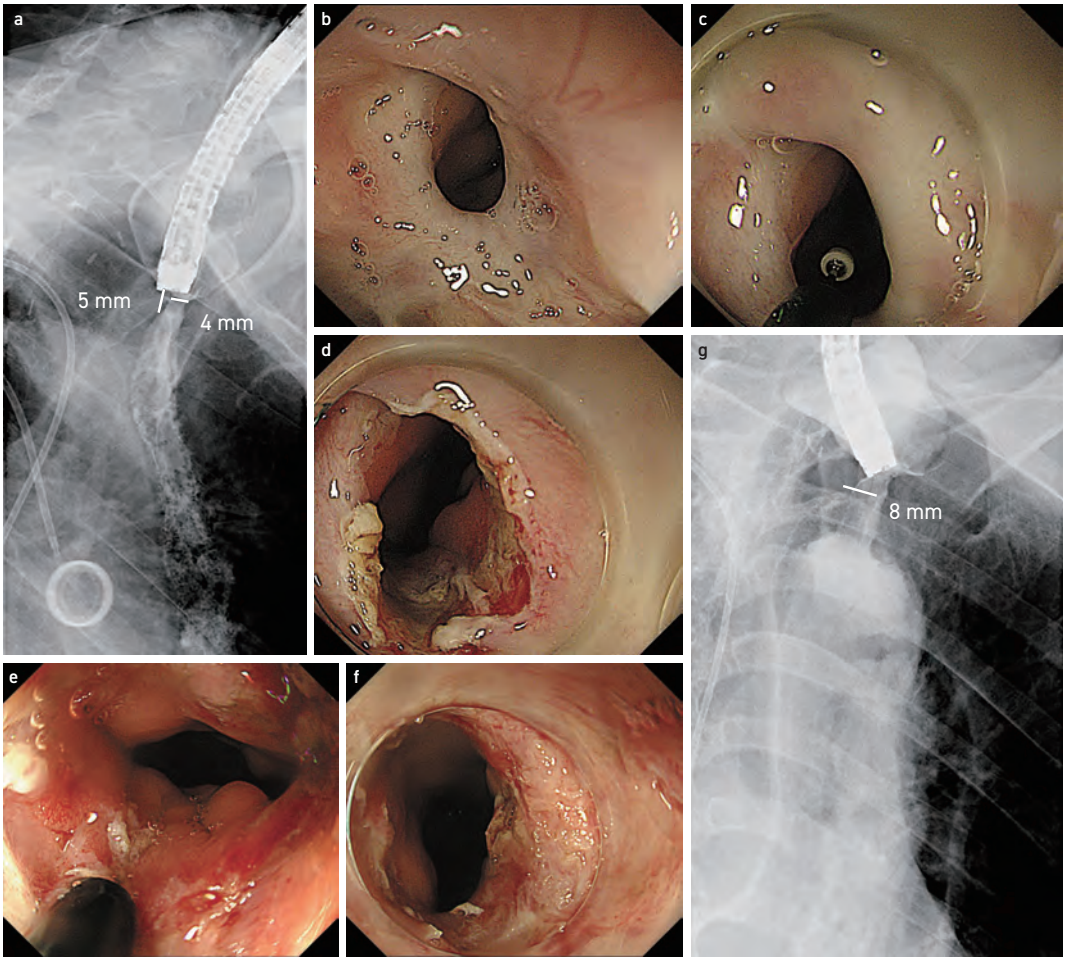


Figure 5 Actual RIC method.

a: Esophageal fluoroscopy before the radial incision and cutting (RIC), method. The narrowing area had a stenosis diameter of 4 mm and length of 5 mm.
b: Endoscopic image of the narrowing area before the RIC method
c: The blade of the ITknife nano was used to make a vertical incision to the lumen.
d: After circumferential dissection of the scar tissue
e: Since the scar tissue could not be removed in one attempt, the scar on the gastric side was also incised.
f: After treatment
g: Esophageal fluoroscopy after the RIC method. The diameter of the narrowing lumen expanded to 8 mm.

intralesional steroid injections.[5] However, a randomized controlled trial is currently underway to scientifically compare the RIC method to the standard treatment.[10] This study will help us determine if the RIC method is hopefully a better option. Yano and colleagues reported on the treatment outcomes of RIC for benign stenosis that were not caused by esophageal cancer surgery.[7] RIC was introduced to treat three cases of stenosis after chemoradiotherapy, three cases of salvage endoscopic treatment for remaining or recurring lesions, and two cases of stenosis after ESD. As a result, there were no serious complications, and dysphagia improved to Grade 0 or 1 in all cases. However, only 37.5% (3 out of 8) of patients demonstrated adequate lumen patency with standard-sized endoscopes three months later, and six patients required further treatment for recurrent stenosis. Outside the esophagus, Moroi and colleagues treated 20 cases of benign stenosis of the lower gastrointestinal tract using the RIC method. They reported

that 55.8% of the cases showed no recurrence of obstructive narrowing after 52 weeks.[11] Therefore, RIC is a treatment method being explored for various benign gastrointestinal stenosis. However, there remain uncertainties regarding risks such as perforation and the criteria for its application, in addition to the limitations of indications. Further research is needed to address these issues.

3. Stent Placement

(1) Indications for esophageal stents

According to the *Guidelines for Gastroenterological Endoscopy*, the basic indications for esophageal stenting include inoperable malignant ES, malignant tracheoesophageal fistulas and esophagobronchial fistulas, and stenosis following radiation therapy or chemotherapy, those which cause difficulty in oral intake.[2]

The *Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus* also state that for unresectable malignant ES or symptoms caused by fistulas, esophageal stenting is the best option for palliative treatment, finding one of the cornerstone treatments for symptom relief.[12]

(2) Types and selection of esophageal stents

Currently, the main self-expanding metal stents (SEMS) used in Japan include Ultraflex™ (Boston Scientific), Niti-S™ (Taewoong Medical), HANAROSTENT® (M.I.Tech), Flexella Plus-J (ELLA-CS), Evolution® (Cook Medical), and EGIS Esophageal Stents (S&G Biotech). These stents come in full-cover, partial-cover, and non-cover types. The cover helps prevent blockage caused by tumor or granulation growth and is also useful for ligating fistulas. Various stent lengths are available to accommodate different lengths of stenosis. Additionally, there are stents with anti-reflux valves and cervical esophageal stents for intubation at the esophagogastric junction. Stents are loaded into delivery systems, but the type of stents and their insertion method vary slightly depending on the location of cancerous stenosis.

(3) Basic and practical techniques for esophageal stent placement

(i) Prior to stent insertion, an esophagography using Gastrografin® is performed to assess the location, length, severity, and axial deviation of the stenosis.

(ii) Vascular access is secured, and pharyngeal anesthesia is performed. With monitoring, a sedative is administered.

(iii) The stenosis site is examined via endoscopy, and a hemostatic clip is placed at the proximal end of the stenting site for marking. At the same time, X-ray fluoroscopy is used for confirmation of the exact position.

(iv) A guidewire is inserted through the endoscopic instrument channel and passed beyond the stenosis into the gastric space. The guidewire is left in place while the endoscope is removed.

(v) The stent delivery system is threaded over the guidewire and inserted under fluoroscopic guidance until it reaches the proximal end of the stenosis.

(vi) The position of the marking on the stent is accurately adjusted with the marker placed at the

proximal site of the stenosis.

(vii) As the stent expands, adjustments are made to ensure both the stent marker and the esophageal marker maintain aligned.

(viii) After the stent deployment, fluoroscopy is used to confirm its position, and the guidewire and delivery system are slowly removed.

(ix) To ensure that the stent is placed in the correct position within the lumen and properly expanded, both X-ray fluoroscopy and endoscopy are used. If the stent is slightly misaligned or not fully expanded and requires fine adjustment, the dangler/safety thread attached to the stent is grasped and gently pulled with a grasper. Once the stent is properly adjusted into position, the procedure is complete.(**Figure 6&7**)

(4) Adverse event and its management of esophageal stent placement

Adverse events and problems associated with stent placement include pain, hemorrhage, perforation, gastroesophageal reflux, stent occlusion, stent migration or dislodgement, and airway compression.

Pain: Severe throat pain or discomfort could occur with stent placement in the cervical esophagus. For insertion into cervical esophagus, a cervical esophageal stent is inserted if there is more than 20 mm from the pharyngoesophageal junction.[13)]

Hemorrhage: This is possibly caused by tumor enlargement or necrosis. If the bleeding source is a large vessel or a direct branch from the aorta, massive bleeding occurs which makes it difficult to manage.

Perforation: This is caused not only by unsuitable insertion of a guidewire or stent in stenting process, but also in severe cancerous stenosis, necrosis associated with tumor enlargement, or fistula formation. Conservative treatment should be introduced while covered stent is inserted in the appropriate position. If pyothorax or pleural effusion develops, chest tube insertion is required.

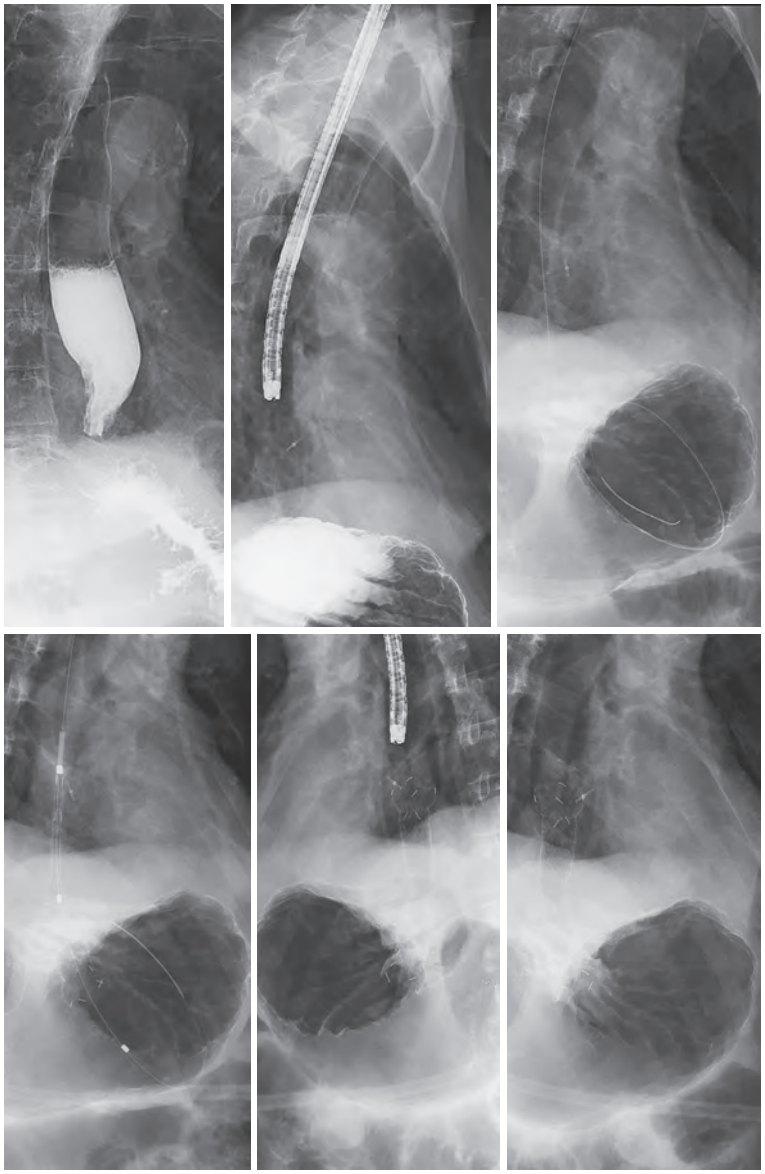
Gastroesophageal reflux: This is caused by stent placement at the esophagogastric junction. To reduce this risk, a stent with an anti-reflux valve should be selected.

Stent migration or dislodgement: Caution is necessary when stents are inserted for the cases with mild stenosis at the esophagogastric junction. The stent is retrieved by securing the dangler/safety thread attached to its proximal end with a grasper, while an overtube or cap is used to protect the mucosa during the process.

Stent occlusion: This is caused by tumor growth or hyperplasia of normal mucosa in the uncovered portion of stents. Hot biopsy or argon plasma coagulation (APC) is applied to treat excessive granulation growth. If this is difficult, additional stent placement (stent-in-stent) is indicated.

Airway compression: If the tumor occupies the upper thoracic esophagus and its primary site is located on the anterior or left wall, there is a possibility of compressing the trachea or left main bronchus during stent intubation or dilation.[14)]

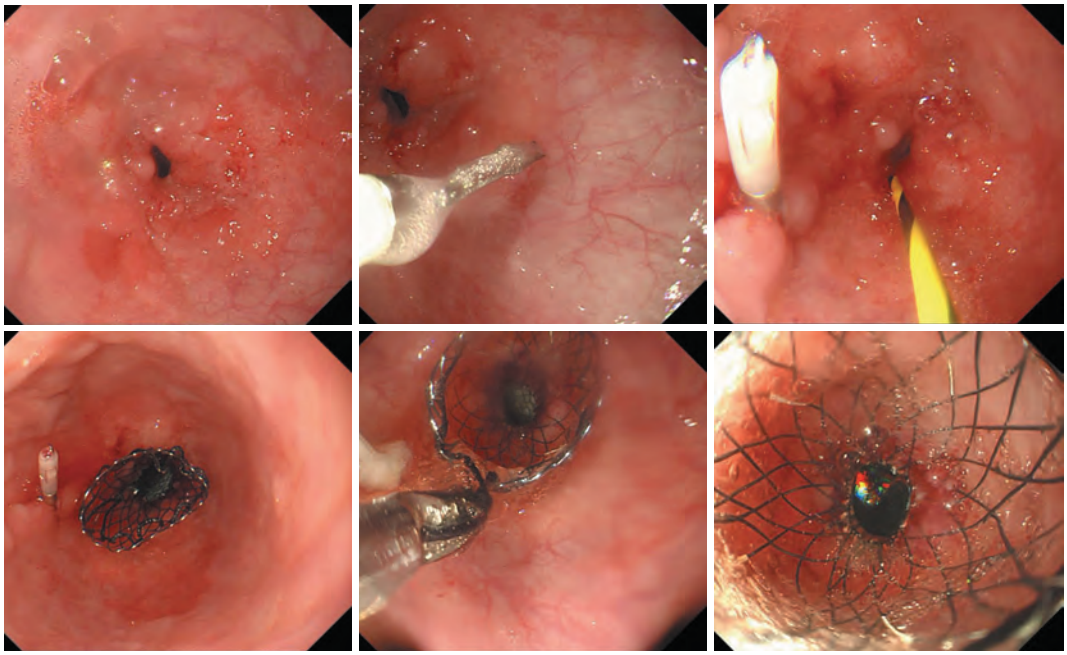
It is important to fully understand and explain the risks of these adverse events to patients before performing esophageal stent placement.



a	b	c
d	e	f

Figure 6 **Esophageal stent insertion and X-ray fluoroscopic findings.**

a: The stenosis condition is assessed using esophageal contrast radiography.
b: The oral side of the narrowing area is marked with endoscopic hemostatic clips.
c: A guide wire is inserted into the stomach through the instrument channel of the endoscope.
d: The delivery system of the esophageal stent is inserted and deployed at the appropriate position.
e: The position is confirmed endoscopically after deployment, and fine adjustments are made, as necessary.
f: After esophageal stent placement



a b c
d e f

Figure 7 Esophageal stent insertion and endoscopic findings.

a: The condition of the narrowing area is confirmed.
b: The position of the oral end is marked with a hemostatic clip.
c: A guide wire is inserted under fluoroscopy.
d: The position is confirmed endoscopically after stent deployment.
e: The dangler/safety thread is grasped with a forceps for fine adjustments.
f: The procedure concludes after confirming both the position and how the device is deployed in relation to the surrounding structures.

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Yuji Urabe, Hideo Shimada and Hiroyuki Okada

9 Endoscopic Treatment for Esophageal Cancer

1. Indications for EMR/ESD in Esophageal Cancer

(1) Invasion depth and indications for EMR/ESD

Lesions confined to the epithelial layer (T1a EP) and lesions confined to lamina propria mucosae (LPM) with a low risk of metastasis have a very high probability of being cured by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).[1] The latest Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus (2022 edition) state that no additional treatment is necessary if the lesion is completely resected histologically.[2] On the other hand, while T1aMM or SM1 lesions confined to the submucosa within 200 μm of the muscularis mucosae can be resected endoscopically, there is a possibility of lymph node metastasis, so their indications are applied conditionally.[3-5] Furthermore, Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus (2012 edition) have been revised, and the management of MM/SM1 lesions has become more stringent (**Table 1**). In case of T1a MM lesions with positive vascular invasion or T1a MM lesions with INFc or positive vertical margins, additional treatments such as surgery or chemoradiotherapy should be considered. In case of T1b SM1 lesions, additional treatment should be carefully considered regardless of the presence or absence of vascular invasion or a positive vertical margin (**Table 1**).

Even if vascular invasion, INFc, and resection margins are all negative on histological examination and follow-up observation is required, careful monitoring is still necessary based upon thorough informed consent.

Since metastases are found in about 50% of T1b SM2 lesions invading the submucosa more than 200 μm from the muscularis mucosae,[6] EMR/ESD is not indicated as a curative treatment. EMR/ESD should only be selected when it is expected to benefit the patient by controlling the local esophageal cancer.

Table 1 Management of MM/SM1 lesions in superficial esophageal cancer.

	Vascular invasion	INF	VM	Treatment policy
MM	(-)	a, b	(-)	Observation
	(+)	c	(+)	Additional treatments*
SM1	Presence or absence of vascular invasion or vertical margin			

These management criteria are based on the revised Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus (April 2012 edition).

*Additional treatments includes surgical treatment, chemoradiotherapy, radiotherapy, or chemotherapy.

(2) Distinguishing between EMR and ESD

For EP/LPM lesions where mucosal resection involves more than three-fourths of the esophageal circumference, postoperative scar-related strictures are likely to develop. Therefore, preventive treatments for strictures, such as steroid administration, and thorough informed consent are necessary.[2] In cases of laterally spreading tumors, deep infiltration tends to occur in multiple locations, thus careful assessment of invasion depth should be taken.

(3) Distinguishing between EMR and ESD

The most important aspect of endoscopic treatment for esophageal cancer is to ensure complete en bloc resection of the lesion to prevent local recurrence, and to perform a histopathological evaluation as rigorously as possible to estimate the possible risk of metastasis. Since EMR has limitations in the size of the resectable area, ESD should be used when en bloc resection is anticipated to be difficult.[7] When performing ESD, it is necessary for endoscopists to be sufficiently familiar with the prevention and management of adverse events such as bleeding and esophageal perforation. On the other hand, small lesions less than 10 mm in size are more likely to be completely resected en bloc with EMR. Thus, EMR is a suitable and quick procedure for such lesions. [8,9]

2. Endoscopic Mucosal Resection of Esophagus

EMR is a possible procedure that is performed quickly, has a high safety profile, and could even be done on an outpatient basis. However, it is difficult for this method to achieve en bloc resection of large cancers. If the resection is performed in multiple stages, the residual disease rate and recurrence rate are as high as 20%. It is desirable to limit its application to small cancers measuring 10 mm or less.

Representative EMR techniques include the two-channel method,[10] EMR-C method,[11] and endoscopic esophageal mucosal resection-tube (EEMR-tube) method.[12] Each of these methods has its own advantages and disadvantages, and it is essential to understand their respective characteristics before selecting the appropriate treatment approach.

3. Endoscopic Submucosal Dissection of Esophagus

(1) Preoperative preparation for endoscopic submucosal dissection

ESD, if bleeding occurs during the procedure, it is difficult to secure a clear field of vision due to the narrow lumen. For this reason, it is advisable to use a scope equipped with a water jet and attach a transparent cap to the tip.

Since the esophageal wall is thin at 4 mm and lacks serosa, this anatomy leads to incidental perforation. Even exposure of the muscularis propria could lead to mediastinal emphysema. Therefore, CO_2 insufflation is essential to prevent mediastinal emphysema or subcutaneous emphysema.

By using a highly viscous, low tissue-damaging sodium hyaluronate solutions [13] or sodium alginate as the submucosal injection solution, it is possible to produce and maintain preferable mucosal elevation.

(2) Basic techniques

1) Marking

After the cancerous area is identified with iodine staining, marks are placed 3–5 mm outside the detected boundary. In the case of Barrett's esophageal cancer, where range diagnosis is challenging, marking is performed at least 5 mm outside the lesion. Furthermore, if the proximal side of such a lesion is in contact with squamous epithelium, Barrett's adenocarcinoma frequently extends beneath the squamous epithelium. In this case, making range diagnosis is even more difficult. Therefore, marking should be performed at least 10 mm outside.

2) Submucosal injection

Since esophageal wall is very thin at approximately 4 mm, vertically inserting a local injection needle easily penetrates the submucosa, and its tip reaches the muscularis propria or adventitia. To ensure proper submucosal injection, the needle should be slightly angled or gently inserted as the solution is injected slowly where the fluid helps to create a space in the submucosal layer.

At the beginning of ESD, the initial injection is typically performed using isotonic saline or Glycerol® (used off-label), because these solutions are safer in the event of an accidental injection into the muscularis propria, allowing for easier recovery from mispuncture. Achieving an appropriate submucosal lift at this stage plays a critical role in the safety and success of the procedure. Subsequently, sodium hyaluronate solutions [13] or sodium alginate is injected into the base of the elevation created by the initial injection to reduce the risk of muscularis propria injection, thereby allowing for safe performance of ESD.

3) Mucosal incision

Sufficient submucosal injection is performed initially, followed by a precise incision through the muscularis mucosa with the first cut. The lateral incision is then made with scope angulation or torque. The knife is slid into the submucosa and gently lifted toward the lumen while current is applied to make the vertical incision. The distal side of the lesion is then carefully trimmed (deep cutting) down into the deep submucosa, while the final point of submucosal dissection is set. On the proximal side of the lesion, trimming is performed to allow the scope to enter the submucosa easily. This process ensures smooth progression of subsequent dissection.

Especially in the esophagus, lateral mucosal incision could lead to significant bleeding. This is because such an incision continuously severs the blood vessels that run longitudinally in that area due to the anatomical arrangement of the esophagus. It is best to reduce the speed of the knife and adjust how you handle the scope. This careful approach helps minimize bleeding, especially when compared to a vertical incision.

4) Submucosal dissection

The endoscopist first guides the endoscope into the submucosa, applies counter-traction using the transparent distal hood, and carefully ensures that both the submucosa and the muscularis propria are clearly visualized. A slightly deeper layer within the middle submucosa is loose and suitable for dissection. When proper esophageal glands are observed, dissection is performed just below them.

To avoid perforation or exposure of the muscularis propria, it is necessary to set the knife as parallel to the muscularis propria as possible and avoid applying current while the knife is in contact with the muscularis propria.

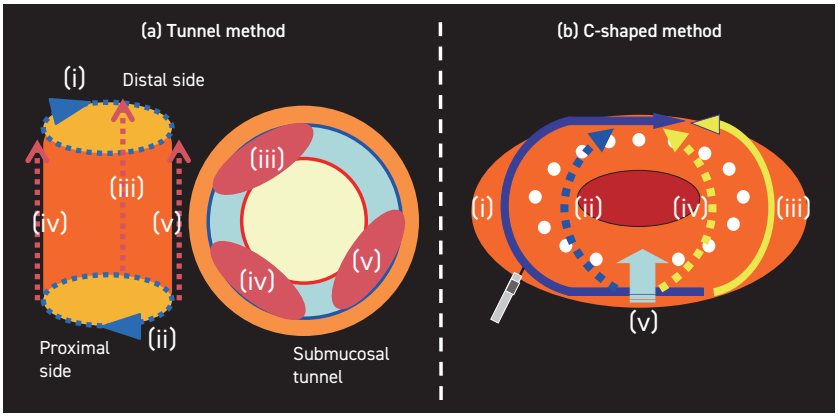


Figure 1 Endoscopic submucosal dissection (ESD) procedures.

For smooth dissection, it is necessary to maintain a clear view and prevent bleeding. Thin blood vessels in the submucosa are coagulated and controlled with the knife, but vessels larger than 1 mm require hemostatic forceps for prevention of bleeding. If bleeding occurs, coagulation and hemostasis are first attempted with the knife used for the incision or dissection. If this action does not stop the bleeding, hemostatic forceps are used to grasp the bleeding source, lift it off from the muscularis propria, and coagulate it with a soft coagulation mode (VIO300D: Effect 3–5, 60–100 W; VIO3: Effect 5.0–7.0).

(3) Procedure of ESD

In esophageal ESD, a consistent approach is applied to most lesions, allowing procedures to follow a standardized pattern. Therefore, it is crucial to establish an optimal procedural framework tailored to individual expertise. As shown in **Figure 1**, two representative techniques for esophageal ESD are the tunnel method[14] and the C-shaped method.

In the tunnel method (**Figure 1a**), mucosal incision and trimming are performed first. The submucosa near the center of the lesion is then dissected to create 2 or 3 tunnels extending from the proximal to the distal side. Typically, tunnels are created at the 7 o'clock (and optionally 4 o'clock) and 11 o'clock orientations, and the submucosa is left intact at the 1 o'clock orientation. This setup utilizes gravity effectively as a countertraction and facilitates submucosal dissection of the remaining submucosa after tunnel creation. The creation of tunnels is both straightforward and efficient, but insufficient trimming of the incision on the distal side leads to difficulties in dissection of the remaining submucosa at the end.

In the C-shaped method (**Figure 1b**), an incision is made in a C-shape on one side of the lesion's mucosa, usually the mucosa near the left wall where water or blood is likely to accumulate and make treatment difficult. The submucosa in this area is then dissected, followed by mucosal incision and submucosal dissection on the opposite side. Finally, the submucosa remaining longitudinally in the center of the lesion is dissected. This method prevents the proximal side of the lesion from collapsing toward the distal side, facilitating smooth dissection.

As submucosal dissection progresses in esophageal ESD, the lesion becomes increasingly mobile, and this makes the procedure difficult to secure and maintain a clear visual field. In such cases, traction techniques using devices like clip with thread are effective.[15] After circumferential mucosal incision, a clip is attached to the proximal edge of the mucosal specimen containing the lesion to create counter



Figure 2 **ESD Knives.**

(Images provided by Olympus and FUJIFILM Medical)

traction and stabilize the lesion. This creates effective countertraction, contributing to shorten the dissection time.[16)]

(4) Selection of ESD knives

Various ESD knives are available for esophageal ESD, as illustrated in **Figure 2**. These include tip-type knives such as the FlashKnife, DualKnife, and HookKnife, as well as insulated-tip knives like the ITKnife nano, and scissor-type knives such as the ClutchCutter. Other options include the B Knife, Splash Needle, SB Knife, ProKnife, and ISSEN. Each of these knives is designed specifically for esophageal ESD. It is essential for effective treatment to understand the strengths and limitations of each type and select the knife that aligns with the practitioners' preferences.

4. Adverse Events and Their Management

(1) Mediastinal emphysema and perforation

The perforation rate of esophageal EMR/ESD is rare, at less than 1%, when performed by skilled practitioners.[7,9,10-12)] However, improper handling or procedures performed under poor visualization easily leads to perforation due to the thin esophageal wall. Esophageal perforation must be avoided, as it results in severe complications like respiratory failure caused by subcutaneous emphysema and pneumothorax, as well as mediastinal abscess and empyema. Maintaining good visualization and performing EMR/ESD with adequate caution are crucial for preventing perforation. Since esophagus lacks serosa, even without visible perforation, exposure of the muscularis propria alone possibly leads to mediastinal or subcutaneous emphysema. It is essential to perform esophageal ESD with CO_2 insufflation.

In cases of perforation or damage to muscularis propria, insufflation should be minimized with carefully monitoring the patient's condition to determine the appropriate response. If the patient's condition is unstable, the procedure should be immediately halted. Moreover, imaging examinations such as chest X-ray or CT should be conducted to evaluate the extent of emphysema or pneumothorax and assess whether the procedure could be safely continued. The procedure could be cautiously resumed while the patient remains stable.

If subcutaneous emphysema is detected, there is a risk of sudden respiratory changes, necessitating prompt resection and retrieval of the lesion. While the patient's condition is stable and no emphysema is observed, ESD could be cautiously continued by first sufficiently dissecting the submucosa around the perforation site, then closing the perforation site with clips. When the muscularis propria around the perforation site is exposed, clipping could exacerbate the perforation. Prolonged process to close the perforation site leads to severe mediastinitis.

Recently, possible methods such as closing a gastrointestinal perforation site with polyglycolic acid (PGA) sheets with fibrin glue have demonstrated benefits. This covering method minimizes the risk of clip-related enlargement of the perforation. Thus, this option should be considered for closing a perforation site.[17)]

Even if endoscopic closure of perforation is not feasible, the perforation often closes within two weeks with fasting, provided there is no associated infection. In cases where the closure appears challenging, prompt termination of the procedure and transition to conservative treatment are viable options to prevent further deterioration before improper treatment for closing the perforation site.

When there is damage to the muscularis propria, oral intake should only be resumed if an endoscopic examination performed several days later confirms there is no delayed perforation. In the event of perforation, postoperative imaging such as chest X-ray or CT should be performed to assess the extent of emphysema, pneumonia, pneumothorax, or pleural effusion. Fasting is necessary, along with intubation of a decompression tube in the esophagus and administration of antibiotics. Conservative treatment continues as the condition gradually improves. However, surgical intervention should be considered while infection control is inadequate. Once infection signs have resolved under conservative treatment, endoscopic or contrast examinations are performed to confirm closure of the perforation before resumption of oral intake.

(2) Postoperative hemorrhage

Even if the ulcer bed is not coagulated after resection, post-EMR/ESD bleeding is rare, with an incidence of less than 1%. To prevent bleeding, it is sufficient to treat only blood vessels protruding from the ulcer bed, and excessive cauterization should be avoided since it increases the risk of delayed perforation.

(3) Stricture

The risk of stricture after esophageal EMR/ESD primarily depends on the extent of circumferential resection. When the mucosal defect exceeds three fourths of the luminal circumference, there is a high risk of stricture,[18,19)] and complete circumferential resection invariably results in severe stricture requiring frequent balloon dilation. Steroids are effective in preventing esophageal stricture, with both local injection and oral administration significantly reducing its occurrence.[20, 21)]

Recently, the combination therapy by oral administration with local injection of steroids has been

CQ4: What is recommended for the prevention of post-endoscopic resection stricture in superficial esophageal cancer?

Recommendation statement:

For prevention of post-endoscopic resection stricture in superficial esophageal cancer, oral administration of prednisolone, submucosal injection of triamcinolone, or a combination of both is strongly recommended.
(Agreement rate: 85.2% [23/27], strength of evidence: C)

Figure 3 ***Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus*** **(2022 edition).**

(Modified from Literature 2)

reported as particularly effective, even in cases of extensive or circumferential resection.[22)]

The efficacy and safety of steroid use after endoscopic resection require further evaluation through accumulated case studies. However, as outlined in the 2022 edition of the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus, a more specific statement is given (**Figure 3**). CQ4: "What is recommended for the prevention of stricture after endoscopic resection of esophageal superficial cancer?" As a recommendation, "It is strongly recommended to perform oral prednisolone, submucosal injection of triamcinolone, or both for the prevention of stricture after endoscopic resection of esophageal superficial cancer (consensus rate: 85.2% [23/27], strength of evidence: C)." It is desirable to select one of the stricture prevention treatments for cases with extensive resection exceeding three fourths of the luminal circumference.

The Japan Clinical Oncology Group (JCOG) is currently conducting a randomized Phase III trial comparing oral steroid administration with local steroid injection therapy, with final results expected in 2024.[23)] Additionally, regenerative medicine technology such as tissue-engineered autologous oral mucosal epithelial cell sheets onto the ulcer surface to prevent stricture[24, 25)] and the use of PGA sheets with fibrin glue for stricture prevention are under investigation, with future clinical applications anticipated.[26, 27)]

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III.Gastroduodenal

1 Definition and Classification of the Stomach and Duodenal Regions

1. Classification of Gastritis

(1) Kimura-Takemoto classification [1)]

The endoscopic classification of chronic gastritis evaluates how far gastric mucosal atrophy has progressed by examination on the boundary between the fundic gland region and the pyloric gland region, as shown in **Figure 1**.[1)] If the fundic gland region remains intact around the entire gastric wall, it is classified as a "closed type" (C-1, C-2, or C-3). In cases where atrophy is severely advanced and the fundic gland region is missing circumferentially, it is categorized as an "open type" (O-1, O-2, or O-3). Recently, due to a decline in *Helicobacter pylori (H. pylori)* infections, some cases show no visible atrophy. For these cases, a new subclassification of C-0 is introduced. However, in autoimmune gastritis, where atrophy mainly affects the fundic gland region, this classification system sometimes does not reflect the accurate extent of mucosal atrophy.

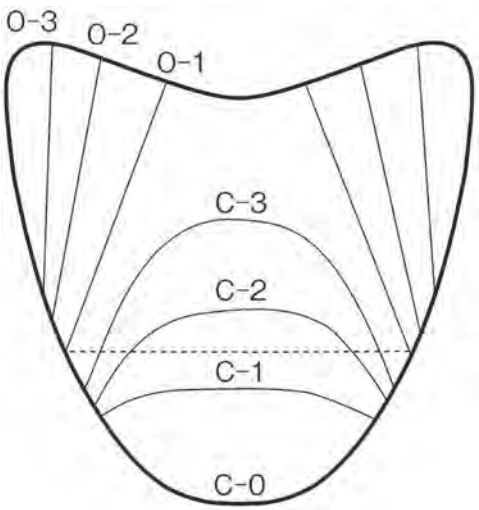


Figure 1 Conceptual diagram of the Kimura–Takemoto classification.

(Cited from Literature 1)
Note: In the original publication, the extent of atrophy is described with the notations C-I, C-II, C-III, O-I, O-II, and O-III. The designation C-0 is not included.

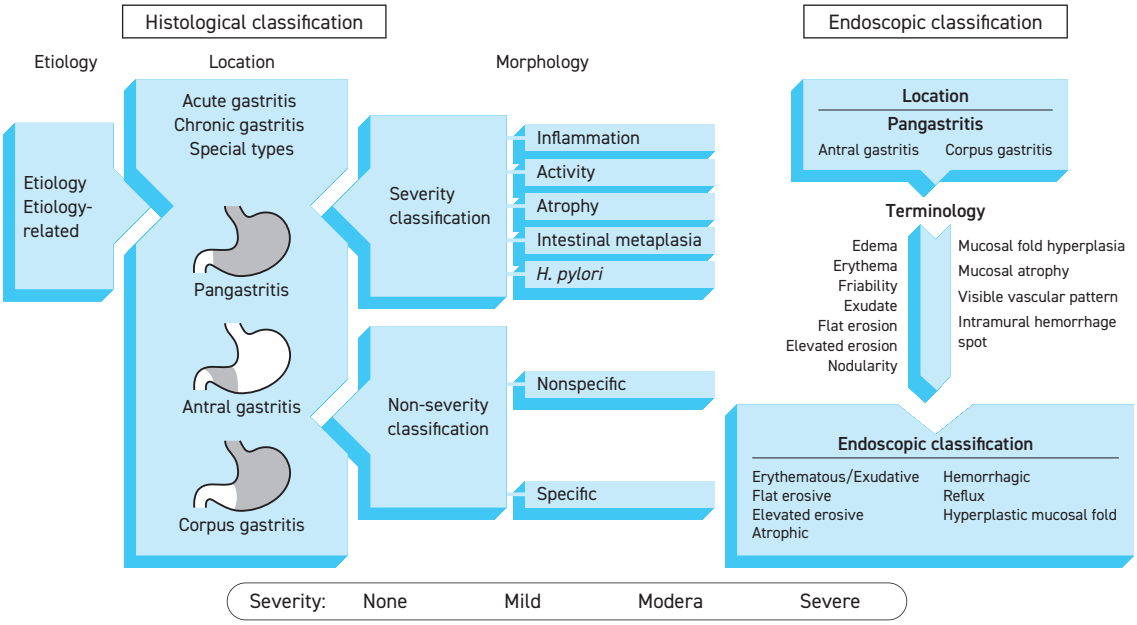


Figure 2 **Correlation between histological and endoscopic classifications in the updated Sydney System.** [2]

(Cited from Literature 3)

(2) Sydney classification [2]

In 1996, Dixon and colleagues introduced the Sydney Classification. It is the global standard for categorizing gastritis and also known as the Updated Sydney System. This system evaluates the etiology, topography and morphology of gastritis, meanwhile including both histological and detailed endoscopic findings (**Figure 2**). [3]

Histological classifications categorize the disease entities by location into pangastritis, antral gastritis, and corpus gastritis. They also focus on five key factors: inflammation (lymphocyte infiltration), activity (neutrophil infiltration), atrophy, intestinal metaplasia, and the presence of *H. pylori*. Each factor is rated on a four-point scale in severity grading: none, mild, moderate, or severe. To ensure thorough diagnosis, biopsies are recommended from five sites: lesser and greater curvatures of the antrum, incisura angularis, and lesser and greater curvatures of the corpus.

Endoscopic classification similarly divides the disease entities into pangastritis, antral gastritis, and corpus gastritis based on their location. It identifies seven categories of endoscopic gastritis: (i) erythematous/exudative gastritis, (ii) flat erosive gastritis, (iii) raised erosive gastritis, (iv) atrophic gastritis, (v) hemorrhagic gastritis, (vi) reflux gastritis, and (vii) rugal hyperplastic gastritis. Additionally, 11 descriptive endoscopic terms are applied for expressing the disease conditions. Aligning the pathohistological and endoscopic classifications surely remains a challenge for future research.

(3) Types A and B gastritis (Table 1 & Figure 3) [4,5]

Type A gastritis is known as autoimmune gastritis, which has been gaining attention in recent years. In

1973, Strickland and colleagues divided atrophic gastritis into Type A and Type B, based on where the damage occurs and the presence of specific antibodies in the blood.[4)]

Type A gastritis typically shows no issues in the mucosa of antrum but involves widespread inflammation in the corpus, high levels of gastrin in the blood, and significantly reduced stomach acid production in addition to positive tests for gastric parietal cell antibodies. Type B gastritis involves inflammation in the antrum, low gastrin levels, patchy inflammation in the corpus, and moderately reduced stomach acid production in addition to no gastric parietal cell antibodies.

In those days, the role of *H. pylori* was unknown for the cause of gastritis. It was thought that Type A was caused by autoimmune processes, whereas Type B was linked to environmental factors. Today, Type A gastritis is recognized as autoimmune gastritis (AIG), and Type B gastritis is associated with *H. pylori* infection.

In 2023, a new proposal was offered for the establishment of diagnostic criteria for Type A gastritis or AIG from the Study Group of the Japan Gastroenterological Endoscopy Society (JGES) (**Table 1**). [5)]

Table 1 **Diagnostic criteria for autoimmune gastritis.**

Confirmed diagnosis:
A) Either endoscopic findings or histological findings (as specified) must meet the criteria for autoimmune gastritis.
B) Positive gastric autoantibodies, such as anti-parietal cell antibodies (as specified) or anti-intrinsic factor antibodies, or both, should be present. A confirmed diagnosis requires both A) and B). In early-stage cases, histological findings and positive gastric autoantibodies are sufficient.

Suspected diagnosis:
Cases fulfilling only criterion A are considered suspected. Among these, early-stage cases are identified solely by histological findings.

-Detailed notes:
Endoscopic findings (Advanced stage):

Main criterion:
Severe atrophy predominantly in the corpus and fundus, with uniform vascular visibility in the corpus.

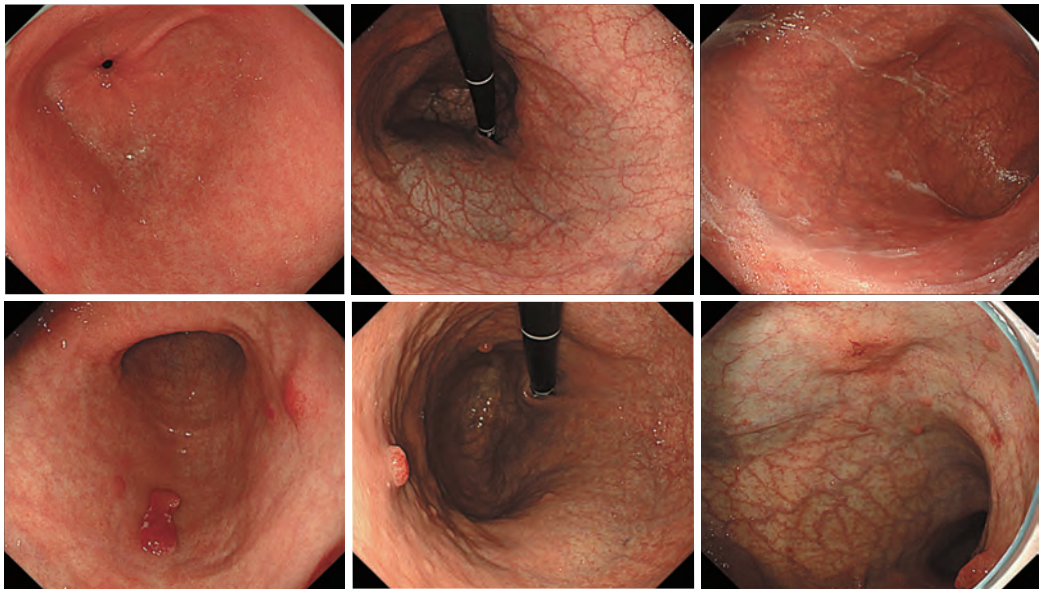
Supporting findings:
Fixed mucus, residual fundic gland mucosa, or hyperplastic polyps are often observed in the corpus and fundus. The antrum does not consistently exhibit normal coloration but sometimes shows patchy redness, ridge-like redness, or ring-like patterns. The main criterion is essential for diagnosis.

Histological findings:
Diagnosis is categorized into three stages: early stage, advanced florid stage, and advanced end stage (see **Table 2**).

Anti-parietal cell antibodies:
A tenfold increase is considered positive, but the potential for false positives should be considered. These criteria are probably subject to future revisions.

(Cited from Literature 5)

Type A gastritis is important to diagnose because it causes low stomach acid, vitamin B12 deficiency, and anemia. It also increases the risk of gastric neuroendocrine tumors (NETs) and stomach cancer. However, diagnosing *H. pylori* infections are tricky for patients with Type A gastritis because low stomach acid allows urease-producing bacteria to thrive, thereby leading to false-positive results in common tests like urease and breath tests.



a b c
d e f

Figure 3 Endoscopic findings of autoimmune gastritis.

(a, b) In type A gastritis, atrophy of the corpus is relatively more pronounced than atrophy in the antrum (a, b).
(c) In many cases, marked mucous adherence is observed in the corpus.
(d) A hyperplastic polyp associated with autoimmune gastritis
(e) A gastric neuroendocrine tumor associated with autoimmune gastritis
(f) An early gastric cancer associated with autoimmune gastritis

(4) Kyoto classification

1) Kyoto classification of gastritis

The 85th Congress of the JGES was held in May 2013 in Kyoto, where the theme of gastritis diagnosis was addressed. The primary aim was to define the findings used to diagnose *H. pylori*-associated gastritis within Japan's standard endoscopic diagnostic framework, incorporating histological findings. This approach was based on the updated Sydney system and sought to improve both objectivity and diagnostic accuracy. Additionally, it intended to assign a score to the presentation of gastritis that poses a risk for developing gastric cancer. This became the current Kyoto classification of gastritis,[6] and the first edition was published in September 2014. In this system, *H. pylori* infection is categorized into uninfected, currently infected, and previously infected (including post-eradication), with corresponding characteristic endoscopic findings organized accordingly.

2. Infection Status and Endoscopic Findings (Table 2 & Figure 4)[7]

(1) *H. pylori*-uninfected gastric mucosa

This refers to gastric mucosa not infected with *H. pylori* and without histological gastritis. A pattern

Table 2 Kyoto Classification of gastritis.
(Endoscopic mucosal findings/ localization related to *H. pylori* infection)

a: Kyoto Classification of Gastritis (Characteristic mucosal findings related to *H. pylori* infection)

Endoscopic findings	Uninfected	After *H.pylori* eradication	*H.pylori* Infected
Regular arrangement of collecting venules	◎	×～○	×
Scratch sign	○	×～○	×
Fundic gland polyp	○	×～○	×
Map-like redness	×	◎	×
Fujitsubo's sign	×	○	△
Diffuse redness	×	×	◎
Mucosal swelling	×	×	◎
Spotty redness	×	△～×	○
Nodularity	×	△～×	○
Enlarged fold, tortuous fold	×	△～×	○
Sticky mucus	×	△～×	○
Atrophy	×	○～×	○
Intestinal metaplasia	×	○～×	○
Foveolar-hyperplastic polyp	×	○～×	○
Xanthoma	×	○	○
Hematin	○	○	△
Red streak	○	○	△
Raised erosion	○	○	△
Multiple white and flat elevated lesions	○	○	△
Patchy redness	○	○	○
Depressive erosion	○	○	○
Erosion of the corpus	○	○	○

◎ : frequently observed ○ : observed × : not observed △ : occasionally observed

known as the regular arrangement of collecting venules (RAC) is observed, primarily at the lesser curvature of the body. It is recommended that RAC be assessed in the lesser curvature of the angulus to the lower body. Additionally, fundic gland polyps, hematin, red streaks, and raised erosions are frequently observed.

(2) Currently *H. pylori*-infected gastric mucosa

This condition is chronic active gastritis, where the gastric mucosa shows neutrophilic infiltration along with mononuclear cells, and chronic changes such as atrophy of the fundic glands and intestinal metaplasia. In the body to fundus of active gastritis, diffuse redness, mucosal swelling, spotty redness, and sticky mucus are basically noted in addition to atrophy, intestinal metaplasia, nodularity, fold

Location of endoscopic mucosal findings associated with *H. pylori* infection.

	Location						
	Fundus	Upper body	Middle body	Lower body	Angulus	Gastric antrum	
						Antrum	Prepyloric region
Regular arrangement of collecting venules				(Diagnostic relevance)	(Diagnostic relevance)		
Scratch sign							
Fundic gland polyp							
Map-like redness							
Fujitsubo's sign							
Diffuse redness							
Mucosal swelling							
Spotty redness							
Nodularity							
Enlarged fold, tortuous fold							
Sticky mucus							
Atrophy							
Intestinal metaplasia							
Foveolar-hyperplastic polyp							
Xanthoma							
Hematin							
Red streak							
Raised erosion							
Multiple white and flat elevated lesions							
Patchy redness							
Depressive erosion							
Erosion of the corpus							

Frequently observed or diagnostically important Usually observed

(Cited from Literature 7)

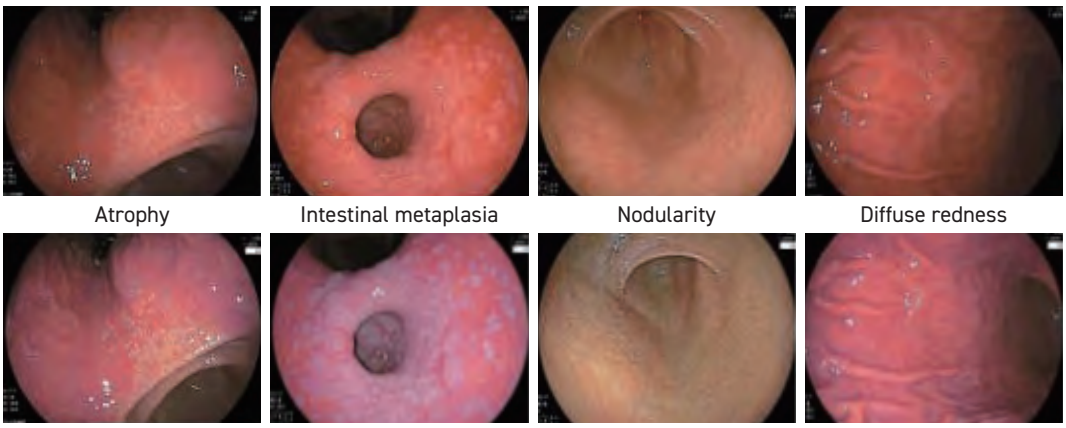


Figure 4 **Image-enhanced endoscopy (LCI) of *H. pylori*-associated gastritis.**

a: Atrophy (white light)
b: Atrophy (LCI)
c: Intestinal metaplasia (white light)
d: Intestinal metaplasia (LCI)
e: Nodularity (white light)
f: Nodularity (LCI)
g: Diffuse redness (white light)
h: Diffuse redness (LCI)

abnormalities, xanthoma, and hyperplastic polyps. Among these, atrophy, intestinal metaplasia, nodularity, and fold hypertrophy are important findings as risk indicators for gastric cancer.

(3) Previously *H. pylori*-infected gastric mucosa

This is chronic inactive gastritis following eradication or natural disappearance of the bacteria due to severe atrophy. Atrophy is recognized, but diffuse redness disappears, and the thickness and course of the folds in the greater curvature of the body become almost normal. Due to the resolution of inflammation by eradication, map-like redness (histologically, intestinal metaplasia) sometimes becomes apparent in severely atrophic gastric mucosa. Although this condition does not necessarily appear after eradication, it is a specific finding considered to be post-eradication mucosa.

3. Staging of Gastric and Duodenal Ulcers (Table 3 & Figure 5) [9,10)]

Table 3 Sakita-Miwa endoscopic classification

4. Diagnosis on Depth of Tumor Invasion

The depth of tumor invasion is diagnosed according to the *Japanese Classification of Gastric Carcinoma*, as shown in Table 4.[12)] The depth of carcinoma invasion is classified with the T classification system, and the different layers of the gastric wall or infiltration into other organs are represented by M, SM, MP, SS, SE, and SI. The clinical and pathological classifications, marked by "c"

Table 3 Sakita-Miwa endoscopic classification.

Active stage	A_1	The ulcer is covered with thick whitish exudate, and the surrounding mucosa shows edematous swelling with no regenerating epithelium.
	A_2	The surrounding edema has decreases, and the ulcer margin becomes clearly defined. A small amount of regenerating epithelium appears in the ulcer margins. A red halo in the marginal zone and a white slough circle in the ulcer margin are commonly observed. The convergence of mucosal folds could be traced to the edge of the ulcer.
Healing stage	H_1	The white coating is becoming thin, and the regenerating epithelium is extending into the ulcer base. The gradient between the ulcer margin and the ulcer floor is becoming flat. The ulcer crater is still evident and the margin of the ulcer is sharp.
	H_2	The ulcer is mostly covered by regenerating epithelium, with only a small amount of white coating remaining.
Healed stage	S_1	The white coating has disappeared, and the ulcer surface is covered with regenerating epithelium. The regenerating region is markedly red (red scar).
	S_2	The redness is reduced to the color of the surrounding mucosa or it shows a slightly white appearance (white scar).

*H3: A small, pinhead-sized white coating remains in the healing ulcer, which is described as the H3 stage.
(Cited from Literatures 9 & 10)

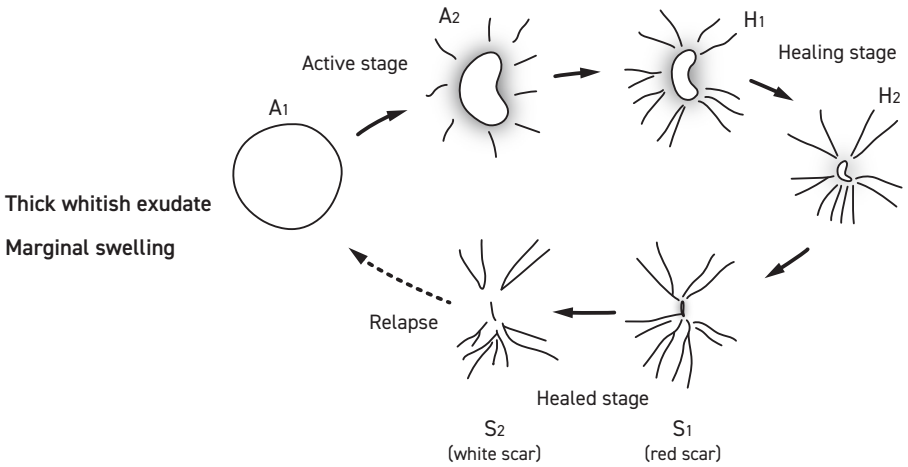


Figure 5 Staging (by Sakita and Miwa) of gastric and duodenal ulcers.

(Cited from Literatures 9 & 11)

and "p," are used with the T classification but not with M, SM, or other similar codes. It is important to note that the mucosa (M) also includes the muscularis mucosae (MM). In cases with multiple lesions, the T classification of the deepest tumor is used to determine the overall stage. Regardless of whether lymph node metastasis is present, T1 tumors are considered early gastric cancer.

5. Macroscopic Classification of Gastric Cancer (Table 5 & Figure 6) [12)]

Table 4 Diagnosis on depth of tumor invasion.

TX: Depth of tumor unknown
T0: No evidence of primary tumor
T1: Tumor confined to the mucosa (M) or submucosa(SM)
T1a: Tumor confined to the mucosa (M)
T1b: Tumor confined to the submucosa (SM)
T2: Tumor invades the muscularis propria (MP)
T3: Tumor invades the subserosa (SS)
T4: T Tumor invasion is contiguous to or exposed beyond the serosa (SE) or tumor invades adjacent structures (SI)
T4a: Tumor invasion is contiguous to the serosa or penetrates the serosa and is exposed to the peritoneal cavity (SE)
T4b: Tumor invades adjacent structures (SI)

For tumor with invasion from the muscularis mucosae of less than 0.5 mm, it is classified as pT1b1 (SM1); for deeper invasion, it is classified as pT1b2 (SM2). The invasion depth is measured from the lower edge of the muscularis mucosae. If the muscularis mucosae is obliterated due to carcinoma invasion, the measurement is taken from the surface.
If the tumor invades the greater omentum or lesser omentum but is not exposed on the serosal surface, it is classified as T3 (not T4a). Other organs refer to the liver, pancreas, transverse colon, spleen, diaphragm, abdominal wall, adrenal glands, kidneys, small intestine, and retroperitoneum.
(Cited from Literature 12)

Table 5 Macroscopic types of gastric cancer.

(1) Basic classification

The macroscopic type of gastric cancer is classified into superficial type and advanced type based on the depth of tumor invasion. The former is typically observed when the invasion depth remains within the submucosa, whereas the latter is observed when the tumor invades beyond the muscularis propria. The tumor is categorized into six types (0-5) based on its appearance viewed from the mucosal surface. Type 0 is further subdivided to describe the macroscopic appearance of early gastric cancer. This classification is determined regardless of the depth of the invasion, but the depth (estimated in clinical classification) is always recorded. In cases treated with preoperative therapy, the prefix "y" is used.

Type 0 (Superficial): Tumors confined to the submucosa
Type 1 (Mass): Polypoid tumors, sharply demarcated from the surrounding mucosa
Type 2 (Ulcerative): Ulcerated tumors with raised margins surrounded by a thickened gastric wall with clear margins
Type 3 (Ulcerative and infiltrative): Ulcerated tumors with raised margins surrounded by a thickened gastric wall without clear margins
Type 4 (Diffuse and infiltrative): Tumors without marked ulceration or raised margins, the gastric wall is thickened and indurated and the margin is unclear
Type 5 (Unclassifiable): Tumors that cannot be classified into any of the above types

(2) Subclassification of 0 type (Superficial type)

Type 0-I (Protruding): Polypoid tumors
Type 0-II (Superficial): Tumors with or without minimal elevation or depression relative to the surrounding mucosa
Type 0-IIa (Superficial elevated): Slightly elevated tumors
Type 0-IIb (Superficial flat): Tumors without elevation or depression
Type 0-IIc: (Superficial depressed): Slightly depressed tumors
Type 0-III (Excavated): Tumors with deep depression

-The distinction between 0-I and 0-IIa types was previously determined based on the height of the elevation. If the elevation was within twice the height of the normal mucosa, it was classified as 0-IIa, and if it exceeded this height, it was 0-I. In practice, tumors with elevations up to about 2 mm are classified as 0-IIa, and those exceeding that height are classified as 0-I.

- Mixed types of the superficial type are described by connecting the different areas of the lesion with the "+" symbol (e.g., 0-IIc+III).

(Cited from Literature 12)

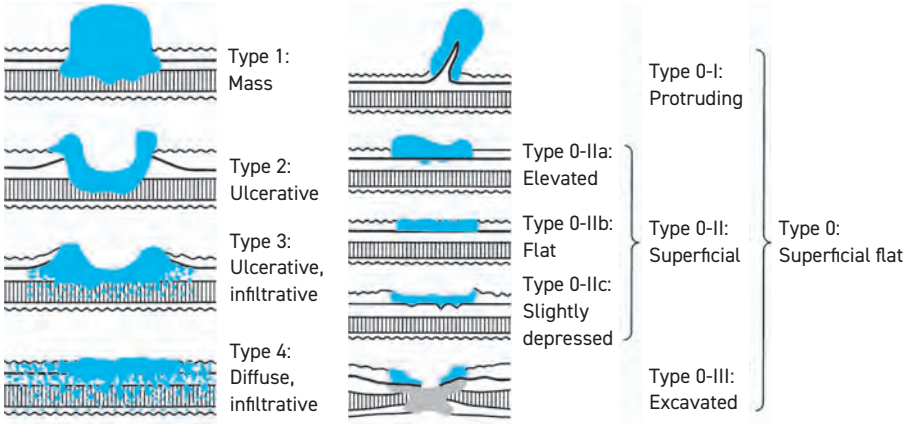


Figure 6 Macroscopic classification of gastric cancer.

(Modified from Literature 9)

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Shinji Kitamura, Naoki Muguruma and Kazunari Murakami

2 Observation Method

1. Gastric Observation

(i) Gastric endoscopic observation is divided into (1) screening endoscopy and routine endoscopic examination for symptomatic patients, and (2) detailed endoscopic examination for lesions already identified. This section provides an overview of screening endoscopy.
(ii) For screening, two subjects should be evaluated as well as the detection of localized lesions.

(1) Infection status of *Helicobacter pylori* (*H. pylori*)

Although the presence or absence of *H. pylori* infection is primarily assessed by bacteriological testing together with a history of the eradication therapy, endoscopic findings are also important. At least, the presence or absence of the regular arrangement of collecting venules (RAC) should be assessed because this sign has the highest reproducibility. RAC refers to the endoscopic appearance in the fundic gland mucosa (**Figure 1**).[1] The RAC should be evaluated at the lesser curvature of angulus. If RAC is present, the likelihood of *H. pylori* infection is extremely low.

(2) Endoscopic gastric mucosal atrophy

The presence and extent of the atrophic border are identified and determined according to the Kimura–Takemoto classification (**Figure 2**).[2]
(iii) The fundamental principle of screening endoscopy is to examine the entire gastric mucosa carefully without blind spots. In fact, the importance of systematic observation was emphasized traditionally in Japan. Observation procedures varied by academic society, institution, and instructor, and no international standardized method had been established. After extensive discussions with specialists worldwide, Yao proposed the systematic screening protocol for the stomach (SSS) in 2013 (**Figure 3**).[3] This protocol outlines a clear method for observing 22 specific areas of the gastric mucosa. In fact, the process has been widely accepted internationally. The SSS is introduced in the Japanese guidelines[4] and is also recommended in the guidelines of the British Society of Gastroenterology.[5]

SSS protocol

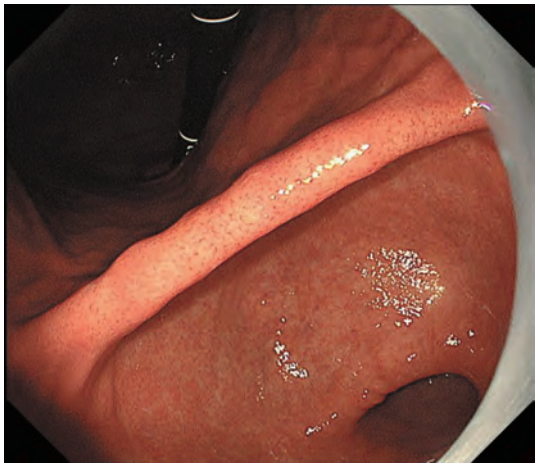


Figure 1 Regular arrangement of collecting venule (RAC).

Regularly arranged collecting venules are observed on the lesser curvature of the gastric incisura. This is determined to be RAC-positive gastric mucosa that is typical findings of *Helicobacter pylori*-uninfected stomach.

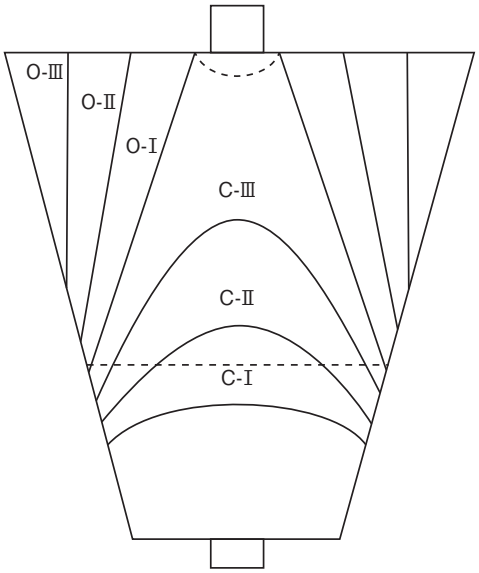


Figure 2 Illustration for endoscopic gastric mucosal atrophy (Kimura-Takemoto classification).

Atrophic mucosa is limited to the antrum in C-I; limited to the lesser curvature of lower corpus in C-II; limited to the upper corpus in C-III, limited to the surroundings of the gastric cardia in O-I, atrophy is present in the entire stomach in O-III, and O-II is an intermediate type between O-I and O-III. (Adapted from Literature 2)

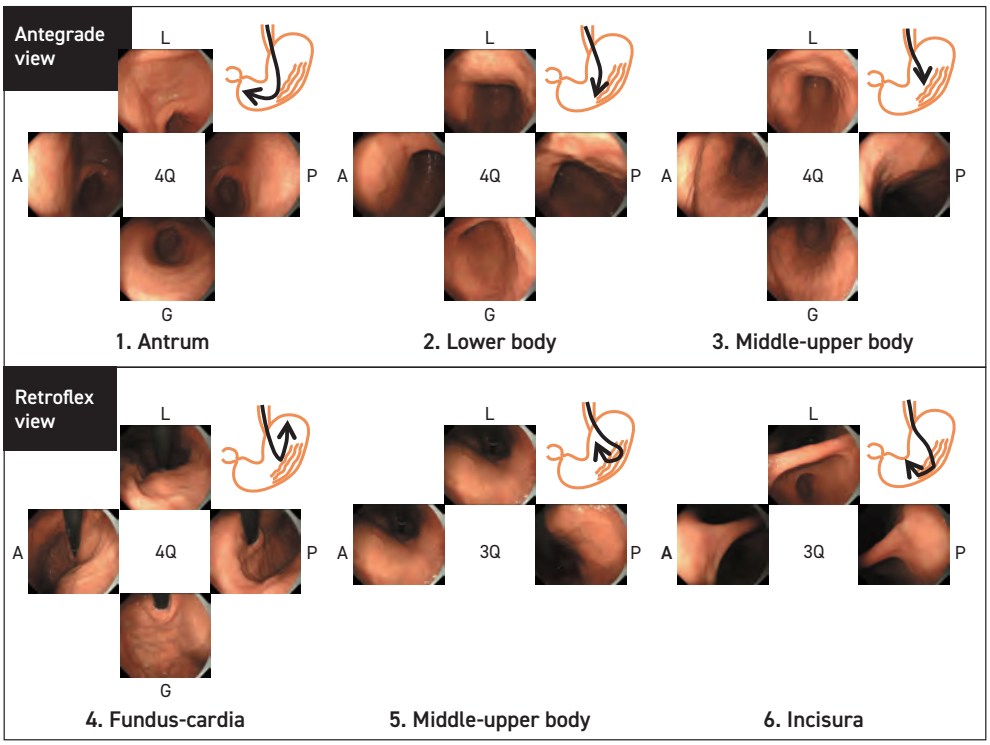


Figure 3 Systematic screening protocol for the stomach (SSS).

L: lesser curvature, A: anterior wall, G: greater curvature, P: posterior wall, Q: quadrant
(Adapted from Literature 3)



a | b | c

Figure 4 Observation of duodenum.

a: Pyloric ring viewed from the antrum
b: Duodenal bulb. The arrow indicates the superior duodenal angle.
c: Descending portion. The yellow arrow indicates the major papilla. The white arrow indicates the inferior duodenal angle.
(Adapted from Literature 6)

(1) Observation by forward-view

(i) Antrum: In forward-viewing, once the endoscope proceeds into the antrum, 4 quadrants of the lesser curvature, anterior wall, greater curvature, and posterior wall are observed and recorded in either clockwise or counterclockwise manner.

(ii) Lower body: Then, after withdrawing the endoscope to the lower body, the same process is repeated.

(iii) Middle to upper body: After the endoscope is withdrawn to the upper body, the same process is repeated.

(2) Observation by retroflex view

(i) Cardia and fundus: By retroflex view, observation begins with the fundus and cardia. Each quadrant of the lesser curvature, anterior wall, greater curvature, and posterior wall is observed and recorded.

(ii) Body: The scope then advances with keeping the retroflex position, and 3 quadrants of the lesser curvature, anterior wall, and posterior wall of the body are observed and recorded.

(iii) Angulus: The scope next proceeds to the angulus, and 3 quadrants of the lesser curvature, anterior wall, and posterior wall are observed and recorded.

When a localized lesion is found during observation, additional close-up images are taken. The fundamental principle is that all 22 sites are systematically examined.

2. Duodenal Observation [6)]

(1) Sequence of observation sites

Observation of duodenum starts from the area before the pylorus (**Figure 4a**). There are two approaches: one involves entering the duodenum after completing the entire observation of the gastric lumen, including retroflexion observation; the other involves entering the duodenum immediately after forward-viewing up to the antrum. Each method has its advantages and disadvantages. In the former, insufflation during gastric observation often causes discomfort on duodenal insertion. In the latter, contact with the mucosa during duodenal insertion could result in reddening on the greater or lesser curvature of the angulus. This causes a problem for evaluation of lesions. In such cases, it is important for endoscopists to carefully observe and image the relevant areas before advancing the scope into the duodenum.

To insert a scope into the duodenal bulb through the pyloric ring, the operator should gently guide the scope while ensuring the pyloric ring remains centered in the view. At this moment, the angle of the scope should slightly raise to help with the passage, and just before it crosses the pyloric ring, the up-angulation should be slightly reduced to facilitate easier insertion. Excessive force on insertion causes strong contact with the mucosa of the bulb, potentially leading to hemorrhage from the damaged site.

Once the scope progresses into the bulb, it should be withdrawn back to the area just before the pyloric ring. This process allows observation of the entire bulb from the anterior to the superior, inferior and posterior walls. Maintaining appropriate distance and avoiding excessive proximity are essential for practitioners to evaluate surface patterns and the presence of scars in the duodenal mucosa (**Figure 4b**).

Subsequently, the scope advances to just before the superior duodenal angle. Then practitioners angle up the scope and simultaneously give clockwise torque to the shaft, and the scope gently advances beyond the superior duodenal angle into the descending part. After the scope enters the descending part, the up-angulation given for insertion process is released to center the field of vision within the lumen. At this point, if the angulation is too strong or too weak, it may cause contact with the mucosa, thereby leading to mucosal bleeding. In fact, meticulous handling skills are required.

The major papilla is typically observed in the upper left quadrant of the field in a downward-looking view. If sufficient visualization is not obtained during insertion, the area can be observed during the withdrawal process (**Figure 4c**). After inserting the scope into the descending part, operators should gently withdraw the scope with clockwise rotation of the shaft, thereby achieving further advancement of the scope. On rightward torque, the scope tip advances near the inferior duodenal angle without creating a bend in the gastric cavity. After sufficient insertion has been achieved, the scope is slowly withdrawn with the active right and left shaft rotation for thorough observation.

In duodenal endoscopy, it is particularly important **to examine areas that are prone to becoming blind spots, such as the area just below the superior duodenal angle and the major papilla. Successful observation is achieved through careful control of insufflation, scope angulation, axial rotation, and push-pull maneuvers**.

3. Practical Application of Contrast Method

The contrast method involves **spraying indigocarmine onto the surface of gastrointestinal mucosa to enhance the visibility of irregularities in surface pattern**. In general, detailed endoscopic examinations such as chromoendoscopy are time-consuming process. Therefore, sufficient pharyngeal anesthesia is applied, and the use of sedatives is also preferred. If a large amount of sticky mucus remains on the mucosal surface in stomach and the dye is applied, the mucus itself becomes stained. This obscures the natural morphology of the mucosa. To avoid this, it is recommended that the patient should drink 100 mL of tap water with mucolytic agent (such as pronase and sodium bicarbonate,) and a defoaming agent in prior to the procedure.

Because stomach has a wide lumen, indigocarmine is equally sprayed over a broad area of mucosal surface using a spray catheter. Careful attention should be paid in order to check mucosal subtle changes in surface within any detected lesions. In addition to such changes, it is also important to evaluate the shape of the margins and whether the surrounding converging folds are continuous or interrupted.

Figures 5 shows endoscopic images of early gastric cancer.[6] By conventional endoscopy in **Figure 5a**, there is a flat lesion with a reddened area in the center accompanying with slightly elevated area

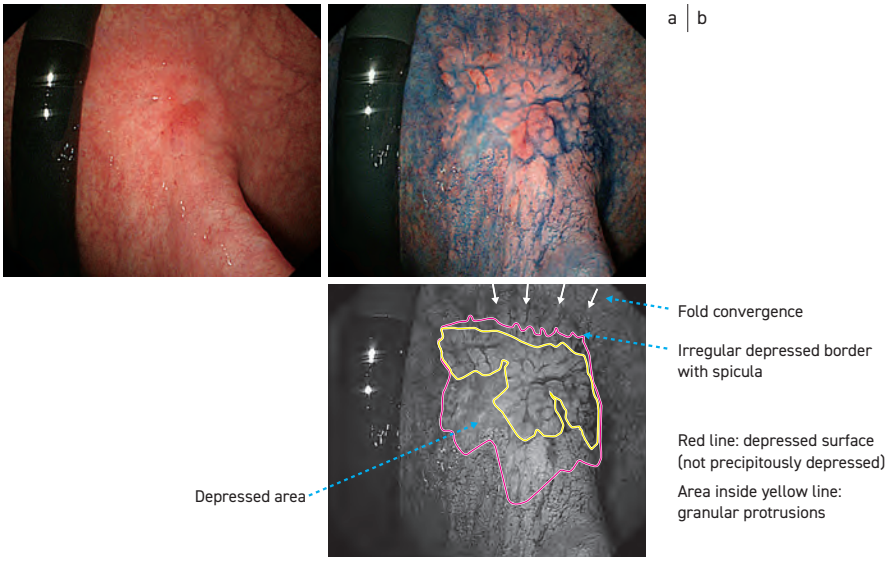


Figure 5 Early gastric cancer of 0-IIa + IIc type.

a: White light endoscopy (routine endoscopy)
b: Contrast method (Chromoendoscopy)
(Adapted from Literature 6)

surrounded by a slightly pale mucosa. However, its diagnosis is difficult. By contrast method (chromoendoscopy) in **Figure 5b**, the area outlined in yellow reveals aggregated granular surface which is surrounded by depressed area extending to the red boundary line. This lesion is diagnosed as early gastric cancer of 0-IIa + IIc type. The red line representing the outer margin of the lesion shows irregular, and the converging folds do not show thickening, fusion, or non-extension sign. This suggests that the lesion is confined to the mucosa. Furthermore, the margin area shows spicula depression and it does not demonstrate steep depression. Accordingly, the lesion is likely a differentiated type of carcinoma.

In duodenum, the key point of observation with a contrast method is to accurately assess the structure of villi. The shape of duodenal villi varies in association with inflammation or neoplastic changes. After application of indigocarmine, the shape of villi is well visualized, and ulcer scars and other findings often become more distinct.

4. Practical Application of Acetic Acid Method

(1) Acetic acid for spraying

While working at Niigata Prefectural Yoshida Hospital, the author, Kazuyoshi Yagi used 1.5% acetic acid prepared by adding distilled water to 1.5 mL of acetic acid, reagent grade, from KANTO CHEMICAL, to make a total volume of 100 mL and sterilizing it at 115°C for 30 minutes, with obtaining approval from the facility's ethics committee. Vinegar and such are also acceptable if the acetic acid concentration is around 1.5%. This is stored in a glass bottle. Care should be taken to ensure that the concentration of acetic acid used does not exceed 1.5%, as high concentrations of acetic acid induce perforation.

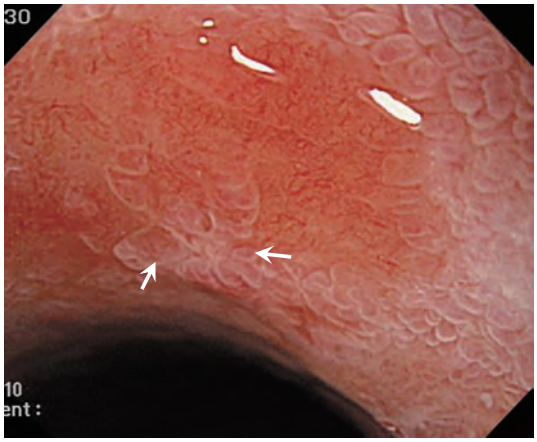


Figure 6 Early gastric cancer of 0-IIb type delineated by acetic acid dynamic chemical method.

(Adapted from Literature 7)

(2) Spraying method

A syringe containing about 10 mL of 1.5% acetic acid is connected to the instrument channel for spraying. Shooting in a mist is not required, as the concentration is sufficient to adhere to the mucosal surface. Another 10 mL could be added if insufficient. Spraying tubes should not be used because they often cause mucosal bleeding.

(3) Endoscopic findings [7,8]

1) Acetic acid-enhanced magnification endoscopy

Acetic acid reversibly denatures cytoplasmic proteins, preventing the transmission of white light. As a result, columnar epithelia appear white, and the red blood vessels beneath the columnar epithelia are no longer visible. Because all light is reflected off the mucosal surface, it is observed like a three-dimensional scanning electron microscope. Magnification endoscopy allows for a clearer recognition of the pit patterns.

2) Acetic acid dynamic chemical method

A few seconds after acetic acid spraying, both cancerous and non-cancerous mucosa turn white. However, they soon return to their original reddish color. The time it takes to return to the original color differs between cancerous and non-cancerous areas. Cancerous areas return to their original color faster. As a result, cancerous areas appear red, and non-cancerous areas remain white, thereby making the cancerous region clearly discernable. This is an observation method that utilizes this optical phenomenon.[9] The time it takes to return to redness also differs depending on the tumor grade of gastric cancer. Moderately differentiated adenocarcinoma returns in a few seconds, well-differentiated adenocarcinoma in 10 to 20 seconds, adenoma in 20 seconds to 3 minutes, and the mucosa of chronic gastritis returns to its original color in 1 to 3 minutes.

Figure 6 shows a type 0-IIb early gastric cancer.[7] The histological type is moderately differentiated



Figure 7 Early gastric cancer of 0-IIb type delineated by acetic acid with indigocarmine method.

(Adapted from Literature 7)

adenocarcinoma. Conventional endoscopy revealed only slight redness, but it is difficult to accurately diagnose the extent of cancerous lesions. Approximately 3 seconds after spraying acetic acid, the magnified endoscopic appearance was observed as shown in **Figure 6**. The area where whitening persists is non-cancerous, and the reddening area is cancerous. The boundary between the cancerous and non-cancerous areas is accurately diagnosed based on the findings of sharp contrast between red and white. The presence of non-cancerous regenerative epithelium in the biopsy scar can also be diagnosed from the persistent pale appearance (white arrow in **Figure 6**). This acetic acid dynamic chemical method is also useful in low magnification observation.

3) Combined acetic acid with indigocarmine method

After acetic acid is sprayed, indigocarmine is applied. Within 10 to 20 seconds, the dye fades from the cancerous area, whereas the blue color of the indigocarmine remains on the non-cancerous tissue. This method is also called the acetic acid indigocarmine sandwich.[8] Indigocarmine is also applied directly through the biopsy channel. For this, about 10 mL of indigocarmine diluted to twice its original volume is prepared in a syringe. The point is to spray evenly over the mucosal surface. Spraying continues until the indigocarmine has adequately coated the lesion and its surrounding area. After 10 seconds or so, imaging is initiated once the dye begins to fade from the cancerous region. Additional spraying is allowed to enhance the blue coloration of indigocarmine on the non-cancerous area. There is also a method of spraying a mixture of 1.5% acetic acid and indigocarmine,[10] or a mixture of 0.6% acetic acid and indigocarmine (acetic acid indigocarmine mixture: AIM).[11] The mechanism by which the adhesion time of indigocarmine differs between cancerous and non-cancerous areas has yet been elucidated.

Figure 7 shows a type 0-IIb early gastric lesion.[7] In conventional endoscopy, the extent of lesion is partially determined from the reddening findings. However, the cancerous lesion is confirmed with spraying acetic acid and indigocarmine and observing for about 10 seconds. The area where indigocarmine is not attached is the cancerous area (the area surrounded by the yellow arrows in **Figure 7**), while the blue area is non-cancerous where indigocarmine is attached.

4) NBI under acetic acid spraying

When observed with NBI after spraying acetic acid, cancerous lesions tend to appear brown, and non-cancerous areas tend to appear greenish.

5. Clinical Application of Magnifying Endoscopy with Narrow-band iaging (M-NBI)

Magnifying endoscopy is often performed in combination with image-enhanced endoscopy (IEE). Endoscopic systems equipped with narrow-band imaging (NBI) from Olympus, or blue laser imaging (BLI) and linked color imaging (LCI) from Fujifilm are commercially available. The following outlines the use of magnifying endoscopy with NBI.[12)]

(1) Preparation

1) Preparation for patients

Preparation for patients is basically same as in routine upper gastrointestinal endoscopy. When a prolonged examination is anticipated, administration of sedatives is recommended.

2) Settings of electronic endoscopy system

The electronic endoscopy system of Olympus has structure enhancement function. This function has two modes: A mode and B mode.

Since in A mode, higher setting levels make diameter of blood vessels appear larger than their actual size, B mode is suitable for M-NBI. Structure enhancement levels are preset to levels 4, 6, and 8. Levels 4 or 6 are used in non-magnifying endoscopy, whereas level 8 is often selected for magnifying observation. For color mode settings under NBI, mode 1 is recommended for upper gastrointestinal observation.

3) Scope and black soft hood

To obtain stable magnifying endoscopic images at maximum magnification for gastric mucosa, **a black soft hood is an essential item**. The use of a black soft hood attached to the distal end of scopes is recommended in both routine and detailed endoscopic examinations using M-NBI. Black soft hood (MAJ-1989, Olympus) is for GIF-XZ1200, GIF-H290Z, and GIF-Q240Z, , whereas Black soft hood (MAJ-1990, Olympus) is for GIF-H260Z.

4) Graph paper

Graph paper cut into 1 cm squares is affixed to the endoscopic trolley or the measurement scale on the specimen spread sheet is used. After the hood is mounted to the scope before the examination, the tip of the hood is placed perpendicularly against the graph paper. Using the zoom lever, the magnifying ratio is increased to the maximal level and adjusted so that the graph paper is displayed on the endoscopy monitor at maximum magnification. If the width of the screen measures 4.5 mm for GIF-XZ1200, 4.75 mm for GIF-H290Z, 4.1 mm for GIF-H260Z, or 3.4 mm for GIF-Q240Z, then the optical zoom function is confirmed to be operating properly, and the positioning of the hood is adjudged to be appropriate.

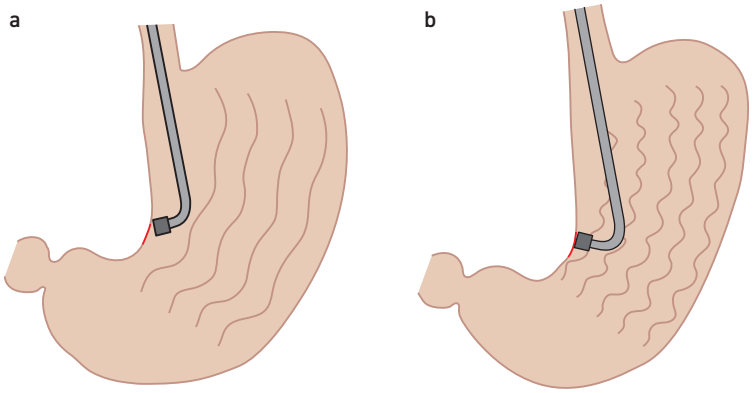


Figure 8 Black soft hood technique for approaching to lesion.

a: Observation during white light endoscopy (routine endoscopy)
b: Observation during magnifying NBI endoscopy
(Adapted from Literature 6)

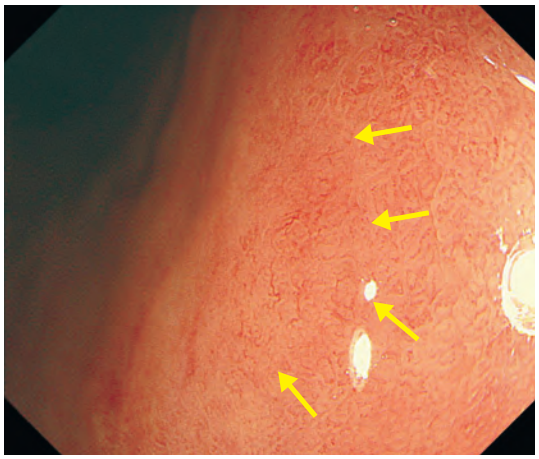


Figure 9 Demarcation line (arrows) observed in white light endoscopy.

(adapted from Literature 6)

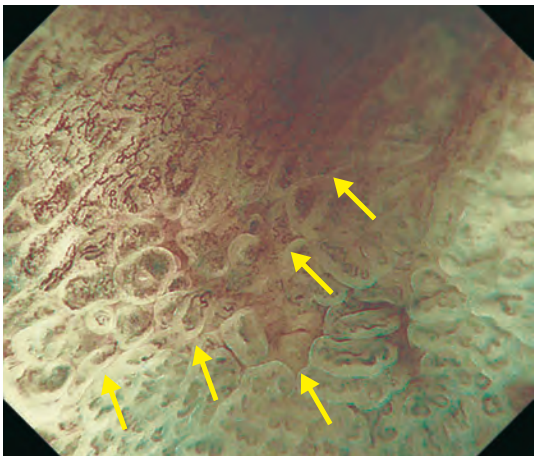


Figure 10 Endoscopic findings of early gastric cancer by M-NBI: a demarcation line (arrows), irregular microvascular and microsurface patterns (area above the arrows).

(Adapted from Literature 6)

(2) Observation

1) Approach to the lesion[6]

(i) When a lesion is detected, the lesion is initially examined with conventional white-light endoscopy. When the scope gets close to the lesion, the tip of the hood is gently brought into contact with the mucosal surface (**Figure 8a**).

(ii) The lesion's demarcation line is detected by moving the endoscope from the outside toward the center of the lesion at low magnification (**Figure 9**, arrows).

(iii) Then, the light is changed to NBI, and the magnification rate is increased to maximum.

(iv) At the maximum magnification, air in the stomach is sucked out, and make the tip of the black soft

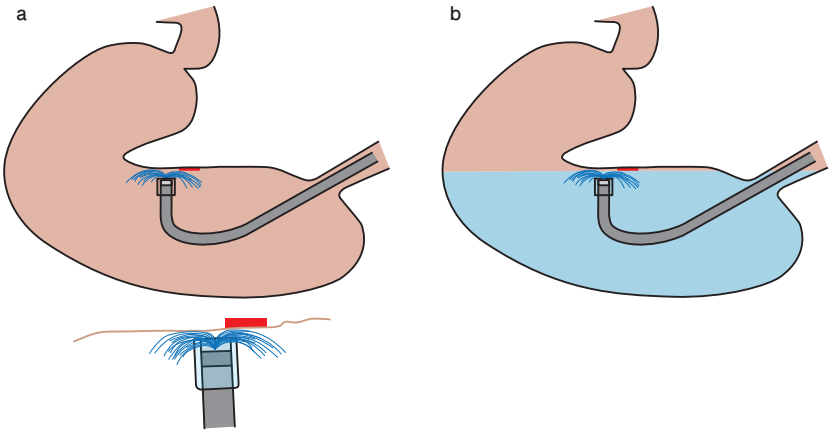


Figure 11 **Water immersion technique.**

a: Water irrigation method; b: Water filling method
(Adapted from Literature 13)

hood of the endoscope become close and perpendicular to the mucosal surface. (**Figure 8b**).
(v) After the demarcation line is identified (**Figure 10**, arrows), **the microvascular pattern and microsurface structure are meticulously examined within the demarcation line. If an irregular microvascular pattern and/or an irregular microsurface pattern are present (the area above the arrows in Figure 10), it is diagnosed as cancer. Otherwise, it is diagnosed as non-cancer.**

2) Tips for making a focus on the mucosal lesion at maximum magnification

(i) If endoscopists approach the lesion by retroflexing the endoscope, it becomes easy to fix the tip of the endoscope against the mucosal surface.
(ii) While keeping the magnification at maximal level, endoscopists adjust the distance between the lesion and the tip of the scope by slightly insufflating air and moving the scope forward and backward with the right hand.
(iii) If the distance to the lesion is too close and if it is out of focus, endoscopists should slightly insufflate air to keep away from the mucosal surface.
(iv) If the distance to the lesion is too long and if it is out of focus, endoscopists should aspirate a small amount of air from the stomach to bring the lesion closer to the tip of the scope.

(3) Water immersion technique

This method involves filling the inside of the hood with water for magnified observation. There are two types of procedures: the water irrigation method, in which water is introduced into the hood using a water pump or syringe during observation (**Figure 11a**); and the water filling method, where not only the hood lumen but also the surrounding gastric lumen is filled with water (**Figure 11b**)[13] The advantages of the water immersion technique are: (i) elimination of light reflection (halation) on the mucosal surface, (ii) increased depth of field, making it easier to focus even at maximum magnification, (iii) increased resolution, (iv) easier horizontal movement of the hood, and (v) reduced mucus adhesion on the lens surface. This method is very useful not only for detailed examinations but also for routine examinations.

6. Clinical Application of Endoscopy with BLI/LCI in the stomach

In LASEREO laser endoscopy system, two types of image enhanced endoscopy (IEE) modes are configured: BLI mode and BLI-bright mode. These are achieved by adjusting the ratio of white light laser to BLI laser according to the observation mode. In the former mode, close-up imaging enables observation of the microsurface pattern and microvascular pattern, which is useful for delineating the extent of cancer and for qualitative diagnosis. Since the latter mode is brighter than BLI mode, it facilitates lesion detection not only in close-up but also from medium and distant views, and is thus expected to be advantageous for lesion detection from various observation distances.[14] Furthermore, LASEREO system incorporates LCI mode, which is considered useful for distinguishing subtle differences in mucosal color. The colors critical for diagnosing normal mucosa, atrophic changes, deep vessels, and redness in the stomach are mostly concentrated within a limited range centered around skin-toned shades. This makes subtle color differences especially distinct in endoscopy. In LCI mode, signal conversion is applied to enhance color separation within this range while brightness is maintained, thereby rendering reddish tones more red and whitish tones more white. As a result, even minimal differences in mucosal color are emphasized. LCI mode has been considered an improved and effective IEE for gastric screening, such as identifying atrophic border, diagnosing *H. pylori* gastritis, and detecting early gastric cancer.[15]

In LCI mode, *H. pylori*-positive gastric mucosa presents with enhanced diffuse reddening, and fundic gland mucosa appears crimson in color (**Figure 12c**).[6] In contrast, *H. pylori*-negative gastric mucosa (whether never infected or post-eradicated) typically shows no diffuse redness, and the fundic gland mucosa appears apricot-colored (**Figure 12a & b**). Thus, LCI mode is expected to be useful for gastric endoscopic diagnosis considering the infection status of *H. pylori*. Early gastric cancer often involves color changes, and LCI mode is expected to improve detection rates. In the multicenter, randomized controlled trial (LCI-FIND Trial) for upper gastrointestinal carcinomas, Dohi and colleagues reported that LCI showed a 1.67-fold higher detection rate than white light imaging (WLI).[16] This study demonstrated that standard WLI endoscopy alone has a high risk of overlooking tumors. Therefore, a non-inferiority trial is underway to prove that LCI alone is not inferior to the combination of WLI and LCI in detecting upper gastrointestinal carcinomas.

An example of early gastric cancer detected using the EG-L590ZW is shown in **Figure 13**.[6] This is a case of a depressed-type early gastric cancer in 4 cm size located in the greater curvature of lower body. LCI mode was useful for identifying the lesion and determining its extent, and BLI magnified observation is effective for providing a definitive diagnosis.

As a routine examination method using the LASEREO laser endoscope system for the stomach, the following approach is expected to be useful: (i) Beginning with, (ii) Checking the state of *H. pylori* gastritis and lesions by color changes in LCI mode, and (iii) Performing qualitative diagnosis with BLI-bright mode for intermediate and long-distance observation and BLI mode for close-up magnified observation.

7. Adverse Event and Its Management

The frequency and details of adverse events are discussed in the *Report on the Seventh National Survey on Gastrointestinal Endoscopy-related Adverse Events for Three Years: From 2019 to 2021*, which is referenced in this handbook. In addition, general principles of risk management and guidelines in

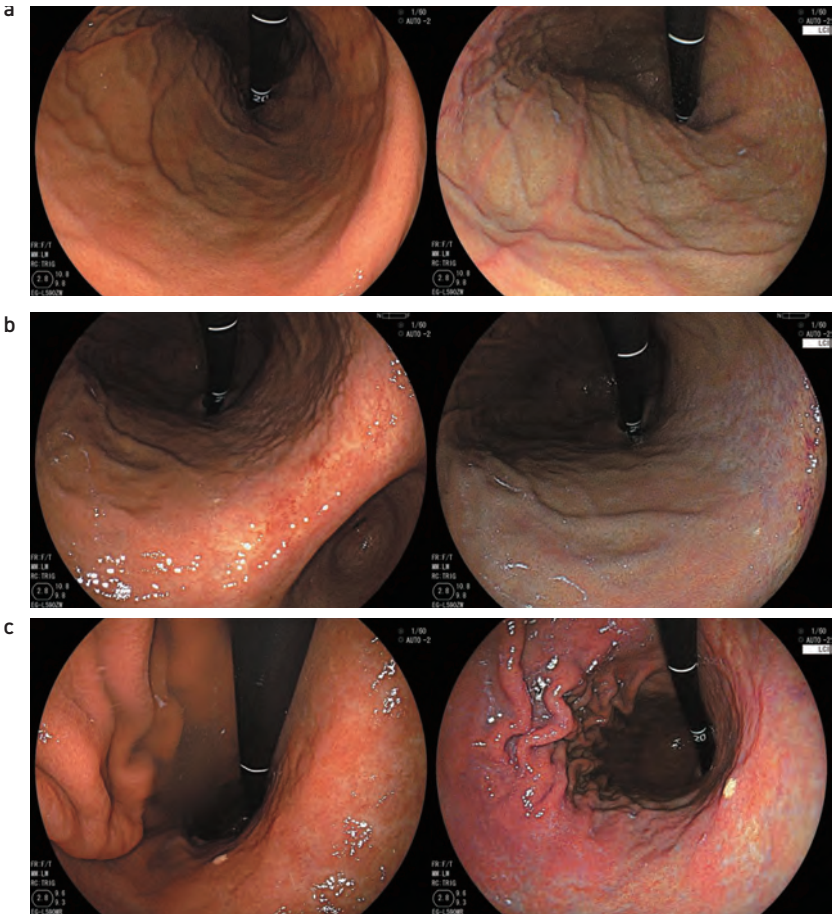


Figure 12 Endoscopic findings of *H. pylori* infection progress.

a: Uninfected; Linear erythema is unclear under white light observation (left), while fundic glands appear apricot-colored and linear erythema becomes distinct under LCI (right).
b: Postinfected; Ulcer scar is seen in the gastric angle under white light observation (left). On LCI (right), fundic glands appear apricot-colored with mild atrophy on the lesser curvature of the body.
c: Currently infected; Diffuse redness is unclear under white light observation (left), but on LCI (right), the fundic glands exhibit diffuse redness and appear crimson.
(Adapted from Literature 6)

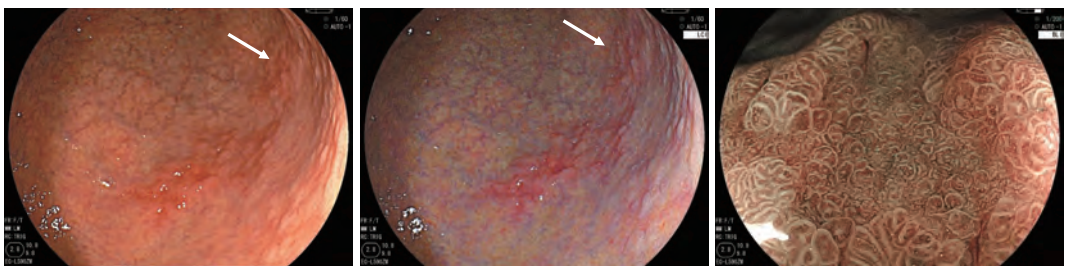


Figure 13 Early gastric cancer (0-IIc).

a: On white light imaging, the reddish depression is seen on the greater curvature of the lower body. Mild reddening is also suspected on the distal posterior wall (white arrow).
b: On LCI, the reddish depression on the greater curvature of the lower body becomes clearer, and the reddening on the distal posterior wall is also easier to diagnose (white arrow).
c: On magnifying BLI, the reddish depression on the greater curvature of the lower body shows a regionally irregular mucosal and vascular patterns.
(Adapted from Literature 6)

endoscopic practice are available in the *Risk Management for Digestive Endoscopy* report prepared by the Risk Management Committee of the Japan Gastroenterological Endoscopy Society in 2004.[17]

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3 Endoscopic Ultrasonography

Introduction

This section discusses the practical application of endoscopic ultrasonography (EUS) for examination of lesions in the stomach and duodenum. This method has been established as a technique for objectively obtaining submucosal information, and this overview also includes EUS-guided fine needle aspiration (EUS-FNA) for tissue diagnosis.

1. Characteristics and Purpose

By observing the ultrasonic tomographic images of the gastrointestinal wall and its surroundings, EUS in the stomach and duodenum allows for assessing the localized layer (mucosa to serosa or extramural) of gastrointestinal lesions, the internal echo pattern of the lesions, the size of the lesion, and peri-gastric lymph nodes. The purpose of EUS is to obtain useful information for determining the treatment plan and evaluating the effectiveness of treatment for lesions. Specifically, EUS is used for the staging of gastroduodenal tumors, including the assessment of the depth of wall invasion and lymph node metastasis. It is also used to evaluate submucosal tumors (SMTs) and subepithelial lesions (SELs), including their actual size, mural location (which layer of the gastrointestinal wall they are in), and internal characteristics. Additionally, for SMTs/SELs and other cases where tissue diagnosis via conventional forceps biopsy is difficult, **EUS-FNA** can be performed to obtain an accurate cytological or histological diagnosis.

2. The five-layered structure of the gastrointestinal wall imaged by EUS

In EUS, the layered structure of the gastrointestinal wall is formed by alternating high-echo interface layers and substantial echo layers. The former layers arise at the interfaces where tissues with differing acoustic impedances meet. The substantial echo layers, whose brightness varies based on their tissue composition, represent structures such as the mucosa, connective tissue, and muscle layer. The basic layered structure of the gastric wall is the five-layered structure imaged by 7.5 MHz echoendoscope. The first layer (high-echo) and the second layer (low-echo) of the five-layered structure correspond to mucosa (M), the third layer (high-echo) corresponds to submucosa (SM), the fourth layer (low-echo) corresponds to muscularis propria (MP), and the fifth layer (high-echo) corresponds to subserosa and serosa (SS, S) (**Figure 1**).[1)]

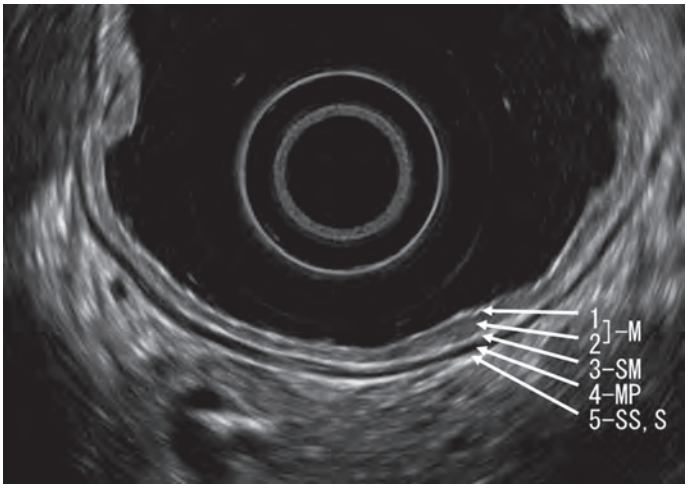


Figure 1 **Five-layered structure of the normal gastric wall imaged by EUS.**

The first (1) and second (2) layers correspond to mucosa (M), the third layer (3) corresponds to submucosa (SM), the fourth layer (4) corresponds to muscularis propria (MP), and the fifth layer (5) corresponds to subserosa and serosa (SS, S).

3. Procedural Details

(1) Equipment selection

For gastrointestinal EUS, either a dedicated echoendoscope equipped with a transducer at the tip or an ultrasound catheter probe inserted through the forceps channel of a standard endoscope is used.

(i) For SMTs/SELs and advanced cancers, endoscopists select a dedicated echoendoscope with a large transducer capable of observing deep within the gastric wall and extramurally or a 12 MHz ultrasound catheter probe.

(ii) For small early gastric cancers and other superficial lesions, endoscopists select a high-frequency ultrasound catheter probe like 15-20 MHz to closely observe the superficial layer of the gastric wall while seeing the lesion with endoscopy.

(2) Scanning techniques for specific purposes

(i) Depth of invasion diagnosis (Deaerated water filling method or balloon-combined deaerated water filling method):

Approximately 500 mL of deaerated water is infused into gastric lumen to distend the lesion and the surrounding normal gastric wall. This helps maintain a suitable distance (5 to 20 mm) between the ultrasound probe and the digestive tract wall for accurate assessment of the invasion depth.

(ii) Lymph node metastasis diagnosis (Balloon method)

Balloon method is performed to obtain deep extramural information from the entire circumference of the stomach and duodenum. Deaerated water infused into gastric lumen for depth of invasion diagnosis is aspirated as much as possible, while the probe covered by inflated balloon with deaerated water is

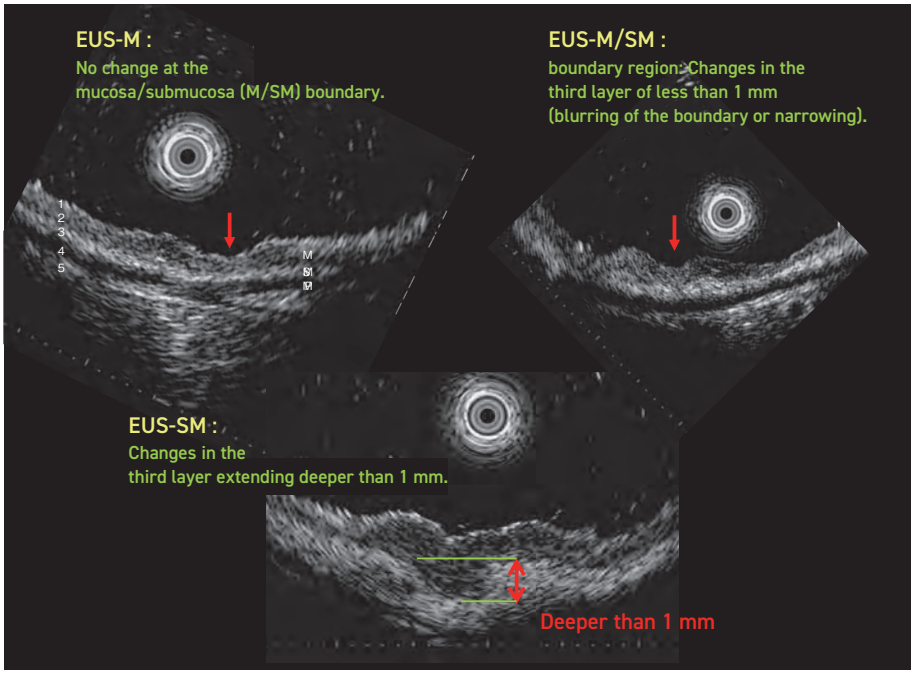


Figure 2 EUS classification of invasion depth in early gastric cancer (Yanai).

EUS-M and EUS-M/SM boundary regions are both determined to be EUS-M.
(Cited from Literature 2)

brought into close contact with the gastric and duodenal wall to perform the diagnosis on peri-gastroduodenal lymph node metastasis. This close contact eliminates any blind spots, enabling a more extensive evaluation for lymph node metastasis.

(3) Efforts and precautions for improving diagnostic accuracy

(i) For scanning the pyloric region and duodenum, the prone position may allow deaerated water to pool, which can result in better images.
(ii) Consider using a two-channel multi-bending scope or an endoscopic hood to add more deaerated water or to expand the Kerckring folds.
iii) When checking for surrounding lymph nodes, slowly withdraw the scope from the deep duodenum to the cardia while using surrounding organs and blood vessels as landmarks to avoid overlooking any nodes.

4. EUS Diagnosis of Gastric and Duodenal Epithelial Tumors: A Practical Approach

(1) Assessing the depth of invasion in early gastric cancer with EUS

Early gastric cancer is categorized into three types based on EUS findings of the depth of tumor

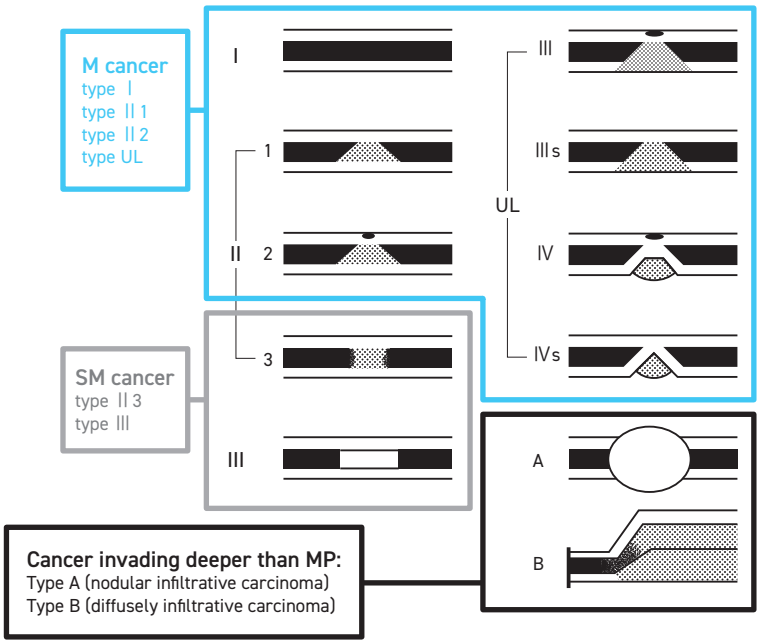


Figure 3 EUS patterns classification of invasion depth in gastric cancer by Yoshino and Nakamura.

(Modified from Literature 5)

invasion.

- EUS-M: No changes at the boundary between the second and third layers
- EUS-M/SM borderline: Changes within the third layer less than 1 mm in depth
- EUS-SM: Changes deeper than 1 mm into the third layer (**Figure 2**)

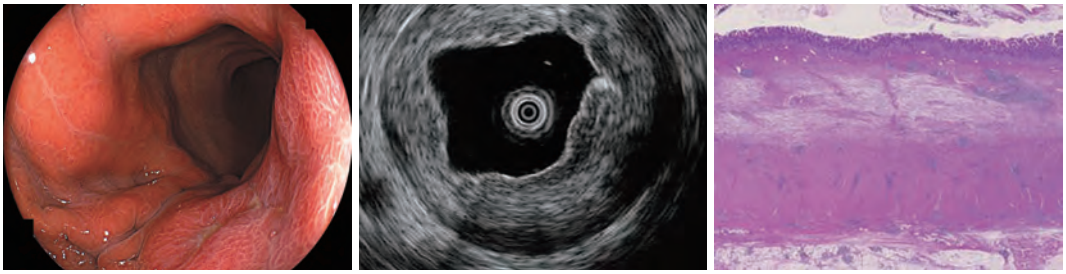
Pathological findings showed that 94.3% (215/228) of cases classified as EUS-M were confirmed as M cancers. In the EUS-M/SM borderline group, 82.9% (58/70) were mucosal cancers, whereas 17.1% (12/70) were submucosal cancers. For EUS-SM, 71.4% (5/7) were pathologically determined to be submucosal cancers.[2,3)]

However, early gastric cancer frequently involves lesions with peptic ulcers or ulcer scars. Both cancerous tissues and fibrosis associated with ulcer (UL) appear as hypoechoic regions on EUS, making it difficult to accurately determine the depth of tumor invasion.[4,5)] Therefore, for cancers with positive ulcerous changes, it is more effective to use the depth classification patterns proposed by various researchers (**Figure 3**) rather than simply interpreting deep changes on EUS as indicative of cancer depth. Studies have reported that this approach improves diagnostic accuracy.

For carcinomas without ulcerous changes, the deepest hypoechoic area of the tumor is used for depth diagnosis. In contrast, for carcinoma with ulcerous changes, the pattern-based classification method is employed to assess invasion depth.

(2) EUS Diagnosis of Invasion Depth and Lymph Node Metastasis in Advanced Gastric Cancer

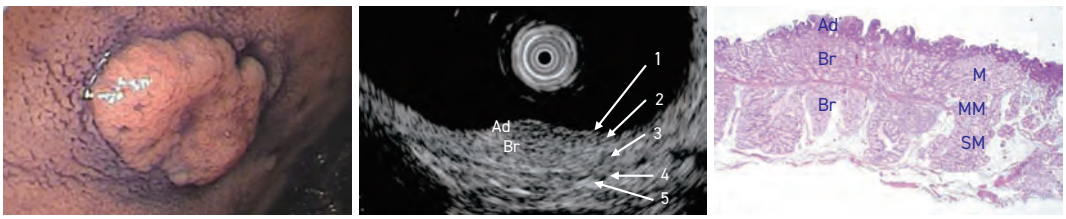
There are two types of advanced gastric cancer: one that infiltrates nodularly into the fourth layer or deeper, and another that infiltrates diffusely (scirrhous fashion). A dedicated 7.5 MHz echoendoscope



a | b | c

Figure 4 **Diffuse infiltrative type advanced gastric cance.r**

(a) Endoscopic image shows poor distensibility of the gastric body, fold thickening, and impaired expanding between folds.
(b) EUS image demonstrates marked thickening of the gastric wall, with preservation though partial blurring of the second to fourth-layers. No clearly defined hypoechoic mass is observed.
(c) Magnified view of the surgical specimen shows significant thickening of the gastric wall while preserving the layered structure. The final pathological diagnosis was diffuse infiltrative type advanced gastric cancer, non-solid type poorly differentiated adenocarcinoma, scirrhous fashion, no lymphatic involvement, and no vascular involvement.
(Cited from Literature 7)



a | b | c

Figure 5 **Duodenal adenoma.**

(a) Endoscopic image shows a flat elevated lesion (type IIa) approximately 10 mm in size on the anterior wall of the duodenal bulb.
(b) EUS image using a 15 MHz ultrasound catheter probe reveals blurring of the first layer and hypoechoic changes in the superficial second layer (Ad: adenoma). The deeper part of the second layer to the mid-third layer shows slightly reduced echogenicity due to the presence of Brunner's glands (Br). Although layer separation is poor, no clear hypoechoic area is observed in the third layer, and the lesion is diagnosed as a mucosal (M) lesion.
Layer identification: 1 = first layer (interface echo), 2 = second layer (mucosa), 3 = third layer (submucosa), 4 = fourth layer (muscularis propria), 5 = fifth layer (serosa).
(c) Magnified view of the ESD resection specimen shows adenoma (Ad) in the superficial mucosa, with Brunner's glands (Br) present from the deep mucosa to mid-submucosa. M: mucosa, MM: muscularis mucosae, SM: submucosa.
(Modified from Literature 8)

with excellent ultrasonic penetration is desirable for deep observation of tumors (**Figure 3**).[5,6] EUS enables the evaluation of serosal (SS, S) changes, assessing serosal invasion, extramural spread, and involvement of adjacent organs such as pancreas. Typically, the former invades in a nodular fashion, appearing as a hypoechoic mass on EUS with a relatively clear boundary at the tumor's leading edge, making depth of invasion diagnosis straightforward. In cases of elevated advanced gastric cancer, scanning from the tumor's apex often causes ultrasound attenuation in deeper regions, making it difficult to accurately assess the depth of invasion. Therefore, it is crucial to scan from both sides of the tumor base to avoid this attenuation and to ensure a thorough evaluation. In scirrhous fashion, undifferentiated advanced cancers do not form a mass, and present a tissue image in which relatively

few cancer cells infiltrate sporadically with fibrosis. Therefore, on EUS, compared with nodular fashion, hypoechoic masses are not depicted, and the thickened gastric wall with an indistinct-layered structure is observed (**Figure 4**).[6,7] This EUS finding is relatively specific to diffuse infiltration and is helpful for diagnosis, even in cases where cancer cells are not easily identified via biopsy due to limited tumor exposure within the gastric lumen.

On EUS, the sensitivity of detecting metastatic lymph nodes in the peri-gastric and duodenal region is adequate, but computed tomography (CT) is more useful for observing a wide range of metastatic lesions. In general, lymph nodes in round shape larger than 1 cm in diameter are considered to be metastatic.

(3) Duodenal lesions

Brunner's glands are located in the duodenal bulb and surrounding areas, and on EUS images, they appear as slightly hypoechoic regions within the deep mucosa and submucosa. Therefore, the boundary between the second layer (M) and the third layer (SM) is unclear even in the normal layered structure depicted by EUS. For this reason, careful attention is required for diagnosing the depth of wall invasion in duodenal lesions (**Figure 5**).[8] Although endoscopic treatment of duodenal tumors has not yet been established, endoscopic resection (ESD/EMR) is often selected if the depth of invasion is within mucosa on preoperative EUS, there is no lymph node enlargement, and endoscopic resection is considered feasible.

5. Diagnosis of Submucosal Tumors (SMT) and Submucosal Epithelial Lesions (SEL) in the Gastroduodenal Area.

(1) Definition of SMT/SEL

The Japan Gastroenterological Endoscopy Society (JGES) uses the term SMT broadly to refer to protrusions caused by lesions located within the wall beneath the mucosa, which result in elevation of the mucosal surface.[9] However, in clinical settings, lesions endoscopically diagnosed as SMT are smooth-surfaced protrusions in many cases. These include not only narrowly defined SMTs but also SELs, which represent a broader definition of SMT. These lesions include epithelial tumors primarily developing in the deep mucosa to submucosa (neuroendocrine tumor (NET), malignant lymphoma, SMT-like cancer), as well as varices and extrinsic compressions (compression by organs, extrinsic lesions, and their infiltration).[10] Differential diagnosis on SMT/SEL covered with normal mucosa is difficult by observing the mucosal surface with conventional optical endoscopy. In practice, it is essential to perform a detailed examination using EUS, a tomographic imaging endoscope with high spatial resolution.

(2) Diagnosis by EUS image

EUS should be used to diagnose SMT/SEL for (i) differential diagnosis between intramural and extramural lesions, (ii) identifying the layer of origin, (iii) estimation of tissue properties by echo level (cyst, lipoma, vessel, or solid tumor), (iv) measurement of SMT/SEL size in tomographic images, and

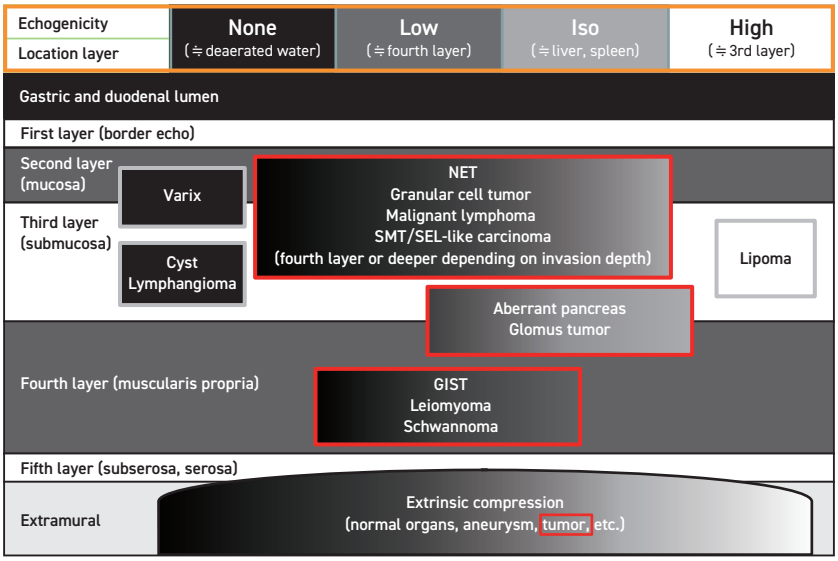


Figure 6 Differential diagnosis of SMT/SEL based on EUS echogenicity and localization.

Tissue diagnosis by EUS-FNA is desirable for lesions outlined in red.
(Modified from Literature 8)

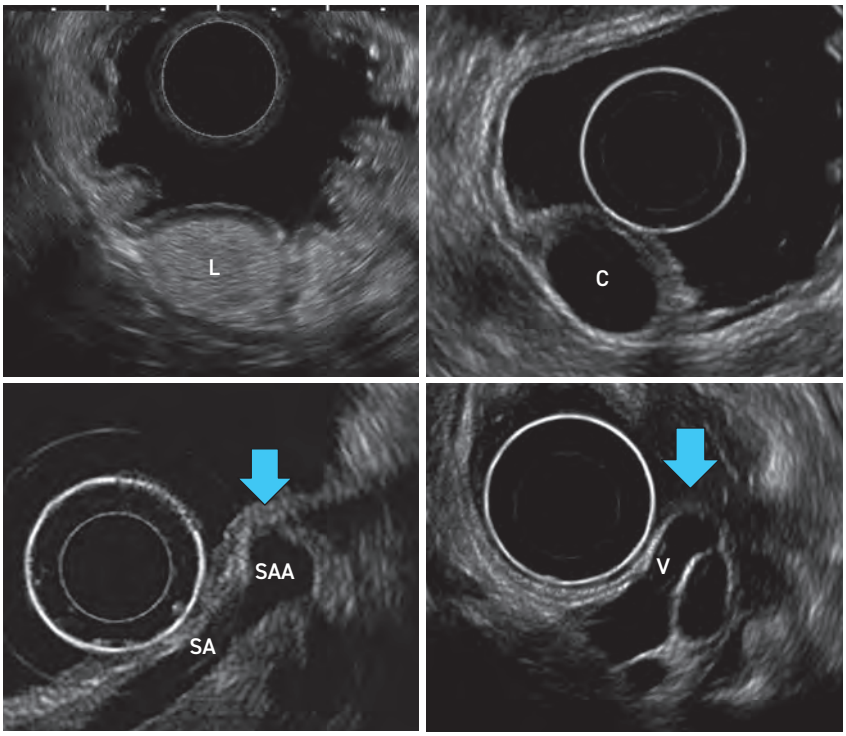
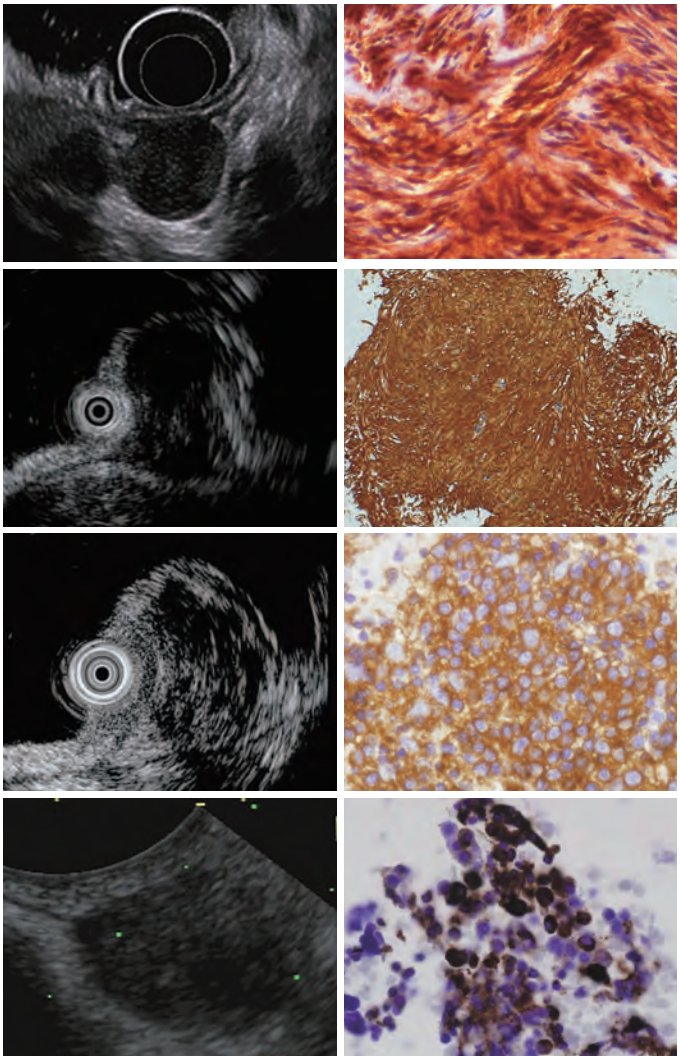


Figure 7 Characteristic EUS findings enabling diagnosis of SMT/SEL by EUS alone.

(a) EUS image of a gastric lipoma showing a hyperechoic mass (L: lipoma)
(b) EUS image of a gastric cyst presenting as an anechoic mass (C: cyst)
(c) EUS image revealing extrinsic compression by a splenic artery aneurysm, appearing as an anechoic mass external to the gastric wall (SA: splenic artery, SAA: splenic artery aneurysm, arrow)
(d) EUS image of gastric varix, indicating an anechoic mass extending from outside the wall into the submucosa (V: varix, arrow)
(Modified from Literature 10)



a	b
c	d
e	f
g	h

Figure 8 **EUS and EUS-FNA histology of SMT/SEL showing hypo- to isoechoic solid masses.**

(a) EUS image of a gastric GIST showing a hypoechoic solid mass growing extramurally
(b) Histologic image of (a): spindle-shaped tumor cells positive for c-kit, confirming diagnosis of GIST
(c) EUS image of a gastric leiomyoma showing a hypo- to isoechoic solid mass with intraluminal growth
(d) Histologic image of (c): spindle-shaped tumor cells positive for α-SMA and negative for c-kit, CD34, and S-100, confirming diagnosis of leiomyoma
(e) EUS image of a gastric malignant lymphoma showing a hypo- to isoechoic solid mass with intraluminal growth
(f) Histologic image of (e): large, blast-like lymphoid cells positive for CD20, leading to diagnosis of diffuse large B-cell lymphoma
(g) EUS image of a duodenal NET showing a hypo- to isoechoic solid mass with intraluminal/extramural growth
(h) Histologic image of (g): epithelial-like cells with round to short spindle-shaped nuclei arranged in irregular nests, positive for chromogranin A, confirming NET
(Modified from Literature 10)

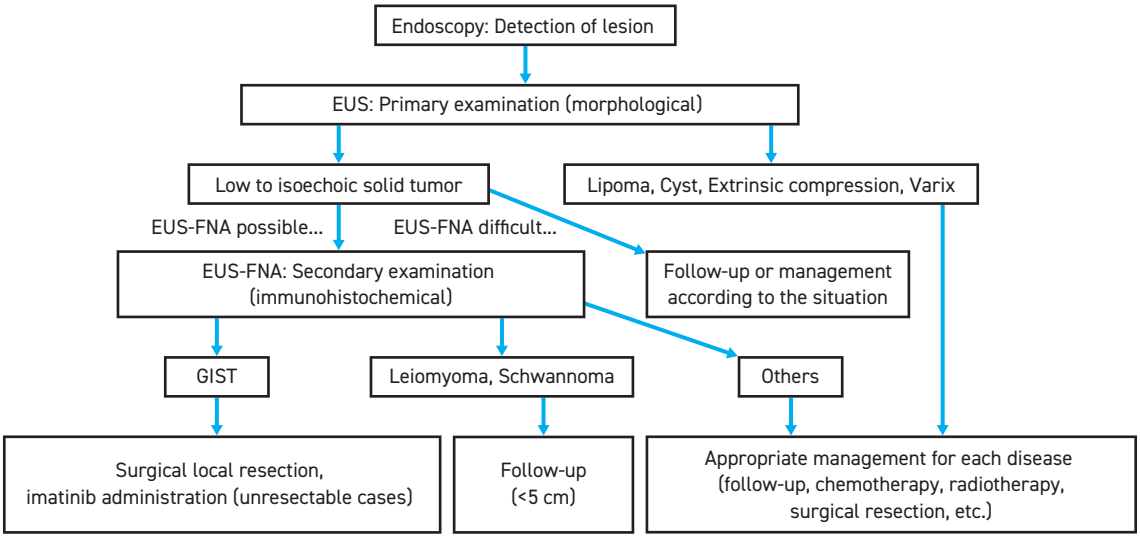


Figure 9 **Differential diagnosis and treatment strategy for gastric and duodenal SMT/SEL.**

(Modified from Literatures 8 & 10)

(v) SMT/SEL growth pattern (intraluminal growth or extraluminal growth). SMT/SEL is differentially diagnosed by the above five findings of EUS (**Figures 6 & 7**).[8,10,11] The echo level is classified as hyperechoic for the third layer of the gastric wall (submucosa), isoechoic for the liver or spleen, hypoechoic for the fourth layer (muscularis propria), and anechoic for degassed water.[11] Lipomas, cysts, varices, and extraluminal compressions (such as those caused by a liver cyst, splenic artery, or splenic artery aneurysm) present with characteristic EUS findings, allowing for a definitive diagnosis based on EUS images alone (**Figure 7**).[10] However, it is difficult to infer the histological diagnosis of lesions such as GIST, leiomyoma, schwannoma, NET, malignant lymphoma, SMT/SEL-like carcinoma, metastatic tumors, or aberrant pancreas which are all depicted mainly as hypoechoic or isoechoic masses on EUS (**Figure 8**).[10,12,13] Differential diagnosis of these lesions is performed by histological diagnosis using EUS-FNA, as described later.

(3) Determining the indications by EUS for endoscopic treatment

EUS allows for easy assessment of the layer of origin and tumor size of SMT/SEL. NET that is less than 1 cm in size, presents as an iso- to hypoechoic solid mass, is confined to the third layer, and shows no regional lymph node enlargement, can be treated with endoscopic resection methods such as endoscopic submucosal dissection (ESD). In the case of GIST, which is an isoechoic or hypoechoic mass with continuity to the fourth layer without metastasis, surgical local excision is generally selected.

6. Histological Diagnosis of Gastric and Duodenal SMT/SEL by EUS-FNA

(1) EUS-FNA

Curved linear array or linear echoendoscopy is employed for visualization of the ultrasound images parallel to the endoscopic axis and observation of the puncture path. These echoendoscopes allow real-time observation of the target SMTs/SELs which are not visible with conventional endoscopy. They also find vessels and adjacent important organs (such as the lungs) that often cause adverse events related to puncture, in addition to the puncture path. Therefore, it is possible to collect tissue samples safely and reliably on puncturing the target lesion. **EUS-FNA is an established examination method that allows safe and reliable histological diagnosis of gastrointestinal SMT/SEL**.

(2) Clinical significance and indications

The treatment strategy for SMT/SEL varies significantly depending on their histological diagnosis, making the role of EUS-FNA extremely important. Furthermore, *the Japanese Clinical Practice Guidelines for Gastrointestinal Stromal Tumors (GIST)* of Japan Society of Clinical Oncology recommend surgery for GIST, a potentially malignant tumor, regardless of size (including 2 cm or less). This is applied if the results of EUS-FNA or biopsy are positive for GIST.[14] If EUS-FNA diagnosis is GIST, surgical local excision is performed. If SMT/SEL-like carcinoma, gastrectomy with lymph node dissection is applied. If malignant lymphoma, chemotherapy is selected. If aberrant pancreas, follow-up observation is induced. Thus, EUS-FNA provides crucial information for selecting the treatment method for SMT/SELs. **Therefore, if malignant lesions such as SMT/SEL-like carcinoma or GIST are suspected based on endoscopic or EUS findings but negative on conventional endoscopic biopsy, EUS-FNA should be performed without delay to obtain early diagnosis and early treatment.**[14,15] As mentioned above, there are many lesions in SMT/SEL that are diagnosed based on EUS findings alone, so these entities should be excluded first by **EUS. EUS-FNA is indicated mainly for hypoechoic or isoechoic solid masses that are hardly diagnosed based on EUS findings alone** (Figures 6 & 9).[8,12]

(3) Procedure (Figure 10)[10]

(i) Visualization: SMT/SEL are visualized on the EUS image.
(ii) Safe puncture route: A safe puncture route is chosen to prevent peritoneal dissemination and bleeding. This route avoids penetrating of the gastroduodenal wall or tumor, and passing through any intervening vessels, which are confirmed using color Doppler.
(iii) Puncture depth: First, measure a safe puncture distance along the chosen route to prevent tumor penetration which can cause intra-abdominal hemorrhage, or peritoneal dissemination. Then, securely fix the handle stopper to ensure the needle's maximum protrusion matches this distance.
(iv) Puncture: The stylet is retracted approximately 10 mm to make the needle tip sharp. When the appropriate puncture route is visualized, the needle is punctured rapidly.
(v) Sample acquisition: Once the needle tip is fully inserted into the target, the stylet within the needle is pushed out to expel any mucosal or submucosal tissues that possibly have been introduced during the puncture. The stylet is then completely removed, and a 20 mL syringe is used to apply negative pressure. The needle is moved back and forth within the SMT/SEL area. This task is repeated more than

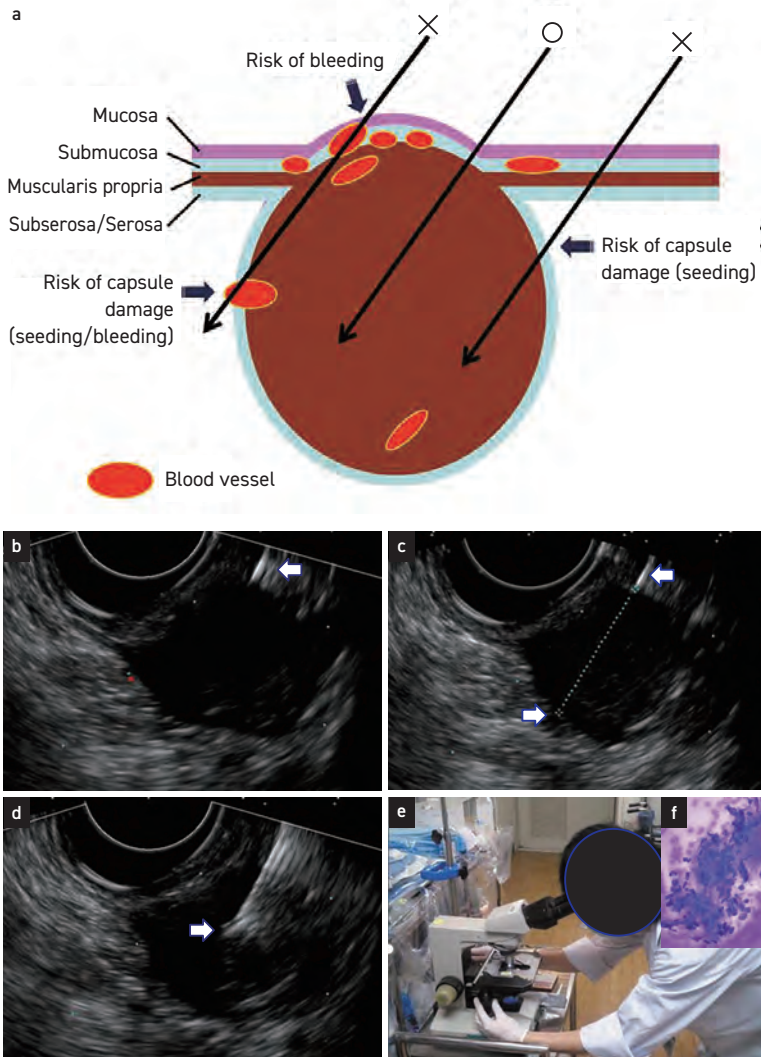


Figure 10 **Procedure of EUS-FNA (Case of a 1.5 cm GIST on greater curvature of the gastric angle).**

(a) Diagram of puncture route selection. The circle indicates appropriate routes; crosses indicate inappropriate ones.
(b) Color Doppler EUS image before FNA shows a 1.5 cm hypoechoic solid mass with continuity to the fourth layer of the gastric wall. The outer sheath of the puncture needle (left arrow) is fixed to the tumor surface, and no vessels are seen along the planned puncture line.
(c) Measurement on EUS image before FNA determines the safe puncture distance between the needle sheath (left arrow) and the opposite tumor surface (right arrow).
(d) EUS image during puncture shows the needle tip (right arrow) within the tumor.
(e) ROSE (rapid on-site evaluation) in the endoscopy suite.
(f) Hemacolor stain during ROSE confirms appropriate specimen with spindle-shaped tumor cells.
(Modified from Literature 10)



Figure 11 Types of puncture needles.

(a) Menghini-type FNA needle: EZ Shot 3 Plus, 22G, Olympus
(b) Franseen-type FNB needle: Acquire, 22G, Boston Scientific
(c) Fork-tip-type FNB needle: SharkCore, 22G, Covidien

20 times while the needle direction is slightly changed, to obtain an adequate sample.

(vi) Rapid on-site cytological examination (ROSE): After needle withdrawal, ROSE is performed in the endoscopy room. If an adequate amount of appropriate specimen is obtained, the examination is completed. ROSE is effective in improving the diagnostic rate of EUS-FNA and should be performed whenever possible.[15] Pathological examination, including immunohistochemical staining, is performed on the obtained specimen.

(4) Needle selection

(i) Needle gauge

Needles with gauges of 25G, 22G, and 19G are commonly used. 19G needles are thicker and stiffer, allowing for a larger sample volume but making angled punctures more difficult and slightly increasing the incidences of adverse events. 25G and 22G needles allow for easier angled punctures and show the lower incidences of adverse events, making them the first choice in routine clinical practice.

(ii) Needle tip shape (**Figure 11**)

Previously, FNA needles (such as the Menghini needle) were commonly used. However, in recent years, fine needle biopsy (FNB) needles with new needle tip shapes such as the Franseen needle and Fork-tip needle, have become more widely used for obtaining larger tissue samples.

(5) Procedural outcomes and adverse events

Studies have reported histologic core procurement rate and diagnostic accuracy of 80.6% vs. 94.9% and 64% vs. 87.9%, respectively, for FNA needles and FNB needles, indicating that FNB needles are superior.[16] Additionally, FNB needles have been reported to have higher diagnostic yield (81% vs. 45%) for small SMT/SELs measuring 2 cm or less.[17] The incidence of adverse events is 3.9% (sepsis) for 19G needles, but nearly 0% for 22G and 25G needles.[10]

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Kazuya Akahoshi and Hideo Yanai

4 Endoscopic Mucosal Resection

Introduction

In recent years, endoscopic treatments for early gastric and esophageal cancer have primarily involved endoscopic submucosal dissection (ESD) which offers a high en bloc resection rate. However, practitioners performing ESD should first master the technique of endoscopic mucosal resection (EMR). For duodenal lesions, the incidence of ESD-related adverse events is high, and the procedure has not become as widely adopted as it has for gastric cancer. Therefore, EMR techniques are crucial and require a thorough understanding of nuts and bolts of EMR techniques, such as underwater EMR (UEMR).
This section provides a detailed explanation about the indications, techniques, and adverse events of EMR in the treatment of gastric and duodenal conditions.

1. EMR for Gastric Diseases

(1) Indications

According to the Guidelines for Endoscopic Submucosal Dissection and Endoscopic Mucosal Resection for Early Gastric Cancer (the second edition), lesions with absolute or expanded indications of ESD for early gastric cancer should be treated with ESD (evidence level B, recommendation grade.[1)] For gastric diseases, lesions deemed amenable to en bloc resection with EMR are candidates for the procedure. The related reports indicate that the en bloc resection rate of EMR decreases for tumors larger than 1 cm in size.[2-4)]
Nevertheless, whereas EMR has a higher local recurrence rate than ESD, studies have shown no significant difference in survival rates between the two methods.[5)] Furthermore, EMR is associated with fewer complications than ESD.[6)] Although EMR has a lower en bloc resection rate, it is a safe and time-efficient technique. Its primary indication is lesions smaller than 1 cm in size, although certain locations and macroscopic types could preclude en bloc resection. In practice, it is critical to select appropriate cases carefully.
The Clinical Practice Guidelines for Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN) (second edition 2019[7)] also highlights the utility of EMR using the suction method or two-channel videoendoscope, demonstrating their effectiveness.[8,9)]

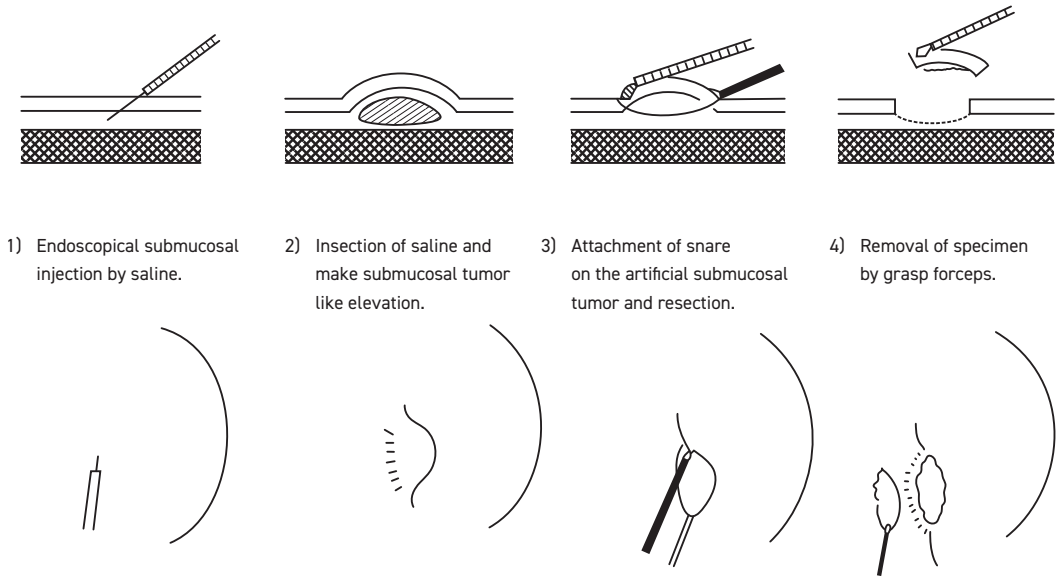


Figure 1 Method of strip biopsy.

(Cited from Literature 10)

(2) Techniques

EMR involves lifting the lesion by submucosal injection of liquid, followed by resection using a snare and electrocautery. This technique is generally categorized into two primary approaches: the strip biopsy method and the suction method.

1) Strip biopsy[10)]

In its original form, this method utilized a two-channel fiberscope (GIF-2T). A saline solution (3–5 mL) was injected submucosally beneath the lesion to elevate it. One side of the lesion used to be fixed with a grasper, followed by snaring the lesion and resection using high-frequency electrocautery (**Figure 1**). Currently, this technique is performed with the multi-bending scope (Olympus GIF-2TQ260M) instead of the two-channel fiberscope (GIF-2T). When a single-channel scope is used, the lesion is bulged similarly to colorectal EMR procedures, and the snare is directly applied (**Figure 2**).

2) Suction method[11-13)]

Several suction-based EMR techniques have been reported, including the endoscopic gastric mucosal resection using a cap-fitted panendoscope (EMR-C), endoscopic aspiration mucosectomy (EAM), and endoscopic mucosal resection using a ligating device (EMR-L) method. [11-13)]

In EMR-C method, a cap is attached to the tip of the endoscope and saline solution is injected locally into the submucosa to bulge the target lesion, which is then suctioned into the cap and resected with a snare (**Figure 3**).[11)] Five types of caps (provided from Olympus) are currently available for this method.

EMR-L method adopts the endoscopic variceal ligation (EVL) technique for treating esophageal varices. After submucosal injection of saline, the target lesion is suctioned, and an O-ring is applied at the base. The lesion is then resected with applying a snare at the base of the O-ring. The EMR-L method has demonstrated effectiveness in managing type I gastric neuroendocrine tumors (Rindi type I NETs).[8)]

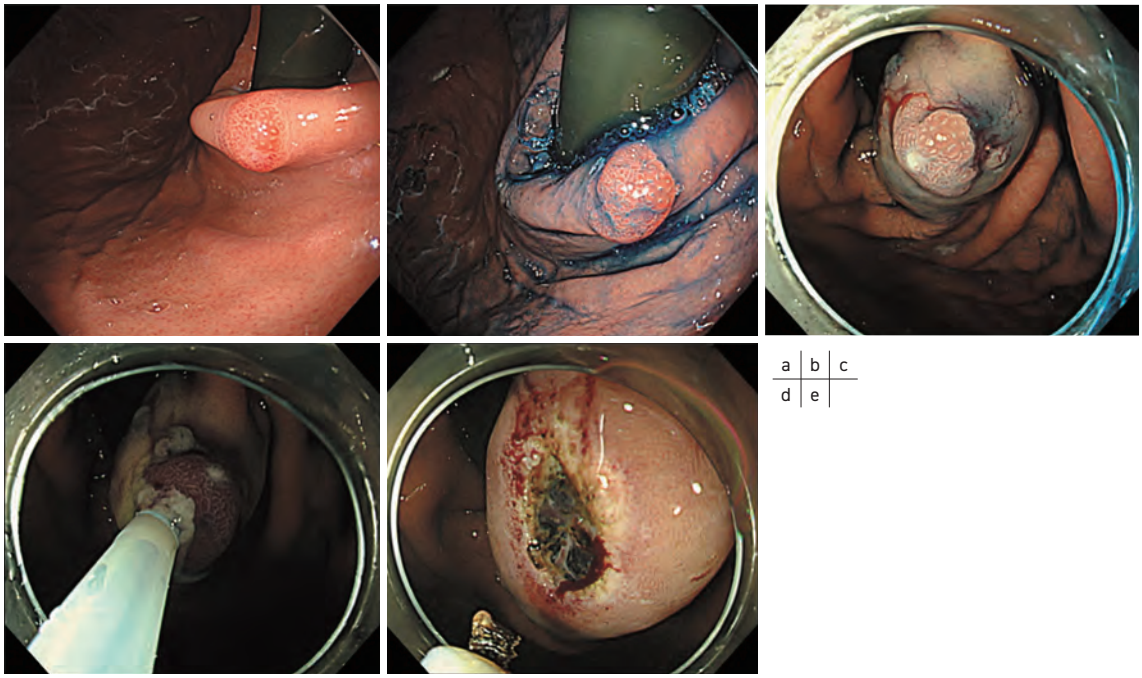


Figure 2 Gastric EMR using a single-channel endoscope.

a: A type 0-IIa lesion, 6 mm in diameter, is located on the anterior wall of the cardia.
b: Indigo carmine dye is sprayed over the target mucosa.
c: Submucosal injection of saline is performed.
d: Snaring of the elevated mucosa is carried out.
e: The ulcer base is observed after resection.

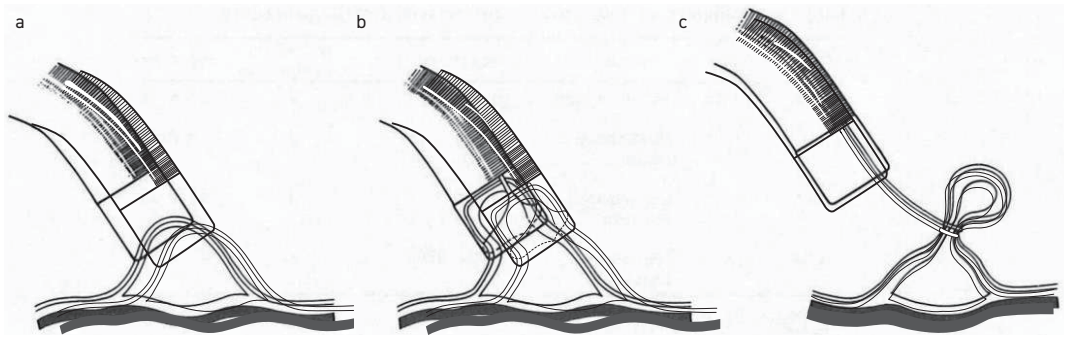


Figure 3 EMR-C method.

a: Target mucosa is fixed to the tip of plastic cap under mild endoscopic suction.
b: A snare is open inside the plastic cap widely.
c: Target mucosa including a lesion is tightly snared and resected by electrocauterization.
(Cited from Literature 11)

(3) Adverse event

1) Perforation

The incidence of perforation following EMR is reported to be 1.2%,[6] significantly lower than 3.6% in ESD. [6] If perforation accident occurs, the site should be immediately sutured with clips. Unlike ESD,

perforation in EMR is typically identified after snaring and resection. This makes post-perforation management easier. To avoid capturing the muscularis mucosae during snaring, the technique involves moving the snare back and forth after it has been tightened, or slightly loosening it first before applying the same motion. This approach helps reduce the risk of involving the muscle layer.

2) Delayed perforation

Though rare in EMR, delayed perforation could occur under circumstances such as difficulty in bleeding control at the ulcer bottom If muscularis propria is exposed at the ulcer bottom, prophylactic closure of the wound using clips is recommended. The feasibility of clip closure decreases depending on when a delayed perforation site is detected. If oral intake has already started by the time the perforation is detected, there is a higher risk of peritonitis. In such cases, early surgical consultation becomes necessary.

3) Hemorrhage

In cases of bleeding, arterial bleeding is typically managed with hemostatic forceps or hemostatic clips. Minor bleeding is often managed by coagulation with the tip of the snare.

2. EMR in Duodenal Diseases

(1) Indications

EMR for superficial duodenal epithelial tumors is only indicated when there are no metastases. Therefore, only lesions diagnosed preoperatively as either adenoma or adenocarcinoma in situ are considered indication for this procedure.[14] However, preoperative biopsy-induced submucosal fibrosis not only complicates endoscopic resection but also results in low diagnostic accuracy rates of 68%–71.6%.[15,16] Furthermore, the accuracy of endoscopic diagnosis using image-enhanced endoscopy (IEE) is limited to approximately 78.8% to 87%,[17-19] reflecting the challenges posed by the rarity of these diseases and the lack of established preoperative diagnostic strategies. Consequently, in clinical practice, the procedure often serves as a diagnostic therapy (complete biopsy). However, due to the anatomical characteristics of duodenum, duodenal EMR is challenging compared to other organs and carries an increased risk for severe adverse events. Thus, the high level of technical proficiency and informed consent are imperative. Regarding duodenal neuroendocrine tumors (NETs), lesions measuring 1 cm or less in diameter that are confined to submucosal invasion (sm) have been shown to have a low metastasis rate. For cases with clinically node-negative status (cN0), endoscopic resection is considered. Techniques such as EMR, ligating-assisted EMR (EMR-L), or ESD are employed, but due to limited evidence, consensus on their use remains unestablished.[7]

(2) Techniques

Typically, EMR for duodenum follows the principles of gastric EMR. This section will focus on the underwater EMR (UEMR) technique.

Duodenal UEMR (Figure 4)

By filling the duodenal lumen with saline or gel, the lesion is buoyed and snared before electrocautery

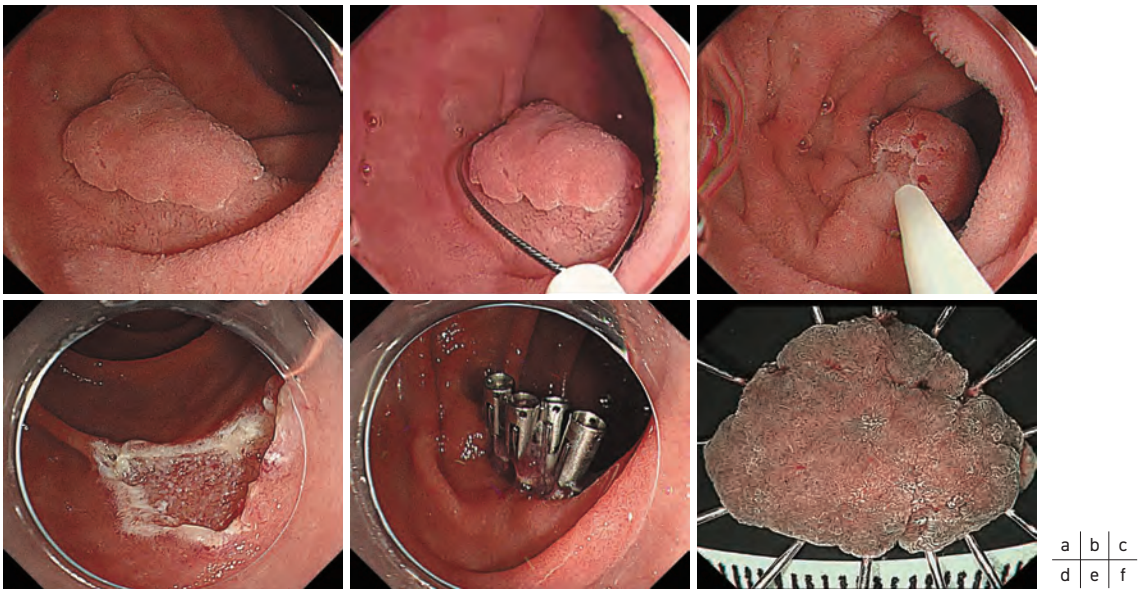


Figure 4 Duodenal UEMR.

a: The lumen is filled with saline.
b: Buoyed up by the saline, the lesion is ensnared.
c: Resection is performed with electrocautery.
d: Residual tissue is confirmed at the margin of the post-resection ulcer.
e: Clips are applied to the ulcer margin to prevent adverse events.
f: A 17x13 mm high-grade adenoma is resected with negative lateral and vertical margins.

resection. The buoyancy effect lifts the lesion, reducing the risk of perforation even without submucosal injection. As submucosal injection is unnecessary, the procedure time is shorter, and the absence of bleeding allows for clear visualization during snaring. In the bulbous region, where Brunner's glands and fibrosis are well-developed, the lesion could not float by buoyancy effect. In the descending and horizontal lumen, the lesion is easily lifted by fluid injection, and this process is suitable for en bloc resection of lesions approximately 15 mm in size.[20)]

(3) Adverse event

1) Intraoperative perforation

The duodenal wall is thin, and the existence of Brunner's glands and fibrosis in the submucosa makes EMR difficult to achieve adequate submucosal lifting through injection. Additionally, the narrow lumen and active peristalsis and respiratory movements limit snaring maneuvers, thereby increasing the risk of perforation (perforation rate: 0.7-1.6%).[21,22)] Once a perforation event occurs, leakage of gastric acid, bile, and pancreatic juice into the retroperitoneum causes to severe adverse events. The perforation site should be immediately closed with endoclips. If the closure is impossible, surgical intervention should be promptly considered.

2) Intraoperative hemorrhage

Hemostasis is achieved with endoclip or hemostatic forceps. Due to the thin muscularis propria, excessive electrocautery increases the risk of perforation, and bipolar forceps is used in some cases. Careful attention is paid for clip usage to avoid tearing the thin muscularis propria with the clip jaws.[23)]

3) Delayed adverse events

A unique adverse event of duodenal EMR is delayed bleeding or perforation due to exposure of the ulcer base to gastric acid, bile, and pancreatic juice (delayed bleeding rate: 1.9-3.0%, delayed perforation rate: 0.15-0.6%).[21, 22)]

While delayed bleeding could often be managed endoscopically, delayed perforation requires surgical intervention due to the risk of severe adverse events. To prevent delayed adverse events, prophylactic measures such as endoclip closure (**Figure 4e**) or covering the ulcer bottom are recommended.[14)]

Conclusion

While ESD has become the standard procedure for gastric lesions, EMR is now selected for a limited range of cases. Recent examples include foveolar-type gastric tumor with a raspberry-like appearance and gastric cancers associated with fundic gland polyps. Although its indications are narrowing, EMR remains a significant procedure, especially for the aging population.

For duodenum malignancy, mastering the underwater EMR technique is essential since the risk of adverse events associated with ESD is high. Lesions measuring 15 mm or less, such as adenomas and adenocarcinomas in situ, are well-suited for UEMR. Given the potential for severe adverse events, constant and close communication with surgical staff is crucial.

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5 Endoscopic Submucosal Dissection

Endoscopic submucosal dissection (ESD), as defined in the Japanese Gastric Cancer Treatment Guidelines,[1] is a procedure utilizing high-frequency devices to incise target mucosal lesions and dissect their submucosae (**Figure 1**). ESD is a technically demanding procedure requiring a considerable variety of devices, compared with endoscopic mucosal resection (EMR) which involves the use of a steel snare to perform electrocautery resection covered under insurance for 6,460 points. Hence, insurance reimbursement for gastric ESD is set at 18,370 points. For duodenal ESD, reimbursement is higher at 21,370 points, because the procedure is even more complex and involves ulcer closure to prevent severe delayed adverse events. This section provides practical and educational instructions for daily clinical practice. For supplemental details, it is helpful to refer to the various guidelines issued by the Japan Gastroenterological Endoscopy Society and explanatory materials on specific techniques and devices.

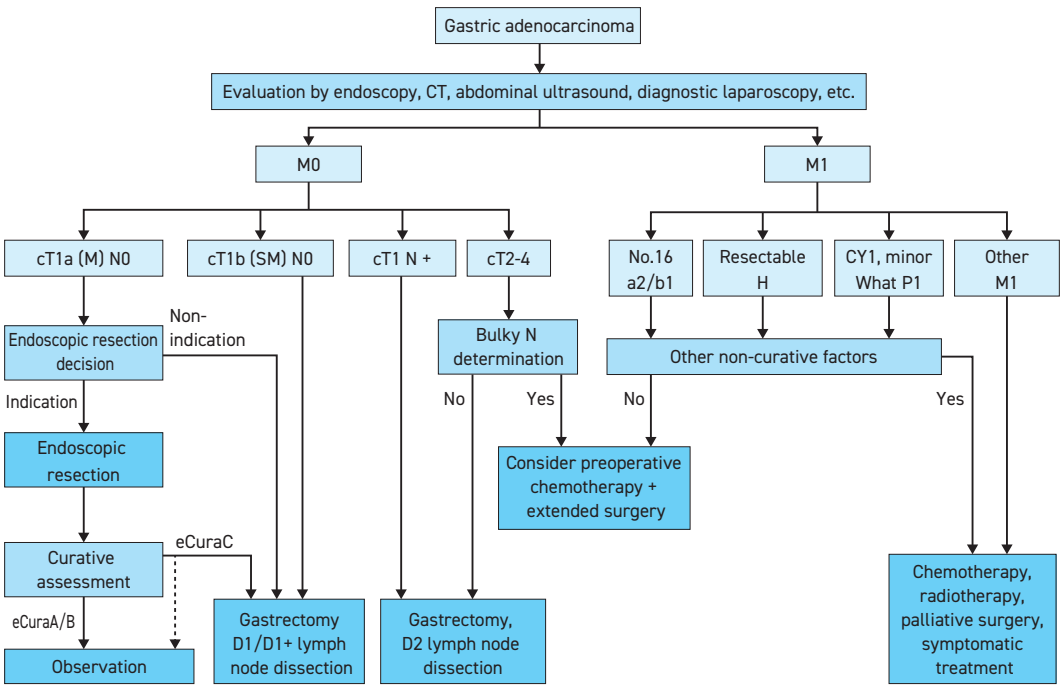


Figure 1 Algorithm for treatment selection recommended in routine clinical practice.

(Modified from Literature 1)

Table 1 Indications for endoscopic resection based on tumor factors.

Invasion depth	Ulcer	Differentiated	Undifferentiated
cT1a (M)	UL0	≤ 2 cm >2 cm	≤ 2 cm >2 cm
		★ ■	■ □
	UL1	≤ 3 cm >3 cm	
		■ □	□
cT1b (SM)		□	□

★ :Absolute indications for EMR/ESD ■ : Absolute indications for ES

□ : Relative indications

cT1a(M): Adenocarcinoma in situ (preoperative diagnosis), cT1b(SM): Submucosal invasion carcinoma (preoperative diagnosis), UL: Ulcer (scar) findings

(Cited from Literature 7)

1. Indications

(1) Treatment selection

- Treatment options for gastric cancers include endoscopic resection, surgical resection (open surgery, laparoscopic surgery, or organ-preserving surgery), chemotherapy (postoperative adjuvant or preoperative neoadjuvant), and palliative care (**Figure 1**).
- For gastric cancers, endoscopic resection (local resection without dissecting lymph nodes) is generally considered for stage IA disease, where the final decision is based on the technical feasibility of the procedure.
- While ESD for duodenal lesions is covered by insurance in Japan (K653), there is no clear evidence-based guideline for selecting patients for this procedure.
- Due to the high technical difficulty and risk of serious adverse events associated with duodenal ESD, it is not yet a widely performed procedure.[2,3)]

(2) Indications for ESD (Table 1)[1)]

- **General principles:**

(i) Extremely low risk of lymph node metastasis (curative)

(ii) yLesion size and location suitable for en bloc resection (local control)

- **Definitive indications:**

The decision to use EMR or ESD is determined by the feasibility of en bloc resection, resulting in distinct indications for each procedure.

EMR/ESD indications:

Lesions meeting the following criteria:

(i) T1a macroscopic carcinoma in situ ≤ 2 cm

(ii) Well-differentiated adenocarcinoma (tubular or papillary)

(iii) Any macroscopic types
(iv) No histological fibrosis (UL)

ESD indications:

Lesions meeting the following criteria:

(i) Well-differentiated T1a with UL0 > 2 cm
(ii) Well-differentiated T1a with UL1 ≤ 3 cm
(iii) Undifferentiated T1a (poorly differentiated adenocarcinoma, signet ring cell carcinoma, mucinous carcinoma) with UL0 ≤ 2 cm

- When both differentiated and undifferentiated types are present, the predominant type should be specified.

- **Expanded indications:**

Recurrent local carcinoma in situ is applicable under the expanded indication when it arises after an initial EMR or ESD performed with absolute indication criteria, and the lesion has been confirmed as a differentiated type and classified as eCuraC-1.

- **Relative indications:**

For early gastric cancer patients who are unsuitable to undergo surgical resection due to age or comorbidities, ESD is applicable based on the estimated risk of lymph node metastasis. When the procedure is to be performed, it is essential to thoroughly explain the risks, such as the possibility of lymph node metastasis, and obtain the patient's understanding and consent.

Indications for duodenal ESD

While there are no clear guidelines, ESD could be considered for early carcinoma or lesions suspected to be carcinoma in situ, where complete resection is difficult with conventional EMR, as well as lesions that could hardly be resected by EMR due to the effects of preoperative biopsy or prior treatments.[4)]

2. Procedural Preparation

(1) Informed consent

- Patients should be provided with comprehensive written explanations about the diagnosis, treatment objectives, procedural details, clinical outcomes, and risks involved, particularly in comparison with EMR. Potential adverse events such as perforation (5%), postoperative bleeding (5%), the need for blood transfusions (less than 1%), emergent surgery for bleeding or perforation (less than 0.3%), and rare mortality should be disclosed, ideally referencing institutional data. Moreover they should also be explained about management approaches, alternative treatments, and risks related to comorbidities and overall health status.
- It is essential to clarify that resection (e.g., ESD) and curative treatment are different. Even if an R0 resection is achieved, there is a chance of 3 to 40% that the resection could be deemed non-curative. In such cases, it is crucial to fully explain that an additional surgical resection process is necessary to achieve a cure.
- It is also important to note that recurrence or metastasis could occur even after curative resection. For lesions falling under expanded or relative indications, surgical resection is still regarded as the standard treatment, whereas ESD is considered an approach within the framework of clinical research.

(2) Medical history assessment

- A thorough review of past medical history is crucial, including prior diagnoses (e.g., cardiac diseases, glaucoma, hypertension, cerebrovascular diseases, prostatic hyperplasia), surgical history, routine medications, drug allergies, and use of pacemakers.
- For patients on **antiplatelet agents** (e.g., aspirin, ticlopidine, clopidogrel) or **anticoagulants** (e.g., warfarin), it is important to refer to the Japan Gastroenterological Endoscopy Society's *Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment*[5] and *Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment: 2017 Appendix on Anticoagulants Including Direct Oral Anticoagulants*.[6] In particular, the prescribing physicians should be called for assessing whether it is necessary to discontinue, interrupt, or substitute the medication.

(3) Preoperative general examinations

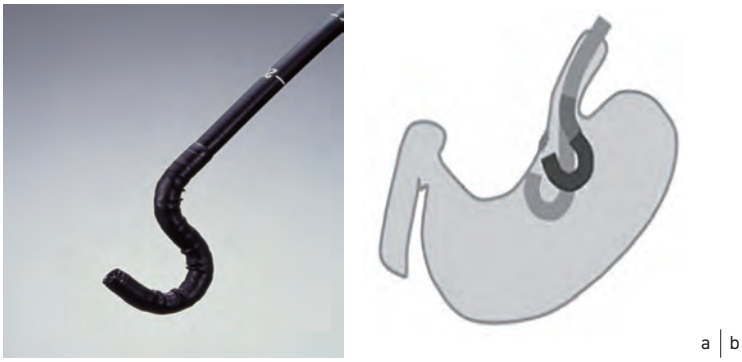
Preoperative assessments should include blood tests (blood typing, infection screening for HBV, HCV, syphilis, etc.), general biochemical and coagulation tests, and *Helicobacter pylori* antibody tests. Additional tests include electrocardiography, pulmonary function tests, chest X-rays, and abdominal CT or ultrasonography if metastasis risks are present.

(4) Preoperative diagnosis[7]

- Detailed preoperative evaluation of the lesion's location, size, invasion depth, histologic type, and ulcer findings is essential, following the ***Japanese Classification of Gastric Carcinoma***.[8]
- The diagnosis of ulcer-related adverse events depends on the presence of active ulcers or ulcer scars. Histopathologically, ulcers are defined as mucosal defects reaching UL-II or deeper. Active ulcers observed during endoscopy are open ulcers with whitish exudates of moderate depth, excluding superficial erosions. Healed or scarred ulcers are identified by mucosal or fold convergence to a single point.
- Indigocarmine or other blue dyes are useful for diagnosis on the horizontal extent of lesions, enabling accurate delineation of about 80% of early gastric cancers suitable for ESD.[9]
- Determining the extent of some differentiated and undifferentiated early gastric cancers could be challenging by regular white light endoscopy alone. It is necessary to take biopsies of non-cancerous appearing tissue outside the tumor and consult pathology to clearly define the incision line.
- If diagnosis of the horizontal extent is challenging with standard white light endoscopy, magnified imaging with image-enhanced endoscopy (IEE) is beneficial.[10]
- While not mandatory, endoscopic ultrasonography probably assists in assessing invasion depth and ulcer findings.

(5) Clinical pathways

- ESD treatment offers a relatively predictable process for inpatient care from admission to discharge, making clinical pathways suitable. The typical hospitalization period ranges from 3 days to a week, depending on regional and institutional capacity, or judgement by practitioners. Medication protocols also vary among institutions.



a | b

Figure 2 **Multi-bending endoscope.**

a: Actual image of the multi-bending endoscope
b: Schematic diagram illustrating the configuration of the multi-bending scope
(Cited from Literature 11)

3. Practical Aspects of ESD

(1) Medical devices and materials

- High frequency electrosurgical units equipped with endoCUT mode or Pulse Cut mode (a combination of soft coagulation and incision waves) are recommended. Such electrosurgical generators include the ESG-100/ESG-300 (Olympus) and VIO300D/VIO3 (ERBE). The ESG-300 supports modes like BlendCut and Power Coag, while the VIO3 offers Swift Coag, Dry Cut, and Twin Coag which is the blended mode of cutting and coagulation waves. The optimal settings for high-frequency knives vary among institutions and users. In reality, consultation of specialized documents is required to obtain detailed information.
- Electronic scopes equipped with forward water-jet function are recommended, though standard forward-viewing scopes are possible. Depending on lesion locations, two-channel scopes or multi-bending scopes prove useful (**Figure 2**).[11] In cases requiring retroflexion, such as in the duodenal bulb or cardia, small-caliber endoscopes with enhanced maneuverability are advantageous. The best scope should be selected based on the nature and condition of lesions.
- There are several types of high-frequency knives with insulated tips:
  IT knives for lateral cuts using the blade such as ITknife from Olympus, SAFEKnife from FUJIFILM (**Figure 3**); Tip-based knives for forward-direction cuts such as DualKnife from Olympus, FlushKnife from FUJIFILM, B-knife from Zeon Medical, Endosaber from SB-KAWASUMI LABORATORIES, ProKnife from Boston Scientific (**Figure 4**); and Scissor-type knives or SB Knife from SB-KAWASUMI LABORATORIES and ClutchCutter from FUJIFILM (**Figure 5**). Please refer to the documentation for each device for specific information and details.
- Traction devices include disposable distal attachments, transparent hoods, EndoLifter (Olympus), and external grasper. When using a hood, endoscopists should account for the difference between the visualized distance and the actual distance. Traction methods using a hemoclip with dental floss, the Multi-Loop Traction Device (Boston Scientific) (**Figure 4**), and the S-O clip (Zeon Medical) are effective for difficult-to-resect areas such as the fundus, greater curvature of the upper gastric body, or duodenum (**Figure 5**).[12,13]

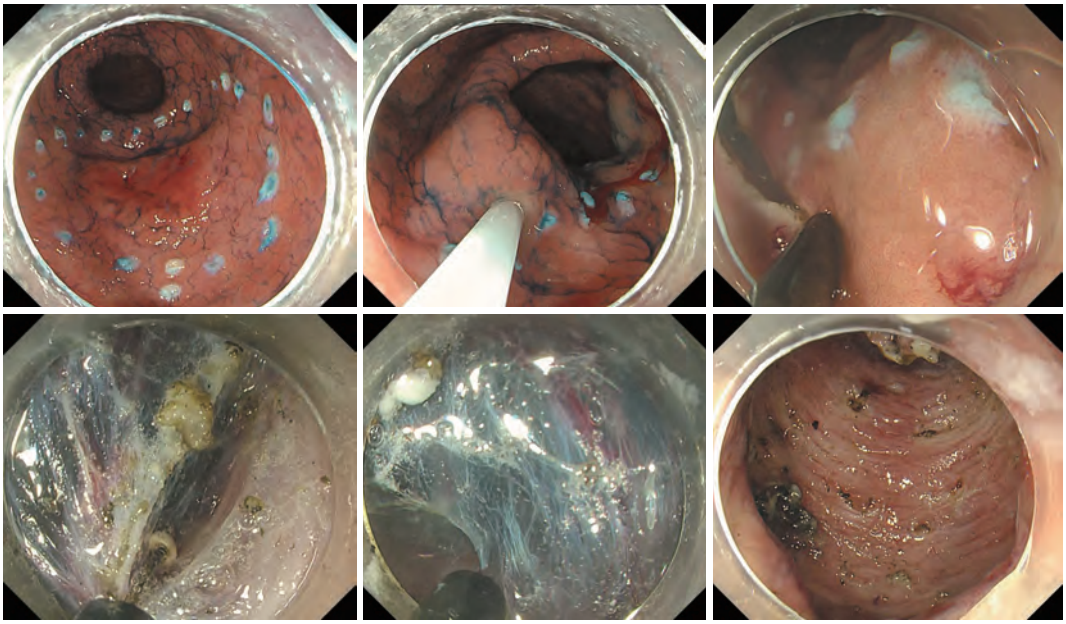


Figure 3 Gastric ESD using an ITknife 2.

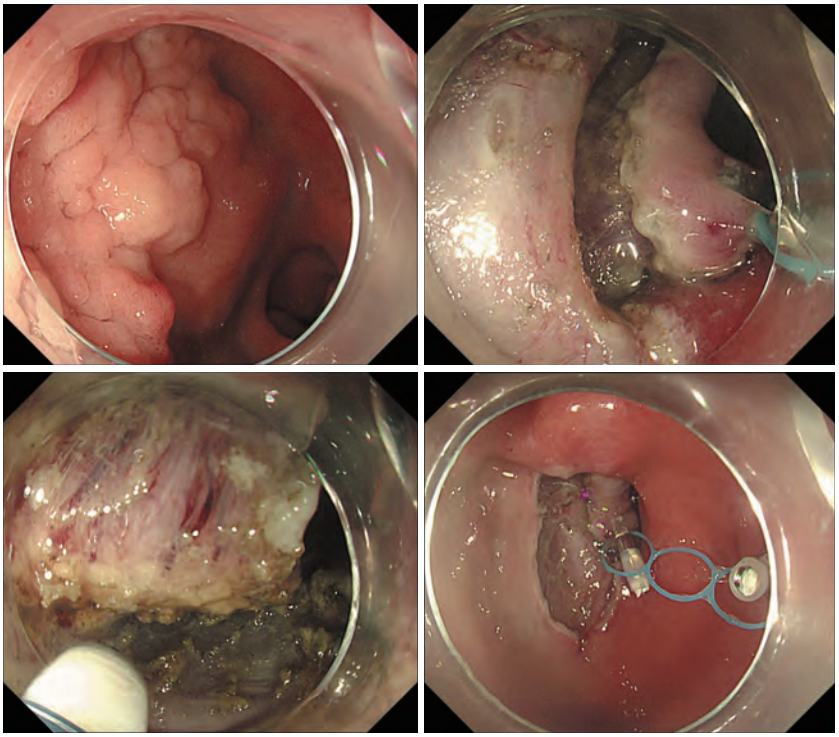
a | b | c
d | e | f

a: Markings are made around the lesion with a tip-type device.
b: Local submucosal injection of hyaluronic acid is performed around the marking area to create an elevation.
c: Using a downward angulation, mucosal incision is performed from the distal to proximal side, with the tip pressed against the gastric wall.
d, e: Submucosal dissection proceeds directly above the muscularis propria while applying sufficient tension to the submucosal connective tissue.
f: After dissection, bleeding source and exposed blood vessels on the ulcer base are managed with preventive hemostasis.

- Techniques like underwater endoscopic mucosal resection (UEMR), water-pressure method, and gel immersion ESD (**Figure 5**) leverage water pressure or buoyancy as traction forces, which are highly effective for lesions in the narrow-lumen of duodenum.[4,14)]
- Common hemostasis tools include hot biopsy forceps, hemostatic forceps, clips, and argon plasma coagulation (APC).
- A 25G needle with high flow rate is recommended. Injection fluids include normal saline, Glyceol® (off-label), **hyaluronic acid preparations,** and **sodium alginate solutions**.
- For patients without respiratory diseases including COPD, **CO_2 insufflation** helps reduce intraoperative and postoperative discomfort and prevents severe adverse events.

(2) Preoperative preparation, intraoperative management, and medication

- It is common practice to administer **proton pump inhibitors (PPIs)** or **potassium-competitive acid blockers (PCABs)** from the day before the procedure to 4 to 8 weeks postoperatively.
- On the day of the procedure, patients are required to fast, although water intake is permitted. Other preparations are consistent with standard preoperative measures for upper gastrointestinal endoscopy.
- Intravenous access is secured, and continuous infusion is maintained. For intraoperative fluid replacement, Ringer's solution is preferred to compensate for blood volume loss caused by bleeding, provided there are no cardiac concerns.
- Antispasmodics: Glucagon is the only antispasmodic agent approved for insurance-covered endoscopic



a | b
c | d

Figure 4 **Duodenal bulb ESD using FlushKnife with multi-loop traction device.**

a: A type 0-IIa lesion is spread across the anterior wall of the duodenal bulb.
b: Following circumferential mucosal incision, the submucosa is exposed from the gastric side by the traction device.
c: For dissection at the lesion's leading edge, the knife is maneuvered under the submucosa with the cap whenever possible, thereby allowing clear visualization of the appropriate dissection plane and proceeding with incision centrally toward the lateral and deeper areas.
d: Even when the lesion extends over the pyloric ring, the traction device allows for adequate visualization and operative field expansion.



a | b | c

Figure 5 **Duodenal ESD using scissor-type knife with gel immersion method.**

a: A type 0-IIa lesion extends over more than half of the inner wall on the cranial side of the papilla. Due to poor access, full observation of the lesion is challenging.
b: After sufficient luminal degassing, gel immersion is achieved via a secondary water delivery channel by a pump. Gel is applied to expose the submucosa, and dissection is carried out at the middle submucosal level with a scissor-type knife.
c: Even when bleeding occurs, the gel-filled environment prevents diffusion of blood, allowing easy identification of the bleeding source in the lower left of the visual field.

treatments, but butylscopolamine (Buscopan®) and l-menthol (Minclea®) are also frequently used in clinical practice. Noticeably, attention must be paid to contraindications and precautions for each drug. For instance, in narrow-angle glaucoma, both butylscopolamine and benzodiazepines are

contraindicated as per their package inserts. Likewise, caution is required with narcotic analgesics such as pethidine hydrochloride, considering their cholinergic properties.

- Typically, modified neuroleptanalgesia (NLA) is employed for producing analgesia without loss of consciousness. Diazepam or midazolam is used for sedation together with pethidine hydrochloride, buprenorphine hydrochloride, or pentazocine for pain-relieving. For prolonged procedures such as ESD, dexmedetomidine is also selected. On use of propofol, attention to sedation depth is critical, and its option is generally restricted to patients classified as ASA-PS I or II, under the supervision of physicians trained in airway management. For detailed recommendations, it is useful to refer to the *Guidelines for Sedation in Gastroenterological Endoscopy* (second edition) from the Japan Gastroenterological Endoscopy Society.[15)]
- In **elderly patients**, especially those with comorbidities, or cases expected to involve lengthy procedures, general anesthesia with closed-circuit intubation should not be avoided.
- Continuous intraoperative monitoring of blood pressure, oxygen saturation, electrocardiogram, and pulse rate is essential with recording data. Recently, capnography-compatible mouthpieces have become available, offering a rapid means to assess respiratory status.

(3) Procedure methodology

1) ESD using ITknife (ITknife 2) (Figure 3)

(I) Lesion observation

Once the endoscope advances into the stomach, and the diagnostic boundaries of the lesion are clarified based on information from the preoperative endoscopic biopsy sites, image-enhanced endoscopy, and dye-based endoscopic findings.

(II) Marking (**Figure 3a**)

Coagulation marks are assigned by a tip knife or APC at intervals of 2–3 mm, positioned approximately 3–5 mm outside the lesion's margin. To facilitate orientation during specimen processing, an additional mark is placed on either the proximal or distal side of the resected tissue.

(III) Submucosal injection (**Figure 3b**)

A submucosal injection is administered with the needle into slightly underneath the marking area, creating a sufficient mucosal protrusion. The injection solution consists of saline or Glycerol®, with small amounts of epinephrine or indigocarmine added depending on the practitioner's intention. According to the situation, such as lesions near the cardia or pylorus, or those with ulcer scars, sodium hyaluronate is used, as necessary.

(IV) Pre-cutting and circumferential mucosal incision

A 1–2 mm precut incision is made with the tip knife into the mucosa approximately 5 mm beyond the marking point to allow insertion of the ITknife 2. In practice, care is taken to approach the muscularis propria without causing perforation.

The ITknife 2 tip is introduced into the precut incision, which makes a circumferential mucosal incision around the marking area with endoCUT mode (Pulse Cut), DRY CUT mode, or Swift Coagulation mode. The mucosal incision reaches a depth that reveals the loose connective tissue of the submucosa, facilitating smoother dissection. During cutting, the knife remains in contact with the gastric wall, thereby allowing sufficient exposure of the submucosa (**Figure 3c**). Notably, attention is taken to the blade orientation. When the rear blade of the insulated tip faces the 6 o'clock orientation, an excessively applied pressure could result in injury to the muscularis propria.

(V) Submucosal dissection

Following the completion of the circumferential incision, an additional submucosal injection produces a well-elevated bulge surrounding the lesion. Submucosal dissection is then carried out with clear visualization of the connective tissue, using endoCUT (Pulse Cut), Dry CUT, or Swift Coagulation mode depending on the procedural context. Effective dissection depends on maintaining sufficient tension on the connective tissue while the ITknife 2 moves in a direction parallel to the gastric wall (**Figure 3d, 3e**).

(VI) Specimen retrieval and mucosal defect management

The resected tissue is collected with a grasper. After retrieval, the endoscope is reinserted to confirm hemostasis. Exposed blood vessels are coagulated by hemostatic forceps, hot biopsy forceps, or APC, regardless of whether active bleeding is present (**Figure 3f**). For injuries of thicker vessels or muscularis propria, hemoclips will offer safer management.

2) ESD using tip knife

(I) Lesion observation

It is useful to refer to the procedure described under "ESD using ITknife."

(II) Marking

For tip knives, markings are performed by the same high-frequency knife intended for incision and dissection. To enhance safety, devices such as hook knives or dual knives should be used with their electrode retracted.

(III) Submucosal injection

It is helpful to refer to the details under "ESD using ITknife." This technique involves administering the submucosal injection over a targeted area of a few centimeters where the mucosal incision is intended, rather than performing the injection circumferentially in a single step. Solutions such as Glycerol® or sodium hyaluronate are preferred which offer superior retention of submucosal elevation compared to saline.

(IV) Mucosal incision and submucosal dissection

For enhanced safety, the knife is operated from the proximal side (near the endoscope) toward the distal side. This is the opposite direction typically selected with IT knives. Mucosal incisions are made gradually within the injected area, advancing a few centimeters at a time. The processes of mucosal incision and submucosal dissection are often repeated seamlessly without separating strictly until the entire circumference is incised.

Submucosal dissection follows immediately after a partial mucosal incision is completed. With the aid of devices such as a transparent cap or traction tools, the targeted mucosa is elevated from the submucosa. This elevation allows the tip of the endoscope to enter the submucosal space, which plays an important role in enabling effective dissection (**Figure 4b & 4c**).

(V) Specimen retrieval and mucosal defect management

It is helpful to refer to the procedure described under "ESD using ITknife" for specimen retrieval and mucosal defect management.

4. Adverse Events and Their Management

The most representative **adverse events** in ESD are **bleeding** and **perforation**. In addition to these, the frequency of adverse events increases with prolonged procedure times. It is important to note that there have been reports of death, although extremely rare. Endoscopists performing ESD should be well-versed in the management of adverse events.

(1) Perforation

- Generally, the incidence of intraoperative perforation is reported to be around 1 to 5%.
- It occurs commonly to problematic lesions, located in the upper body or greater curvature of the body, or accompanied by ulcer scars.
- Several treatment options are possible depending on the extent of perforation site and the patient's condition. If the patient is stable and the perforation area is not large, ESD could be continued after creating a suture line and closing it with hemoclips. If the perforation area is large and the patient is moving around seriously, the procedure should be discontinued just after closing the perforation site. Alternatively, the possibility of emergency surgery should also be considered.
- After closing the perforation site, urgent treatment should be induced including continuous negative pressure suction through a nasogastric tube, administration of antibiotics, and intravenous administration of PPIs. In most cases, conservative treatment is possible, and the perforation site is often closed spontaneously the next day.
- If signs of peritoneal irritation appear, an emergency aid should be consulted with surgeons to determine the need for laparotomy.
- Although **delayed perforation** is considered to be less than 0.1%, it often could not be treated conservatively and requires laparotomy in principle.
- Excessive cauterization of the ulcer surface contributes to **delayed perforation**. Indeed, care should be taken to avoid over-coagulation.
- Preventive measures include:

(i) Not performing incision and dissection if endoscopists feel unsure.

(ii) The plane of incision and dissection should be aligned parallelly to the curved surface of the gastric wall.

(iii) Excessive coagulation should be avoided.

(iv) Coagulation procedures are performed diligently to prevent bleeding. Should bleeding occur, it is promptly stopped, as bleeding impairs visibility and leads to blind manipulation, thereby increasing the risk of perforation.

(v) A well-considered treatment strategy is established in advance. When the strategy requires beyond the endoscopist's level of expertise, the treatment should be avoided.

(vi) Closure of the ulcer after resection for non-papillary duodenal tumors is recommended to prevent severe delayed perforation and bleeding. In addition to ordinary hemoclips, various methods such as threaded hemoclips and over-the-scope clips (OTSC) are used for closure.[4)]

When target lesions are removed from the distal side of the descending part of the duodenum and it is challenging to close the defect primarily, external drainage of the pancreatic or bile duct is also considered.

(2) Hemorrhage

1) Intraoperative

- Intraoperative bleeding is almost inevitable.
- Venous bleeding and bleeding from small arteries are often controlled with a high-frequency knife. For bleeding from large arteries, hemostatic forceps and hot biopsy forceps are selected.
- Use of hemoclips should be avoided as much as possible since they hinder subsequent procedures.

However, if hemostasis could not be achieved with high-frequency coagulation, they should be applied before the over-coagulation occurs.

- Severe bleeding that proves difficult to control could become life-threatening in some cases. In such cases, it is necessary to consider blood transfusion or emergency surgical intervention.
- It is important to note that air embolism from blood vessels could also occur, although rarely.

2) Postoperative

- Postoperative bleeding has been reported to occur up to three weeks after treatment.
- It is known that the frequency of postoperative bleeding could be reduced by coagulating visible vessels on the resected ulcer surface with hemostatic forceps, hot biopsy forceps, APC, or hemoclips.[16] However, even if the electrical current reaches the muscularis propria or serosa slightly, the patients experience abdominal pain, fever, and elevated inflammatory markers for several days.
- There have been reports that use of PPIs reduces postoperative bleeding compared to H_2 receptor antagonists.

(3) Stricture

- The frequency of stricture increases when more than half of the cardia or pylorus is resected or when dissection is performed in the anterior-posterior direction for more than 5 cm.
- Extensive resection of the antrum causes obstruction due to impaired peristalsis even without stricture of the pyloric ring. In reality, particular attention should be paid to the elderly.
- In the case of the gastric stricture, its degree is often mild and usually improves with one or several dilations, but perforation events due to dilation have been reported. Thus caution is required. There are no reports of effective stricture prevention with steroid injection which is applied after esophageal ESD.
- Malnutrition due to long-term dilation or prolonged poor emptying of gastric content could require a pyloric gastrectomy.

(4) Others

- Aspiration pneumonia, atelectasis, pulmonary embolism, abscess, and air embolism have been reported.

5. Curative Assessment

- Endoscopic resection is considered complete when the resected specimen is properly handled and a reliable pathological assessment is performed for curability.
- Pathological findings should be described according to the ***Japanese Classification of Gastric Carcinoma (15th edition)***. Elastic fiber staining like Elastica van Gieson stain or Victoria-blue/Hematoxylin-Eosin double staining is useful for identifying veins, and immunohistochemical staining with anti-lymphatic endothelial antibody (D2-40) is effective for identifying lymphatic vessels.
- Based on the pathological information of the ESD specimen, the curability is evaluated according to the ***Japanese Gastric Cancer Treatment Guidelines (6th edition)*** (Table 2),[7] and is classified into

Table 2 Assessment of curability based on tumor factors.

Invasion depth	Ulcer	Differentiated	Undifferentiated
pT1a (M)	UL0		≤ 2 cm > 2 cm
	UL1	≤ 3 cm > 3 cm	
pT1b1 (SM1)		≤ 3 cm > 3 cm	
pT1b2 (SM2)			

eCuraA eCuraB eCuraC-2

*Curability is assessed as eCuraA or eCuraB only when en bloc resection is achieved, with negative horizontal and vertical margins (HM0, VM0), and no lymphovascular invasion (Ly0, V0). pT1a (M) refers to carcinoma in situ confirmed by pathology, while pT1b (SM) denotes submucosal invasive carcinoma. UL indicates presence of ulcer or ulcer scar.
(Cited from Literature 7)

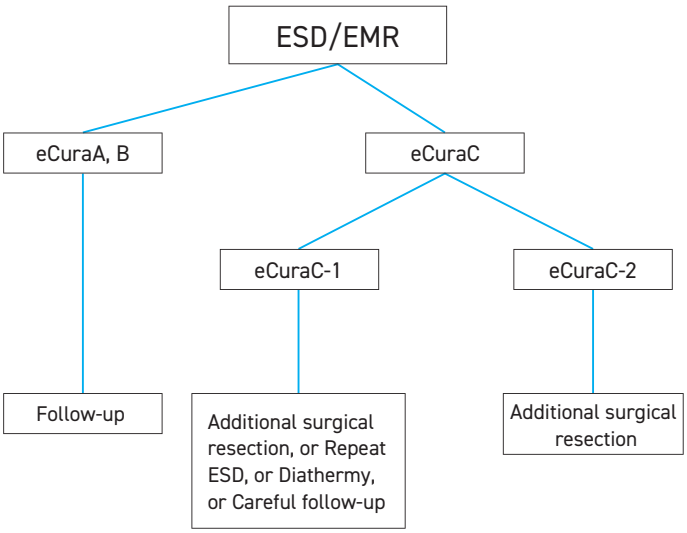


Figure 6 Therapeutic flowchart following ESD/EMR.
(Cited from Literature 7)

curative resection, curative resection beyond the absolute indication, and non-curative resection (**Figure 6**). [7]

(1) Endoscopic curability A (eCuraA): Curative resection

When the tumor is completely resected and UL0;

(i) Regardless of tumor size, if differentiated adenocarcinoma predominates and pT1a, HM0, VM0, Ly0, V0

(ii) If the undifferentiated type predominates and is 2 cm or less in long diameter, pT1a, HM0, VM0, Ly0, V0
If UL1;

(iii) If differentiated adenocarcinoma predominates and is 3 cm or less in long diameter, pT1a, HM0, VM0, Ly0, V0
However, if the undifferentiated component exceeds 2 cm in long diameter in (i), it is classified as eCuraC-2.

(2) Endoscopic curability B (eCuraB)

Although long-term results have yet been obtained, cure is expected. It refers to cases where the tumor is completely resected, differentiated adenocarcinoma predominates, and it is pT1b1 (SM1) (less than 500 μm from the muscularis mucosae), HM0, VM0, Ly0, V0, and with a long diameter of 3 cm or less. However, if there is an undifferentiated component in the SM invasion, it is classified as eCuraC-2.

(3) Endoscopic curability C (eCuraC)

This applies to cases that do not meet the criteria for eCuraA or eCuraB, and there is a possibility of residual disease. Among them, if a complete resection of differentiated adenocarcinoma is performed and only the lateral margin or piecemeal resection deviates from the criteria for eCuraA or eCuraB, it is classified as eCuraC-1. Otherwise, it is classified as eCuraC-2.

- In the case of eCuraC-1, repeat ESD, ablation, or follow-up observation could be options, depending on the facility's policy, even if informed consent is obtained from the patients.
- In the case of eCuraC-2, additional surgical resection is generally selected. If surgical resection is not performed due to reasons such as age or concomitant diseases, it is necessary to evaluate the curability with the data on risks of lymph node metastasis, local recurrence, and distant metastasis.[17] It is also required to fully explain and obtain consent from the patient that the prognosis is poor if recurrence occurs.

6. Long-term Follow-up After ESD

- After treatment, eradication of *H. pylori* infection is recommended for *H. pylori*-positive cases. Even after eradication, upper gastrointestinal endoscopy should be performed 1 or 2 times a year to check the occurrence of second primary multiple gastric cancers.
- In the case of eCuraB, it is desirable to examine the presence or absence of metastasis with upper gastrointestinal endoscopy, abdominal ultrasonography, and CT.
- If additional surgical resection is not performed but follow-up observation is selected for eCuraC-1, careful follow-up should be performed using upper gastrointestinal endoscopy.

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6 Hemostasis
(Local Injection, Clipping, Cauterization, and Hemostatic Forceps)

1. Indications for Endoscopic Hemostasis

When upper gastrointestinal bleeding is suspected, emergency endoscopy is indicated. To stratify the risk of patients with upper gastrointestinal bleeding, the Glasgow-Blatchford score (GBS)[1] and the Rockall score (RS)[2] are known. These scores are considered useful for predicting the need for therapeutic intervention, the risk of rebleeding, and the risk of death.[3]

The Forrest classification[4,5] is used to evaluate the bleeding characteristics, and endoscopic hemostasis is indicated for Forrest classification Ia (spurting bleeding), Ib (oozing bleeding), and IIa (visible vessel) (**Table 1** & **Figure 1**). Forrest classification Ia and Ib are strong indications for endoscopic hemostasis. For IIa with a protruding vessel or fresh clot at the tip, the risk of rebleeding is high, and endoscopic hemostasis is required.[6]

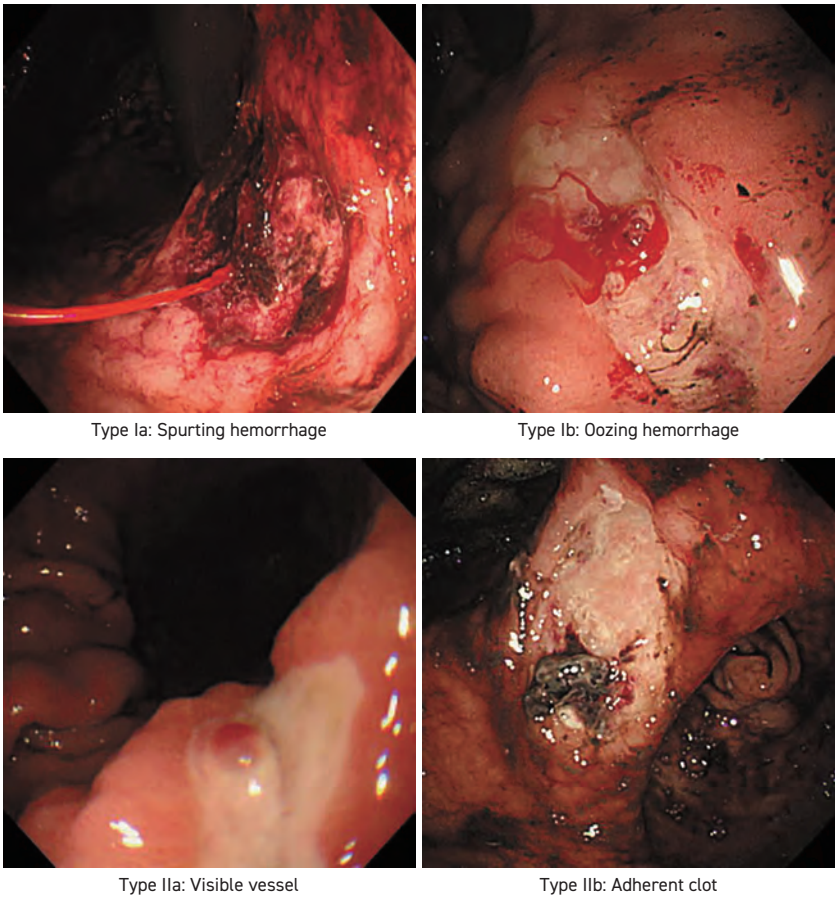
2. Types of Endoscopic Hemostasis

Based on their hemostatic mechanisms, a list of various endoscopic hemostasis methods is shown in **Table 2**.[7] Hemostatic methods are classified into local injection, mechanical hemostasis, thermal coagulation, and drug spraying. The characteristics and practical aspects of each hemostatic method will

Table 1 Forrest classification of endoscopic hemorrhagic findings.

Active bleeding
Ia Spurting hemorrhage
Ib Oozing hemorrhage *
Recent bleeding
IIa Visible vessel **
IIb Adherent clot ***
IIc Hematin-covered lesion ****
No bleeding
III No signs of recent hemorrhage

Footnotes: The terminology used is from the Society's glossary, but other terms are also frequently used.
*: Gushing bleeding, oozing bleeding
**: Non-bleeding visible vessel
***: Adherent clot
****: Black base
(Cited from Literature 5)



Type Ia: Spurting hemorrhage
Type Ib: Oozing hemorrhage
Type IIa: Visible vessel
Type IIb: Adherent clot

Figure 1 **Forrest classification of endoscopic hemorrhagic findings.**

be described. Additionally, it is useful to refer to the guidelines[8] issued by the Japan Gastroenterological Endoscopy Society for the evaluation and treatment of non-variceal upper gastrointestinal bleeding.

(1) Local injection

1) Absolute ethanol

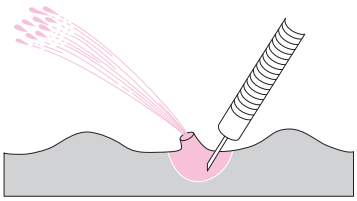
Hemostatic characteristics and mechanism: Developed by Asaki, this method utilizes the dehydrating and fixing properties of absolute ethanol (95.5%) to constrict blood vessels, damage vascular endothelial cells, and form thrombi to achieve hemostasis.[9] The advantage is that it could be performed anywhere with a 1 mL syringe and injection needle.

Actual hemostatic technique: As shown in **Figure 2**,[10] 0.1-0.2 mL of absolute ethanol is injected shallowly into 3 or 4 sites around the bleeding vessel (1-2 mm away). This is performed until the bleeding vessel turns white or brownish. To avoid perforation, the total volume of absolute ethanol injected should not exceed 3 mL.

Table 2 Classification of endoscopic hemostasis techniques according to hemostatic mechanism.

1) Injection method
   (a) Absolute ethanol injection method
   (b) Hypertonic saline epinephrine (HSE) injection method (1:10,000 epinephrine)
2) Mechanical hemostasis method
   (a) Clipping hemostasis method
   (b) Endoscopic variceal ligation (EVL, deployed snare)
   (c) Over-The-Scope clip (OTSC)
3) Thermal coagulation method
   (a) High-frequency hemostatic forceps
   (b) Argon plasma coagulation (APC)
   (c) Heater probe method
4) Drug spraying method
   (a) Thrombin solution/powder
   (b) Sodium alginate
   (c) Absorbable local hemostatic material (Purestat®)

(Modified from Literature 7)



- Absolute ethanol is injected shallowly and accurately in 0.1 to 0.2 mL increments around the vessel.
- The total amount of absolute ethanol should not exceed 3 mL.

Figure 2 Absolute ethanol injection method.

(From: Satoshi Tanabe et al., Guidelines for endoscopic hemostasis, *Guidelines for Gastroenterological Endoscopy*, 3rd Edition, p.198)

2) Hypertonic saline epinephrine (HSE)

Hemostatic characteristics and mechanism: Hirao and colleagues reported this method is simple and highly effective for hemostasis.[11] HSE achieves hemostasis through the vasoconstrictive effect of epinephrine and the physicochemical tissue swelling, fibrinoid degeneration of the vessel wall, and thrombus formation caused by hypertonic saline. It is applicable for all types of lesions and bleeding situations.

Actual hemostatic technique: Two types of HSE solution are prepared; HSE 1 solution (20 mL of 5% NaCl + 1 mL of 0.1% epinephrine) and HSE 2 solution (20 mL of 10% NaCl + 1 mL of 0.1% epinephrine).

For initial hemostasis, when it is difficult to identify the bleeding source due to severe bleeding, 4 mL of HSE 1 solution is injected into 4 or 5 sites near the bleeding source to reduce the bleeding rate. For complete hemostasis, the visible vessel is identified, and 1 mL of HSE 2 solution is injected into 4 or 5 sites near the exposed blood vessel to reduce bleeding intensity. Since it does not have a strong

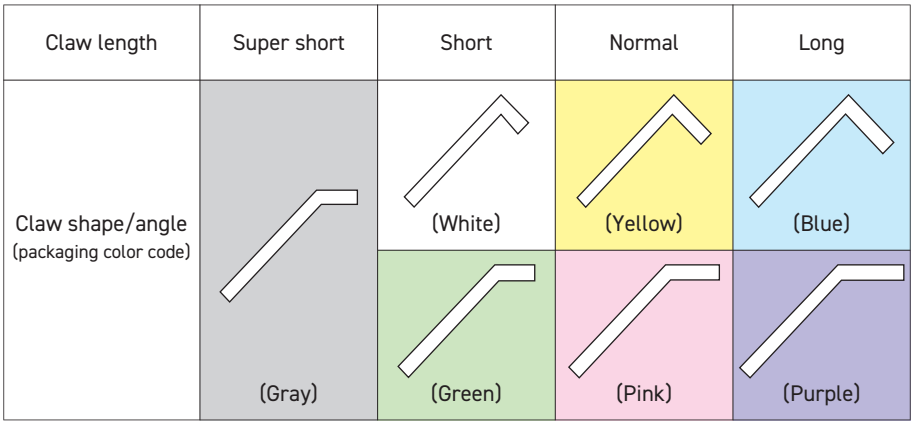


Figure 3 **Types of hemostatic clips.**

(Source: Olympus Medical Systems)

dehydrating and fixing effect like ethanol, endoscopic examinations are performed 24 and 48 hours after the injection to check for any remaining visible vessels and perform additional treatment if necessary. In cases of severe bleeding, the bleeding rate is reduced by injecting HSE, and additional hemostatic methods are selected for effective hemostasis.

(2) Mechanical hemostasis

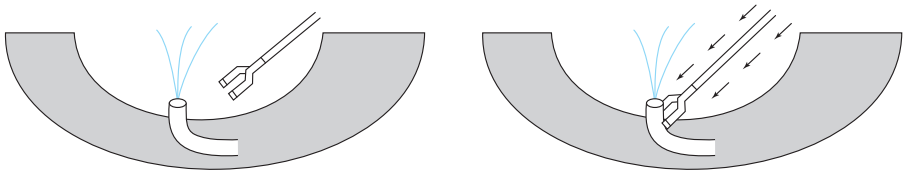
1) Clip hemostasis

Hemostatic characteristics and mechanism: This is a safe and simple method that directly grasps and compresses the bleeding source or visible vessel. It is a mechanical closure method that blocks blood flow. Developed by Hayashi and colleagues,[12] and further improved by Hachisu and colleagues[13] with the addition of a rotating function, this method is now widely used. It is well-suited for cases where the bleeding source is identified, such as arterial bleeding or visible vessels.[14] Clips are available with long and short arms, and obtuse (135 degrees) and acute (90 degrees) angles (**Figure 3**). For soft lesions such as Mallory-Weiss syndrome, long-arm, acute-angle clips are suitable for suturing, while for hard lesions such as peptic ulcers, short-arm, obtuse-angle clips are useful as they transmit sufficient grasping force to the tip.

Actual hemostatic technique: The bleeding source or visible vessel is directly grasped with an endoscopic hemostasis clip device. The key is to place the clip over the visible vessel with the tissue edges. For hard ulcer base such as chronic ulcers, the “woodpecker method” devised by Hachisu and colleagues is useful.[15] This method involves narrowing the opening of the short clip or hemostatic clip and compressing it against the ulcer base like a woodpecker to grasp the edges of a bleeding vessel (**Figure 4**).

When hemostasis is performed on the lesser curvature or posterior wall of the stomach, a downward approach is unstable, so endoscope retroflexion from the distal side is preferred (**Figure 5**). While a bleeding source is gently compressed with a clip and the scope is then slightly pulled back, the clip will become perpendicular to the bleeding source. This process ensures a good clipping and effective hemostasis.

Precautions for clip hemostasis: The first clip is very important, and should be applied carefully after



(a) The tip of the hemostatic clip is narrowed during the approach.

(b) The clip is pressed against the ulcer base in a motion resembling that of a woodpecker, while grasping the margin of the visible vessel.

Figure 4 Woodpecker technique.

(Cited from Literature 15)

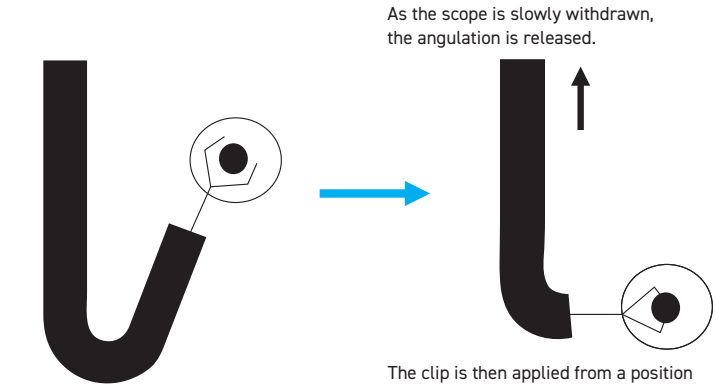


Figure 5 Approach to lesions on the lesser curvature.

the confirmation of bleeding source. Subsequent clips become increasingly difficult to apply, so the approach should be carefully considered. Previously, repositionable clips were expensive, but relatively inexpensive reusable SureClip® is now available. SureClip® allows recapture, making it possible to securely grasp a bleeding source (**Figure 6**). The device allows repositioning for precise targeting of bleeding source, proving especially useful in cases of heavy bleeding where the first clip placement is crucial. It is important not to damage the endoscope by aspirating a detached clip.

Over-The-Scope clip (OTSC) (**Figure 7**) was developed as a full-thickness endoscopic suturing device but is considered useful for cases where hemostasis is difficult with other methods or for duodenal ulcer bleeding accompanied by perforation.[16)]

2) Endoscopic ligation

Hemostatic characteristics and mechanism: This is a mechanical hemostasis method that uses O-rings to ligate the lesion, applying the endoscopic variceal ligation (EVL) technique used for treating esophageal varices.

Actual hemostatic technique: The procedure is similar to EVL. While it is not suitable for hard lesions, it has been reported to be useful for hemostasis in cases such as Dieulafoy's ulcer, Mallory-Weiss syndrome, gastric antral vascular ectasia (GAVE), and diffuse antral vascular ectasia (DAVE).[17)] Since EVL is not indicated for Mallory-Weiss syndrome, GAVE, etc., it is advisable to obtain approval before



Figure 6 SureClip®
(Provided by MC Medical)

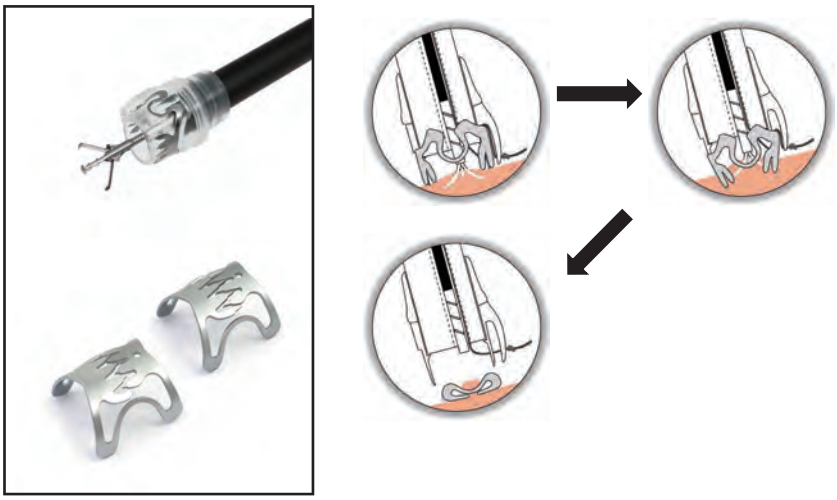


Figure 7 Over-The-Scope clip (OTSC).
(Provided by Century Medical)

use in each facility.

(3) Thermal coagulation method

1) High-frequency hemostatic forceps

Hemostatic characteristics and mechanism: High-frequency hemostatic forceps are used for hemostasis during endoscopic submucosal dissection (ESD) for early gastric cancer and early esophageal cancer, and have also come to be used for ulcer bleeding. This method achieves hemostasis

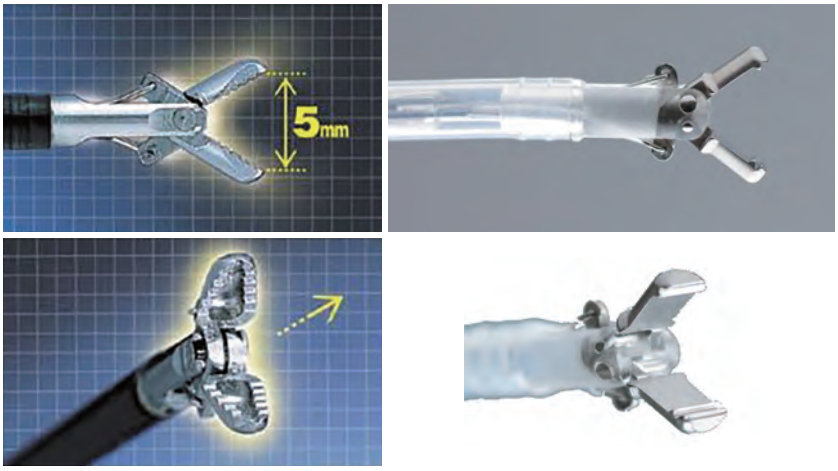


Figure 8 **High-frequency hemostatic forceps.**

Monopolar hemostatic forceps (Coagrasper, manufactured by Olympus Medical Systems)
Bipolar hemostatic forceps (HemoStat-Y, manufactured by HOYA)

by dehydrating the bleeding vessel and coagulating the blood within the vessel, causing the surrounding tissue to contract through Joule heat. By controlling the voltage to 200 V or less and preventing sparking, the tissue is devitalized without carbonization. There are two types of forceps on the market: monopolar and bipolar (**Figure 8**). The operation of the hemostatic forceps is simple and reliable, as it involves grasping the bleeding source or visible vessel with the hemostatic forceps and delivering heat. With the monopolar type, the forceps require careful handling, as pressing the tip during electrification impacts deeper tissues with increasing perforation risks. On the other hand, the bipolar type provides current flows only between the tips of the cups, allowing for safe hemostasis at low power. However, since only the area grasped by the cups is coagulated, this limitation requires to accurately visualize the bleeding source and securely grasp the bleeding vessel to achieve adequate hemostasis. It is appropriate to use for organs with thin walls, such as the esophagus, duodenum, and colon.

Actual hemostatic technique: For the monopolar type, the power settings are for soft coagulation by 80 W in ICC200, by 100W for effect 5 in VIO300D, and for effect 3.0-3.5 in VIO3. For the bipolar type, the power settings are soft bipolar by 20-30 W in ICC200, by 20-30 W for effect 3 in VIO300D, and bipolar soft coagulation by 2.0-3.0 in VIO3.[18,19)]

If there is no active bleeding and the exposed blood vessel is clearly visible, the vessel is grasped and heat is delivered. If there is active bleeding and the bleeding source or exposed blood vessel is not clearly visible, the target vessel should be grasped with the hemostatic forceps to slow down the bleeding. If the active bleeding does not decrease, the bleeding vessel should be grasped again to apply heat. Repeated application of heat without success not only fails to achieve hemostasis but also causes the tissue to coagulate or leads to perforation due to excessive burning.

2) Argon plasma coagulation (APC) method

Hemostatic characteristics and mechanism: This method is a non-contact electrocoagulation introduced by Grund and colleagues into the field of endoscopy.[20)] APC allows for coagulation of a wide area to a uniform shallow penetration depth, making it useful for diffuse bleeding from GAVE and

tumors. By releasing ionized argon gas (argon plasma) while simultaneously discharging high-frequency current, an argon plasma beam is generated to coagulate and hemostat tissue.

Actual hemostatic technique: The APC device has evolved from APC300 to APC2 and more recently APC3 (provided from ERBE). The power settings are typically 40-60 W for heat and 1-2 L/min for argon gas flow. On the other hand, the power setting of forcedAPC mode in APC3 uses effect 3.0, 30 W for applying heat, and 0.8 mL/min for providing argon gas flow. The probe tip is placed as close as possible to the target site without touching it to perform coagulation. If the probe is pressed against the mucosa while creating coagulation, submucosal emphysema could occur, so care must be taken. The second-generation APC device (APC2) currently in widespread use has an added ignition assist function that makes discharge easier. Today, APC3 is available, and improvements in the basic performance of the device allow for the formation of discharges from a greater distance than APC2. The newly added pulsedAPC mode allows for the maintenance of a more uniform cloud-like beam, enabling shallower and wider-area coagulation than the forcedAPC mode. This feature is useful for GAVE and other conditions.[21)]

3) Heater probe method

Hemostatic characteristics and mechanism: This thermal coagulation method was developed by Protell and colleagues, and involves applying a probe equipped with a heating diode to the bleeding site to achieve hemostasis.[22)] The procedure is simple and the device is portable. The hemostatic mechanism involves tissue devitalization by heat, narrowing of the vessel lumen, and thrombus formation.[23)]

Actual hemostatic technique: The heater probe device should be set based on the target organ and the bleeding condition. For organs with thinner walls, such as the esophagus, duodenum, or colon, a setting of 20 to 25 J is appropriate. In the case of the stomach, a setting of 25 to 30 J is suitable, and coagulation is applied accordingly.

The tip of the probe is placed in contact with the bleeding source, such as the cut end of a vessel, and heat is applied continuously one to three times at the appropriate setting. This process is repeated until hemostasis is confirmed. After hemostasis has been achieved, heat is carefully applied to the surrounding area to ensure adequate coagulation.[24)]

In cases with severe movement due to respiratory fluctuations, a stable and effective burn should be performed by joining an attachment to secure the field of vision. One of the characteristics of this method is that it also allows hemostasis for lesions oriented tangentially, by applying pressure from the side. The criteria for hemostasis are blackening and shrinking of the visible vessel.

(4) Drug spraying method

Substances such as thrombin solution, thrombin powder, sodium alginate, and epinephrine are nebulized for spraying. This method is often used for diffuse bleeding from a wide mucosal surface, as an adjunct to other endoscopic hemostatic methods, or as a combined therapy, and some effectiveness of this method has been confirmed.[3)]

Recently, a synthetic hemostatic material (PuraStat®) has attracted attention as a new hemostatic material.[25)] This synthetic hemostatic material utilizes self-assembled peptide technology and reacts with blood to form a hydrogel. This hydrogel physically occludes a bleeding source to achieve hemostasis. It is considered useful for oozing bleeding and is also effectively combined with other hemostatic methods such as clips and high-frequency hemostatic forceps.

3. Adverse Events and Their Management

(1) Inductions of active bleeding

When hemostatic procedures are performed on exposed blood vessels that are already in a hemostatic state, active bleeding is sometimes triggered. This could occur with any type of hemostatic procedure. In local injection methods like absolute ethanol or HSE, bleeding could occur if the injection needle is directly inserted into the edge of vessel. This is especially concerning in cases of duodenal bleeding, as the lumen is narrow, and once bleeding occurs, maintaining a clear vision of field becomes difficult.
With clip hemostasis, if the clip is deployed from the endoscope near the edge of vessel, the vessel could be damaged by the clip and cause bleeding.
For thermal coagulation methods, such as high-frequency hemostatic forceps, heater probe, and APC, it is important to be cautious in treating large vessels. In the case of large vessels, blood flow could be blocked in advance by first injecting HSE around the vessel. This approach allows thermal coagulation to proceed without causing bleeding.

(2) Ulcer expansion

Hemostatic procedures sometimes cause ulcer expansion. This could occur with local injection methods and thermal coagulation methods, but not in clip hemostasis. In local injection methods, particularly when absolute ethanol dehydration and fixation effects cause the closure of the branches around the exposed blood vessels, ulcer expansion occurs. In thermal coagulation methods, excessive heat at the ulcer margin with APC or heater probe methods cause ulcer enlargement. However, the expansion of the ulcer itself does not significantly worsen bleeding or increase the risk of rebleeding, and it is not a major clinical issue.

(3) Perforation

Perforation occur either directly as a result of damage to the ulcer base during hemostatic procedures, or after some time has passed following the procedure, when the tissue of the ulcer base devitalizes and sloughs off to cause perforation. In absolute ethanol local injection, care must be taken to ensure that the total volume of absolute ethanol does not exceed 3 mL. In heater probe methods, excessive pressure or overcoagulation should be avoided. Similarly, in thermal coagulation modalities like APC or hemostatic forceps, excessive burning should be avoided. Perforation risk is particularly higher in the thin-walled duodenum, so care must be taken when performing hemostatic techniques with high tissue damage potential.

4. Selection of Hemostatic Methods and Hemostatic Outcomes

Currently, various endoscopic hemostatic methods are used in Japan, but it is difficult to determine which method is superior. In particular, there has been no significant difference in efficacy among epinephrine injection, absolute ethanol injection, heater probe method, and clip method regarding initial hemostasis and rebleeding.[26,27] Although the addition of epinephrine injection to endoscopic hemostasis

has been reported to have an additive effect in preventing rebleeding,[28] drug injection therapy alone using epinephrine has a high rebleeding rate, and the addition of other endoscopic hemostatic methods is recommended. Furthermore, although absolute ethanol injection is simple and inexpensive, the amount of ethanol that should be used is limited due to the possibility of tissue necrosis after injection. Thus it could be insufficient to achieve adequate hemostasis for active bleeding when ethanol injection is applied alone. On the other hand, the benefit of high-frequency hemostatic forceps used during ESD has also been reported recently.[29] High-frequency hemostatic forceps are easy to use and applied for various bleeding conditions. They are expected to be one of the promising hemostatic methods in the future.

By understanding the characteristics of each hemostatic method and selecting the appropriate technique while considering the disease and the site and conditions of the bleeding, it is expected that hemostatic rates will improve. It is important to be proficient in one technique, but it is also helpful to acquire different hemostatic methods in case of need.

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Satoshi Tanabe, Chika Kusano and Mitsuru Kaise

7 Foreign Body Removal

Gastrointestinal foreign bodies are not at all rare but encountered daily. Most cases occur in children, whereas in adults, they are more common in the elderly, especially those with dementia, and patients with mental illness. In children, coins and batteries are the most frequent cause, whereas in adults, the most frequent cause is a food bolus. In recent years, the number of elderly individuals who have swallowed dentures or press-through packs (PTPs) has been increasing.[1,2] Although 80 to 90% of foreign bodies pass through the gastrointestinal tract without intervention, approximately 10 to 20% are removed by endoscopy. Surgical treatment becomes necessary in 1% or fewer of the cases. In general, the mortality rate is reported to be extremely low.[1,2] There are several reports on the classification of upper gastrointestinal foreign bodies, but Akamatsu and colleagues classify them according to urgency, that is, the necessity of removal (**Table 1**).[3]

1. Diagnosis of gastrointestinal foreign bodies

The management of gastrointestinal foreign bodies is shown in **Figure 1**.[3]

Table 1 Classification of gastrointestinal foreign bodies.

1. Urgent
a. Those that may damage the gastrointestinal wall Hooked dentures, press-through packs, fish bones, needles, glass fragments, dental instruments, multiple magnets, and Anisakis b. Those that may obstruct the gastrointestinal tract Food boluses, bezoars, coins, plastic bags, endoscopically resected large specimens, and roundworms c. Those containing toxic contents Dry cell batteries (manganese, alkaline) and button batteries (alkaline manganese, mercury, lithium)
2. Non-urgent
Pachinko balls, buttons, marbles, Go stones, and mercury in thermometers

(Modified from: Taiji Akamatsu et al., Guidelines for endoscopic removal of foreign bodies, *Gastroenterological Endoscopy Guidelines*, 3rd Edition, p206)

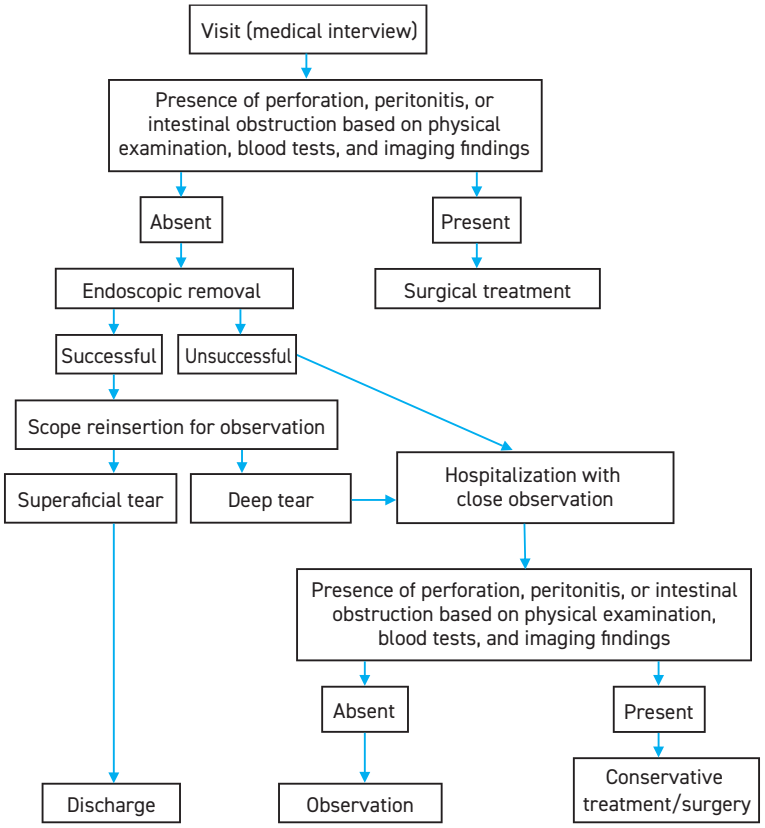


Figure 1 **Management of gastrointestinal foreign bodies.**

(Modified from: Taiji Akamatsu et al., *Guidelines for Endoscopic Removal of Foreign Bodies*, *Gastroenterological Endoscopy Guidelines*, 3rd Edition, p.212)

(1) Diagnosis of gastrointestinal foreign bodies

1) Medical interview

In conscious and understanding patients, the type and location of the foreign body are possibly identified. However, it is difficult in most cases, where patients with no symptoms are unaware of ingesting foreign body. Confirmation of the most recent time food was taken is also considered important, along with details such as intake of large portions of meat or raw seafood.

2) Physical findings

When a patient has swelling or tenderness in the neck, especially if a crackling sensation under the skin or crepitus is obvious, these are signs that strongly suggest there might be perforation somewhere. In the abdomen, attention should be paid to the signs of peritonitis and ileus. When these are observed, surgical treatment should be considered promptly.

3) Imaging findings

Multidirectional X-ray examination is useful to confirm mediastinal emphysema and abdominal free air as well as the location of the foreign body. CT examination should be performed **because this modality adequately identifies even radiolucent foreign bodies**, although radiation exposure is a concern in

children. Recently, CT examination with reduced tube voltage is recommended to control exposure. Notably, contrast examination is not preferred, because it could cause aspiration and hinder subsequent endoscopic examination.

4) Informed consent

All necessary information about a medical procedure should be explained to obtain consent including: (i) risks of leaving the foreign body untreated, (ii) urgency of the extraction procedure, (iii) premedication/sedation together with its adverse events, (iv) appropriate extraction procedures, (v) procedure related adverse events (mucosal injury, perforation, bleeding, and aspiration) and their management, and (vi) the post-extraction management.

(2) Preparation for endoscopic removal of foreign body

1) Location

The procedure should be performed in a fluoroscopy room if a radiopaque foreign body is expected with food residues.

2) Scope selection

In addition to a forward-viewing endoscope, an endoscope with a water jet function and a double-channel endoscope should also be prepared.

3) Instruments

Biopsy forceps, various graspers, tripod/quadripod forceps, basket forceps, snares, and retrieval nets should be prepared first. It is advisable to check in advance whether these devices appropriately grasp the foreign body if the same one is available.

4) Mucosal injury prevention

Over-tubes for securing the airway and retrieving multiple foreign bodies or transparent distal hoods are available for preventing mucosal injury. If these devices are unavailable, a temporary hood made of rubber gloves is acceptable.[4] A ballon is also helpful for securing the lumen during retrieval.

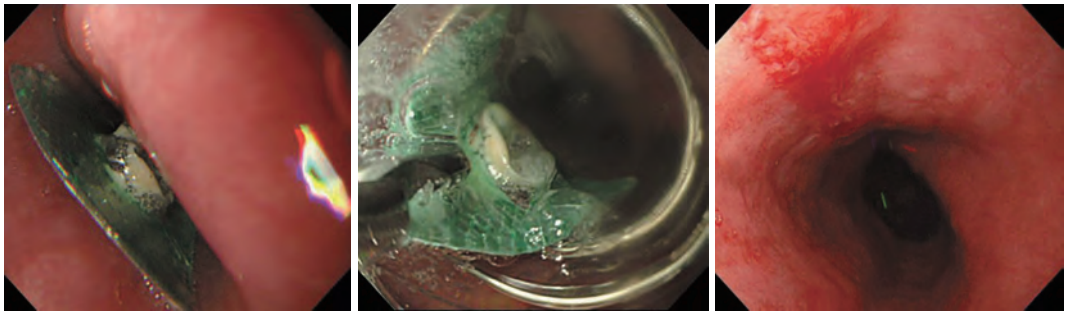
5) Premedication/sedation

While securing intravenous access with monitoring is essential, sedation should be considered if the procedure is likely to become lengthy. In children, especially infants, it is preferable to perform the procedure under general anesthesia. Considering the risk of aspiration, tracheal intubation should be arranged before the procedure as a precaution.

(3) Practical points for endoscopic removal of foreign body

1) Potential to damage the gastrointestinal wall

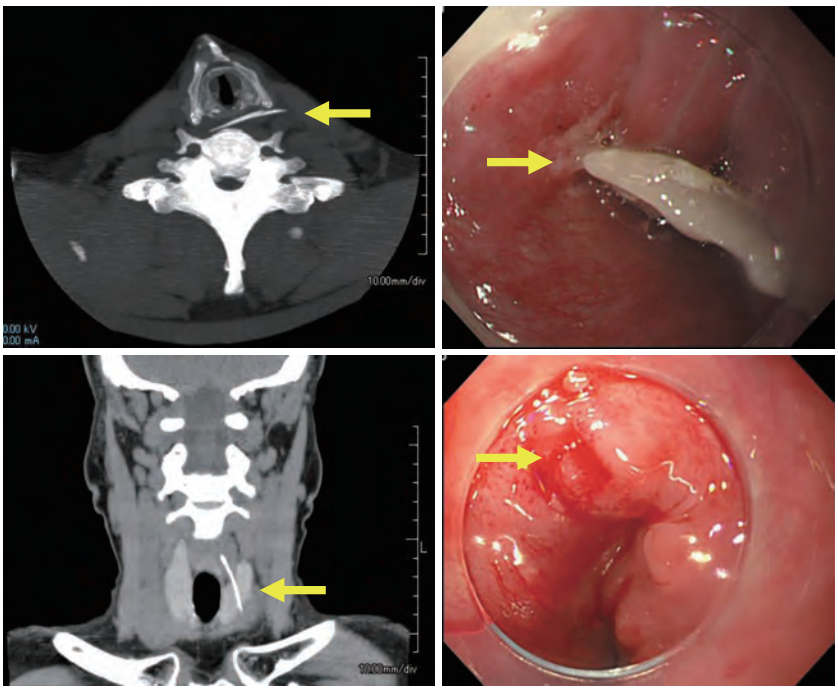
Sharp, irregularly shaped foreign bodies or needle-like objects have a high risk of causing gastrointestinal perforation. Endoscopists should try to remove these objects whenever feasible, if they are located in the gastric cavity or the upper part of the duodenum. PTPs could be safely removed with a hood attached to



a | b | c

Figure 2 Case of PTP aspiration.

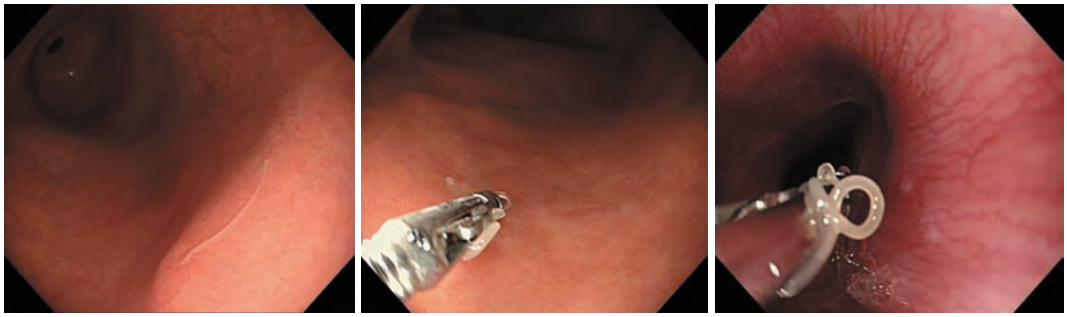
a: A press-through package (PTP) was identified at the esophageal-tracheal bifurcation.
b: It was grasped with alligator forceps and drawn into the transparent cap at the distal tip, of the scope which was then withdrawn together with the foreign body.
c: Upon reinsertion of the scope for observation, no deep tears were noted, and the patient was considered eligible for discharge.
(Cited from Literature 5)



a | b
c | d

Figure 3 Case of fish bone aspiration.

a: The patient was referred to the facility after sudden onset of pharyngeal pain following consumption of cod on the previous day. A computed tomography (CT) examination revealed a fish bone (arrow) extending from the left cervical region to the pharyngoesophageal junction.
b: Insertion of a scope via the left piriform sinus revealed penetration of a fish bone (arrow) into the left esophageal wall at the pharyngoesophageal junction. However, as most of the foreign body was located outside the esophagus, endoscopic removal was deemed hazardous. On the same day, the otolaryngology department performed extraction using a rigid endoscope under general anesthesia.
c: Another patient developed persistent pharyngeal pain during swallowing after eating tempura of beltfish five days earlier and was referred to the facility. CT examination revealed a fish bone (arrow) in the left cervical area penetrating the thyroid gland.
d: Insertion of a scope via the left piriform sinus revealed the entry site of the fish bone (arrow) at the pharyngoesophageal junction, but the bone itself could not be visualized. On the same day, the otolaryngology department performed a cervical external incision under general anesthesia to remove the bone.
(Cited from Literature 5)



a | b | c

Figure 4 Case of anisakiasis.

a. The patient consumed vinegared mackerel the day before and presented with severe epigastric pain. A larval body of Anisakis was observed penetrating the posterior wall near the greater curvature of the gastric antrum.
b. The area around the site of penetration (the head) was grasped with biopsy forceps and slowly extracted.
c. The larva was retrieved along with the endoscope.

the distal tip (**Figure 2**).[5] CT is useful for diagnosing fish bones, and their endoscopic removal is indicated only when the condition is very localized, or when there is neither peritonitis nor damage to adjacent organs and vessels. If these undesirable findings are present, surgical removal or extraction with a rigid endoscope under general anesthesia should be considered (**Figure 3**).[5] Dentures also generally resolve with conservative treatment, but hooked dentures impacted in the second esophageal constriction pose a risk of damage to the bronchi, lungs, or aorta. This case is indicated for surgical intervention. A single magnet is often spontaneously egested, but multiple magnets attract each other across the intestinal wall and damage it. Thus, their early removal is required. Anisakiasis occurs most frequently in gastric cavity, but possibly occurs in all parts of the gastrointestinal tract, including the esophagus.[6] The head of the parasite is observed to be embedded, appearing like threads or coils or multiple larvae are also possible. **During removal, it is important to grasp the parasite near the embedded site, pull it out without breaking it, and retrieve it together with the scope** (**Figure 4**).

2) Potential to obstruct the gastrointestinal tract

Food boluses often pass spontaneously. However, they could remain impacted and cause obstruction in patients with underlying conditions. In such cases, an overtube is useful for repeated manipulations and removal with endoscope. This device prevents the risk of pushing the bolus from the esophageal tract into the gastric cavity. Since large bezoars are likely to cause ileus, they are crushed with forceps, snares, or electrohydraulic lithotripsy device,[7] but the hard surface often makes the process difficult. Coca-Cola lavage therapy is also beneficial,[8] but it is not always successful in a short period of time, so combined use with endoscopic fragmentation is safer. Crushed fragments could also cause ileus, requiring to be crushed to 2 cm or less. In fact, caution is necessary even after treatment in patients with impaired motor function. Blunt foreign bodies like coins often pass spontaneously in adults, but in children they could be lodged in the esophagus and pose a risk of ulcers or perforation. In such cases, indications for the removal are provided.

3) Potential leakage of toxic substance

Button batteries contain an alkaline solution and cause corrosive injury. Their smooth surface makes them difficult to grasp, but retrieval nets are useful. Lithium batteries have become particularly common in recent years. Since they are large with a high electromotive force, they are prone to lodging and

causing gastrointestinal damage in a short period of time. In reality, early prompt removal is recommended.

2. Adverse Events and Their Management

During foreign body removal, there is a risk of damaging the digestive tract and causing perforation or bleeding when passing through physiological constrictions such as the esophagogastric junction and cervical esophagus. To prevent such incidents, utmost caution is required.

(1) Perforation

If conditions allow, endoscopic closure using clips or other comparable methods is applicable. After the procedure, conservative treatment should begin without delay, including nasogastric tube placement, withholding of oral intake (nil per os (NPO)), intravenous fluid administration, and antibiotics. This postprocedure management requires close monitoring, and a consultation with a surgeon should also take place. When perforation is not observed but a deep tear is found, the patient should be admitted, and oral intake should be started only if the symptom, blood tests, physical examination, and imaging findings are appropriate.

(2) Hemorrhage

When spurting or oozing bleeding, or exposed blood vessels within the tear are identified, immediate endoscopic hemostasis becomes necessary.

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Seisuke Okamura

8 Percutaneous Endoscopic Gastrostomy

1. Indications

The indications and contraindications for percutaneous endoscopic gastrostomy (PEG) are summarized in **Tables 1 and 2**.[1–5] In determining appropriateness, both clinical and ethical considerations must be addressed.

(1) Indications based on physical perspectives

PEG is indicated when the patient's physical condition allows safe placement and when enteral nutrition is expected to provide clinical benefit. It is not recommended in patients with extremely short life expectancy or severely compromised general condition.

Table 1 Indications for PEG.

1. Swallowing and feeding disorder
- Involuntary feeding due to cerebrovascular disease, dementia, etc. - Inability or difficulty in feeding due to neurological or muscular diseases, etc. - Difficulty in feeding due to head and neck or facial trauma - Difficulty in feeding due to chemoradiotherapy for head and neck cancer or esophageal cancer - Laryngopharyngeal, esophageal, or gastric cardia stenosis - Esophageal perforation
2. Repeated aspiration pneumonia
- Repeated aspiration events involved with food intake - Aspiration associated with nasogastric tube placement
3. Inflammatory bowel disease
- Inflammatory bowel disease requiring long-term enteral nutrition, especially Crohn's disease patients
4. Decompression therapy
- Pyloric stenosis - Upper small intestinal obstruction
5. Other special treatments

(Modified from Suzuki Y, et al.: Guidelines for Percutaneous Endoscopic Gastrostomy, *Gastroenterological Endoscopy Guidelines*, 3rd Edition. p311.)

Table 2 Absolute and relative contraindications for PEG.

Absolute contraindications
- Absolute contraindications for routine endoscopic examination - Pharyngeal or esophageal stenosis that does not allow endoscope passage - Inability to approximate the anterior gastric wall to the abdominal wall - Uncorrectable bleeding tendency - Gastrointestinal obstruction (except for decompression drainage purposes)
Relative contraindications
- Massive ascites - Extreme obesity - Significant hepatomegaly - Tumorous lesions or acute mucosal lesions of the stomach - Hiatal hernia - Bleeding tendency - Pregnancy - Portal hypertension - Peritoneal dialysis - Carcinomatous peritonitis - Poor general condition - Poor prognosis - History of gastric surgery - Lack of explanation and consent

(Modified from Suzuki Y, et al.: Guidelines for Percutaneous Endoscopic Gastrostomy, *Gastrointestinal Endoscopy Guidelines* 3rd Edition. p311.)

1) Route of nutritional administration

According to the *Guideline for Parenteral and Enteral Nutrition (3rd Edition)* from the Japanese Society for Parenteral and Enteral Nutrition Therapy, enteral nutrition should be the preferred option when intestinal function is preserved.[2] In patients who cannot maintain oral intake and require tube feeding for more than four weeks, gastrostomy is considered the first-line approach.

2) Life expectancy

Although strict numerical criteria are lacking, patients with an expected survival of more than one month are conventionally considered appropriate candidates for PEG.

3) General condition tolerable to PEG

Although PEG is minimally invasive, it may be relatively invasive in patients with severely impaired general status. In cases of severe malnutrition (serum albumin $\leq$ 2.5 g/dL), anemia (hemoglobin $\leq$ 8.0 g/dL), or uncontrolled infection, correction of these conditions should take precedence. Preoperative nutritional status has been reported to correlate with prognosis after gastrostomy, and Onodera's prognostic nutritional index (PNI) is considered useful as a predictive factor.[6] Conversely, in patients with malnutrition due to poor oral intake, improvement can be achieved with enteral nutrition via gastrostomy.[7] In such patients, the decision requires careful consideration of risks and expected benefits.

(2) Indications based on ethical perspectives

The *Guidelines for the Decision-Making Process in Elderly Care Focusing on Indications of Artificial Hydration and Nutrition* (2012 Edition) from the Japan Geriatrics Society emphasize the need to evaluate artificial hydration and nutrition (AHN) in terms of benefits and burdens for each patient.[8] The therapeutic purpose of AHN should be clarified, and the most appropriate method selected accordingly.

The use of PEG in very elderly patients or in those with end-stage dementia has been questioned. Applicability must be determined on a case-by-case basis, recognizing PEG as a potential form of nutritional therapy within both ethical and social contexts. Because many elderly or severely ill patients lack decision-making capacity, decisions are frequently entrusted to family members or other surrogates. Such delegation may diverge from the principle of self-determination, highlighting the necessity for careful and balanced judgment shared between healthcare providers and the patient's family.

2. Preoperative Management

(1) Preoperative examination

Preoperative evaluation equivalent to that for surgical procedures is necessary. Laboratory assessment should include coagulation function and nutritional status. Imaging studies such as plain abdominal radiography, computed tomography (CT), and ultrasonography are useful. For CT, inflating the stomach with air via a nasogastric tube can improve visualization, especially in conditions such as Chilaiditi syndrome, by resolving gastrointestinal interposition.[9]

(2) Evaluating swallowing function

In patients requiring swallowing assessment, videofluoroscopic (VF) or videoendoscopic (VE) evaluation should be performed before PEG. Preoperative multidisciplinary discussion is desirable, involving physicians from relevant specialties (e.g., otolaryngology, neurology), dentists, nurses, speech-language pathologists, and registered dietitians. This team develops a plan regarding the likelihood of recovery of oral intake and explains the findings to the patient and family.[10]

- **Videofluoroscopic examination (VF):** Allows indirect observation of the oral, pharyngeal, and esophageal phases using barium-mixed test food.
- **Videoendoscopic examination (VE):** Allows direct observation of the pharyngeal phase using actual food. The Hyodo and Hyodo-Komagane scores are used to assess dysphagia severity by evaluating saliva pooling, cough reflex, swallowing reflex, and post-swallow clearance.[11,12]

(3) Antiplatelet and anticoagulant therapy

According to the *Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment* (2012 Edition and 2017 Supplement) from the Japan Gastroenterological Endoscopy Society, PEG is classified as a high-risk procedure for gastrointestinal hemorrhage.[13,14]

- **Antiplatelet agents:** Aspirin can generally be continued. Other agents (excluding thienopyridines) should be withheld for one day. If combined therapy is required, continuation with aspirin or

cilostazol alone is recommended.

- **Anticoagulants:** For warfarin, discontinuation for 3–5 days with temporary heparin substitution has been standard, but bleeding risk with heparin bridging is recognized. For direct oral anticoagulants (DOACs), administration is withheld from the morning of the procedure. Unfractionated heparin should be discontinued at least 3 hours before the procedure and restarted only after confirming hemostasis. Alternative approaches include continuing warfarin within therapeutic INR or temporary switching to DOACs in cases of non-valvular atrial fibrillation.

3. Selection and Placement of Gastrostomy Catheters

(1) Catheter types

Gastrostomy catheters are classified by intragastric shape into bumper type and balloon type (**Table 3**), and by external shape into button type and tube type (**Figure 1**).[1,15]

- **Bumper type:** Durable and less prone to accidental removal, but replacement can cause discomfort and usually requires endoscopy.
- **Balloon type:** Easier to replace but more prone to accidental dislodgement.
- **Button type:** More hygienic and aesthetically acceptable than tube type, but shaft length cannot be adjusted.

  A gastrostomy catheter incorporating a shape-memory alloy was released in 2023, designed to maintain durability while reducing resistance during insertion and removal. Clinical data are still being accumulated.

(2) Placement procedures

Placement is classified by whether the catheter passes through the oral cavity. In the Pull/Push method, the catheter passes through the mouth; in the Introducer method, it does not. The choice of method depends on procedural characteristics (**Tables 4 and 5**).[5]

- **Pull/Push method:** A guide wire is inserted from the abdominal wall and retrieved orally. The gastrostomy catheter is attached to the guide wire and pulled into place.
- **Introducer method:** A puncture needle or guide wire is inserted into the stomach, the tract is dilated, and the catheter is placed directly.

(3) Determination of puncture site

After gastric insufflation brings the stomach into contact with the abdominal wall, the puncture site is confirmed using finger indentation and transillumination. The preferred site is in the left hypochondrium, above the umbilicus, over the rectus abdominis muscle.

(4) Gastric wall fixation

Fixation of the gastric wall to the abdominal wall is performed before the main puncture. It is essential for Introducer methods and, since the 2022 revision of medical service fees, has been recommended even

Table 3 Comparison between bumper-type and balloon-type catheters.

	Bumper type	Balloon type
Advantage	- High durability - Low frequency of replacement - Low risk of accidental removal	- Almost no pain during replacement - Easy replacement procedure - Low risk of tube damage or intraperitoneal misinsertion during replacement
Disadvantage	- Pain during replacement - Difficult replacement procedure - Risk of tube damage or intraperitoneal misinsertion during replacement	- Low durability - High frequency of replacement (must be replaced within 1 month) - Risk of accidental removal

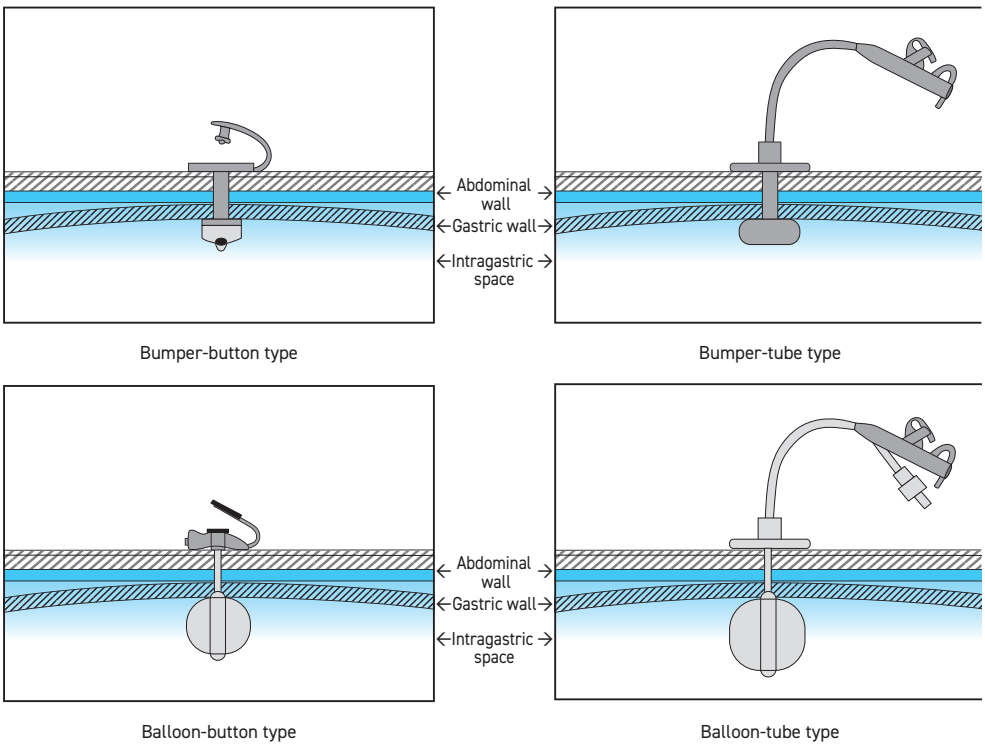


Figure 1 Types of catheters.

(Cited from Literature 15)

Table 4 Comparison among insertion methods.

	Pull/Push method	Original Introducer method	Modified Introducer method
Advantage	- Thin puncture needle - Stable procedure - Large inner diameter of PEG catheter - Surrounding tissue is compressed for hemostasis by the pulled-out catheter	- Only one endoscopic insertion is required - Clean surgery	- Thin puncture needle - Only one endoscopic insertion is required - Clean surgery - Large inner diameter of catheter
Disadvantage	- Two endoscopic insertions are required - Unclean surgery	- Small inner diameter of catheter - Risk of dislodgement due to balloon type catheter	- Button type catheter with a shaft length matching the abdominal wall thickness is necessary

(Modified from Suzuki Y, et al.: *Guidelines for Percutaneous Endoscopic Gastrostomy, Gastrointestinal Endoscopy Guidelines* 3rd Edition. p311.)

Table 5 Indications for insertion techniques in special cases.

	Pull/Push method	Original Introducer method	Modified Introducer method
Residual gastric cases	○	△	△
Tumors or stenoses of the head, neck, and esophagus	×	○[3]	○[3]
Ascites cases (Small amount)	○[1]	○	○[4]
Decompression gastrostomy	○	△	○
Pharyngeal MRSA	△[2]	○	○

1: Gastric wall fixation is essential.

2: Combined use of infection prevention kit is desirable.

3: Small-diameter, nasogastric endoscope is useful.

4: If an increase in ascites is expected, use a longer button type catheter or replace it with a tube type catheter.

(Modified from Literatures 5 & 16)

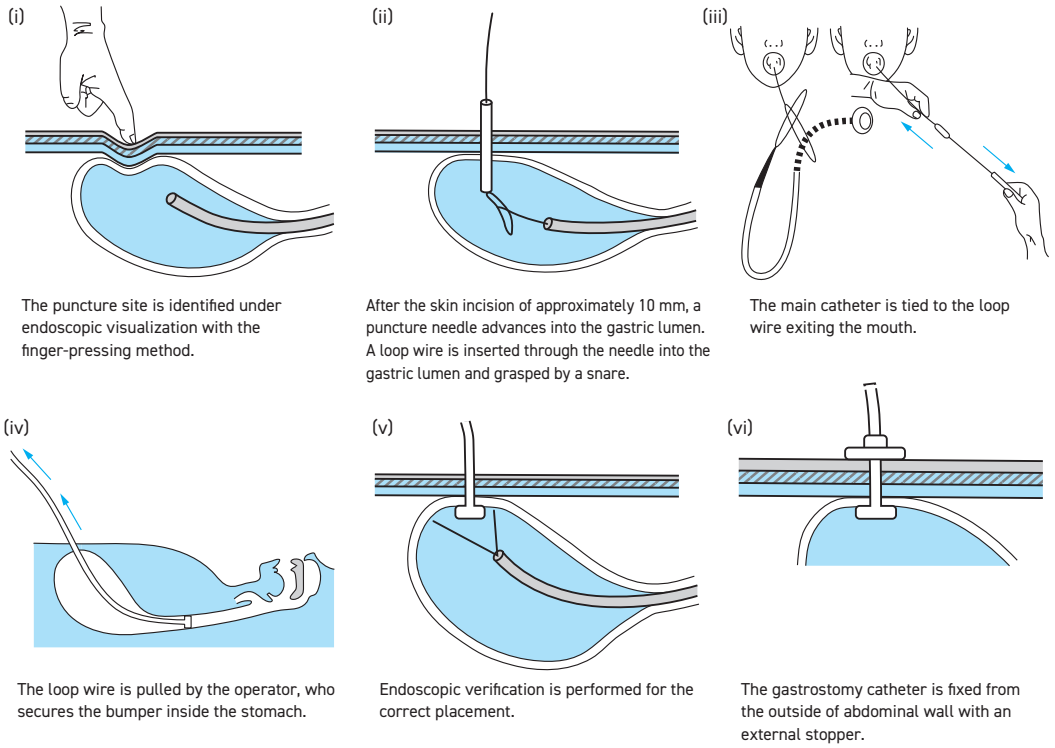


Figure 2 Insertion procedure using pull method.

(Cited from Literature 15)

for Pull/Push methods. Fixation prevents early separation and facilitates management of accidental removal. Risks include bleeding due to additional punctures, inadvertent injury to adjacent organs in narrow fields, and local ischemia from overtightening. Sutures are generally removed one week after placement.

- **Suture ligation method:** Two needles are introduced into the stomach. A nylon thread is inserted through one needle and retrieved externally with a snare through the other, after which both walls are tied together.

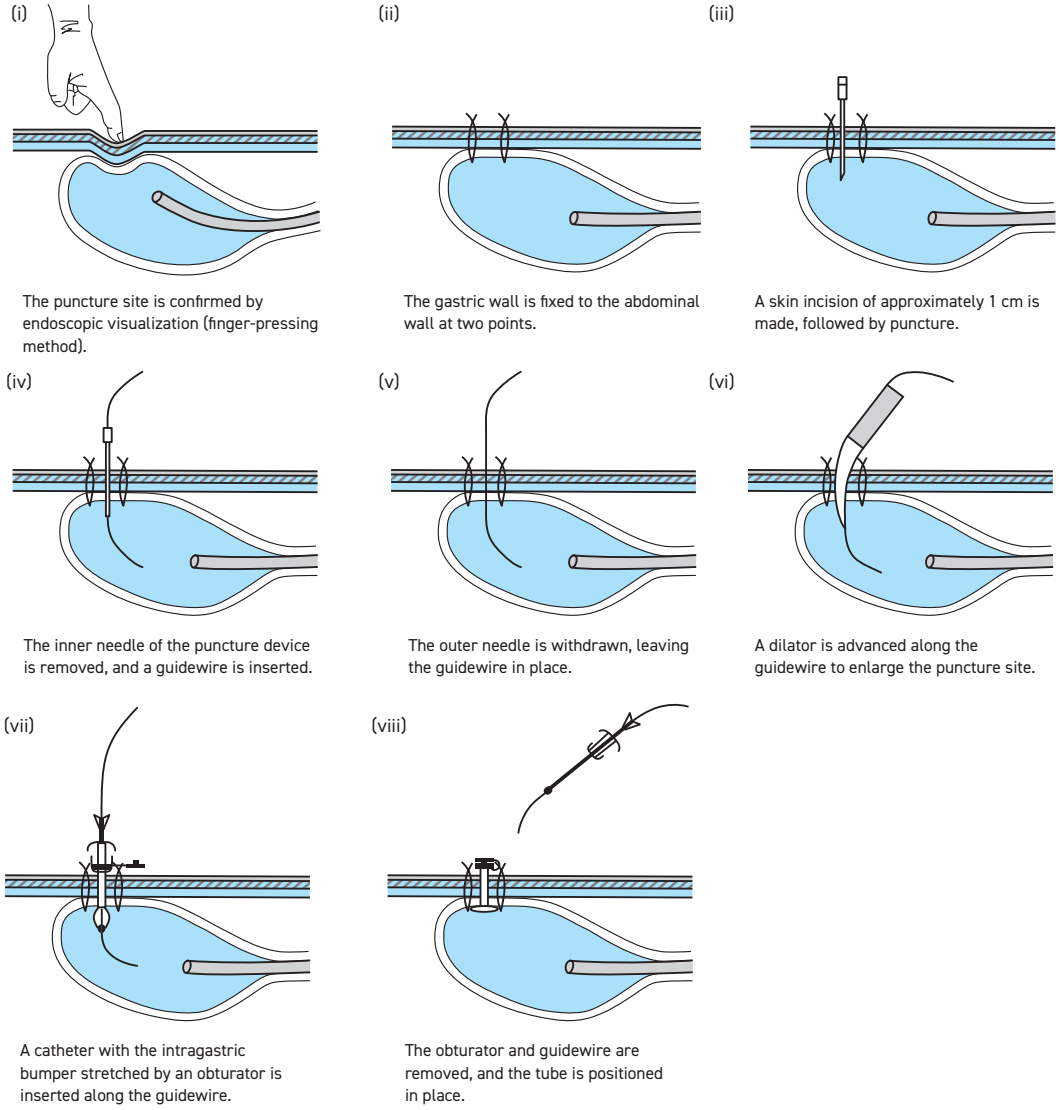


Figure 3 Insertion procedure using modified introducer method.

(Cited from Literature 15)

- **T-fastener method:** A T-shaped anchor attached to a nylon thread is deployed into the gastric lumen via a puncture needle.

4. Early and Late Management After PEG [16-18]

(1) Early stage

- **Infection control:** Prophylactic antibiotics are recommended for the Pull/Push method; not mandatory for the Introducer method.
- **Nutritional schedule:** Feeding typically begins 24–48 hours after placement at 10–20 mL/h,

increasing every 1–3 days to reach the target within 5–10 days. In patients with disuse of the gastrointestinal tract for more than one month, initial administration consists of 50–100 mL water or 5% glucose, followed by diluted enteral formula delivered by pump at 10–50 mL/h.

(2) Late stage

- **Catheter maintenance:** Flush with 20–50 mL lukewarm water after feeding or medication. For balloon catheters, balloon water should be replaced every 1–2 weeks.
- **Skin care:** The area around the stoma should be cleaned with water or mildly acidic soap. Approximately 1 cm of external shaft length should be maintained to prevent pressure injury and allow smooth rotation.

(3) Catheter replacement

- **Schedule:** Bumper-type catheters are exchanged every 4–6 months; balloon-type within one month. For button catheters, shaft length may require adjustment as subcutaneous tissue increases with improved nutrition.
- **Technique:** A mature tract is generally established within 2–3 weeks. Endoscopic replacement is recommended to avoid malposition, confirmed by direct methods (upper gastrointestinal endoscopy or ultrathin transgastrostomic endoscopy) or indirect methods (fluoroscopy, dye-based techniques such as the "sky blue method").[17)]

5. Adverse Events and Their Management[16-18)]

(1) Submucosal hematoma and bleeding during placement

These occur relatively frequently and are usually controlled with compression. If hemostasis is not achieved, local hemostatic injection, clipping, or surgical intervention may be required. Visible vessels in the gastric or abdominal wall should be avoided during puncture. After placement, the catheter should be left open under decompression until feeding begins to allow early detection of bleeding.

(2) Mispuncture of the transverse colon

Although uncommon, mispuncture of the transverse colon is a serious complication. It is typically asymptomatic at the time of placement but may be revealed at the first tube exchange or by severe diarrhea after feeding through a replaced tube. If infection such as peritonitis is absent, emergency surgery is not indicated and careful observation is appropriate.

Prevention includes: (i) placement under fluoroscopic guidance, (ii) identification of the transverse colon's position with preoperative endoscopy and three-dimensional CT, and (iii) contrast imaging of the transverse colon after oral administration of gastrografin several hours before the procedure.

(3) Mispuncture of the liver

Depending on the site, hemostasis may occur spontaneously or with compression. If bleeding persists, the catheter should be cut externally and the internal bumper removed endoscopically. Continued bleeding, intragastric hematoma, or suspected peritonitis requires prompt laparotomy.

(4) Buried bumper syndrome

This occurs when the internal bumper becomes embedded in gastric mucosa due to excessive tension on the external bumper or mismatch in shaft length. Management depends on the depth of embedding and may require reinsertion of a new PEG tube. To prevent this, external fixation should be released after the immediate postoperative period, usually by the following day. In daily care, it is important to confirm that the catheter rotates smoothly and moves up and down without resistance.

(5) Accidental dislodgement

Accidental removal rarely results in chronic complications but can lead to rapid closure of the tract within hours. A PEG tube, urinary catheter, or Nelaton catheter should be inserted immediately to maintain patency. Reinsertion of the PEG catheter should be performed under endoscopic guidance whenever possible.

(6) Excessive granulation tissue around the stoma

This often improves with hygiene management and application of topical steroid ointment. If refractory, silver nitrate cauterization or surgical excision is performed.

(7) Leakage around the tube

Leakage can be managed by adjusting catheter angle. Replacement with a larger-diameter catheter is generally avoided, as this often enlarges the stoma and worsens leakage.

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Junji Takahashi, Yutaka Suzuki and Shinsaku Fukuda

IV. Small intestine

1-(I) Balloon-Assisted Endoscopy

- Diagnosis

1. Characteristics

Balloon-assisted endoscopy (BAE) is a special type of endoscopy that uses a long endoscope together with a flexible overtube to help the scope reach deep into the intestines. The overtube always has a balloon at its tip, and the endoscope may or may not have an additional balloon at its own tip. This system makes it possible to grip the intestinal wall and straighten the intestine.[1)] It is particularly well suited for insertion into the jejunum and ileum, where stable anchoring within the abdominal cavity is lacking. By employing both peroral and peranal approaches, BAE achieves a high success rate in accessing the entire small intestine.[2)] It is also effective for endoscopic retrograde cholangiopancreatography (ERCP) in cases with postoperative reconstructed intestinal tracts, such as Roux-en-Y anastomosis, and for challenging cases in colonic insertion or treatment. Due to its stable operability, BAE is highly valuable as a therapeutic endoscopy tool. Currently, two types of balloon-assisted endoscopy are available: double-balloon endoscopy (DBE) and single-balloon endoscopy (SBE). As guidelines related to small bowel endoscopy, the Japan Gastroenterological Endoscopy Society has published the *Clinical Practice Guidelines for Enteroscopy* in 2015 and *Guidelines for Endoscopic Balloon Dilation in Treating Crohn's Disease-associated Small Intestinal Strictures*, as a supplement in 2021.[3,4)]

(1) Double-balloon endoscopy

The DBE is equipped with two balloons; one attached to the tip of the scope and the other at the distal end of the overtube (**Figure 1a**). A balloon controller regulates the pressure of the two balloons by alternately inflating and deflating them, thereby stabilizing and grasping the intestine during endoscopic insertion (**Figure 1b**). The balloons are available in latex as well as silicone (latex-free) materials.

Pre-examination preparation is somewhat more complicated since a balloon is attached to the tip of the endoscope.

However, either of the balloons grasps the intestine at each step of the insertion cycle, which ensures that insertion proceeds in a stable and reliable manner.[5)] Various DBE models are available (**Table 1**). The EN-580XP is a thin type with an instrument port diameter of 2.2 mm and mainly used for observation purposes. The EN-580T has an instrument port with a diameter of 3.2 mm and commonly accommodates various devices, including dilation balloons and clips, making it suitable for endoscopic treatment. The EI-580BT is a short type with an instrument port diameter of 3.2 mm. This model is



a | b

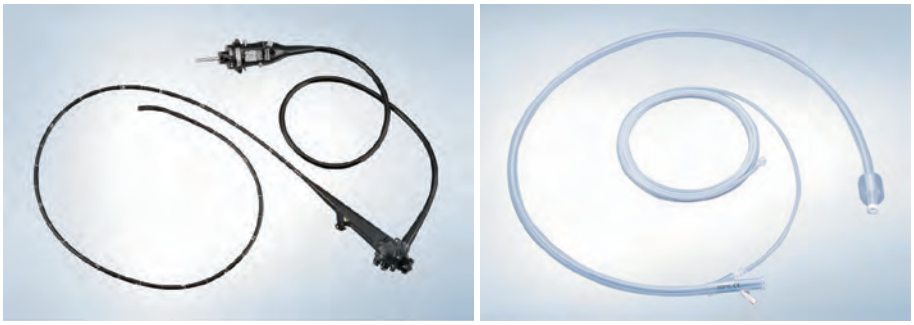
Figure 1 **Components of double-balloon endoscope.**

a: Scope body (EN-580T) with overtube (TS-13140) (FujiFilm)
b: Balloon controller (PB-30) (FujiFilm)

Table 1 **Specifications of latest balloon endoscopes (as of July 2023).**

	EN-580XP	EN-580T	EN-840T	EI-580BT	SIF-H190	SIF-H290S
Field of view	140°					
Observation depth (mm)	2 ~ 100				3 ~ 100	
Distal-end outer diameter	7.5	9.4			9.2	
Insertion tube outer diameter (mm)	7.7	9.3			9.2	
Instrument port diameter (mm)	2.2	3.2				
Angulation range (up/down/left/right)	180°/180°/160°/160°					
Effective length (mm)	2,000			1,550	2,000	1,520
Total length (mm)	2,300			1,850	2,280	1,830
Anti-sticking mechanism	None		Curve tracking		Passive bending	
Torque control	None		High force transmission		High force transmission	
Image enhancement	FICE		LCI/BLI/ FICE	FICE	NBI, TXI*, RDI*	
Compatible overtubes	TS-1114	TS-13140,TS-1314B**		TS-13101	ST-SB1	ST-SB1S
Overtube outer diameter	11.6B	13.2				
Remarks	For double ballon observation	For double	For double ballon	For double ballon	For general use of single ballon	Single ballon short type

*U: up, D: down, L: left, R: right
FICE: flexible spectral imaging color enhancement
NBI: narrow band imaging
TXI: texture and color enhancement imaging
RDI: red dichromatic imaging
*: SIF-H290S is compatible with EVIS X1
**: made of silicone rubber



a | b

Figure 2 Components of single-balloon endoscope.

a: Scope body (SIF-H190) (Olympus)
b: Overtube (ST-SB1) (Olympus)

particularly useful for examinations of colon, distal ileum, and surgically reconstructed intestinal tracts. In addition, the technology uses a curve tracking function that addresses the problem of a walking-stick-shaped scope, in which the tip bends and cannot advance during insertion. It also features a high-force transmission tube designed to improve torque performance, allowing smoother and more precise maneuvering.

(2) Single-balloon endoscopy

SBE uses an endoscope with a silicone balloon attached only to the overtube. Since there is no need to attach another balloon to the body of the endoscope, pre-examination preparation is simple (**Figure 2**). It is latex-free, since both the overtube and the balloon are produced from silicone. As there is no balloon on the endoscope itself, advancement of the overtube is achieved by anchoring the bowel wall with scope angulation; during this maneuver, hooking the tip of the scope onto the outer curvature of the bowel ("outer wrapping") stabilizes the tip position so that it becomes less likely to slip back even when the overtube is advanced.[6,7] Two devices are available: SIF-H190 and SIF-H290S. Their instrument port diameter is 3.2 mm. Notably, both have a passive bending mechanism and a high-force transmission tube (**Table 1**). The SIF-H190 is used for general small intestine examinations. The SIF-H290S is a short type and useful for examinations of the large intestine and distal ileum, as well as post-surgical reconstructed intestinal tracts.

2. Indications and Contraindications

Indications:
Patients suspected of having small-intestinal lesions based on medical history, clinical symptoms, or other diagnostic findings are candidate for BAE. Specifically, it is indicated for the evaluation and treatment of suspected small bowel bleeding (SSBB) without an identified source on upper and lower endoscopy, suspected or diagnosed small intestinal strictures, small intestine tumors, and inflammatory bowel diseases such as Crohn's disease.[2] In addition to endoscopic visualization, BAE enables tissue sampling by biopsy, endoscopic ultrasonography using a miniature probe, and target enteroclysis using water-soluble contrast agent (Gastrografin®). Furthermore, therapeutic interventions such as hemostasis, endoscopic balloon dilation, polypectomy and EMR, foreign body retrieval, and marking with tattooing

or clips are also within the indications of BAE. BAE is additionally useful in challenging cases of colonoscopy such as difficulty in advancing the scope or performing treatments,[3] as well as for evaluation of surgically reconstructed intestinal tracts that are otherwise inaccessible by conventional endoscopes, including ERCP in such reconstructed anatomies.[8]

Contraindications:

Contraindications to BAE are essentially the same as those for upper and lower endoscopy, particularly when the procedure carries a high risk of severe complications and life-threatening events. These include patients with acute abdomen or severe acute inflammation. Since the peroral approach for BAE is more invasive compared with standard upper or lower endoscopy, its indication should be considered carefully.

The procedure should only be performed when the potential benefit outweighs the risk in patients with severely compromised general condition, intestinal obstruction, gastrointestinal perforation, suspected intestinal fragility, Ehlers-Danlos syndrome, or markedly impaired respiratory or circulatory function. In addition, patients with hypersensitivity to natural rubber must undergo the procedure using silicone-based products.

3. Examination Method

(1) Determination of insertion route

For diagnostic methods, the insertion route is determined based on the location of lesions. Generally, the peroral approach is chosen for jejunal lesions and the peranal approach for ileal lesions. If the lesion's location is unclear, the peranal route is initially selected, whereas the peroral approach is preferred in cases of overt bleeding. The insertion route is decided by reference to prior diagnostic findings, such as CT scans or capsule endoscopy.

(2) Preparation, pretreatment, and premedication

Prior tasks differ depending on the approach. For the peroral approach, patients fast from the night before, same as upper gastrointestinal endoscopy. For the peranal approach, bowel preparation is performed according to the protocol for colonoscopy. Although fluoroscopic guidance is not an absolute requirement, it is preferable to have fluoroscopy available in order to confirm the insertion course and facilitate concomitant contrast imaging. The patient's position during the examination is similar to the position used for upper gastrointestinal or endoscopic retrograde cholangiopancreatography when a peroral approach is taken. When the peranal approach is selected, the patient's position is the same as that for colonoscopy. In cases of difficult insertion, changing the patient's position or applying manual abdominal pressure may alter bowel configuration and facilitate scope advancement.

Before the procedure, venous access is secured, and blood pressure and oxygen saturation are monitored. The use of sedatives is recommended, since enteroscopy often involves prolonged procedures. The peroral approach is more invasive than the peranal route, necessitating sufficient sedation and analgesia.

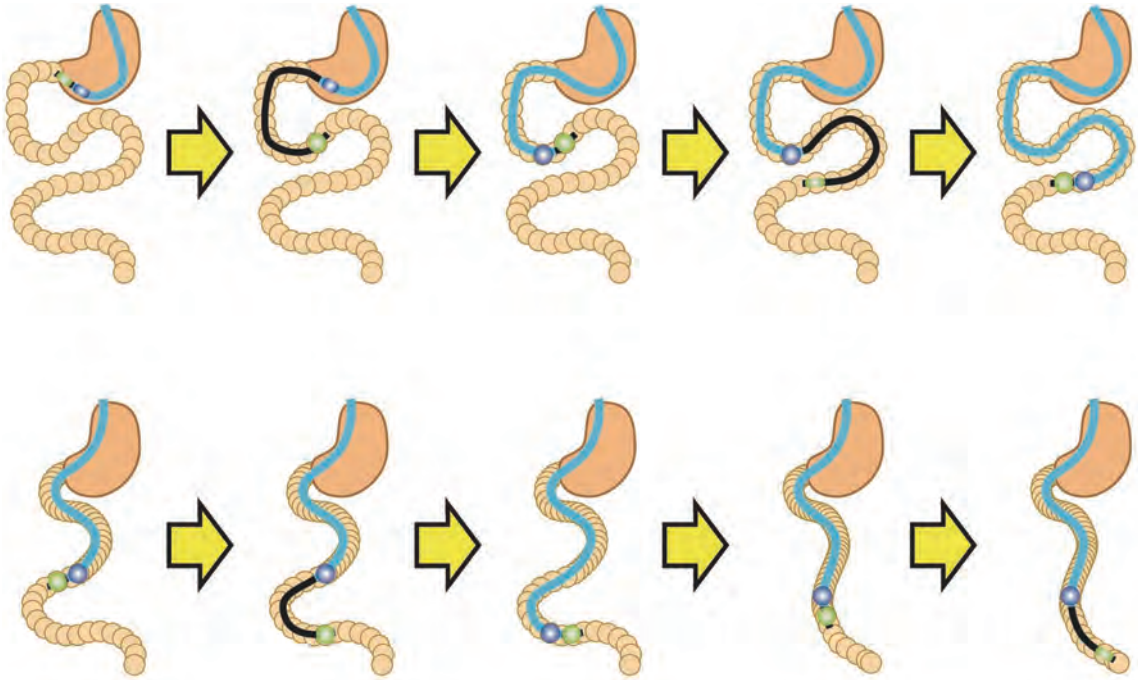


Figure 3 Peroral insertion of double-balloon endoscope.
(Courtesy of Dr. Tomonori Yano, Jichi Medical University)

(3) Insertion of DBE

DBE will advance forward through the intestinal tract by sequentially inflating and deflating the balloons located at the tips of both the overtube and the endoscope. This mechanism enables the endoscope to anchor itself at different points, drawing the intestine toward the scope. The manipulation allows gradual advancement through simplifying the configuration of intestine for deeper insertion as shown in **Figure 3.** It is important for endoscopists to understand this principle well and guide the endoscope while carefully adjusting the intestine to an appropriate shape that does not require excessive force. The balloon pressure is regulated by a controller to prevent excessive force on the intestinal wall. If the scope or overtube does not properly assume the correct shape during insertion, the balloon might slip, thereby causing it to retract. The problem prevents deep insertion of the instrument. The insertion is proceeded with implementing the small intestine shortening procedure little by little while adjusting the shortening position. It is also useful to employ incorporating techniques like changing the patient's position or applying manual abdominal pressure. To minimize strain on the intestine, it is critical to sterically maintain a configuration resembling large concentric loops during insertion.[9)]

Figures 3 & 4 show the insertion cycle for DBE step by step.

- The overtube balloon anchors the intestine as the starting point for advancement of the endoscope.
- Once the endoscope reaches deeper sections, its balloon inflates to hold the intestine in place.
- The overtube balloon should be deflated and the overtube can be advanced to follow the endoscope.
- The overtube balloon should be inflated to anchor the intestine.
- Both balloons are used to hold and shorten the intestine.

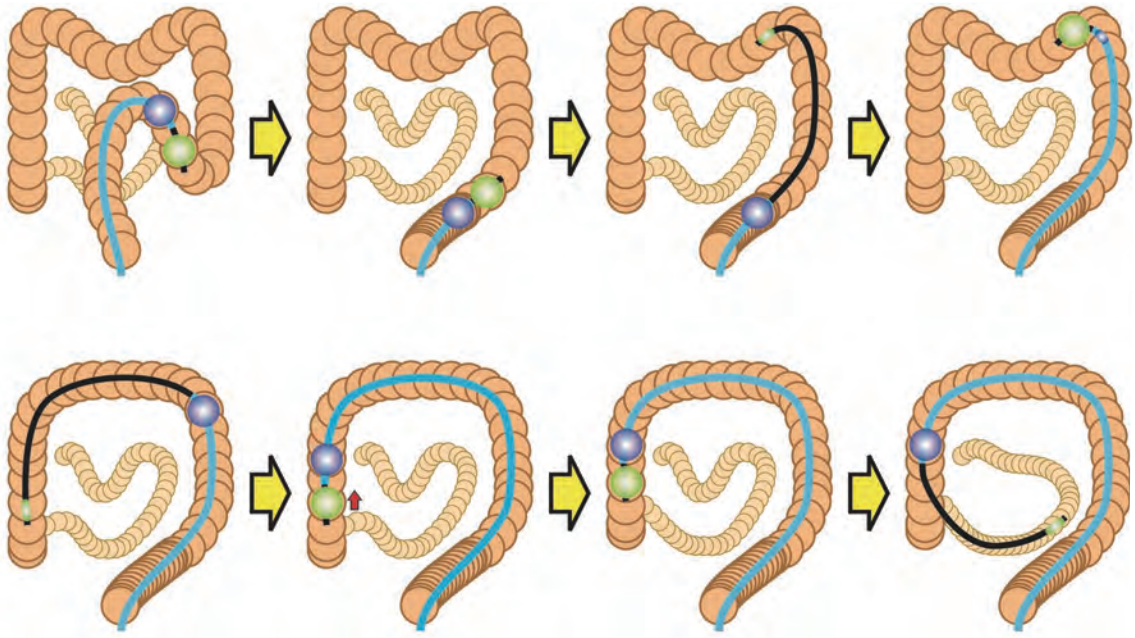


Figure 4 Peranal insertion of double-balloon endoscope.
(Courtesy of Dr. Tomonori Yano, Jichi Medical University)

- The endoscope balloon should be deflated and the endoscope can be advanced again.
- Repeat of this cycle enables deeper insertion. Unlike SBE, DBE features a balloon at the endoscope tip that fixes the intestine in place even while the overtube balloon is deflated. This makes DBE particularly suitable for stable advancement in difficult cases and for achieving deeper insertion.

(4) Insertion of SBE

In SBE, the overtube is similarly used to simplify the configuration of intestine and facilitate its shortening on insertion. Figure 5 shows the insertion cycle:

- The endoscope can be advanced with the fixation provided by the balloon at the tip of the overtube.
- The intestine should be anchored through the application of scope angulation. Because the small intestine is advanced in concentric loop, rotation of the tip outward helps to anchor the bowel (**Figure 6**).
- The overtube balloon should be deflated and the overtube can be advanced to follow the endoscope.
- The overtube balloon should be inflated to anchor the intestine.
- While shortening the intestine, the endoscopist should gradually release the rotation of the endoscope.

By repeating this cycle, the intestine is progressively shortened and the endoscope can be advanced.[10] During overtube insertion, care is taken to slightly retract the endoscope but not push it forward to avoid excessive pressure on the intestinal wall.

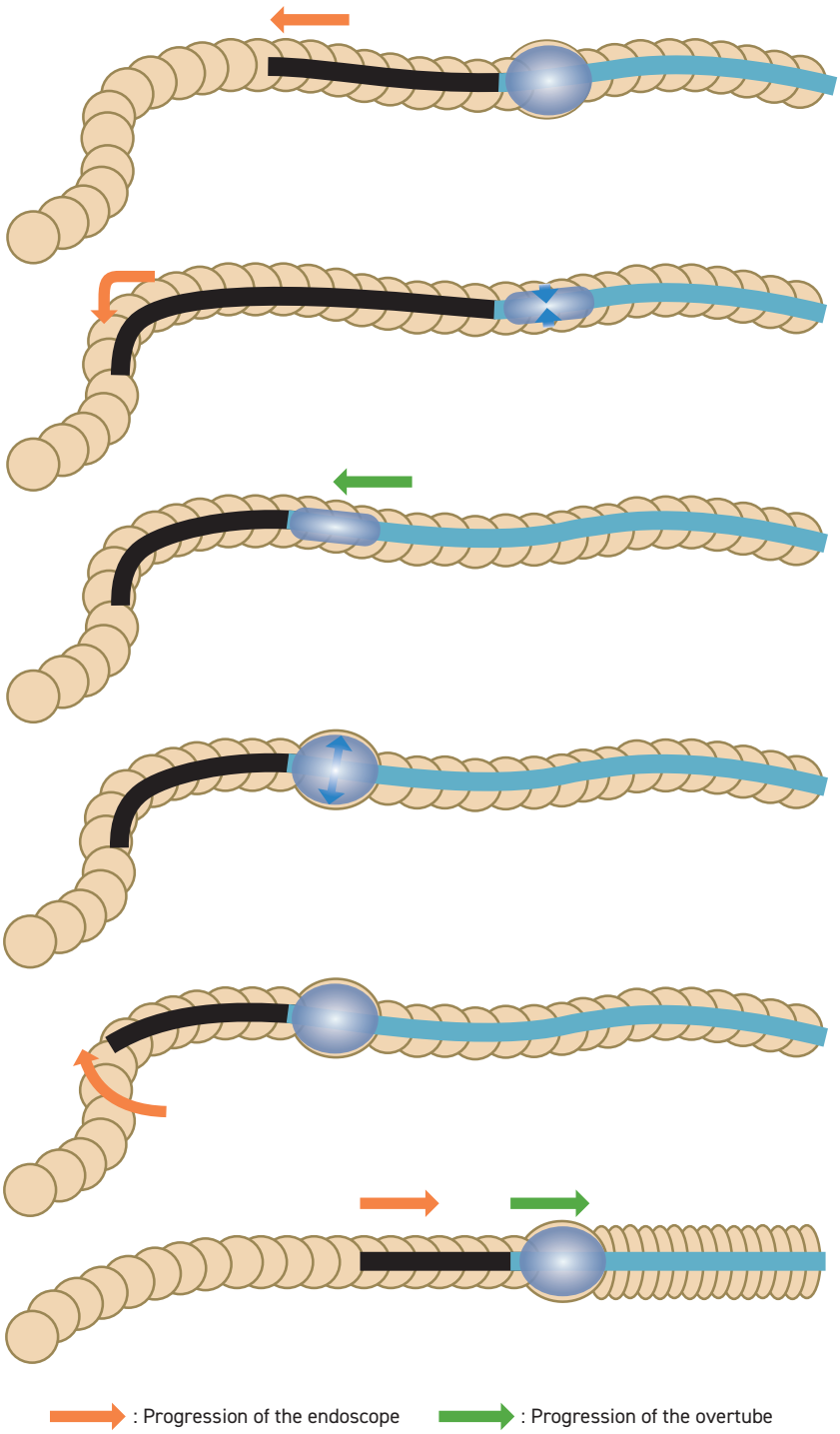


Figure 5 Insertion of single-balloon endoscope.

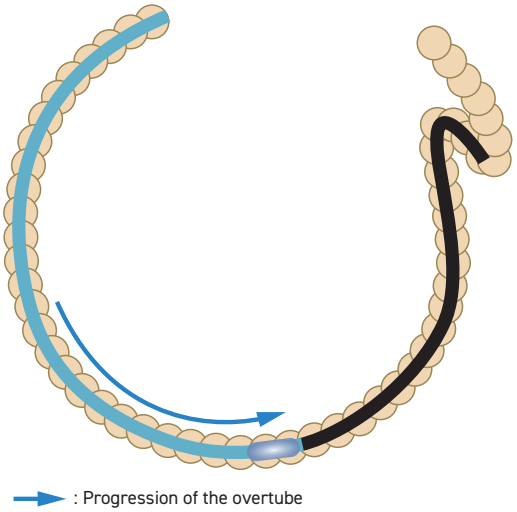


Figure 6 Intestinal fixation by rotation of the distal angulated portion from inward to outward direction.

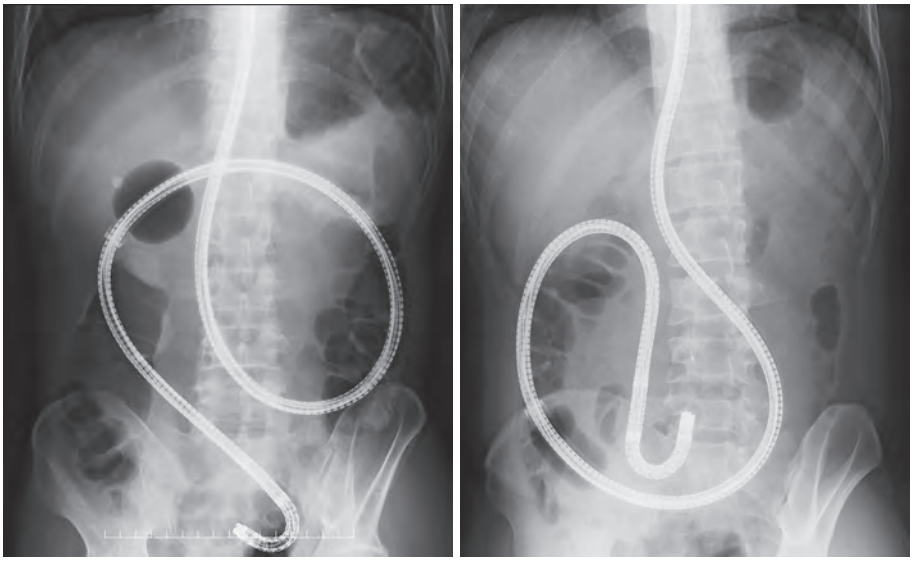
(5) Key points for insertion and observation in BAE

In principle, a significant level of experience with upper and lower gastrointestinal endoscopy is required for operators. In particular, proficiency in performing colonoscopy is essential, as this skill should be applied to the procedure. Although the procedure is often performed using a two-operator method, in which the endoscopist manipulates the scope and the assistant manages the overtube. However, a skilled endoscopist controls both the endoscope and overtube operations alone in single-operator method.[10,11)]

Several key points exist for deep insertion. Carbon dioxide should be used for insufflation as a rule, but the insufflation volume should be kept to a minimum level. To achieve deep insertion, it is essential for an endoscopist to sufficiently shorten the small intestine. However, in air insufflation, gas tends to remain within the intestine. This reduces the effectiveness of shortening. To minimize insufflation, endoscopists should use a transparent cap at the tip of the endoscope. It is also useful to apply water rather than air for insufflation to maintain the lumen. The water exchange method is a process where residual gas and intestinal fluid are aspirated and replaced with water. This method has been reported in colonoscopy to maintain low intestinal pressure and minimize discomfort for the patients.[12)] In a report using SBE, the water exchange method has been shown to improve the total enteroscopy rate compared to carbon dioxide insufflation.[13)]

In the peroral approach, pancreatitis sometimes occurs as a complication. Risk factors for postprocedural hyperamylasemia include elderly, deep insertion, and clockwise insertion.[14)] Therefore, in elderly patients, when insertion is performed in a clockwise direction, deep insertion should preferably be avoided (**Figure 7**).

In the peranal approach, passing through the ileocecal valve tends to present some difficulty. In such cases, the balloon is inflated just above the ileocecal valve, and both the endoscope and overtube are sufficiently withdrawn toward the anal side, thereby widening the angle between the ascending colon



a | b

Figure 7 Peroral insertion direction.

a: Counterclockwise
b: Clockwise

and terminal ileum to facilitate insertion. Additionally, manual abdominal pressure on the anterosuperior or inner side of the ileocecal valve causes the terminal ileum to shift downward and help blunt the angle. Once the endoscope passes through the ileocecal valve, it should advance as far as possible into the deep ileum to prevent the endoscope from retracting while the overtube advances.

On removal, the overtube and endoscope should be alternately removed step by step. The distance for each overtube removal should be limited to 10 to 15 cm. Withdrawing further may cause sudden slippage of the endoscope, resulting in insufficient observation.

4. Endoscopic Observation and Diagnosis

Endoscopic observation with BAE is primarily conducted on white light. Although BAE scopes are not equipped with optical magnification, underwater observation affords a slight magnifying effect and makes the villi stand erect, often yielding clearer images. For image enhancement with DBE, the EN-580 series offers FICE (Flexible Spectral Imaging Color Enhancement), and the latest EN-840T additionally supports LCI (Linked Color Imaging) and BLI (Blue Laser Imaging). With the latest SBE model (SIF-H190), NBI (Narrow Band Imaging), TXI (Texture and Color Enhancement Imaging), and RDI (Red Dichromatic Imaging) are available. Indigocarmine spray can also be used when necessary. Because small intestine exhibits stronger peristalsis than colon, antispasmodic agents are used as needed.

In addition to endoscopic diagnosis, target enteroclysis using water-soluble contrast agent (Gastrografin®) is also useful. With DBE, efficient opacification of segments beyond the reach of the scope can be achieved by inflating the distal endoscope balloon to create a wedge seal. However, excessive contrast agent injection possibly leads to intestinal perforation, so caution is especially

needed in patients with mucosal fragility.

Biopsy is also important for diagnosis and is generally effective for neoplastic lesions. However, in cases of GIST, there have been reports of significant bleeding from the biopsy site. When biopsy is performed from a GIST lesion, it should be undertaken with adequate backup in place. Additionally, a vascular lesion in the small intestine should be carefully observed for its shape along with presentation of pulsation. In practice, biopsies should be performed with caution.

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Shigeki Bamba, Kazuo Ohtsuka and Hironori Yamamoto

1-(II) Balloon-Assisted Endoscopy

- Treatment

1. Therapeutic Procedures Related with Balloon Assisted Endoscopy

Balloon assisted endoscopy (BAE) with an instrument channel enables various endoscopic procedures due to its ability to maintain excellent maneuverability deep within the small intestine.

(1) Endoscopic resection

Similar to upper and lower endoscopy, BAE is useful for resection procedures such as polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). Polyposis syndromes such as Peutz-Jeghers syndrome (PJS) and familial adenomatous polyposis (FAP), which develop numerous polyps in the small intestine, are recognized as indications for this treatment using BAE. Polyps in PJS can be resected using polypectomy and EMR with a snare, but those procedures pose the risks of perforation and bleeding. As hamartomatous polyps presented in PJS generally have a low risk of malignancy, ischemic polypectomy with BAE is also recommended.[1,2] This approach, with the placement of a detachable snare or endoclips, is preferable because it tends to have lower risks of perforation and bleeding. In general, in FAP, polyps are resected because they are adenomatous. For small lesions, cold snare polypectomy (CSP) with BAE is recommended due to its safety and efficiency.[3]

(2) Endoscopic hemostasis

Vascular lesions, which are often treated using hemostasis procedures with clipping or argon plasma coagulation (APC), are responsible for about 40% of small bowel bleeding events.[4] According to the endoscopic classification of small intestinal vascular lesions,[5] the treatments are recommended for Type 1a lesions when bleeding continues, and for lesions except Type 1a regardless of whether bleeding persists. In cases of massive bleeding where the narrow lumen of the small intestine is filled with blood, it is impossible to obtain a clear visual field; gel immersion endoscopy (GIE), with injection of transparent gel, is helpful to secure the visual field.[6,7]

(3) Endoscopic balloon dilation

Endoscopic balloon dilation (EBD) is indicated for benign strictures, such as Crohn's disease-related small intestinal strictures, post-ischemic enteritis, and diaphragm-like strictures caused by non-steroidal anti-inflammatory drugs (NSAIDs). In strictures via Crohn's disease, this procedure is appropriate for the strictures that extend 5 cm or less in the longitudinal length. The patients who have the strictures present with symptoms related to the stricture, or the images show dilation of the intestinal proximal to the stricture. Furthermore, these strictures should not be accompanied with fistulas, fissures, abscesses, deep ulcers, or strong angulation with adhesions.[8,9)]

(4) Endoscopic foreign body removal

Various objects such as a capsule endoscope remaining in the lumen, accidentally-swallowed PTP sheets, toothpicks, dentures, enteroliths, or biliary drainage tubes can be retrieved with BAE. A transparent cylindrical hood should be attached to the tip of the endoscope. This distal attachment is useful not only to secure the visual field during the procedure, but also to house the sharp edges of foreign bodies, preventing injury to the intestinal wall during retrieval.

(5) Endoscopic retrograde cholangiopancreatography-related procedures

It was difficult to approach the duodenal papilla or hepaticojejunostomy site with conventional endoscopy. Currently, endoscopic retrograde cholangiopancreatography (ERCP)-related procedures with BAE for postoperative intestinal tracts have become feasible. A high success rate of endoscopic retrograde cholangiography (ERC) using short-type double-balloon enteroscopy (DBE) has been reported with a low incidence of adverse events.[10)]

The lumen of the afferent loop is a semi-closed space, enclosed between the blind end of the loop and the balloon situated at the tip of the overtube. The narrow space easily increases the intraluminal pressure of the space when air is insufflated. The risk results in the development of gas embolism, a complication that possibly becomes fatal. Therefore, great care must be taken to avoid excessive insufflation.

(6) Endoscopic reduction of intussusception

Intussusception with intestinal ischemia requires emergency surgery. However, reduction with BAE may be possible if intestinal blood flow is maintained. Endoscopic reduction of intussusception with DBE has been reported for PJS polyps and inflammatory fibroid polyps (IFP),[11)] and removal of the polyps after intussusception reduction prevents recurrence.[12-14)]

2. Therapeutic Scopes

The selection of therapeutic scopes depends on the intended usage. Therapeutic scopes typically have an instrument channel with a diameter of 3.2 mm, allowing to use a wide range of instruments. When equipped with the BioShield® Irrigator biopsy valve (STERIS) for endoscopic irrigation, these scopes gain the function to continue injecting water, water-soluble contrast agents, or gel even while the

Type	Short		Cylindrical			Small-caliber tip
Intended use	Observation/biopsy		Hemostasis/polyp treatment		Observation/treatment	Balloon dilation
Product no.	DH-32EN	DH-17EN	D-201-10704	Space adjuster	Elastic touch S	CAST hood
Manufacturer	Fujifilm	Fujifilm	Olympus	TOP	TOP	TOP
Tip length	1 mm	1 mm	4 mm	4 mm	Adjustable	6 mm
						

Figure 1 Main distal attachments used in balloon assisted endoscopy.

instruments are in use. The observation scope is thinner than the therapeutic scope and offers good insertion capability with minimal invasiveness. However, due to its narrower instrument channel with a diameter of 2.2 mm, the range of available instruments is limited; therefore, creative approaches for therapeutic procedures are required.

There are several scopes in the long model (working length: 2,000 mm) and the short model (working length: 1,520 to 1,550 mm) for single-balloon enteroscopy (SBE) and DBE. When the location of a lesion is unclear or deep insertion is needed, choosing a longer scope is preferable. However, shorter scopes offer a few benefits. They allow for a wider array of instruments with quicker insertion, and the scope itself is easier to handle outside the patient's body. These advantages are helpful in cases where the target site is near the insertion start point, as well as for ERCP in post-surgical reconstructed intestines.

3. Distal Attachments

Selection of the appropriate distal attachment based on the intended usage (**Figure 1**) is essential for safe and efficient examinations and treatments. For diagnostic purposes such as observation and biopsy, a short hood is selected not to obstruct the visual field. This design helps maintain a small gap between the lens and the mucosal surface, preventing red-out phenomenon and ensuring a clear visual field. For hemostasis or polypectomy, a cylindrical hood is recommended. The hood maintains an appropriate distance from lesions even when instruments such as clips are deployed inside it, ensuring safe scope maneuverability. For observing small intestinal strictures or performing balloon dilation, a calibrated, small-caliber-tip, transparent (CAST) hood® [15] having calibration lines along its side is useful. It allows for measuring the inner diameter of a stricture by placing the hood against the narrowed area. The design of the CAST hood offers additional advantages, enhancing procedural efficiency and safety. It smoothly guides a guidewire along its inner surface, allowing the guidewire to pass through its opening and to access a narrowing site. Additionally, it helps the scope to pass through the stricture after balloon dilation.[16]

4. Insertion Route

Selection of the antegrade or retrograde insertion is based on the results of the pre-procedural examinations. If the location of a lesion is unknown and there is a possibility of examining the entire small intestine, a retrograde approach is preferable because it is less invasive and carries a lower risk of pancreatitis. In such a case, the deepest point is marked via the retrograde approach before implementing

the antegrade approach. For active bleeding in the small intestine, the antegrade approach is generally preferable as it is useful for gaining a clear visual field and then identifying the source of bleeding by recognizing the hemorrhagic intestinal fluid. If CT scans reveal the source of bleeding in the distal ileum, a retrograde approach is selected. GIE from the start of the anal insertion is effective to ensure a clear visual field. This method reduces reflux of hemorrhagic intestinal fluid, improves maneuverability of the endoscope, and alleviates patient discomfort by maintaining low intraluminal pressure.

5. Bowel preparation

Bowel preparation for BAE differs depending on the insertion routes. In the antegrade approach, patients are required fasting from the night before, similar to upper gastrointestinal endoscopy. In the retrograde approach, patients need to follow the colonoscopy protocol, taking the bowel-cleansing solution. In cases of PJS or mild to moderate strictures, bowel preparation could require more time; a split-dose bowel preparation regimen[17], where the cleansing solution is divided into one liter the day before and one liter on the morning of the procedure, should be used. In cases of severe gastrointestinal strictures, oral administration of the cleansing solution is contraindicated. Instead, a high-pressure enema with one liter of warm water is used for bowel preparation in such cases. Then, the scope is inserted using GIE to ensure visualization.

6. Clear Visual Field

Requirements for ensuring a clear visual field include carbon dioxide insufflation, water exchange (WE) method,[18] and GIE. These methods are selected depending on the situation. WE and GIE provide several benefits which include not only maintaining a clear visual field but also improving maneuverability by keeping intraluminal pressure low. They also help lower the risk of adverse events such as perforation and gas embolism. Moreover, the dosage of analgesics and sedatives can be reduced due to these methods. However, if a larger space is required, for example, such as for the treatment of large polyps, insufflation should be necessary to expand the lumen. GIE is particularly effective for ensuring a clear visual field in cases of persistent bleeding or inadequate bowel preparation, as viscous gel prevents mixing with hemorrhagic intestinal fluid or residue.

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2 Capsule Endoscopy

1. Characteristics

Capsule endoscopy is a minimally invasive procedure that allows for examination of the gastrointestinal tract while the subject swallows a small, capsule-shaped endoscope (**Figure 1**). The capsule continuously captures still images, which are stored either in the capsule itself or on an external recording device. These images are not only reviewed as video by specialized software after the process,[1] but also observed during the process in real time manner. The small bowel capsule endoscopy achieves a high rate of full small bowel observation, approximately 85%, in patients with obscure gastrointestinal bleeding (OGIB).[2] **Figure 2** shows the diagnostic algorithm for OGIB in Japan.[3] In 2012, a new capsule became available called the PillCam® Patency Capsule or also known as the patency capsule as shown in **Figure 3**. This capsule helps to determine if there are any obstructions in the gastrointestinal tract. [3] Initially, this device was used to assess gastrointestinal patency before operation. Its use has since broadened, and it now helps evaluate not only individuals who might have gastrointestinal stenosis but also patients with known or suspected small bowel disease. Recently, it has also come to be widely used for the diagnosis and severity assessment of Crohn's disease.[4]

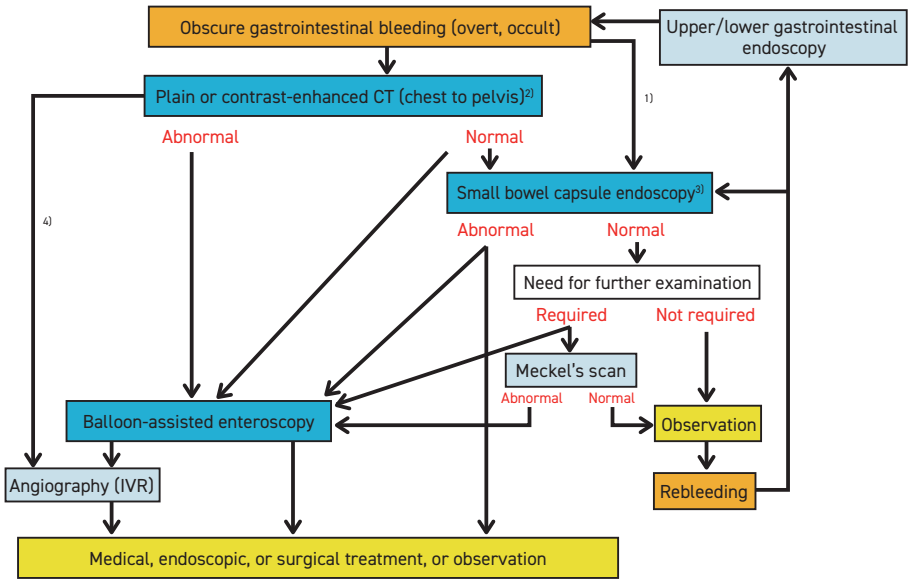
Currently, the small bowel capsule endoscopes approved and primarily used in Japan are PillCam® SB 3 manufactured by Covidien, EndoCapsule® manufactured by Olympus, and CapsoCam Plus® manufactured by Nagase. While the systems and examination methods of the three companies are almost identical, there are two types of mechanisms: a system that transmits images captured by the capsule endoscope to an external recording device attached to the patient's body in real-time (PillCam® SB 3 and EndoCapsule®) and a system that stores captured images in the flash memory built into the capsule endoscope to read them after recovery of the excreted capsule (CapsoCam Plus®). There are differences in insurance coverage in Japan (see section 2. Indications and Contraindications). **Table 1** compares the capsule endoscopy systems and components of the three companies.[5]

Capsule endoscopy is an examination in which a patient simply swallows an 11 × 26 mm (PillCam® SB 3, EndoCapsule®) or 11 × 31 mm (CapsoCam Plus®) capsule-type endoscope. It is a simple, safe, and easy examination for patients, but there is a possibility that lesions are overlooked. **Therefore it is necessary to understand its characteristics properly and interpret the examination results accordingly.** Unlike conventional gastrointestinal endoscopy where clinicians perform the examination directly, nurses or other medical professionals are often involved in the examination process including assistant nurses, clinical laboratory technicians, radiologic technologists, and clinical engineers.



Figure 1 Small bowel capsule endoscopy.

a: ENDOCAPSULE EC-S10 (Olympus)
b: PillCam SB 3 (Covidien)
c: CapsoCam Plus (Nagase)



Delphi method evaluation Median: 7.5, Minimum: 6, Maximum: 9
Evidence level: IVb–V, Recommendation grade: C1

Figure 2 Diagnostic algorithm for OGIB.

1) In facilities without CT, capsule endoscopy could be performed first, but CT scanning should be performed subsequently.
2) It is important to note that some lesions could not be visualized without dynamic CT.
3) It is advisable to first use a patency capsule to evaluate gastrointestinal patency if Crohn's disease is suspected, the patient experiences abdominal pain or distension, or the case has a history of long-term NSAID use, abdominal radiation, or abdominal surgery. Following this assessment, small bowel capsule endoscopy would then be performed. Note that capsule endoscopy and gastrointestinal patency testing with patency capsule should not be performed in cases of intestinal obstruction including suspected cases.
4) When endoscopic procedures are difficult.
(Cited from Literature 3)

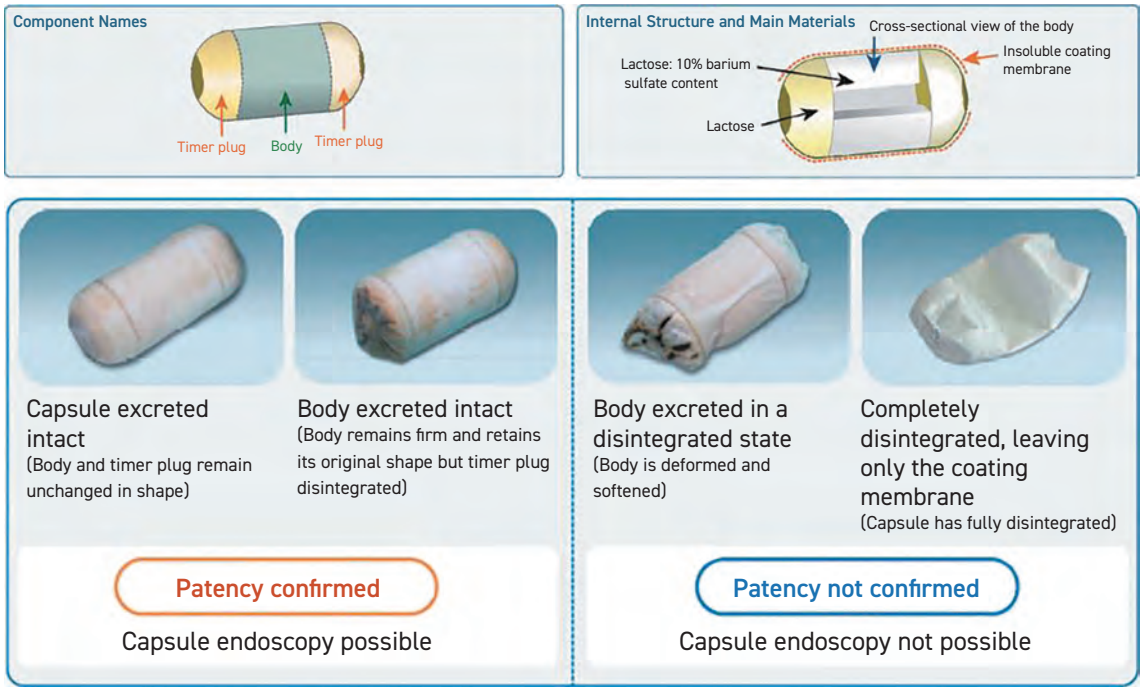


Figure 3 Structure of PillCam® patency capsule and gastrointestinal patency assessment.

(Cited from Literature 3)

Table 1 Comparison of small bowel capsule endoscopy devices and equipment .

Name	Covidien Japan	Olympus	Nagase
Capsule endoscope	PillCam® SB 3 Capsule	ENDOCAPSULE® (EC-S10)	CapsoCam Plus®
Antenna	PillCam® Sensor Array or PillCam® SB 3 Sensor Belt	Antenna unit	-
Recorder & Receiver	PillCam® Recorder DR3	ENDOCAPSULE® (RE-10)	- (Built-in flash memory)
Workstation	RAPID® Workstation		-
Software		ENDOCAPSULE® SOFTWARE 10	CapsoView®

(Modified from Literature 5)

2. Indications and Contraindications

As of June 2023, the insurance coverage for capsule endoscopy is as follows:

(i) **To be used in patients with obscure gastrointestinal bleeding after upper and lower gastrointestinal examinations including endoscopic examinations.** For insurance purposes, upper and lower gastrointestinal examinations are not limited to endoscopic examinations. If the cause of bleeding is unclear after barium enema or other X-ray contrast examinations, capsule endoscopy is also covered by insurance (EndoCapsule®, PillCam® SB 3, and CapsoCam Plus®).

Table 2 Contraindications for capsule endoscopy.

- Patients with known or suspected gastrointestinal obstruction or fistulas based on abdominal X-ray, ultrasound, medical history, surgical history, or clinical findings
- Patients with known gastrointestinal strictures where capsule retention is clearly anticipated during capsule endoscopy
- Patients with Crohn's disease involving lesions in the small bowel (EndoCapsule® only)
- Patients with implanted cardiac pacemakers or other electronic medical devices (PillCam® SB 3 capsule and EndoCapsule®)
- Patients with dysphagia or patients who cannot take capsules
- Patients with a history of hypersensitivity to barium sulfate preparations (patency capsule only)
- Pregnant patients (EndoCapsule® and CapsoCam Plus®)
- Patients with Zenker's diverticulum or Meckel's diverticulum (EndoCapsule® only)
- Patients with gastrointestinal bypass surgery or implanted devices such as stents that could obstruct passage (EndoCapsule® only)
- Patients with gastroparesis (CapsoCam Plus® only)

Contraindicated Combination: Do not use magnetic resonance imaging (MRI) concurrently
(Modified from Literatures 6 to 8)

(ii) **A patency capsule is used to evaluate the patency of the gastrointestinal tract before capsule endoscopy in patients with or suspected of having gastrointestinal stenosis or narrowing. Once the gastrointestinal tract has been assessed through the patency capsule, the capsule endoscope is then swallowed.** (PillCam® SB 3 only).

There are also differences in the contraindications for EndoCapsule®, PillCam® SB 3, and CapsoCam Plus® (**Table 2**).[6-8)]

3. Actual Examination Procedures

Table 3 shows the actual examination procedures,[3,6-8)] and the followings are supplemented information.

(1) Initial visit

Eligibility for the procedure is confirmed, and the written informed consent is obtained.
Patients are informed of the examination schedule and given necessary precautions.
For patients with or suspected of having a gastrointestinal stenosis or narrowing, a patency capsule is used for preoperative patency assessment. Patency is determined 30 to 33 hours after a patency capsule is swallowed. Patency is confirmed when the excreted capsule remains completely intact, or its main body is intact with only the timer plug dissolved. Generally, this condition is verified through both visual and tactile inspection (**Figure 3**).[3)] Patency is also ensured if the capsule is confirmed to have reached the large bowel by X-ray examination. This verification is performed with computed tomography (CT) scanning.

(2) Preparation

Patients are given instruction to eat nothing for approximately 8 hours or more before the examination.

Table 3 Flow of the examination process.

1. Initial visit
Selecting subjects and obtaining consent; Registering examination
Scheduling; Pre-examination explanation
*Patency assessment (if applicable): If the patient has or is suspected of having a narrowing in the digestive tract, a patency capsule is swallowed to check if the digestive tract is obstructed.

2. Before examination
Equipment check
Patient preparation: Patients should stop taking certain medications prior to the examination and fast for at least 8 hours before the procedure

3. Examination day
Preparation for examination
Swallowing a capsule endoscope
Equipment removal: After the examination, removal of the recording device and other equipment; collecting the capsule endoscope
Data transfer from the recording device to the workstation (for PillCam® SB 3 and EndoCapsule®)
Maintenance of the examination equipment and devices (for PillCam® SB 3 and EndoCapsule®)

4. Image diagnosis on the same day or the following day
Preliminary review
Detailed examination
Report generation
Data management

5. Post-examination (Or the examination to be complete when the capsule is excreted)
Confirmation of capsule excretion
Confirmation of no retention
Explanation of examination results

* Applicable only to a patency capsule
(Modified from Literatures 3, 6 to 8)

(3) Examination day

(i) A medical interview is conducted to assess gastrointestinal symptoms, bowel habits, stool characteristics, and the time of the last meal.
(ii) Vital signs are recorded including blood pressure, pulse, and temperature.
(iii) Patient information is entered into the workstation.
(iv) A sensor array (antenna unit) is attached to designated areas of the patient's body.
(v) A recording device is secured to the patient using a pouch and belt.
(vi) The patient then swallows the capsule. While no standard bowel preparation has been established for small bowel capsule endoscopy, if appropriate, agents could be used such as polyethylene glycol electrolyte solution, simethicone, or prokinetic agents because they are reported helpful. The patient is allowed to drink water two hours after swallowing the capsule and have a light meal four hours afterward.
(vii) After the arrival of the capsule is confirmed in the colon on the real-time monitor, the recording device and sensor array are removed.
(viii) Data is then transferred from the recording device to the workstation.
*The steps ((viii) to (v), (vii), and (viii)) are only necessary for PillCam® SB 3 and EndoCapsule.

(4) Post-examination

1) For PillCam® SB 3 and EndoCapsule®

(i) Image analysis, report creation, and data management are performed with workstation-integrated computer-aided software to enhance diagnostic efficiency.

(ii) Capsule excretion and retrieval are also confirmed.

2) For CapsoCam Plus®

(i) The capsule is retrieved using a dedicated kit.

(ii) The capsule is disinfected, and connected to a PC equipped with specialized software to transfer the image data.

(iii) The subsequent steps include image diagnosis, report creation, and data management.

3) Patient explanation and precautions

The patient are provided with the examination results and instructions for any additional testing or treatments, such as balloon-assisted endoscopy, if necessary. Given the possibility that some findings could be overlooked, additional tests should be considered even when results from a small bowel capsule endoscopy appear normal but symptoms continue.

4. Prevention and Management of Adverse Events

A distinctive complication associated with capsule endoscopy is capsule retention.

Retention is defined as a condition in which the capsule remains in the body for more than two weeks or is expected not to be excreted without endoscopic or surgical removal.[9] The incidence of retention has been reported to be 1.4% in patients with OGIB, 7.4% in confirmed cases of Crohn's disease, and 6.3% in suspected cases.[10,11] In cases using patency capsules for suspected small bowel stenosis, retention occurred in 0.51% of cases.[12]

While retention does not typically lead to emergencies such as intestinal obstruction, retrieval through balloon assisted endoscopy or surgery is necessary if natural excretion does not occur. Additionally, incidents of capsule aspiration into the airway have been reported. Therefore, for patients with swallowing disorders, it is prudent to perform capsule endoscopy with the aid of upper gastrointestinal endoscopy (**Figure 4**).[3,6]

This section has been created in accordance with the *Clinical Practice Guideline for Enteroscopy*.[3]

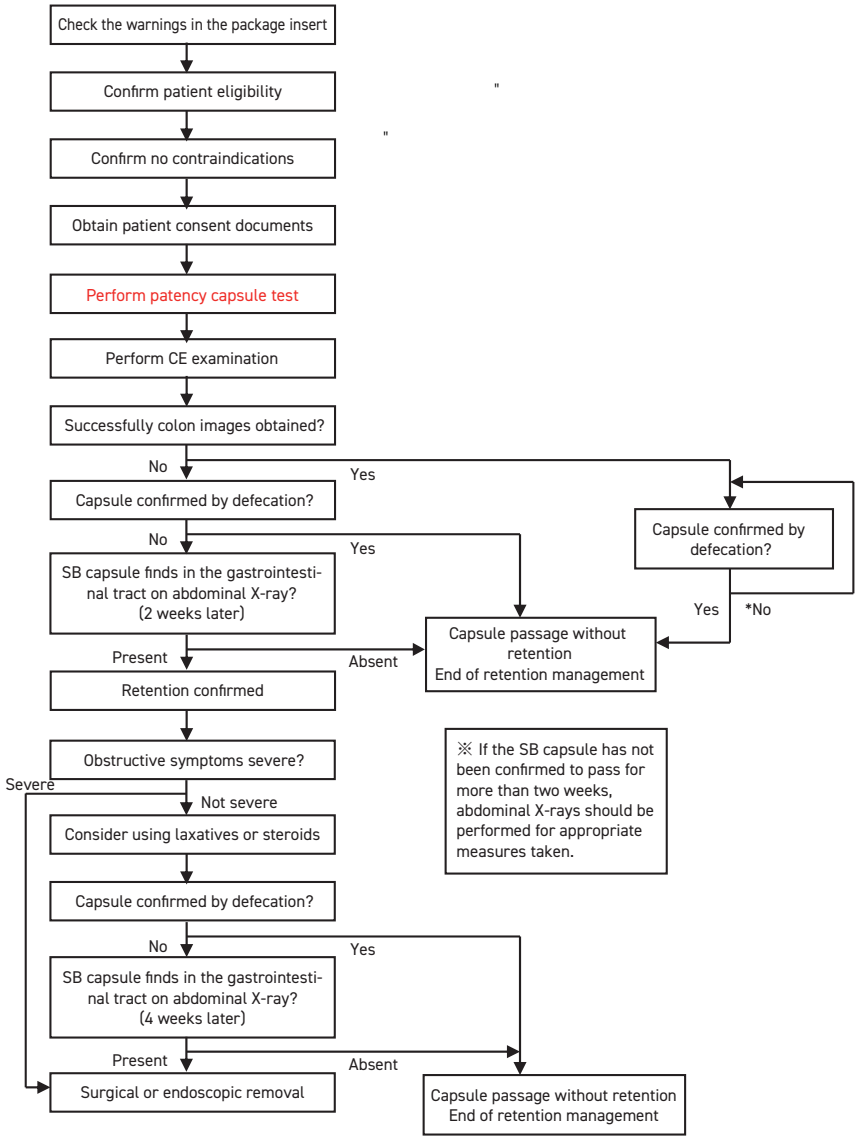


Figure 4 SB capsule retention management flowchart.

(Cited from Literature 6)

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Masanao Nakamura, Mikihiro Fujiya and Kazuhide Higuchi

V. Large intestine

1 Definition and Classification of Colorectal Regions

1. Depth of Tumor Invasion

In the 9th Edition of the *Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma*,[1] the depth of tumor invasion in large intestine is classified using the T classification system (**Table 1**). Abbreviations such as M, SM, MP, SS, A, SI, and AI are used to describe tumor invasion into the layers of colorectal wall and the extent of spread to surrounding organs. Among them, SI indicates that the tumor has penetrated beyond the serosa in regions where the layer is present and has invaded adjacent structures. AI describes cases where the tumor in regions without serosa spreads into other organs. Rectal-type adenocarcinoma in the anal canal is treated differently because its anatomy differs from other parts of the colon, and tumor invasion is defined separately (**Table 2**).

Tis cancer typically refers to carcinoma *in situ*, namely cancer confined to mucosa without invading deeper layers, and has a unique definition in colorectal cancer. This includes intramucosal carcinoma, which is not just limited to the mucosa but stays in the submucosa, regardless of its actual invasion.

In Japan, Tis and T1 are defined as early cancer, whereas tumors that infiltrate deeper than the muscularis propria is defined as advanced cancer.[1] In cases of T1 tumors, deciding how deeply the cancerous tissue has invaded is crucial to determine the treatment. Two methods are used for the classification: relative depth and absolute depth. The former divides the distance from the muscularis mucosae to the muscularis propria into three layers (SM1, SM2, and SM3).[2] This method is simple and does not rely on exact measurements, but can only be applied when the muscularis propria is present thus more appropriate for assessing specimens that have been surgically resected. The latter measures the invasion depth in micrometers, and has become the standard due to the increasing operations of endoscopic resection. In addition to the given guideline, the *JSCCR Guidelines 2022 for the Treatment of Colorectal Cancer* [3] also recommends further surgery if the invasion depth exceeds 1,000 μm after endoscopic resection, highlighting the importance of exact measurement.

According to 9th Edition of the *Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma*,[1] the method for measuring the tumor invasion is determined regardless of the macroscopic type. In cases where the course of the muscularis mucosae is reliably identified or reasonably estimated, measurement is performed from the lower border of the affected muscularis mucosae. In cases where the muscularis mucosae are not noticeably identified or estimated, measurement is performed from the surface of the lesion (**Figure 1**). For pedunculated lesions, where the muscularis mucosae is often distorted, it is challenging to find a reference point for measurement. When invasion is limited within the lesion's head, it is treated as head invasion.

Table 1 Classification of invasion depth for colorectal cancer.

TX : Primary tumor cannot be assessed.
T0 : No evidence of primary tumor
Tis : Tumor is confined to the mucosa (M) and does not invade the submucosa (SM).
T1 : Tumor is confined to the SM and does not invade the muscularis propria (MP).
T1a: Tumor is confined to the SM, and invasion is within 1,000 μm.
T1b: Tumor is confined to the SM, and invasion is 1,000μm or more, but it does not extend to the MP.
T2 : Tumor invasion to, but not beyond, the MP
T3 : Tumor invades beyond the MP
In sites with serosa, the tumor grows into the subserosa (SS).
In sites with no serosa, the tumor grows into the adventitia (A).
T4 : Tumor invades or perforates the serosa (SE) or directly invades other organs or structures (SI/AI).
T4a : Tumor invades or perforates the serosa (SE).
T4b : Tumor directly invades adjacent organs or structures (SI/AI).

Notes:
- In areas without serosa, the perienteric/perirectal tissues corresponding to the subserosa in areas with serosa are called adventitia (A).
- Clinical (c) and pathological (p) prefixes are used only for T classifications and not for additional descriptors such as M or SI/AI (for describing pathological mucosal cancer, description by pTis is used but not pM).
- For pT4b, the name of the invaded organ is also included, for example pT4b (prostate).
- The histopathological depth of the invasion is evaluated at the deepest part of tumor invasion.
  However, if the deepest point of the invasion is within a vessel or nerve, this should be explicitly noted.
  Example 1: If tumor invades in the muscularis propria and venous invasion is observed in the subserosa, this is referred to as pT3 (V)-MP.
  Example 2: If tumor invades in the submucosa with the invasion depth of 1,500 μm and its lymphatic invasion is found in the subserosa, this is referred to as pT3 (Ly)-SM: 1,500 μm.
- The criteria for determining the invasion depth have been defined in consideration of consistency with classifications used for other gastrointestinal tumors.
- In TNM classification, vascular invasion is not included in the assessment on the depth of tumor invasion. Therefore, there are cases where it could occasionally result in discrepancies between the two classification systems.

(Modified from Literature 1)

Table 2 Classification of the invasion depth for rectal-type anal adenocarcinomas.

TX : Primary tumor cannot be assessed.
T0 : No evidence of primary tumor
Tis : Tumor is confined to the mucosa (M) and does not extend to the submucosa (SM).
T1 : Tumor is confined to the SM and does not extend to the internal sphincter.
T1a : Tumor is confined to the SM, and the distance of submucosal invasion is less than 1,000 μm.
T1b : Tumor is confined to the SM, and the distance of submucosal invasion is 1,000 μm or greater.
T2 : Tumor extends to the internal sphincter but not to the conjoined longitudinal muscle.
T3 : Tumor has invaded beyond the conjoined longitudinal muscle.
T4 : Tumor has invaded the puborectal muscles or adjacent organs or structures.

(Modified from Literature 1)

2. Macroscopic Classification of Colorectal Cancer

(1) Early colorectal cancer

The macroscopic classification of early tumors in colorectal regions includes the classification of the *Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma* and the *Paris Endoscopic*

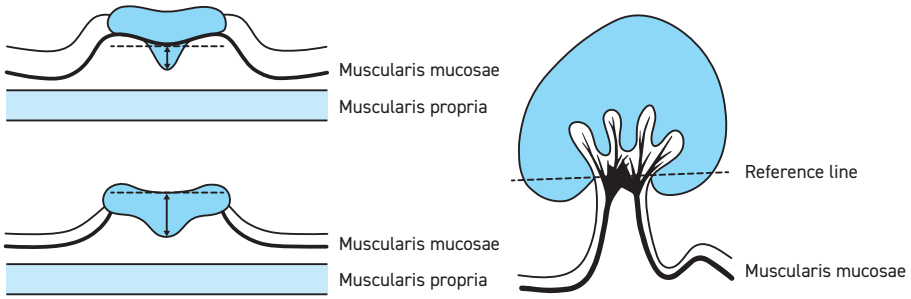


Figure 1 **Measuring invasion depth of T1 cancer.**
(Cited from Literature 1)

Classification,[4] as well as the morphological development classification including laterally spreading tumors (LSTs) and the growth pattern classification by polypoid growth (PG) / non polypoid growth (NPG). Each classification is useful as follows.

1) Classic classification

The *Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma*[1] has classified the macroscopic types of colorectal cancer.

Type 0: Superficial type
Type 1: Polypoid type
Type 2: Ulcerated type with clear margin
Type 3: Ulcerated type with infiltration
Type 4: Diffusely infiltrating type
Type 5: Unclassified type

Superficial type (Type 0) is lesions estimated to be Tis and T1 cancers and is classified by morphology. Protruded tumors are classified as 0-I, and superficial tumors are classified as 0-II. The latter one is further classified as 0-Ip (pedunculated), 0-Isp (semi-pedunculated), 0-Is (sessile), 0-IIa (superficial elevated type), 0-IIb (superficial flat type), and 0-IIc (superficial depressed type). In addition, since it is often difficult to distinguish between adenomas and carcinomas based on macroscopic findings in colorectal tumors, the macroscopic type of adenomas also follows the superficial type subclassification. Previously, it was written simply as “IIa” without adding “0-”, but this has been changed since the 9th edition of the classification.

The classification prioritizes endoscopic findings over histopathological results. It is described in the *Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma*[1] to primarily capture the shape of lesions as a whole image without considering tissue origin, tumor, and non-tumor differences.

2) Paris Endoscopic Classification[4]

In November 2002, a workshop was held to examine the usefulness and clinical significance of the Japanese macroscopic classification for superficial tumors of esophagus, stomach, and colon, and was compiled as the Paris Endoscopic Classification for superficial neoplastic lesions of the digestive tract (**Figure 2**).

Superficial lesion Type 0 is broadly divided into polypoid and non-polypoid. Polypoid is classified into 0-Ip (protruded, pedunculated) and 0-Is (protruded, sessile); and non-polypoid is divided into 0-IIa

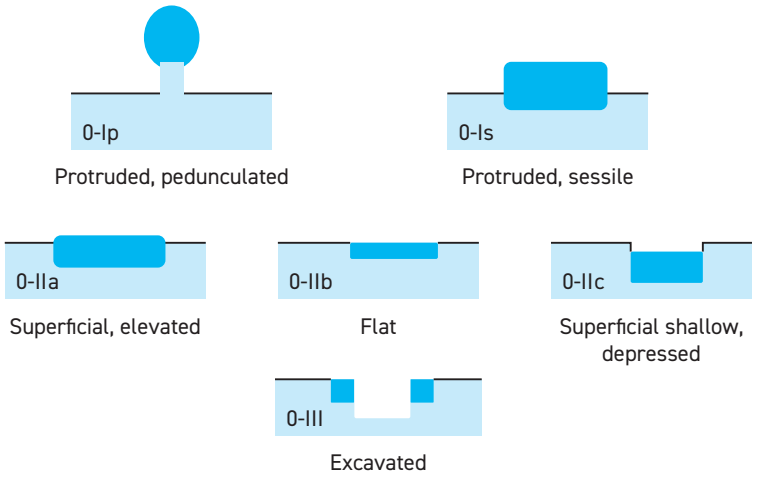


Figure 2 Paris Endoscopic Classification

(Modified from Literature 4)

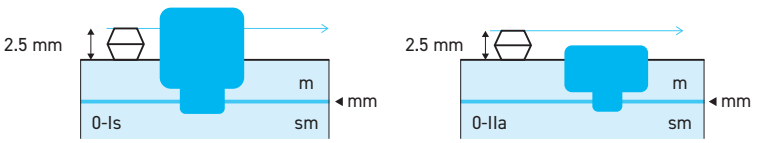


Figure 3 Definition of Types 0-Is and 0-IIa in Paris Endoscopic Classification.

(Modified from Literature 4)

(superficial, elevated), 0-IIb (flat), 0-IIc (superficial shallow, depressed), and 0-III (excavated). In practice, 0-III type is not applied for colonic lesions.

In this classification, a difference from the *Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma*[1] is found that the height definition of 0-IIa and 0-Is is distinct. The diameter of biopsy forceps is 2.5 mm and when tumors are not higher than 2.5 mm, they are classified as 0-IIa, and when higher than that, classified as 0-Is (**Figure 3**).

This classification assesses the macroscopic type based on the findings in endoscopic diagnosis and should not be changed according to the histopathological results, as it is in the *Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma.*[1]

3) Morphological development classification

This is a classification proposed by Kudo and colleagues for adenomas and early carcinomas in colorectal regions and provides important information for predicting biological malignancy as shown in **Figure 4**.[5] It introduces the concept of laterally spreading tumors (LSTs) and depressed lesions (IIc, IIc + IIa, IIa + IIc, Is + IIc).

LST is an inclusive term for carcinomas that mainly grow laterally with a diameter exceeding 10 mm. It is broadly divided into granular type (G) and non-granular type (NG). LST-G is in the shape of nodular and granular protruding lesions clustered and is further classified into homogenous type and nodular

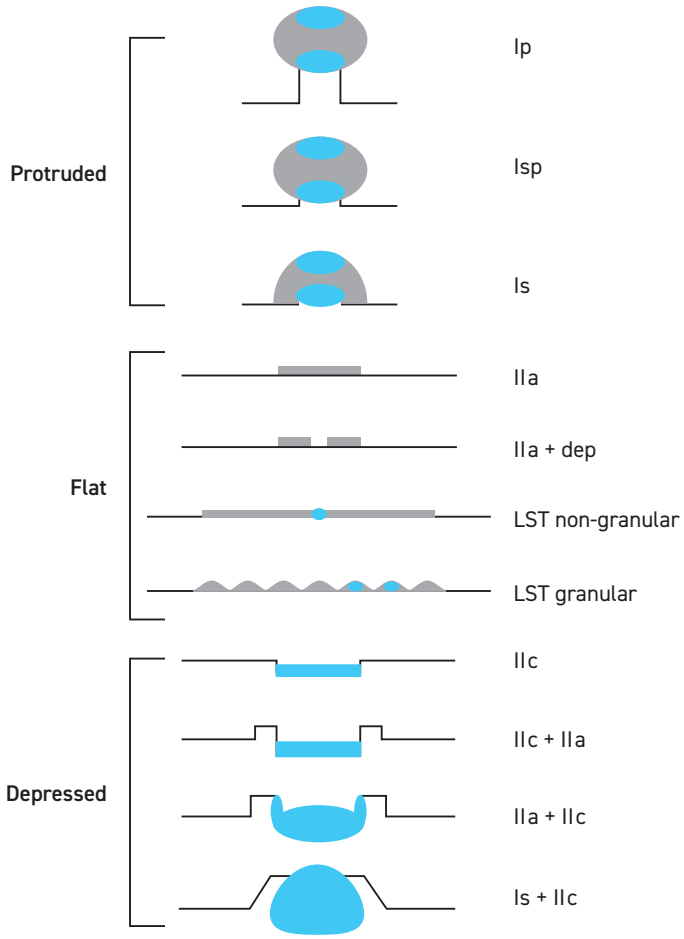
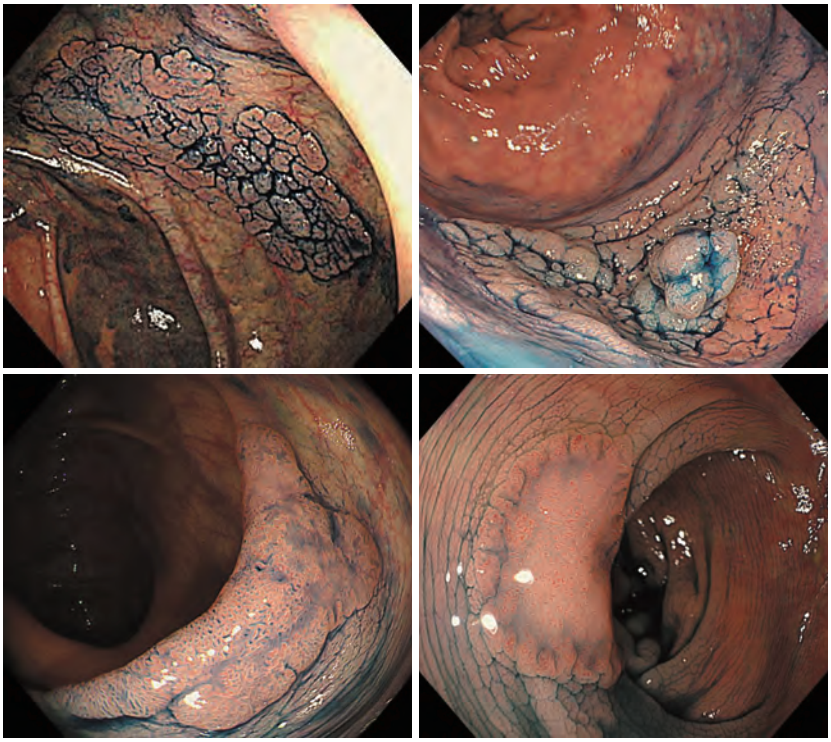


Figure 4 Morphological development classification.
(From Shinei Kudo: *New Diagnosis and New Treatment*, p. 26)

mixed type. LST-NG is flat with serrated margins and is classified into flat elevated type and pseudo-depressed type (**Figure 5**). According to the classification of the *Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma*[1] and the Paris Endoscopic Classification,[4] the LST-G homogeneous type and the LST-NG flat elevated type are defined as 0-IIa; the LST-G nodular-mixed type as 0-IIa, 0-Is + IIa or 0-IIa + Is; and the LST-NG pseudo-depressed type as 0-IIa + IIc or 0-IIc + IIa (**Figure 6**).[6] This classification was not originally created for macroscopic diagnosis, but it is widely used for deciding the macroscopic types because it is easy to recognize the tumor type just by the defined terms. In addition, the depressed type is recognized as a tumor with a high degree of malignancy, and in particular, Is + IIc is known as a macroscopic shape that suggests T1b cancer. In this classification, the depressed areas of IIc and IIc + IIa are defined as absolute depressions.

4) PG/NPG classification

This is a classification proposed by Ikegami and colleagues,[7] and classifies adenomas and carcinomas into two groups, polypoid growth (PG) and non-polypoid growth (NPG), based on the intramucosal growth.[7] This classification uses tissue specimens, unlike the classification of the *Japanese*

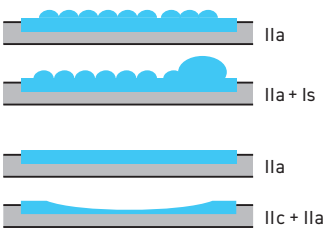


a | b
c | d

Figure 5 LST subclassification.

a: LST-G homogeneous type
b: LST-G nodular mixed type
c: LST-NG flat elevated type
d: LST-NG pseudo-depressed type

Subtypes of LST	Classification in type 0
LST granular (LST-G)	
Homogenous type	0-IIa
Nodular mixed type	0-IIa, 0-Is + IIa, 0-IIa + Is
LST non-granular (LST-NG)	
Flat elevated	0-IIa
Pseudo-depressed type	0-IIa + IIc, 0-IIc + IIa



The term "LST laterally spreading tumour" refers to the lateral glowth of lesions at least 10 mm in diameter; this is in opposition to traditional polypoid upward growth or flat and depressed lesions downward growth.

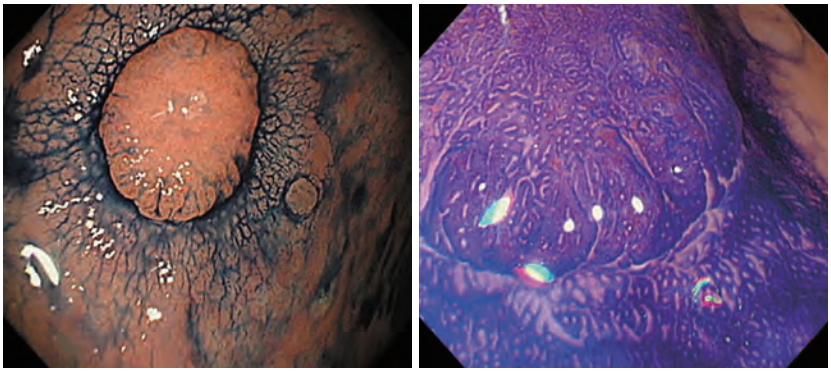
Figure 6 Relationship between LST subclassification and macroscopic type.

(Cited from Literature 6)

Classification of Colorectal, Appendiceal and Anal Carcinoma and the Paris Endoscopic Classification.[4)]

Polypoid growth type is when adenoma or carcinoma grows within the mucosa, making the edges of tumor-covered mucosa noticeably protruded compared to the surrounding normal mucosa.

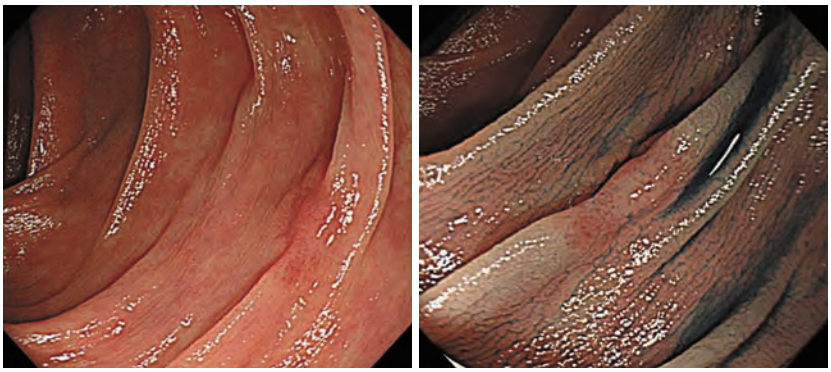
Non-polypoid growth type is observed when the affected mucosa is about the same thickness or thinner than the surrounding normal mucosa, or when the tumor mucosa is slightly raised but blends smoothly



a | b

Figure 7 Non-polypoid growth.

a: Indigocarmine spraying
b: Crystal violet staining. Type I pit at the margin, indicating normal mucosa



a | b

Figure 8 Early-stage cancer Type IIc.

a: White light endoscopy
b: Indigocarmine spraying

into the surrounding tissue.

In NPG, its depressed lesions develop through de novo pathway. While this type is usually classified based on tissue samples, it can also be detected by endoscopy if the depressed lesion abuts on normal mucosa (**Figure 7**).

(2) Morphological development classification of type IIc

In this classification, type IIc lesions in the colon are characterized by the depressed morphology, which is associated with higher histological malignancy and a greater risk of being overlooked. The histological definition of type IIc in the colon finds a depressed lesion mainly with absolute depression, but if a lesion is relatively depressed, it is generally treated as IIa + IIc. Therefore, true IIc lesions have slightly or no marginal elevation, whereas IIc lesions with some distinct marginal elevation are classified as IIc + IIa. **Figure 8** shows a typical example of IIc.

(3) Macroscopic classification of advanced colorectal cancer

The *Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma*[1] classifies the macroscopic types of advanced colorectal cancer into Type 1 (protruded type), Type 2 (well-defined ulcerative type), Type 3 (ill-defined ulcerative type), Type 4 (diffusely infiltrating type), and Type 5 (unclassifiable), among which Type 2 is observed most frequently.

Type 1 finds protruding lesion without ulceration. Their macroscopic appearance and surface characteristics often make it difficult to diagnose as advanced cancer. Some cases require differentiation from 0-Isp and 0-Is types. On the other hand, Type 2 is easy to diagnose due to its clearly demarcated surrounding elevation, but when the well-defined ulcerative lesion is located in bending sites or becomes nearly circumferential, it is difficult to endoscopically recognize the entire lesion. In such cases, radiographic contrast enema examination is useful and able to distinctly display the apple core sign. Type 3 is less common and is distinguished from Type 2 by their gradual transition from the normal tissue without forming the distinct ulcer mound. The surrounding area of ulcer could exhibit submucosal invasion with submucosal tumor-like elevation or luminal narrowing. Type 4 does not exhibit distinct ulceration or mass formation but instead demonstrates diffuse infiltrative growth throughout the entire colonic wall, and frequently leads to luminal narrowing. In such cases, endoscopic evaluation alone is often insufficient, and differentiation from inflammatory bowel disease is necessary. Moreover, the tumor tissue could not be detected even on biopsy. Therefore it is essential to employ multiple imaging modalities to establish a diagnosis, such as radiographic contrast enema examination and contrast-enhanced CT in addition to endoscopy.

3. Endoscopic Classification of Inflammatory Bowel Disease

(1) Ulcerative colitis (UC)

UC typically involves lesions in the distal colon and rectum in many cases, making it relatively easy to observe lesions through endoscopy. Moreover, endoscopic findings correlate with clinical severity, so endoscopic classification has been used for assessing severity and treatment effectiveness.[8] The endoscopic features of UC include diffuse mucosal lesion, loss of the visible vascular pattern, rough-surfaced or finely-granular mucosa, friability, mucopurulent discharge, multiple erosions, ulcers, or pseudopolyposis. Typically, the lesions are observed consecutively from the rectum.[9] Commonly used classifications for the disease entities include the *Clinical Practice Guidelines for Inflammatory Bowel Disease*,[9] which is produced based on the internationally recognized Truelove's classification[10] for endoscopically assessing active stage (**Table 3**, **Figures 9-11**).[11] The Mayo Endoscopic Subscore (MES)[12] (**Table 4**), and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[13] (**Table 5**) are also used as endoscopic scoring systems. The diagnostic classification for endoscopically assessing active stage and MES are quite similar, based on the visible vascular pattern, friability, and hemorrhage in the severely affected sites. UCEIS focuses on three evaluation parameters: vascular pattern, hemorrhage, and mucosal lesions (erosions and ulcers), and it deliberately excludes subjective aspects like redness, edema, and mucus to minimize inter-observer variabilities. Furthermore, there are classical classifications such as the Baron Index[14] and the Rachmilewitz Endoscopic Index.[15] Baron's classification is based on the extent of hemorrhage, while Rachmilewitz's classification evaluates granularity, visible vascular patterns, mucosal fragility, and mucosal damage, but both are less commonly used in recent years.

Table 3 Classification based on endoscopic findings in active phase.

Inflammation	Endoscopic findings
Mild	Loss of vascular pattern, granular mucosa Redness, aphthae, small yellow dots
Moderate	Rough-surfaced mucosa, erosion, small ulcers Friability (contact bleeding) Mucopurulent discharge
Severe	Extensive ulceration, marked spontaneous bleeding

*Diagnosis is based on the most severe findings within the observed range. Endoscopy should be conducted without preparation mostly in a short time, and there is no requirement to examine the entire colon.

(Cited from Literature 9)



Figure 9 Mild UC.

(Cited from Literature 11)



Figure 10 Moderate UC.

(Cited from Literature 11)

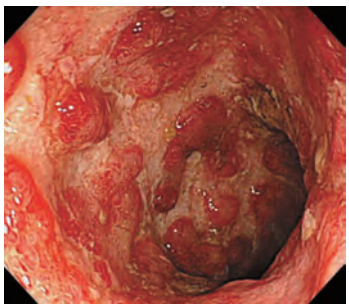


Figure 11 Severe UC.

(Cited from Literature 11)

Table 4 Mayo Endoscopic Subscore (MES).

Endoscopic appearance	Mayo endoscopic subscore
Normal mucosa	0
Decreased vascularity, mild friability, erythema	1
Absent vascular pattern, marked erythema, severe friability, erosions	2
Spontaneous bleeding, ulceration	3

(Cited from Literature 12)

(2) Crohn's disease (CD)

Recent research has shown that mucosal healing is related to long-term outcomes in CD, thus endoscopic evaluation is vital. The endoscopic findings in CD include longitudinally aligned ulcerous furrows, cobblestone appearance, skip lesions, irregularly arranged or round ulcers, and multiple aphthous lesions. Gastrointestinal manifestations include bamboo-joint like appearance and notch-like depressions (**Figures 12-16**).[11] Endoscopic classifications commonly used for CD include the Crohn's

Table 5 Ulcerative Colitis Endoscopic Index of Severity (UCEIS).

Descriptor (score most severe lesions)	Likert scale anchor points	Definition
Vascular pattern	Normal (1)	Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (2)	Patchy obliteration of vascular pattern
	Obliterated (3)	Complete obliteration of vascular pattern
Bleeding	None (1)	No visible blood
	Mucosal (2)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (3)	Some free liquid blood in the lumen
	Luminal moderate or severe (4)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a haemorrhagic mucosa
Erosions and ulcers	None (1)	Normal mucosa, no visible erosions or ulcers
	Erosions (2)	Tiny (≤5 mm) defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer (3)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial
	Deep ulcer (4)	Deeper excavated defects in the mucosa, with a slightly raised edge

(Cited from Literature 13)



Figure 12 Longitudinal ulcers.

(Cited from Literature 11)

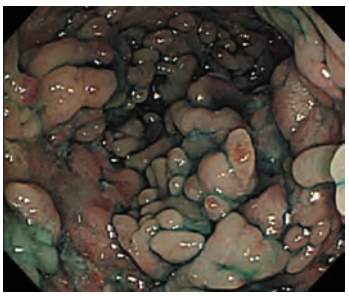


Figure 13 Cobblestone appearance.

(Cited from Literature 11)



Figure 14 Irregularly arranged ulcers.

(Cited from Literature 11)

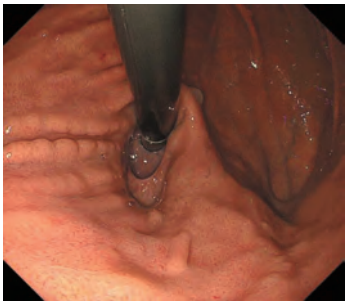


Figure 15 Bamboo-joint appearance.

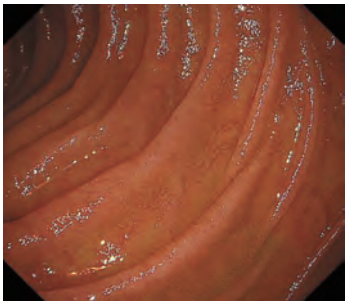


Figure 16 Notch-like depressions.

Table 6 Crohn's disease endoscopic index of severity (CDEIS).

1	ISRCF (Frequency of Deep Ulcers in Each Rectum-Colon Segment) *1 X1 = (Number of segments with deep ulcers *2) / (Number of observed segments)	X1×12 = Y1
2	ISRCF (Frequency of Superficial Ulcers in Each Rectum-Colon Segment)X2 = (Number of segments with superficial ulcers) / (Number of observed segments)	X2×6 = Y2
3	ASSD (Extent of Lesions per Segment, Including Ulcerative Lesions (cm)) *3 X3 = (Total extent (cm) of lesions (including ulcerative lesions) per segment) / (Number of observed segments)	X3×1 = Y3
4	ASSU (Extent of Ulcerative Lesions per Segment (cm)) X4 = (Total extent (cm) of ulcerative lesions per segment) / (Number of observed segments)	X4×1 = Y4
5	PRES (Presence of Non-Ulcerative Strictures) X5 = Presence of non-ulcerative strictures in the observed	X5×3 = Y5

*1: ISRCF is calculated through dividing the number of lesion segments by the number of observed segments.
ISRCF ranges from 0 (no lesions in any observed segments) to 1 (lesions present in all observed segments).
*2: Segments = Rectum, S-shaped colon, left colon, transverse colon, right colon, ileum
*3: The proportion of the segmental surface involved by the nine lesions or ulcerative lesions listed in the next table is assessed through a 10 cm visual analog scale.
0: No lesions or ulcerative lesions, 10: Entire segment surface finds lesions or ulcerative lesions.
*4: Ulcerative lesions = Aphthous ulcers, superficial ulcers, deep ulcers, ulcerative strictures.

ISRCF, individual segmental rectocolonic frequency; ASSD, average of segmental surfaces involved by the disease; ASSU, average of segmental surfaces involved by ulcerations; PRES, presence

List of 9 Mucosal lesions

Lesion Type	Definitions or Remarks
1 Pseudopolyps	—
2 Healed ulcers	With pale scar
3 Apparent erythema (spot, banded, or diffuse)	Excluding mild or moderate erythema
4 Apparent mucosal edema	Excluding mild or moderate mucosal edema
5 Aphthous ulceration	Small (2 or 3 mm), protruded or flat red lesions (with whitish center)
6 Superficial ulceration	All ulcers except aphthous and deep ulcers
7 Deep ulceration	Clearly visible deep ulcers only
8 Non-ulcerative narrowing	Difficult or impossible passage of adult endoscopes
9 Ulcerative narrowing	Difficult or impossible passage of adult endoscopes

(Cited from Literature 16)

Table 7 Simple endoscopic score for Crohn's disease (SES-CD).

Parameter	Simple Endoscopic Score for Crohn's Disease values			
	0	1	2	3
Size	None	Aphthous ulceration (Φ 0.1–0.5 cm)	Ulceration (Φ 0.5–2 cm)	Large ulceration (Φ >2 cm)
Ulcerative area	None	<10%	30%	>30%
Lesion area	None	<50%	50 - 70%	>75%
Narrowing	None	1 site, passable	Multiple, passable	Impassable

Φ: Diameter
Section from small to large intestine is predefined in five segments, and endoscopic evaluation is performed for section.
1: Ileum. The ileum is scored up to the observable range, but the ileocecal valve or ileocolonic anastomosis are out of evaluation.
2: Right colon. The right colon includes the ileocecal valve, cecum, and ascending colon up to the hepatic flexure; for Crohn's disease limited to the cecum, scoring is done for this segment.
3: Transverse colon. The transverse colon is defined as the area between the hepatic flexure and the splenic flexure.
4: Left colon. The left colon includes the descending colon (from the splenic flexure) to the rectosigmoid junction.
5: Rectum. The rectum is defined as from the rectosigmoid junction to the terminal rectum.
(Cited from Literature 16)

Table 8 Rutgeerts' score.

Grade	Endoscopic finding
i0	No lesions in the distal ileum
i1	≦5 aphthous lesions
i2	＞5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to ileocolonic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

(Created from Literature 19)

Disease Endoscopic Index of Severity (CDEIS) (**Table 6**),[16,17] Simple Endoscopic Score for Crohn's Disease (SES-CD) (**Table 7**),[16, 18] and Rutgeerts' score (**Table 8**).[19] The CDEIS, proposed by Mary and Modigliani, considers ulcer depth, lesion area, ulcer area, and the presence of complications such as narrowing in specific regions. However, its calculation is highly complex, and Daperno and colleagues simplified it by proposing the SES-CD, which scores four items of CDEIS. While the SES-CD is now more commonly used in recent years, Rutgeerts' score is generally used to assess postoperative recurrence.

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Keigo Suzuki and Shinichiro Yoshioka

2 Insertion Technique (Total Colonoscopy)

1. Types and Selection of Endoscopes

Choosing the appropriate endoscope based on its characteristics and the clinical situation is essential for safe insertion in colonoscopy. In general, a smaller outer diameter of the insertion tube finds the scope more flexible, whereas a larger diameter makes it more rigid.

(1) Flexible endoscope

Flexible endoscopes are particularly indicated for elderly patients, petite women, history of abdominal surgery, and adhesions related to diverticula. It is also indicated for screening examinations where minimizing discomfort is a priority. Ultrathin endoscopes with a distal outer diameter of 9.2 mm (Olympus PCF-PQ260I/L, Fujifilm EC-L600XP7/L) are commercially available. These scopes are equipped with passive bending and curve tracking functions that allow the scope to bend spontaneously when lightly pressed against the intestinal wall. These properties enable smooth insertion even in sharp flexures of large intestine.

Furthermore, small-caliber magnifying endoscopes with a distal outer diameter of 11.7 mm are on the market. The devices offer high-definition imaging with a wide field of view of 170°(Olympus PCF-H290ZL/I) or field of view of 140° (Fujifilm EC-L600ZP7). These scopes are useful to perform magnification for screening observations.

(2) Rigid endoscope

Many rigid endoscopes incorporate magnifying observation capabilities. The rigidity reduces the scope's susceptibility to flexed bowels, enabling it to maintain a straight configuration during insertion and providing excellent followability while the operator twists or pushes/pulls the scope. However, in colons with pronounced flexures or in cases with adhesions, the rigid types tend to be less easily inserted than the flexible types. Therefore, they are more likely to cause pain due to overextension of the bowel and carry a higher risk of mechanical perforation due to forceful insertion.

Recently, colonoscopes with changing their rigidity have become available. Such devices with adjustable stiffness offer high-definition imaging capabilities, with the Olympus CF-XZ1200L/I providing a distal outer diameter of 13.2 mm and a 170-degree field of view, and the Fujifilm EC-

Table 1 Indications and contraindications for colonoscopy.

Indications	Contraindications
<Diagnostic purposes> (i) Screening and detailed examination of tumors (ii) nflammatory bowel disease Differential diagnosis, staging, evaluation of treatment effectiveness, follow-up observation (iii) Others Vascular lesions, intestinal lesions associated with systemic diseases, etc. <Therapeutic purposes> (i) Tumor resection Hot biopsy, polypectomy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), etc. (ii) Hemostasis Clipping, band ligation, local injection of hemostatic agents, APC, etc. (iii) Decompression, stent insertion (iv) Stricture dilation (v) Foreign body removal (vi) Reduction of intestinal volvulus, intussusception (vii) Local injection of anticancer drugs (viii) reoperative marking, clipping, ink-injection, etc.	<Absolute contraindications> (i) Acute abdomen (ii Intestinal perforation (iii) Respiratory and circulatory failure If examination is necessary, systemic management with strict monitoring is performed. (iv) Abdominal aortic aneurysm (when impending rupture is suspected) <Relative contraindications> (i) Severe inflammatory bowel disease As the condition could worsen with pretreatment or examination, observation should be limited to the minimum level if necessary. (ii) Intestinal obstruction (ii) Pregnancy Examination should be avoided, especially during the unstable period up to 12 weeks of gestation. (iv) Significant ascites (v) Significant intestinal adhesion (vi Poor bowel preparation (vii) Patients unable to cooperate with the examination (viii) Large amount of intestinal bleeding Management of circulatory dynamics takes top priority. If shock due to rapid bleeding does not improve, vascular bleeding could be suspected, and embolization via angiography is often necessary.

(Modified from Literature 3)

L600ZW7 providing a distal outer diameter of 12.8 mm and a 140-degree field of view. They are beneficial for very detailed observation. The function to change the rigidity of the endoscope enables to adjust the stiffness according to the actual situation; for example, reducing stiffness in flexures to prevent loop formation while increasing stiffness in other areas. This property is helpful for insertion. Scopes with a water jet function are particularly helpful during endoscopic treatments, such as endoscopic submucosal dissection, and in identifying bleeding sites during examination.

2. Indications and Contraindications

Colonoscopy is indispensable for diagnosing and determining treatment strategies in patients suspected of having colonic symptoms such as abdominal pain, constipation, diarrhea, or hematochezia.[1,2] In particular, detailed examination of patients with positive for fecal occult blood is the most appropriate indication. The indications and contraindications for colonoscopy are detailed in **Table 1**.[3] Absolute contraindications include acute peritonitis, intestinal perforation, respiratory or circulatory failure, and suspected impending rupture of an abdominal aortic aneurysm.[1,2]

In cases of bleeding, the first consideration involves determining whether the patient's overall circulatory status remains stable. When the general condition is unstable, for example blood pressure, colonoscopy should not be performed.

3. Bowel Preparation

Adequate preparation is essential not only to facilitate the insertion of a colonoscope but also to improve the cecal intubation rate and adenoma detection rate (ADR). Several pretreatment methods are available, including (i) Niflec method, (ii) large-volume Magcorol method, (iii) Visiclear method, (iv) Mobiprep method, (v) Picoprep method, and (vi) Salprep method.[3] These methods should be selected individually or in combination. They are often combined with other conditions such as consuming a special test meal or semi-digested nutritional supplements on the day before the procedure. Laxatives like sodium picosulfate hydrate could also be added to the preoperation regimen. These combined approaches help reduce the amount of bowel preparation medication needed on the day of the colonoscopy. The choice of pretreatment is made according to the policies of each facility and the background conditions of patients. It should be noted that these agents other than Niflec® and Mobiprep® are contraindicated for severe renal dysfunction. In fact, caution is necessary in administering medicines for loosening the bowels.

Pretreatment for hematochezia

In cases where moderate or large amount of hematochezia is observed, emergency colonoscopy is indicated, but pretreatment is generally not necessary. However, if the bleeding originates from the deeper tracts of the colon, it is preferable to perform an enema before the examination. This is useful to wash away stool and blood in the rectum and facilitate observation and intervention. On the other hand, for a small amount of fresh blood or tarry stool, it is not necessary to perform emergency colonoscopy if it is suspected that time has passed since the bleeding event. In this case, colonoscopy is performed after normal pretreatment. In patients with ulcerative colitis, symptoms could be exacerbated by use of laxatives or washing solutions during the active phase when hematochezia or bloody and mucus stools are frequently observed. Therefore, colonoscopy for ulcerative colitis is performed either without pretreatment or with minor pretreatment such as an enema. In the remission phase, it is better to perform the usual pretreatment for the detailed observation on the mucosal surface.

4. Practical Techniques

(1) Basics for insertion

- The fundamental technique for colonoscope insertion is to align the axis of the scope with the axis of the colorectum to achieve shortening and straightening along the entire intestinal tract, a process known as shaft retention and shortening method (**Figure 1**).[3, 4-6]
- It is crucial to understand the course and anatomical characteristics of large intestine. Specifically, the ascending colon, descending colon, and lower rectum (Rb) are fixed to the retroperitoneum, while the transverse colon and sigmoid colon are supported only by the mesentery and remain free within the abdominal cavity. The ascending and descending parts of the colon are located in the retroperitoneal space and lie toward the back of the body.
- The scope insertion lengths in the shaft retention and shortening method are approximately 15 cm for the rectosigmoid junction (RS), 30 cm for the sigmoid-descending junction (S-D junction), 40 cm for the splenic flexure, 60 cm for the hepatic flexure, and 70 cm for the cecum.

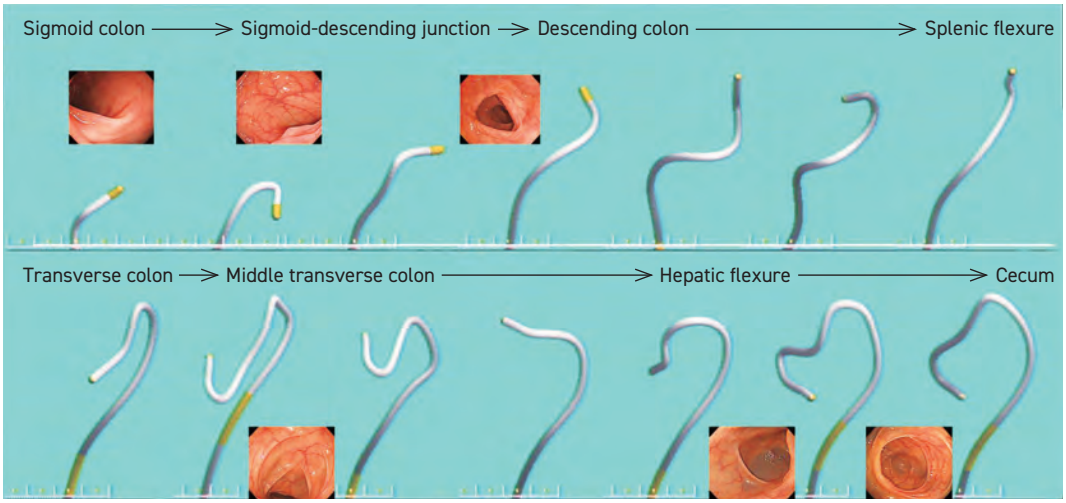


Figure 1 **Scope movement using insertion shape device (UPD) with shaft retention and shortening method.**

The scope is inserted by aligning its axis with that of the colon while extending the intestinal tract to avoid loop formation.
(Cited from Literature 3)

- In scope manipulation, the left hand is used for manipulating the angle of the scope, while the right hand is dedicated to inserting and rotating the scope. It is important to always maintain the feeling of free movement, where the right hand's movement is infallibly transmitted to the tip of the scope through repeated shortening maneuvers.
- Insufflation with CO2 is more helpful than air because it reduces abdominal distension. It is useful to avoid insufflation as much as possible, aspirate air as much as possible to collapse the intestinal lumen, and advance the scope over the crowded folds: a method called the hooking the fold technique[4-7] as shown in **Figure 2**.[3] There is another method called right turn shortening technique[8-10] as shown in **Figure 3**,[3] which keeps the scope constantly straightened and maintains a free feeling.
  It is loop formation that represents one of the factors that contribute to difficulty during insertion. In such cases, manual compression after loop formation is ineffective, so manual compression and repositioning before loop formation are important.
- When a standard scope is difficult to insert because of adhesions, it's possible to achieve insertion by switching to a softer, thinner scope and avoiding any forceful maneuvers.

(2) Rectum

- Before the insertion into rectum, it is essential to perform transrectal palpation. Subsequently, the scope is inserted into the rectum in the left lateral posture because anatomically, air collects in the rectum in this position.
- The scope should be inserted with a left rotation from lower rectum (Rb) up to upper rectum (Ra), and once the scope reaches rectosigmoid (RS), it should rotate further to pass the RS junction, so that the sigmoid colon lumen is visible to the right side. In this process, insufflation should be minimized.
- Excessive air inflation or forceful insertion should be avoided, as these actions complicate the shortening process during insertion into sigmoid colon.

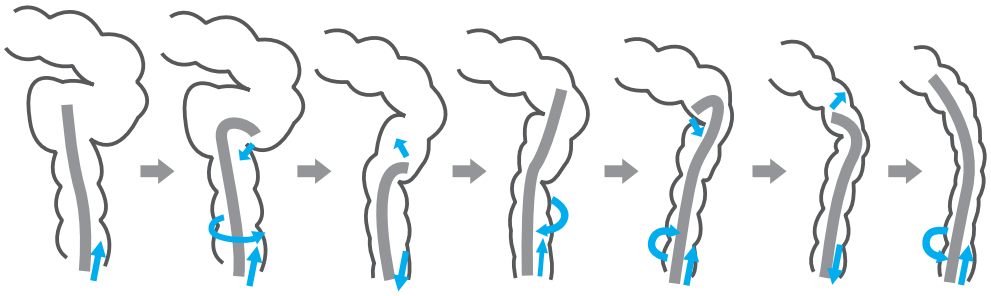


Figure 2 Hooking the fold technique.

The tip of the scope is used to hook and compress the fold. Each time the fold is passed, the scope is pulled back. This process is repeated while avoiding loop formation. When advancing the scope with right torque, it is essential to return the axis with left torque to maintain a neutral position at all times.
(Cited from Literature 3)

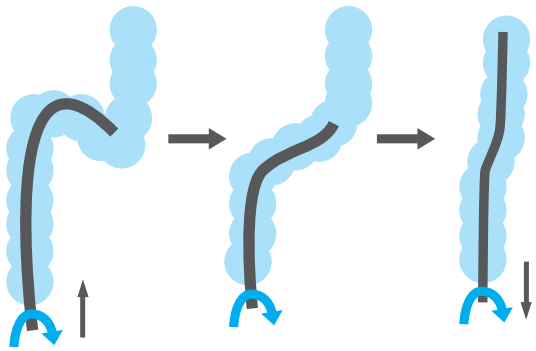
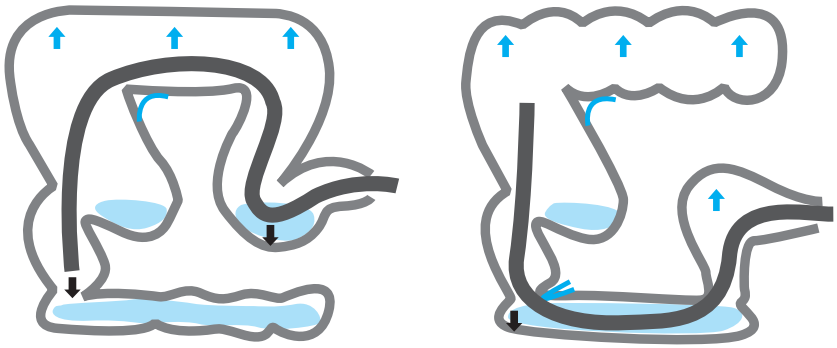


Figure 3 Right turn shortening technique.

By hooking the scope's tip onto a flexure and rotating the scope axis to the right while pulling the scope back, operators straighten the scope and simultaneously pass it through the flexure.
(Cited from Literature 3)

(3) Sigmoid colon

- It is acceptable to remain in the left lateral posture, but once the scope has reached sigmoid colon, changing to supine posture is usually helpful to insert in deeper tract.
- It is necessary to reach the S-D junction in the shortest possible length and try to pass the S-D junction with the right turn shortening technique[4-6] (**Figure 3**) [3] while the axis should be maintained.
- When the sigmoid colon is likely to become stretching, the part of colon tract approaching over the pubic bone is lightly compressed manually to assist the insertion. At this stage, careful attention to minimizing insufflation allows the scope to advance more easily, aiming to glide naturally into the next segment of the lumen.
- If a loop is formed, especially an N loop, it is important to release the loop as soon as possible.
- Even if an α or a reverse α loop is formed naturally but the patient exhibits no discomfort, the scope should be inserted into the descending colon and then straightened. In order to straighten the scope, it is important to control the tip of the scope with the coordinated manipulation of the angle operation with the left hand and the rotation with the right hand, so that the scope does not slip off.



a: Right lateral decubitus position　　b: Left lateral decubitus position

Figure 4 **Methods of passing the splenic and hepatic flexures.**

a: In right lateral decubitus position. In cases with a sharply angled splenic flexure or extremely long sigmoid colon where shortening the scope is challenging, placing the patient in a right lateral decubitus position could blunt the splenic flexure. Additionally, the transverse colon is straightened by the weight of the scope or the intestinal tract with maintaining a blunt splenic flexure, thereby allowing the tip to advance more easily.

b: In left lateral decubitus position. When the space at the hepatic flexure is limited, insertion into the ascending colon often becomes difficult. In such cases, placing the patient in the left lateral decubitus position allows air to move from the transverse colon toward the hepatic flexure and ascending colon. This shift in air helps expand the lumen and makes it easier to advance the scope into the ascending colon.

(Cited from Literature 3)

(4) Splenic flexure

- In passing through splenic flexure, it is necessary for the scope to be straightened from the rectum to the descending colon.
- If the scope has trouble navigating the splenic flexure, the flexure could become stretched towards the left lung. Pushing the scope in this situation won't work and causes significant pain. It is a trouble called the walking-stick shaped scope. These problems also occur due to the stretched splenic flexure. To make the splenic flexure less sharp, air is removed from the bowel. Additionally, the patient takes deep breaths, which compress the space with the diaphragm. Simultaneously, gentle manual pressure is applied to the lower abdomen, and the patient is turned from lying on their back to lying on their right side (**Figure 4b**).[3)]

(5) Transverse colon

- Aspiration of air as much as possible from the left transverse colon results in a shortened, less sharp flexure.
- When passing through the middle of the transverse colon, it is preferable for the scope to be rotated 180 degrees to the left and advanced with an up angle.
- After the scope passes the middle of the transverse colon, it reaches the hepatic flexure. This involves aspirating air, pulling back the scope, and rotating it to the left.
- If the sigmoid colon is sagging, manual compression of the lower abdomen or repositioning the patient to the right lateral posture is helpful.
- In cases where the transverse colon is long or in cases where it has strong flexure due to adhesions

after abdominal surgery, loop formation (γ loop) often occurs. In addition, the intestinal tract often becomes twisted, and the patient typically experiences pain. This also reduces the chance to reach the cecum because the scope's length becomes insufficient. In such situations, the best approach is to remove as much air as possible from the bowel space between the splenic flexure and the left side of the transverse colon and advance further the scope. When the scope slowly reaches the bending point in the middle of the transverse colon, a combination of leftward rotation and upward angulation is used. Simultaneously, the scope is pulled back slightly. This combined maneuver helps to shorten the previously lengthened transverse colon.

(6) Hepatic flexure

- With air aspiration and the patient's deep breathing, the scope should be rotated rightward to advance toward the ascending colon.
- If there is sufficient space in the hepatic flexure, the operator easily inserts the scope into ascending colon by simply rotating the scope to the right while aspirating air.
- If there is not enough space in the hepatic flexure, the operator mostly inserts the scope into ascending colon through placing the patient in the left lateral posture to move air from the transverse colon to the hepatic flexure and aspirate it (**Figure 5b**).[3)]
- When the scope does not easily enter the ascending colon, manual pressure should be applied to the area near the hepatic flexure, typically around the right hypochondrium. This approach reduces sagging of the transverse colon, which allows the endoscopist to advance the scope into the ascending colon more smoothly while the pressure is maintained.

(7) Cecum and terminal ileum

- When the scope reaches the cecum, the ileocecal valve and the appendiceal orifice should be confirmed.
- After the scope is positioned at the base of cecum, the ileocecal valve is examined as the scope is withdrawn slightly. The scope is then angled to the left so that it contacts the lower lip of the ileocecal valve, and it is gently advanced forward in a manner resembling hooking onto the upper lip. Accordingly, insertion into the terminal ileum becomes easier.

Angling the scope to the left so that it touches the lower lip of the ileocecal valve helps insertion into the terminal ileum. The operator then gently advances the scope forward as if hooking it onto the upper lip.

- Introduction of a small amount of air expands the intestinal lumen and improves visibility. In this state, the operator angles the tip of the scope downward to follow the natural curvature of the bowel, making deeper insertion easier and smoother. Generally, the terminal ileum is visible at a distance of approximately 10 to 15 cm beyond the ileocecal orifice.

5. Postoperative Management

Post-procedure management is an important aspect of colonoscopy, requiring attention to the residual intraluminal air, the effects of sedatives, and the care following a biopsy.

(1) Residual air in intestinal tract

In order to prevent abdominal pain and nausea caused by bloating after the examination, it is essential to deairing as much as possible during scope withdrawal. However, it's important not to remove too much air in the examination process, as this could make the endoscopy harder to observe and identify lesions. Instead of air, carbon dioxide is preferable because it undergoes absorption by tissues at a rate over 100 times faster than that of air. It proves beneficial in reducing post-procedural discomfort.

(2) Sedatives and analgesics

Administration of sedatives and analgesics sometimes induces dizziness. Thus patients should remain in the hospital bed until these symptoms improve, and not operate a car or bicycle when leaving. Antagonists usually facilitate rapid awakening, such as flumazenil for benzodiazepine sedatives and naloxone hydrochloride for narcotic analgesics or pentazocine. However, because their half-lives are short, patients often experience a renewed decline in consciousness after initial recovery. It is necessary to pay attention to the characteristics of these agents.

(3) Biopsy and endoscopic treatment

Following biopsy or endoscopic treatment, vigilance for bleeding is warranted. In particular, active ulcerative colitis and other conditions cause the mucosa to become fragile and bleeding after biopsy. In general, there is no particular problem with eating or bathing after a biopsy, but it is better to refrain from drinking alcohol and strenuous exercise on the day of biopsy and for one week after endoscopic treatment. For antithrombotic drugs, it is necessary to be careful because the period of discontinuation and resumption varies depending on the agents.

6. Adverse Events and Their Management

(1) Perforation

According to the nationwide survey by the Japan Gastroenterological Endoscopy Society (2008-2012), the incidence of adverse events associated with colonoscopy including observation alone and biopsy is 0.011% (1 case per 8,710 procedures), and the mortality rate is 0.0004% (16/3,815,118).[8] Among the adverse events associated with colonoscopy, intestinal perforation is the most frequent at 60.7%,[9] but the accidents include many perforation events relating-not-to endoscopic treatments. Endoscopic perforation results not only from the tip of the scope but also from the excessive extension during colonoscopy, particularly in patients with adhesions. The majority of these events occur in the sigmoid colon.[10]

In cases where the perforation site is not notably confirmed and severe abdominal pain or bloating appears and worsens during the examination, perforation is suspected and the examination is immediately discontinued. At that time, it is important not to forget to aspirate intestinal contents such as air and food residues. Blunt perforation during insertion often results in tearing that extends deep beyond the muscularis propria in the area surrounding the perforation site. In such cases, clip closure is

ineffective, and surgical treatment is required in principle.[11] In order to prevent perforation during insertion, a scope should never be pushed further if the endoscope feels strong resistance during insertion. When the scope and the intestinal wall are in close proximity, the screen often shows a reddish circular image known as the red-out sign. This indicates that the tip of the scope is pressed against the intestinal wall. Advancing the scope in this state carries a risk of injury, so avoiding push maneuvers is important.

Recently, there have been reports of deaths due to intestinal perforation caused by increased intraluminal pressure after administration of oral bowel cleansing agents before examination. It is necessary to pay attention to the presence or absence of intestinal obstruction symptoms by medical history and imaging findings before performing pretreatment.

(2) Other adverse events

In elderly patients with underlying diseases, acute myocardial infarction, cerebral infarction, ischemic colitis, or mesenteric venous thrombosis could occur due to dehydration. Prior to the examination, it is important to conduct a detailed medical interview for understanding the underlying diseases in advance. It is also necessary to sufficiently replenish fluids before the examination for these patients to prevent dehydration.

Caution is required for shock due to medications (xylocaine®, anticholinergic drugs) , especially pre-treatment drugs such as sedatives (diazepam, flunitrazepam) and analgesics (pethidine hydrochloride), as their related-deaths have been reported.

Shock caused by premedication with Xylocaine® or anticholinergic agents has been linked to fatal outcomes. Particularly, fatal adverse events have been reported in association with the use of sedatives such as diazepam or flunitrazepam, as well as analgesics like pethidine hydrochloride. Therefore, careful monitoring is critical. Attention should also be paid to vagal reflex and hyperventilation caused not only by excessive insufflation or pain stimulation but also anxiety or tension on the examination. In order to prevent these events, it is necessary to make reassuring comments to alleviate patient anxiety during the endoscopic examination and ensure that the insertion is performed with appropriate care. In practice, a monitoring system should be in place to continuously observe patients' vital signs, including blood pressure and SpO_2, so that abnormal findings are detected early during the examination.

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3 Observation Methods

Endoscopic observation methods are broadly classified into five categories depending on the purpose: (i) conventional (white light) endoscopy, (ii) image-enhanced endoscopy (IEE), (iii) magnified endoscopy, (iv) microscopic endoscopy, and (v) tomographic endoscopy.[1)] This section focuses on explaining (i) and (ii), specifically narrow-band imaging (NBI), blue laser/light imaging (BLI), texture and color enhancement imaging (TXI), red dichromatic imaging (RDI), and chromoscopy (contrast method).
As for (i), chromoscopy using indigocarmine which falls under (ii) will also be explained.

1. Conventional (White Light) Endoscopy of Colon

With respect to the observation of colon using conventional (white light) endoscopy, recent developments have led to the widespread use of magnified endoscopy for pit pattern diagnosis of colorectal lesions and the combined application of narrow band imaging with magnified endoscopy to assess microvascular and surface patterns.
However, conventional (white light) endoscopy using the indigocarmine spraying method remains the basis of diagnosis, and the use of other imaging methods should not be expected without mastering the standard endoscopic diagnosis.

(1) Lesion detection

Before the examination, it is essential to ensure that the colon is free of any residue by using sufficient laxative agents. Then, after confirming any existing medical conditions as much as possible, observation is performed under the administration of anticholinergic drugs or glucagon for the purpose of suppressing peristalsis. To avoid overlooking any lesions, it is important to thoroughly inspect the entire colon. Although efforts are made to detect colonic lesions that measure only a few millimeters, it is known that the lesion detection rate during a single endoscopic examination varies with the experience and skill of both facilities and endoscopists. Factors related to the adenoma detection include the quality of bowel preparation, the presence of lesions in areas that are difficult to anatomically observe, such as behind haustral folds or at the hepatic and splenic flexures, as well as the endoscopist's detection ability and concentration. It is also known that the lesion detection rate is usually improved by changes in patient position during the examination and colonoscopic retroflexion in the ascending colon and rectum.

Furthermore, maintaining a high level of awareness for detecting superficial type lesions is important. These lesions are not easy to detect and tend to be more malignant than protruded type ones. Superficial depressed type frequently invades the submucosa even when it is small, so it is important to pay attention to not only slight deformations of the wall but subtle differences in visible vascular pattern and change in color relative to normal mucosa. Mucus adhering on normal mucosa particularly serves as a cue for detecting sessile serrated lesions (SSLs), and is recognized as one of the precursor lesions of colorectal carcinoma. The latest endoscopes now offer improved resolution and a wider field of view, realizing more efficient lesion detection. When a lesion is detected, irrigation is performed with the water jet function or a syringe. In either case, care should be taken to gradually clean from around the lesion, and not apply water directly onto the lesion to avoid hemorrhage.

(2) Qualitative diagnosis

Colonic lesions discovered by endoscopy include epithelial lesions, both tumorous and non-tumorous, and submucosal tumors. Submucosal tumors could be easily distinguished from epithelial lesions because they elevate smoothly and are covered with normal epithelium in endoscopic findings. This section describes the diagnosis of epithelial lesions.

1) Differentiation between tumors and non-tumors

Tumors and non-tumors are differentiated by focusing on change in color and surface characteristics of the lesion. Protruded type tumors often appear red or bright red compared to the surrounding normal mucosa, and the surface often exhibits lobular grooves. Superficial elevated type tumors often appear red or light red, and the surface is smooth or uneven, often exhibiting a petal-like structure on the periphery. Superficial depressed type tumors often exhibit faint redness, and the depressed margins become more distinct after spraying indigocarmine. On the other hand, hyperplastic polyps are broad-based and often have the same color as or slightly paler than the surrounding normal mucosa and mucus adhesion could be observed on the surface.

Non-magnified pit pattern imaging with spraying indigocarmine is also useful for differentiating between tumors and non-tumors, but this process is not comparable with magnified endoscopy.

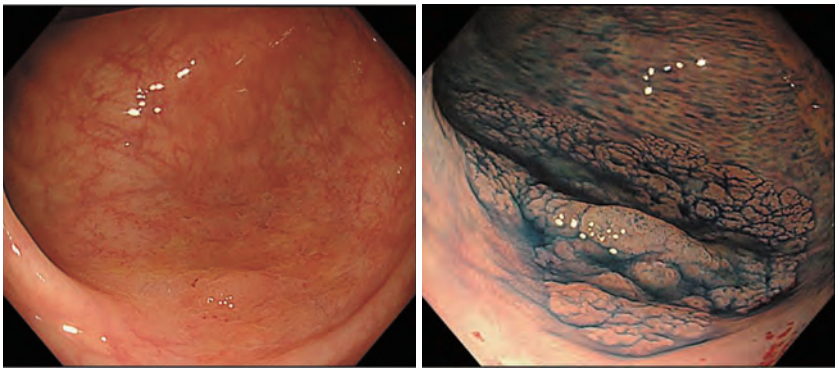
2) Differentiation between sessile serrated lesion and hyperplastic polyp

In endoscopic imaging, SSL is white or pale in color, broad-based shape, and frequently shows mucus adhesion on the surface. Its features are similar to hyperplastic polyps but SSLs are generally larger and more frequently detected in the right colon than hyperplastic polyps. SSL is strongly suspected when the lesion in the right colon is white or pale in color, flat in shape, and 10 mm or more in size (**Figure 1**).[2] In order to confirm the margins of the lesion and to accurately determine its diameter, conventional observation alone is insufficient and chromoendoscopy using indigocarmine is necessary.

3) Differentiation between adenoma and carcinoma

When a lesion is deemed neoplastic, it becomes essential to differentiate between adenoma and carcinoma. However, it is often difficult to differentiate between adenoma and intramucosal carcinoma. In general, findings such as change in color, double elevation, and the presence of depression are helpful for the differential diagnosis.[3]

Regarding change in color, the area with strong redness frequently shows a higher degree of dysplasia



White light observation　　Chromoendoscopy with indigocarminespraying

Figure 1 Endoscopic observation of sessile serrated lesion (SSL).

than the area without redness. In lesions with double elevation, the upper area often shows greater dysplasia than the lower one. In case of a depressed area with stronger redness than the surrounding elevated area, the depressed area often has a higher degree of dysplasia than the surroundings.
When the presence of depression is suspected during conventional endoscopy, indigocarmine is always applied to assess the depressed shape, depth, distinctness of its demarcation, and appearance of its surface.

(3) Quantitative (depth of invasion) diagnosis

1) Conventional endoscopic findings of cT1b (high-grade SM invasion cancer: SM invasion depth 1,000 μm or more)

In diagnosis of invasion depth, a fundamental approach is to assess the distensibility of lesion by alternately insufflating and deflating air. Evaluation of the distensibility of superficial type is relatively easy, but evaluation of the distensibility of protruded type is extremely difficult. In conventional endoscopic findings, in addition to changes in the distensibility of the lesion, there are characteristics that appear due to cancer invasion into the submucosa. Along with changes in the lesion including (i) a clear depression with a flat surface, (ii) firm fullness, and (iii) a submucosal tumor-like elevation, (iv) poor distensibility in the normal mucosa around the lesion could be observed (**Figure 2**).[3-6]

(I) Clear depression with a flat surface

For detecting a depression, a depressed surface with strong redness relative to the surrounding mucosa is often observed. It is desirable to perform indigocarmine spraying after conventional endoscopy to confirm a clear depression.

(II) Firm fullness

Firm fullness refers to the appearance seen in adenomas, where the lobular grooves disappear, leaving a shiny, mostly flat surface. This is attributed to cancer invading the submucosa and the increased cancerous tissue in the submucosa pushing up the surface of the lesion from below. Although this finding is not very objective and has a lot of subjective elements, this condition is generally recognized with experience.

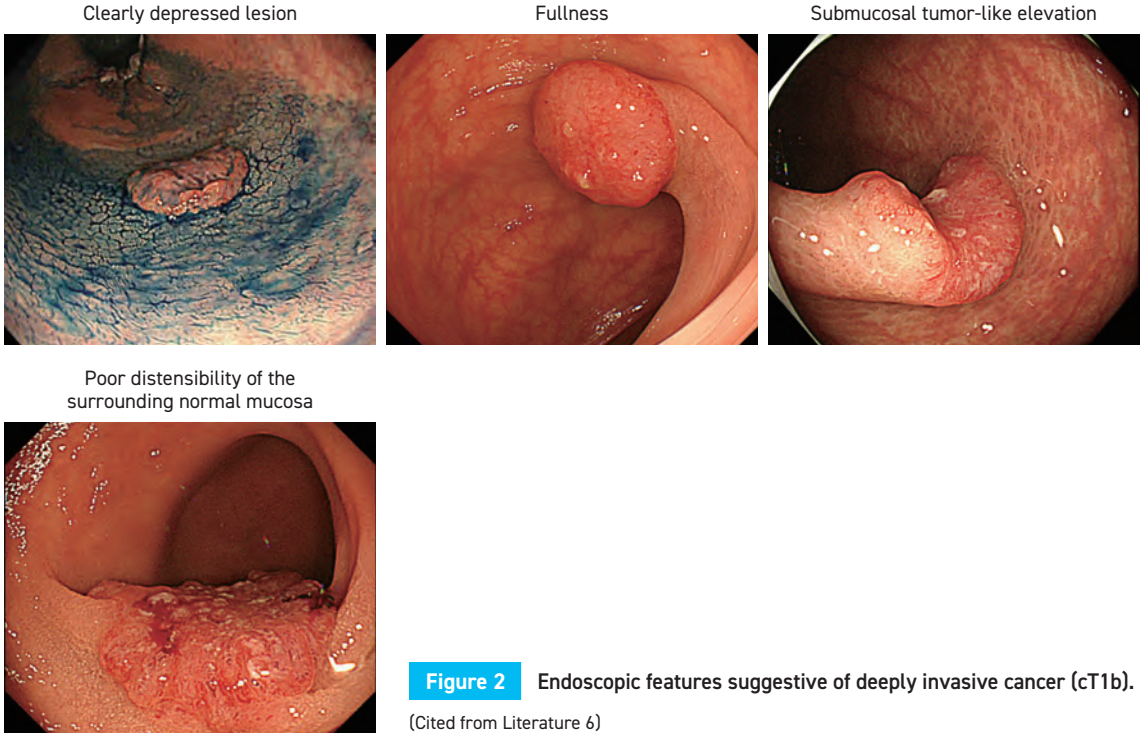


Figure 2 **Endoscopic features suggestive of deeply invasive cancer (cT1b).**
(Cited from Literature 6)

(III) Submucosal tumor-like elevation

Some elevated part of protruded lesions looks normal on the surface, resembling non-cancerous tumor. However, these elevations often find T1 high-grade invasive cancers. The cancer's aggressive nature is masked because while it invades the submucosa near the lesion's center, it also spreads extensively underneath the surrounding normal-looking mucosa at the edges. This submucosal spread creates the appearance of benign elevation while actually representing advanced cancer.

(IV) Poor distensibility in the normal mucosa around the lesion

This findings include fold convergence, rigidity of arc, and non-extension sign. Fold convergence refers to a finding that exhibits concentrated folds from three or more directions. In this case, cancer often invades deep into the submucosa with fibrosis. Rigidity of arc describes a situation where, instead of folds converging towards a lesion the one or more folds appear to be pulled in a straight line toward the lesion. In non-extension sign, both the lesion and the surrounding normal mucosa are raised, resembling a submucosal tumor. It occurs when cancer that has deeply invaded the submucosa lifts the intramucosal lesion upward.

2) Diagnosis of invasion depth

If one or more of these four findings is observed, T1 high-grade invasive cancer is suspected. In conventional endoscopy, about 70 to 80% of T1 high-grade invasive cancers could definitively be diagnosed.[4] Therefore, in cases where the depth of invasion is difficult to determine with conventional endoscopy, or in order to increase the certainty of the diagnosis, it is necessary to perform a diagnosis using other tests in combination, such as magnified endoscopy, endoscopic ultrasonography, or radiographic contrast enema examination.

2. Chromoendoscopy

(1) Non-magnified imaging

Even when observing the large intestine, it is essential to fully utilize electronic endoscopy equipped with a magnifying function. Non-magnified imaging involves performing white light endoscopy, followed by narrow band imaging, and then detailed examination using chromoendoscopy.

(2) Dye-based image enhanced endoscopy

1) Importance of magnified chromoendoscopy

Chromoendoscopy is divided into the contrast method and the staining method. In the former, by spraying indigocarmine (0.2 to 0.4%), the dye accumulates on the lesion surface and the area demarcated with the healthy mucosa, making the difference in elevation clear. The staining solution is useful for magnified endoscopy, and generally crystal violet (0.05%) or methylene blue (10%) is selected. By staining the marginal crypt epithelium, the crypt opening is clearly depicted, and the histological type of the target lesion is predicted from the findings. The Japan Gastroenterological Endoscopy Society (JGES) recommends using crystal violet as it is useful in magnified chromoendoscopy for determining the treatment policy for colonic epithelial lesions.

In 2019, based on the results of animal experiments, Health Canada recognized that gentian violet has a carcinogenic risk. This product is a mixture of triphenylmethane-based basic dyes, and equivalent to crystal violet. No carcinogenesis has been observed in clinical use of crystal violet or gentian violet. Based on this finding, the JGES stated that crystal violet should be used only when its benefits to patients clearly outweigh the risks, and that the minimal necessary amount should be employed under the responsibility of the physician and facility performing the procedure. The academic society also stated that further progress in endoscopic research is important so that dye-based image enhanced endoscopy should eventually serve as an alternative to the current chromoendoscopy.[7)]

2) Technique and observation method

To make an accurate observation, it is helpful to use syringe with lukewarm water containing a defoaming agent and proteolytics to gradually remove mucus from the lesion surface immediately before staining. The amount of staining solution should be kept as low as possible so that the surrounding normal mucosa remains unstained, and any excess dye is immediately suctioned away, both to prevent increased peristalsis from mucosal irritation and to minimize any potential carcinogenic risk. The magnified endoscopy involves first performing non-magnified imaging, then gradually increasing the magnification while observing, and finally checking the deepest part with the highest magnification.

3) Magnified findings by crystal violet (Kudo-Tsuruta classification)[8)]

Since the development of magnified endoscopy, histopathological prediction of colorectal lesions before treatment has been attempted by closely observing the openings of the crypts. This technique led to the establishment of the Kudo-Tsuruta classification, a system for categorizing these patterns, which was formalized after the Hakone Agreement.[9)] Previously, observation of the crypt opening was performed on resected specimens using a light microscope.[10)] The pit pattern classification divides

lesions into five types, from Type I to Type V, with subtypes specified for Types III and V. Normal crypt openings are classified as Type I pits, a pattern that is also seen in juvenile or inflammatory polyps. Openings classified as Type II pits, which typically display a star-shaped pattern as shown in Figure 3b, are characteristic of serrated lesions such as hyperplastic polyps. Such pit patterns are occasionally observed in sessile serrated lesions (SSLs) as well,[11] and lesions larger than 1 cm require careful differentiation through meticulous observation. Types III through V are defined as tumorous lesion. Type III pits are further divided into two subtypes; adenomas often exhibit a tubular pit pattern, referred to as Type IIIL (**Figure 3c**), although superficial low-grade adenomas display a mixture of Type I and Type III patterns. In contrast, depressed lesions have a distinctive pit pattern, designated as Type IIIS, characterized by small, densely packed, round pits that are smaller than normal Type I pits (**Figure 3d**). This feature is difficult to recognize without microscopic observations followed by crystal violet staining. Type IV pits show a villous structure, a characteristic pattern seen in relatively large protruding lesions and laterally spreading tumors (LSTs) of the granular type. Descriptions of these patterns vary including gyrus-, branch-, or pinecone-like, but they all share the feature of deep grooves in the crypt openings. Due to strong mucus adherence, thorough water irrigation is necessary prior to staining. Finally, Type V pits are subclassified based on the pattern of the crypt openings into Type VI and Type VN. Moreover, Type VI pits are broadly grouped into mildly or severely irregular based on the degree of irregularity in crypt morphology. Mild type is characterized by an irregular pit pattern that still retains the staining quality of crystal violet, with the margins of the openings remaining clearly delineated. In contrast, when the crypt lumens appear narrowed with irregular margins, obscure delineation, the pattern is defined as severely irregular. If the crypt opening pattern is lost entirely and hardly recognized, it is designated as Type VN, which serves as an indicator of deep submucosal invasion (**Figure 4**).[6]

4) Super-magnifying endoscopy

The usefulness of magnifying endoscopes that allow imaging at higher magnifications than the usual magnified imaging has been reported,[12] and a super-magnifying endoscope or endocytoscope (EC) has been released by Olympus. Similar to a normal magnifying endoscope, optical magnification of up to 520 times is possible by operating the zoom lever. Observation is performed after applying methylene blue stain.

Findings obtained through endocytoscopic (EC) imaging are organized into three major categories or five subtypes. Based on these findings, an EC classification system has been proposed to correspond with the predicted histological tissue type.[12] Endoscopic images in each lesion are shown in **Figure 5**. In normal crypts, perfect circular openings are observed at equal intervals (**Figure 5a**). In hyperplastic polyps, the nuclei are small and difficult to observe as in normal crypts, but possibly recognized as enlargement of the crypt opening (**Figure 5b**). In normal adenomas, the tubular crypts have slit shaped openings surrounded by the nuclei (**Figure 5c**). On the other hand, in depressed adenomas, the openings are smaller than those of normal crypts and uniformly aligned, and this appearance corresponds to Type IIIS in the pit pattern classification (**Figure 5d**). Moreover, the nuclei are miniaturized and hardly recognized. In highly invasive SM cancer, the openings are obscure, as is the shape of crypt (**Figure 5e**).

In super-magnifying endoscopy, the tissue characteristics of the lesion surface are generally understood in real time as in histopathological findings. It will be widely used as one of the modalities for differentiating tumors from non-tumors or diagnosing the depth of invasion to select a treatment method.

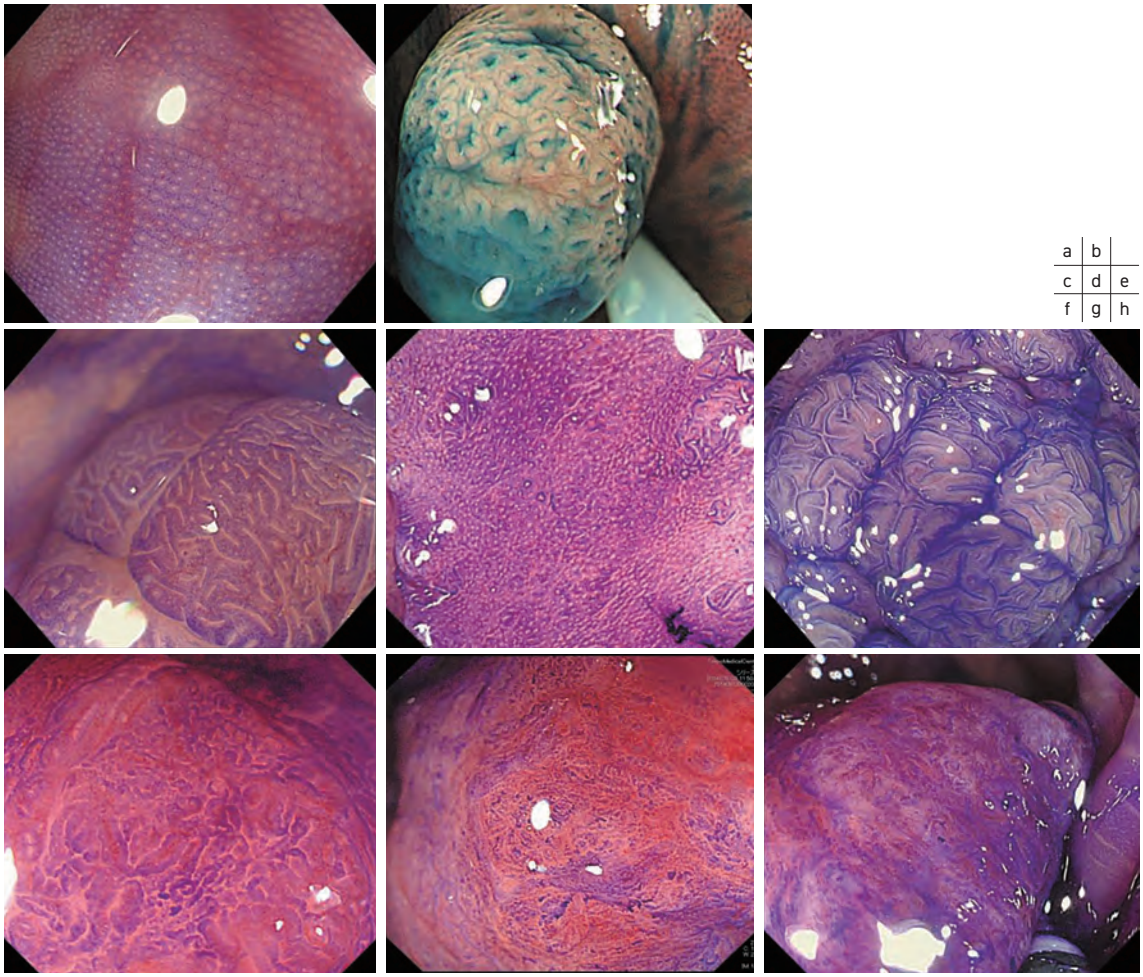


Figure 3 Pit pattern classification.

a: Type I pit represents normal crypt architecture.
b: Type II pit is seen in serrated lesions including hyperplastic polyps.
c: Type IIIL pit shows tubular pits.
d: Type IIIS pit is characterized by pit patterns typical of depressed lesions.
e: Type IV pit presents a villous structure and is typically found in relatively large protruding lesions.
f: Type VI pit (mild irregularity) has irregular openings lacking the regularity seen in types III and IV.
g: Type VI pit (severe irregularity) shows markedly indistinct openings.
h: Type VN pit lacks recognizable pit patterns, and crypt openings are hardly identified.

3. Image Enhanced Endoscopy with NBI, BLI/LCI, TXI, and RDI

Image enhanced endoscopy (IEE) is a technique that enhances images obtained from endoscopes for improving the detection of lesions. It is classified into three types: optical digital method using light other than white light, digital method in which images obtained by white light are processed computationally, and chromoendoscopy method using dyes. In this section, the first two types are explained.

The optical digital method clearly depicts the mucosal surface, its deeper profile, and surface pattern by

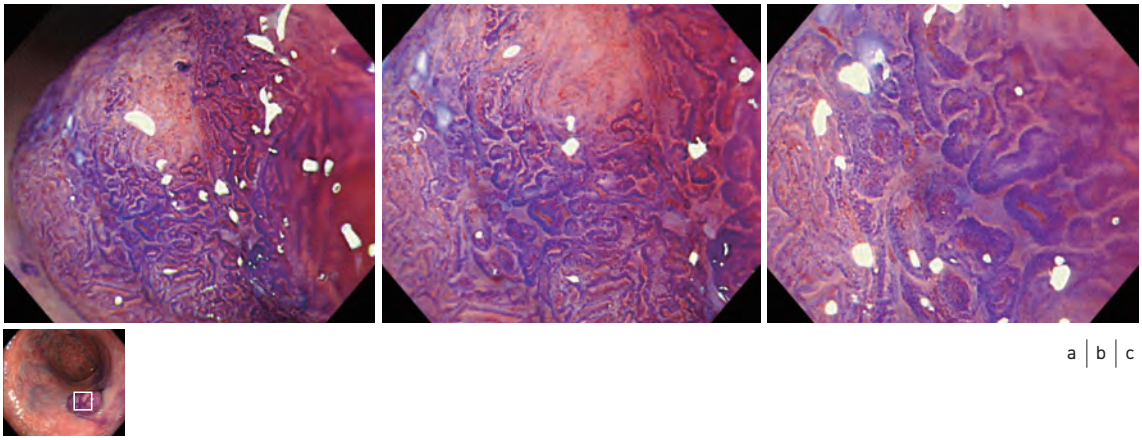


Figure 4 Differences in magnified images with electronic zoom.

a: Magnified image with optical zoom only
b: Image magnified 1.4 x with electronic zoom
c: Image magnified 2.0 x with electronic zoom
(Cited from Literature 6)

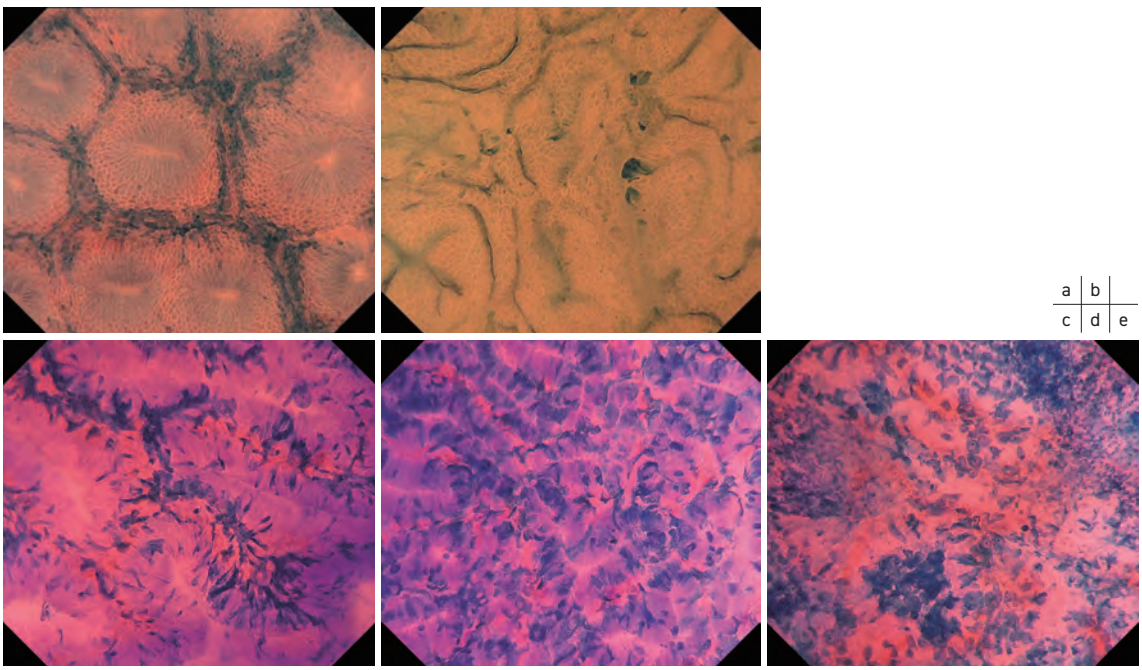


Figure 5 Endoscopic images of various lesions.

a: EC1a corresponds to normal colorectal mucosa, with clearly visible round glandular lumens, smooth glandular margins, and uniformly arranged small round or slightly spindle-shaped nuclei radially aligned along the glandular edge.
b: EC1b corresponds to hyperplastic polyp, showing serrated glandular lumens and small round granules within the cytoplasm.
c: EC2 corresponds to adenoma or carcinoma in situ, presenting with clearly defined slit-like glandular lumens, smooth margins, and slightly enlarged spindle or oval nuclei.
d: EC3a corresponds to Tis to T1a carcinoma, with irregular glandular lumens and methylene blue-stained round nuclei.
e: EC3b corresponds to T1b or deeper invasion, characterized by indistinct glandular structures and irregular nuclei.

using non-white light; the typical modalities include narrow band imaging (NBI), linked color imaging (LCI), blue laser/light imaging (BLI), and red dichromatic imaging (RDI). The digital method improves the visibility of lesions by processing images computationally, such as texture and color enhancement imaging (TXI).

(1) Observation with NBI

NBI was introduced in 2006, and diagnostics based on vessel pattern and surface pattern have rapidly developed and become widely used; both patterns of the digestive tract mucosal surface are captured under NBI magnifying endoscopy.[13)]

1) Findings and classification of NBI magnifying endoscopy in large intestine

(I) NBI presentation and histological findings

i. Vessel pattern and histopathology

In colonic epithelial lesions, it is known that angiogenesis is enhanced and the thickness and density of microvessels increase as the histological tumor grade increases.[14)] In reality, there are some differences between histological images and magnified NBI (narrow-band imaging) findings. For example, in normal colorectal mucosa, histologically, microvessels run in a honeycomb-like pattern surrounding the pits. However, under NBI, these microvessels are often not visible. When they are visible, they appear as an orderly honeycomb-like vascular pattern surrounding the crypts. In hyperplastic polyps, it is usually difficult to recognize microvessels with NBI magnifying endoscopy because the microvessels in the superficial mucosa are very thin and sparse. In adenomas, the caliber and density increase compared to normal mucosa and hyperplastic polyps, and the microvessels show a relatively uniform network pattern. In carcinomas, compared with adenomas, microvessels surrounding the crypts often become irregular and thick with varied calibers, interrupted pattern, and tortuous appearance. Furthermore, in SM cancers where the cancerous tissue that has invaded the submucosa has surfaced, vessel patterns is hardly recognized, or thick vessels is clearly observed (**Figure 6**).[6)]

ii. Surface pattern and histopathology

Regarding surface pattern in NBI magnifying endoscopy, marginal crypt epithelium (MCE) is recognized as white zone (WZ), and sometimes the true pit (crypt opening, CO) is observed at the center of WZ. Only WZ, or the combination of WZ and CO, is regarded as the surface pattern and used for diagnosis. In practice, the surface pattern in adenomas is relatively distinct and the pattern is well-ordered. In contrast, the surface pattern in carcinoma becomes obscure and irregular as the dysplasia progresses, and in SM cancer when the invasive cancerous tissue is exposed on the surface, the surface pattern becomes unrecognizable (**Figure 6**).[6)] In general, since the surface pattern of protruded type is clearly depicted, there are a few difficulties in judging the distinctness and regularity. In superficial type, the surface pattern is not clearly depicted, and it is difficult to judge the distinctness and regularity. It is necessary to understand that the surface pattern in superficial type shows limitations in differentiating adenomas from carcinomas and diagnosing the depth of invasion.

(II) NBI classification

The classification of NBI magnifying endoscopy findings in the large intestine was first reported in 2006 by Sano focusing on vascular findings, followed by the Hiroshima classification in 2008, and the Showa classification and Jikei classification in 2009. In 2011, the Japan NBI Expert Team (JNET), a group of colorectal endoscopy specialists nationwide, was organized to integrate various classifications

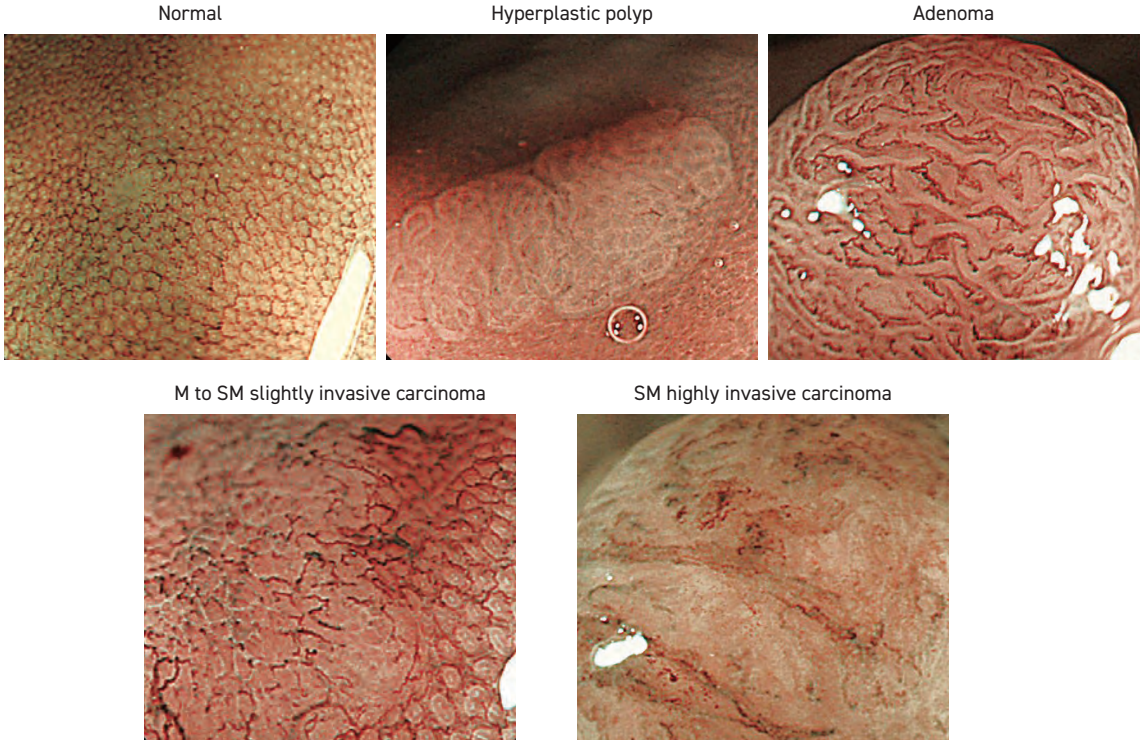


Figure 6 **NBI images of colonic lesions.**

- In normal colonic mucosa, microvessels are often not observed, but when visible, they are observed as orderly honeycomb-like vessels surrounding the crypts.
- It is usually difficult to recognize microvessels under NBI magnified observation in hyperplastic polyps.
- In adenomas, microvessels are recognized as a relatively uniform mesh-like vascular pattern. The surface pattern is clear and the pattern is also orderly.
- In carcinomas, thick vessels irregularly surround the crypts, and variations in caliber, interruptions, and tortuosity are often observed, compared to adenomas. The surface pattern becomes obscure and the pattern irregular.
- In SM carcinomas where the submucosal invasion is exposed on the surface, the vessel pattern is rarely recognized, or clearly thick vessels are often observed. Also, the surface pattern is no longer recognized.

(Cited from Literature 6)

of NBI magnifying endoscopy, and the JNET classification was created in 2014. This diagnostic classification consists of two indicators: vessel pattern and surface pattern. Furthermore, both are divided into four categories: Type 1, 2A, 2B, and 3 (**Table 1**).[15)]

2) System settings for NBI

In evaluating vessel pattern and surface pattern under NBI magnifying endoscopy, it is important to optimally set the structure enhancement function and color mode to the video processor of electronic endoscopy. The system employes a digital method for image enhanced endoscopy to perform structure enhancement function, which has two types: A mode and B mode. Both modes can be set at levels from 0 to 8. The difference between A mode and B mode lies in the fineness of the emphasized structures, A mode for relatively coarse patterns and B mode for finer ones. Although settings could vary slightly among facilities and according to the target lesion, levels A5 to A8 are most commonly used in the lower gastrointestinal tract. There are three color modes, and compared to mode 1, mode 3 decreases the red and blue tones while increasing the green tone; mode 3 is recommended in the large intestine.[16)]

Table 1 JNET classification for magnified NBI of colorectal lesions.

	Type 1	Type 2A	Type 2B	Type 3
Vesse pattern	-Invisible*1	-Regular caliber - Regular distribution (meshed/ spiral pattern) *2	- Variable caliber - Irregular distribution	- Loose vessel areas - Interruption of thick vessels
Surface pattern	- Regular dark or white spots - Similar to surrounding normal mucosa	- Regular dark or white spots - Similar to surrounding normal mucosa - Regular (tubular/ branched/papillary)	- Irregular or obscure	- Amorphous area
Most likely histology	Hyperplastic polyp	Low-grade intramucosal neoplasia (Tis)	High-grade intramucosal neoplasia/ Shallow submucosal invasive cancer (Tis/T1a) *3	Deep submucosal invasive cancer (T1b or deeper)

*1 If visible, the caliber in the lesion is similar to surrounding normal mucosa.
*2 Microvessels are often distributed in a punctuate pattern and well-ordered reticular or spiral vessels may not be observed in depressed lesions.
*3 Deep submucosal invasive cancer may be included.
(Cited from Literature 15)

3) NBI magnifying endoscopic procedure for large intestine tumor

In clinical application of NBI magnifying endoscopy for colonic tumors, prior to lesion observation, the lesion and its surrounding mucosa laden with residual debris or mucus should be thoroughly washed. In this process, care should be taken not to induce bleeding from the lesion since hemorrhage usually interferes with subsequent NBI observation. In particular, aggressive irrigation with a spraying tube too close to the lesion could easily cause bleeding. After the lesion is well washed and residual debris and intestinal contents are thoroughly aspirated, white light endoscopy is performed. For dye-based image enhanced endoscopy using indigocarmine, it is helpful to conduct dye spraying after NBI observation to avoid the extra step of washing off the dye.

Once white light endoscopy has provided an adequate image regarding the quality and invasion depth, NBI process begins.

During NBI magnifying endoscopy, even for relatively large lesions it is desirable to capture images covering the entire lesion. It is helpful to concentrate on regions that display signs of significant histological dysplasia under white light endoscopy, such as redness, depression, or unusual protrusions. In addition, viewing the lesion at an oblique angle often produces unclear images and interferes with accurate assessment of NBI findings. Therefore, it is important to observe the lesion frontally as much as possible by compression of the mucosa surrounding the lesion with a non-traumatic tube (from Olympus) as well as by adjusting air volume. If peristalsis is present, it is important to wait for the lesion to be positioned for a frontal view during the peristaltic movement. Moreover, instead of immediately using full zoom, it is important to gradually zoom in with distant to close-up viewing, and then at the next shooting point to transition from distant again gradually to close-up viewing. Through this imaging method, it becomes easier to identify which part of the lesion corresponds to the magnified image in the later review. When white light and NBI endoscopy conclude a lesion as non-tumorous,

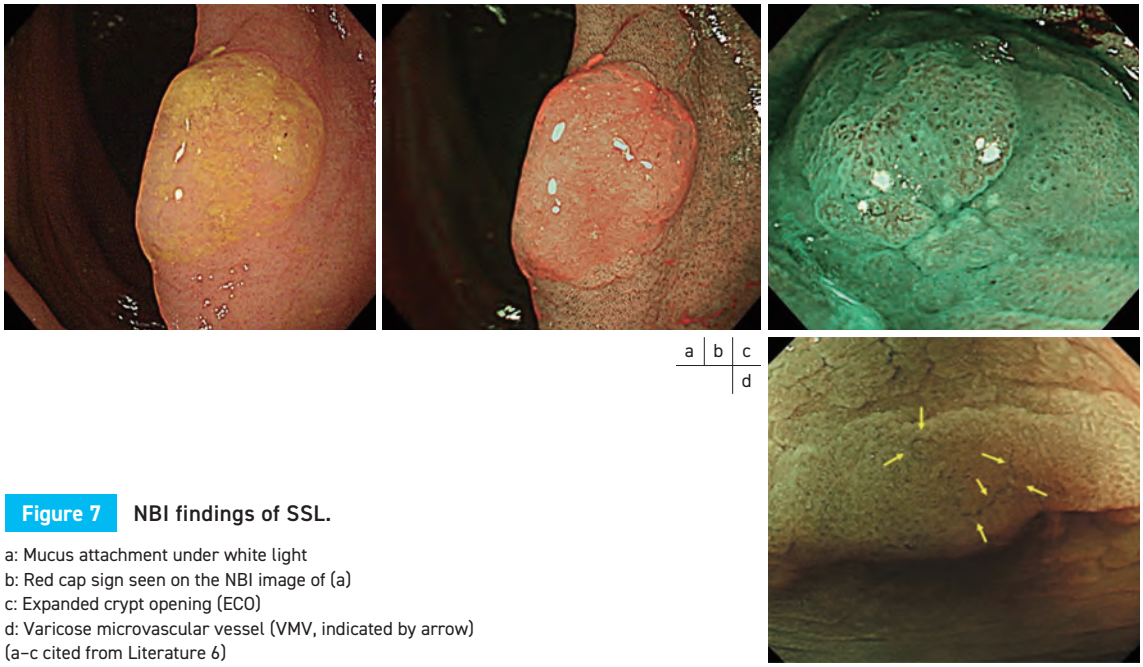


Figure 7 NBI findings of SSL.

a: Mucus attachment under white light
b: Red cap sign seen on the NBI image of (a)
c: Expanded crypt opening (ECO)
d: Varicose microvascular vessel (VMV, indicated by arrow)
(a–c cited from Literature 6)

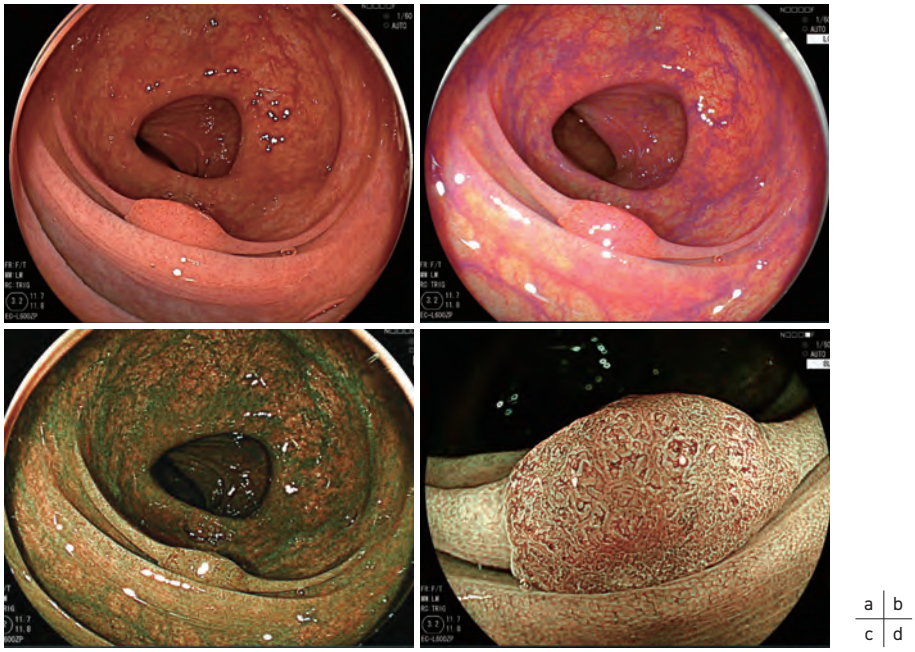
follow-up observation should be induced; when diagnosed as an adenoma, follow-up observation or endoscopic resection is undertaken; and when diagnosed as cancer or suspected cancer, it is recommended to observe the surface structure of the lesion in detailed imaging and to perform dye-based image enhanced magnified endoscopy to improve diagnostic accuracy.

4) Differentiation between SSL and hyperplastic polyp

Both sessile serrated lesions (SSLs) and hyperplastic polyps show a non-tumorous pattern (JNET classification Type 1) on NBI endoscopy. However, there is a report to provide the characteristic findings in SSL that are useful for differentiating between the two conditions. The characteristics of SSL include red cap sign[17] corresponding to mucus adhesion in white light endoscopy, expanded crypt opening (ECO)[18] corresponding to Type II pit opening in dye observation, and vascular features for dilated, meandering, or branch-like vessels such as varicose microvascular vessel (VMV)[2] and dilated and branching vessel (DBV),[19] as shown in **Figure 7**.[6]

(2) Observation with BLI/LC

In the endoscopic system that was released in 2012 utilizing a laser light source, it is possible to perform BLI endoscopy, a narrow-band light observation technique that emphasizes microvessels and surface patterns. The BLI mode increases the proportion of laser light used for narrow-band light observation, thereby maximizing the contrast of the vessels on mucosal surface and making it suitable for close-up imaging as well as magnified viewing. BLI-bright mode enhances the white light component compared with BLI, resulting in brighter images and improved contrast through narrow-band light imaging even at relatively distant views. It has been reported that this mode improves the visibility of polyps compared with white light endoscopy.[20]



a | b
c | d

Figure 8 **Endoscopic images using BLI/LCI.**

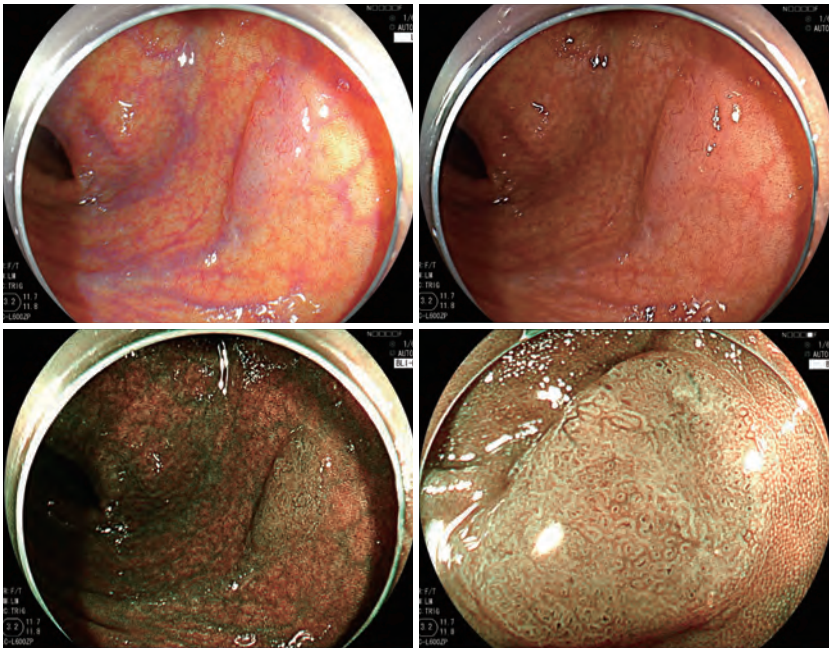
a: White light image of IIa lesion in the descending colon (8 mm, low-grade adenoma)
b: LCI image
c: BLI-bright image
d: Magnified BLI image
(Cited from Literature 6)

LCI emphasizes the differences in mucosal color by adding red light components to the illumination light of BLI-bright for processing the images clearly. LCI endoscopy is even brighter than white light endoscopy and is capable of capturing subtle changes in the color of mucosal surface (**Figures 8** & **9**).[6)]

1) Diagnosis of colorectal tumorous lesion by BLI/LCI

For the diagnosis of colonic tumors using BLI/LCI, it is possible to employ the same NBI magnified endoscopic classification that is used in narrow-band light imaging technique, and BLI has been reported to have diagnostic capability equivalent to that of NBI for differentiating neoplastic and non-neoplastic polyps as well as for diagnosing the depth of cancer invasion.[21,22)] The JNET classification is also applicable to BLI endoscopy.

Currently, various reports have been published on the surveillance of colorectal polyps using LCI, showing that LCI not only increases the adenoma detection rate (ADR) and polyp detection rate (PDR) but is also useful for enhancing the detection rate of serrated polyps, compared with white light endoscopy.[23-25)] BLI-bright mode also has been reported to be useful in improving the adenoma detection rate.[26)] However, few reports suggest that it does not contribute to an increase in ADR, so further investigation is warranted.



a | b
c | d

Figure 9 Endoscopic images using BLI/LCI.

a: White light image of IIa lesion in the ascending colon (8 mm, SSL)
b: LCI image
c: BLI-bright image
d: Magnified BLI image
(Cited from Literature 6)

2) Evaluation of inflammation by BLI/LCI

Recently, LCI has also been reported to be potentially effective for evaluating colonic mucosal inflammation in ulcerative colitis (UC).[27-29] Until now, the evaluation of inflammatory activity in UC had been performed with scoring systems based on conventional endoscopy, such as the Mayo Endoscopic Sub-score (MES) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Today, a scoring system is developed based on observations made using LCI. This score is calculated by assessing the degree of mucosa redness enhanced by LCI and visible vascular pattern reduced by LCI, compared with conventional endoscopy. This scoring system is possibly more effective for predicting prognosis than conventional white light-based evaluation methods.[27]

(3) Observation with TXI

TXI is a novel image-enhanced endoscopy (IEE) released in 2020. This imaging technology optimizes three elements based on standard white light information: structure enhancement, color, and brightness correction. This modality brightens dark areas without causing halation, to visually specify subtle changes in color and structure on the image. TXI has two modes: standard TXI mode 1 and TXI mode 2 which is close to white light. TXI mode 1 produces an image with all three elements optimized, whereas TXI mode 2 produces the color tone close to white light with improved structure enhancement and brightness correction. These features provide an image close to white light that enhances the visibility of mucosal structure (**Figure 10**). Since its release, it has been used in many facilities for tumor



Figure 10 Endoscopic observation using TXI.

a: Standard white light observation
b: TXI Mode 1 observation, optimized with structure enhancement, color, and brightness correction
c: TXI Mode 2 provides a color tone similar to white light, but with improved structure enhancement and brightness correction, allowing improved visibility of mucosal morphology while maintaining a white light-like image

detection and inflammation assessment, and reports on its effectiveness should be available soon.

1) Diagnosis of colorectal tumorous lesions by TXI (Figure 11)

Regarding the diagnosis of colorectal neoplasms by TXI, reports are still scarce, and evidence demonstrating its effectiveness is insufficient. There are reports that TXI showed a higher tumor detection rate in studies comparing adenoma detection rate (ADR) and polyp detection rate (PDR) between TXI and conventional endoscopy,[30,31] while a report suggests that TXI detection ability could be inferior to the endoscopy with narrow-band imaging (NBI).[32] Thus further verification is warranted in the future.

2) Evaluation of inflammation by TXI (Figure 12)

Regarding inflammation, evaluation by TXI is similar to inflammation evaluation by linked color imaging (LCI). There are reports proposing a scoring system based on the enhanced mucosa redness and visible vascular pattern reduced, which are emphasized when endoscopy is performed using TXI mode 1.[33] TXI endoscopy suggests the possibility of detecting mucosa with the potential for recurrence even if the lesion is evaluated as being in remission with conventional endoscopy. However, further research is needed as reports regarding inflammation are insufficient at the moment.

(4) Observation with RDI (Figure 13)

RDI is a modality of image-enhanced endoscopy (IEE) released in 2020, together with TXI. This imaging technology creates contrast between deep and superficial vessels with three types of narrow-band light of red, amber, and green that have different light absorption characteristics. It was developed to improve bleeding management during treatment by displaying deep vessels around 1 to 1.5 mm deep with amber light and superficial blood vessels more clearly with green light. RDI has three modes, and the enhancement level of deep vessels is changed by each mode. In Mode 1, the whole image appears in yellowish amber, but deep vessels are depicted in darker amber, so it is helpful for identifying the

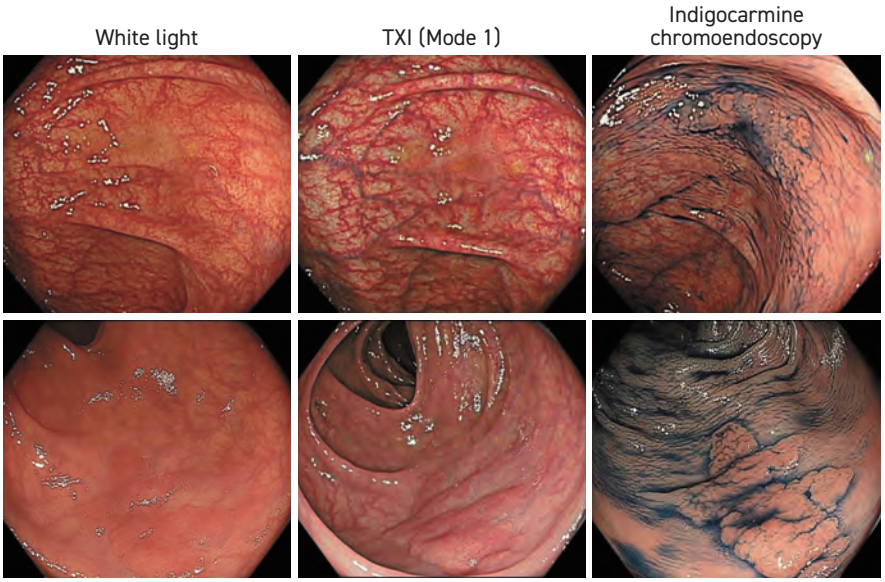


Figure 11 Diagnosis of colorectal neoplastic lesions using TXI.

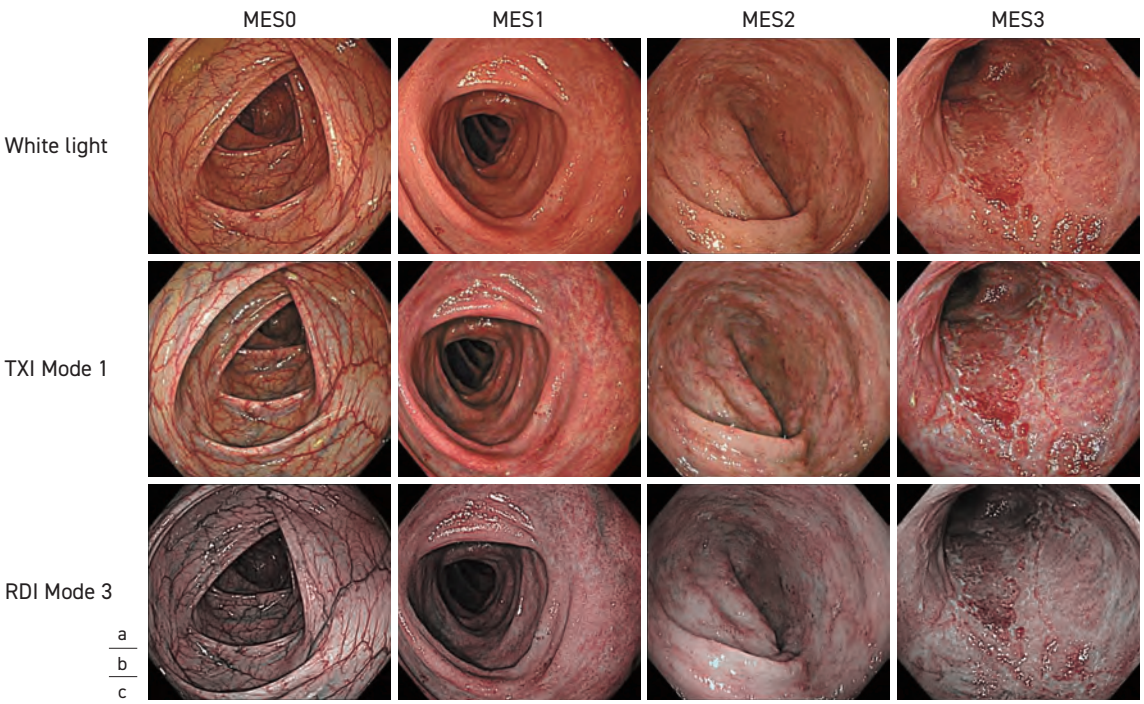
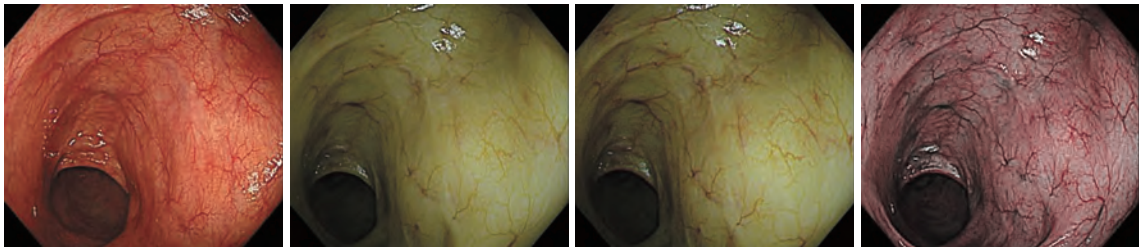


Figure 12 Inflammation assessment using TXI/RDI.

Appearance of inflammation under each imaging mode
a: White light
b: TXI Mode 1
c: RDI Mode 3



White light | RDI (Mode 1) | RDI (Mode 2) | RDI (Mode 3)

a | b | c | d

Figure 13 **Endoscopic observation using RDI.**

a: Standard white light image
b: In Mode 1, the image appears amber in tone, with deeper vessels appearing in a darker amber shade.
c: Mode 2 enhances the reddish appearance of deeper vessels compared with Mode 1.
d: In Mode 3, deeper vessels are further emphasized and appear green, while superficial vessels appear red.

source of bleeding. In Mode 2, the redness of deep vessels is more pronounced than in Mode 1. It is expected to improve the visibility of vessels for local injection in endoscopic treatment. In Mode 3, the deep vessel enhancement level is further increased. Deep blood vessels are observed in green and superficial ones in red, so the difference in visible vascular pattern is clear. The effectiveness of RDI is expected to be demonstrated when evaluation of visible vascular pattern is vital for inflammation disease such as ulcerative colitis (UC).

Since RDI is a technology that clarifies the contrast of vessels, most of its reports evaluate the usefulness of Mode 1 for gastrointestinal bleeding. However, there are no reports of study examining the effectiveness for detecting neoplastic lesions. On the other hand, some studies using Mode 3 reported that RDI is useful for evaluating the activity of UC.[34,35] It has been reported that scoring the difference in visibility between superficial and deep vessels is effective for predicting prognosis, but since there are still few reports, further studies are necessary.

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4 Colon Capsule Endoscopy

1. Characteristics

The first generation of colon capsule endoscopy (PillCam® COLON 1) was released in 2006, followed by the second generation (PillCam® COLON 2) in 2009.

The colon capsules are 5 mm longer than small bowel capsules, with a length of 31.5 mm and a width of 11.6 mm (Figure 1a). Because the capsule incorporates a camera at each end, providing a 172-degree field of view on both sides, it is possible to capture images in all directions. The device is equipped with an **adaptive frame rate (AFR) function** as a tool to automatically adjust the number of images taken. When the capsule is moving slowly through an intestinal tract, it takes 4 frames per second (fps), but it takes 35 images per second while moving quickly. This function reduces the risk of overlooking lesions, which was a concern with the first generation with a fixed capture rate of 4 fps. The **data recorder (DR3)** (Figure 1b) is equipped with a function that automatically recognizes the shapes of mucosal surface in small intestine and large intestine. When the colon capsule endoscopy determines



Figure 1 Components of colon capsule endoscopy

a: PillCam® COLON 2 capsule (Covidien)
b: PillCam® recorder DR3 (Covidien)
c: PillCam® sensor array (Covidien)
d: RAPID® workstation (Covidien)

that the capsule goes in the small intestine, it takes 14 images per minute for conserving battery. The DR3 usually not only specifies capsule images in real time but also has a **regimen reminder function**. This function makes it possible to accurately inform patients of the timing for taking booster medication and the timing of prokinetics. The reading software has been upgraded to include a **polyp size estimation (PSE) function**. This feature allows for the measurement of lesion sizes regardless of the distance between a lesion and the capsule. Capsule endoscopy is a modality that permits observation of the digestive tract in a physiological condition after a patient simply swallows the capsule. The greatest advantage is that it is simple and painless for the patient. On the other hand, it is necessary to perform colon capsule endoscopy with an adequate understanding on its characteristics, such as a large amount of bowel preparation and the risk of overlooking lesions, compared to standard colonoscopy.

2. Indications in Japan

In July 2013, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan approved the use of colon capsule endoscopy for patients with known or suspected colonic diseases. Its intended use involved capturing images of the colonic mucosa and providing visual information to support the diagnosis on colonic diseases in situations where colonoscopy is necessary but not easily performed. These situations involve individuals with a positive fecal occult blood test who face difficulty undergoing colonoscopy, mainly due to factors such as adhesions. It is difficult to perform colon capsule endoscopy as a secondary examination for colorectal cancer screening in all cases with the current Japanese indications, while some Japanese facilities are performing the examination with non-insurance or self-pay medical treatment. However, its safety has not been fully confirmed for pregnant women and patients under 18 years old or with severe diverticular disease of the digestive tract, even though the indication of colon capsule endoscopy is patients with known or suspected colonic diseases.

3. Contraindications and Precaution

The contraindications for colon capsule endoscopy are almost the same as those for small bowel capsule endoscopy. Precaution is required for **capsule retention, a condition in which the capsule remains in the same site of organ for more than two weeks**, in particular for: (i) patients with known or suspected gastrointestinal obstruction, stenosis, or fistula through abdominal X-ray examination, abdominal ultrasonography, medical history, surgical history and clinical findings (excluding cases where no stenosis is confirmed by contrast examination although it is not confirmed by the above examination methods), (ii) patients with a confirmed diagnosis of Crohn's disease (because there is no patency capsule dedicated to the large intestine), (iii) patients who have received radiation therapy to pelvic organs and are suspected of having stenosis due to radiation enteritis, and (iv) patients with a history of abdominal surgery and an unconfirmed status for contrast examination. Moreover, precautions for incidents unrelated to retention include (i) patients with a cardiac pacemaker or other implanted electrical medical device, and (ii) patients with swallowing difficulty or at risk for it. It is contraindicated to use colon capsule endoscopy in conjunction with MRI examination because this combination may cause injury to the intestinal tract or abdomen when the colon capsule goes through the tract.

Colon capsules past their expiration date should not be used for safety precaution. In particular, they should not be used if there is a suspicion of quality impairment due to dropping the colon capsule or the

patient biting it, or if there are other unforeseen circumstances. Unlike small bowel capsule endoscopy, laxatives and oral medications are essential for the examination. Therefore it is important to always check for allergies and contraindications to the related drugs. Because of the large amount of pre-treatment medication, sufficient care should be taken when the patients take these medications. When a patient complains of abdominal symptoms, it is necessary to immediately discontinue administration.

4. Colonic Preparation

The quality of the colonic preparation is extremely important for highly accurate diagnosis. Unlike standard colonoscopy, it is impossible to aspirate or wash away residue, and a large amount of residue often leads to lesions being overlooked. Unlike small bowel capsule endoscopy, it is difficult to observe the entire colon within the battery life using intestinal peristalsis alone, so after the capsule reaches the small intestine, it is essential to clear the colon lumen and then take a booster, such as an additional laxative, to flush the capsule toward the anus. Regarding the amount of laxative, it has been reported in western countries that 4.5 to 6 L of laxative is required over two days, including the booster,[1] while the excessive amount of laxative posed a problem for its introduction into Japan in terms of patient acceptability. In Japan, the regimen for preparing for an examination has typically involved using a reduced amount of a polyethylene glycol-containing electrolyte solution, or PEG-ELS, on the day of the procedure. The one-day method uses three to four liters of the solution.[2] Currently, a pre-treatment method using high-concentration polyethylene glycol (sodium, potassium, and ascorbic acid combination powder) is effective, but the combination with castor oil is also useful,[3,4] the oil which has been used in Japan for a long time. *The Japanese Association for Capsule Endoscopy* recommends regimens using the laxatives together with castor oil for surveillance of colonic polyps and evaluation of the degree of inflammation in ulcerative colitis (**Table 1**). However, even if the recommended regimen is selected, there are cases where the cleansing level is inadequate or cases where the entire large intestine is hardly observed. In practice, the issue regarding how to improve the pre-treatment regimen remains unresolved.

5. Basics and Practice of Reading

Differences of colon from the small intestine include: (i) wider lumen, (ii) many blind spots due to the presence of folds, (iii) reading accuracy is affected by the level of cleanliness, (iv) the capsule moves within the same region from proximal to distal, and (v) reading is required twice for one case since that cameras are mounted on both ends of the capsule. Unlike colonoscopy, capsule endoscopy is not performed with the lumen sufficiently expanded by air insufflation, and capsule images are taken with fluid present in the large bowel (submarine view), and there are many close-up images in contact with the intestinal mucosa. The basic principles and specific procedures for reading will be described separately for the diagnosis of colon polyps and the evaluation of inflammation in ulcerative colitis.

(1) Colonic polyp (Figure 2) [5]

1) Basic principles for reading

(i) It is essential to follow the recommended method. An efficient procedure for reading the colon capsule involves **three sequential steps**: beginning with a **preview using quick view (QV)**, then

Table 1-1 Medication and instructions for colon capsule endoscopy (for colorectal polyp)

		Regimen
Two days prior	Before bedtime	Sennoside 3 tablets (36 mg): for constipation (patients with chronic constipation should take laxatives daily starting 1 week prior).
One day before	Morning, noon, evening	Low-residue diet
	7-10 PM	1 packet (50 g) of Magcorol powder® dissolved in 180 mL of water (high osmotic method)
	Before bedtime	1 bottle of Laxoberon® + 80 mL of water (1 cup)
Examination day	9 AM	Moviprep® 1000 (up to 500) mL + 500 (up to 250) mL of water: until bowel movements are clear
	10-11 AM	4 tablets of Gasmotin® → A capsule endoscope swallowed
		Walking or lying in the right lateral position
		If the capsule has not reached the small intestine after 1 hour → intramuscular injection of 1 ampule of Primperan (10 mg) (optional)
		If the capsule has still not reached the small intestine after another 1 hour → intramuscular injection of 1 ampule of Primperan (10 mg) (optional).
	After reaching the small intestine	1 bottle (30 mL) of flavored castor oil + 100 mL of Moviprep®
		400 mL of Moviprep® + 250 mL of water
		500 mL of Moviprep® + 250 mL of water
	By 5:00 PM, if no excretion	(i) Intramuscular injection of 1 ampule of Primperan (10 mg) (optional)
		(ii) 30 mL of flavored castor oil + 100 mL of water (optional)
		(iii) 1 packet (50 g) of Magcorol powder® dissolved in 180 mL of water (optional)
		(iv) 60 mL glycerin enema

*Water: water, tea, apple juice, sports drinks are acceptable.
(Source: Japanese Association for Capsule Endoscopy website)

proceeding to a **review with display**, and finally **performing analysis and report**.

(ii) It is important to **adjust the reading speed and avoid interpreting at an excessively fast frame rate**; when the capsule moves rapidly, one should reduce the display speed as needed or scroll through frames one by one using the mouse wheel.

(iii) **Judgments should not be based on a single image**.

(iv) **Evaluation is performed with reference to the vascular pattern of mucosa**. The vessels are primarily distinguished from the lesion boundaries, and suspicious lesions are tracked according to the vascular pattern with reviewing a series of varying images.

(v) Attention should be paid to folds and the ileocecal valve, which could resemble polyps.

(vi) Caution is required for captured bubbles, since the light reflected from them possibly resembles polypoid structures.

2) Reading procedure

(I) Preview

The reading process begins with a preview using QV and dual-head view. The entire journey from mouth to anus is scanned as quickly as possible while maintaining clarity. At the outset, four anatomical landmarks are identified and annotated: the first cecal image, the hepatic flexure, the splenic flexure,

Table 1-2 Medication and instructions for colon capsule endoscopy (for ulcerative colitis)

		Regimen
One day before		Dietary restrictions, no bowel preparation
Examination day	6:30 AM	Moviprep® 500 mL + 250 mL of water
	9:00 AM	Capsule endoscope is swallowed after 2 mL of Gascon Drops
	After reaching the small intestine (10:00 AM)	20 mL of castor oil
		Moviprep® 500 mL + 250 mL of water
	If no excretion by 0:00 PM	Moviprep® 500 mL + 250 mL of water
	If no excretion by 3:00 PM	Moviprep® 500 mL + 250 mL of water
	4:00 PM	Start eating

*Water: water, tea, apple juice, sports drinks are acceptable.
(Source: Japanese Association for Capsule Endoscopy website)

and the final rectal images. Following this, **the cleansing quality of the colon is evaluated for each region, applying a four-grade scale for the five colon segments: poor, fair, good, and excellent.**[6] Any images that raise concern should be captured for later analysis.

(II) Review (Display)

The next phase is the review process. In this step, the entire images is played back by a single-head (green head) display at a speed of 8 frames per second or less, during which any lesions are captured. After this, the review returns to the initial cecal image and switches to the second capsule head (yellow head), as two readings per case are required. In anatomically complex regions or when the capsule is moving quickly, it is critical to slow down the display speed or manually scroll frame by frame to avoid missing a polyp that appears in only a single frame.

(III) Analysis/Report

After the review process, the captured images are analyzed and the findings are concluded. The main findings include the lesion site, gross type, lesion diameter, tumor/non-tumor and whether it is tumorous or not. Because the same lesion is often imaged multiple times by the capsule's dual cameras, a comprehensive judgment is needed to determine whether the appearances represent the same lesion or another one. The lesion diameter is measured by the PSE function, and when multiple images of the same lesion are available, the largest measurement is recorded.

While protruded lesions such as polyps are relatively easy to detect, flat lesions are more likely to be overlooked and therefore require special attention (**Figure 3**).[5] **In identifying flat lesions, one should carefully note features such as a mucus cap, margin formation caused by residue or bubbles, interruption of vascular pattern, and contour deformation of the folds.** Although vessels tend to be less visible on lesions, the boundaries of flat type sometimes mimic vascular patterns. Thus, it is important not to confuse the borders of lesions with vessels. In cases where there is uncertainty regarding a lesion, endoscopists should review consecutive images by scrolling back and forth rather than relying on a single frame.

According to a study conducting meta-analysis in 2021, the detection sensitivity of colorectal polyps with a diameter of 6 mm or more by the second-generation colon capsule was reported to be 87% (95% CI: 83-90%), and the specificity was 87% (95% CI: 76-93%).[7] It is a useful modality for identifying

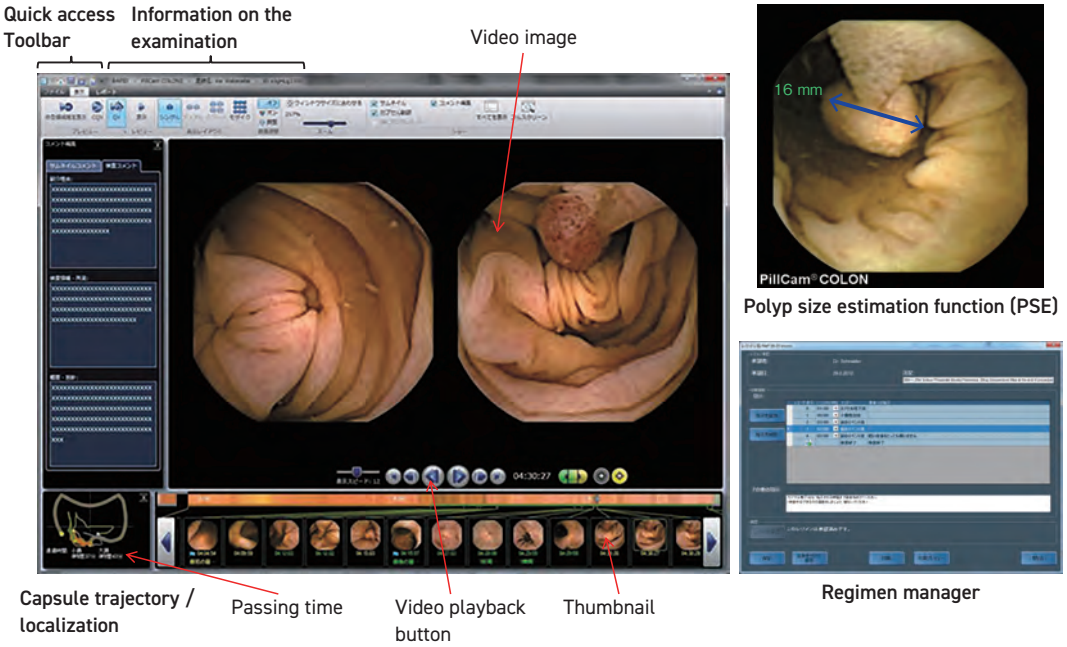


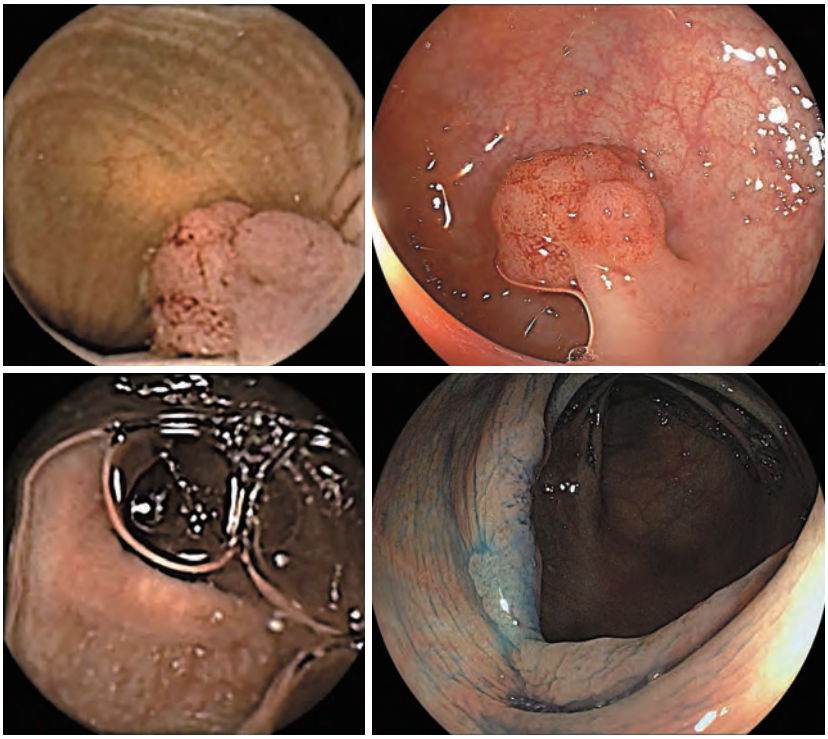
Figure 2 Display screen of PillCam® workstation (RAPID®)

(Cited from Literature 5)

and diagnosing colorectal polyps. On the other hand, a multi-center study conducted in Japan reported a 94% detection rate for treatable lesions using colon capsule endoscopy. These lesions included polyps measuring 6 mm or more in diameter, as well as other morphological abnormalities that required endoscopic or surgical intervention. This result was beneficial to the lesions with a diameter of 6 mm or more in the sigmoid colon compared with colonoscopy, while there was no difference in the detection rate for protruding and superficial types.[8)]

(2) Ulcerative colitis (Figure 4)

Western guidelines currently do not recommend colon capsule endoscopy for ulcerative colitis. However, its clinical usefulness has been reported for diagnosing the severity and extent of inflammation in the follow-up of patients with ulcerative colitis for confirmation of treatment effect and confirmation of severity.[9,10)] The roles of endoscopy in ulcerative colitis include: (i) diagnosis at the time of the first visit, (ii) judgment of treatment effect and monitoring of inflammation, and (iii) surveillance of ulcerative colitis-related colorectal tumors.[11)] Although the usefulness of colon capsule endoscopy has been reported for diagnosing the severity and extent of inflammation in ulcerative colitis, there are no reports on surveillance of ulcerative colitis-related colorectal tumors, and its use for that purpose is not recommended. Therefore, in cases of long-term ulcerative colitis, it is necessary to use not only colon capsule endoscopy but colonoscopy as appropriate, to pay attention to ulcerative colitis-related colorectal tumors. In clinical practice, the modality is beneficial for evaluation on the effect of treatment intervention. For the evaluation on inflammation, the process becomes similar to reading for colon polyps but requires additional attention to the capsule's position to gauge the extent of inflammation. Specifically, it is crucial to determine whether the inflammation has spread beyond the

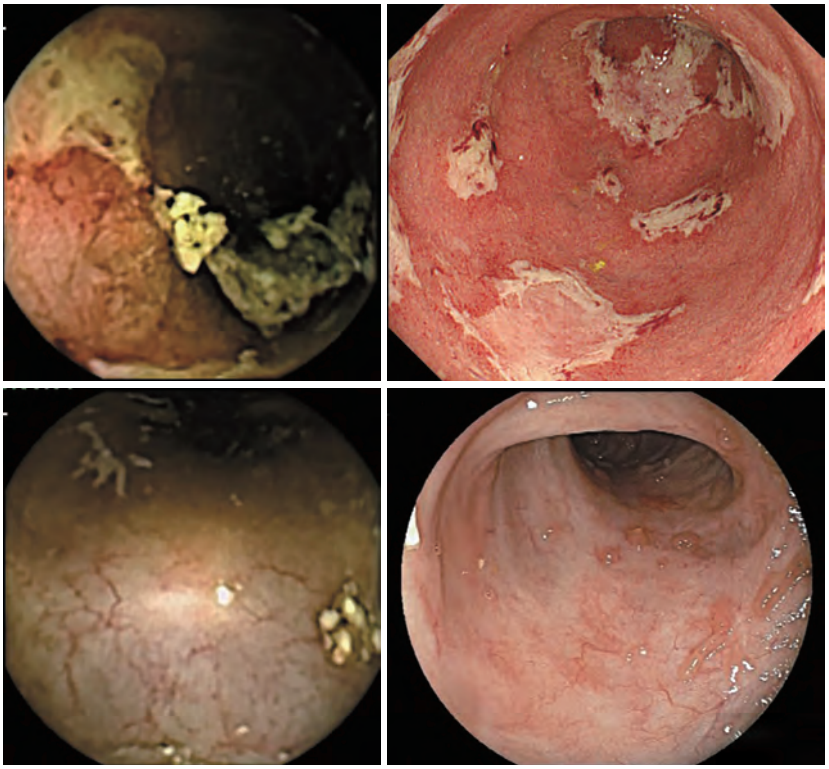


a | b
c | d

Figure 3 Two cases of colonic lesions identified by colon capsule endoscopy

a: Capsule endoscopic image. A 12 mm, type 0-Isp lesion in the sigmoid colon
b: Conventional endoscopic image of lesion (a). Histopathological diagnosis revealed carcinoma *in situ* (Tis).
c: Capsule endoscopic image. A 25 mm, type 0-IIa lesion in the transverse colon
d: Conventional endoscopic image of lesion (c). Histopathological diagnosis revealed carcinoma *in situ* (Tis).
(Cited from Literature 5)

splenic flexure. It is difficult for colon capsule endoscopy to distinguish the boundaries between the rectum and the sigmoid colon, as well as the sigmoid colon and the descending colon, so a rough estimate is sufficient. If the extent of involvement is unclear, it is generally helpful to retrogressively review the video from the anal side. This process provides clearer images of the affected extent, similar to the colonoscopy procedure conducted from the distal side. Regarding the severity of inflammation, obvious findings such as ulcers or erosions are relatively easy to assess (**Figure 4a**). However, in the remission phase without active inflammation, the mucosa still looks granular in texture. This appearance makes it difficult to definitively confirm that true remission has been reached. Additionally, the visible vascular pattern could appear blurred or indistinct. To accurately assess remission, it is best to focus on images where the capsule is in close proximity to the mucosa.



a | b
c | d

Figure 4 **Inflammatory appearance of ulcerative colitis observed by colon capsule endoscopy**

a: Capsule endoscopic image. Geographic ulcer in the sigmoid colon, corresponding to Mayo endoscopic subscore 3.
b: Conventional endoscopic image of lesion (a).
c: Capsule endoscopic image. Scarred mucosa without active inflammation in the descending colon, corresponding to Mayo endoscopic subscore 0.
d: Conventional endoscopic image of lesion (c).

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Naoki Hosoe and Shiro Oka

5 Endoscopic Ultrasonography

Endoscopic ultrasonography (EUS) is an examination method that depicts the digestive tract wall and its surrounding area as an ultrasonic tomographic image from the lumen of digestive tract. This technology is widely used for the diagnosis of digestive tract diseases as well as pancreatic and biliary tract diseases. In the lower digestive tract region, it is also used for diagnosis of invasion depth and submucosal infiltration of cancer, qualitative diagnosis of submucosal tumors, and evaluation on severity of inflammatory bowel disease. EUS is a useful examination method applied for identification of the pathological condition if it is possible to obtain a constant and reproducible clear ultrasonic tomographic image of target lesions.

This section will explain the devices used for EUS examination of colorectal diseases, examination methods, and the practical diagnostic methods.

1. Available Devices

Currently, the main EUS devices used for the diagnosis of colorectal diseases are ultrasonic probes (USPs), but echoendoscope for large intestine are not commercially available. After deaerated water fills in the area around the lesion of large intestine, a USP is inserted through the forceps channel of the endoscope. The USP is a mechanical radial type, and ultrasound scanning is performed after insertion of the probe tip directly above the lesion. The frequency of the USP can be selected either 12 MHz or 20 MHz. In addition to regular radial images, three-dimensional ultrasonic probes are commercially available to give linear images or three-dimensional images at arbitrary phases.

Regarding the frequency used in EUS, higher frequencies yield higher image resolution but are more prone to ultrasound attenuation. Such frequencies are less suitable for observation of the deeper layers of the bowel wall and surrounding areas. Therefore, high-frequency devices are selected for scanning flat lesions on the surface, whereas low-frequency devices are chosen when higher lesions need to be scanned or lymph node metastasis in pericolic tissues needs to be assessed.

2. EUS Examination Methods and Key Points

For EUS examinations of colorectal diseases, even for rectal lesions, bowel preparation should be performed using oral bowel cleansing solution. Residues generally create artifacts in the EUS images and interfere with accurate diagnosis. Unless contraindicated, pre-procedure medications such as butylscopolamine or glucagon are typically administered to suppress intestinal peristalsis. This is because

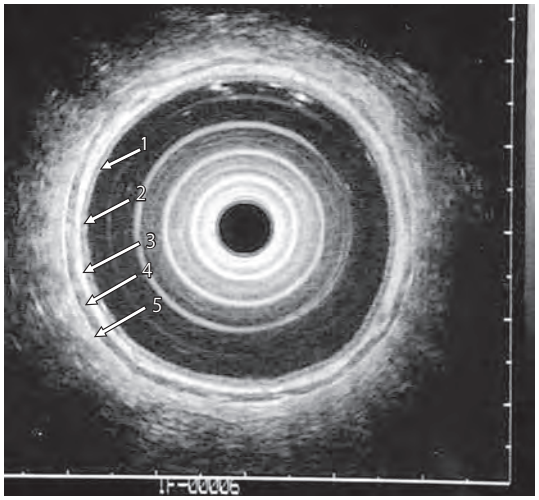


Figure 1 EUS image of the colorectal wall.

The colorectal wall is visualized as a five-layered structure under endoscopic ultrasonography.
(Cited from Literature 1)

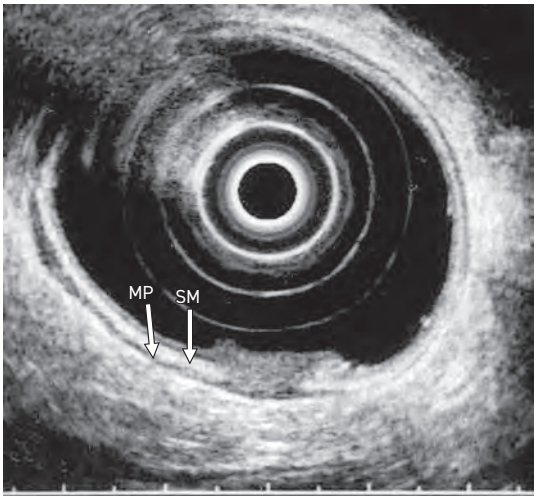


Figure 2 EUS image of cT2 cancer (muscularis invasive carcinoma).

(Cited from Literature 1)

active peristalsis interfere with adequate filling of the bowel with deaerated water. The deaerated water should also be warmed to body temperature. In EUS, the lesion should be scanned as vertically as possible to obtain clear ultrasonic images. The EUS image is the primary guide for positioning the probe over the lesion while the endoscopic image serves as a reference to help for the fine adjustment.

3. Ultrasonic Layer Structure of the Colorectal Wall

The normal colorectal wall is visualized as a 5-layered structure in EUS. From the inner side of the lumen, the first layer shows high echo with the second one, low (mucosa), the third, high (submucosa: SM), the fourth, low (muscularis propria: MP); and the fifth, high of subserosa and serosa (or adventitia in areas without serosa), respectively (**Figure 1**).[1)] In EUS, the colorectal diseases are diagnosed by comparison with the normal 5-layered structure, based on the location or qualitative diagnosis.

4. Diagnosis of Colorectal Cancer

(1) Invasion depth

In EUS, the cancerous lesion is depicted as a hypoechoic mass, and the depth of invasion is determined by the findings of destruction and preservation of the layered structure.2-4) If the mass remains within the second layer and the third layer is preserved, it is diagnosed as cTis cancer (M type). If the mass remains up to the third layer and the fourth layer is preserved, it is diagnosed as cT1 cancer (SM type). If the mass remains up to the fourth layer and the fifth layer is preserved, it is diagnosed as cT2 cancer (MP type) (**Figure 2**).[1)] If the mass destroys the fourth layer and reaches the fifth layer, it is diagnosed as cT3 cancer (SS or A type). If the mass is depicted as extending the wall, it is diagnosed as cT4a cancer (SE type). Furthermore, if the mass is in continuity with the surrounding organs, it is diagnosed as cT4b

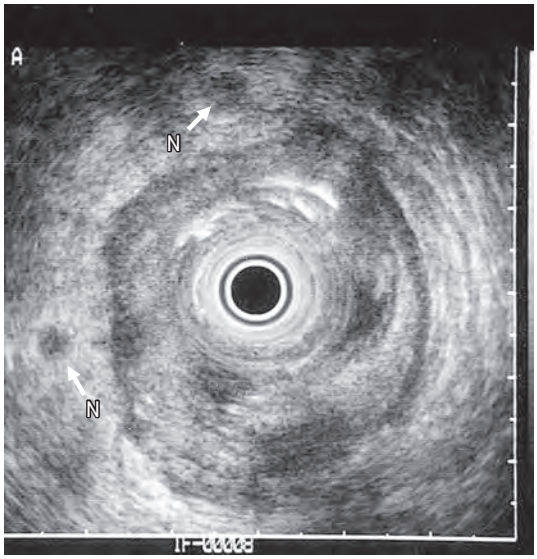


Figure 3 EUS image of metastatic lymph nodes (N positive).

(Cited from Literature 1)

cancer (SI or AI type).

(2) Lymph node metastasis

In EUS, lymph nodes are depicted only in the paracolic lymph nodes, but even small lymph nodes of 5 mm or less are usually diagnosed thanks to the resolution (**Figure 3**).[1)] The diagnosis by EUS is primarily provided according to the size of depicted lymph nodes same as with MRI and CT, so the diagnostic accuracy for metastasis is limited.

(3) Diagnosis of SM infiltration of T1 cancer

Among early colorectal cancers, intramucosal cancer (pTis cancer) and submucosal infiltrative cancer (pT1a cancer) with invasion depth of less than 1,000 μm from the lower edge of the muscularis mucosae have extremely rare lymph node metastasis. In general, surgical intestinal resection with lymph node dissection is not required, and in many cases, it is completely cured endoscopically.

The depth of submucosal (SM) invasion in colorectal T1 cancer is assessed on EUS through comparison of the hypoechoic mass, which represents the cancerous lesion, with the surrounding SM layer. However, accurately measuring the vertical extent of invasion prior to the procedure remains challenging. This is because the muscularis mucosae is not clearly identified on EUS, and the measurement accuracy is not high on the ultrasound transducer. Therefore, relative classification is employed with EUS for determining the depth of invasion into submucosa before the treatment of colorectal T1 cancer. A cancer is defined as SM1 when its deepest part, which appears as a hypoechoic mass, is comparable to the upper third level of the adjacent submucosa (**Figure 4a**).[1)] When it remains in the middle third, it is defined as SM2 cancer (**Figure 4b**). When it invades in the lower third but the boundary with the fourth layer (MP layer) is

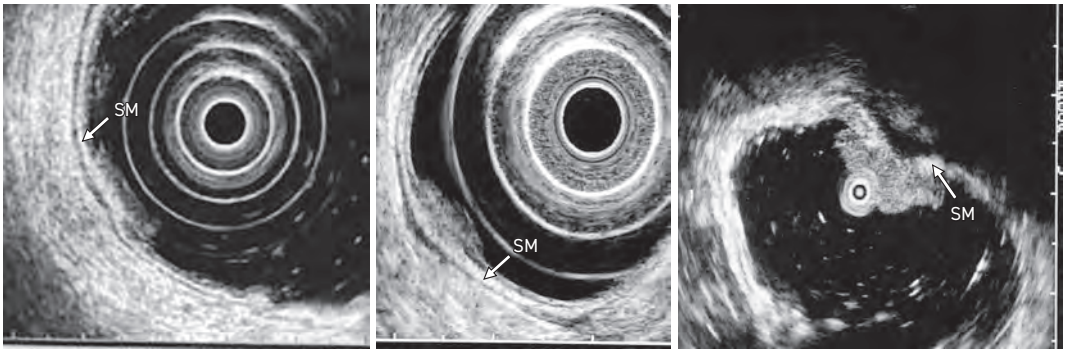


Figure 4 EUS image of cT1 cancer (submucosal invasive carcinoma).

a: SM1 cancer
b: SM2 cancer
c: SM3 cancer
(Cited from Literature 1)

preserved, it is defined as SM3 cancer (**Figure 4c**).[1,5] The role of EUS in clinical practice is to differentiate whether the cancer is confined to SM1 or extends beyond SM2. When M or SM1 cancer is diagnosed preoperatively with EUS, endoscopic resection is performed if technically feasible. Curative assessment is performed through the detailed histological examination including the invasion depth for the obtained resected specimen. In cases where there is suspicion of cancer invading beyond SM2, the presence or absence of lymph nodes around the intestine near the cancer lesion is also evaluated, and surgical resection is considered in combination with other diagnostic methods.

5. Diagnosis of Submucosal Tumors

EUS is also applied for qualitative diagnosis of submucosal tumors (SMTs) / subepithelial lesions (SELs), selection of treatment methods, and differentiation from extraluminal compression, because it obtains vertical tomographic images of the tumor.[6]

(1) Diagnostic method by EUS

In the diagnosis of colorectal SMT/SEL, the intraluminal localization and the internal structure (echo level and echo pattern) are evaluated based on the EUS findings. The echo level is evaluated as hyperechoic when it is comparable with the third layer (submucosa), hypoechoic when it is comparable with the fourth layer (muscularis propria), isoecho when it is between the third and fourth, and anechoic when it is comparable with deaerated water. The echo pattern is evaluated as homogeneous or heterogeneous.

Table 1 outlines the characteristics of the intraluminal localization and the internal structure evaluated by EUS for colorectal SMT/SEL and SMT/SEL-like lesions.[1] Among these, especially lipomas, lymphangiomas, and pneumatosis cystoides intestinalis provide characteristic EUS findings, and qualitative diagnosis is possible with EUS. Hypoecho indicates cancerous entities including gastrointestinal stromal tumor (GIST), lymphoma, carcinoid (well-differentiated neuroendocrine tumor), and granular cell tumor. In GIST, if there is bleeding or necrosis within the tumor, the internal echo

Table 1 EUS findings in submucosal tumors and submucosal tumor-like lesions in the colon.

Lesion	Location	Tomography
Lipoma	3rd layer	Hyperechoic, with possible deep echo attenuation
Lymphangioma	3rd layer mainly	Cystic, with septation; anechoic lumen
Hemangioma	3rd layer mainly	Hyperechoic, with mixed anechoic to hypoechoic areas
Carcinoid	Depends on invasion depth	Homogeneously hypoechoic
Lymphoma	Depends on invasion depth	Homogeneously hypoechoic to nearly anechoic
GIST	3rd/4th layer	Hypoechoic predominantly, with mixed hyperechoic and anechoic areas
Granular cell tumor	3rd layer	Hypoechoic, often heterogeneously
Appendiceal mucocele	3rd layer	Anechoic to hypoechoic with mixed hyperechoic areas
Pneumatosis cystoides intestinalis	3rd layer or deeper	Plate-like hyperechoic structure, with acoustic shadowing
Intestinal endometriosis	3rd to 4th layers	Fusiform thickening of the 4th layer

(Cited from Literature 1)

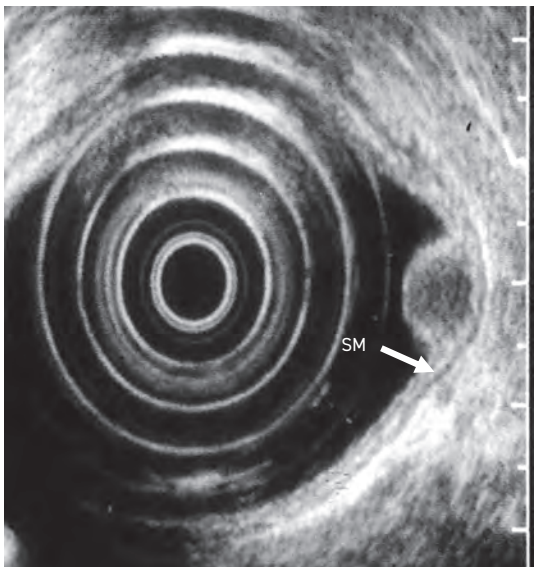
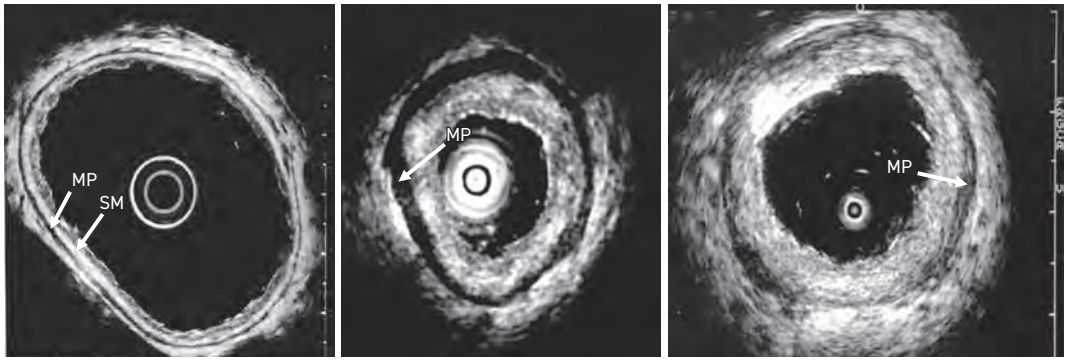


Figure 5 EUS image of rectal carcinoid.

(Cited from Literature 1)

becomes complex, thereby indicating malignancy. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is sometimes used to get a tissue sample for a pathological diagnosis of GIST and other rectal submucosal tumors/subepithelial lesions located near the anus.[6)]



a | b | c

Figure 6 EUS image of ulcerative colitis.

a: Inflammation is confined to the mucosa.
b: Inflammation extends to the submucosa.
c: Inflammation reaches from the muscularis propria to the serosa.
(Cited from Literature 1)

(2) Indications for endoscopic treatment

Among colorectal SMT/SELs, carcinoids are quite common in the lower rectum. Endoscopic resection is often possible,[7] if the tumor is confined to the third layer (submucosa) with no enlargement of the lymph nodes near rectum on EUS as shown in **Figure 5**.[1]

6. Diagnosis of Inflammatory Bowel Disease

Acute enteritis includes ischemic colitis, bacterial enteritis, and drug-induced enteritis (acute hemorrhagic colitis type and pseudomembranous colitis type). In the acute phase, edema and erosion are observed on the mucosal surface in all of these conditions. EUS demonstrates marked thickening of the large intestinal wall, the main cause of which is hypoechoic change and thickening of the submucosa. In pseudomembranous colitis, the findings reflect that a hypoechoic irregular mass corresponding to the pseudomembrane is attached to the mucosal layer.

Chronic enteritis includes ulcerative colitis, Crohn's disease, and radiation-induced enteritis.

In ulcerative colitis, the EUS image in the active phase manifests that the wall is thickened throughout, inflammation is observed as hypoechoic change, and ulcers are observed as defects on the wall surface. As the severity increases, the hypoechoic change of inflammation is observed up to the deeper part of the wall. EUS is useful as auxiliary diagnostic tool for determining the severity because it observes the depth of inflammation in the active phase.[8] **Figure 6** shows EUS images of depth of inflammation.[1] In **Figure 6a**, the wall is slightly thickened, but the layered structure is preserved. Inflammation looks to remain within the mucosa. In **Figure 6b**, the wall is moderately thickened, the layer boundaries from the first to the third layer are indistinct, and the hypoechoic change extends to the third one. Thus, the inflammation appears to extend into the submucosa. In **Figure 6c**, the wall is markedly thickened, the layer boundaries from the first to the fourth layer are indistinct, and the outer edge of the fourth layer is irregular with hypoechoic change. The inflammation extends from the muscularis propria to the serosa. In ulcerative colitis, enlarged lymph nodes, dilated blood vessels, and localized ascites are frequently found around the intestinal tract in active phase. As the inflammation progresses and affects deeper layers of the intestine, it is typically associated with a higher occurrence rate of more severe findings or complications.[9]

In Crohn's disease, changes are mainly observed in the submucosa, with thickening of the submucosa and irregular thickening of the muscularis propria corresponding to the lesional area.
In radiation-induced enteritis, EUS demonstrates many small hypoechoic or anechoic findings thought to be dilated vascular networks from the mucosa to the submucosa, while this finding corresponds to the extensive telangiectasia on the mucosal surface confirmed by endoscopy.

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6 Polypectomy, Cold Polypectomy, EMR, and Underwater EMR

In endoscopic resection there are some techniques such as polypectomy, cold (snare) polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). Polypectomy generally refers to resecting polyps by applying electrocautery to a steel wire of the snare, although historically there was a period when resection was performed by physical cutting without electrocautery. In recent years, the method of resection without electrocautery has been revisited, having rapidly become popular under the name cold (snare) polypectomy. To distinguish this technique, the electrocautery method is sometimes called hot (snare) polypectomy.

For small polyps, removal is sometimes completed using the biopsy forceps or similar ones. Those performed with electrocautery have traditionally been called hot forceps polypectomy or hot biopsy, although they are rarely performed in these days. The technique of resection without electrocautery is termed cold forceps polypectomy to differentiate it from biopsy performed solely for diagnostic purpose. For lesions such as broad-based and flat depressed types, endoscopic mucosal resection (EMR) where the lesion is resected using electrocautery after being elevated by the injection of liquid iinto the submucosa underneath has been applied Furthermore, the so-called underwater EMR is also gaining popularity, in which the lumen of gastrointestinal tract is filled with water without performing submucosal injection, while the lesion is strangulated with a snare before resection with electrocautery. This section will explain the indications, procedures, and management of adverse events for each technique other than ESD.

1. Indications and Contraindications

(1) Overview

1) Basic concept

When early colon cancer is diagnosed, endoscopic treatment or surgical treatment should be recommended. **The treatment should be abandoned if the risks of endoscopic treatment outweigh its benefits, in cases where the patient's general condition is poor or the patient does not have the ability to cooperate.**[1] A lateral spreading tumor (LST) in the colorectum is considered a suitable candidate for endoscopic treatment. They are common among elderly patients, but the rate of high-grade dysplasia is low and depth of invasion, if ever, is usually shallow, despite their size. Elderly patients, who often have poor general conditions and underlying diseases, face a higher possibility of complications during endoscopic treatment. Therefore, the decision on whether to conduct the treatment

requires careful judgment. In contrast, some reports have indicated that endoscopic treatment could be safely carried out even for elderly patients. **For very elderly patients, endoscopic treatment should be done only when the expected advantage is likely to outweigh the risk of complications associated with the resection, while also considering the average life expectancy, comorbidities, and body age of the patient.** Prior to the endoscopic treatments, it is necessary to thoroughly assess the concomitant diseases and current medications. Particularly, when the patient is on antithrombotics such as anticoagulant or antiplatelet, it is important to understand that the patient has the risks of bleeding if the medication is continued on the endoscopic treatment and the risks of cerebrovascular events if the medication is suspended. Based on this consideration, it should be decided whether to suspend the antithrombotic(s) and how long the suspension period should be.[2] **Endoscopic treatment should be conducted only after an adequate informed consent is obtained.**[1]

2) Principles behind the indications for endoscopic resection

(I) Cancerous lesions

Among early colorectal carcinomas, lesions with little possibility of lymph node metastasis and higher expectancy of curability with en bloc resection on the basis of the size and the location are usually treated endoscopically because such cases are expected to be curable.[1] When endoscopic treatment is carried out for colorectal carcinomas, en bloc resection is the principal approach; however, piecemeal resection is also acceptable when the possibility of submucosal invasion can be definitively excluded and if the treatment is appropriately carried out. In such cases, thorough magnified endoscopy is essential before resection, but the cancerous area should not be resected in a fragmented way. Obvious clinical T1b carcinomas (submucosal invasion depth ≥1000 μm) are usually treated surgically.

(II) Non-cancerous lesions

Resection is recommended for adenomas ›6 mm in size. Resection is recommended for superficial depressed-type lesions (type 0–IIc) even when the lesion is ‹5 mm in size. Typical hyperplastic polyps ‹5 mm in size that are present in the distal colon may be left untreated.[1,3] The carcinoma rate of protruded-type and superficial elevated-type lesions ≤5 mm in size is low, and these adenomas are extremely unlikely to become a T1 (submucosal [SM]) carcinoma. However, the rate of SM invasion (i.e. the T1 [SM] carcinoma ate) of lesions >6 mm increases as the size of the lesion increases. Despite there is no clear evidence regarding the prognosis of diminutive lesions ≤5 mm in size that had been followed for several years showed minimal changes. Therefore, **prompt treatment is not required for protruded-type and superficial elevated-type adenomas ‹5 mm in size.**[1,3] Superficial depressed-type lesions exhibit a certain carcinoma rate and a certain rate of SM invasion even when their size is ≤5 mm. Based on the combined use of pit pattern on magnified endoscopy with the findings from image-enhanced endoscopy (IEE), lesions suggestive of malignancy should be treated regardless of the tumor diameter. Although adenomas themselves are benign, it is expected that their removal will prevent the development of colorectal carcinoma. Most colorectal neoplasms are adenomas, and these adenomas can be cured by endoscopic resection. In recent years, the so-called resect and discard policy has been proposed in the Western countries, where adenomas smaller than 5 mm are resected and discarded without being sent to histopathological examination.[4] This management aims to reduce substantial medical costs by omitting the process of histopathological diagnosis. This concept was put forward based on the data that show there exists almost no carcinoma within adenomas of 5 mm or less in size. Hence, pathology examination is often deemed unnecessary. Although a diagnostic accuracy of 90% or more is required as the threshold,[5] it is premised that the endoscopic diagnosis is made by an

Table 1 Selection of colorectal tumor resection methods.

Lesion	Tumor diameter (mm)				
	≤3	4-5	6-9	10-19	20≤
Pedunculated		H snare	H snare	H snare	H snare
Flat, broad-based	C forceps	C snare	C snare EMR	EMR	ESD pEMR
susupected to be carcinoma or HGD		EMR	EMR	EMR	ESD

H snare: hot snare polypectomy, C snare: cold snare polypectomy, C forceps: cold forceps polypectomy, H forceps: hot forceps polypectomy, pEMR: piecemeal endoscopic mucosal resection
(Cited from Literature 7)

experienced practitioner using the latest endoscopic modalities including IEE. Thus, there are still challenges concerning the feasibility and widespread applications of this policy into clinical practice. It is also proposed that hyperplastic polyps in the sigmoid colon and rectum do not need to be removed, but the prerequisite is that the negative predictive value for adenomas should be 90% or more.[5] According to genetic-molecular-pathological analysis, certain colorectal carcinomas are assumed to develop from serrated lesions through the so-called serrated pathway. Serrated lesions are classified into three types: hyperplastic polyp (HP), traditional serrated adenoma (TSA), and sessile serrated lesion (SSL). Both TSA and SSL with a size of 10 mm or more or those suspected to harbor dysplasia should be removed.[6] Since SSLs are often ill-defined, careful observation with magnified endoscopy is necessary before the treatment to avoid the resection margin becoming positive during endoscopic treatment.

(2) Specific indications for each resection techniques

1) Polypectomy and EMR (Table 1) [7]

(I) Hot forceps polypectomy (Hot biopsy)

Previously, it was common to perform hot forceps polypectomy (HFP) for resecting polyps 5 mm or less in size. Recently, cold snare polypectomy (CSP) and cold forceps polypectomy (CFP) have gained widespread use, while HFP has become less common. However, HFP is occasionally applied for treating not only minute residues during piecemeal resection with EMR, but also locally recurrent lesions after endoscopic resection, especially in benign cases.

(II) Polypectomy (Hot snare polypectomy)

Basically, this procedure is applied for pedunculated or semipedunculated protruded lesions. For pedunculated lesions, hot snare polypectomy is a preferable indication, since cold snare polypectomy has a high risk of causing intraprocedural bleeding. For lesions suspected to be cancer invading into the stalk, surgical treatment is selected in principle.

(III) Cold polypectomy [8]

For complete resection of lesions, it is recommended that the target for cold polypectomy be limited to preoperatively diagnosed to be adenomas less than 10 mm in size. CSP has a benefit of shorter procedure time compared with HSP. CSP is associated with lower rate of en bloc resection with

negative margin. Hence, it is not recommended for resection of polyps of 10 mm or more in size. Considering all the circumstances, the indication for CSP should be limited to adenomas, whereas EMR should be adopted for lesions suspected to be cancer (or high-grade dysplasia) for which complete en bloc resection is required. Before the resection, highly accurate qualitative diagnosis is required with image-enhanced/magnified endoscopy to rule out the possibility of cancer. Cold polypectomy is performed with not only snares (CSP) but also forceps (CFP). Forceps are acceptable for polyps 3 mm or less in size because of simplicity of the technique and high rate of successful retrieval of the resected specimen.

(IV) Conventional EMR and piecemeal EMR

EMR is a technique in which physiological saline or sodium hyaluronate is locally injected into the submucosa beneath the lesion, and the lesions are strangulated with a snare wire and resected with an electric current generated by a high frequency electrosurgical unit. It is mainly performed for superficial or broad-based lesions. Large sessile (0-Isp, Is) or flat (0-IIa) lesions are indicated for EMR or ESD. How small they are, lesions suspected to be cancer should be resected with injection in order to secure lateral and vertical margins. For small lesions not suspected to be cancer, polypectomy is acceptable, but the surrounding normal mucosa should be grasped with a snare even without injection.

(V) So-called underwater EMR (UEMR) [9]

This is a method of resecting a tumor while filling the digestive tract lumen with water, snaring the tumor without submucosal injection, and applying electric cautery with a high frequency electrosurgical unit. The target lesions include adenomas, sessile serrated lesions (SSLs), and any cancerous lesions that are expected not to have spread into the submucosa. Lesions larger than 10 mm can be resected with UEMR technique, whereas lesions smaller than 10 mm in diameter are candidates for CSP. However, even UEMR carries a risk of involving the muscularis propria when the lesion is associated with significant fibrosis. Even if a lesion is difficult to lift with submucosal injection, this procedure is worth trying. For example, a recurrent lesion associated with scar tissue after previous endoscopic resection is a potential candidate. Since UEMR does not include submucosal injection, it does not strictly align with the definition of EMR provided in the ESD/EMR guidelines issued by the Japan Gastroenterological Endoscopy Society.[1]

2) Selection of HSP or CSP

For lesions up to about 5mm in diameter, CSP is adequate, enabling a quick procedure. In HSP, there is a risk of causing thermal cautery to the resected specimen and there are also concerns about adverse events. In lesions 10 mm or more in size, CSP requires a large force for resection, and the risk of incomplete resection increases, so it is generally contraindicated.

3) Selection of EMR or ESD

According to the *SCCR Guidelines 2022 for the Treatment of Colorectal Cancer*, [10] the indication for ESD goes to early malignant tumor, while **it is determined in consideration of accurate preoperative endoscopic diagnosis and the operator's proficiency in endoscopic resection. Most colorectal tumors are adenomas and generally treated with en bloc EMR or piecemeal EMR.** In practice, ESD is technically more difficult than EMR, requires a longer treatment time, is associated with a higher perforation rate, and is more expensive. In cases of carcinoma, lesions less than 2 cm in size are generally resected en bloc by EMR using a snare. Thus in Japan, application of insurance to ESD is limited to carcinoma (HGD or T1) with a maximum diameter of 2 cm or more.

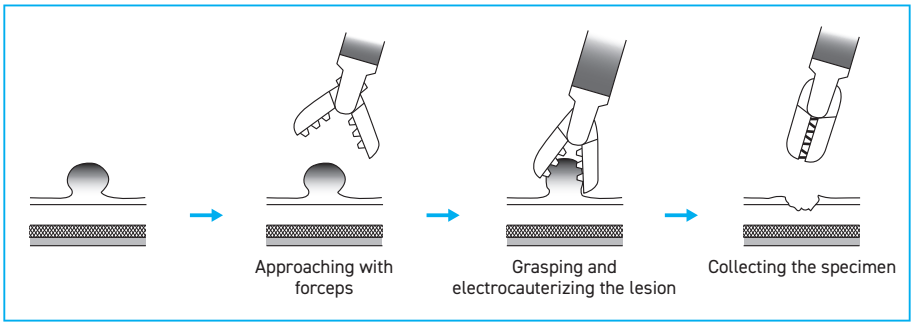


Figure 1 Schematic presentation of endoscopic resection: Hot biopsy.

(Cited from Literature 11)

However, intramucosal tumors with submucosal fibrosis, sporadic localized tumors associated with chronic inflammation such as in ulcerative colitis, and recurrent early carcinoma after endoscopic resection often present with poor lifting in response to injection, even when measuring less than 2 cm. These types of lesions are therefore sometimes considered suitable for endoscopic submucosal dissection (ESD).[1)] Lesions with fibrosis, such as recurrent lesions after piecemeal EMR, are often difficult to resect with ordinary EMR. Such lesions are considered to be indicated for ESD if they are large. However, a high level of proficiency is required because there is a risk of perforation. In practice, it should be addressed carefully. When recurrence from the deep margin is suspected, the lesion is likely to represent a deeply invasive submucosal cancer. Surgical treatment is appropriate in such cases, even if the lesion is small.

In endoscopic resection, en bloc resection is recommended as much as possible even for lesions with a large tumor diameter in order to obtain accurate pathohistological evaluation thereafter. The limit of en bloc resection with snaring is considered to be about 20 mm in tumor diameter. While en bloc resection with a snare is generally more challenging for larger lesions, it may be possible depending on the specific location and shape of the lesion, the kind of solution used for injection, the instruments, and the proficiency of endoscopists performing the procedure. **When the lesion is large but clearly a benign adenoma, it can be considered to be candidate for piecemeal EMR.** Compared with complete en bloc resection, piecemeal resection tends to make pathohistological evaluation difficult and the local residual recurrence rate is high. **Endoscopic removal for early colorectal cancer should basically be completed with en bloc resection.**[1)] Piecemeal EMR is acceptable only when it is performed appropriately, but this means that the number of resected pieces is kept to a minimum and the lesion should be completely removed so that there is no residue. Adherence to the following points is critical.

(i) Resection be carefully planned and completed based on endoscopic diagnosis, ensuring that normal mucosa is included in the specimens to avoid any lesion resideu.

(ii) The cancerous area be predicted with accuracy, and efforts be made to minimize the number of pieces of fragments.

(iii) All removed tissue specimens be collected and reassembled as completely as possible for accurate pathohistological assessment.

(iv) A follow-up endoscopic evaluation be scheduled several months after the procedure.

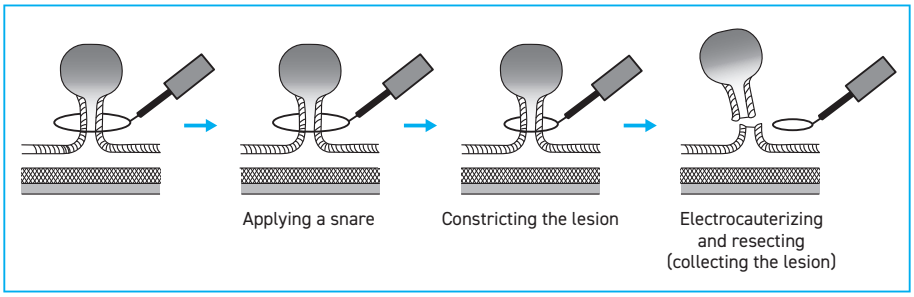


Figure 2 Schematic presentation of endoscopic resection: Polypectomy.

(Cited from Literature 11)

2. Practical Procedure

(1) Hot biopsy (Figure 1)[11)]

A lesion is grasped with the dedicated forceps and lifted from the mucosa. The lesion is lightly electrocauterized, and when the base of the lesion turns white, the forceps are pulled to dissect the lesion. The resected specimen remains in the forceps cup to be retrieved through the working channel of the scope.

(2) Polypectomy (Figure 2) [11)]

(i) In cases of pedunculated polyp, the snare is placed around the stalk. In cases of semipedunculated polyp, the snare is placed at the base.
(ii) The snare is closed around the polyp. The neck of polyp is strangulated until the polyp head becomes discolored due to ischemia.
(iii) The snare is further closed while electrocautery is applied to dissect the polyp.
(iv) The resected specimen is retrieved with tripod, pentapod or a snare. In the case of multiple small lesions, retrieval by aspiration is acceptable, but attention must be taken not to crush the specimen with the suction valve. When there are several resected specimens or when a piece is large, a net retriever is useful. When retrieving multiple lesions, care should be taken so that each lesion can be discriminated.

<Key points>

- In cases where the entire view of a polyp or a stalk is not clearly visible, the posture of the patient should be changed. Attention is required to avoid placing the snare in the middle of the polyp head. In addition, the snare might capture excessive amount of normal mucosa if the snare is pressed too much to the polyp base. Then, when the stalk is grasped, the snare and its sheath should be pulled slightly toward the scope before the snare is closed.
- In cases of a pedunculated polyp without malignancy, **the snare is placed closer to the head** to prevent perforation on electrocautery. Preserving part of the stalk during the resection also makes it easier to apply clips to the stump in order to prevent post-polypectomy bleeding.
- When the head invasion of carcinoma is suspected, the snare is placed slightly closer to the base for

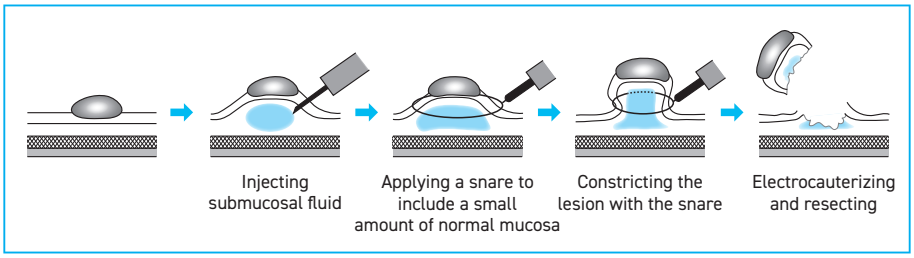


Figure 3 Schematic presentation of endoscopic resection: EMR.

(Cited from Literature 11)

the purpose of securing a negative margin. Some endoscopists inject small amount of saline to the stalk in advance for the purpose of preventing perforation and bleeding. **When the stalk invasion is suspected, surgery is basically the choice of treatment.**

- If the polyp head is in contact with the opposite wall, electrocautery may injure the relevant part. When the contact on the opposite side is unavoidable, paradoxically, making the contact area larger leads to less cautery of the wall as a result of reduced density of current.
- When the resection process is too quick, bleeding is likely to occur. Reversely, when electrocautery is applied too long a time, there is a risk of perforation or transmural burn. When the stalk is thick and hardly resected, the voltage should be raised or the current mode should be changed before the energizing time becomes too long. Primarily, when the patient complains of pain, the procedure should be discontinued and the underlying cause be immediately evaluated.
- When the stalk is thick, it is ligated with a detachable snare before resection for the purpose of preventing bleeding. In a polyp with a short stalk, however, the use of a detachable snare often hinders resection.

In a combined use of an electrocautery snare and a detachable snare, the cross-sectional area captured by the former should be smaller than that by the latter. Otherwise, the current density at the part strangulated by the detachable snare becomes higher, resulting in thermal injury to the tissue. During electrocautery, attention should be paid to changes in the color of the ligated site.

(3) Cold polypectomy

(i) A snare is applied around the target polyp.
(ii) The snare is tightened, strangulating the polyp.
(iii) The snare is further closed, and the polyp is dissected.
(iv) The resected specimen is retrieved.

<Key points>

- Since it is necessary **to include some of the normal mucosa surrounding the polyp**, the tip of snare is placed slightly away from the polyp.
- If the speed of closing the snare is too fast, it will slip off and the polyp will not be caught. Instead, it should be tightened slowly. Moreover, when a snare lifts a polyp inappropriately, the lesion will escape. In contrast, if the base of the snare is pressed too firmly against the polyp, the snare tends to

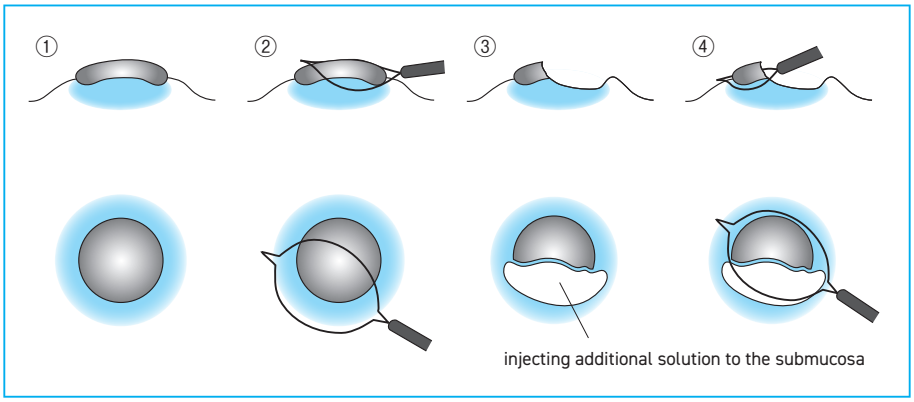


Figure 4 Schematic presentation of endoscopic resection: Piecemeal EMR.
(Cited from Literature 11)

slip toward the oral side. The operator should make appropriate adjustments to keep the lesion at the center of the snare throughout the process until the snare is fully closed.
- Once the lesion is caught, it is resected quickly. When it is hard and difficult to cut, the sheath is straightened or the sheath is pulled into the working channel of the scope, thereby cutting off the polyp.
- After resection, the oozing blood is washed away with water, and magnified endoscopy using IEE such as dye spraying should be employed to confirm that the margin is free from any residue.

(4) Conventional EMR and piecemeal EMR (Figures 3 & 4) [11)]

Treatment strategy should be determined in advance whether to employ en bloc EMR or piecemeal EMR. **When the lesion appears to have cancerous focus/foci on magnified endoscopy, the strategy is determined so that the relevant region be not cut into pieces.** The scope is so held that the lesion is kept in the 4 to 8 o'clock direction on the screen.

1) Injection

There are several types of injection solution, but saline is sufficient for relatively small lesions that are usually treated in a short time. For large lesions or cases where piecemeal EMR is employed and treatment is expected to take time, sodium hyaluronate (MucoUp®, KSmart®) or sodium alginate (Liftal® K) is suitable for maintaining the elevation and lifting of such lesions. The highly viscous solution is generally used undiluted for ESD, but for en bloc EMR and piecemeal EMR, the viscosity is too much, making the snare to slip or requiring more time for electrocautery. Thus, it is better to dilute the solution with saline. Concentrated glycerin-fructose (Glyceol®) is sometimes used, but it is not covered by insurance. The above-mentioned kinds of solution are commercially available in Japan but may not in other parts of the world.

The injection is the key factor for EMR, though the technique slightly varies depending on the tumor diameter and the location of lesion. The injection should be conducted so that the lesion is located in the center of the bulge created by injection and faces slightly anally toward the scope.

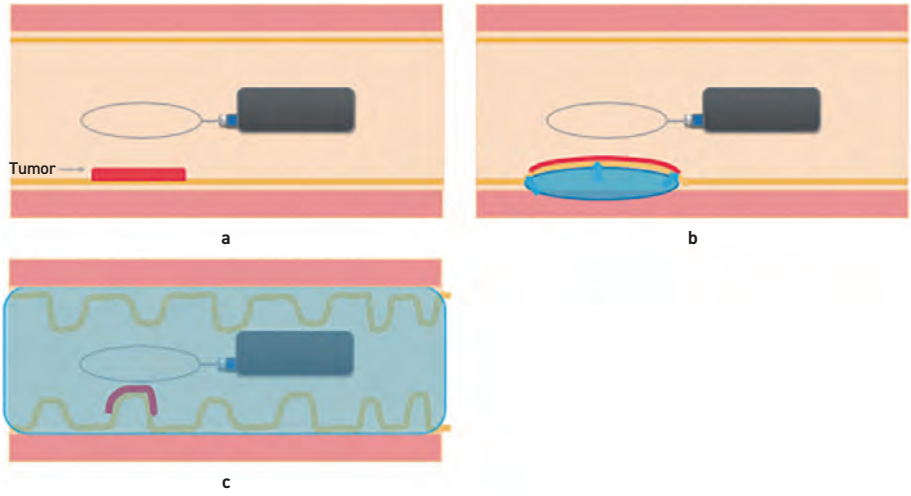


Figure 5 Schematic presentation of endoscopic resection: Underwater EMR (UEMR).

a: Prior to submucosal injection, the tumor is smaller than the diameter of the snare.
b: If submucosal injection is performed, the elevation reduces the height difference between the lesion and the surrounding mucosa, thereby making the snare to slip over the lesion. Also, the volume of the lesion gets increased due to the injected solution, thus the resection may result in piecemeal.
c: Under immersion without submucosal injection, the mucosal layer gets relaxed in tension, and the tumor floats upward in the lumen, thereby the lesion is captured more easily with the snare.
(Cited from Literature 9)

The needle length should be selected appropriately according to the conditions for injection. If the puncture is too shallow, it will cause leakage of the solution or intramucosal injection. Conversely, if the puncture is too deep, it will penetrate the muscularis propria or serosa, resulting in the failure of lesion lifting. Moreover, the patient may even complain of pain. After a slight elevation of the lesion is confirmed by injection of minimal amount of solution, injection is continued slowly. When the injected solution is too much in amount, or spreads too much to the surrounding tissue, capturing the lesion with a snare becomes more difficult.

2) Snaring

The snare is applied to include a small portion of the surrounding normal mucosal tissue, thereby reducing the risk of a positive lateral margin. Normally, the tip of snare is gently put in contact with the oral side of the lesion, and the snare wire is opened slowly. The snare is closed while its base is gently pushed against the anal side of the lesion. Just before starting resection, the snare wire is loosened slightly while air being insufflated and tightened again. **This process eliminates the involvement of the muscularis propria or excess amount of normal mucosa.**

In piecemeal EMR, it is advisable to use a large snare initially to resect much tissue at once. This approach aims to minimize the number of resected pieces. However, the snare becomes less effective for maintaining downward pressure on the lesion as its diameter increases. This possibly causes slippage and difficulty in grasping the targeted area. For early cancers, resection is conducted to ensure that the area suspected to be the deepest be resected in one piece.

3) Electrocautery resection

Electrocautery resection is executed without pushing the snare against the colonic wall, while the lesion being lifted slightly. When pain, prolonged electrocautery, or bouncy resistance are encountered during snaring with electrocautery, there is a high possibility that the muscularis propria is involved.

In large lesions, piecemeal EMR is safer than reckless en bloc EMR. Particularly, **en bloc resection of large LSTs such as one lying over folds face risk for perforation when the proximal side is poorly observed.** In general, resection should be started with a larger snare to remove as much of the area as possible, followed by the use of a smaller snare for eradication of remaining tissue.

Snaring should be repeated as necessary to prevent to leave any residue. At this point, the risk of perforation increases as the snare touches or involves the proper muscle layer. Thorough confirmation of the cut surface is necessary to identify any residue of the lesion, if ever. When a residual lesion is found, additional treatment using hot forceps polypectomy (HFP) and/or argon plasma coagulation (APC) may be required. Magnifying endoscopy is useful for assessing the lateral margin of the mucosal defect.

4) Specimen retrieval

The resected specimen is retrieved with tripod or pentapod. A net retriever is introduced when the resected specimen is either large or divided into fragments. After the retrieval, the collected specimen is unrolled and securely fixed onto a rubber or cork board with thin stainless-steel pins.

(5) So-called UEMR (Figure 5)[9]

To facilitate visualization and lesion removal during endoscopic procedures, injection solution can be delivered either through endoscope's water-jet channel or through an external water-jet device connected to the working channel of the scope, just like in ultrasound endoscopy. It's crucial to use physiological saline for injection but not distilled water. Injecting large amount of distilled water may cause water intoxication or hyponatremia. When the target area becomes submerged in the injected fluid the submucosal tissue tends to relax. This makes the lesion to bulge into the intestinal lumen as if floated, making it easier for a snare to grasp it. The setting of the electrosurgical unit can be the same as in conventional EMR. It should be noted however, that there's a risk of accidentally grasping the muscularis propria along with the lesion if the lesion is located on a fold or associated with significant fibrosis.

3. Adverse Events and Their Management

Adverse events consist of those generally encountered in colonoscopy and those specifically related to lesion resection. This section emphasizes the latter, as the former is addressed in other chapters of this book. Residue/recurrence of lesions is not mentioned in this chapter, either, though it is one of the concerns in endoscopic treatment.

(1) Hemorrhage

Bleeding related to endoscopic treatment includes intraprocedural bleeding and postprocedural bleeding. Measures against bleeding are broadly divided into prophylaxis and hemostasis. Intraprocedural bleeding in ESD literally means bleeding during mucosal incision or submucosal dissection, whereas in polypectomy and EMR, it refers to bleeding developed just after the resection. Although even a small amount of bleeding events in a short time is bleeding, it is difficult to determine the exact number of intraprocedural bleeding since it is usually controlled immediately on the spot. Postprocedural bleeding is often defined as obvious hematochezia, a decrease in hemoglobin of 2 g/dL or more, or hemorrage requiring transfusion or some hemostatic procedure.[12] The postprocedural bleeding rate has been reported to be 1.1 to 1.3% and 1.4% for polypectomy and EMR, respectively.[13-17] Cold polypectomy is less likely to cause postprocedural bleeding than endoscopic resection with electrocautery.[8]

1) Bleeding prevention

(I) Antithrombotics

For details on suspension of antithrombotic agents like antiplatelets and anticoagulants, *Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment*[2,18] are helpful and the readers are advised to refer to other sections of this book.

(II) Prevention of intraprocedural bleeding

With advances in hemostatic devices and modern electrosurgical generators where the current can be adjusted optimally, bleeding control is now easier and requires less concern. However, if the resection time is too short or too long, intraprocedural bleeding or postpolypectomy syndrome (described below) may occur, respectively.

In the case of pedunculated polyps with a thick stalk, there are techniques such as using an electrocautery snare together with a detachable snare or local injection. Some practitioners use clips as a substitute for a detachable snare before resection. It should be noted that when the stalk is thick, clipping sometimes fails to completely block blood flow. The electric current may easily flow through the clips, resulting in too much cautery through the stalk. Therefore, cautions are required.

(III) Prevention of postprocedural bleeding

i) Polypectomy

Immediately after the resection of a pedunculated polyp, a clip is, or clips are applied to prevent postprocedural bleeding. The clip(s) should be placed onto a site where the tissue is not thermally degenerated since the thermally affected area may fall off later. When the base of the polyp is thick, clip application from two or three directions is better in prevention of postprocedural bleeding than application from only one direction. Clipping is easier when the stalk is relatively long, and snaring is performed as close to the polyp head as possible. A detachable snare generally prevents not only intraprocedural bleeding but also postprocedural bleeding.

Cold snare polypectomy hardly causes postprocedural bleeding for small, non-pedunculated or flat polyps, compared with hot snare polypectomy, hot forceps polypectomy, or EMR. Since the incident of postprocedural bleeding is extremely low in cold polypectomy, clipping is hardly required for preventive purposes.

ii) Conventional EMR and piecemeal EMR

A randomized controlled trial for prophylactic clip placement immediately after EMR was reported. It

suggests the preventive measure does not contribute to reducing the postprocedural bleeding rate. The trial involved lesions with a relatively small median tumor diameter of 7.8 mm.[19] On the other hand, some studies have reported that the prophylactic clipping of resection sites is effective for lesions exceeding 2 cm,[20,21] and a retrospective study suggests the feasibility of outpatient treatment with clipping.[22] Thus, postprocedural clipping is considered somewhat effective in EMR for large lesions or in patients with a high risk of postprocedural bleeding due to antithrombotic treatment. If a residual lesion could not be ruled out in piecemeal EMR, the resection site should not be closed as there is a possibility that residual/recurrent lesion might get sealed and hidden by the closure.

2) Management of bleeding

(I) Intraprocedural bleeding

Hemostasis should be performed with a hemostatic device or hemoclip after identification of the bleeding point. In recent years, there are also methods such as using gel immersion for securing good endoscopic view[23] and absorbable topical hemostatic material (self-assembling peptide) for stopping non-spouting bleeding.[24] Even if intraprocedural bleeding is encountered in cold polypectomy, clipping closure is not required. It will stop spontaneously, unless it is pulsating bleeding.

(II) Postprocedural bleeding

Postprocedural bleeding is typically defined as overt bleeding/overt bloody stool which requires electrocautery hemostasis or which is accompanied with a hemoglobin drop of at least 2 g/dL.[12] Minor hemorrhage, such as occasional traces of blood in stool, does not fall under this definition. Generally, postprocedural bleeding usually occurs within two or three days to one week after the procedure. There is even a possibility of bleeding until around ten days after the procedure. Severe postprocedural bleeding requiring transfusion is uncommon in colorectal procedures. However, in cases where persistent obvious hematochezia is observed, an urgent endoscopic examination is warranted to locate the exposed blood vessels and stop bleeding. Identification of the bleeding point is critical. When the lesion was proximal to the rectum and the bleeding event occurred after the resumption of oral intake, bowel preparation should be conducted before endoscopy to improve the view of the colon lumen, if the patient's condition permits. When a blood clot is adhering to the mucosal defect, thorough irrigation using the endoscope's water jet function is necessary to remove it. Once the bleeding point is confirmed, hemostasis is generally achieved with hemoclips or other hemostatic devices, or by closing the entire mucosal defect with clips.

(2) Perforation

Perforation is defined as a full-thickness tissue defect in the intestinal wall that creates an open communication with the body cavity, regardless of whether free air is detected on radiographic imaging.[1] When the full-thickness tissue defect is sealed with another organ and there is no free communication with the body cavity, it is defined as penetration. In the case of the lower rectum, perforation into the abdominal cavity does not occur due to anatomical characteristics, but perforation into the pelvic cavity does occur. This may lead to retroperitoneal/mediastinal or subcutaneous emphysema.[25] In areas without serosa, such as the lower rectum and the posterior side of the ascending and descending colons, perforation occurs immediately when the muscularis propria is penetrated. Intraprocedural perforation occurs due to the direct damage to the muscularis propria during resection, while delayed perforation occurs as a result of over-electrocautery to it. The intraprocedural perforation

rate has been reported to be 0.05% and 0.58-0.8% for polypectomy and EMR, respectively,[13-17] whereas delayed perforation is extremely rare. In cold polypectomy, perforation almost never occurs.

1) Prevention of Perforation

(I) Intraprocedural perforation

The large intestine has a thinner wall than the stomach. Therefore the risk of perforation during treatment is high. Before the endoscopic procedure, it is necessary to perform adequate bowel preparation to make a possible damage by perforation to the minimum. During the procedure, it is essential to ensure good scope maneuverability. Scopes should be selected according to the location of the lesion, its shape, and the presence of fibrosisand selection of appropriate devices, injection fluid and CO2 insufflators are very important.[1]

In hot snare polypectomy for pedunculated lesions, intraprocedural perforation rarely occurs. However, in non-pedunculated or flat lesions, the risk of perforation is lower in EMR or cold polypectomy than in HSP. Even in EMR, though, intraprocedural perforation may occur if the muscularis propria is involved. For the prevention of the incident, it is important to adequately lift the lesion by injection, not to push the snare excessively against the colorectal wall, and not to apply excessive aspiration during snaring. When the assistant feels much resistance and difficulty in cutting during electrocautery, or when the patient complains of pain, there is a high possibility that the muscularis propria is involved. In such a situation, the procedure should be stopped immediately, and additional injection or repositioning of the snare should be considered. When the en bloc resection of a large lesion with a large snare is performed forcibly, the muscularis propria may become involved and grasped, thereby increasing the risk of perforation. In such cases, piecemeal EMR is less likely to cause perforation, or even ESD could be safer. In lesions associated with fibrosis, it is difficult to obtain elevation by injection, hence ESD or hybrid ESD is employed in order to dissect the submucosa under direct vision. For small lesions, cold polypectomy without electrocautery carries a lower risk for intraprocedural perforation.[8]

(II) Delayed perforation

In polypectomy of pedunculated lesions, a snare should be placed closer to the head of the polyp. In non-pedunculated or flat lesions, EMR is less likely to affect the muscularis propria by electrocautery nor does it cause delayed perforation compared with hot snare polypectomy. In EMR, it is important to sufficiently lift up the lesion by injection while the snare is placed without excessive pressure to the colonic wall. Bipolar snare does not allow coagulation current to flow deeply and therefore it is less likely to cause delayed perforation. On the other hand, if the resection is too quick, a bleeding event is more likely to occur. In small lesions, cold polypectomy without electrocautery has a lower risk of delayed perforation.

Wound closure using clips immediately after resection is effective in preventing delayed perforation. However, wound closure should not be performed when possibility of residue/recurrence of lesion cannot be ruled out, especially in piecemeal EMR, because it may cover up the residue/recurrence.

2) Management of perforation

(I) Intraprocedural perforation

Endoscopic mucosal resection carries a risk for involving the muscularis propria together with the serosa, resulting in a large perforation. In such cases, the muscularis propria and serosa are often attached onto the underside of the resected specimen, which makes an appearance like a pillar of scallop which is sometimes called “target sign.” If intraprocedural perforation occurs, the perforated area or the entire wound should be immediately closed with clipping. When its closure is difficult to achieve, the

emergency surgery is required.

If complete suturing is possible, surgery would be probably avoided by administration of antibiotics and fasting.[1,15,26,27] After the successful wound closure, the scope is withdrawn while stool juice and excessive air being aspirated. After the procedure, the patient is closely observed under rest, fasting, administration of drip infusion and antibiotics. The presence of free air in the abdominal cavity on CT is not an absolute indicator for deciding whether or not to proceed to surgery.[27] Inflammatory reaction should be monitored with blood tests. If a fever, abdominal pain or peritoneal irritation sign appear, consultation with surgeon is needed in order not to miss the golden time for an urgent surgery.

(II) Delayed perforation

Delayed perforation is defined as a complication that becomes apparent only after the endoscopic procedure is finished and the scope is withdrawn. It is diagnosed based on symptoms such as fever, abdominal pain, physical abdominal findings, and inflammatory reaction. While the majority of cases occur within 24 hours after the procedure, approximately one-third are confirmed after a longer postprocedure interval. Since free air is not always visible on plain X-ray but usually detected on abdominal CT, CT examinations should be actively performed when delayed perforation is suspected. Although no reports provide the precise incidences, delayed perforation is considered extremely rare.

In cases where delayed perforation is confirmed, reinsertion of the endoscope is basically contraindicated, regardless of the underlying cause. An emergency surgery will be usually required. A surgeon should be consulted immediately, and the decision of whether to proceed to surgery or not should be made without delay, based on clinical indicators such as fever, abdominal pain, signs of peritoneal irritation, elevated inflammatory markers in blood tests, and results of imaging modalities.

(3) Postpolypectomy electrocoagulation syndrome

When electrocautery reaches the deeper layers, it may cause tissue degeneration in the proper muscle layer and even the serosa in the absence of perforation. This leads to localized peritonitis with symptoms such as fever and abdominal pain.[28] In general, conservative treatment is possible in the majority of cases, but considering the possibility of progression to delayed perforation, it may be necessary to take careful measures such as extending the fasting period.

(4) Posttreatment surveillance and its schedule

Differences between Western countries and Japan in the management of diminutive lesions, together with variations in diagnostic accuracy among endoscopists, have resulted in the absence of a standardized consensus on surveillance intervals in Japan. According to the *Colonoscopy Screening and Surveillance Guidelines*, the suggested intervals for total colonoscopy surveillance (TCS) are as follows: 3 to 5 years after resection of two or less adenomas that do not meet the criteria for advanced adenoma*; 3 years after removal of three to nine adenomas that do not meet the criteria for advanced adenoma; and 1 to 3 years following the resection of advanced neoplasia including cases with ten or more non-advanced adenomas. The strength of this recommendation is considered weak while the evidence level is classified as B. [6]

*: Adenoma with a diameter of 10 mm or more, those associated with histopathologically villous or tubulovillous components, or high-grade dysplasia (almost equivalent to mucosal cancer (Tis) in Japan).

Conclusion

This section explained the various endoscopic treatments for large intestine, aside from endoscopic submucosal dissection (ESD). It covers when to use each technique, how to perform the procedures, and what actions help manage any adverse events. It is important for not only beginners but also practitioners involved in endoscopic treatment to reconfirm the basics to prevent adverse events. We hope this section would be of help to the readers

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7 Endoscopic Submucosal Dissection

1. Indications and Contraindications

Endoscopic submucosal dissection (ESD)[1-4] of the large intestine was only available as advanced medical care since 2009, unlike esophageal and gastric ESDs. Following the release of the *Statement on colorectal endoscopic submucosal dissection conducted as an advanced medical treatment*, the Japan Gastroenterological Endoscopy Society (JGES) initiated a prospective evaluation since June 2010. This multi-center prospective cohort study assessed the efficacy and safety of colorectal ESD performed as an advanced medical procedure. With approximately 1,600 cases registered, advancements in related devices and improvements in technical proficiency demonstrated favorable treatment outcomes in terms of both safety and efficacy. Based on the research results in 2012, JGES Pharmaceutical Affairs and Social Insurance Committee submitted a pharmaceutical application for this procedure, and it has been covered by insurance since April 2012. Colorectal ESD is the first procedure approved as advanced medical care in the field of gastrointestinal endoscopy and has become a model case for system building for future insurance integration via the advanced medical care framework.

(1) Expansion of indications for colorectal ESD

- The indications for advanced medical treatment before insurance coverage were summarized as follows:

(i) Indicated for cases in which en bloc resection with endoscopic mucosal resection (EMR) is considered challenging, specifically for early colorectal cancerous lesions exceeding 2 cm in size that have been thoroughly evaluated preoperatively with magnifying or ultrasonic endoscopy, and for which curative resection is generally expected.

(ii) Indicated for adenomas that exhibit poor lesion lifting upon EMR or for those with residual or recurrent lesions after EMR, where the lesion is at least 1 cm in size and resection via EMR is infeasible.

- Indications for colorectal ESD after insurance coverage (April 2012)

Early malignant tumors of colorectum with a maximum diameter of 2 cm to 5 cm

Even if the preoperative diagnosis suggested carcinoma but the final pathological diagnosis confirmed adenoma, reimbursement remained applicable.

- Revision in April 2018

The upper limit of tumor size has been removed, and the indications have been expanded to include

early colorectal carcinomas with a minimum diameter of 2 cm, as well as neuroendocrine tumors ranging from 5 mm to 1 cm in diameter. Furthermore, early colorectal cancerous lesions smaller than 2 cm that exhibit fibrosis have become also suitable for ESD. Although the revised criteria limits ESD to cases of carcinoma, the initial diagnosis as carcinoma should influence the ESD reimbursement. Some lesions are initially assessed as early colorectal carcinomas based on endoscopic or histopathological findings but even if the final pathological diagnosis identifies these lesions as adenomas, they could still remain eligible for ESD reimbursement.

Regarding the indications of neuroendocrine tumors with a maximum diameter of 5 mm to 1 cm, endoscopic submucosal resection using a ligation device (ESMR-L) or endoscopic mucosal resection using a cap (EMR-C) enables easy and R0 resection with outpatient treatment. It is necessary to discuss whether to make it an indication for ESD. Even in the results of a recent multicenter prospective study,[5] the time required for ESMR-L or EMR-C is significantly shorter than ESD, whereas the resection outcomes are comparable to those of ESD.

- Institutional criteria for colorectal ESD

Facilities that perform colorectal ESD are obliged to meet the following criteria: (i) conducting at least 20 ESD operations annually, (ii) having a designated department specializing in gastroenterology, gastrointestinal surgery, endoscopic medicine, or endoscopic surgery, (iii) employing full-time medical practitioners with over five years of experience in gastrointestinal endoscopic surgery, and (iv) maintaining a system capable of performing emergent operation.

It is essential that medical specialists performing colorectal ESD hold board certification from the Japan Gastroenterological Endoscopy Society. In addition, the procedure should be conducted at facilities equipped with a surgical department and available beds, as emergency surgery could become necessary in cases of adverse events such as perforation. Therefore, this procedure is not regarded as suitable for clinics that do not have inpatient capacity.

(2) Contraindications for colorectal ESD

Colorectal ESD is contraindicated for lesions diagnosed endoscopically as deeply invasive submucosal carcinoma or massive submucosal invasion. Endoscopic diagnosis typically includes assessments by conventional endoscopy, magnifying colonoscopy,[6,7] and endoscopic ultrasonography (EUS). In magnifying colonoscopy, lesions classified as type V_N pit in the Kudo-Tsuruta classification or type V_I (invasive pattern)/V_N in the Fujii and colleagues clinical classification[6,7] are diagnosed as highly advanced submucosal invasive carcinoma. However, diagnostic ESD is considered a relative indication, even when deep submucosal invasion could not be entirely excluded. This is particularly relevant in cases involving high-risk surgical patients or lesions located in the lower rectum where preservation of the anus is desired. Decisions on diagnostic ESD should be made through discussion in a multidisciplinary team (MDT) conference and only after obtaining sufficient informed consent.

Other absolute contraindications for ESD include patients with bleeding tendencies where hemostasis is expected to be difficult, those in poor general condition, and those who do not have ability to cooperate with or consent to the procedure. Patients on antithrombotic therapy should be managed according to the *Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment and the 2017 Appendix on Anticoagulants Including Direct Oral Anticoagulants (DOACs)*. Additionally, ESD is relatively contraindicated in anatomically challenging locations where endoscopic maneuverability is complicated since it is commonly difficult to manage adverse events such as

perforation with endoscopic ligation techniques like clipping.

(3) Lesions indicated for ESD

According to the second edition of the *JGES Guidelines for Colorectal Endoscopic Submucosal Dissection/Endoscopic Mucosal Resection*, indications for colorectal ESD include: early colorectal carcinoma in an extremely low risk of lymph node metastasis for which en bloc resection with snare EMR is difficult to apply; mucosal tumors with submucosal fibrosis; sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis; and local residual or recurrent early carcinomas after endoscopic resection. The primary advantage of ESD is its high en bloc resection rate. EMR technique is simpler with a lower risk of adverse events than ESD, but its en bloc resection is often difficult for lesions larger than 2 cm or those with submucosal fibrosis presenting with a non-lifting sign. Piecemeal EMR poses challenges in pathological assessment of resection margins and invasion depth, and reveals a high local recurrence rate of 20% for lesions larger than 2 cm.[8] However, results from the multicenter cohort study CREATE-J demonstrated an extremely low local recurrence rate of 0.5% after colorectal ESD for early colorectal carcinomas larger than 2 cm, with favorable long-term outcomes and a high rate of intestinal preservation.[9] Therefore, ESD is indicated for lesions that contain carcinoma and are expected to be difficult to resect en bloc with EMR.

1) Treatment guidelines for LST

Laterally spreading tumors (LSTs) account for the majority of lesions classified as lesions larger than 2 cm that are hardly resected en bloc with EMR. LSTs are categorized into granular type (LST-G) and non-granular type (LST-NG), with differences in biological behavior on macroscopic observation. Subclassification of LSTs is also useful in determining the treatment strategy.

(i) Homogeneous granular-type LSTs are predominantly adenomas or intramucosal adenocarcinomas, even when large in size. Lesions measuring 3 cm or less are primarily adenomas and generally managed with scheduled piecemeal EMR (p-EMR).[10] However, as ESD techniques have become quite standardized, p-EMR is now rarely performed at institutions with established ESD expertise.

(ii) Nodular mixed-type LST-G lesions have a higher risk of SM invasion, and the invasion site proves to be under a large nodule or depressed area. Approximately 16% of this type also exhibit SM invasion outside these regions. Thus, en bloc resection with ESD is beneficial for these lesions.[11]

(iii) Pseudodepressed-type LST-NG lesions show a high rate of SM invasion,[11,12] often with fibrosis and multifocal SM invasion. Thus, en bloc ESD is suitable for these lesions.[13,14]

(iv) For flat elevated-type LST-NG lesions, treatment strategy is determined based on preoperative diagnosis but facilities proficient in endoscopic submucosal dissection (ESD) generally avoid piecemeal endoscopic mucosal resection (EMR), same as homogeneous granular-type laterally spreading tumors (LSTs).

2) ESD for non-LST

As ESD indications for lesions other than LST, large villous-type (Is) lesions of 20 mm or more and 0-IIc lesions that are difficult to remove en bloc by EMR are also applicable. However, it is necessary to be careful because even in the short-term results of the CREATE-J multicenter study, these lesions have been reported with a high rate of submucosal invasion (26.3%) or massive submucosal invasion (19.4%) compared with LST.[15] Additionally, large villous-type lesions often exhibit complex

interwoven arrangements of the muscularis mucosae, making ESD technically challenging.

For neuroendocrine tumors (NETs) measuring 5–10 mm, endoscopic submucosal resection using a ligation device (ESMR-L) and endoscopic mucosal resection using a cap (EMR-C) are adequate options. However, for NETs measuring 10–15 mm, ESD is feasible when diagnostic endoscopic treatment is considered, as this method allows secure submucosal margins. Nevertheless, colorectal ESD has not yet been formally established as an indication for these lesions, which remains a challenge to overcome.

Lesions with submucosal fibrosis presenting with a non-lifting sign are unsuitable for en bloc EMR and therefore good candidates for ESD. The causes of submucosal fibrosis include tumor invasion into the submucosa, prior biopsy, chronic inflammation from conditions such as ulcerative colitis, proximity to an anastomotic site, and residual or recurrent malignancy after previous endoscopic treatment.

ESD is also applicable for lesions extending over diverticula or the appendiceal orifice, as careful incision and dissection allow operators to minimize the risks through direct visualization of these structures. Similarly, in en bloc EMR for lesions extending across colonic folds, the snare placement often grips the lesion only superficially, which leads to piecemeal resection. Positioning the snare too much onto a fold increases the risk of muscularis injury or perforation. In such cases, meticulous dissection with ESD is a more appropriate approach.

- When a patient has a lesion requiring endoscopic submucosal dissection (ESD), and the procedure is infeasible for the current facility, a referral to another hospital equipped for ESD should be arranged. The arrangement ensures the patient receives the necessary specialized care. If such a referral is impossible, laparoscopic assisted colectomy (LAC) serves as an alternative.
- The decision to perform ESD depends on the absence of deep submucosal invasion as observed during conventional endoscopy, along with no presence of VI (invasive pattern) or VN features on magnifying colonoscopy. According to these findings, the choice of ESD should be made considering macroscopic classification, tumor size, and technical proficiency of endoscopists.

2. Practical Procedure

Colorectal endoscopic submucosal dissection (ESD) involves a circumferential incision of the mucosa around the target lesion, followed by direct visualization and dissection of the submucosa. This approach enables en bloc resection regardless of the tumor size, location, or macroscopic type.[16] However, the complexity of the procedure is heightened due to the natural curvature of the intestine and the presence of folds. This increases the risk of bleeding and perforation. To ensure safe and effective colorectal ESD, selection of proper techniques and strategic planning are essential.

(1) Selection and preparation of scope

Preoperative evaluation includes assessing lesion location, tumor size, scope maneuverability, and the need for colonoscopic retroflexion. In certain locations, such as behind the folds or in the rectum, a retroflexed approach not only provides a better field of view but improves scope stability. Thin-caliber endoscopes equipped with water-jet function are commonly used in these cases. However, some operators prefer conventional endoscopes due to better axial stability. Esophagogastroduodenoscopes are an option for rectal lesions, but their limited downward angulation possibly makes procedures more difficult.

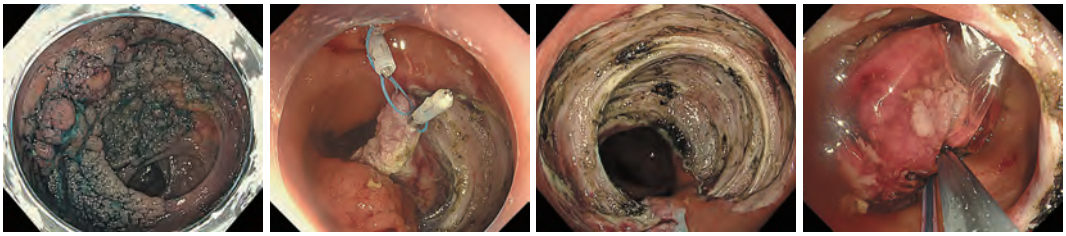
It is critical to maintain a clear field of view during the procedure, and this requires the use of a transparent distal attachment. Given the high risk of perforation and the extended procedure time, continuous CO_2 insufflation is essential.[17] A preoperative check should be conducted with the chosen endoscopes. When its stable maneuverability is inadequate, additional devices should be introduced, such as a single-balloon overtube[18] or a double-balloon endoscope.[19] If these options are not viable, colorectal ESD should be avoided.

(2) Selection and usage of injectate

Since the large intestine wall is thin, a submucosal injection solution with appropriate lesion-lifting ability is desirable. Physiological saline is not beneficial for colorectal ESD because it diffuses quickly and the lifted lesion becomes flat. Glycerol is recommended as a standard submucosal injection solution because it is inexpensive, has a good lesion-lifting ability, and shows no tissue damage.[20] For more challenging cases, sodium hyaluronate (MucoUp®) is useful to enhance safety.[21] Other options include hyaluronic acid-based preparations such as Ksmart® and sodium alginate-based Liftal® K, which became available in 2018. If the injection accidentally reaches beyond the muscularis propria, this makes the subsequent procedure difficult. Therefore, the solution should be injected precisely into the submucosa. If injecting from the mucosal surface, physiological saline or glycerol should first be used to confirm that the solution has entered the submucosa. Only after this confirmation, an agent such as a hyaluronic acid preparation should be injected. A small amount of indigocarmine is helpful to visualize the submucosa, but the concentration should be kept low to maintain the visibility of vascular pattern and muscularis propria.

(3) Selection and usage of knife

Each ESD knife has its own characteristics, and it is necessary to select an appropriate device depending on the conditions and situations. It is important to select a knife that is familiar to the facility as each type of the device offers unique advantages. Common monopolar tip knives include DualKnife/DualKnife J, FlushKnife, ProKnife, and HookKnife/HookKnife J. Currently these knives incorporate a jet injection function, and there are few differences between devices. The HookKnife differs from other tip knives in that it hooks onto the submucosa before making an incision. This provides stable traction for the submucosal dissection, which proves especially helpful in cases involving fibrotic lesions or limited endoscopic maneuverability. Among bipolar tip knives, the Jet B Knife is widely used. It features a positive electrode at the tip and a negative electrode at the sheath's distal end, thereby allowing current to flow between them for safer dissection. Blade-type monopolar knives such as ITknife nano and Mucosectom 2 are available. The former has an insulating tip and ablates with the blade part. For the situations where the muscularis propria being pulled upward is anticipated or where greater efficiency in dissection is desired, this device is regarded as a suitable option. Scissor-type knives like the SB Knife and ClutchCutter offer a biopsy-like grasping action before they start to cut. This design allows for precise and safe dissection.



a | b | c | d

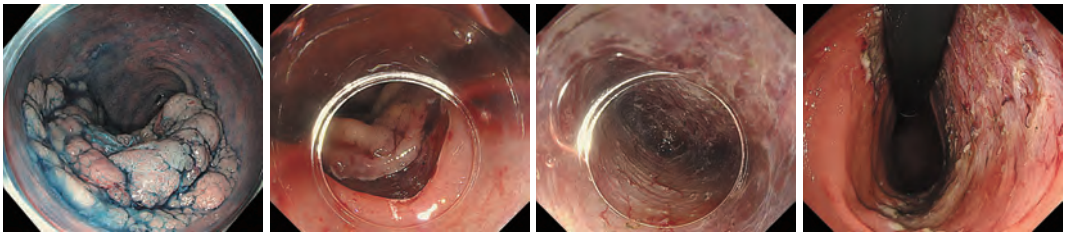
Figure 1 **Colorectal ESD using Multi-loop traction device and Endo Carry Large Type.**

a: A laterally spreading tumor of granular mixed type (LST-G-M) involving approximately four-fifths of the rectum from Ra to Rb.
b: Following full circumferential incision and submucosal dissection on the distal side, a multi-loop traction device was attached to achieve adequate submucosal exposure.
c: Dissection was completed in a short time.
d: Although the lesion exceeded 80 mm in diameter, it was retrieved from distal side with the Endo Carry Large Type.

(4) Treatment strategy based on anatomy of large intestine

Colorectum has a thin mucosa and the boundary of the lesion is clear. Thus electrocautery marking is basically unnecessary. When lesions have unclear borders, like in the case of sessile serrated lesions, it becomes necessary to mark them. A full circumferential incision at the outset frequently complicates additional submucosal injection, so a stepwise approach combining partial incision and dissection is suggested for better procedural control. Once the dissection process is somewhat advanced under the target lesion, the insertion of the colonoscope with the transparent hood into the submucosal layer greatly improves visibility. Not only does this provide a clear view, but it also applies appropriate traction to the fibers. This advantage makes the dissection much easier. The direction of gravity should always be taken into consideration during the dissection process. When the lesion is positioned against gravity, the incised tissue tends to open more easily, which makes dissection smoother. Combined with the cut tissue flipping over, a clear field of view is secured to make treatment easier. Conversely, if the lesion lies on the gravity-dependent side, the incision site won't open easily. Additionally, fluid and blood accumulate easily, where it is difficult to maintain a good field of view. This situation requires repositioning the patient.

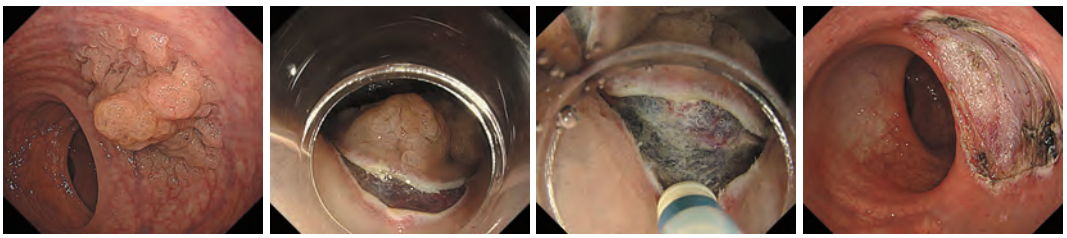
The complexity of ESD is primarily determined by the difficulty of submucosal dissection. Traction techniques provides a clear submucosal view and facilitates safer and more efficient dissection. Various traction methods are employed in colorectal ESD, including clip with line method, spring S-O clip traction device, and multi-loop traction device (**Figure 1**).[22-25] Furthermore, innovative techniques such as tunneling method, bridge formation method (BFM), water pressure method, and pocket creation method utilizing natural traction have been reported.[26,27] The pocket creation method employs a transparent, long, thin hood attached to the endoscopic tip, minimizes the first mucosal incision, allows all submucosal dissection directly below the lesion, and finally completes the remaining mucosal incision. This technique minimizes the effects of respiratory fluctuations and cardiac movement artifacts in the pocket, prevents unnecessary loss of submucosal injection solutions, provides effective traction via the distal hood, and ensures a controlled submucosal dissection parallel to the muscularis propria (**Figure 2**). The tunneling method is a technique where submucosal dissection progresses linearly, creating a tunnel-like space through the submucosal layer. By linearly dissecting, the colonoscope is stable and a clear field of vision is created. The technique becomes easy because the



a | b | c | d

Figure 2 **Colorectal ESD using pocket creation method.**

a: A laterally spreading tumor of granular mixed type (LST-G-M) involving approximately half of the circumference of the sigmoid colon.
b: A short ST hood was employed, and approximately 2 cm of mucosal incision was made on the distal side of the lesion.
c: Submucosal dissection was performed under a stable field of view within the pocket.
d: En bloc resection was completed in a short time.



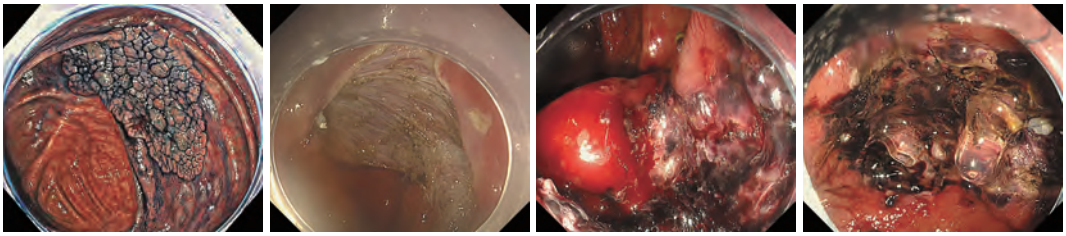
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Figure 3 **Colorectal ESD using water pressure method.**

a: A laterally spreading tumor of granular mixed type (LST-G-M) measuring approximately 30 mm in diameter, located in the rectum (Rb).
b: Visibility of the submucosal layer was poor under air insufflation.
c: Upon immersion, buoyancy was generated, and water pressure created by flow facilitated submucosal expansion.
d: En bloc resection was achieved in a short time.

submucosa at the deepest part of dissection is simply pulled up with the tip hood. Unlike the pocket creation method, the tunneling method requires a larger initial mucosal incision to allow direct observation of the entire submucosa beneath the lesion. An appropriate submucosal depth could be reached with maintaining a good field of view. However, given the extensive luminal space of the colorectum compared to the esophagus, the pocket creation method is more commonly employed. The water pressure method involves filling the lumen with saline while utilizing a water-jet system to expand the submucosal space. This approach eliminates the effects of gravity, reduces the need for positional changes, and provides buoyancy for traction. In addition, as an advantage of water pressure, it is possible to create a water flow and improve the visibility of the submucosa to be dissected (**Figure 3**).

Advancements in colorectal ESD techniques have made en bloc resection of large tumors feasible. As a result, conventional net retrievers have become inadequate for handling large specimens.[28,29] In response, the Endo Carry Large Type retrieval bag has been developed. This device features a transparent film net with a 60 mm diameter and 40 mm depth, allowing for larger retrieval. The retrieval device is inserted into the rectum alongside the endoscope. Once the retrieval net is deployed, a clear view of inside the net is maintained. By inserting a grasper from the instrument port to control bagging, it has become possible to retrieve large colorectal lesions (**Figure 1**).



a | b | c | d

Figure 4 Delayed bleeding on the day after colorectal ESD.

a: A laterally spreading tumor of granular homogeneous type (LST-G-H) measuring approximately 40 mm in size, located in the cecum.
b: Ulcer base after en bloc resection.
c: Arterial bleeding from the ulcer base was observed on the day after ESD.
d: Hemostasis was achieved by coagulation with hemostatic forceps on the exposed blood vessel, followed by application of the absorbable topical hemostatic agent PuraStat.

3. Adverse Events and Their Management

(1) Hemorrhage

1) Intraoperative bleeding

Even in colorectal ESD, lower rectum lesions, large protruding lesions, and high-grade dysplasia cancerous lesions have abundant nutrient vessels, and the frequency of bleeding is by no means low. During submucosal dissection, it is important to visually identify vessels under direct observation and perform accurate vascular hemostasis. When it is arterial and the bleeding source is clear, coagulation with hemostatic forceps is very reliable. Applying electrocautery in the same way as in the stomach carries a high risk of delayed perforation because the large intestinal wall is thin. Therefore, specialized hemostatic forceps with a small cup designed for colorectum are introduced. Electricity is then applied only after the vessel is sufficiently lifted. In cases where a thick penetrating vessel is difficult to grasp with small-cup forceps, gastric-type hemostatic forceps should be used. However, since these forceps have larger cups, it is recommended to grasp only the minimum necessary tissue with the tip to reduce the risk of delayed perforation.

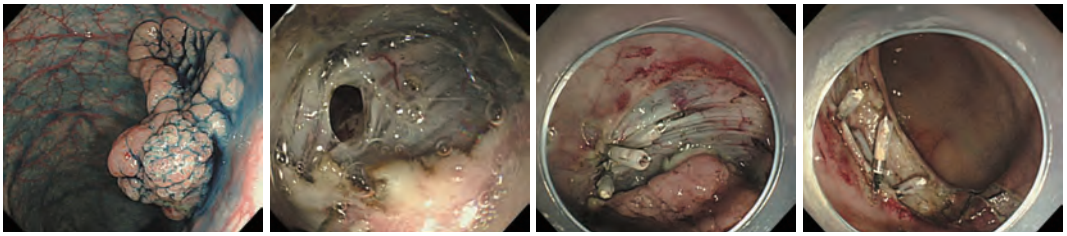
2) Postoperative bleeding

Post-procedural bleeding is defined as a hemoglobin drop of over 2 g/dL or the occurrence of hematemesis or melena following endoscopic treatment.[30] It has been reported in 0.7% to 3.1% of cases. To prevent delayed bleeding, hemostatic forceps are employed to manage exposed blood vessels at the ulcer base immediately after ESD.[31] Although the risk of postoperative bleeding with ESD is relatively low due to meticulous intraoperative hemostasis, excessive coagulation causes tissue necrosis, resulting in exposure of deeper vessels and subsequent delayed bleeding (**Figure 4**).

(2) Perforation

1) Intraoperative perforation

In ESD, since the large intestinal wall is thin and the muscularis propria is sparse, a perforation event easily occurs if the tip knife comes into contact with the ulcer base even slightly while electrifying. The



a | b | c | d

Figure 5 **Clip closure for intraoperative perforation during colorectal ESD.**

a: A laterally spreading tumor of granular mixed type (LST-G-M) involving approximately one-third of the circumference of the sigmoid colon.
b: Muscularis propria injury occurred during circumferential mucosal incision.
c: Dissection was continued to secure the operative field, and then clipping was performed.
d: Perforation was closed with clips while en bloc resection is completed.

incident rate is reported to be 2 to 14%. Therefore, extreme care must be taken to prevent the knife from coming into contact with the ulcer base. If a perforation site is observed, the perforated area should be closed with clips as soon as possible. In ESD, perforation often occurs during treatment, and the perforation site looks like a small pinhole. The site is endoscopically ligated after the dissection has been partially completed and the hemoclips used to hold tissue do not obstruct the view or instruments during the remaining dissection process (**Figure 5**). At the time of perforation, air and intestinal fluid in the intestinal tract are aspirated as much as possible for the purpose of decompression and preventing leakage of intestinal fluid outside the intestinal tract. The patient's position is adjusted so that gravity pulls the intestinal fluids away from the operative field. If perforation is suspected, an upright chest and abdominal X-ray or CT scan is performed to check for the presence of free air since symptoms are difficult to appear in the case of microperforation. For microperforation, conservative healing is often achieved by fasting and administration of antibiotics. It is important not to forget to adequately cooperate with the surgeon. If the closure of the perforated area is incomplete, surgical operation should be considered. The use of a CO2 insufflation device is essential for colorectal ESD to control the increase in intra-intestinal pressure during and after the treatment. The devise is also useful for preventing leakage of intestinal contents into the abdominal cavity during perforation. It is also important to perform good bowel preparation so that stool juice does not leak out of the intestinal tract when perforation occurs.

2) Delayed perforation

Delayed perforation is a rare but serious adverse event. Usually, the perforated area is large, and intestinal contents leak into the abdominal cavity, often accompanied by generalized peritonitis. If delayed perforation is diagnosed, surgical treatment is indicated in principle. The causes of delayed perforation are excessive current delivery and damage to the muscularis propria. After removal of the submucosa, specific features of the ulcer base indicate an increased risk of delayed perforation. These changes include damage or fissures within the muscularis propria, along with hyperemia of that muscle layer. If these findings are observed, strict follow-up is necessary with preventive clipping, prolongation of the fasting period after treatment, and administration of antibiotics.

Symptoms of delayed perforation are indistinct immediately after its onset, but become severe over time and exhibit signs of generalized peritoneal irritation. It should be noted that when inflammation reaches

the muscularis propria, localized peritoneal irritation symptoms could be present, but precise differentiation from delayed perforation is difficult. If delayed perforation is suspected, blood tests including a complete blood count and CRP are carried out, and an IV line is started. Imaging modalities including X-rays of the chest and abdomen and potentially a CT scan of the abdomen are then introduced to look for free air, signs of inflammation near the suspected perforation site, and any abscesses. Additionally, patients should be informed beforehand that straining during defecation, drinking, and exercising after surgery could act as triggers for delayed perforation.

3) Necrotizing fasciitis

If a bacterial infection spreads during delayed perforation of the rectum, pus usually accumulates in the fascia and muscles of the perineum, around the anus, and in the thigh. This possibly leads to necrotizing fasciitis, a rapidly worsening condition caused by a mixed infection of anaerobic and aerobic bacteria. It's important to remember that a perforation site could associate with areas other than the abdominal cavity. A bacterial infection affecting the perineum and scrotum is known as Fournier's gangrene. Diagnosis is evident if subcutaneous pneumatosis is observed in the perineum, thigh, and inguinal region on simple abdominal X-ray or CT examination. Subsequently, it is necessary to immediately perform surgical operation, endotoxin adsorption therapy, γ-globulin preparation administration, and hyperbaric oxygen therapy, after diagnosis. In particular, the invasive type extends to the retroperitoneum through the connective tissue in the pelvis and is often difficult to diagnose. This infection finds a poor prognosis. Thus early diagnosis is extremely important.

(3) Abdominal compartment syndrome

When pneumoperitoneum occurs due to perforation, abdominal compartment syndrome due to vagal reflex often develops. If a perforation site develops, closure should be performed with a clip as soon as possible in a situation where it does not hinder the continuation of ESD. Although pneumoperitoneum is less likely to occur with the wide use of CO2 insufflation devices, pneumoperitoneum still occurs if insufflation is continued for a long time. For the prevention of pneumoperitoneum, degassing is induced by abdominal puncture with a 48 G Medicut needle at the right McBurney's point, while free air is confirmed on abdominal X-ray examination before the puncture.

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8 Large Intestine Hemostasis

1. Differential Diagnosis and Treatment of Hematochezia

In recent years, much evidence has been building regarding the diagnosis and treatment of lower gastrointestinal bleeding or hematochezia, thanks to *ESGE Guideline Diagnosis and Management of Acute Lower Gastrointestinal Bleeding* in Europa and America, *Guidelines for Colonic Diverticular Bleeding and Colonic Diverticulitis* by The Japanese Gastroenterological Association, and the results of the Colonic Diverticular Bleeding Leaders Update Evidence from Multicenter Japanese Study (CODE BLUE-J Study).[1-4] A flowchart for the diagnosis and treatment of hematochezia according to each guideline and cohort study is shown in **Figure 1**.

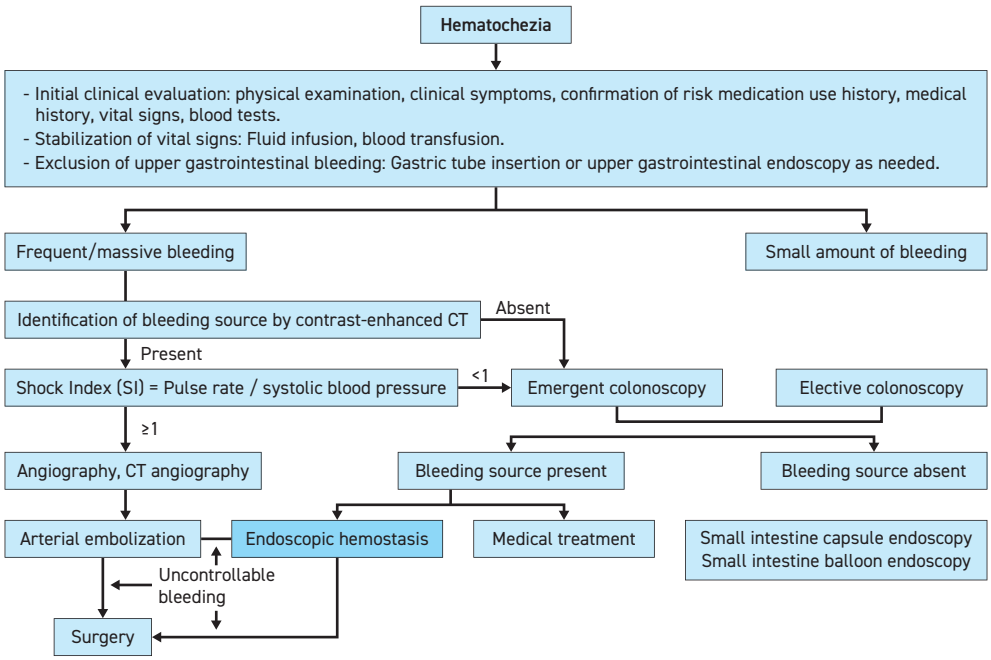


Figure 1 Hematochezia diagnosis and treatment flowchart.

(Created from Literatures 1-4)

(1) Understanding the causes and evaluation of hematochezia

In large intestine hemostasis, it is important to differentiate hematochezia. The most common cause of lower gastrointestinal bleeding is diverticular bleeding in the large intestine (63.6%), followed by ischemic colitis (9.1%), postendoscopy bleeding (4.5%), and rectal ulcer (2.5%).[5] Therefore, in order to estimate the causative disease of hematochezia, it is important to conduct a detailed medical interview regarding the nature of the hematochezia, accompanying symptoms such as abdominal pain, diarrhea, fever, and vomiting, the history of taking drugs such as antithrombotic drugs, NSAIDs, antibiotics, and antitumor drugs and the history of radiation therapy, or abdominal surgery, and daily life activities.

If a patient presents with clinical symptoms such as altered mental status or unstable vital signs, a practitioner should order immediately laboratory tests while working to stabilize their hemodynamic status. This requires establishing circulatory monitoring, administering oxygen, securing intravenous access, and promptly obtaining blood samples.[1] In addition, randomized controlled trials revealed that the bleeding source was present in the upper gastrointestinal tract in 3.6% to 15.3% of patients presenting with a large amount of hematochezia.[6,7] Thus it is also important to rule out upper gastrointestinal bleeding. Insertion of a gastric tube or upper gastrointestinal endoscopy should be considered, as necessary.

(2) Diagnostic procedure and treatment of hematochezia

In cases of frequent or massive hematochezia, if possible, evaluation of the bleeding source by contrast-enhanced CT and evaluation of circulatory dynamics by the shock index (SI = pulse rate / systolic blood pressure) are performed. The British Society of Gastroenterology guidelines for acute lower gastrointestinal bleeding recommend the use of the SI,[3] as it has been reported to show an association with mortality. [8] In lower gastrointestinal bleeding, there are reports that SI of 1 or more is a predictor of contrast extravasation under angiography.[9] According to the guidelines for diverticular bleeding, the detection rate of extravasation on contrast-enhanced CT is relatively low, ranging from 15% to 36%. Therefore, performing contrast-enhanced CT for all cases of diverticular bleeding is not recommended.[4] On the other hand, a meta-analysis on lower gastrointestinal bleeding exhibited that contrast-enhanced CT has good diagnostic performance with a sensitivity of 0.90 and a specificity of 0.92.[10] From these facts, it is considered appropriate to describe guidelines such as (i) emergency colonoscopy is given priority for hemostasis if the bleeding source is difficult to identify by contrast-enhanced CT, or if it is identified with an SI of less than 1 and is suitable for such treatment, and (ii) arterial embolization should be performed after detection of the responsible vessel with angiography or CT angiography for contrast-enhanced CT-positive cases with SI of 1 or more. Furthermore, surgical hemostasis should be considered if hemostasis is impossible with endoscopy or angiography. If hematochezia is minimal, an elective colonoscopy is performed, and endoscopic hemostasis is considered if necessary.

2. Endoscopic Hemostasis

Various methods exist for endoscopic hemostasis, but this section will focus on representative hemostasis techniques for colonic lesions.

(1) Mechanical hemostasis

1) Clipping

This hemostasis method is employed relatively easily regardless of whether the bleeding is arterial or venous, provided the bleeding site is identified. It is also a safe method that is applicable to the thin colonic wall. A study of direct clipping to the responsible vessel has revealed significant reduction of rebleeding rate within 30 days and 1 year compared to the indirect method which sutures the diverticular opening.[11] Therefore, the direct method should be used whenever possible. One drawback of clipping method is the problem of transition to alternative hemostasis techniques if clipping proves ineffective. Another limitation is that clips often fail to hold the target vessel securely, as they tend to slip off blood vessels exposed on a hard ulcer base.

2) Band litigation/detachable snare ligation

There are endoscopic band ligation (EBL) and endoscopic detachable snare ligation (EDSL), which have recently become popular as hemostasis methods for colonic diverticular bleeding.

A comparison of EBL and endoscopic clipping[12] manifested no difference in the initial hemostasis rate between them, but the recurrent bleeding rate up to 30 days or 1 year was significantly lower with EBL. Although the usefulness of EBL has been confirmed in this way, it is necessary to keep in mind the risk of adverse events such as perforation and diverticulitis.[12] A technical problem with this method is that the scope should be removed once to attach this ligation device.

EDSL is a ligation technique employing a detachable snare that is originally used as preventive hemostasis for resecting pedunculated polyps. It has shown promise in treating colonic diverticular bleeding, and its future use is of considerable interest.[13] Recent studies comparing EBL and EDSL have not found any significant difference in initial hemostasis rates or rebleeding rates in Japan.[13]

3) Over-the-scope clip

Case reports have sometimes described hemostasis for colonic diverticular bleeding using an over-the-scope clip (OTSC).[14,15] Reports on the treatment outcomes with a large number of cases are expected.

(2) Local injection

This is a method of achieving hemostasis by injecting a drug directly into the tissue, using the physical or chemical properties of the drug. The drug mainly used for hemostasis in the colon is hypertonic saline-epinephrine (HSE). The hemostatic mechanism of HSE is the vasoconstrictive effect of epinephrine, tissue swelling due to hypertonic saline, thrombus formation in the vessels, and local retention of epinephrine. However, it is necessary to pay attention to the injection volume because the possibility of tissue damage increases as the total injection volume increases. In contrast, ethanol is a representative local injection drug for upper gastrointestinal bleeding, but is contraindicated because it

has strong tissue damaging properties and increases the risk of colonic perforation.

(3) Thermal coagulation

This method achieves hemostasis by thermally coagulating the tissue at the bleeding site. It applies electrocoagulation, argon plasma coagulation (APC), heater probe therapy, microwave coagulation, and laser. In recent years, electrocoagulation and APC are the first-line for colonic hemostasis.

1) Electrocoagulation

This method is used for bleeding from ulcerative lesions with exposed blood vessels, bleeding during endoscopic submucosal dissection (ESD), and postendoscopy bleeding. It is a contact electrocoagulation modality using hemostatic forceps, and there are monopolar and bipolar types. When bleeding occurs, the site is grasped with hemostatic forceps, and current is provided for several seconds per application. This process is repeated several times until hemostasis is achieved. Notably, excessive use of electrocautery should be avoided because it carries a risk of perforation.

2) Argon plasma coagulation

This method applies high frequency using argon gas as a medium for coagulating a targeted tissue surface layer. It is a non-contact electrocoagulation. This enables coagulation of a wide range of tissues in a relatively short time, while the risk of perforation is controlled because the coagulation remains superficial. However, the hemostatic effect on active bleeding with exposed blood vessels is inadequate. Bleeding due to telangiectasia or radiation colitis is considered a good indication.

(4) Hemostatic agents

This is a method of directly spraying hemostatic agents onto the bleeding site. Thrombin, sodium alginate, and epinephrine-added saline are practically applied. Since the hemostatic effect of any of these alone is insufficient, they are often used in combination with other hemostasis modalities.

After the approvement in Western countries, recently, self-assembling peptide solution (PuraStat®) has been approved and launched in Japan as a novel hemostatic agent for the drug spraying method.[16] PuraStat® is an artificial synthetic peptide consisting of three amino acids: arginine, alanine, and aspartic acid. After coming in contact with body fluids, the peptides change from acidic to neutral, self-assembling into gel aggregates and acting as a medical device for hemostasis of bleeding sources.[16] In addition to bleeding control during ESD and prevention of postendoscopy bleeding, it has been reported to be useful for lower gastrointestinal bleeding unrelated to endoscopic treatments.[17,18]

3. Principles of Endoscopic Hemostasis According to Disease Type

The indications for endoscopic hemostasis and the selection of hemostatic techniques are summarized by disease type in **Table 1**.

Table 1 Indications for endoscopic hemostasis and corresponding hemostatic methods.

Disease	Hemostasis
Colonic diverticular bleeding	Clipping, EBL, EDSL, HSE (OTSC)
Post-EMR/(Cold) polypectomy	Clipping (first-line), electrocoagulation, hemostatic agents
Bleeding post-ESD bleeding	Electrocoagulation (first-line), clipping, hemostatic agents
Acute hemorrhagic rectal ulcer	Clipping or electrocoagulation (first-line), APC, HSE
Telangiectasia	APC method (first-line), clipping (adjunct), HSE (adjunct)
Dieulafoy ulcer	Clipping (first-line), HSE (adjunct), electrocoagulation, EBL
Radiation colitis	APC (low power, short-duration ablation)

(1) Colonic diverticular bleeding

Colonic diverticular bleeding accounts for approximately two-thirds of cases of acute lower gastrointestinal bleeding and has been increasing in recent years.[5] If a patient is taking antithrombotic agents, discontinuation should be taken whenever possible. This condition is characterized by the difficulty in identifying the bleeding diverticulum[19] and by both a high rate of spontaneous hemostasis (70% to 90%) and a high rebleeding rate (20% to 40%).[20] Given these challenges, the establishment of a treatment strategy has been required for some time. Since the publication of the *Japanese Gastroenterological Association Guidelines* in 2017, a large-scale, multicenter cohort study called CODE BLUE-J Study has provided a substantial body of evidence on the management of diverticular bleeding.[4]

1) Endoscopic diagnosis

The criteria for endoscopic intervention in colonic diverticular bleeding are based on three key findings collectively referred to as stigmata of recent hemorrhage (SRH): active bleeding, visible vessels, and adherent clots.[19] The identification of SRH requires careful consideration of the optimal timing of colonoscopy and bowel preparation, as well as the use of an endoscopic distal attachment and water jet irrigation. Several reports suggest that early colonoscopy within 24 hours increases the detection rate of SRH and shortens length of stay, although it does not significantly influence rebleeding or mortality rates.[21,22] Further investigation is needed to clarify these findings.

For bowel preparation, both the *Japanese Guidelines for Colonic Diverticular Bleeding and Colonic Diverticulitis and the American Society for Gastrointestinal Endoscopy Guidelines* recommend the use of polyethylene glycol-based bowel cleansing solutions.[2,4] The application of a distal attachment facilitates the visualization of diverticula that is possibly concealed behind colonic folds. Additionally, water jet irrigation improves luminal expansion and enhances visibility within diverticula, aiding in the identification of bleeding sources.

2) Selection of endoscopic hemostasis techniques

The primary endoscopic hemostasis methods for colonic diverticular bleeding include clipping, endoscopic band ligation (EBL), endoscopic detachable snare ligation (EDSL), and hypertonic saline-

epinephrine (HSE) injection.[11-13] In addition, the use of mechanical hemostasis techniques has recently gained attention. The selection of an appropriate hemostasis technique depends on several factors:

a. Active bleeding status

- For active bleeding, EBL is preferred over direct clipping, as it has been associated with decreased rebleeding.
- For non-active bleeding, both EBL and direct clipping offer similar efficacy in preventing rebleeding. However, given the potential risk of perforation associated with EBL, albeit low, direct clipping is the preferred option due to its minimal risk of adverse events.

b. Bleeding site

- For right-sided colonic bleeding, EBL is recommended over the direct clipping due to its lower rebleeding rate and the absence of reported perforation cases.
- For left-sided colonic bleeding, no significant difference in rebleeding rates has been observed between EBL and hemoclipping, or direct clipping and indirect clipping. Given the potential risk of perforation with EBL, albeit low, hemoclipping is considered the preferred option.

c. The efficacy of EDSL in hemostasis and rebleeding prevention is comparable to EBL, and EDSL is regarded as an equivalent treatment option.

d. In cases where bleeding control is challenging, HSE injection into the area surrounding the diverticulum should be performed to reduce bleeding before the implementation of definitive hemostasis.

(2) Post-endoscopic polypectomy bleeding

This category includes bleeding after endoscopic submucosal dissection (ESD), endoscopic mucosal resection (EMR), hot polypectomy, and cold polypectomy. According to the JGES Guidelines for Colorectal Endoscopic Submucosal Dissection/Endoscopic Mucosal Resection (2nd Edition), the incidence of postendoscopy bleeding is 0.7% to 3.1% for ESD, 1.1% to 1.7% for EMR, and 1.6% for polypectomy.[23] The risk is particularly higher in patients taking antithrombotic medications, requiring careful attention. If adherent clots are present, it is crucial to remove them completely before identification of the bleeding sources.

Due to the large resection area, post-ESD bleeding should be managed primarily with hemostatic forceps for pinpoint hemostasis. For post-EMR and post-hot polypectomy bleedings, clipping is the first-line approach, with hemostatic forceps being an alternative when clipping fails. Post-cold polypectomy bleeding is extremely rare. However, if active bleeding occurs, management follows the same approach as post-EMR or post-hot polypectomy bleedings. Hemostatic powder application with agents such as thrombin or PuraStat® is effective for oozing.

(3) Acute hemorrhagic rectal ulcer

Acute hemorrhagic rectal ulcer (AHRU) is an ulcerative lesion limited to the lower rectum, which occurs frequently in long-term bedridden patients with serious underlying diseases. It often presents with sudden-onset of painless hematochezia. The primary endoscopic hemostasis for this condition is clipping or electrocoagulation with hemostatic forceps, whereas reports also exist on the use of HSE injection or argon plasma coagulation (APC).[24] The rebleeding rate is relatively high, ranging from 16.7% to 50.0%. In fact, careful monitoring is required.[25-29]

(4) Telangiectasia

Endoscopically, telangiectasia appears as a flat, bright redness, with capillaries visible upon close observation. Argon plasma coagulation therapy (APC) is the first-line treatment, but if hemostasis is unsuccessful, clipping or HSE injection is effective as adjunctive methods.

(5) Dieulafoy ulcer

Dieulafoy ulcer is characterized by a large, tortuous submucosal artery that causes massive bleeding when an ulcer develops in the overlying mucosa. The lesion predominantly occurs in the lower rectum, where endoscopic findings typically include arterial bleeding or visible vessels within a minor mucosal defect. Clipping is the first-line treatment, though HSE injection is applicable to reduce blood flow. Related reports also support the efficacy of electrocoagulation with hemostatic forceps and endoscopic band ligation (EBL).

(6) Radiation colitis

Radiation colitis is a condition caused by radiation-induced damage to the intestinal vessels, leading to microcirculatory disorders such as arteritis or vascular occlusion. This often results in complications like angioectasia, ulceration, stenosis, and fistulas. They are broadly classified into early and late stages based on the time of onset. Among these, oozing bleeding from dilated vessels associated with advanced-stage disorders is frequently observed, where APC is commonly used for thermal coagulation. However, post-APC adverse events have been reported, such as ulceration, stenosis, perforation, and fistula formation,[30,31] and thus cautious hemostasis is required. To minimize these risks, low-power settings (30 to 40 W, flow rate 0.6 to 1.0 L/min) and short-duration electrocoagulation are recommended. When angioectasia is extensive and diffuse, a staged treatment approach with sessions spaced 2 or 3 months apart is preferable to preserve normal mucosa. This approach proves to be quite an effective option compared to a single session of complete ablation.[32]

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9 Treatment of Stricture

For benign diseases causing colonic strictures, endoscopic balloon dilation (EBD) is primarily preferred for the treatment.[1] There are reports concerning endoscopic interventions for difficult-to-treat cases such as the radial incision cutting (RIC) method with an electrosurgical knife or argon plasma laser or stent placement, but they are in the clinical research. Therefore, there is no consensus on their effectiveness and safety.[2-6]

In malignant diseases, balloon dilation alone is not only insufficient but also carries a high risk of perforation due to damage in cases of colorectal cancer.[7] Therefore, balloon dilation is not indicated, while surgical treatment or **stent placement** is generally completed.[8] Stents used in the gastrointestinal tract are basically all self-expandable metal stents.[9]

1. Endoscopic Balloon Dilation for Benign Colonic Strictures

(1) Indications and contraindications

Indications include **postoperative anastomotic strictures, post-endoscopic treatment strictures** (especially after endoscopic submucosal dissection for extensive lesions), high-grade strictures due to **inflammatory diseases** (colonic diverticulitis, ischemic colitis, Crohn's disease, intestinal tuberculosis, and radiation enterocolitis), **post-hemorrhoidectomy stricture**, and **strictures that do not allow passage of a thin endoscope** with diameter less than 1 cm.[10]

Contraindications and cases considered unsuitable include those with severely angulated strictures, long-segment strictures, the presence of fistulas or abscesses, as well as strictures accompanied by active inflammation or ulceration.[11,12]

(2) Preparation for procedure

It is necessary to obtain informed consent from patients through both verbal explanation and written consent in all cases. An intravenous route should be secured, and fluid infusion should be administered. Conscious sedation is used if necessary. Since the presentation of pain serves as an indicator, the dosage of the sedative is adjusted so that the patient has the ability to adequately express any pain during balloon dilation.[12] The endoscopic procedure should be performed in a fluoroscopy room. The following items are the equipment to be prepared.

i) Electronic endoscope, gascon solution, infusion fluids, monitor, and disposable syringes, which are

necessary for endoscopy.

ii) Water-soluble contrast medium such as Gastrografin®

iii) Balloon for dilation: The following are available as balloons for the lower digestive tract: CRE PRO (Boston Scientific), Hercules (Cook Medical), EZDilate (Olympus), Elation (Merit Medical), and Multi-Stage Dilation Balloon (Century Medical). These are all through-the-scope (TTS) balloons equipped with a guide wire lumen and correspond to the instrument port diameter of 2.8 mm. The catheter length is 240 cm, in some cases 230 cm, while the effective length of the balloon is 5.5 cm, in some cases 6.5 cm. There are 6 types of balloon dilation diameters from 6 to 18 mm, up to 20 mm (5 types in Hercules®, 8 to 18 mm up to 20 mm), and three expansion diameters is available with adjustment of the expansion pressure. A pressure measuring device is required during the expansion process. The balloon is expanded with sterile water, sterile saline, or a mixture of both with a contrast medium.

iv) Dilator, pressure monitor, guide wire: The expansion pressure should be monitored. In the expansion process, pressure is applied slowly and maintained so as not to exceed the specification limit of each balloon. Attention is simultaneously paid to both the patient's pain and the degree of balloon dilation under X-ray fluoroscopy.[12] The guide wire is attached to the dilation balloon.

(3) Practical Procedure and Tips (Figure 1)

After inserting the colonoscope up to the stricture, an endoscopist should evaluate the degree of the narrowing, the presence of severe inflammation, bleeding, or active ulcers (**Figure 1a**). After that, contrast imaging with Gastrografin® is performed to assess the length and angulation of the stricture and to confirm the absence of deep ulcers or fistulas (**Figure 1b**).

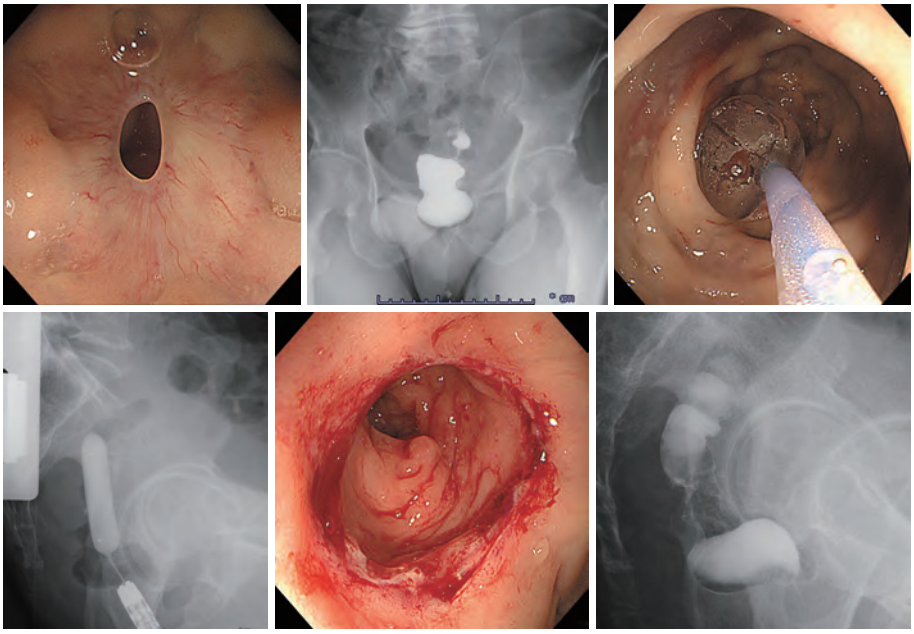
A guidewire is then gently advanced through the stenotic area to the proximal side, and a through-the-scope (TTS) balloon is inserted along the guidewire under fluoroscopic guidance. In cases with short, non-angulated strictures, it is possible to insert the balloon directly without using a guidewire.

Once the balloon is correctly positioned, dilation is initiated gradually (**Figures 1c&d**). **Dilation should be maintained for approximately one to two minutes, followed by deflation for about one minute. This cycle is repeated two to three times.** The target diameter should be achieved in a stepwise manner over multiple dilations rather than maximum pressure is applied at once. The goal of dilation is to ensure endoscopic passage, but if a single session is inadequate, additional dilation should be performed after a few days. After dilation, the treated area is examined for mucosal tearing and bleeding to confirm the absence of perforation (**Figures 1e&f**).

(4) Treatment outcomes, adverse events and their countermeasures

Balloon dilation for Crohn's disease achieves technical success in approximately 90% of cases and is clinically effective in about 60%.[13-15] Long-term follow-up studies have reported that surgery was avoided in 80% to 90% of patients at 12 months, 70% to 80% at 36 months, and 60% to 70% at 60 months.[11,15]

The main adverse events associated with endoscopic balloon dilation are perforation and bleeding, while mild bleeding is common but severe bleeding rarely occurs. Perforation is reported in approximately 1% to 3%, so careful technique is essential for its prevention.[13,15] Understanding the profiles of the stricture is critical for selecting an appropriate balloon, for example its angulation, length, associated inflammation,



a | b | c
d | e | f

Figure 1 **Endoscopic balloon dilation using a through-the-scope (TTS) balloon for anastomotic stricture following low anterior resection.**

a and b: After endoscopic confirmation of the absence of inflammation or ulceration at the site of stricture, the balloon is directly inserted under endoscopic guidance.
c and d: The first dilation is performed using a 12 mm balloon inflated to 3 atm, and the second using a 15 mm balloon at 8 atm. The balloon is inflated for approximately two minutes in each instance, until the patient begins to feel discomfort—typically described as mild pain or a sense of pressure, though still tolerable. As a dilating process of the fibrotic and granulation tissue surrounding the stricture is required, the dilation is performed to an extent to cause slight bleeding.
e and f: The final step involves confirming endoscopic passage and the absence of perforation or active bleeding.

and ulcer depth. Additionally, if the patient complains about excessive pain, the trouble probably indicates excessive dilation. Thus, immediate deflation should be performed.[12)]

2. Endoscopic Stenting for Malignant Colonic Strictures

(1) Indications and contraindications

Endoscopic stenting is indicated for malignant colonic strictures presenting with obstructive symptoms. This includes strictures caused by malignant diseases such as anastomotic recurrence following colorectal cancer surgery, metastatic recurrence, and unresectable colorectal cancer **for palliative treatment.** Stent placement is also performed **to avoid emergency surgery in obstructive colorectal cancer and called elective bridge to surgery (BTS) for decompression.**[16)]

Contraindications and ineligible cases include perforation or impending perforation, complex strictures such as long or fistulous strictures, strictures with inflammation such as bleeding or abscess formation, and cases with a strong bleeding tendency.[9,16)] Moreover, lesions in the lower rectum near the anal verge tend to cause discomfort or pain if the stent's end extends over the dentate line. Lower rectal lesions

Table 1 ColoRectal Obstruction Scoring System: CROSS.

Level of oral intake	Score
Requiring continuous decompressive procedure	0
No oral intake	1
Liquid or enteral nutrient*	2
Soft solids, low-residue, and full diet with symptoms of stricture†	3
Soft solids, low-residue, and full diet without symptoms of stricture†	4

*: Enteral nutrition includes a complete liquid diet in which the substances are easily taken through a straw.
†: Symptoms of stricture contain abdominal pain/cramps, abdominal distension, nausea, vomiting, constipation, and diarrhea which are related to gastrointestinal transit.
(Cited from Literature 18)

suitable for stenting could vary from person to person. However, there isn't a universally consensus on the extent of these lesions that are applicable to stenting. If someone has this type of lesion, they're considered relatively ineligible for stenting in general.[9,17)]

(2) Assessment of colonic obstruction and stricture

Accurate assessment on colonic obstruction and stricture is essential for safe procedures. However, there is no established method for evaluation. The Japan Colonic Stent Safe Procedure Research Group has developed the ColoRectal Obstruction Scoring System (**CROSS**) as a widely applicable and straightforward assessment tool, which is available on their website (https://colon-stent.com/).[9,17,18)] CROSS assigns scores based on dietary intake and abdominal symptoms. For palliative treatment of obstructive colorectal cancer, scores of 0 to 3 are considered appropriate indications, while scores of 0 to 1 are regarded as suitable for the preoperative resolution to colorectal cancer obstruction.[9)]

(3) Procedural preparation

The preparatory steps and procedural settings are similar to those for EBD procedures. The required equipment includes:

(i) Endoscope: The delivery system for colorectal stents is predominantly 9 Fr. (3.0 mm), while many thin or standard endoscopes have an instrument port of at least 3.2 mm, making them compatible. However, some delivery systems exceed 10 Fr. (3.3 mm), so the instrument port size should be ensured before procedure.

(ii) Water-soluble contrast medium (e.g. Gastrografin®) is required for visualization, along with endoscopic clips for marking the stricture site.

(iii) Guidewire: A thin and flexible guidewire (0.025 or 0.035 inch) is necessary for navigating the stenotic area.

(iv) ERCP sheath: This is essential for contrast imaging of stricture to guide the guidewire through the narrowing, and for visualizing the proximal side of the stricture.

(v) Stent and delivery system: The commonly used stent is a distal-release, through-the-scope (TTS) type, non-covered, flare-less model with a diameter of 22 mm. There are some available options including HANAROSTENT® Naturfit™ (Boston Scientific), Niti-S™ (Century Medical),

JENTLLY® NEO (Japan Lifeline), and AJIRO® (JIMRO). Additionally, a proximal-release type, covered, flared model with a diameter of 18 mm is also available. These stents should be selected appropriately depending on the narrowing conditions. Since the stent length is determined according to the stricture length, several types are kept available to match the required length appropriately.

(4) Practical procedure and Tips[19)]

Since stent types are distinguished by delivery release methods, marking positions, and guidewire compatibility, it is essential for an endoscopist to thoroughly review and fully understand the instructions for each product before use.

The procedure begins with the insertion of a colonoscope up to the stricture site to confirm that the underlying cause is a malignant disease (**Figure 2a**). Generally, when a stricture is present, residual stool on the distal side is minimal. In fact, pretreatment is unnecessary, but enema is required if appropriate. Sedation is not administered unless the patient experiences pain.

Contrast imaging with Gastrografin® is first implemented with the endoscope to assess the severity of the stricture (**Figure 2b**). A metal clip is then placed on the distal side of the stricture to serve as an internal marker, ensuring clear visualization of the site under fluoroscopy (**Figure 2c**). A thin guidewire inserted through the ERCP sheath advances through the stenotic lumen to proximal side (**Figure 2d**). Subsequently, the sheath advances beyond the stricture, which allows contrast imaging of the bowel on the proximal side of the narrowing. The imaging confirms correct guidewire positioning and allows for measurement of the stricture's length (**Figure 2e**).

When the guidewire extends sufficiently beyond the stricture, the sheath is removed, after that, the stent delivery system is inserted directly into the stricture through the guidewire from the instrument port (**Figure 2f**). Using not only endoscopic and fluoroscopic views but the internal marker, the endoscopist carefully monitor the stent's position relative to the stricture as it is gradually deployed. Once properly aligned, the stent is fully deployed and secured in the appropriate position (**Figures 2g&h**).

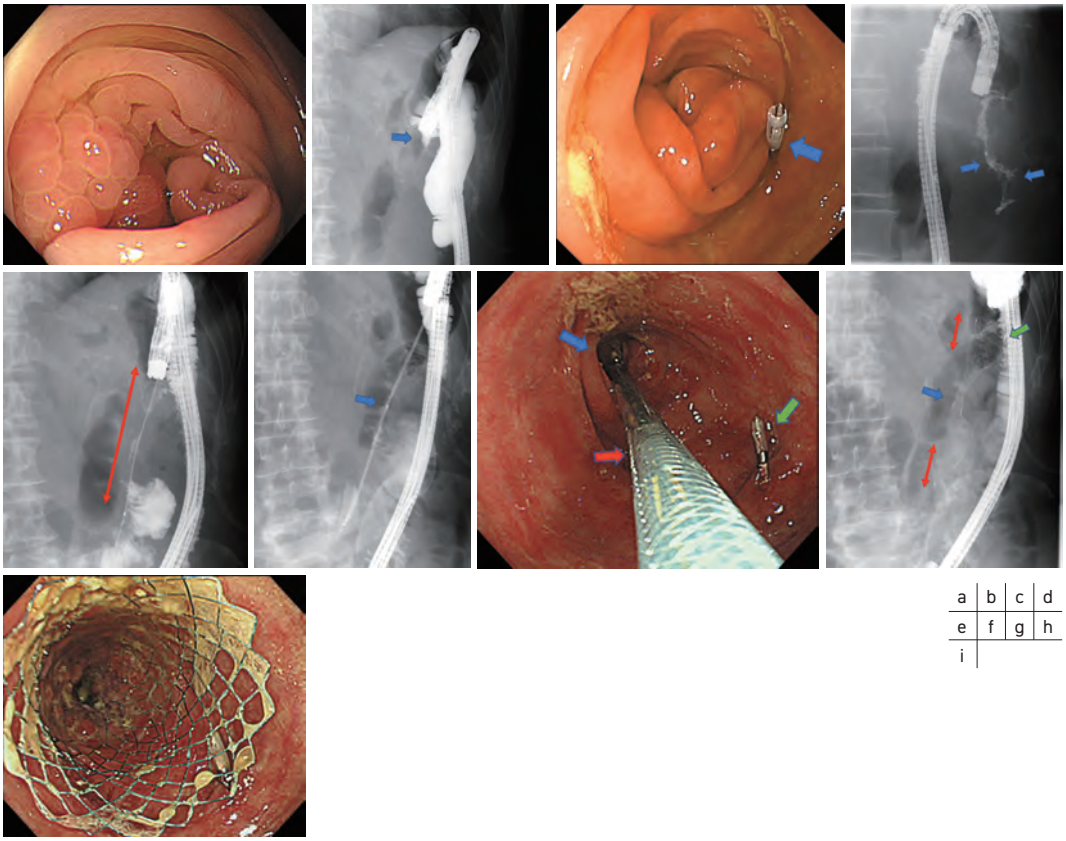
Although a balloon is useful to dilate a narrowed area for stent placement in the upper gastrointestinal tract, it is pointed out this method to expand a stricture for stent placement in the lower GI tract carries a high risk of perforation. It is essential to exercise extreme caution and avoid forceful balloon dilation.[20)]

The final step involves endoscopic and fluoroscopic confirmation of the stent's position while checking for adverse events such as bleeding or perforation (**Figure 2i**). It is particularly important to position the patient in a semi-upright stance in the fluoroscopy room to ensure no signs of free gas. Patients are generally permitted to drink fluids within a few hours after placement, following confirmation of normal findings on plain X-ray. Oral intake is also resumed the following day after an additional radiographic confirmation.

(5) Treatment outcomes, adverse events and their countermeasures

The technical success rate of colorectal stent placement exceeds 90%, and successful deployment allows for the effective decompression in almost all cases.[21)] In palliative stenting, the duration of stent retention ranges from 1 to 576 days, with an average of 145 days.[20,22)] For bridge to surgery (BTS) cases, postoperative adverse events and the necessity for decompressing stomas were reduced, compared with emergency surgery.[23)]

Short-term adverse events within seven days of the stent placement include the following risks: 2.1% for



a	b	c	d
e	f	g	h
i			

Figure 2 **Procedure for colonic stent placement: 64-year-old male with transverse colon obstruction due to peritoneal dissemination of gastric cancer (for palliative treatment).**

a: A colonoscope is advanced to the stricture, and the lesion is identified.
b: Gastrografin contrast imaging reveals complete obstruction with no contrast filling in the stricture or proximal side of the bowel (arrow).
c: The distal side of the stricture is marked with a metallic clip (arrow).
d: The contrast is injected through the ERCP sheath to identify the lumen of the stricture (arrow), which guides the guidewire advancement toward the proximal side.
e: After crossing the stricture with a 0.035 inch guidewire, the sheath is advanced to the proximal bowel, followed by contrast imaging to assess length of the stricture measured to be 6.5 cm (arrow length) upon positional adjustment.
f: The stent delivery system is introduced along the guidewire, aligning the central marker of the stent (arrow) with the midpoint of the stricture, and the stent is carefully deployed. In this case, due to disseminated lesions, a 12 cm stent is selected to ensure a 2 cm margin coverage beyond both ends of the stricture.
g: The endoscopic image during stent deployment reveals the distal side of the lesion (blue arrow), internal marking (green arrow), and the delivery system (red arrow).
h: After deployment, the central marker of the stent (blue arrow) aligns approximately with the midpoint of the stricture based on internal marking (green arrow), thereby covering 1.5 to 2 cm (red arrow length) beyond both ends.
i: The final endoscopic image confirms stent position and absence of adverse events, with additional confirmation using radiography.
(Modified from Literature 19)

perforation, 1.0% for stent migration, and 0.8% for reobstruction.[21] In long-term palliative stenting, perforation, migration, and reobstruction rates have been reported at 3%, 7%, and 13%, respectively.[22] Although no unified consensus exists regarding the concurrent use of chemotherapy with stent placement, several reports demonstrate an increased risk of perforation when **bevacizumab** is administered before or after the stent placements, requiring careful attention.[24,25] Reobstruction due to tumor ingrowth is effectively managed with secondary stent insertion using the stent-in-stent technique.[17,26]

In 2014, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines stated that BTS was

not applicable as a standard treatment for potentially curable left-sided obstructing colon cancer due to potential deterioration in long-term prognosis.[27] However, subsequent advancements in procedural techniques and stent improvements have led to a reduction in perforation rates. Recent meta-analyses have clarified no significant difference in overall survival (OS) or disease-free survival (DFS) between BTS and emergency surgery groups. Furthermore, randomized controlled trials in Italy and Spain (ESCO trial)[28] and the UK (CReST study)[29] found no difference in OS or postoperative mortality between the two approaches. Based on these findings, the 2020 update of the ESGE guideline revised its recommendation, favoring colorectal stenting as a bridge to surgery discussed within shared decision-making process, instead of emergency surgery.[17] In the *JSCCR Guidelines 2022 for the Treatment of Colorectal Cancer,* no clear statement is made regarding the pros and cons of BTS, although it is "not recommended."[24] However, a multicenter prospective study conducted by the Japan Colonic Stent Safe Procedure Research Group demonstrated outcomes comparable to or even superior to not only emergency surgery but the outcomes reported in ESCO trial and CReST study.[30]

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VI. Biliary-pancreatic

1 Endoscopic Retrograde Cholangiopancreatography(ERCP)

1. Indications and Contraindications

(1) Indications

Endoscopic retrograde cholangiopancreatography (ERCP) is indicated for conditions affecting the entire biliary system, from the papillary region to the intrahepatic bile duct, as well as the pancreatic duct. The conditions include tumors, inflammatory diseases, trauma, and congenital anomalies. If diagnostic imaging modalities such as ultrasonography (US), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), or endoscopic ultrasonography (EUS) make a definitive diagnosis possible, the ERCP procedure is generally unnecessary.

For diagnostic purposes, ERCP is utilized for evaluating pancreatic and biliary duct shapes, obtaining pathological samples for cytology or histology, and conducting differential diagnosis of pancreaticobiliary diseases and tumor staging using intraductal ultrasound (IDUS) or peroral pancreatoscopy and choledochoscopy.

Therapeutic indications include endoscopic removal of stones and drainage of the biliary or pancreatic duct. Advances in endoscopic techniques and improvements in devices have led to increased use of endoscopic transpapillary interventions. Additionally, balloon-assisted endoscopy has expanded the indications to include patients with surgically altered anatomy following gastrointestinal reconstruction.

(2) Contraindications

ERCP is contraindicated in patients with poor general condition that makes endoscopic procedures unsafe, as well as in cases where passage of the endoscope is obstructed due to severe upper gastrointestinal stricture.

Regarding iodine hypersensitivity, since ERCP does not involve intravenous injection of contrast agents, the procedure is feasible with careful precaution. Acute pancreatitis is generally a contraindication for ERCP. In cases where gallstone pancreatitis complicated by acute cholangitis, urgent endoscopic management (typically ERCP) should be considered after careful assessment of the indications. The goal is to quickly relieve the pressure in the bile duct and remove the source of the infection, which is critical for the patient's survival, even though ERCP is usually not indicated in uncomplicated acute pancreatitis.

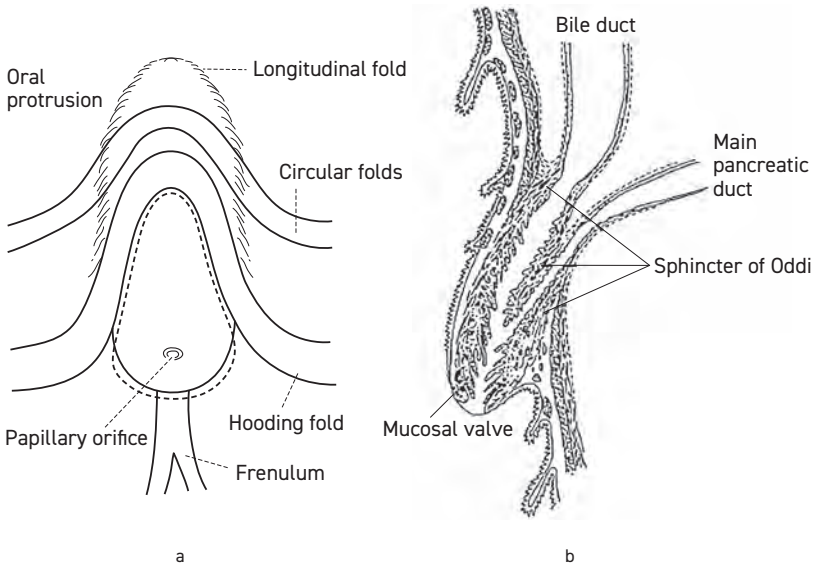


Figure 1 **Anatomy of duodenal papilla.**

a: Frontal view (Modified from Literature 1)
b: Cross-sectional view (Modified from Literature 2)

2. Anatomy of Papillary Region for ERCP

The bile duct and pancreatic duct open into the papillary region which is located almost in the center or slightly below the descending part of the duodenum. The santorini's duct opens at the minor papilla which is located on the anterior wall proximal to the major papilla.

Figure 1a schematically describes the papillary region as observed from the duodenal lumen. The major papilla consists of three anatomical features: the oral protrusion located proximal to the opening, a transverse fold referred to as the hooding fold that intersects the oral protrusion, and a vertically oriented ridge known as the frenulum on the distal side of the opening.[1)] There is considerable individual variation in the shape of the opening, the dimensions of the oral protrusion, and the morphology of the frenulum.

Figure 1b illustrates a cross-section of the tissue structure of major papilla.[2)] Within papillary region, bile duct and pancreatic duct transition into the common duct. Both ducts are surrounded by the sphincter of Oddi, which regulates the discharge of bile and pancreatic juice and prevents reflux of duodenal contents together with the mucosal valve in the lumen. In cases of pancreaticobiliary maljunction, a congenital anomaly, the pancreatic duct and bile duct merge outside the duodenal wall, forming an abnormally long common channel.

3. Pretreatment

As in the usual upper gastrointestinal endoscopy, pharyngeal anesthesia is provided, and then a spasmolytic, butylscopolamine bromide (Buscopan®) is administered, but for patients with ischemic heart disease, glaucoma, prostatic hypertrophy, or the elderly, glucagon is administered before the examination. Furthermore, after establishment of an infusion route to reduce the patient's pain, sedation

is implemented with a sedative or an analgesic or both. Regarding sedation, it is necessary to be well versed in the *Guidelines for Sedation in Gastroenterological Endoscopy* (second edition) provided by the Japan Gastroenterological Endoscopy Society.[3)]

In Japan, the sedatives most commonly used are the benzodiazepines midazolam (Dormicum®), diazepam (Horizon®/ Cercine®), and flunitrazepam (Silece®). According to the guidelines, propofol should be administered with strict attention to sedation depth and is limited to patients classified as ASA-PS I or II. The agent is appropriately administered by specialists trained in airway management. Notably, its insurance coverage is restricted to "induction and maintenance of general anesthesia" and "sedation during mechanical ventilation in intensive care," thus it requires careful consideration. Dexmedetomidine hydrochloride is useful for procedures requiring prolonged sedation during endoscopic therapy.

Regarding analgesia, agents such as pethidine hydrochloride and pentazocine (Sosegon®) are commonly used.

During the procedure, since respiratory depression and hypotension are likely to occur, a nasal cannula is applied before the examination, and continuous monitoring is required for ECG, pulse oximeter, and blood pressure. To counteract respiratory depression, flumazenil (Anexate®) and naloxone hydrochloride should be readily available.

4. Practical Techniques and Key Point in ERCP Procedure

(1) Monitor setup

For ERCP, the endoscopy monitor and the fluoroscopy monitor should be positioned adjacent to each other at the head end of the table (on the operator's side) so that both the endoscopist and the assistant can view both screens simultaneously.[4)] Continuous monitoring is essential for the patient's condition throughout the procedure.

(2) Scope

A duodenoscope with backward side viewing is employed for ERCP. Previously, duodenoscopes with an instrument channel diameter of 3.7 mm were commonly used. However, a widely adopted duodenoscope with a 15-degree retrograde field of view and an instrument port diameter of 4.2 mm has become the standard, because it is suitable for various therapeutic procedures.

(3) Cannula

A variety of cannulas with different tip shapes and stiffness levels are commercially available. With the widespread use of wire-guided cannulation (WGC), cannulas that allow injection and aspiration of contrast medium even with the guidewire (GW) indwelling are now widely used. In cases where stone removal is expected, endoscopic sphincterotomy (EST) knife such as papillotome, should be selected from the outset.

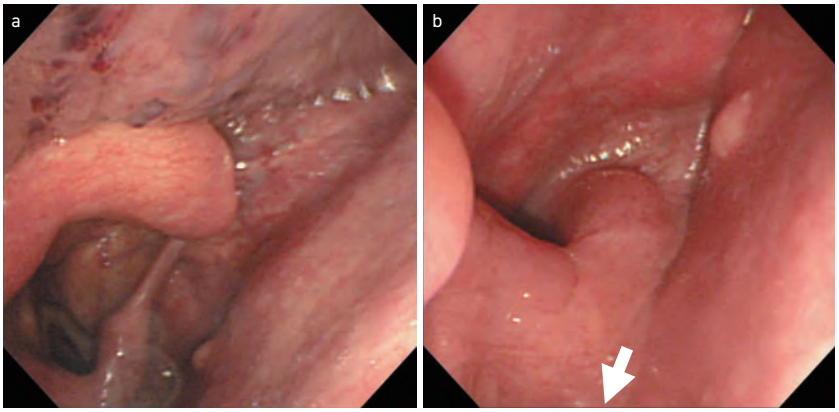


Figure 2 **Pharyngeal manipulation.**

Once the tip of the endoscope passes over the base of the tongue, reducing the upward angulation and gently pushing the scope from the left side of the hypopharynx toward the midline (indicated by the arrow) enables insertion into the pharyngoesophageal junction.

(4) Insertion of scope

In retrograde backward side viewing endoscopy, the lower center of visible field aligns with the direction in which the scope advances. Therefore, down angulation is adjusted as needed as the scope advances, and the endoscopist continuously confirms the direction in which the scope is moving. If the operator feel resistance, the endoscope should never be forced forward.

1) Pharynx and esophagus

The patient should be placed in a prone position from the beginning, with the chin slightly protruding. In cases where it is difficult to pass through the pharynx, it is easier to insert the scope as the assistant raises the right shoulder slightly to make the patient semi-prone. Pharyngeal observation is feasible, even in the prone position. After the tip of the scope passes the base of the tongue, up angulation should be gradually released. At this point, the tip can be gently guided from the left hypopharyngeal wall toward the midline, allowing the scope to enter the pharyngoesophageal junction (**Figure 2**). While traversing the esophagus, the scope is advanced with slight insufflation so that the distal lens does not contact the mucosa, thereby preventing red-out.

2) Stomach

When the tip of the scope reaches the stomach, it is rotated counterclockwise to avoid the posterior wall of the lesser curvature of the upper body, and the direction of scope insertion is changed from the lesser curvature to the anterior wall. Subsequently, it is rotated clockwise and the scope is advanced to the lower body while the operator views at the lesser curvature. Thereafter, the scope is advanced along the greater curvature to the antrum. The pyloric ring is positioned on the lower side of the screen, and when the angulation is returned from up to down, the scope passes through the pyloric ring (**Figure 3**).[5] In the prone position, air tends to accumulate in the fundus, thus it is important to keep the amount of insufflation as low as possible and navigate through the available luminal space.

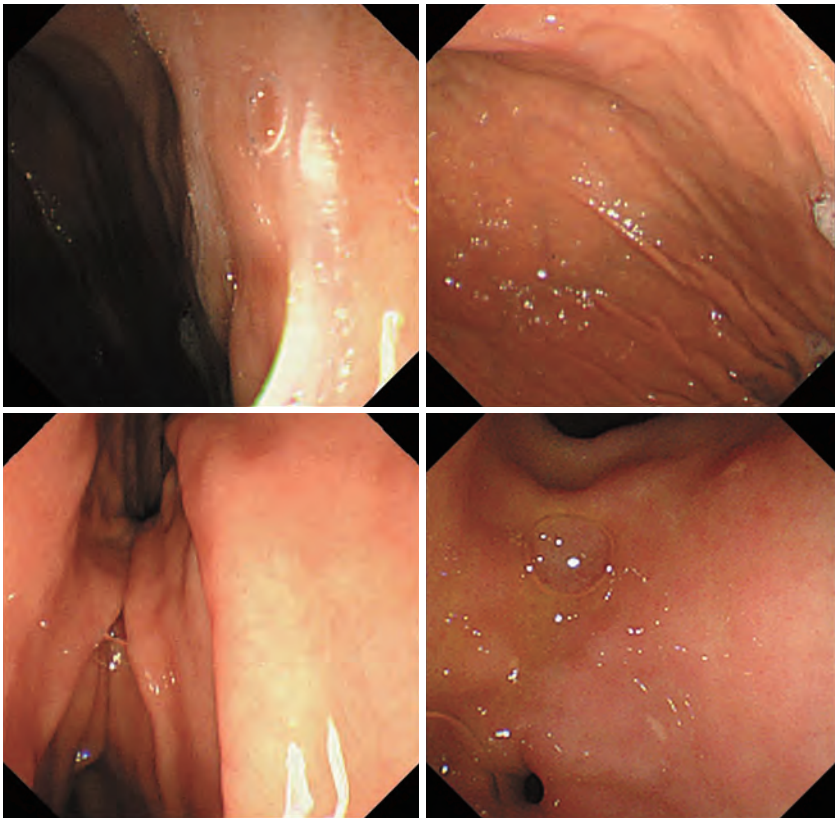


Figure 3 Intracorporeal gastric maneuvering.

a: Counterclockwise rotation helps avoid the lesser curvature posterior wall.
b: Advancing the scope toward the lower body while rotating it clockwise.
c: Advancing the scope along the greater curvature into the antrum.
d: Aligning the pyloric ring at the lower part of the screen and transitioning the angulation from upward to downward allows passage through the pyloric ring.
(Cited from Literature 5)

3) Duodenum

The final process begins with confirming the superior duodenal angle (SDA). Once the first section of duodenum has been confirmed, the endoscope is gently angulated downward and rotated clockwise while it is slowly guided toward the descending (second) portion of the duodenum. After the scope reached the SDA, the right angle of the scope is locked, and the scope remains angulated upwards. Subsequently, the scope is either carefully withdrawn in a straight line or rotated slightly clockwise. This helps to position the tip of the scope into the deeper part of the descending duodenum. At this point, the scope is slowly withdrawn based on the distal-side frenulum as a landmark to guiding it towards the major papilla. Finally, with rightward angulation relaxed, the papillary orifice is visualized in a frontal view (**Figure 4**).

(5) Selective cannulation

The configuration of the confluence of bile duct and pancreatic duct within the papilla is estimated to some extent by carefully observing the papillary orifice (**Figure 5**).[6] The fundamental approach to selective cannulation involves adjusting the position of the papilla through scope manipulation, including insertion and withdrawal, angulation control, and insufflation management. The key to successful

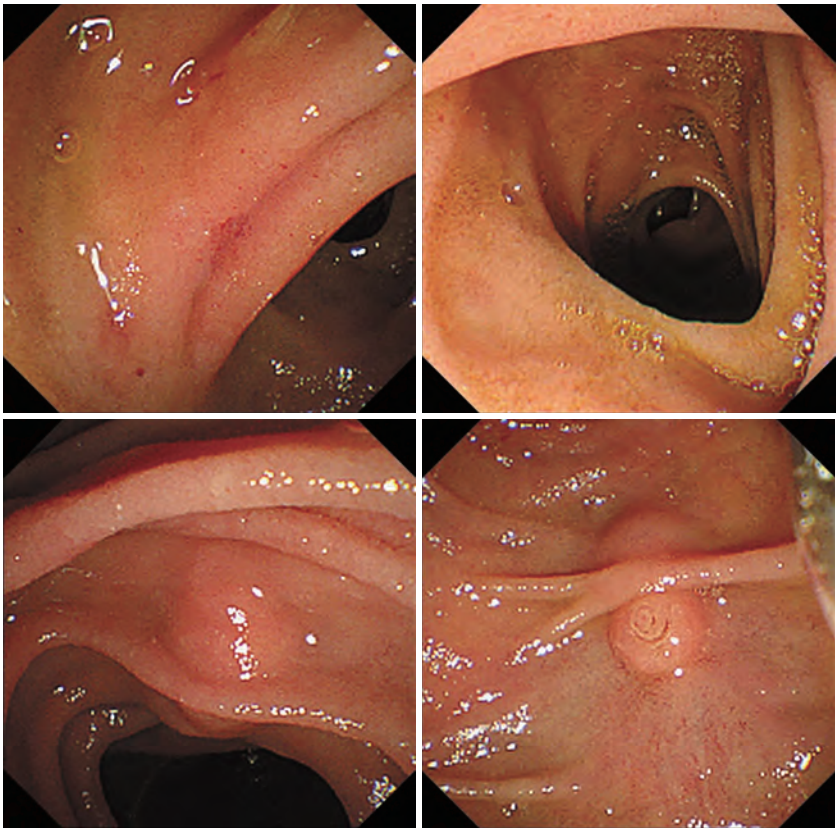


Figure 4 Maneuver in the duodenum duodenum.

a: Inserting the scope into the duodenal bulb to identify the superior duodenal angle (SDA).
b: After reaching the SDA, the right angle is locked.
c: Pulling back the scope with upward angulation and clockwise rotation usually brings the minor papilla into view, typically at the 1 to 2 o'clock orientation on the screen.
d: With further withdrawal, the major papilla is visualized centrally, and the scope is inserted deep into the descending part of the duodenum.
(Cited from Literature 5)

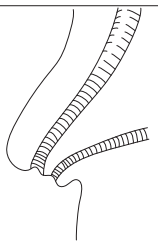
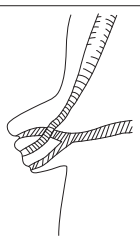
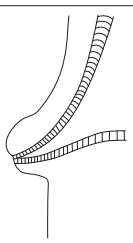
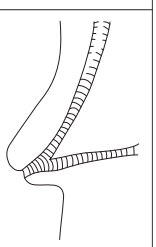
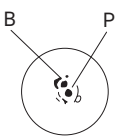
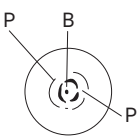
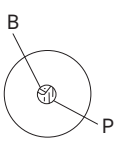
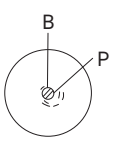
Classification	Separate type		Septal type	Common channel type
	Separate opening type	Onion type		
Intrapapillary confluence pattern of bile duct and pancreatic duct				
Shape of papillary orifice				

Figure 5 Confluence pattern of bile duct and pancreatic duct within papilla and shape of orifice .

(Cited from Literature 6)



Figure 6 **Pancreatic duct cannulation.**

Cannulation is attempted in the 3 to 4 o'clock orientation with a slight downward view of the papilla.

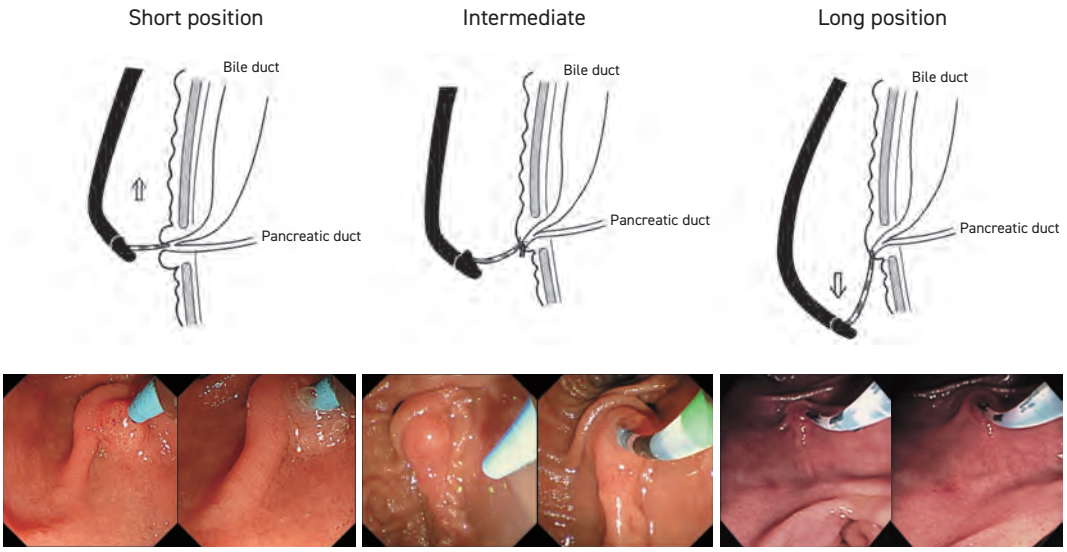


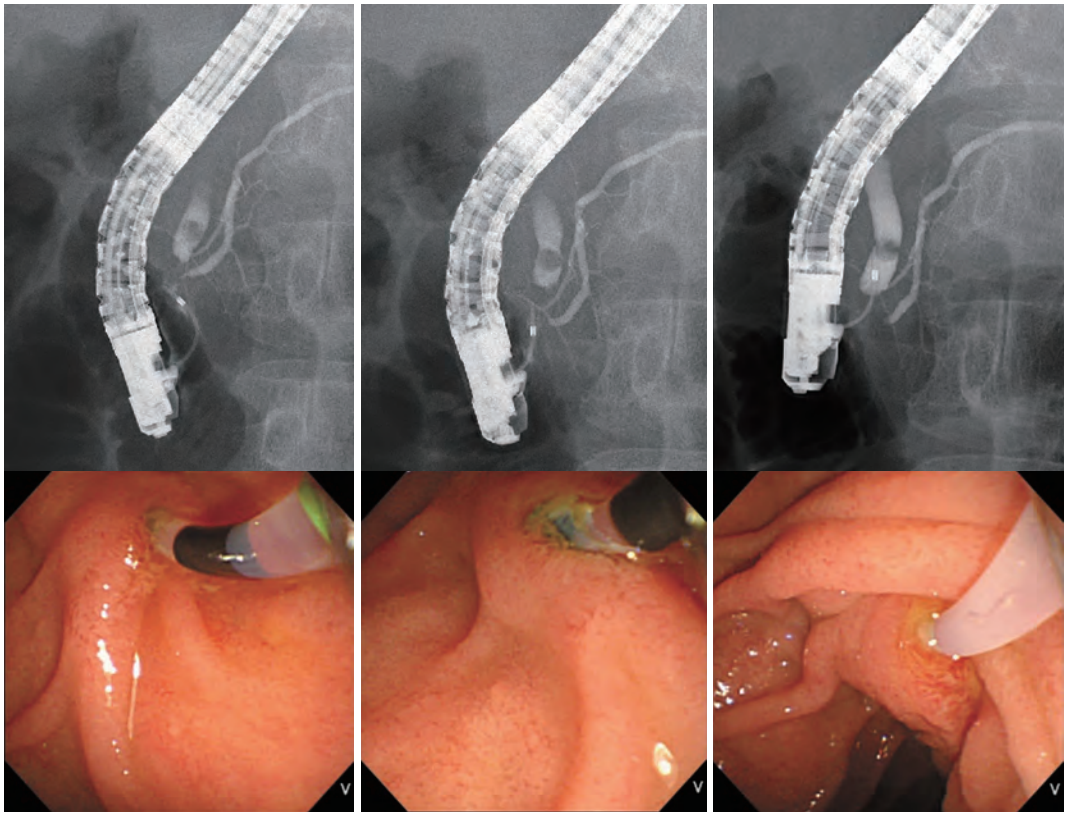
Figure 7 **Basic techniques for biliary cannulation – Short and long scope position.**

(Cited from Literature 5)

cannulation lies in adjusting the angle of the cannula with the elevator mechanism and aligning it with the axis of bile duct or pancreatic duct.

1) Pancreatic duct cannulation

The pancreatic duct opening is located at the front of papillary orifice and often oriented nearly perpendicular to the duodenum. If smooth cannulation is not achieved, the cannula should be directed toward the 1-2 o'clock position or toward the 3-4 o'clock orientation if the papilla is viewed slightly downward (**Figure 6**). During contrast injection, the cannula tip should be monitored to prevent acinarization. Air injection into the pancreatic duct should be avoided since it usually results in pancreatitis or poor contrast filling. To prevent this, the contrast medium should be thoroughly flushed immediately before cannulation to expel any residual air in the cannula. Although guidewire-assisted (GW) techniques are now frequently employed, caution is required to avoid misinsertion into the branch of the pancreatic duct.



a | b | c

Figure 8 **Axis alignment for selective biliary cannulation.**

While slightly withdrawing the cannula proximally (a, b), relaxing the up angle and slowly pulling the scope aligns the axis of the cannula with the long axis of the bile duct, facilitating deep cannulation (c).
(Cited from Literature 5)

2) Biliary cannulation

(I) Contrast-assisted cannulation

Cannulation should be performed in an upward direction from the 11 o'clock orientation of the papillary orifice. At this point, proper distance adjustment between the endoscope and the papilla is crucial. Depending on the relative position of the papilla and the endoscope, different approaches have been described, as shown in **Figure 7**: a close-range approach (short position/direct view), a long-range approach (long position/indirect view),[5-7] and an intermediate-range approach.[4,7] However, there is no standardized consensus on these techniques. The essential consideration is to adjust the scope's position and orientation as the endoscopist assesses papillary morphology and the bile duct axis.

For deep biliary cannulation, rather than pushing the cannula forcefully into the bile duct, the operator should gently withdraw the scope while gradually reducing the upward angulation and slightly pulling back the cannula. This maneuver helps align the cannula with the axis of the bile duct, thereby facilitating deeper cannulation (**Figure 8**).[5]

(II) Guidewire-assisted cannulation

Wire-guided cannulation (WGC) is a technique for deep biliary cannulation performed without contrast medium injection, using a preloaded guide wire (GW) in advance.[8] There are two approaches to advancing the guidewire into the bile duct: one method involves gently contacting the papilla with the cannula while maneuvering the GW to locate the bile duct, and the other involves extending the GW

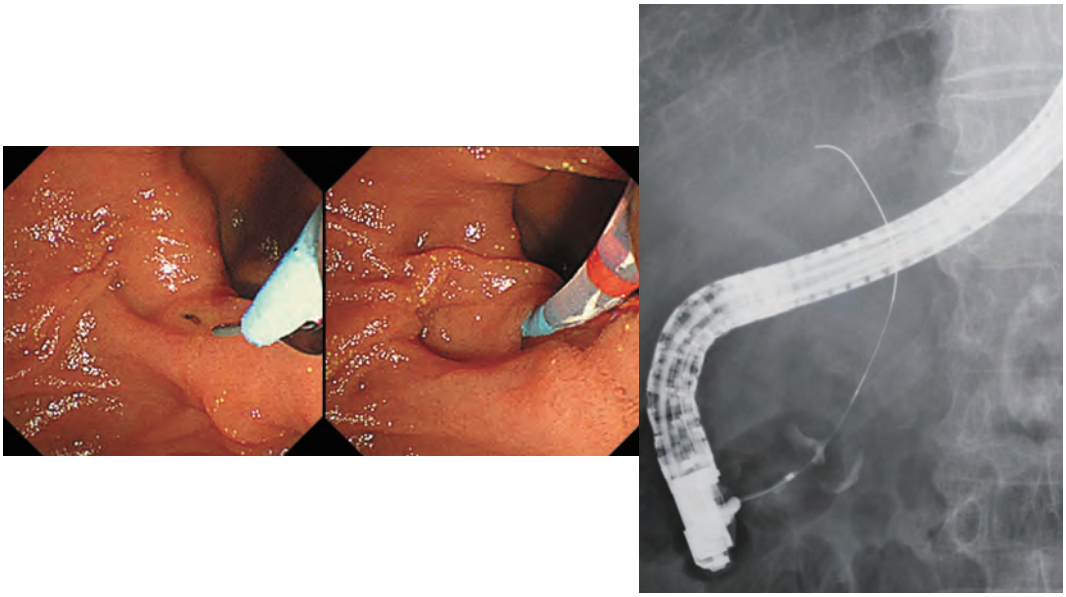


Figure 9 Wire-guided cannulation (WGC) approach.
(Cited from Literature 5)

slightly from the catheter tip and advancing it into the bile duct without contacting the papilla with the cannula (**Figure 9**).[5] In addition to standard cannulas, an endoscopic sphincterotomy (EST) knife is also useful for wire-guided cannulation. When using an EST knife, it is important to extend it into the duodenal lumen to allow fine adjustments to the blade tension.

Once the cannula or EST knife is properly directed toward the bile duct, the preloaded GW should be advanced separately. If the GW proceeds smoothly without resistance, it is likely correctly positioned within the bile duct. After advancing the GW to a certain extent, fluoroscopic confirmation should be made to verify its direction. As the GW is correctly oriented toward the bile duct, a catheter should then be inserted along the wire.

A potential issue with wire-guided cannulation is the risk of edema of papilla or perforation, particularly when the guidewire is manipulated by an inexperienced endoscopist or assistant. Therefore, careful and delicate handling of the GW is vital.

5. Techniques for Challenging Biliary Cannulation

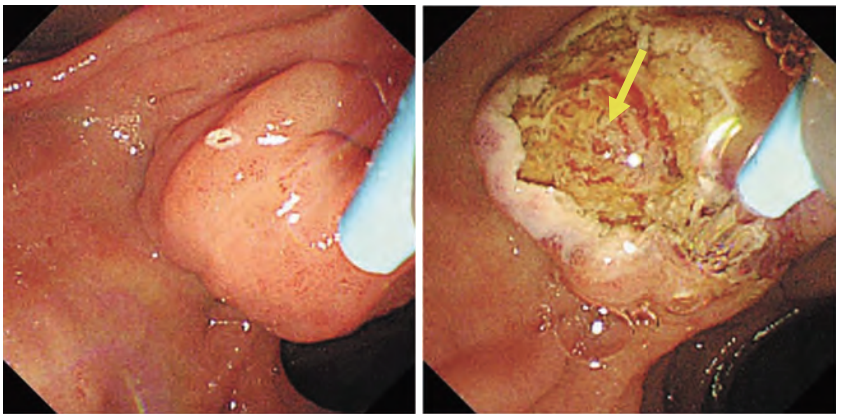
(1) Cannula exchange

Switching to a different cannulation device often improves the success rate of biliary cannulation by allowing more precise control of tip orientation, in addition to standard maneuvers such as scope manipulation, angulation, and elevator use. In particular, devices such as an endoscopic sphincterotomy (EST) knife[9] or a bendable catheter facilitate cannulation, thereby allowing directional changes at the tip (**Figure 10**).



Figure 10 Papilla located inside a diverticulum.

Biliary cannulation was achieved using the SwingTip® catheter.



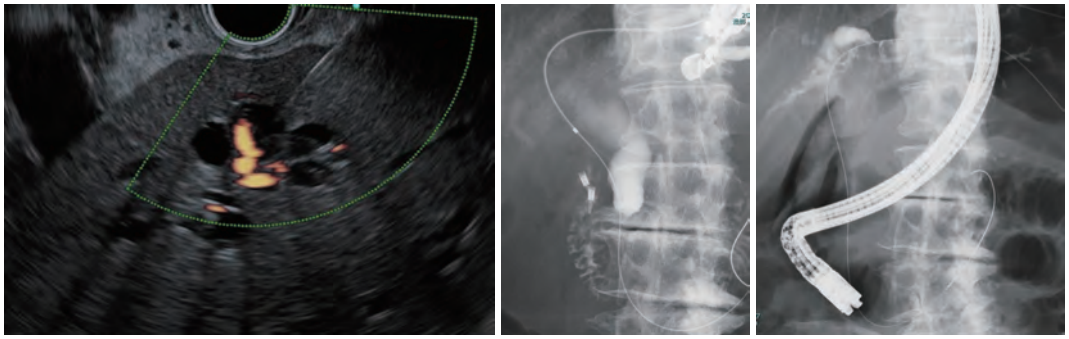
a | b

Figure 11 Precut method (Freehand technique).

Using a needle knife, a shallow incision is made starting from the mucosal surface of the papilla (a), allowing identification of the bile duct orifice and enabling biliary cannulation (b).

Table 1 Precut techniques.

1. Using a needle knife
1) Freehand starting at orifice
2) Freehand fistulostomy starting above orifice (infundibulotomy)
3) Over pancreatic stent
2. Using a sphincterotome
1) Papillary roof incision
2) Pancreatic sphincter precutting
3) Intramural incision technique



a | b | c

Figure 12 EUS-guided rendezvous technique.

a: The intrahepatic bile duct is punctured with a convex-type EUS.
b: A guidewire is advanced across the papilla into the duodenum.
c: The endoscope is switched to a duodenoscope to perform biliary cannulation.

(2) Pancreatic guidewire–assisted cannulation

A technique in which a guidewire (GW) is placed in the pancreatic duct can also assist biliary cannulation.[10] In this approach, a GW is first placed in the pancreatic duct, and then a cannula is inserted through the same channel, targeting the left upper side of the already positioned GW. This method is particularly useful in cases where the papilla is highly mobile, the oral protrusion is pronounced, the lower bile duct has a long narrow distal segment, or there is a parapapillary diverticulum. However, because pancreatography and guidewire (GW) placement are involved, the risk of post-ERCP pancreatitis (PEP) should be anticipated.

(3) Precut (access) sphincterotomy

Another approach is a precut technique in which a needle-knife[11] is used to incise the papillary roof (papillotomy) to obtain biliary access. There are two main variations: direct incision at the papillary orifice and creation of an artificial fistula at the oral protrusion (infundibulotomy). The former is performed either freehand or with a pancreatic stent in place (**Figure 11**). If a guidewire (GW) has been placed in the pancreatic duct, a needle-knife (or sphincterotome) is used to perform a transpancreatic precut, incising from the pancreatic orifice toward the bile duct axis (11-12 o'clock) to obtain biliary access. Infundibulotomy is also effective in treating impacted stones (**Table 1**).

(4) Two-device-in-one-channel method

For cases involving a periampullary diverticulum, the two-device-in-one-channel method is effective. This technique involves grasping the duodenal mucosa at the distal rim of the diverticulum with biopsy forceps or bowel grasper and applying downward traction. This maneuver allows a papilla located within the diverticulum to be pulled out into the duodenal lumen,[12] making biliary cannulation more feasible.

(5) Rendezvous technique

When percutaneous biliary access such as percutaneous transhepatic biliary drainage (PTBD) or percutaneous transhepatic gallbladder drainage (PTGBD) is already in place, a rendezvous approach is used. A guidewire is advanced antegrade through the percutaneous tract and across the papilla into the duodenal lumen. The wire is then captured with the duodenoscope (e.g., snare or grasping forceps) and externalized through the instrument channel to facilitate retrograde biliary cannulation. The approach facilitates bile duct access. More recently, the EUS-guided rendezvous technique has been introduced, in which a GW is guided into the duodenal lumen after the puncture in the intrahepatic bile duct or extrahepatic bile duct under endoscopic ultrasonography (EUS) guidance, followed by duodenoscope-assisted biliary access (**Figure 12**).[13)]

6. Adverse Events and Postprocedural Management

Adverse events associated with ERCP include acute pancreatitis, bleeding, and perforation. According to *Report on the Seventh National Survey on Gastrointesinal Endoscopy- related Adverse Events for Three Years: From 2019 to 2021*, the adverse event rates were 0.169% for diagnostic ERCP and 1.619% for therapeutic ERCP. Among therapeutic procedures, the adverse event rates were 1.258% for endoscopic biliary stenting (EBS) / endoscopic naso-biliary drainage (ENBD) / endoscopic nasogallbladder drainage (ENGBD), 1.776% for endoscopic sphincterotomy (EST) /precutting, 1.797% for endoscopic lithotripsy, 0.348% for endoscopic pancreatic stenting (EPS) / endoscopic nasopancreatic drainage (ENPD), 3.462% for endoscopic papillary balloon dilation (EPBD), and 2.899% for endoscopic papillary large balloon dilation (EPLBD). The overall mortality rate for diagnostic and therapeutic ERCP combined was 0.031%.[14)] Acute pancreatitis is the most common ERCP-related adverse event and carries a risk of severe disease. Careful attention to prevention and early recognition is required.

Post-ERCP pancreatitis (PEP) is thought to be multifactorial. One proposed mechanism involves obstruction of pancreatic juice outflow due to papillary edema or spasm of sphincter of Oddi, which increases pancreatic ductal pressure and causes microvascular injury. These changes may be precipitated by contrast injection into the pancreatic duct or by cannulation-related trauma. ultimately resulting in injury to ductal epithelial and acinar cells.

Risk factors for post-ERCP pancreatitis include sphincter of Oddi dysfunction (SOD), female, and a history of pancreatitis as patient-related factors.[15)] Procedure-related factors include precutting, pancreatic duct contrast injection, repeated cannulation (over 5 attempts), endoscopic pancreatic sphincterotomy (EPST), endoscopic papillary balloon dilation (EPBD), and retained bile duct stones.[16)]

Regarding post-ERCP pancreatitis prevention, evidence for the efficacy of protease inhibitors in preventing PEP remains inconclusive, thus further evaluation of indications for their use is needed.[17)] The efficacy of rectal non-steroidal anti-inflammatory drugs (NSAIDs) (indomethacin or diclofenac sodium, 50–100 mg) for post-ERCP pancreatitis prevention has been reported.[18)]

Prophylactic pancreatic stent (EPS) is effective in preventing post-ERCP pancreatitis in high-risk patients and is highly recommended.[19)] A spontaneous dislodgement stent without a distal flap has been reported as beneficial. However, there is a risk of failure to dislodge or premature dislodgment, so caution is required for its use.

Post-ERCP pancreatitis is generally diagnosed based on the presence of abdominal or back pain lasting over 24 hours and hyperamylasemia (serum amylase over 3 times the upper normal limit).[20)]

For early detection, measurement of serum pancreatic enzymes (primarily amylase, and often lipase) 2 to 6 hours after ERCP is commonly recommended, with a threshold of 2 or 3 times the upper limit of normal (ULN).[16] CT imaging also should be performed in patients presenting with abdominal symptoms.

For postprocedural management, patients should be fasted on the day of the procedure and receive intravenous fluid therapy, with continuous monitoring of vital signs and abdominal symptoms. In cases where pancreatitis is suspected, immediate fasting should be initiated along with adequate intravenous fluid administration, including antibiotics and protein synthesis inhibitors. Furthermore, measures should be taken to ensure respiratory and circulatory stabilization as well as pain control.

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Akio Katanuma and Shinji Okaniwa

2 ERCP-Related Procedures in Surgically altered anatomy

1. Indications and Contraindications

(1) Indications

Endoscopic retrograde cholangiopancreatography (ERCP) is indicated for diseases affecting the biliary tract (bile duct and gallbladder), pancreatic duct, papillary region, and anastomotic sites (biliary/pancreatic-jejunal). The indications are similar to those for ERCP in patients with normal anatomy and include biliary tract tumors, pancreatic tumors, ampullary tumors, bile duct stones, pancreatic stones, biliary obstruction or bile duct dilatation, and pancreatic duct stenosis or dilatation. Meanwhile, ERCP is indicated in cases of anastomotic stricture at the hepaticojejunostomy or pancreaticojejunostomy site, as well as in cases of intrahepatic stones.

(2) Contraindications

Contraindications are the same as those for other endoscopic procedures and apply in situations where the potential risks outweigh the expected benefits. The complexity of reaching the papilla or the hepaticojejunostomy or pancreaticojejunostomy site varies significantly depending on the surgical reconstruction, and a prolonged procedure time is required in some cases. Therefore, the indications for ERCP in patients with surgically altered anatomy should be carefully determined based on the expertise and experience of endoscopists as well as the patients' conditions. The following are generally accepted contraindications:

- Severely compromised general condition
- Recent surgery or gastrointestinal perforation
- Severe cardiovascular or respiratory disease
- History of anaphylactic shock due to iodine allergy
- Severe inflammatory conditions, such as acute pancreatitis, when the procedure could exacerbate the condition. Even so, ERCP is useful in cases of common bile duct stone-induced pancreatitis or acute obstructive suppurative cholangitis.
- Failure in obtaining informed consent for the procedure

2. Reconstruction Methods

Common gastric reconstruction methods after gastrectomy with Billroth I, Billroth II, Roux-en-Y with hepaticojejunostomy, double-tract reconstruction, and jejunal interposition. In recent years, Roux-en-Y reconstruction has been increasingly adopted. Reconstruction methods following pancreaticoduodenectomy include variations such as the modified Child method, the Whipple method, and the Imanaga method. In choledochectomy, reconstruction is often performed using Roux-en-Y hepaticojejunostomy, particularly in cases of hilar cholangiocarcinoma, upper bile duct carcinoma, or congenital biliary dilatation, where gastric preservation is preferred. A schematic representation of these reconstruction methods is provided in **Figure 1**.

3. Selecting the Appropriate Endoscope for Different Reconstructions

(1) Billroth I reconstruction

A retrograde-viewing endoscope (JF-260V or TJF-Q290V, Olympus) is used in patients with bowel reconstruction, allowing procedures to be performed in a manner largely similar to standard ERCP. Stretching within the duodenum is generally unnecessary, and the endoscope typically advances linearly from the gastric remnant to the major papilla. However, postoperative altered anatomy tends to make it difficult to align the endoscope with the bile duct axis. In such cases, biliary cannulation is performed using a sphincterotome.

(2) Billroth II reconstruction and Child reconstruction

There are reports of successful use of retrograde-viewing endoscopes for ERCP-related procedures. However, in cases with a long and sharply angulated afferent loop, the risk of intestinal perforation increases, making the procedure challenging.[1)] Other reports also describe the use of forward-viewing endoscopes (standard esophagogastroduodenoscope) or oblique-viewing endoscopes (GIF-XK240, Olympus) for ERCP-related interventions. Compared with the standard forward-viewing endoscope, the oblique-viewing endoscope positions the instrument channel at the 11 o'clock orientation and includes an elevator mechanism, which facilitates alignment with the bile duct axis.[2)] More recently, balloon-assisted enteroscope (BAE) has come into use.[3-5)]

(3) Roux-en-Y reconstruction

In patients with Roux-en-Y , reaching the blind end with retrograde-viewing, forward-viewing (upper gastrointestinal), or oblique-viewing endoscopes is generally challenging because of the long distance, pronounced angulation, and adhesions of the small bowel.[6-8)] In particular, Roux-en-Y with hepaticojejunostomy accompanied with gastric preservation is often challenging, compared with total gastrectomy.[9,10)] Although previous reports have described techniques using a small-caliber colonoscope, the success rate has been suboptimal. Recently, more reports have demonstrated the usefulness of BAE for various procedures.[11-18)]

a



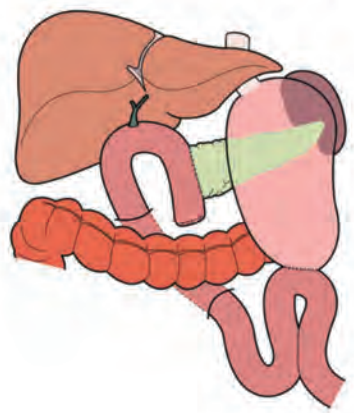
Total gastrectomy with
Roux-en-Y (TG + RY)

b



Distal gastrectomy with
Billroth II (DG + BII)

c



Pancreatoduodenostomy
with hepaticojejunostomy
(PD + HJ)

Figure 1 **Representative methods of gastrointestinal reconstruction**

a: Total gastrectomy with Roux-en-Y (TG + RY)
Based on Scott HW Jr, Law DH 4th, Gobbel WG Jr, et al: Clinical and metabolic studies after total gastrectomy with a Hunt-Lawrence jejunal food pouch. Am J Surg 1968; 115:148–156

b: Distal gastrectomy with Billroth (DG + BII)
Based on Wirts CW, Templeton JY 3rd, Fineberg C, et al: The correction of postgastrectomy malabsorption following a jejunal interposition operation. Gastroenterology 1965; 49:141–149

c: Pancreatoduodenostomy with hepaticojejunostomy (PD + HJ)
Based on Edward LB III, Robert Z: The Pancreas. Textbook of Surgery, 13th ed. WB Saunders Company, Philadelphia, 1986, p.1196

Table 1 Specifications of balloon-assisted endoscopes.

	DBE		SBE		
Model	EN-450T5	EI-580BT	SIF-Q260	SIF-H290S	SIF-H190
Tip diameter (mm)	9.4	9.4	9.2	9.2	9.2
Insertion tube diameter (mm)	9.3	9.3	9.2	9.2	9.2
Working length (mm)	2,000	1,550	2,000	1,520	2,000
Total length (mm)	2,300	1,850	2,345	1,830	2,280
Instrument port diameter (mm)	2.8	3.2	2.8	3.2	3.2

BE: Double-balloon endoscope
SBE: Single-balloon endoscope

4. Practical Procedures Using Balloon Assisted Enteroscope

(1) Balloon assisted enteroscope

ERCP-related procedures in patients with surgically altered anatomy are often performed using balloon-assisted enteroscope (BAE). The following provides an overview of procedures using BAE. Currently, additional reimbursement is granted for ERCP performed with BAE, allowing an extra 3,500 points to be added to the conventional ERCP procedure score. As a result, the use of BAE for ERCP is expected to become increasingly widespread.

Two commercially available BAEs include the double-balloon enteroscopes (DBEs) from Fujifilm and the single-balloon enteroscopes (SBEs) from Olympus (**Table 1**). Both systems offer two endoscope lengths: the standard type with a working length of 200 cm and the short type measuring approximately 150 cm (DBE: 155 cm and SBE: 152 cm). Although standard-type BAE is effective in reaching the target site, it has limitations related to the length of devices used in endoscopic retrograde cholangiopancreatography (ERCP). These devices are often not long enough to pass through the instrument channel, which restricts the procedure's effectiveness. When using the standard type, one technique involves inflating the overtube balloon to anchor the endoscope in the intestine, then withdrawing the endoscope alone. The overtube is then cut in its midsection, and a conventional forward-viewing endoscope is inserted for ERCP. However, this method is not commonly practiced.[13)]

Numerous reports in recent years have demonstrated the usefulness of BAE for ERCP-related procedures in patients with surgically altered anatomy, leading to the introduction of short-type BAEs to enhance procedural efficiency and success. With a working length of approximately 150 cm and an instrument port diameter of 3.2 mm, these short-type BAEs allow the use of various ERCP devices. They have become the first option at many institutions today. Both short DBEs and short SBEs have been evaluated in Japanese multicenter studies, demonstrating their efficacy.[15,18)] In a study using short DBEs for 311 cases, the overall procedural success rate was reported to be 92.3%.[15)] In cases using short SBEs to access an intact papilla in patients with surgically altered anatomy, the analysis showed a procedural success rate of 74.9% based on 1,318 cases.[18)] Both techniques have shown favorable outcomes.

The latest short-type DBE as shown in **Figure 2a** (working length: 155 cm, instrument port diameter: 3.2 mm, EI-580BT) is equipped with an advanced force transmission function and an adaptive bending system, which improves insertion capability, compared with conventional models. Furthermore, enhancements in angulation mobility and in the design of the instrument channel facilitate successful



a | b

Figure 2 **Balloon-assisted enteroscopes.**

a: Double-balloon enteroscope (Fujifilm)
b: Single-balloon enteroscope (Olympus)

completion of ERCP-related procedures. The latest short-type SBE as shown in **Figure 2b** (working length: 152 cm, instrument port diameter: 3.2 mm, SIF-H290S) features a passive bending function that allows the endoscope to navigate sharp angulations more smoothly by adapting to intestinal angulation.[19)]

(2) Procedural technique and tips

1) Intraoperative and postoperative patient management

(I) Preprocedure

Comprehensive informed consent should be obtained for both balloon-assisted enteroscope (BAE) and ERCP-related procedures, ensuring that patients fully understand the difficulty in surgically altered anatomy. Furthermore, additional explanations should be sufficiently given such as alternative treatment options, the facility's success rate, and potential adverse events such as bleeding, gastrointestinal perforation, and post-ERCP pancreatitis. As with ERCP-related procedures in patients with normal anatomy, premedications such as analgesics, sedatives, and antispasmodics could be used.

For analgesia, 35 mg of pethidine hydrochloride and 2 mg of midazolam are intravenously administered, after that additionally administered if needed. For antispasmodics, scopolamine butylbromide is prepared for use. Glucagon is used in elderly patients or in those with ischemic heart disease, prostatic hypertrophy, or glaucoma. Flumazenil is prepared as an antagonist. Patients are required to fast on the day of the procedure, with intravenous fluids administered as necessary.

(II) Postprocedure

After the procedure, symptoms, vital signs, and blood tests including white blood cell count, serum amylase, and C-reactive protein (CRP) should be monitored to ensure appropriate postoperative care. Although there is no definitive evidence supporting the use of protease inhibitors or antibiotics, they could be administered when necessary.

2) Scope insertion to the blind end (Afferent loop)

To perform ERCP-related procedures in patients with surgically altered anatomy, it is essential to reach the target site. Before scope insertion, it is important not only to review the surgical history and reconstruction method but also to predict the length from the branching point to the target site. If the endoscopist initiates insertion without this information, unexpected branching, such as Braun anastomosis,

may be encountered during the procedure, causing confusion.

(I) Billroth II reconstruction and Child reconstruction

In Billroth II reconstruction and Child reconstruction, the afferent loop typically runs superiorly and to the left beyond the anastomotic site. However, it is difficult for the endoscope to enter because the lumen exists in a collapsed state. To facilitate insertion, an overtube should be inserted carefully to prevent the endoscope from bending. Subsequently, similar to colonoscopy, the procedure involves carefully navigating angulated sites in the intestine, shortening the intestine, and advancing towards the blind end while minimizing the amount of air introduced.

Although reaching the deeper parts is usually easier in these cases, longer afferent loops could be complicated by adhesions. Braun anastomosis often results in a complex and winding passage. However, if utilized strategically, Braun anastomosis could actually facilitate reaching the blind end.

(II) Roux-en-Y reconstruction

In Roux-en-Y Reconstruction, it is often challenging to identify the Y anastomosis and guide the endoscope into the afferent loop. There are some methods that are helpful in identifying the afferent loop, such as using the suture line of the Y-limb anastomosis as a guide for insertion,[20] or spraying indigo carmine.[21] When the Y-limb has a steep angle, the endoscope tip tends to kink, and the applied force does not effectively reach the distal end of the endoscope. This makes it difficult to advance the endoscope. A basic technique in balloon-assisted endoscopy (BAE) that is helpful in such situations is the alternating maneuver of the endoscope and overtube, often referred to as juggling. Insertion is carried out gently, with particular attention to minimizing air insufflation throughout the process.[22] In Roux-en-Y reconstruction with gastrectomy, the endoscope should be inserted with caution, gently advancing it while forming a large loop and making sure not to shorten the intestinal tract during the process. However, in Roux-en-Y with hepaticojejunostomy, when the stomach is preserved, the goal is to achieve deep insertion by shortening the intestine. In this setting, excessive pushing is avoided, instead, angle manipulation is used effectively and the balloon is skillfully employed to aid insertion. In single balloon enteroscopy (SBE), the endoscope does not have a balloon at the tip, unlike double balloon enteroscopy (DBE). Therefore, after passing through an angulated site of the intestinal tract, the tip of the endoscope is sharply angulated to create a point of resistance by hooking onto the intestinal wall. While maintaining this position, the inflated overtube balloon is used to pull both the overtube and the endoscope together. This allows the intestine to be shortened and facilities further advancement.[23] The introduction of CO_2 is also an effective method. When insertion becomes difficult, CO_2 insufflation is used and abdominal compression is applied to the abdomen. Throughout the procedure, fluoroscopic guidance is used to monitor progress and ensure accuracy.

3) Biliary cannulation

The type of BAE determines the orientation and angle at which the catheter exits the endoscope. With a double-balloon endoscope (DBE), the catheter typically emerges towards the 5 to 6 o'clock orientation, whereas with a single-balloon endoscope (SBE), its generally emerges at the 7 to 8 o'clock orientation. These information should be confirmed before starting ERCP. A cannula with a straight, unbent tip should be selected to facilitate the procedure.

(I) Transpapillary approach

In Billroth II reconstruction, the papilla is typically observed in an upward-facing position, located on the left or upper side of the screen when the endoscope reaches the blind end. Since this orientation is the reverse of that in standard ERCP, the bile duct runs toward the 5 o'clock orientation. In DBE, deep

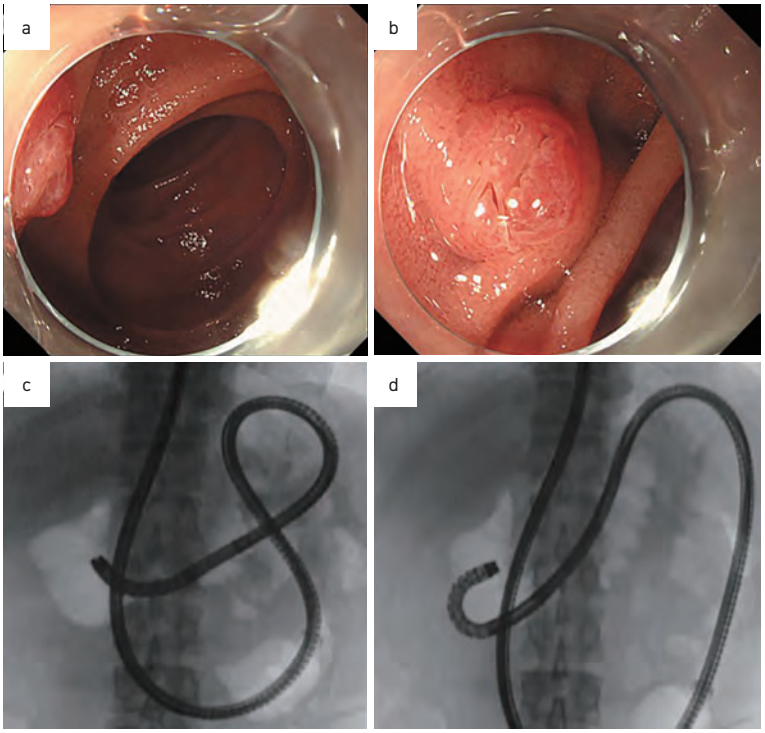


Figure 3 **Retroflex positioning using SBE.**

When the papilla is observed tangentially, biliary cannulation becomes difficult (a, c).
By applying the upward angulation and advancing the endoscope, retroflex position is achieved, allowing a frontal view of the papilla (b, d).

insertion of the overtube with loop reduction stabilizes the endoscope by securing the intestine with both the overtube balloon and the endoscope tip balloon. This positioning allows the papilla to be aligned properly so that the bile duct oriented toward the 11 o'clock orientation, allowing selective biliary cannulation. In SBE, the catheter exits from the 7 to 8 o'clock orientation of the endoscope. As a result, the catheter aligns naturally with the 5 o'clock orientation. Therefore, bile duct cannulation is attempted from the same endoscope position at which the papilla was first reached, without the need to significant angle or position adjustments.

In Roux-en-Y gastrectomy, the papilla is often visualized in an upward-facing position between the 11 and 1 o'clock orientations when the endoscope reaches the blind end, though its position could vary. When performing a procedure with an SBE, encountering a papilla positioned between 11 and 1 o'clock orientations could be challenging. This specific orientation typically requires a tangential endoscope approach. This makes cannulation more challenging. Attaching a distal cover on the endoscope tip helps in producing a frontal view. By angulating the endoscope upward at the inferior duodenal angulus and advancing it, the endoscope is rotated to create a J-turn (retroflex position). This allows for direct visualization of the papilla from the front, which is often useful for cannulation (**Figure 3**).[24] In DBE, an overtube is inserted deeply to stabilize the endoscope by gripping the intestine. The endoscope is then maneuvered to position the papilla at the 6 o'clock spot on the endoscopic screen, with the bile duct running in the 11 o'clock orientation. The position and direction typically make it easier to view the papilla directly. However, when the direct visualization is difficult, the retroflex position is selected to view the papilla directly (**Figure 4**). In challenging cases, even in surgically altered anatomy, cannulation

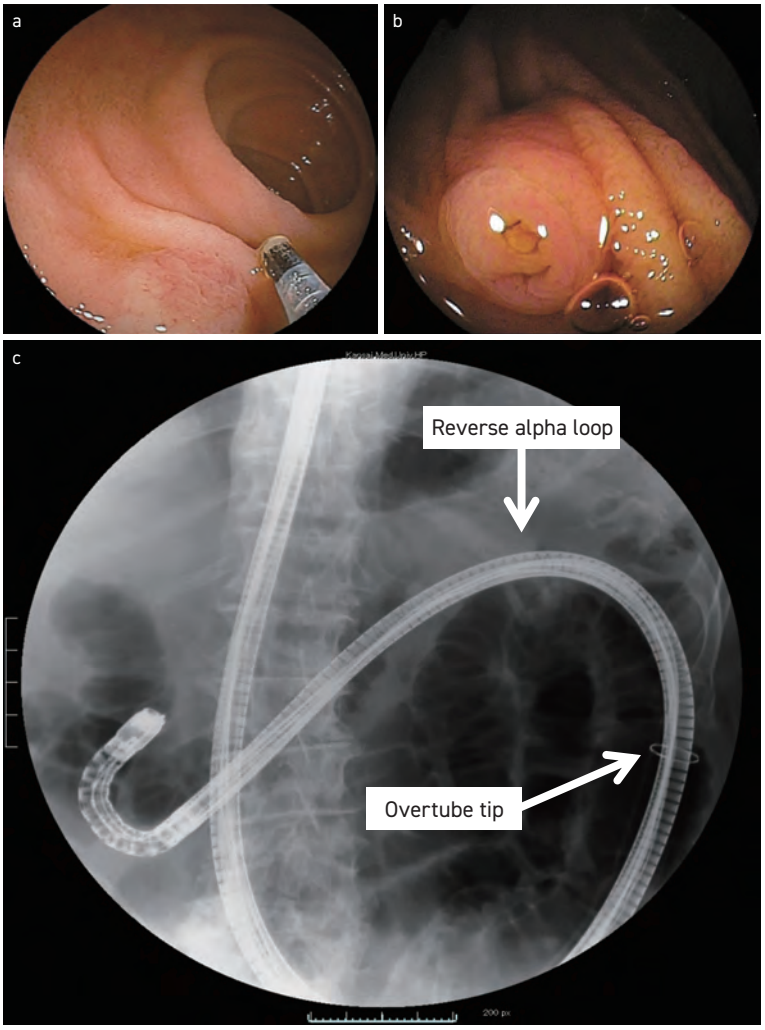


Figure 4 **Biliary cannulation in Roux-en-Y reconstruction using DBE.**

Even when the papilla is positioned at 6 o'clock, it is seen tangentially (a).
Retroflex positioning enables frontal visualization of the papilla (b, c).

via the pancreatic duct is effective. When a guidewire is placed in the pancreatic duct, pancreatic duct guidewire-assisted biliary cannulation is performed. As in standard ERCP, guidewire placement involves stabilizing the papilla and straightening the oral protrusion. In this approach, the pancreatic duct guidewire serves as a landmark indicating the direction of the pancreatic duct. This offers multiple advantages, especially in helping to maintain an appropriate distance from the papilla and enabling smoother execution of the procedure. In DBE, as in standard ERCP, the bile duct lies superior and to the left of the pancreatic duct, and this position facilitates biliary cannulation (**Figure 5**).

(II) Post-hepaticojejunostomy cases

In cases where hepaticojejunal anastomosis has been performed, detection of the anastomotic site is critical, such as after Roux-en-Y with hepaticojejunostomy following liver transplantation or congenital biliary dilatation surgery. In benign anastomotic strictures, the anastomotic opening is pinhole-sized, requiring careful identification. Even a small amount of bile leakage serves as a guide. Moreover, ulcer scar-like mucosa around the anastomosis could provide a promising lead.[25] In the malignant obstructions,

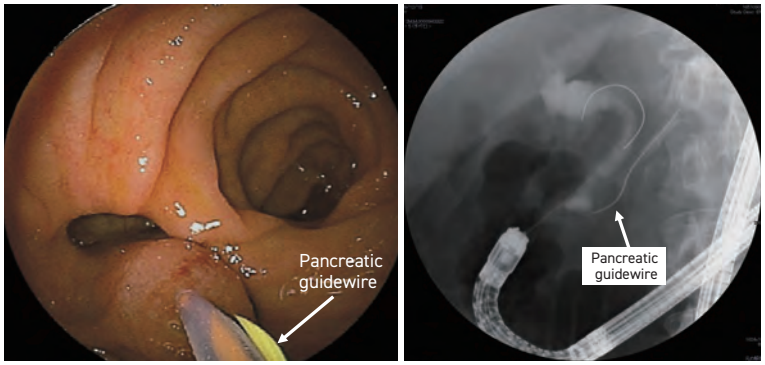


Figure 5 **Biliary cannulation via pancreatic guidewire placement using DBE.**

The upper left direction of the pancreatic guidewire indicates the bile duct (a).
Deep biliary cannulation was achieved (b).

the anastomotic site is usually more readily identifiable. Biliary cannulation through the site is often easier than through the papilla, but when the bile duct takes a steep course, a sphincterotome is required to adjust the cannulation angle.

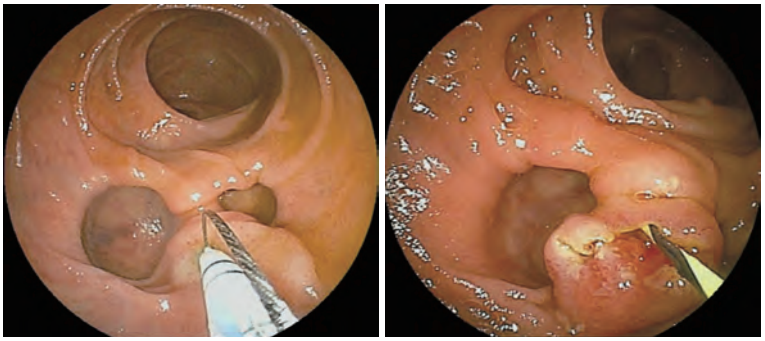
(III) Post-pancreaticojejunostomy cases

Reports on BAE-assisted pancreaticojejunostomy access remain limited, whereas endoscopic ultrasound (EUS) interventions have been more widely documented. The primary challenges in BAE-assisted endoscopic access include the tangential orientation of the pancreaticojejunostomy relative to the endoscopic field and the concealment of anastomotic site within mucosal folds. This makes the identification extremely difficult. Furthermore, the narrow intestinal lumen offers limited space for maneuvering, resulting in blind manipulation that complicates access to the pancreatic duct. However, recent reports offer endoscopic techniques utilizing a clear long cap attachment,[26] gel immersion,[27] and texture and color enhancement imaging to improve visibility.[5,28]

4) Papillary intervention

Papillary intervention includes endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), and endoscopic papillary large balloon dilation (EPLBD). In balloon-assisted enteroscope (BAE), EST is complicated due to difficulty in securing a clear view of the papilla and manipulating the sphincterotome. Therefore, this procedure should only be performed at facilities with highly experienced ERCP endoscopists. EST should be performed ideally using a device that allows guidewire-assisted placement, but the incision direction does not always align optimally. In such cases, switching to EPBD or EPLBD is recommended rather than persisting the procedure. Since BAE lacks an elevator mechanism, fine endoscope manipulation is required for incision. However, in double-balloon enteroscopy (DBE), positioning the papilla at the 6 o'clock orientation on the endoscopic view helps stabilize the papilla, allowing for safer EST with a stable field of view (**Figure 6**). In these days, a dedicated sphincterotome (CleverCut 3V, Olympus) designed for surgically altered anatomy has become commercially available, showing promise for using in single-balloon enteroscopy (**Figure 7**).[29]

For EPBD and EPLBD, the balloon size should be selected based on the bile duct diameter, under guidewire assistance. If the guidewire remains in place within the bile duct, inserting the balloon into the duct is straightforward.



a | b

Figure 6 **Endoscopic sphincterotomy (EST) using DBE.**

Positioning the major papilla at 6 o'clock orientation in the endoscopic field stabilizes the papilla and secures a stable view (a).
EST was safely performed (b).

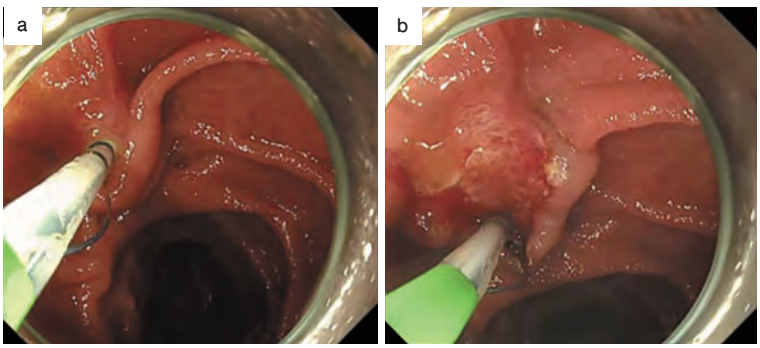


Figure 7 **SEST using a dedicated sphincterotome for reconstructed gastrointestine via SBE.**

Using the CleverCut 3V (Olympus), the blade was oriented toward the bile duct at the 5 o'clock orientation, enabling safe performance of EST.

5) Dilation at the site of hepaticojejunostomy

Dilation of the hepaticojejunostomy site is performed using a balloon dilation catheter (**Figure 8**). In cases where insertion is impossible, a dilator catheter is inserted first, followed by the dilation balloon. The balloon diameter should be selected according to the bile duct diameter, ranging from 4 to 10 mm.

6) Lithotripsy

In short-type BAE, almost all guidewire-assisted devices used for cases with normal anatomy are acceptable, such as mechanical lithotripters, basket catheters, and stone extraction balloon catheters. Endoscopic papillary large balloon dilation (EPLBD) is particularly effective for the removal of large stones or stacked stones (**Figure 9**). In BAE, controlling the axis while grasping stones with a retrieval basket is challenging, especially in cases with a dilated bile duct. As a result, stone retrieval is difficult, and complete removal in the initial procedure is mostly impossible.[30] If the procedure is expected to be prolonged, bile duct stent placement is preferred, allowing for a staged approach with stone removal performed in the next step.

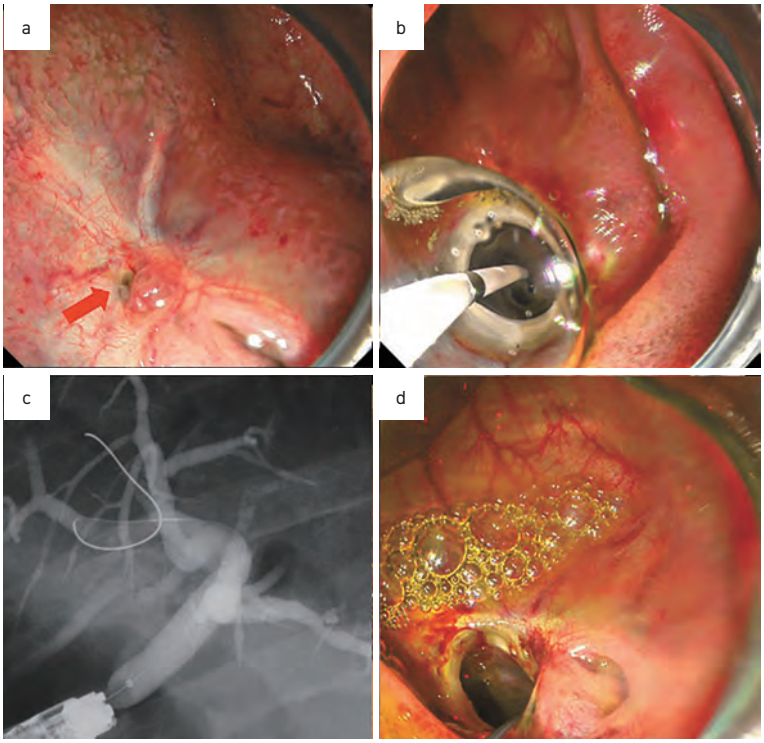


Figure 8 **Hepaticojejunostomy dilation.**

An obstruction at the hepaticojejunostomy site is distinct (arrow) (a).
Dilation was performed using an 8 mm balloon catheter designed for biliary dilation (b, c).
Significant improvement of the anastomotic stricture was confirmed (d).

7) Endoscopic biliary drainage

Biliary drainage using BAE has become increasingly common for bile duct obstructions. When placing a plastic stent or an endoscopic nasobiliary drainage (ENBD) tube, the choice between internal and external drainage should be decided based on the intended purpose and the patient's condition. The required stent length and shape should also be selected according to the target drainage area. During ENBD tube placement, the distance from the insertion site to the external body is longer than in typical anatomy. When the tube is advanced while the endoscope is being withdrawn, as in the usual method, it could end up too short. If no further adjustments are made before removing the endoscope, the successfully placed tube could be accidentally pulled out. In such cases, using a contrast catheter as a pusher helps ensure proper tube placement. For metal stent placement, the introduction of short-type BAE with a 3.2 mm instrument channel has expanded the range of available stents and placement techniques.[31,32] In cases of unresectable malignant biliary obstruction, a covered metal stent is placed for distal biliary obstructions (**Figure 10**). For perihilar biliary obstructions, multiple stents are deployed using the partial stent-in-stent technique to accommodate the necessary drainage area (**Figure 11**).

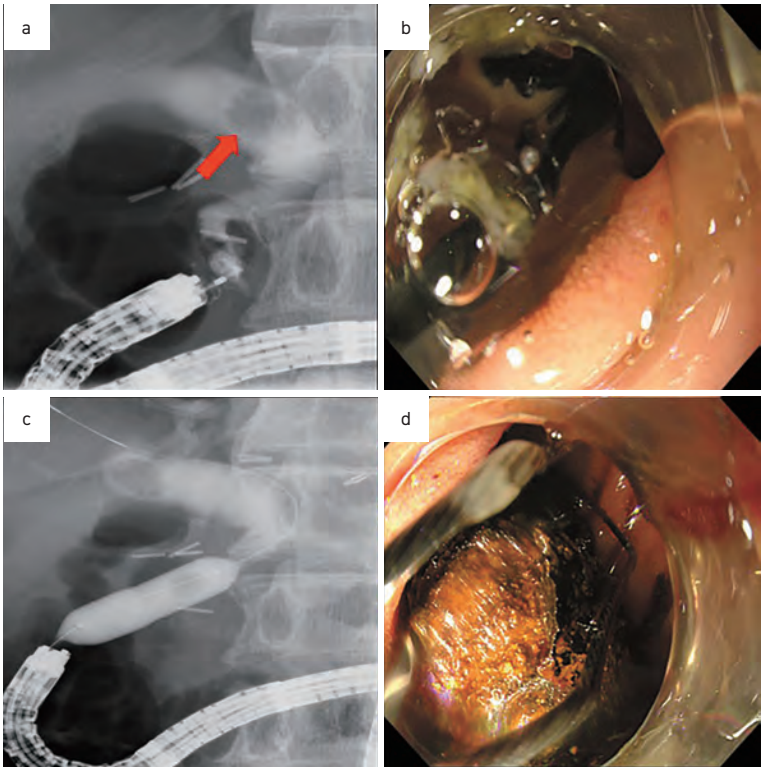


Figure 9 EPLBD with stone extraction.

Cholangiography shows a slightly less than 2 cm radiolucent area (arrow) (a).
Endoscopic papillary large balloon dilation (EPLBD) was performed (b, c).
Following EPLBD, the stone was successfully removed without fragmentation (d).

5. Precaution for Adverse Events

When performing ERCP-related procedures in patients with surgically altered anatomy, it is necessary to keep in mind that various adverse events may occur.

In a multicenter collaborative study, the rate of adverse events with double-balloon enteroscopy (DBE) was reported at 10.6%,[15] while in a similar study using single-balloon enteroscopy (SBE), the rate was 7.7%.[18] Complications could occur during or after the procedure. In ERCP-related procedures using balloon enteroscopy, attention should be paid to gastrointestinal perforation. When inserting the endoscope or shortening the intestinal tract, it should be kept in mind that the intestinal tract is in a post-surgical state and probably has adhesions. Therefore, forced insertion or shortening should be avoided. When strong resistance is encountered during endoscope insertion, the endoscope should be withdrawn until the resistance is relieved, rather than continuing to advance against resistance. After that, reinsertion could be performed. This resistance could be detected only through the endoscope in use, so the endoscopist is required to make careful assessment. In Billroth II reconstruction, it is reported that patients with short afferent loops were prone to perforation,[33-35] so the procedure should be performed very carefully. In cases where this procedure is difficult, it is necessary to consider treatment using other modalities such as percutaneous procedures or procedures using endoscopic ultrasound, instead of BAE.

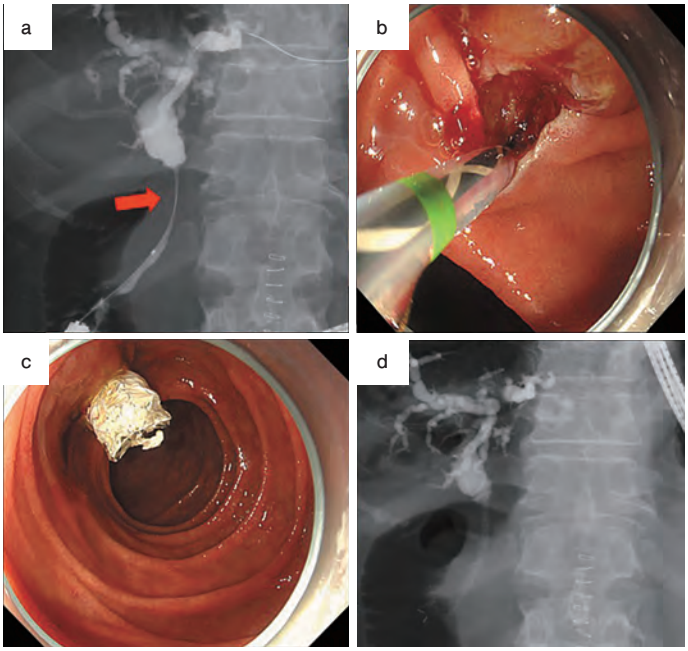


Figure 10 **Distal malignant biliary obstruction treated with covered metal stent.**

Cholangiography reveals a distal malignant biliary obstruction (arrow) (a).
EST was performed (b).
A covered metal stent was deployed (c, d).

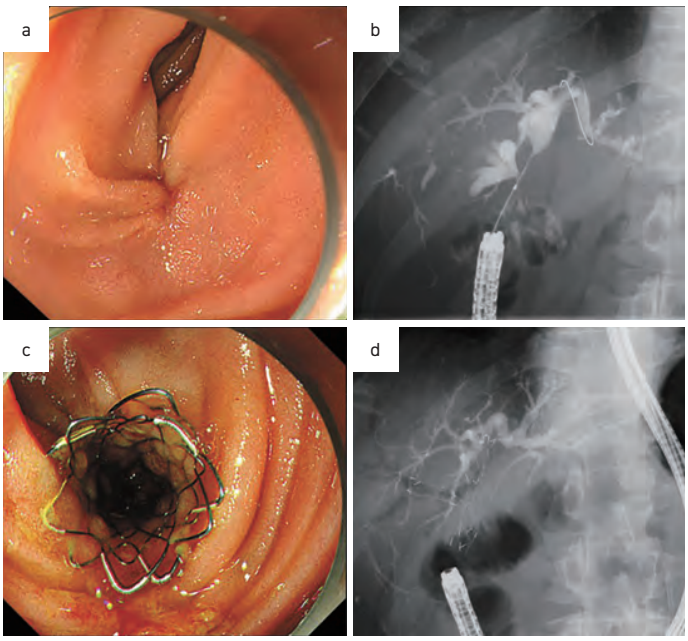


Figure 11 **Hilar malignant biliary obstruction managed by multi-stenting with partial stent-in-stent technique.**

The hepaticojejunostomy site is obstructed (a).
Cholangiography shows no communication between the right and left intrahepatic bile ducts, presenting a complete separation (b).
Uncovered metal stents were deployed using the partial stent-in-stent technique (c, d).

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Yuki Tanisaka and Masaaki Shimatani

3 Peroral Cholangioscopy and Peroral Pancreatoscopy

1. Overview

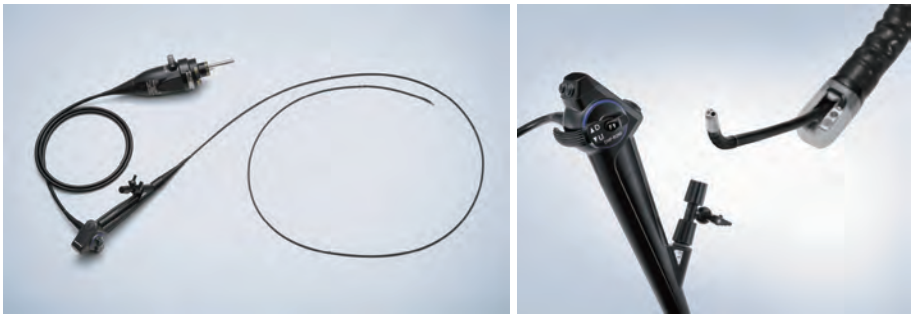
Peroral cholangioscopy (POCS) and peroral pancreatoscopy (POPS) involve the direct insertion of a slim endoscope into the bile duct or pancreatic duct, allowing the acquisition of high-resolution images of the biliary and pancreatic mucosa. These procedures are particularly valuable for the diagnosis of biliary and pancreatic diseases. In addition to direct visualization, they enable targeted biopsy sampling under direct vision, thereby facilitating both detailed morphological and pathological assessment of biliary and pancreatic lesions. Moreover, beyond diagnostic applications, these endoscopic techniques have been increasingly adopted for therapeutic interventions, such as lithotripsy for biliary stones and pancreatic stones.[1,2)]

2. Type

POCS is broadly categorized into two types: one is mother-baby POCS, in which a cholangioscope is introduced through the instrument channel of the duodenoscope for transpapillary insertion, and the other is peroral direct cholangioscopy (PDCS), in which a slim endoscope is inserted directly into the bile duct via the papilla. In POPS, mother-baby pancreatoscopy is common, whereas direct pancreatoscopy has only been reported in a limited number of cases.[3-6)] Since these endoscopes were first developed in the 1970s using fiberoptic technology, the early cholangioscopes had poor image quality and limited diagnostic utility, and could not accommodate many therapeutic instruments because of their narrow instrument channels.[7)] In 2003, the transition to electronic cholangiopancreatoscopy significantly improved image resolution, and the integration of narrow-band imaging (NBI) (available in Olympus CHF-B290, CHF-B260, and CHF-BP260) further enhanced mucosal visualization.[8,9)]

Traditional mother-baby systems required two operators to manipulate both endoscopes. However, in 2005, a single-operator system was developed, using a disposable cholangioscope (SpyGlass™ System from Boston Scientific). This innovation enabled a single endoscopist to operate the baby endoscope.[10)] Initially fiberoptic-based, the SpyGlass™ system was upgraded in 2015 to a digital version (SpyGlass™ DS Cholangiopancreatoscopy System), offering enhanced image quality, improved safety, and greater ease of navigation.[11,12)] Today, the products of these two companies are primarily used. The Olympus CHF-B290 (**Figure 1**) and CHF-B260 are electronic endoscopes with a two-way steerable catheter tip, NBI capability, high-resolution imaging, and superior light intensity.

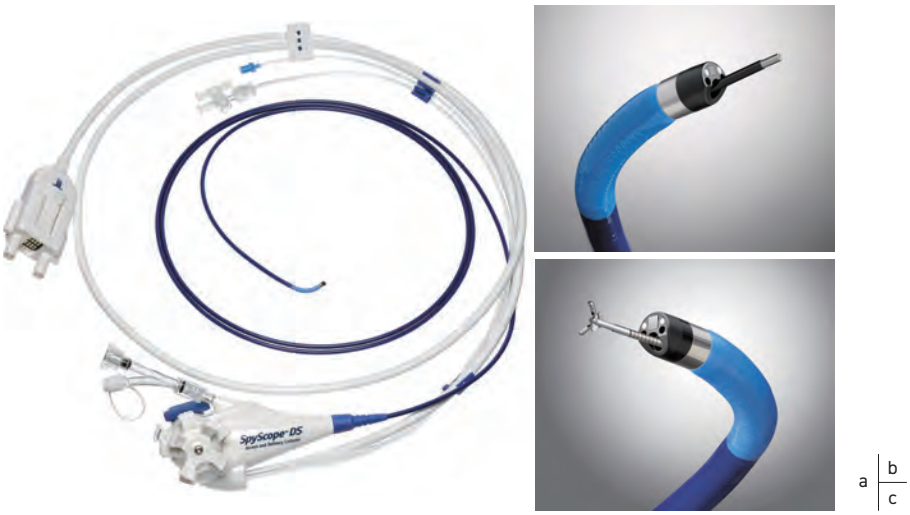
In contrast, the SpyGlass™ DS is disposable (**Figure 2**), eliminating concerns regarding water leakage



a | b

Figure 1 External view of the biliary cholangioscope CHF-B290 from Olympus.

a: Overall appearance of the device
b: On the left, the control section is shown; on the right, the baby endoscope (CHF-B290) is being inserted into the instrument channel of the mother endoscope (TJF-Q290V).



a | b / c

Figure 2 External view of the SpyGlass™ DS biliary cholangioscope from Boston Scientific.

a: General appearance
b: The tip of the cholangioscope along with an electrohydraulic lithotripsy (EHL) probe
c: The distal tip of the cholangioscope and dedicated biopsy forceps (SpyBite™ Max) are shown.

due to endoscope damage. Its catheter tip is steerable in four directions, thereby improving operability. New cholangioscopy systems were also introduced in 2022 and 2023, reflecting continued advancements in the field (**Figures 3 & 4**).

3. Indications for Peroral Cholangioscopy

POCS is primarily used for the differential diagnosis of biliary strictures, obstructions, and bile duct lesions. In cases of localized cholangiocarcinoma (nodular or papillary tumors with villous features), where the tumor tends to spread superficially along the mucosa, POCS is particularly useful in determining the extent of tumor invasion for surgical planning. Among cholangiocarcinomas, distal bile duct tumors often present with a papillary growth pattern, making localized distal cholangiocarcinomas ideal candidates for POCS.



a | b

Figure 3 **External view of the eyeMAX biliary cholangioscopy system from M.C. Medical.**

a: The control section of the device
b: The tip of the cholangioscope along with its dedicated biopsy forceps



a | b

Figure 4 **External view of the DRES cholangioscopy system from Japan Lifeline.**

a: The control section of the device
b: The tip of the cholangioscope shows both the dedicated biopsy forceps and a detachable CMOS camera.

Since cholangiography performed during endoscopic retrograde cholangiopancreatography (ERCP) provides only indirect imaging of intraductal lesions, direct visualization with cholangioscopy offers significant diagnostic advantages. However, in some cases especially in benign conditions direct visual findings may remain inconclusive.

In therapeutic applications, POCS is employed for the treatment of bile duct stones that are difficult to remove with conventional ERCP techniques such as basket or balloon catheters, or standard lithotripsy devices. Under cholangioscopic guidance, electrohydraulic lithotripsy (EHL) or laser lithotripsy can be performed to fragment the stones for extraction. Cholangioscopy is also useful for the retrieval of migrated or difficult-to-remove plastic stents from the bile duct under direct vision using biopsy or basket forceps. Additionally, in cases where guidewire placement into the cystic duct during endoscopic gallbladder drainage (EGBD) is challenging, cholangioscopy enables direct visualization and precise guidewire placement into the cystic duct. Other therapeutic applications include local treatments for biliary tumors, such as photodynamic therapy (PDT) and radiofrequency ablation (RFA).

4. Indications for Peroral Pancreatoscopy

POPS is primarily used for the evaluation of intraductal pancreatic lesions. In particular, intraductal papillary mucinous neoplasms (IPMNs) frequently exhibit intraductal extension and skip lesions, making pancreatoscopy especially valuable for determining the extent of tumor involvement. However, POPS is not always indicated for patients with IPMN. Its application is mainly reserved for situations in which surgical resection is planned and preoperative assessment of lesion extent is required. This includes not only main duct-type IPMN but also branch duct-type and mixed-type IPMN when tumor extension into the main pancreatic duct is suspected.

In therapeutic applications, POPS is used for pancreatic stone removal and retrieval of migrated pancreatic duct stents. However, the procedure is feasible only in cases where the main pancreatic duct is sufficiently dilated to allow POPS insertion. Since direct observation of strictured segments poses a risk of post-ERCP pancreatitis, careful patient selection is required.

5. Practical Application of Peroral Cholangioscopy and Pancreatoscopy

In mother-baby digital cholangiopancreatoscopy, the Olympus duodenoscopes TJF-Q290V and TJF-260V (both with a 4.2-mm instrument channel) are commonly used as the mother endoscope. The use of a baby endoscope with an outer diameter ranging from 2.6 mm to 3.3 mm is theoretically possible with the JF-260V. However, the larger-channel TJF-260V is recommended for safe handling. Care should be taken with this duodenoscope, as its V-system has an internal guidewire lock at the elevator of the duodenoscope, which increases the risk of damaging the rubber portion at the baby endoscope tip during elevator manipulation. When using the disposable SpyGlass™ DS, the JF-260V is an acceptable choice as the mother endoscope, and the elevator mechanism can generally be used safely. A summary of currently available peroral cholangioscopy systems is presented in **Table 1**.

The Olympus CHF-B290, CHF-B260, and CHF-BP260 cholangioscopes feature a two-way steerable catheter tip, with a field of view of 80 degrees for the CHF-B290 and 90 degrees for the CHF-B260 and CHF-BP260. These electronic cholangioscopes support narrow-band imaging (NBI), offering high image quality and excellent illumination. The instrument channels of the CHF-B290 (1.3 mm) and CHF-B260 (1.2 mm) allow the insertion of up to 3 Fr biopsy forceps, as well as other therapeutic devices. The CHF-BP260, a slim endoscope designed for pancreatic cannulation, facilitates easier insertion but has a smaller instrument channel of 0.5 mm. This size prevents the use of biopsy forceps. Additionally, its lower irrigation flow rate impairs washing capability, occasionally compromising image clarity. These cholangioscopes have a single instrument channel, and a Y-connector is attached when simultaneous irrigation and instrument insertion are necessary.[7)]

The SpyGlass™ DS from Boston Scientific has several notable features:

(i) Being disposable, it eliminates concerns about water leakage and damage.

(ii) Its tapered, highly flexible tip allows for safe papillary insertion and superior passage through strictures.

(iii) With a four-way steerable catheter tip, it provides improved maneuverability and precise targeting for biopsy or lithotripsy probes.

(iv) Separate channels for suction and irrigation enable effective washing without excessive pressure, maintaining clear visualization even in the presence of bile, pancreatic juice, mucinous material, or bleeding.

Table 1 Specifications of peroral cholangioscopes.

	Mother-baby system				
	Digital cholangioscope				
	CHF-B290	CHF-B260	SpyScope DS	eyeMAX (2 types with different outer diameters)	DRES
Manufacturer	Olympus	Olympus	Boston Scientific	MC Medical	Japan Lifeline
Operated by	2persons	2persons	1-2persons	2persons	2persons
Instrument port diameter (mm)	1.3	1.2	1.2 & 0.6# & 0.6#	1.1 1.8	2.0
Tip outer diameter (mm)	3.3	3.4	3.6 10.8 Fr)	3.2 3.9	3.5
Insertion tube outer diameter (mm)	3.53 mm (tip to 1,390 mm) 3.75 mm (after 1,390 mm)	33.5 mm (tip to 1,800 mm) 3.9 mm (after 1,800 mm)	3.6 10.8 Fr)	3.2 3.9	3.8
Field of view	80°	90°	120°	120°	96°
Angulation	2 direction + α	2 directions	4 directions	4	4 directions
Up-down	70°- 70°	70°- 70°	90°- 90°	90°- 90°	90°- 90°
Right-left	RL passive bending function	×	90°- 90°	90°- 90°	90°- 90°
Effective length (mm)	1,920	2,000	2,140	2,190	1,900
Water channel (separate)	×	×	○	○	○
Image quality	◎	◎	○	◎	○
Operability	○	○	◎	◎	○
Breakable	Medium	High	Low	Low	Low

#: Irrigation and aspiration

(v) The half-lock function allows for stable positioning within the duct.

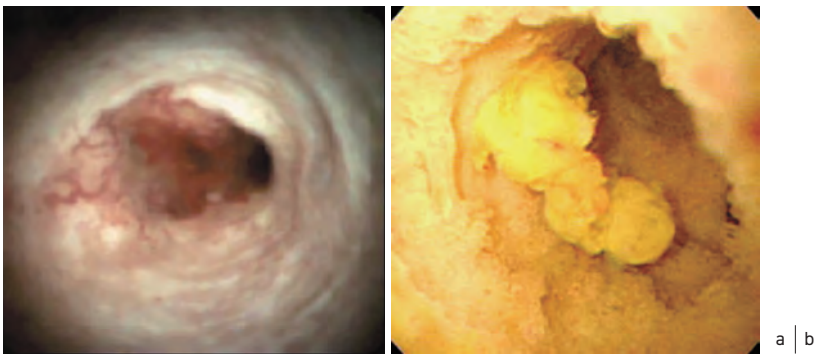
(vi) Its compact light source is compatible with existing trolleys, minimizing space requirements.

Although the system is expensive, it offers easier control and enhanced safety compared with traditional POCS. Tanaka reported that the SpyGlass™ DS enables safe and reliable procedures and is effectively utilized by experienced endoscopists in biliary and pancreatic endoscopy.[11)]

In actual procedures, a medium- to large-endoscopic sphincterotomy (EST) is performed to facilitate access prior to insertion. When resistance is encountered at the papilla, an additional 8-mm endoscopic papillary balloon dilation (EPBD) is performed to facilitate smooth insertion. In cases where insertion remains difficult, guidewire-assisted insertion is recommended to improve safety. Once the baby endoscope is inserted into the bile or pancreatic duct, lumen visualization is optimized by adjusting the angulation of both the mother and baby endoscopes. Bile or mucus is suctioned and irrigated to achieve a clear visual field. With two-way steerable cholangioscopes, fine adjustments are performed through rotation and angulation of the mother endoscope. In contrast, the SpyGlass™ DS offers four-way steerability, enabling fine control of the endoscope to enter the target duct primarily through coordinated movement of the baby and mother endoscopes. Subsequently, irrigation is performed by injecting saline through the irrigation port and suctioning via the instrument channel. Suction and irrigation should be performed simultaneously to keep the lumen clear of mucus and enable observation of the target site. Since the suction power is excellent, intraluminal pressure in the pancreatic and bile ducts is not elevated by water infusion. However, care should be taken, because excessive irrigation may cause pancreatitis and cholangitis. For targeted biopsies, the SpyBite™ Max biopsy forceps (**Figure 2c**), specifically

Table 2 Differentiating benign and malignant biliary mucosa.

Benign	Malignant
Microvasculature (normal) Uneven changes (dimple sign) (Normal) Uniformly low granular mucosa (hyperplastic) Diverticular unevenness (primary sclerosing cholangitis) White scar with fold concentration (Sclerosing cholangitis)	Partially enlarged and fused tumor vessels Friable mucosa Irregular papillary protrusions Nodular masses Submucosal tumor-like nodular elevations (bile duct invasion of gallbladder carcinoma, etc.)



a | b

Figure 5 POCS of cholangiocarcinoma.

a: Partially enlarged and tortuous vessels are observed.
b: Irregular papillary protrusions are noted with surrounding granular mucosa, indicating lateral extension of the lesion.

designed for the SpyGlass™ DS, have an outer diameter of 1.0 mm and a jaw opening of 4.1 mm. Despite their small size, they enable precise biopsy under direct visualization and provide sufficient tissue samples due to their serrated teeth profile.

6. Differentiating Benign from Malignant Using Cholangioscopy

The differentiation between benign and malignant biliary strictures is based on an assessment of biliary mucosal and vascular characteristics (**Table 2**).[13] The Olympus cholangioscopy system, which incorporates NBI, enhances visualization of mucosal structures and vascular patterns, allowing for detailed observation of surface irregularities. The presence of small papillary tumors, mucosal irregularities, and capillary vessel changes has been reported as useful diagnostic markers, particularly for intraductal papillary neoplasms of the bile duct (IPNB).[9,14,15]

Normal biliary mucosa appears smooth and white, with a visible network of fine capillaries and a relatively flat surface. The dimple sign, characterized by shallow depressions resembling thumbprint impressions, is a distinct feature.

Malignant choledochoscopic findings include tumor vessels that are irregularly dilated and fused, friable mucosa, irregular papillary protrusions, and nodular protrusions resembling submucosal tumors. **Figure**

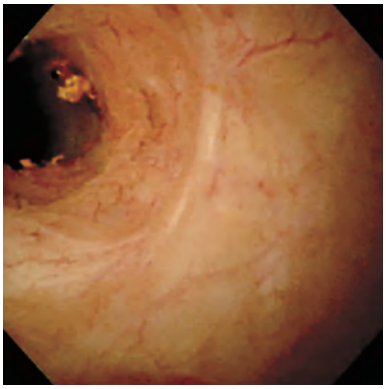


Figure 6 **POCS of sclerosing cholangitis caused by bile duct stones.**

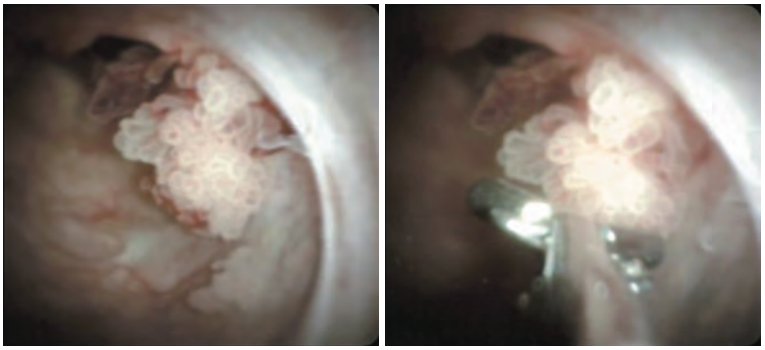
White scarring is observed in the affected bile duct.

5 shows a POCS profile of cholangiocarcinoma. **Figure 5a** illustrates a cholangioscopic image of cholangiocarcinoma, showing tortuous, fused, and irregularly dilated blood vessels. **Figure 5b** depicts a papillary-type cholangiocarcinoma, presenting as an irregular central elevation with a granular or papillary appearance, along with superficial spread into the surrounding mucosa.

In contrast, **Figure 6** shows benign findings, including flat non-irregular mucosa and white scar lesions with converging folds. However, inflammatory conditions may also present with dilated, mildly tortuous vessels, necessitating careful interpretation to avoid misdiagnosis.

Minami et al. evaluated the diagnostic accuracy of POCS for differentiating benign and malignant lesions in 93 cases, reporting a sensitivity of 94.7%, a specificity of 83.3%, and an accuracy of 90.3%.[12] Furthermore, Itoi et al. investigated the differentiation of IgG4-related sclerosing cholangitis and cholangiocarcinoma using POCS. They reported that approximately 60% of IgG4-related sclerosing cholangitis cases exhibited dilated and tortuous vessels, whereas partially enlarged vessels were significantly more common in extrahepatic cholangiocarcinoma.[16] A comparative analysis of primary sclerosing cholangitis (PSC) and IgG4-related sclerosing cholangitis using POCS demonstrated that dilated and tortuous vessels were more frequently observed in IgG4-related sclerosing cholangitis, whereas scarring and pseudodiverticula were significantly more common in PSC.

In addition to visual findings, targeted biopsy under direct vision improves the diagnostic yield compared with fluoroscopic-guided biopsy during ERCP.[17,18] Minami et al. found that adding targeted biopsy to visual assessment significantly improved diagnostic accuracy. Specifically, this combined approach increased sensitivity to 96.5%, specificity to 91.7%, and overall accuracy to 94.6%. They concluded that combining biopsy with visual observation enhanced the diagnostic utility of POCS in differentiating benign from malignant lesions.[12] Kawakami et al. demonstrated that POCS improved the assessment of intraepithelial tumor spread in bile duct carcinoma, with an accuracy of 77% compared with ERCP alone, and increasing to 100% when combined with mapping biopsies.[19]



a | b

Figure 7 POPS of IPMN.

a: Fish egg-like granular neoplasms are visible.
b: Endoscopic image showing biopsy of the granular neoplasms using dedicated pancreatic duct biopsy forceps.

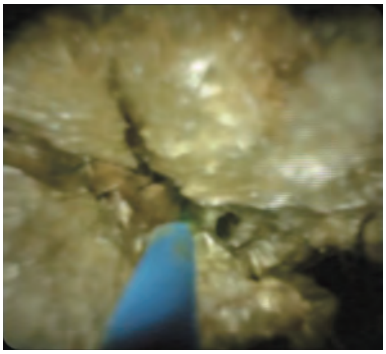


Figure 8 POCS of bile duct stones undergoing fragmentation with YAG laser.

7. Diagnostic Ability of Intraductal Papillary Mucinous Neoplasm(IPMN) by Peroral Pancreatoscopy

POPS has been reported to have a diagnostic accuracy of 76–94% for IPMNs. Hara et al. classified intraductal endoscopic findings of IPMNs into granular, fish egg-like, villous, and nodular types.[20] noting that malignant cases were more often characterized by villous and nodular protrusions. The reported frequencies were 36% for granular, 65% for fish egg-like, 88% for villous, and 85% for nodular types.[21] A recent meta-analysis revealed that pancreatoscopy resulted in changes to surgical strategy in 13–62% of cases, but the adverse event rate was also 12%, with pancreatitis being the most common complication.[22] **Figure 7** shows villous and fish egg-like lesions observed in IPMN cases via POPS.

Intraductal papillary mucinous neoplasms (IPMNs) often show not only widespread extension from the main lesion but also skip lesions. Therefore, whenever possible, it is recommended to examine the area downstream of the main lesion to accurately evaluate the extent of disease progression and determine the appropriate range for surgical resection. In practice, highly viscous mucus cannot be adequately aspirated through the instrument channel of the pancreatoscope. Therefore, techniques such as mucus drainage using a balloon catheter should be performed before inserting the pancreatoscope.

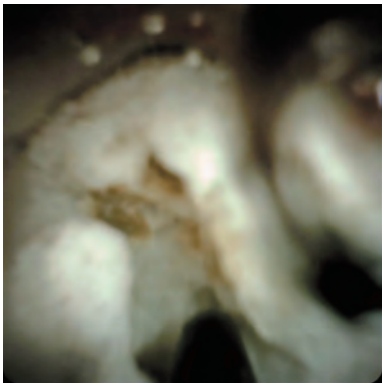


Figure 9 POPS of pancreatic stones fragmented by EHL.

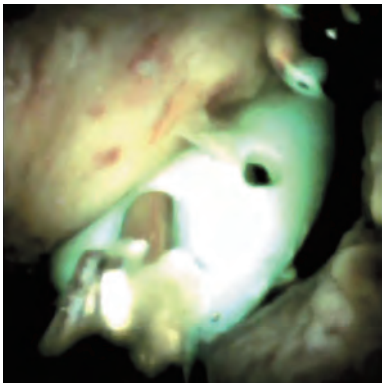


Figure 10 POCS of a migrated biliary plastic stent
The migrated stent is grasped with cholangioscopic biopsy forceps.

The migrated stent is grasped with cholangioscopic biopsy forceps.

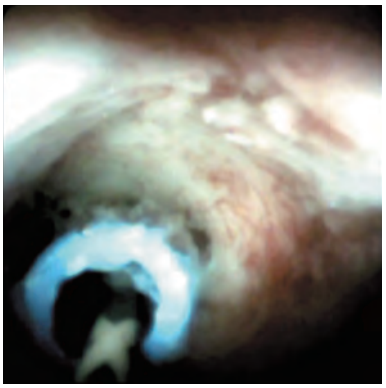


Figure 11 POPS of a migrated pancreatic plastic stent
Under endoscopic vision, successful passage of a guidewire into the lumen of the migrated pancreatic stent is confirmed.

Under endoscopic vision, successful passage of a guidewire into the lumen of the migrated pancreatic stent is confirmed.

8. Treatment with Peroral Cholangioscopy/ Peroral Pancreatoscopy

For cases of bile duct stones that are difficult to treat with standard ERCP, lithotripsy under POCS using an electrohydraulic lithotripter (EHL) or an yttrium aluminum garnet (YAG) laser enables effective stone fragmentation. These devices are introduced through the instrument channel of the POCS. Under direct vision, the YAG laser is applied in contact with the stone (**Figure 8**), while the EHL fragments the stone by generating a shock wave at the stone surface during saline immersion.

During endoscopic transpapillary gallbladder drainage, inserting the guidewire into the cystic duct is often challenging under fluoroscopic guidance. In such cases, POCS can be used to directly identify the cystic duct orifice, thereby enabling guidewire insertion under direct endoscopic visualization.

In chronic pancreatitis requiring pancreatic duct decompression due to pancreatic stones, extracorporeal shock wave lithotripsy (ESWL) is not always sufficient for complete stone fragmentation. If the stones are visible, lithotripsy can be performed using EHL or a YAG laser under direct visualization with POPS. In practice, POPS is inserted after papillary procedures such as pancreatic sphincterotomy and balloon

dilation. Using the SpyGlass™ DS system, our team achieved stone visualization in 71.4% of cases and complete removal in 42.9%.[11] **Figure 9** shows POPS-guided lithotripsy with EHL.

In cases where stent retrieval from the bile or pancreatic duct is difficult with conventional baskets or balloon catheters, POCS alone or POPS combined with SpyBite™ Max can facilitate extraction (**Figure 10**).[23-25] If the stent wall is too thick to grasp, a guidewire is inserted into the stent (**Figure 11**), followed by retrieval with a dedicated retrieval catheter or snare.

Conclusion

The role, indications, and practical applications of cholangioscopy and pancreatoscopy in biliary and pancreatic diseases have been discussed. The incidence of adverse events is comparable to that of standard ERCP; nevertheless, special attention is required for the prevention of pancreatitis during pancreatoscopy. Additionally, due to saline irrigation used to maintain a clear visual field, care should be taken to prevent cholangitis resulting from elevated intrabiliary pressure. Air embolism has also been reported as a severe complication, and caution remains essential in this regard. With ongoing improvements in endoscopic resolution and the development of specialized therapeutic devices, both diagnostic accuracy and treatment outcomes continue to improve, and further technological advancements are expected.

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Takayoshi Tsuchiya and Shomei Ryozawa

4-(I) Endoscopic Ultrasonography (EUS)

- EUS

Introduction

Endoscopic ultrasonography (EUS) is a diagnostic imaging technique that uses an echoendoscope equipped with an ultrasound transducer at its tip to obtain sonographic images of the gastrointestinal wall and surrounding organs from the gastrointestinal lumen. In general, ultrasound waves cannot travel through air, and clear images cannot be obtained when air is present. To perform EUS observation, the air in the digestive tract is replaced with water to eliminate interference and the ultrasound transducer is pressed against the wall. Alternatively, the transducer with water-filled balloon makes direct contact with the digestive tract wall. EUS provides high-resolution images, making it a valuable tool in clinical practice for detailed evaluation of various conditions in the pancreas and biliary tract. For closer examination of lesions within the bile and pancreatic ducts, a technique called intraductal ultrasonography is used, where a thin-caliber ultrasound is directly inserted into these ducts for observation.

1. Types of EUS

There are two main types of EUS. The first is an echoendoscope, in which the ultrasound probe is directly attached to the tip of the endoscope. The second type is a catheter-type device (thin-caliber ultrasound probe), which is inserted through the instrument channel of a standard endoscope for use.

Echoendoscopes for EUS are classified into radial-scanning and curved linear-scanning types based on the ultrasound beam direction. Radial-scanning EUS emits ultrasound beams perpendicularly from the axis of the endoscope shaft, providing a 360-degree circumferential tomographic image (**Figure 1**). In contrast, curved linear-scanning EUS generates cross-sectional images along the longitudinal axis, covering an approximately 180-degree field (**Figure 2**). The curved linear-scanning type enables endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and various therapeutic procedures performed under EUS guidance. Initially, radial-scanning EUS used a mechanical system that rotated the ultrasound transducer to obtain circumferential imaging. Notably, an electronic radial-scanning system has since been developed, offering higher image clarity, reduced artifacts, and compatibility with Doppler imaging.[1)] Currently, only the electronic radial echoendoscopes are commercially available. Although the frequency varies depending on the model, echoendoscopes typically operate within the 5 to 12 MHz range.

Ultrasound probes with thin-caliber are commercially available. They employ a mechanical radial-

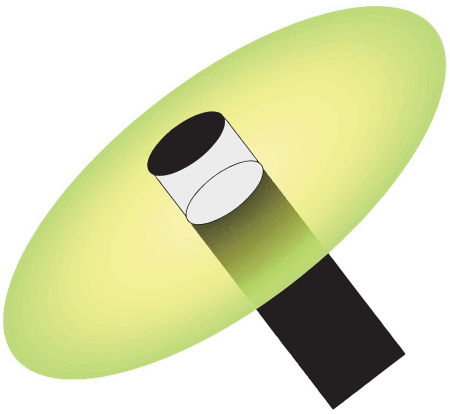


Figure 1 Diagram of radial-scanning endoscopic ultrasonography.

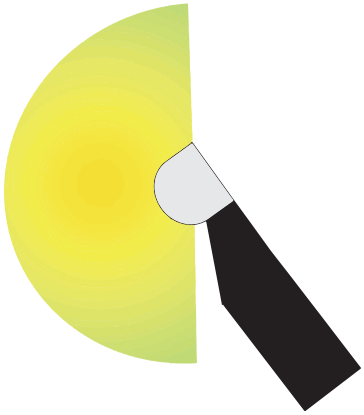


Figure 2 Diagram of curved linear-scanning endoscopic ultrasonography.

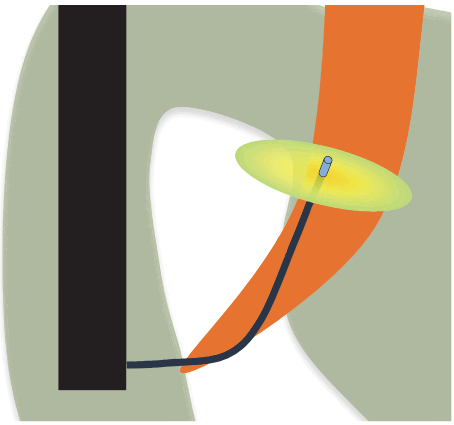


Figure 3 Diagram of endoscopic ultrasonography using a thin-caliber ultrasound probe.



Figure 4 Guidewire-assisted thin-caliber ultrasound probe (Courtesy of Olympus).

scanning system, producing 360-degree circumferential tomographic images (**Figure 3**). The available probes have an outer diameter of 1.4 to 2.6 mm and operate at frequencies of 12 MHz, 15 MHz, and 20 MHz. Higher frequencies provide greater spatial resolution and image precision but higher frequencies, while offering greater resolution, limit penetration into deeper tissues. In the pancreaticobiliary junction, guidewire-assisted ultrasound probes are also available to improve insertion into the bile and pancreatic ducts (**Figure 4**).

2. Indications and Contraindications

Although most biliary and pancreatic lesions are indicated for EUS for detection of lesions, qualitative diagnosis, and staging and depth of invasion, main indications are listed below.

- Diagnosis of common bile duct stone and gallbladder stone
- Diagnosis and pathogenesis of cholecystitis

- Pathogenesis of cholangitis
- Differential diagnosis of bile duct stricture
- Detailed examination of the obstruction site and cause in obstructive jaundice
- Differential diagnosis of gallbladder polyps and protruded lesions
- Invasion depth and staging of gallbladder carcinoma
- Invasion depth and staging of bile duct carcinoma
- Diagnosis of pancreaticobiliary maljunction
- Invasion depth and staging of carcinoma of the papilla of Vater
- Diagnosis of chronic pancreatitis and its early stage
- Diagnosis and cause investigation of pancreatitis
- Cause investigation of pancreatic duct dilatation
- Differential diagnosis and detailed examination of pancreatic cyst
- Detection and differential diagnosis of pancreatic tumor
- Staging of pancreatic carcinoma

Contraindications for endoscopic ultrasonography are the same as those for regular endoscopy. It is contraindicated when the risks of performing the examination outweighs its benefits, with specific contraindications including the following cases.[2)]

- Extremely poor general condition
- Ileus
- Immediately after surgery or suspected gastrointestinal perforation
- Accompanied by severe cardiovascular or respiratory disease
- Cases where informed consent for the examination has not been obtained

3. Pretreatment and Preparation

Pretreatment for EUS using an echoendoscope is the same as that for standard upper gastrointestinal endoscopy. The risk of bleeding in patients taking antithrombotic drugs is also considered to be similar to that for diagnostic upper gastrointestinal endoscopy. There is no need to stop taking antithrombotic drugs. In fact, discontinuation of antithrombotic therapy does not reduce thromboembolic risk, rather, it increases the risk.[3)]

Sedation is administered in most facilities, as the echoendoscope has a relatively large diameter and the procedure time may be prolonged. Moreover, an intravenous line should be secured, as additional medications are often administered as needed. During the examination, blood pressure and oxygen saturation are monitored, and antagonists appropriate for the administered sedatives are prepared in case of oversedation.

Antispasmodics are occasionally administered for observation of duodenal papillary lesions but are rarely used in other situations.

In addition, intraductal ultrasound (IDUS) is performed in conjunction with endoscopic retrograde cholangiopancreatography (ERCP), and its pretreatment and preparation follow the standard protocols for ERCP.

4. Observation Method

Regardless of whether a radial-scanning or curved linear-scanning endoscopic ultrasonography system

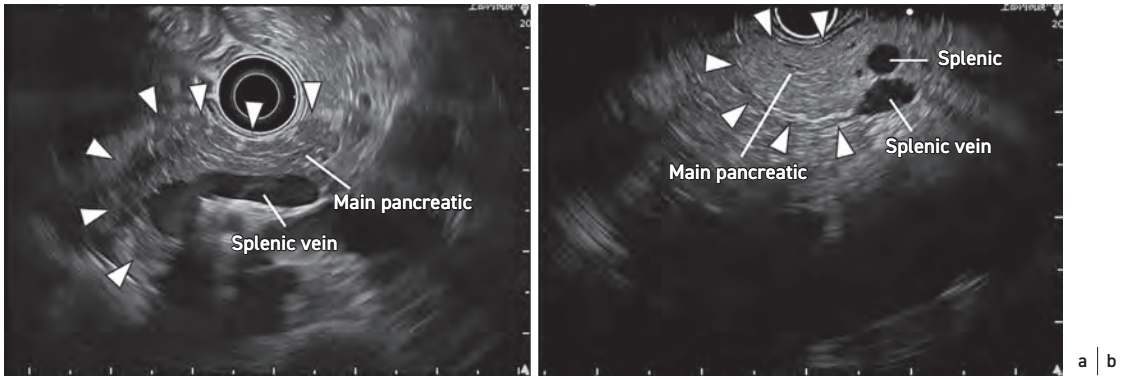


Figure 5 EUS imaging of the pancreas from the stomach.

(a) With radial scanning, the pancreatic body and tail (arrowhead) are visualized in the longitudinal plane.
(b) With curved linear scanning, the pancreatic body (arrowhead) is visualized in cross-section.

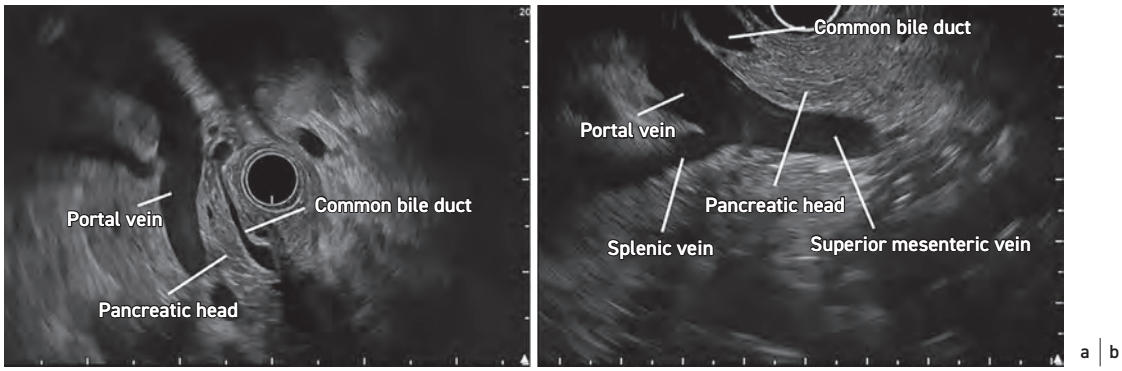


Figure 6 EUS imaging of the common bile duct and pancreatic head from the duodenal bulb.

(a) With radial scanning, the longitudinal axis of the common bile duct and the pancreatic head are visualized between the portal vein and the transducer.
(b) With curved linear scanning, the common bile duct and pancreatic head are visualized between the portal vein–superior mesenteric vein axis and the transducer.

is used, the scanning sites are the same, and focusing on the stomach, the duodenal bulb, and the descending duodenum. From these sites, endoscopists observe the targeted areas of pancreas, bile duct, gallbladder, and papilla. The ultrasound images obtained differ between the two scanning methods. When scanning through the stomach, the body and tail of the pancreas are the primary targets. The radial-scanning system produces a longitudinal image of the pancreas (**Figure 5a**), whereas the curved linear-scanning system provides a cross-sectional (short-axis) image (**Figure 5b**). From the duodenal bulb, the bile duct, gallbladder, and pancreatic head are visualized. In radial scanning, the bile duct is visualized longitudinally (**Figure 6a**), while in curved linear scanning, it is visualized in a short-axis view (**Figure 6b**). When scanning from the descending part, the papillary region and head of the pancreas are the main targets. As the scope is withdrawn while being kept straight without slack, the bile and pancreatic ducts near the papilla are visualized as cross-sectional images in the radial-scanning system (**Figure 7a**), whereas the curved linear-scanning system provides a longitudinal view (**Figure 7b**).

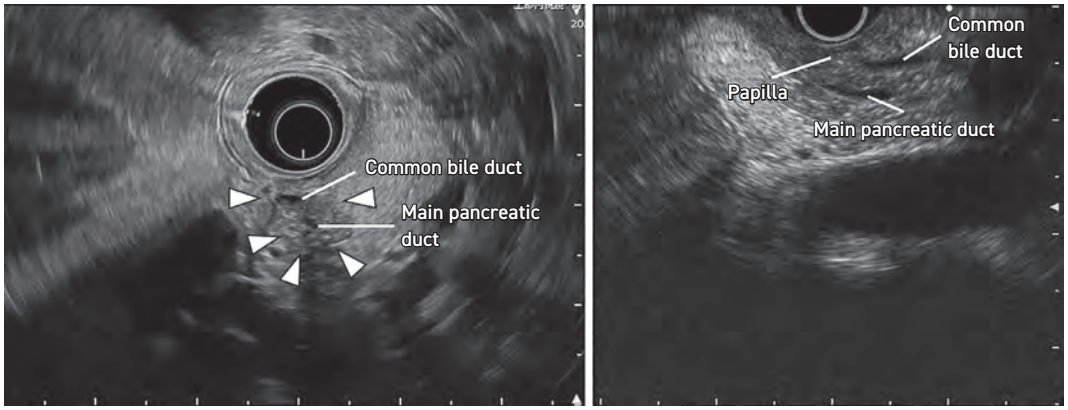


Figure 7 **EUS imaging of the common bile duct and main pancreatic duct near the papilla from the descending duodenum.**

(a) With radial scanning, a hypoechoic area near the papilla (arrowhead) demonstrates cross-sectional images of the common bile duct and main pancreatic duct.
(b) With curved linear scanning, the longitudinal views of the common bile duct and main pancreatic duct near the papilla are visualized.

5. Adverse Events and Its Management

A prospective study conducted between 2019 and 2021 investigated adverse events associated with gastrointestinal endoscopic procedures and treatments over one week at various facilities.[4] Of 2,829 EUS procedures performed in the pancreaticobiliary region with echoendoscopes, 13 (0.46%) were associated with adverse events. Detailed adverse events were reported in seven cases: one perforation, one gastrointestinal tear, one temporomandibular joint dislocation, one dental injury, one intraoral hematoma, one episode of respiratory depression, and one episode of elevated blood pressure. Adverse events related to IDUS are difficult to assess independently, since IDUS is performed as part of the ERCP. However, among 247 cases of biliary IDUS and 48 cases of pancreatic IDUS, no adverse events were reported.

The design of echoendoscope systems presents technical challenges because the ultrasound transducer at the distal tip results in a longer rigid section and a more limited angulation range compared with standard endoscopes. Additionally, the oblique-viewing design of most EUS scopes further restricts the endoscopic field of view. These factors cause a reduction in maneuverability, requiring careful handling to prevent mucosal injury, tear, or perforation. As for IDUS, adverse event management follows the same protocols as those established for ERCP.

6. Imaging Diagnosis

(1) Gallbladder

Endoscopic ultrasonography depicts the gallbladder wall as a two-layered structure, with a hypoechoic inner layer and a hyperechoic outer layer. The inner layer corresponds to the mucosa, muscularis mucosae, muscularis propria, and the superficial layer of the subserosa, whereas the outer layer

Table 1 Types of gallbladder lesions.

	High to medium frequency		Low frequency
Neoplastic		Adenocarcinoma Adenosquamous carcinoma	Adenoma Carcinosarcoma Metastatic tumor Neuroendocrine tumor Malignant lymphoma
Non-neoplastic	Protruding:	Cholesterol polyp	Hyperplastic polyp Metaplastic polyp Inflammatory polyp Fibroid polyp
	Flat to thickened:	Cholangitis Adenomyomatosis, Cholesterol deposition (cholesterolosis)	Hyperplastic change

represents the deep layer of the subserosa and the serosa.[5] When assessing the depth of tumor invasion, even if a lesion appears confined to the inner hypoechoic layer, subserosal infiltration cannot be entirely excluded.

Movable lesions are usually identified as gallstones or solid biliary sludge, regardless of the presence or absence of acoustic shadowing whereas non-mobile lesions should be evaluated according to their appearance, echogenicity, and occurrence frequency.[6] Cholesterol polyps are the most common type and typically appear as multiple, pedunculated, mulberry-like lesions. Adenomyomatosis appears as focal or diffuse gallbladder wall thickening with comet-tail artifacts, which indicate intramural gallstones, along with small anechoic cystic spaces corresponding to dilated Rokitansky-Aschoff sinuses (RAS). Diffuse gallbladder wall thickening with preserved layering suggests inflammation, whereas focal thickening or broad-based polyps with solid internal echogenicity, particularly when exceeding 10 mm, should prompt thorough evaluation for gallbladder carcinoma.

(2) Bile duct

In EUS imaging, the bile duct is usually depicted as a two-layered structure with echoendoscopes and as a three-layered structure with IDUS. The two-layered appearance consists of an inner hypoechoic layer corresponding to the mucosa, fibromuscular layer, and the superficial layer of subserosa, whereas the outer hyperechoic layer represents the deep layer of subserosa and serosa. When visualized as three layers, the innermost hyperechoic layer corresponds to the interface echo and the mucosa.[7]

Movable structures within the bile duct suggest bile duct stones or biliary sludge, whereas immobile lesions raise suspicion for neoplastic changes such as localized cholangiocarcinoma or biliary intraepithelial neoplasia. Diffuse wall thickening is associated with bacterial cholangitis or sclerosing cholangitis, including primary, secondary, and IgG4-related, whereas localized thickening suggests infiltrative cholangiocarcinoma.

(3) Papilla of Vater

EUS is also useful for evaluating tumor invasion of the duodenal papilla into the bile and pancreatic

ducts. Ultrasound imaging of the muscularis propria of duodenum serves as a reference point for assessing tumor extension into these ducts and determining the presence of invasion into the duodenal wall or pancreatic parenchyma. This modality is critical for determining the appropriateness of endoscopic papillectomy.[2)]

(4) Pancreas

Pancreatic carcinoma typically appears on EUS as an irregular, hypoechoic lesion with poorly defined margins and heterogeneous internal echogenicity. In contrast, pancreatic neuroendocrine neoplasms (NENs) are usually well-defined, round, and hypoechoic, with relatively homogeneous internal echogenicity and increased echogenic contrast compared with pancreatic carcinoma.[2)] However, imaging findings alone are often insufficient to differentiate pancreatic masses, making pathological diagnosis by EUS-FNA necessary.

EUS is also valuable for evaluating pancreatic cystic lesions in both diagnosis and treatment planning. Branch duct-type intraductal papillary mucinous neoplasms (BD-IPMNs) typically exhibit a bunch-of-grapes-like cyst-by-cyst configuration, mucinous cystic neoplasms (MCNs) present as cyst-in-cyst formations, and serous cystic neoplasms (SCNs) are characterized by a microcystic honeycomb-like appearance.[8)] EUS provides high-resolution assessment of BD-IPMN, including mural nodules, irregular wall thickening, and ductal communication, thereby offering essential information for treatment planning.

EUS is also instrumental in diagnosing early-stage chronic pancreatitis. Characteristic findings include hyperechoic foci or strands, lobularity, a hyperechoic main pancreatic duct margin, and dilated side branches, all suggestive of early chronic pancreatitis.[9)]

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Takuji Iwashita and Ichiro Yasuda

4-(II) Endoscopic Ultrasonography (EUS)

- EUS-Guided Samplling (EUS-sampling, EUS-FNA)

Introduction

In recent years, procedures involving puncture under endoscopic ultrasonography (EUS) guidance to acquiring samples like tissues, cells, or fluid have come to be referred to as EUS-guided sampling.[1)] However, the original procedural name, EUS-guided fine needle aspiration (EUS-FNA) remains in use, along with EUS-guided fine needle acquisition (EUS-FNA). In this section, the procedure is referred to as EUS-sampling/FNA. When specifying the collection of tissue and cytology samples, the term EUS-guided tissue acquisition (EUS-TA) is used, distinguishing it from EUS-guided fluid sampling, which refers specifically to fluid collection.

This technique has first applied clinically in 1992 for pancreatic mass evaluation, and since then has been recognized for its value in pathological diagnosis. It has been recognized as a technique for obtaining pathological diagnosis of various lesions, and has made steady advancements.[2-7)] In cases where lesion detection has been previously feasible but qualitative diagnosis has remained challenging, the primary advantage of this method lies in its ability to provide pathological and genetic assessments. A variety of puncture needles are now commercially available, and numerous refinements have been made to the procedure. EUS-guided puncture techniques have also been adapted for various drainage procedures, including pancreatic cysts, bile ducts, gallbladders, pancreatic ducts, and intraperitoneal abscesses, as well as for drug injection techniques such as celiac plexus block. These evolving techniques continue to be developed rapidly and are collectively referred to as interventional EUS (I-EUS), encompassing a wide range of diagnostic and therapeutic procedures.

1. Indications and Contraindications

(1) Indications for EUS-guided sampling/FNA

The primary indications for EUS-guided sampling/FNA include (i) differential diagnosis of tumorous lesions, (ii) staging of cancer progression, (iii) definitive tissue diagnosis before treatment (surgery, chemotherapy, or radiology), and (iv) genetic analysis for selecting targeted therapies. The procedure is applicable to all lesions visualized by EUS that require differentiation between benign and malignant conditions, but it should only be performed when it can be safely and easily executed and when it provides useful information for treatment decision-making.

This procedure is applicable to the following key targets: (i) pancreatic and peripancreatic tumorous

Table 1 Indications for EUS-guided Sampling. (EUS-Sampling, EUS-FNA)

The following lesions can be visualized by EUS:
- Mediastinal mass-forming lesion - Intraperitoneal mass-forming lesion ▪ Pancreatic and peri-pancreatic lesion ▪ Biliary tract lesion ▪ Submucosal tumor of gastrointestinal tract ▪ Left adrenal lesion (especially pheochromocytoma) ▪ Hepatic space-occupying lesions and chronic liver diseases ▪ Other mass-forming lesions - It is also applicable to subepithelial epithelial lesions of the gastrointestinal tract where histological diagnosis is difficult using conventional endoscopic biopsy - Pelvic mass-forming lesion - Cystic lesion - Enlarged lymph nodes

lesion, (ii) biliary tract lesion, (iii) submucosal tumor of gastrointestinal tract, (iv) mediastinal tumorous lesion, (v) enlarged lymph node that can be visualized around the gastrointestinal tract, (vi) small amounts of ascitic or pleural fluid detectable only by EUS, (vii) epithelial neoplasm of gastrointestinal tract that is difficult to diagnose via conventional endoscopic biopsy, (viii) left adrenal lesion (not for suspected pheochromocytoma), (ix) hepatic space-occupying lesions and chronic liver diseases identifiable by EUS, (x) pelvic mass observable via transcolonic examination, and (xi) cystic lesion requiring differentiation through EUS-guided sampling/FNA. These indications are summarized in Table 1. Lesions identified by EUS are considered for this procedure if they necessitate pathological or biochemical evaluation, and only if the procedure can be performed safely. For pancreatic cystic lesion, aggressive use of EUS-guided sampling/FNA is more common, including analysis of fluid viscosity, cytology, and carcinoembryonic antigen (CEA) measurement. However, puncture of neoplastic cysts is approached with caution due to the limited diagnostic accuracy of cytology, the low likelihood of altering treatment plans, and concerns about tumor seeding. Nevertheless, reports on the utility of EUS-guided sampling/FNA in these cases are increasing, and the number of procedures performed is rising. In fact, indications should be determined based on the potential impact on treatment decisions. With advances in puncture needle technology, this procedure is now expected to address smaller lesions (≤10 mm), thickened biliary or vascular walls, and genetic panel testing of specimens, expanding its applications.

(2) Contraindication for EUS-guided sampling/FNA

Previous guidelines have not explicitly defined contraindications, but such guidelines recommend that the procedure be avoided when safe puncture is not feasible.[8)] Specific contraindications include patients with bleeding tendencies, lesions that cannot be adequately captured, cases where a safe puncture route cannot be established, and suspected paragangliomas or pheochromocytomas. Since EUS-guided sampling/FNA is regarded as a high-risk procedure for bleeding, if the patient has a bleeding tendency, it should only be performed once coagulation status has been optimized with platelet

or plasma transfusion. Moreover, the procedure should follow the Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment by the Japan Gastroenterological Endoscopy Society.[9] In technically challenging cases, prioritizing safety is essential. Puncturing catecholamine-producing tumors like paragangliomas or pheochromocytomas is generally contraindicated due to the risk of hypertensive crisis.

When performing EUS-guided sampling/FNA on tumors, particularly cystic neoplasms, the potential risk of tumor seeding along the puncture tract or into the peritoneal cavity should be considered. Studies examining peritoneal recurrence after EUS-guided sampling/FNA for pancreatic carcinomas and pancreatic cystic neoplasms have reported that the procedure does not contribute to increased peritoneal dissemination postoperatively. However, some studies have detected tumor cells in gastrointestinal fluid from the puncture site following EUS-guided sampling/FNA for carcinoma of the pancreas.[10,11]

In a retrospective multicenter cohort study, Yane analyzed 301 patients with carcinoma of the pancreas undergoing distal pancreatectomy, comparing 176 cases with preoperative EUS-guided sampling/FNA and 125 cases without it. Needle tract seeding (NTS) was observed in six cases (3.4%) of the EUS-guided sampling/FNA group, but there was no significant difference between the two cohorts in recurrence-free survival (23.7 vs. 16.9 months, p=0.205) or overall survival (48.0 vs. 43.9 months, p=0.392).[12] Additionally, a nationwide survey by Kitano from the Japan Pancreas Society reported an overall NTS incidence of 0.330% among 12,109 patients who underwent surgical resection of primary pancreatic tumors following EUS-guided sampling/FNA, with a significantly higher rate in pancreatic ductal adenocarcinomas than other tumor types (0.409%, p=0.004).[13] NTS was observed in 0.857% of patients undergoing transgastric EUS-guided sampling/FNA but was not detected in those who underwent the procedure via the transduodenal route. The median time to NTS occurrence was 19.3 months, with a median survival of 44.7 months. NTS was found in the gastric wall in 97.4% of cases, and 65.8% of them underwent resection. Survival was significantly extended in patients who had NTS resected, compared with those who did not (p=0.037). These findings highlight the potential impact on treatment strategies aimed at curative and long-term survival. On the other hand, performing highly invasive pancreatic resection or systemic chemotherapy without definitive pathological confirmation is generally not acceptable in current clinical practice unless there are exceptional circumstances. As a result, EUS-guided sampling/FNA remains an essential diagnostic procedure for treatment planning. Future technological advancements are warranted to further address these concerns.

2. Practical Procedure

(1) Understanding EUS imaging

A thorough understanding of ultrasound anatomy using a curved linear array echoendoscope is essential for performing EUS-guided puncture. For detailed anatomical knowledge required for EUS-guided puncture, the standard textbook is useful.[14] Since curved linear array echoendoscope provides images parallel to the endoscope axis, it is crucial to recognize that scanning should be performed while rotating the endoscope axis clockwise and counterclockwise (**Figure 1**).

(2) Understanding how to use the equipment

Although EUS-guided puncture is minimally invasive, it is still an interventional procedure. Therefore,

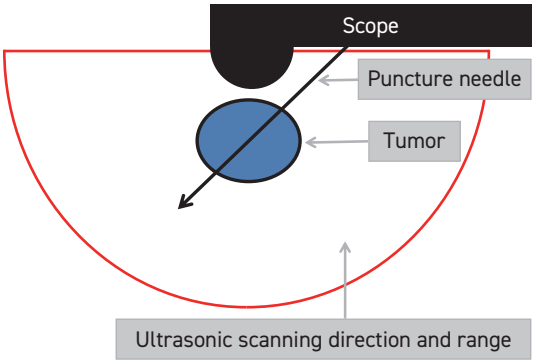


Figure 1 Scanning range and needle direction of curved linear array type EUS.

endoscopists should be fully proficient in handling the instruments and performing the procedure efficiently. The role of their assistant is particularly important, requiring expertise in manipulating the device during puncture and handling specimens after the procedure.

(3) Training methods

A thorough understanding of ultrasound anatomy as visualized by curved linear array echoendoscope, proficiency in interpreting EUS images, and accurate knowledge of device operation are essential for ensuring safe and effective examinations.

Regarding practical training, the American Society for Gastrointestinal Endoscopy (ASGE) guidelines recommend that the first 25 cases of EUS-guided sampling/FNA for pancreatic masses be performed under the supervision of a trained endosonographer. Supporting this, reports indicate that diagnostic accuracy and stability improve significantly after approximately 30 cases of EUS-guided sampling/FNA for pancreatic masses.[15)]

Before performing the procedure, acquiring a dynamic image-based understanding is essential. The given textbook provides instructional DVDs demonstrating the procedure.[14)] The most recommended training approach is to develop an image-based comprehension using these resources and then observe the procedure in a clinical setting to learn from both the specialist and the assistant's actual movements.

(4) Device and equipment

1) EUS for puncture

The endoscope used in this procedure is a curved linear array echoendoscope, which provides ultrasound images parallel to the endoscope axis, with a scanning range of 90° to 180°. This allows the puncture needle and the target lesion to be displayed on the same screen in real-time (**Figure 1**).

Additionally, curved linear array echoendoscope is equipped with Doppler mode, enabling blood flow assessment within the mass and visualization of surrounding vascular courses before puncture. This is crucial for preventing adverse events such as bleeding associated with the procedure (**Table 2**).

Currently, Olympus and Fujifilm manufacture ultrasound endoscopes capable of puncturing (**Figure 2**). Both companies offer their improved ultrasound transducers that are commonly mounted on an endoscopic equipment trolley. Furthermore, their endoscopes are compatible with Fujifilm's diagnostic

Table 2 Adverse events and their management in EUS-guided sampling. (EUS-sampling, EUS-FNA)

-Bleeding	Intraoperative: Detected by Doppler, compressed with the scope, endoscopic hemostasis, administration of hemostatic agents Postoperative: Investigation of the bleeding point and cause with dynamic CT, IVR
-Abdominal pain	Search for the cause with CT, while administering analgesics
-Pancreatitis	Refer to guidelines
-Pancreatic juice leakage	If small, observe the course; consider drainage if infection or increasing tendency
-Infection	Search for the source of infection, blood culture, administration of antibiotics
-Perforation	Perforation due to the puncture needle has not been reported; consult surgery for perforation due to the scope
-Tumor cell seeding along the puncture tract	Surgical treatment or chemotherapy



Figure 2 Curved linear array type EUS scopes.

(a) GF-UCT260 by Olympus
(b) EG-740UT by Fujifilm

ultrasound system (ARIETTA). Advances in imaging technology from both manufacturers have resulted in clearer images, with support for tissue harmonic imaging, elastography, and contrast-enhanced ultrasound.

2) Puncture needle

Various types of needles are used for this procedure. The most commonly used sizes are 25G, 22G, and 19G (**Table 3** & **Figure 3**). The 19G needle allows for a greater sample volume, due to its larger diameter. It has a high diagnostic value, including for histological analysis. However, its stiffness makes puncture difficult when the endoscope is angled.[16] In contrast, the 22G and 25G needles remain maneuverable even when the endoscope is angled, with the 25G needle being particularly suitable for lesions in difficult-to-access areas, such as the uncinate process of pancreas.[16]

Table 3 Puncture Needles.

	Puncture needle	Size	Features
Features	EZ Shot 3 Plus (Olympus)	25 G, 22 G, 19 G	Has a coil sheath. Made of stainless steel (25 G) and nitinol (22 G, 19 G).
	NA-11J-KB (Olympus)	22 G	Automatic puncture needle. Suitable for mobile lesions and hard lesions.
	Sonopsy CY (Hakko)	21 G	Has the structure of a percutaneous biopsy needle, less blood contamination. Made of stainless steel.
	EchoTip Ultra (Cook Medical)	25 G, 22 G, 19 G	Made of stainless steel.
	Expect (Boston Scientific)	25 G, 22 G, 19 G	Made of cobalt chromium and nitinol (19 G).
	SonoTip (Medi-Globe)	25 G, 22 G, 19 G	Made of stainless steel.
	Areus (Micro-tec)	25 G, 22 G	Made of cobalt chromium.
	Beacon (Medtronic)	25 G, 22 G, 19 G	Made of stainless steel and nitinol (19 G).
EUS-FNB needle	EchoTip ProCore (Cook Medical)	25 G, 22 G, 20 G, 19 G	Scrapes tissue using a front or reverse cutting edge side hole. Made of stainless steel.
	Acquire (Boston Scientific)	25 G, 22 G, 19 G	Has three blades of the same length at the tip. Made of cobalt chromium and nitinol (19 G).
	SonoTip TopGain (Medi-Globe)	25 G, 22 G, 19 G	Has three blades of the same length at the tip. Made of stainless steel.
	Trident (Micro-tec)	25 G, 22 G	Has three blades. One blade is longer than the others. Made of cobalt chromium.
	SharkCore (Medtronic)	25 G, 22 G, 19 G	Has two blades of different lengths at the tip. Made of stainless steel and nitinol (19 G).

EUS-FNA : EUS-guided fine needle aspiration, EUS-FNB : EUS-guided fine needle biopsy

A range of puncture needles is now commercially available, differing in materials and properties. Stainless steel provides sharp cutting ability but bends easily, whereas nitinol or cobalt-chromium offers high flexibility and resistance to bending, albeit with slightly reduced sharpness. Olympus' EZ Shot 3 Plus needle, made of nitinol, features improved cutting performance and incorporates a coil sheath for enhanced flexibility and reduced bending (**Figure 3a**).

Conventionally, pathology diagnosis was based on cytology, and needles used for EUS-guided fine needle aspiration (EUS-FNA) were referred to as EUS-FNA needles. Recent advancements have introduced specialized needles designed for histological sampling (EUS-guided fine needle biopsy, EUS-FNB), which are now distinguished from conventional EUS-FNA needles. Cook Medical's ProCore® needle features a side hole with forward- or reverse-facing blades, designed to increase tissue yield by shaving off samples during puncture (**Figure 3b**). Boston Scientific's Acquire™ needle has a three-blade tip and has demonstrated superior tissue sampling capability and diagnostic accuracy for pancreatic tumors compared with EUS-FNA needles (**Figure 3c**).[17] Other manufacturers, such as Medi-Globe (SonoTip TopGain®) and Micro-Tech (Trident™), also offer three-blade needles. The SonoTip TopGain® needle has evenly positioned three blades (**Figure 3d**), similar to the Acquire™ needle, while the Trident™ needle has one elongated blade (**Figure 3e**). Medtronic's SharkCore™ needle features a two-blade design (**Figure 3f**). However, evidence is still limited regarding which EUS-FNB needle offers the best balance of penetration efficiency and tissue yield, and further clinical trials are expected to give good evidence.



a	b	c
d	e	f

Figure 3 **Puncture needles.**

(a) EZ Shot 3 Plus (25 G, 22 G, 19 G) from Olympus
(b) EchoTip ProCore (20 G, with forward-facing blade) from Cook Medical
(c) Acquire (25 G, 22 G, 19 G) from Boston Scientific
(d) SonoTip TopGain (25 G, 22 G, 19 G) from Medi-Globe
(e) Trident (25 G, 22 G) from Micro-Tech
(f) SharkCore (25 G, 22 G, 19 G) from Medtronic

Most available puncture needles include a syringe with adjustable aspiration pressure, typically a 20 mL model with lockable settings at 10 mL or 20 mL to regulate negative pressure.

(5) Preoperative and postoperative treatments

1) Preoperative examination and procedures

Since this is an interventional procedure, preoperative blood tests are mandatory. These include peripheral blood counts, biochemical tests (with amylase or lipase being essential for pancreatic puncture), coagulation parameters, bleeding time, and blood type. A medication review should also be conducted, checking for anticoagulants or antiplatelet agents. If such medications are being taken, the patient should be discontinued following the *Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment*.[9)]

Hospitalization is generally preferred, but for diagnostic punctures, outpatient procedures are also feasible. However, adequate sedation is required. Therefore, a short hospital stay of about one night is advisable. Regardless of inpatient or outpatient settings, vascular access should be secured before the procedure.

Pre-procedure preparation follows standard endoscopic protocols, but because EUS-guided puncture tends to be more time-consuming, sufficient sedation is necessary. Many facilities also perform the procedure under general anesthesia.

2) Perioperative treatment

During the procedure, sedation and antispasmodic agents may be administered as needed, and continuous respiratory and circulatory monitoring is essential.

3) Postoperative treatment

For outpatient cases, post-procedure observation under the physician's supervision is required for at least two hours. Although routine antibiotic administration is discouraged in the United States due to concerns about antimicrobial resistance, reports of localized infections at puncture sites suggest that prophylactic antibiotics should be considered when the gastrointestinal wall is punctured through or when submucosal tumors of the colon are targeted. Patients should fast for one meal after the examination, while water intake is resumed if no issues arise within two hours post-procedure.

(6) Examination method and procedure

1) Staff arrangement

At least two personnel are required for the procedure: a main endoscopist and an assistant endoscopist responsible for handling the instruments. Since it is essential to maintain continuous visualization of the puncture needle, the presence of the assistant to stabilize the endoscope and support the puncture process is recommended. To ensure patient safety, nurses should be assigned to monitor vital signs, assist the endoscopists, and perform necessary interventions.

2) Practical procedure (Figure 4)

(i) The endoscopist guides an endoscopic ultrasound (EUS) to an appropriate site within the gastrointestinal tract (esophagus, stomach, duodenum, large intestine) based on the lesion's location, ensuring optimal visualization of the target lesion, its relationship with surrounding vessels, and the ideal puncture position and angle.

(ii) Before puncture, color Doppler or power Doppler imaging is used to confirm that no vessels are

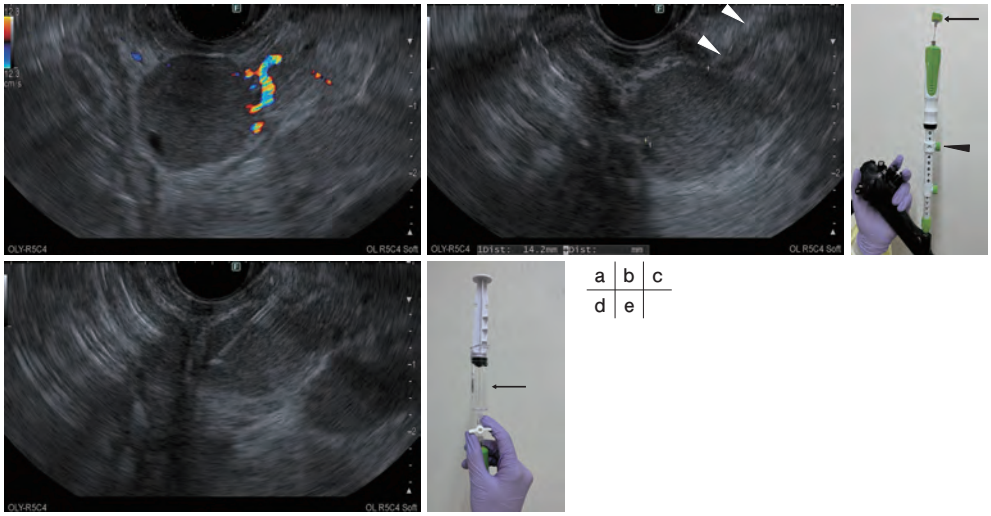


Figure 4 **Standard procedural technique.**

(a) Because a vessel is identified along the initial puncture line, an alternative puncture trajectory is selected to avoid vascular injury.
(b) The tip of the puncture needle is confirmed, and while anticipating the puncture trajectory, the distance to the target lesion is measured. The arrowheads indicate the distal cap of the puncture needle.
(c) The stylet is slightly retracted, and the stopper is secured before proceeding with the puncture. The arrow shows the puncture needle, while the arrowhead indicates the stopper.
(d) The tip of the puncture needle is shown inserted within the tumor. The arrow points to the distal end of the needle.
(e) The stylet is withdrawn, and a dedicated aspiration syringe with negative pressure is connected. The arrow indicates the aspiration syringe.

present along the intended puncture line (**Figure 4a**).

(iii) The puncture needle is then inserted through the instrument port and secured. At this time, the distal cap of the puncture needle appears as a hyperechoic (bright) area on the ultrasound image. This echogenic distal cap serves as a landmark, allowing the operator to anticipate the expected puncture line (**Figure 4b**). If the visibility of the tip of distal cap is unclear, minor manipulations of the forceps elevator may help identify the movement of the tip. The distance from the tip of distal cap (gastrointestinal wall surface) to the target lesion is measured (**Figure 4b**), and the needle stopper is set accordingly (**Figure 4c**). To enhance the visibility of the puncture needle, the stylet is partially withdrawn by approximately 10 to 15 mm (**Figure 4c**).

(iv) To ensure a stable position between the gastrointestinal wall and the endoscope tip, continuous aspiration is applied through the endoscope. While maintaining this stable contact, the endoscopist carefully monitors the needle tip on the ultrasound image and proceeds with the puncture, precisely considering both the angle of insertion and the location of the lesion (**Figure 4d**).

(v) Once the tip is punctured, the slightly withdrawn stylet is reinserted to expel any gastrointestinal mucosal tissue that could have entered the needle lumen. The assistant then removes the stylet and attaches an aspiration syringe to create negative pressure (**Figure 4e**).

(vi) Under ultrasound guidance, the endoscopist moves the needle back and forth within the lesion multiple times (up to 20 times) to acquire samples.

(vii) Once the sampling is complete, the assistant releases the negative pressure by detaching the aspiration syringe, and the endoscopist removes the needle from the lesion. The assistant then fully

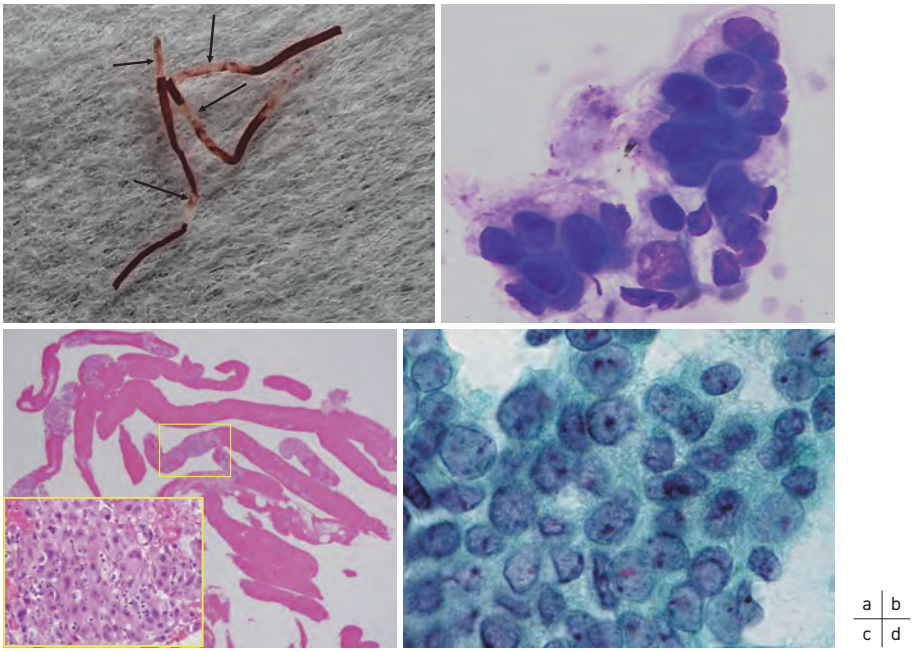


Figure 5 **Processing of acquired specimens.**

(a) The collected specimen shows yellow-white areas (arrows), suspected to contain tumor cells.
(b) Rapid onsite evaluation using Diff-Quik staining reveals cellular clusters with marked nuclear size variation, indicating sufficient tumor tissue for pathological diagnosis, allowing termination of the procedure.
(c) Histological examination with hematoxylin and eosin staining finds tumor tissue with a high nuclear-to-cytoplasmic ratio, distinct nucleoli, and mitotic figures among red blood cells.
(d) Cytological analysis with Papanicolaou staining reveals clusters of cells with nuclear atypia such as notching and prominent nucleoli.

withdraws the scope probe from the endoscope.

(viii) The collected specimen is expelled onto a glass slide or Petri dish, by use of either air pressure or the stylet to extract any remaining material from the needle lumen. Rapid staining is required to assess sample adequacy.

(ix) If the obtained sample is deemed insufficient, the puncture is repeated following the same steps. Once an adequate specimen is collected, the procedure is completed after the confirmation that there is no gastrointestinal bleeding on endoscopic examination and no hypoechoic area suggestive of a hematoma on ultrasound imaging.

3) Specimen handling (Figure 5)

(i) Reliable sample collection improves diagnostic accuracy and reduces the need for repunctures. Rapid on-site pathologic evaluation (ROSE) by a pathologist or cytotechnologist during EUS-sampling/FNA is preferred to assess whether an adequate specimen has been acquired. After visual confirmation, blood components are removed from the collected samples, and portions suspected to contain tumor cells (yellow-white areas in **Figure 5a**) are subjected to Diff-Quik or Cyto Quick staining (**Figure 5b**). This method is highly practical and enables microscopic examination within five minutes. False-negative results are a concern with EUS-sampling/FNA, but the presence of a pathologist or cytotechnologist should reduce the risk. If ROSE is unavailable, the endoscopist may perform staining

and microscopy respectively to determine sample cellularity.

(ii) For institutions where ROSE is not available, adequately collected samples deemed suitable for histological evaluation are submitted for tissue diagnosis (**Figure 5c**). While blood contamination is unavoidable, excessive blood content can be removed manually before submitting the specimen in formalin. This process is called macroscopic on-site evaluation (MOSE) for collecting portions assumed to contain tumor cells (yellow-white areas). In cases where ROSE is not performed, multiple needle passes are required for a puncture process. However, it has been reported that there is no significant difference in the positive diagnostic accuracy with or without ROSE when three passes are performed with an EUS-FNB needle.[18] Additionally, the target sample check illuminator may assist in verifying the presence of tumor tissue in the collected sample.[19]

(iii) For the remaining unused specimen or specimen insufficient for tissue diagnosis, wet fixation with 95% ethanol (for Giemsa staining) and dry fixation (for Papanicolaou staining) are performed and submitted to pathology (**Figure 5d**). Moreover, cell block method consolidates cells and small tissue fragments into a single specimen for histological evaluation. This allows for efficient sample utilization.[20] Liquid-based cytology method has gained attention for minimizing blood contamination and preventing cell desiccation or damage. In this method, cells are suspended in a liquid medium before being evenly smeared onto a slide.[21]

4) Improvements in EUS-sampling/FNA technique

Various techniques have been developed to optimize sample collection efficiency. Door knocking technique involves rapid needle movements. Woodpecker technique uses fine, repetitive needle motions. Funning technique adjusts the needle angle to sample different regions of a tumor. Several aspiration strategies exist, for example, no aspiration, high negative pressure aspiration using a 50 mL syringe, the slow-pull technique where the stylet is gradually withdrawn, and the wet aspiration technique which fills the needle lumen with saline before aspiration. No single approach is universally superior, and adjustments to the sampling method are necessary when specimen collection is inadequate.

(7) Endoscope cleaning and infection control

Since this is an interventional procedure, endoscopes and puncture needles should be replaced for each patient. Puncture needles are prone to contamination due to their length, requiring careful handling. Standard precautions should be observed to ensure healthcare worker safety, same as with other endoscopic interventions.

3. Study Result of Diagnosis

(1) Solid pancreatic masses

A meta-analysis of pathological and histological studies using EUS-sampling/FNA for solid pancreatic masses has reported a sensitivity of 84 to 92%, specificity of 96 to 98%, and an overall diagnostic accuracy of 86 to 91%, demonstrating high diagnostic performance.[22-24]

The development of EUS-FNB needles which allow for larger tissue sampling, has further improved histological analysis of solid tumors. A meta-analysis comparing EUS-FNB and EUS-FNA needles

indicated that EUS-FNB achieved a higher diagnostic accuracy (87% vs. 80%, p=0.02) and a greater tissue core rate (80% vs. 62%, p=0.002).[25]

(2) Biliary tract

For malignant biliary strictures, a meta-analysis of EUS-TA including 20 studies with 957 cases found a sensitivity of 80% (95% CI: 74–86%), specificity of 97% (95% CI: 94–99%), and a diagnostic odds ratio of 70.53 (95% CI: 38.62–128.82),[26] indicating that EUS-TA is a valuable diagnostic tool in cases where ERCP-based diagnosis is challenging. The rate of adverse events was low, at 1% (4 cases) across 11 studies involving 383 cases.

Hijioka reported that EUS-TA achieved 100% sensitivity in diagnosing 19 cases of gallbladder mass.[27] In another study involving 50 cases suspected of gallbladder carcinoma, EUS-TA targeting regional lymph nodes or gallbladder carcinomas demonstrated a sensitivity of 94.8%, confirming its high diagnostic yield.

(3) Duodenal ampullary tumors

For ampullary lesions, EUS-TA is particularly useful for non-exposed submucosal tumor types. A study by Defrain evaluating 35 cases of suspected ampullary tumors reported a sensitivity of 82%, specificity of 100%, and diagnostic accuracy of 89%.[28] Ogura further demonstrated that EUS-TA achieved 100% diagnostic accuracy in cases of suspected non-exposed submucosal tumors without causing adverse events, compared with ERCP-guided biopsy (70%).[29]

(4) Lymphadenopathy

In cases of lymphadenopathy, Yasuda evaluated 104 cases of intra-abdominal lymphadenopathy of unknown origin with EUS-sampling/FNA, reporting an overall diagnostic accuracy of 98%. Among these cases, 16 were metastasis, 48 were lymphomas, and 40 were benign/reactive lymphadenopathies.[30] EUS-sampling/FNA was particularly valuable for staging malignant tumors and for cases where primary lesions were difficult to approach. In lymphoma cases, EUS-sampling/FNA enabled subclassification in 88% of cases, which contributed to treatment selection.

(5) Submucosal tumors

For subepithelial lesions (SELs), rates of tissue acquisition by EUS-sampling/FNA needles have been reported as low. A meta-analysis including studies on EUS-FNA needles showed a polled diagnostic rate of 59.9%.[31] Since immunostaining is necessary for diagnosing subepithelial tumors, EUS-FNB needles allow for greater sample collection and have been shown to be beneficial. In a meta-analysis comparing EUS-FNB and EUS-FNA needles, EUS-FNB needle demonstrated a pooled rate of adequate samples (94.9% vs. 80.6%) and a higher diagnostic accuracy (87.9% vs. 64%).[32]

(6) Genetic analysis of FNA sample

Advancements in next-generation sequencing (NGS) technology have enabled comprehensive genetic analysis, facilitating the application of genomic medicine for cancer treatment. In Japan, two cancer gene panel tests, OncoGuide™ NCC Oncopanel (NCC) and FoundationOne® CDx Cancer Genomic Profile (F1Cdx), are available and generally performed with specimens acquired via EUS-sampling/FNA. For pancreatic carcinoma, genomic profiling has allowed for targeted therapies, including pembrolizumab for high microsatellite instability (MSI-High) and high tumor mutation burden (>10 mut/Mb), as well as TRK inhibitors for NTRK fusion gene-positive tumors. Although EUS-sampling/FNA-based genomic profiling has become feasible, further studies are needed to evaluate its clinical utility and outcomes.[33)]

4. Adverse Events

The overall adverse event rate for EUS-sampling/FNA is approximately 1%, and it is recognized as a very safe procedure. Reported complications include bleeding, abdominal pain, pancreatitis, pancreatic juice leakage, infection, tumor seeding along the puncture tract, and gastrointestinal perforation caused by the endoscope. In a systematic review in 2011, the analysis of 10,941 cases of EUS-sampling/FNA with a 22G needle revealed a pancreatitis rate of 0.44%, a postprocedure pain rate of 0.34%, and a mortality rate of 0.02% (2/10,941 cases).[34)] One potential concern is the risk of tumor seeding following puncture, which is discussed in the section of Contraindications for EUS-Guided Sampling/FNA. EUS-sampling/FNA for intraductal papillary mucinous tumors has been associated with an increased adverse event rate compared with solid pancreatic tumors, and cases of peritoneal dissemination also have been reported in Japan.[35)] As a result, the routine use of EUS-sampling/FNA for papillary mucinous tumors in clinical practice remains limited. A summary of major adverse events and their management is provided in **Table 2**.

While EUS-sampling/FNA is a valuable and relatively safe procedure, complications such as bleeding sometimes occur, and there are concerns regarding peritoneal dissemination and recurrence along the puncture tract. Therefore, its application should be limited to cases where the diagnostic outcome directly impacts treatment decisions.

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Hiroyuki Isayama and Masayuki Kitano

5 Endoscopic Sphincterotomy, EPBD, and EPLBD (Including Stone Removal)

1. Indications and Contraindications

The indications for endoscopic sphincterotomy (EST) are outlined in **Table 1**.[1,5] Endoscopic papillary balloon dilation (EPBD) is primarily indicated for the management of common bile duct stones, particularly in cases with bleeding tendency, papillae located within diverticula, or surgically altered anatomy. In high-risk cases for post-ERCP pancreatitis, such as those with a history of acute pancreatitis or suspected sphincter of Oddi dysfunction, EST is the preferred option.[3] When stone removal is difficult with EST or EPBD alone, such as in cases of large or stacked stones, endoscopic papillary large balloon dilation (EPLBD) is indicated.[4]

In general, EST should be avoided in patients with acute pancreatitis, unless their pancreatitis is caused by gallstones. It's also usually not recommended for patients who are prone to bleeding because they're taking anticoagulant medications. However, these contraindications may be reconsidered if the patient's condition improves. According to the *Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment*,[5,6] EST is classified as a high-risk procedure for bleeding, although certain antiplatelet agents may be continued during the procedure. It is generally recommended to follow the guidelines. EPBD is classified as a low-risk procedure for bleeding, whereas EPLBD is considered a high-risk procedure. Therefore, EPLBD is generally not recommended for patients who have an increased risk of bleeding, such as those taking antithrombotic medications. Furthermore, EPLBD should be avoided in cases with significant distal bile duct strictures or a non-dilated bile duct, since these conditions increase the risk of perforation.

Table 1 Indication for EST.

Treatment	1. Stone removal and bile duct drainage for common bile duct stone, intrahepatic stone, gallstone pancreatitis, and acute cholangitis 2. Bile duct drainage for benign and malignant bile duct stricture and papillary tumor 3. Stricture release for benign papillary stricture 4. Gallbladder drainage for acute cholecystitis
Diagnosis	1. Transpapillary bile duct biopsy 2. Biopsy of non-exposed mass-forming ampullary carcinoma 3. Peroral choledochoscopy 4. Intraductal ultrasonography

(Modified from Literature 1)

2. Pretreatment and Sedation

For patients on antithrombotic therapy, the preoperative related-management should be guided by the relevant guidelines.[5,6] When performing endoscopic sphincterotomy (EST) in patients with an implanted pacemaker, it is necessary to check the pacemaker both before and after the procedure. Endoscopic procedures for the biliary and pancreatic ducts, including papillary interventions and stone removal, often require additional intraoperative techniques. Therefore, all anticipated equipment should be prepared and checked in advance, including scopes and therapeutic instruments. Continuous monitoring including capnography is essential for patient safety and comfort during the procedure. Sedation should be administered according to the *Guidelines for Sedation in Gastroenterological Endoscopy* (second edition).[7] Generally, a combination of sedatives such as midazolam or flunitrazepam and analgesics such as meperidine hydrochloride or pentazocine is available, with dosage adjustments for elderly patients. Given the risks of respiratory depression and hypotension, supplemental oxygen should be administered via nasal cannula at 2 L/min, and antagonists such as flumazenil and naloxone hydrochloride should be readily available. To achieve more stable sedation, dexmedetomidine hydrochloride and propofol are acceptable. However, due to their higher risk of respiratory and cardiovascular adverse effects, they should be administered in accordance with institutional protocols and safety guidelines.

3. Practical Procedure

(1) Endoscopic sphincterotomy

1) Device and equipment

For endoscopic sphincterotomy (EST), a sphincterotome is inserted into the bile duct through the papilla, and the intraduodenal bile duct including the common channel is incised with high-frequency current. To ensure reliable access to the bile duct, the use of a guidewire-assisted sphincterotome is recommended. Sphincterotomes with a short distal end (5-7 mm) or with a short cutting wire (20 mm) offer superior maneuverability. The preferred high-frequency current setting is the endocut mode. This function automatically alternates between cutting and coagulation waves, thereby minimizing bleeding and the risk of an abrupt, uncontrolled incision (zipper cut).

2) Incision range and direction

Once biliary cannulation is achieved, the sphincterotome is gently advanced into the bile duct and then pulled back slightly. The incision is made using the distal one-third of the cutting wire. A steady, controlled incision with moderate tension ensures efficiency while reducing energy application time. A small incision is confined within the hooding fold, a large incision extends up to the upper border of the oral protrusion, and a medium incision is between these two extends (**Figure 1**).

- To minimize the risk of bleeding and perforation, the incision should be directed between the 11 o'clock and 12 o'clock orientations, with the 12 o'clock orientation serving as the reference line connecting the papillary orifice to the oral protrusion.
- The scope should be slightly withdrawn to center the papilla on the screen, and the blade should be tensioned against the mucosa. Gradual elevation of the forceps elevator with maintaining the

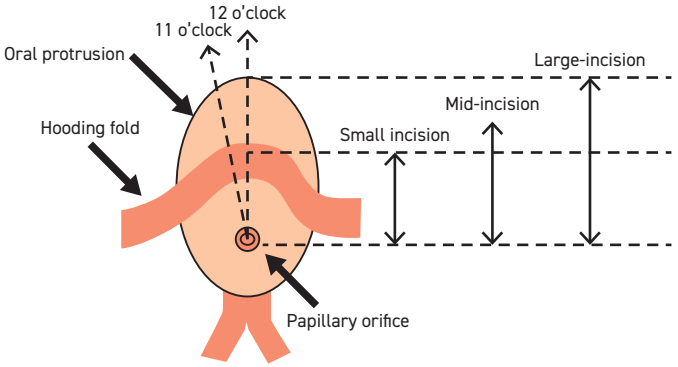


Figure 1 **Incision range and direction for EST.**

The recommended direction of incision for endoscopic sphincterotomy (EST) is between the 11 o'clock and 12 o'clock orientations. The extent of the incision should ideally be of medium size.

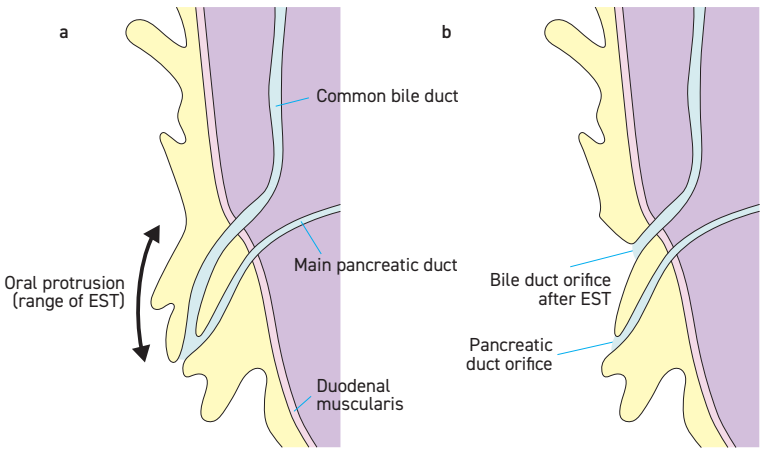


Figure 2 **Cross-sectional view of the papilla before and after a midline incision.**

(a) Prior to EST, the oral protrusion of the duodenal papilla is formed by the intramural portion of the bile duct penetrating the muscular layer of the duodenum. Incision of this region does not cause perforation due to its anatomical structure.
(b) After a mid-incision, the orifice of the bile duct and the pancreatic duct become separated.

mucosa under tension helps ensure a controlled and accurate incision.

- In general, the pancreatic orifice should be exposed, and the incision should extend slightly beyond the hooding fold to stay within the medium incision range (**Figure 2**).
- The bile duct course initially follows the 11 or 12 o'clock orientation near the hooding fold and then shifts toward the 12 o'clock orientation. Therefore, the initial incision should be made at the 11 o'clock orientation, but from the hooding fold to the oral protrusion, a midline incision is preferable.

(2) EPBD (Endoscopic papillary balloon dilation)

- For endoscopic papillary balloon dilation (EPBD), a dilation balloon with an expansion diameter of 8 to 10 mm is advanced over a guidewire into the bile duct. It is gradually inflated at low pressure over approximately two minutes using contrast medium diluted two- to three-fold.
- In the inflation process, the sphincter of Oddi creates a centrally depressed area or notch in the balloon. Once this notch disappears and the balloon becomes evenly expanded, that pressure is maintained, usually at around 2 to 4 atm, for about 15 seconds before gradually deflating the balloon.
- For patients with a narrow bile duct, a dilation balloon with an expansion diameter of 6 mm or less should be selected, or dilation should be terminated before the notch disappears to reduce the risk of bile duct perforation.[8)]

(3) EPLBD (Endoscopic papillary large balloon dilation)

- For endoscopic papillary large-balloon dilation (EPLBD), a small or medium EST is usually performed prior to balloon dilation.
- A dilation balloon with an expansion diameter of 12 to 18 mm is inserted over a guidewire into the bile duct, and the center of the balloon should be positioned at the papilla. It is then gradually inflated at low pressure (2 to 3 atm) with use of contrast medium diluted two to three times.
- Once the central notch of the balloon disappears or a pressure of 2 to 3 atm is reached, that pressure is maintained for 15 to 30 seconds. The dilation is then slowly released while the absence of bleeding is confirmed.
- If the notch does not disappear even when the pressure exceeds 2 to 3 atm, further pressurization should be avoided.[9)]

4. Technical Tips for Difficult Cases

(1) Precut sphincterotomy

This technique is employed in cases where biliary cannulation through the papillary orifice is difficult by the standard approach. This process involves directly incising the duodenal papillary mucosa to expose the bile duct orifice for deep cannulation. There are two methods for this approach: a needle-knife technique and a conventional sphincterotome technique. Due to the high risk of adverse events such as bleeding, perforation, and pancreatitis, this procedure requires a high level of technical proficiency.[10,11)]

1) Precutting with needle knifes

(I) Incision from papillary orifice (precut papillotomy)

- In precut papillotomy using a needle-knife, the incision is made from the upper margin of the

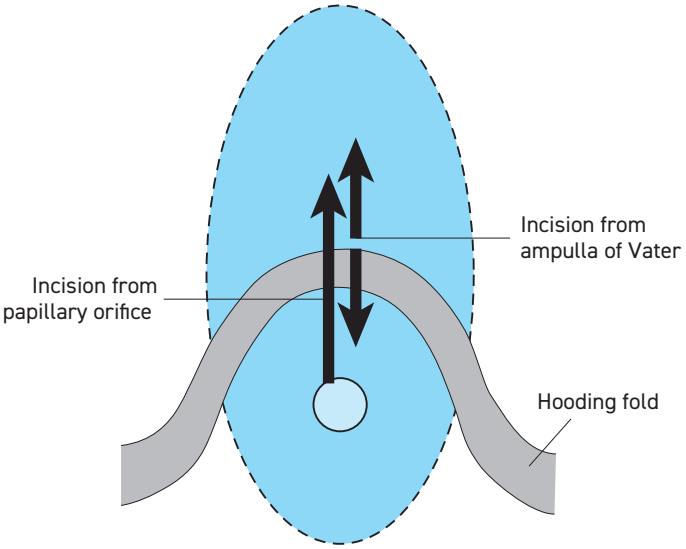


Figure 3 **Precut using needle knifes.**

Precut techniques include precut papillotomy, in which the incision starts at the orifice of the papilla, and fistulotomy (infundibulotomy), in which the incision is performed at the papillary bulge.
(Cited from Literature 1)

papillary orifice toward the midline of the oral protrusion in the 12 o'clock orientation (**Figure 3**).

- The incision is progressively deepened from just before the hooding fold, typically reaching the papillary bile duct slightly beyond this fold.
- Once bile flow is observed, the bile duct orifice is usually identified, thereby enabling cholangiography with an injection catheter. If necessary, an additional sphincterotome or a dilation balloon is used to enlarge the orifice. When initial biliary cannulation fails, the procedure involves repeated small incisions combined with injection of small amounts of contrast medium.
- In cases where biliary cannulation remains unsuccessful, another attempt should be made after 48 hours once the swelling has subsided. At that point, tissue sloughing at the incision site facilitates identification of bile duct orifice.

(II) Incision from the papillary roof of the ampulla of Vater (fistulotomy or infundibulotomy)

For fistulotomy or infundibulotomy, the incision is made either from just before the hooding fold toward the midline of the oral protrusion in the 12 o'clock orientation or from the ampulla in a downward direction (**Figure 3**). This approach is particularly useful when the papillary orifice is not visible in the frontal view or in cases of impacted papillary stones. However, it should be reserved for cases with ampullary hypertrophy.

(III) Incision under pancreatic duct stent placement

Precut sphincterotomy is also performed under pancreatic stent placement to reduce the risk of pancreatitis.[12] A 5-Fr pancreatic stent is placed, and the needle-knife is guided along the stent while an incision from the upper margin of the papillary orifice toward the 12 o'clock orientation is performed. This approach helps maintain pancreatic juice drainage and aids in estimating the location of the papillary bile duct.

(IV) Incision under bile duct stent placement

For patients with surgically altered anatomy, such as those with Billroth II or Roux-en-Y reconstruction, the procedure is facilitated using a normal upper gastrointestinal endoscope or a balloon-assisted enteroscope. In these cases, a 5 or 7 Fr biliary stent is placed to simplify the procedure, and the incision is made using a needle-knife to expose the stent. Given the reverse approach, careful incision along the stent ensures safer completion.

2) Precut with a standard sphincterotome

Precut sphincterotomy with a standard sphincterotome includes techniques such as the transpancreatic sphincter precut method, where the sphincterotome is inserted into the pancreatic orifice to make an incision. Another approach involves using a short-tipped sphincterotome (with a 0-3 mm tip) to make an incision directly at the openings of the bile and pancreatic ducts. Both methods primarily aim for incision toward the bile duct. However, the anatomy of the pancreaticobiliary junction may vary, with some patients having a very short or even absent common channel. Therefore, accurate assessment of the three-dimensional course of the bile duct is crucial for making an effective incision and achieving successful biliary cannulation.

(2) Intradiverticular papilla and periampullary diverticulum

In cases where the papilla is located within a diverticulum or adjacent to it (parapapillary diverticulum), a ridge or oral protrusion representing the course of the bile duct is often observed inside the diverticulum. When this ridge is present, the incision should be made along its path. By applying appropriate tension to the guidewire during withdrawal, the direction of the bile duct can be clearly identified. This also helps in determining the upper margin where the incision should be made. In cases where the papilla is displaced by a parapapillary diverticulum or when the oral protrusion is obscured by an intradiverticular opening, determination of the appropriate direction and length of the incision becomes challenging. This increases the risk of bleeding and perforation events.[13] One method to address this is to inflate a retrieval balloon within the papilla to visualize the oral protrusion and determine the correct incision direction.[14] In cases where the bile duct direction remains unclear, it is safer to limit the incision and combine the procedure with EPBD rather than continuing endoscopic sphincterotomy (EST) alone. EPLBD is feasible for cases involving an intradiverticular papilla or a parapapillary diverticulum. Although the risk of perforation may be higher than in patients with a normal papilla. Therefore, careful and gradual low-pressure balloon dilation is necessary to minimize adverse events.[4]

5. Stone removal after EST, EPBD, and EPLBD

(1) Common bile duct stone

1) Treatment method

(I) Asymptomatic to severe cholangitis

For asymptomatic or mild to moderate cholangitis, single session endoscopic stone removal is attempted. In cases of severe cholangitis, biliary drainage should be introduced initially, and endoscopic biliary stenting (EBS) or endoscopic nasobiliary drainage (ENBD) should be performed. Even in

patients taking antithrombotic medications or those with coagulation disorders, the initial priority is to perform biliary drainage to relieve obstruction. Once coagulation function has been corrected or antithrombotic medications have been temporarily withheld, stone removal is performed as a second session procedure.[15]

(II) Gallstone pancreatitis

In gallstone pancreatitis, the extent to which the stone is lodged in the papilla varies among patients. Some cases are resolved by displacement of the impacted stone into the bile duct during biliary cannulation, while others require precut sphincterotomy for stone release. Regardless of the severity, endoscopic sphincterotomy (EST) is performed before stone removal or biliary drainage.[16] EPBD and EPLBD are not used due to the risk of exacerbating pancreatitis.

(III) Concomitant gallbladder and common bile duct stones

For patients with concurrent gallbladder and common bile duct stones, endoscopic stone removal is generally indicated first, followed by laparoscopic cholecystectomy for residual gallbladder stones. It is reported that residual gallbladder stones have a high risk of symptom recurrence.[17]

(IV) Choledochoduodenal fistula

In patients with a choledochoduodenal fistula due to spontaneous passage of common bile duct stones, a fistulous opening may be observed at the papilla orifice. If no residual stones are present, only observation is adequate. However, if residual or recurrent stones are detected and the fistula opening is narrow, an incision to facilitate stone extraction should be performed along the midline from the papillary orifice up to, but not beyond, the oral protrusion. When the fistula is located at the oral protrusion, EST is sometimes performed from the fistula without extending beyond the midline of the oral protrusion.

2) Endoscopic stone removal

For endoscopic stone removal, stones measuring larger than 7 or 8 mm or presence of multiple stones increase the risk of basket impaction, necessitating the use of mechanical lithotripsy. Stone removal should proceed in order from the papillary side. For stones smaller than 7 or 8 mm, a four-wire basket catheter is safer and more useful since it facilitates release from impaction, and stone removal is effectively performed with the basket open. For stones smaller than 3 mm, a multi-wire basket is preferred, while a balloon catheter is effective for biliary sludge. An endotriptor should be kept on hand to address basket impaction. For larger stones, mechanical lithotriptor is selected to fragment the stones before removal. If mechanical lithotripsy fails to grasp the stone, peroral cholangioscopy-guided lithotripsy or extracorporeal shock wave lithotripsy should be introduced.[18]

3) Comparison of EST and EPBD

In comparing EST and EPBD, EST is superior in complete stone removal rate and mechanical lithotriptor usage rate. However, EST is associated with a significantly higher rate of stone recurrence.[8,19] Risk factors for recurrence include papillary dysfunction, the presence of a parapapillary diverticulum, decreased gallbladder motility and persistent dilatation of the common bile duct. These conditions lead to bile stasis or retrograde biliary infection, both of which are considered to increase the risk of stone recurrence. Additionally, EST is associated with an increased incidence of pneumobilia, whereas EPBD may better preserve papillary function.

4) Comparison of EST and EPLBD

Regarding comparisons between EST combined with EPLBD and EST alone for bile duct stones, previous reports have indicated that there is no significant difference in the overall successful stone removal rate.[20] However, EPLBD has been reported not only to significantly reduce the need for mechanical lithotripsy in cases of large stones but also to shorten both operation time and radiation exposure.[21]

6. Adverse Events and Postoperative Management

- Early adverse event reports[2,3,22] following post-endoscopic sphincterotomy indicate the incidence of (EST) pancreatitis ranges from 0.8% to 6.9%, bleeding from 0% to 27%, perforation from 0% to 1.8%, cholangitis from 0% to 4.2%, and cholecystitis from 0% to 4.2%. Following endoscopic papillary balloon dilation (EPBD), the reported incidence of pancreatitis ranges from 4.8% to 15.4%, bleeding from 0% to 0.2%, perforation from 0% to 0.4%, cholangitis from 0.9% to 2.7%, and cholecystitis from 0% to 2.2%. Following endoscopic papillary large-balloon dilation (EPLBD), the incidence of pancreatitis ranges from 0% to 13.2%, bleeding from 0% to 10.0%, perforation from 0% to 2.5%, and cholangitis from 0% to 5.0%.
- No significant difference has been observed in the overall adverse event rate between EST and EPBD, but pancreatitis is the most concerning adverse event, and occurs significantly higher in EPBD.[23,24] In contrast, the incidence of pancreatitis in EPLBD is comparable to that of EST.[20]
- Precut sphincterotomy is associated with a higher risk of adverse events than standard EST, particularly post-procedural pancreatitis.[10,25]

(1) Acute pancreatitis (Post-ERCP pancreatitis)

Post-ERCP pancreatitis occurs due to mechanical stimulation caused by insertion of an injection catheter, sphincterotome, or dilation balloon; injuries from incision, thermal injury, or dilation; direct irritation from contrast medium or increased intraductal pressure; and retrograde infection. These factors contribute to papillary edema, sphincter spasm, pancreatic duct epithelial injury, and pancreatic duct spasm, resulting in impaired pancreatic juice outflow and acinar cell damage.

- Preventive measures include gentle and efficient cannulation while minimizing repeated intubations.
- During EST, incision should be performed smoothly to expose the opening of the pancreatic duct. In EPBD and EPLBD, dilation balloons in proper size should be selected, and the dilation should be performed slowly at low pressure.
- EPBD and precut sphincterotomy are identified as risk factors, and therefore their use should be carefully indicated.
- Temporary pancreatic stent placement is a useful preventive measure against transient obstruction of pancreatic outflow.[26,27]

The prophylactic use of rectally administered NSAIDs before or after ERCP has been reported to be effective in reducing post-ERCP pancreatitis.[26] Postoperative monitoring for symptoms and vital signs is essential, and when pancreatitis is suspected, laboratory tests and CT imaging should be performed as

appropriate. Early diagnosis and timely initiation of treatment are crucial for preventing disease progression.[26)]

(2) Hemorrhage

- The central vessel at the apex of the oral protrusion is thin and generally coagulated during a standard midline incision. It is important to avoid rapid incision or excessive enlargement of the incision.
- Careful monitoring is required for not only late bleeding a few days after EST but also early post-EST bleeding due to the resumption of antithrombotic therapy.

When managing post-EST bleeding, precise identification of the bleeding source is crucial. Hemostatic techniques include local injection of hypertonic saline-epinephrine (HSE), argon plasma coagulation (APC), coagulation using high-frequency current, balloon tamponade, and mechanical hemostasis with clipping.[2)] Recently, the use of self-assembling peptide hemostatic gel has been reported as a safe and effective method for achieving hemostasis.[28,29)] In cases where conventional methods fail to achieve hemostasis, temporary placement of covered self-expandable metal stent for compression hemostasis has been reported as a useful option.[30)]

(3) Perforation

- Particular attention should be given to the direction and depth of precut incisions, the incision direction in cases of intradiverticular or parapapillary diverticulum papilla, and the use of balloons larger than the bile duct diameter in EPLBD.
- Perforation could also occur during the insertion of therapeutic instruments such as mechanical lithotripters. To minimize its risk, guidewire-assisted instruments should be used, and devices should be advanced gently along the indwelling guidewire.

X-ray fluoroscopy should be applied to check for free air in the peritoneal cavity, particularly beneath the liver or around the right kidney. However, free air is less readily detected on fluoroscopy, and when perforation is suspected based on contrast medium leakage or improper positioning of instruments, CT evaluation should be undertaken. Conservative management is possible for cases of stable general conditions, localized peritonitis in the upper abdomen, and minimal contrast medium leakage or minimal ascites. For papillary perforation due to EST, endoscopic nasobiliary drainage (ENBD) should be selected to prevent bile leakage, and treatment should include gastric tube placement and continuous aspiration. If clinical symptoms or findings do not improve within 24 hours, surgical intervention is required with the close coordination of a surgical team.[31)]

(4) Biliary infection

- Biliary infections, such as cholangitis and cholecystitis, develop primarily when bile flow is obstructed by residual common bile duct stones or swelling of the papilla after a procedure. They

may also result from retrograde infection caused by contrast injection proximal to biliary stricture or into the gallbladder.

In such cases, antibiotic therapy and biliary or gallbladder drainage should be considered.

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Shuntaro Mukai, Takao Itoi and Yoshinori Igarashi

6-(I) Endoscopic Biliary Drainage

- Transpapillary Biliary Drainage

1. Indications and Contraindications

Endoscopic biliary drainage (EBD) is indicated for malignant or benign biliary strictures, bile duct stones, and inflammatory conditions leading to biliary obstruction. Specific conditions include biliary tract cancer, pancreatic cancer, chronic pancreatitis, sclerosing cholangitis, common bile duct stones, acute cholangitis, cholecystitis, and biliary injury. Contraindications include poor general condition and allergy to contrast agents or history of anaphylactic shock, and any other contraindications related to ERCP.[1)]

2. Drainage Methods

Transpapillary EBD consists of two drainage approaches: endoscopic biliary stenting (EBS), which involves stent placement for internal drainage, and endoscopic nasobiliary drainage (ENBD), which provides external drainage (**Figure 1**).[2,3)] The choice of which of these methods to employ depends on the clinical situation, patient-specific factors, and the endoscopist's preference.



a | b | c

Figure 1 Drainage techniques.

a: Endoscopic biliary stenting with plastic stent (EBS with PS), b: Endoscopic biliary stenting with self-expandable metallic stent (EBS with SEMS), c: Endoscopic nasobiliary drainage (ENBD)

3. Practical Procedure and Key Points

Basic techniques

Before performing EBD, imaging modalities such as ultrasound (US), computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) should be conducted to assess the biliary system. This assessment helps determine the appropriate drainage method and select the proper devices. Careful planning of each procedural step is essential. The procedure is considered successful once biliary cannulation is achieved and cholangiography is performed to assess bile duct strictures and confirm stone location. Based on pre-procedural planning and cholangiographic findings, the drainage strategy is determined, an appropriate device is selected, and stent placement is performed with a clear understanding of its properties.[4] Failure at any stage of this process may compromise adequate biliary drainage.

1) Preprocedural planning

The purpose of EBD varies, from emergency drainage for acute cholangitis to jaundice reduction drainage.

In acute cholangitis, the drainage approach is determined depending on the cause. In cases of common bile duct stones, the number and characteristics of the stones are primarily assessed, and the drainage catheter should be advanced beyond the stones toward the hepatic hilum. In cases of biliary strictures, the location and length of the stricture are primarily determined, and the drainage catheter should be placed across the narrowed segment towards the hepatic hilum. Although the final decision is made after direct evaluation of the bile duct, the choice between EBS and ENBD should be discussed in advance. Given the possibility of biliary cannulation failure, backup planning for percutaneous transhepatic biliary drainage (PTBD) should be considered. For severe acute cholangitis, the volume of contrast injection should be minimized, and the suitability of EBD compared with PTBD should be carefully discussed.

In obstructive jaundice, the location and length of the stricture are primarily assessed to select whether a plastic stent (PS) or a SEMS should be placed. In hilar biliary strictures that require multiple stents, it is essential to determine which branches should be drained first and last. Furthermore, when placing multiple SEMSs in hilar strictures, it is crucial to decide in advance whether to use the stent-in-stent or side-by-side technique.

2) Biliary cannulation

For successful biliary cannulation, several methods are available (e.g., contrast method, wire-guided method, wire-loaded method). The choice of method should be based not on the endoscopist's preference, but on the anatomical characteristics of the Vater papilla and the shape of the endoscope, with the optimal insertion technique selected accordingly. When wire-guided or wire-loaded method is used, the endoscopist/assistant should carefully handle the guidewire, using torque control in combination with precise manipulation.

When a PS is placed in advance, there are two methods of performing biliary cannulation: Alongside the PS method and the snare-over-the-guidewire (SOG) method. The latter technique involves navigating a guidewire through the PS lumen to access the drainage area, followed by stent removal alone using a snare (**Figure 2**). The SOG technique is particularly useful for proximal hilar bile duct

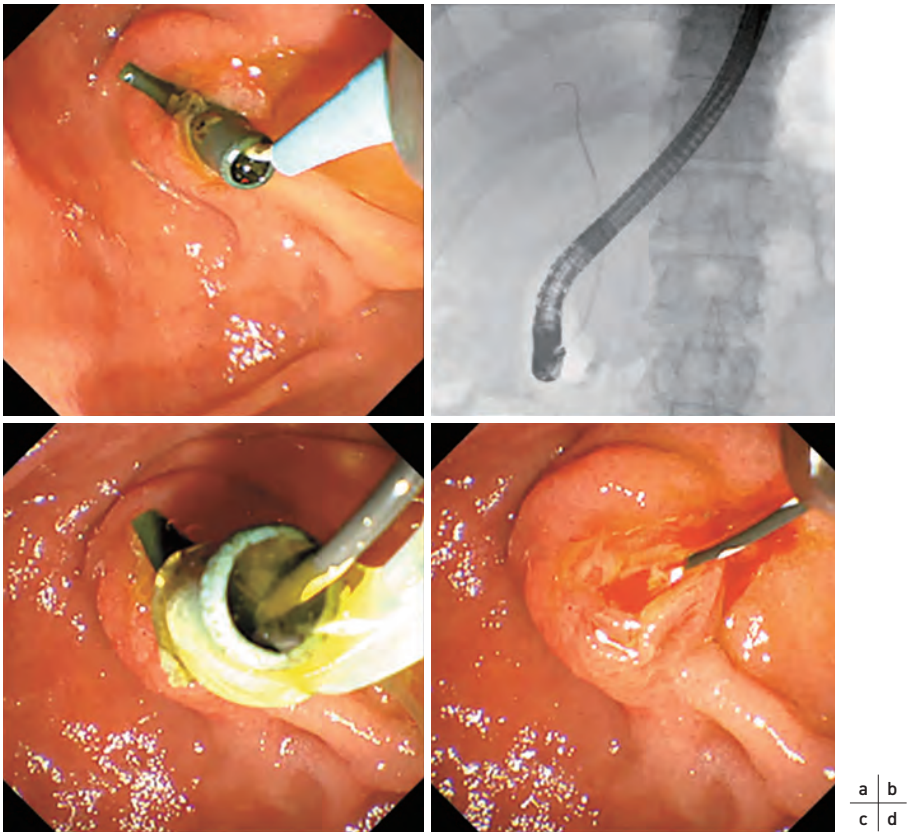


Figure 2 Snare-over-the-guidewire method.

(a) A guidewire is inserted into the bile duct through the lumen of the indwelling PS.
(b) The guidewire is visualized on fluoroscopy.
(c) A snare is inserted along the guidewire to grasp the PS.
(d) The PS is removed while guidewire position is maintained.

strictures because it ensures accurate guidewire placement in the targeted bile duct.[5] However, this technique should only be used with straight-type plastic stents. For pigtail-type plastic stents, the guidewire needs to be inserted alongside the stent instead.

3) Cholangiography

Proper cholangiographic assessment is critical for successful stent placement in both endoscopic biliary stenting (EBS) and endoscopic nasobiliary drainage (ENBD). Each stent has its own optimal resting position, and if the stent's shape and size do not conform to the bile duct anatomy, there is a risk of dislocation into the duodenum. For stent placement in the intrahepatic bile duct, a straight-type stent is generally more suitable for the anterior branch of the right hepatic duct or the B2 segmental branch, whereas a pigtail-type stent is less appropriate for these ductal structures. Conversely, for the posterior branch of the right hepatic duct or the B3 segmental branch, where the branch is more curved, a straight stent tends not to fit, and a pigtail stent is selected.

For multiple SEMS insertion in distal malignant biliary strictures, the distance between the stent tip and the hepatic hilum is a crucial factor. Therefore, cholangiography should be performed to identify the exact position of the hepatic hilum, which facilitates appropriate selection of stent length and type.



a b c
d e f

Figure 3 **Selecting right plastic stent based on bile duct anatomy (Cited from Literature 3).**

When placing a stent in the common bile duct, a pig-tail type PS with a smaller loop is preferable for optimal fit, as a large loop will not adapt well to the duct contour (a–c).
When placing the stent in the peripheral intrahepatic bile ducts, a pig-tail with a larger loop is required to ensure proper anchoring. A small loop will not provide adequate fixation (d–f).

When multiple SEMSs are placed for hilar biliary strictures, cholangiography is also necessary to determine the sequential order of stent placement (**Figure 3**).[3] Although cholangiography is essential for these procedures, excessive contrast injection should be avoided in cases of cholangitis. Even in patients without inflammation, a prolonged examination time often makes it difficult to obtain the sufficient cholangiographic findings. Thus preprocedural planning is essential for making evaluation.

4) Selecting appropriate devices

(I) Endoscopic biliary stenting with PSs

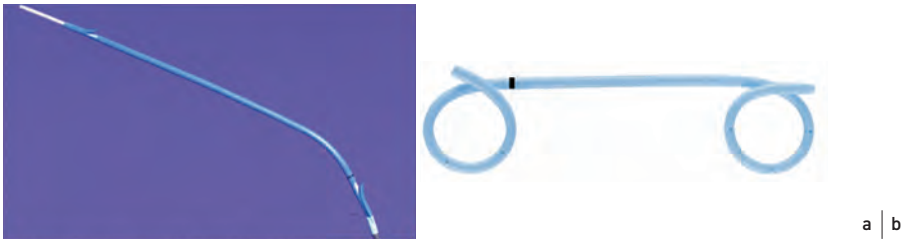
PSs offer advantages such as easy placement, replaceability, and affordability, but their main limitation is short patency. They are available in straight-type and pigtail-type configurations with outer diameters most commonly of 7 Fr, 8.5 Fr, and 10 Fr (**Figure 4**).[6]

For stent exchange, 7 Fr stents are usually removed through the working channel of most endoscopes. In contrast, 8.5 Fr and 10 Fr stents often require removal of the endoscope for replacement, particularly if a guidewire is in place. In some cases, this necessitates the removal of the stent together with the endoscope. Therefore, when stent replacement is anticipated, the placement of multiple 7Fr stents is a favorable option. Various manufacturers produce many PSs that differ in material, flap structure, hole number, and shape. Thus, it is important to understand the specific characteristics of the stents used at each facility. In particular, pigtail-type stents vary in loop length depending on the manufacturer. Additionally, some are sized by the length of the pigtail loops, whereas others are sized by total stent length. Understanding of these specifications is essential to ensure correct placement.

(II) Endoscopic biliary stenting with SEMSs

SEMSs provide excellent patency due to their self-expanding properties and wide lumen, reducing the likelihood of biliary sludge accumulation. However, they are expensive and typically indicated only for malignant biliary strictures.

SEMSs are categorized into braided-type and laser-cut-type, depending on the mesh structure and knitting method (**Figure 5**).[6]



a | b

Figure 4 **Straight-type and pig-tail-type PSs (Cited from Literature 6).**

(a) Straight-type PSs (Flexima, Boston Scientific)
(b) Pig-tail-type PSs (Medi-Globe, Medi-Globe GmbH)

The main features of SEMSs are:

- Relatively little unevenness in the stent lumen, making sludge accumulation difficult.
- More shortening effect than laser cut type
- Large delivery system diameter

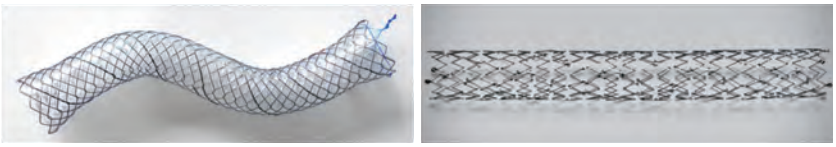
The laser-cut type is manufactured by cutting a nitinol tube into a mesh pattern with a laser. The mesh is subsequently expanded, and the crown-shaped ends are secured at three or four fixed points. The main features are:

- The delivery system diameter is smaller than the braided type.
- High bile duct tracking ability, enabling smooth placement even in bile ducts with complex branching structure in the hepatic hilum.
- Unevenness in the inner lumen of the stent predisposes to sludge accumulation.

Both types are available in covered SEMS (CSEMS) and uncovered SEMS (UCSEMS) forms, with fully covered SEMS (FCSEMS) and partially covered SEMS (PCSEMS) variants. CSEMSs prevent tumor ingrowth, and FCSEMSs can usually be removed if necessary. UCSEMSs are the first choice when stents are placed in bile duct branches, and are particularly preferred when multiple stentings are required in the hepatic hilum to avoid obstruction of bile duct branches.

(III) Endoscopic nasobiliary drainage

Endoscopic nasobiliary drainage (ENBD) tubes are classified based on whether they have a preformed α-shape or a straight configuration. When properly positioned, the α-shaped ENBD tube conforms to the natural α-curve extending from the papillary region into the stomach. Although α-shaped tubes are easier to position, their fixed length for bile duct placement restricts their ability to reach peripheral intrahepatic bile ducts. It is necessary to recognize that it has the property of being placed in the bile duct based on the design. They are further categorized into long-type, short-type, and reverse α-type, depending on the bile duct anatomy. ENBD and ENPD tubes used for the left intrahepatic bile duct adopt a reverse α-shape to fit the anatomical course. Although these all share the same α-shaped structure, the portion inserted into the bile duct beyond that point varies in length and shape. (**Figure 6**).[3] In contrast, non-α-shaped ENBD tubes are straight and can be freely positioned even into peripheral intrahepatic bile ducts. However, they require manual shaping to form the α-curve, which makes their placement more technically challenging.[3]



a | b

Figure 5 Self-expandable metallic stent (Cited from Literature 6).

(a) Braided-type (BONASTENT Standard Sci-Tech Inc.)
(b) Laser-cut-type (Zilber Cook Medical)

5) Understanding of device characteristics

(I) Endoscopic biliary stenting with PSs

Straight-type PSs are relatively straightforward to place. However, for pigtail-type PSs, it is important to understand that they remain **straightened within the inner sheath** inside the endoscope. Once the operator removes the inner sheath **and only the guidewire remains, the previously straightened shape gradually returns to its original form, as the tension that had kept it straight is released and the guidewire starts to recoil. As the guidewire transitions from its rigid section to the flexible portion, the winding strength becomes completely strong, and the pigtail loop fully forms.** This requires the endoscopist to anticipate this effect and determine the final placement site accordingly (**Figure 8**).[3)]

(II) Endoscopic biliary stenting with SEMSs

In clinical settings, several key factors should be considered when placing SEMS.

i) **Axial force and radial force**

Axial force (AF) refers to the stent's tendency to straighten after placement. When appropriately balanced, AF allows the stent to conform to the bile duct's curvature while maintaining its position through self-expansion. However, excessive AF may cause dislocation due to the straightening force, whereas insufficient AF may result in stent migration. Some SEMSs have relatively high AF, which increases the risk of misalignment in highly curved bile ducts (**Figure 9a**).[3)]

Radial force (RF) represents the outward pressure exerted by the stent after placement. Insufficient RF may lead to incomplete stricture dilation, while excessive RF increases the risk of dislocation or migration. Therefore, a moderate level of RF is considered optimal (**Figure 9b**). Understanding of the AF and RF characteristics of the SEMSs used in each facility is essential for appropriate selection.

ii) **Shortening effect**

The shortening effect refers to the reduction in stent length upon deployment, with some SEMS shortening to approximately two-thirds of their pre-deployment length (**Figure 12**).[3)] This occurrence is specific to the braided-type SEMSs. When using a braided-type SEMS, the initial deployment position should be carefully planned. In contrast, laser-cut-type SEMSs do not exhibit significant shortening effect, thus length selection is more straightforward.

Before an SEMS placement, confirm the shape of the outer sheath tip, the location and number of fluoroscopic markers, and the endoscopically visible indicator (often a yellow marker). An endoscopist

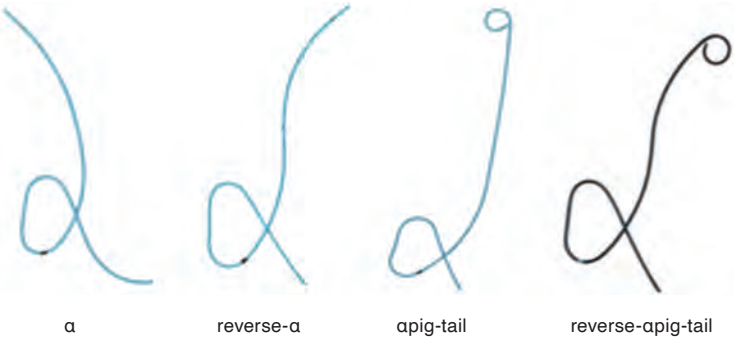


Figure 6 **Endoscopic nasobiliary drainage tubes (Cited from Literature 3).**

This figure shows alpha-type, reverse-alpha-type, alpha pig-tail-type, and reverse-alpha pig-tail-type ENBD tubes by Gadelius Medical.

performs stable SEMS deployment by holding the end of the inner sheath with the right hand and pressing it against the abdomen, then slowly withdrawing the outer sheath with the left hand to deploy it. The forward push of the inner sheath during deployment should be strictly avoided (**Figure 11**).

During deployment, the stent's self-expanding tip gradually emerges in a tulip-like fashion. Occasionally, a phenomenon termed “jumping” occurs, where the expanding stent suddenly protrudes forward. After partial deployment, the upper margin of the stent should be aligned with the intended position. As deployment progresses, the yellow marker becomes visible on the endoscopic screen, guiding accurate placement. Complete deployment should be performed while keeping the yellow marker in a fixed position to achieve stable placement. (iii) Placing endoscopic nasobiliary drainage tube

The placement difficulty of an endoscopic nasobiliary drainage tube (ENBD) tube depends on the type of drainage tubes:α-shape or straight type.

An α-shaped ENBD tube maintains its preformed curvature, making it less likely to collapse and resistant to dislocation. Placement is guided by black reference markers on the tube, which ensure proper formation of the α-loop. Importantly, this marker should be positioned at the bottom of the α-shape, rather than at the papilla, to confirm accurate placement. In contrast, the straight ENBD tube lacks a preformed curve, requiring endoscopists to manually create an α-loop during placement, which increases the technical difficulty.

A commonly used placement technique involves a two-person approach, where an assistant or nurse gradually withdraws the endoscope at the mouth of patients, while the endoscopist gently advances the ENBD tube. This synchronized movement ensures controlled placement. However, if both movements are not well-coordinated, the ENBD tube could dislodge, particularly when the scope moves from the bulb into the gastric cavity, it could fall out into the antrum.

A single-operator technique is also possible, but it involves alternating between slight withdrawal of the endoscope and gradual advancement of the tube in small steps. As the endoscope approaches the oral cavity, it may move unpredictably, increasing the risk of misalignment.

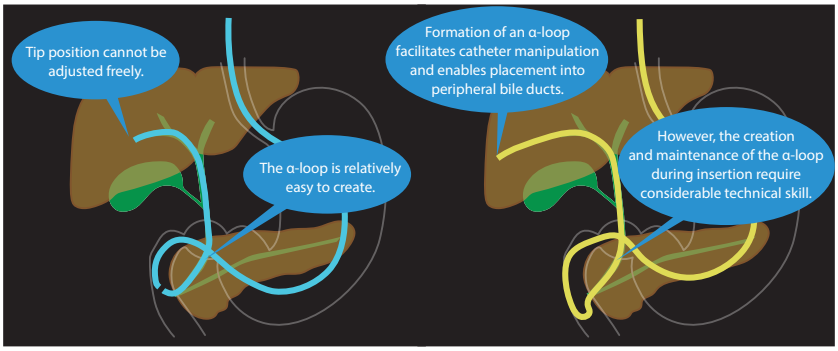


Figure 7 Influence of the αloop on the procedure (Cited from Literature 3).

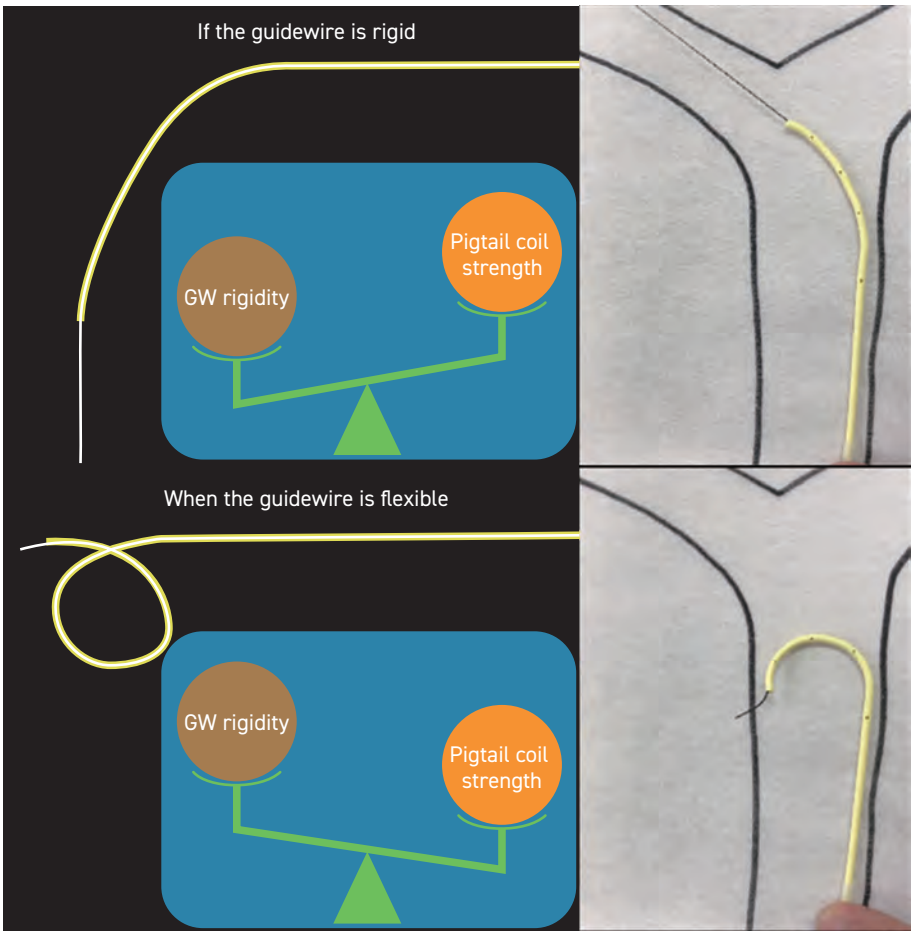


Figure 8 How the pigtail loop forms (Cited from Literature 3).

4. Adverse Events and Its Management

Endoscopic transpapillary biliary drainage carries the risk of adverse events such as cholangitis, cholecystitis, and post-procedural pancreatitis. Therefore, careful preventive measures, early detection,

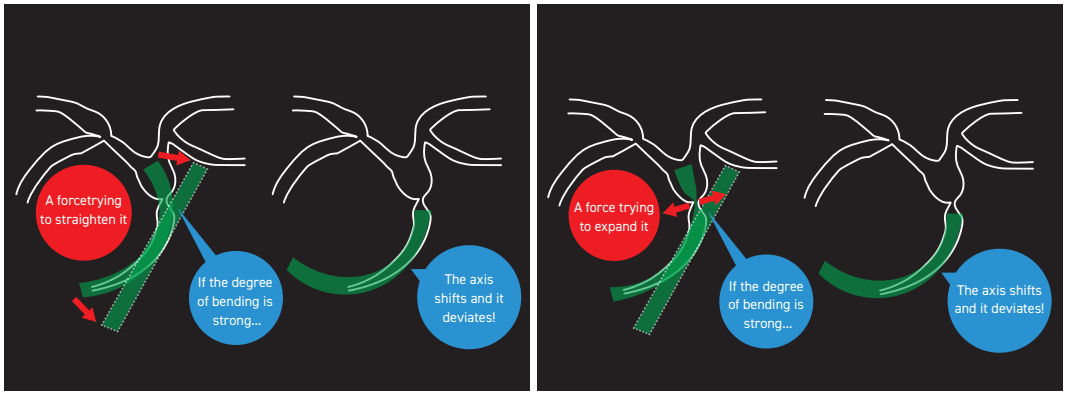


Figure 9 **Axial force and radial force (Cited from Literature 3).**

(a) If AF is excessive, it exerts a straightening force on the stent, increasing the risk of stent dislocation. If AF is insufficient, the stent may slip out.
(b) If RF is too strong, it similarly raises the risk of dislocation or deviation, particularly in highly curved ducts.

and timely treatment are essential. Informed consent concerning potential adverse events should be obtained in advance from the patient and family members.

(1) Cholangitis

Cholangitis may develop after EBS or ENBD, or when preexisting cholangitis fails to improve. When cholangitis occurs shortly after stent placement, it is important first to assess whether the final position and configuration of the stent are appropriate. Reevaluation of stent placement is essential to confirm proper function. To avoid inappropriate placement, thorough pre-procedural planning and discussion are required. For ENBD, accidental self-removal should be excluded first. In addition, because ENBD tubes are relatively thin (5–7 Fr), kinking or twisting along their course should also be considered.

When it is confirmed that the stent placement was unsuitable, the stent should be removed as soon as possible and replaced with a new one. This procedure requires using a more precise and effective placement technique.

In cases where cholangitis develops after a longer period following stent placement, stent occlusion, dislocation, or migration should be suspected. When stent occlusion is suspected, stent replacement is required. In cases of SEMS insertion for malignant biliary strictures, obstruction could occur due to tumor ingrowth or tumor overgrowth. When a CSEMS is in place, it should be removed and replaced. When a UCSEMS is in place, additional SEMSs or PSs should be inserted within the occluded stent.

In stent migration, retrieval should be performed using devices such as basket forceps, balloons, biopsy forceps, or graspers for PSs. For SEMS, stent migration often results in its expansion on the hepatic side of the stricture or just above the papilla. In such cases, the lower end of the stent may become embedded in the pancreatic parenchyma, making retrieval difficult. If the lower end of the SEMS is successfully grasped, the stent can be thinned to be removed safely. Another approach is to grasp the upper end of the SEMS with forceps and turn it inward to facilitate removal. It is important that excessive force should be avoided to prevent unintended adverse events.

A 7 Fr PS or an FCSEMS can usually be removed through the endoscopic instrument channel. In

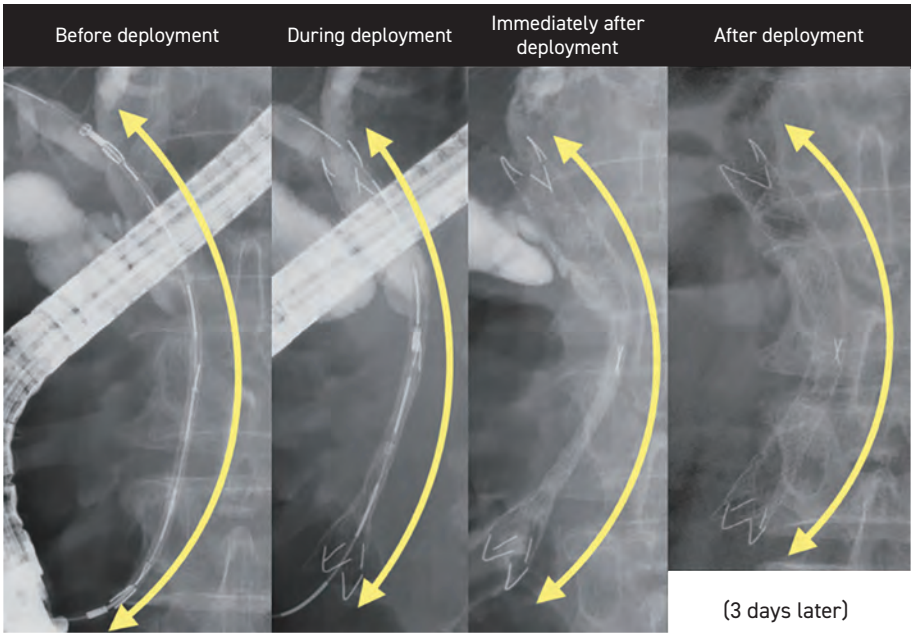


Figure 10 Shortening by deployment of SEMS (Cited from Literature 3).

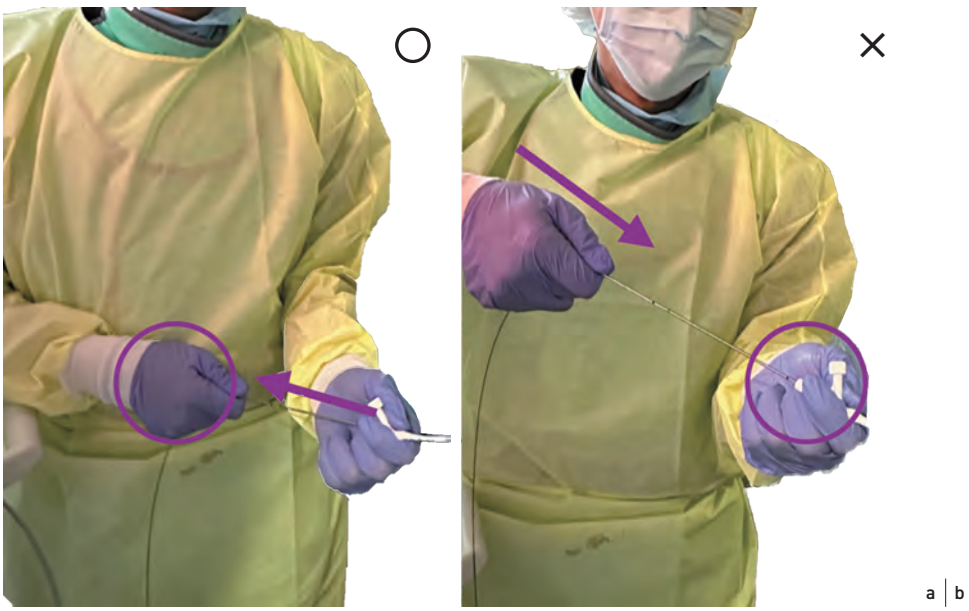


Figure 11 Technique of SEMS deployment.

(a) The end of the inner sheath is held with the right hand and fixed against the abdomen (marked section), while the outer sheath is gradually withdrawn with the left hand to deploy the stent.
(b) Incorrect technique: fixing the outer sheath (marked section) and pushing the inner sheath forward with the left hand, which may result in misdeployment.

contrast, an 8.5–10 Fr PS or a UCSEMS that has migrated into the gastrointestinal lumen generally requires removal together with the endoscope. Care should be taken during retrieval to avoid injury to the gastrointestinal mucosa.

In cases where this procedure is difficult, it is necessary to consider treatment with drainage first, and an endoscopic biliary stent or endoscopic nasobiliary drainage should be placed to manage cholangitis. Subsequently, an operation is usually performed to remove the migrated stent.

(2) Cholecystitis

Cholecystitis may occur when a CSEMS extends across the junction of the cystic duct and common bile duct, resulting in cystic duct obstruction. Initial management consists of fasting and antibiotic therapy. If symptoms do not improve, the CSEMS should be removed and replaced with a PS to relieve the obstruction. When feasible, endoscopic transpapillary gallbladder drainage should be performed. In cases of severe inflammation, percutaneous transhepatic gallbladder aspiration or drainage is required as the initial step to control infection.

(3) Postoperative pancreatitis

When pancreatitis develops after endoscopic biliary stenting or endoscopic nasobiliary drainage, post-ERCP pancreatitis should be considered first. If an FCSEMS has been placed, pancreatic duct obstruction by the stent may also cause obstructive pancreatitis. Even with PSs, those with a diameter of 10 Fr or larger may obstruct the pancreatic orifice. Therefore, adequate endoscopic sphincterotomy (EST) at the time of placement is recommended to minimize this risk.

Regardless of the cause, early management significantly improves the clinical course of pancreatitis. Treatment should be initiated in accordance with guideline-based management protocols to ensure optimal patient outcomes.[7)]

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6-(II) Endoscopic Biliary Drainage

- Endoscopic ultrasound-guided biliary drainage

1. Drainage Method

Endoscopic ultrasound-guided biliary drainage (EUS-BD) encompasses two major approaches: one is introducing a stent along the puncture route; and the other techniques such as antegrade drainage (AG) and the rendezvous technique. Among these, endoscopic ultrasound-guided hepatico-gastrostomy (EUS-HGS) and endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) are the most commonly performed in clinical practice. Additional procedures include endoscopic ultrasound-guided hepatico-jejunostomy (EUS-HJS) and endoscopic ultrasound-guided hepatico-duodenostomy (EUS-HDS). The nomenclature of these techniques is based on the target puncture site, followed by the gastrointestinal segment through which access is achieved. The selection between EUS-HGS and EUS-CDS remains in controversy. In general, the presence or absence of obstructive narrowing in duodenum serves as a criterion. EUS-CDS is not feasible for cases with duodenal stenosis, whereas EUS-HGS is preferred. Since diseases that cause obstructive jaundice frequently involve duodenal invasion, EUS-HGS usually becomes the clinical choice. Endoscopic ultrasound-guided antegrade stenting (EUS-AGS) is performed to place a stent across the biliary stricture, often in combination with EUS-HGS rather than as a standalone procedure. Although this combination can improve drainage efficiency, careful consideration is required when distal bile duct stenosis is present, as placement of a stent across the major duodenal papilla may induce pancreatitis. Endoscopic ultrasound-guided rendezvous (EUS-RV) technique involves placing a guidewire in the target site under endoscopic ultrasound guidance, followed by the exchange of the endoscope to perform endoscopic retrograde cholangiopancreatography (ERCP). This technique is considered in cases such as those with ascites or resectable disease, where standard endoscopic ultrasound-guided biliary drainage (EUS-BD) is avoided. The choice of procedure depends on patient condition, the nature of the stenosis, the endoscopist's expertise, and available resources. The most appropriate approach should be selected for each case.

2. EUS guided Biliary Drainage Devices

Conventionally, devices used for endoscopic ultrasound-guided biliary drainage (EUS-BD) were adapted from those originally designed for endoscopic retrograde cholangiopancreatography (ERCP). In recent years, dedicated endoscopic ultrasound-guided biliary drainage stents have received regulatory approval, with certain models now reimbursed by insurance. As of September 2023, the regulatory approval status

Table 1 Regulatory approval status of devices.

	Device type
Insurance coverage	Guidewire, dilator (bougie, electrocautery), catheter
Off-label use	Puncture needle*, dilation balloon**, stent (metal***, plastic)

*For puncture needles, EZ Shot 3 (Olympus) received regulatory approval in February 2023.
**For balloon catheters, REN (Kaneka Medix) received regulatory approval in April 2023.
*** Niti-S stent has regulatory approval and is covered by insurance.



Figure 1 Spring stopper stent (Century Medical).

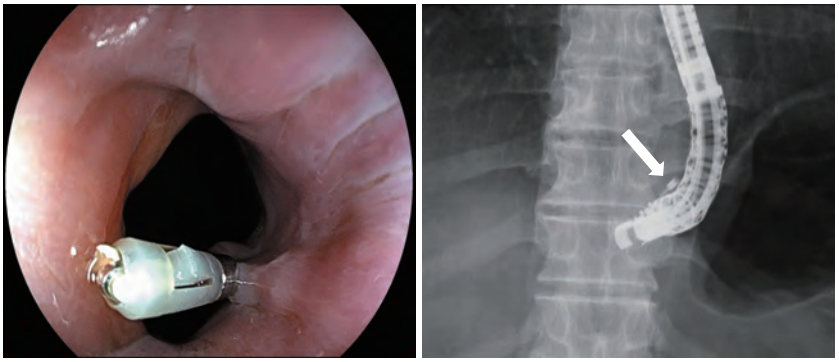
The stent has an uncovered distal end and a proximal end with a spring-like stopper positioned on the luminal side of the gastrointestinal tract. This structure is intended to prevent migration into the lumen.

of these devices is summarized in **Table 1**. Among the devices covered by insurance are guidewires, dilators including bougie dilators and electrocautery dilators, and catheters, whereas puncture needles, balloon catheters, and stents remain uncovered. However, among the available stents, the Niti-S Stent (Century Medical) is covered by insurance. The Spring Stopper Stent (**Figure 1**) has been reported to provide safety and efficacy as a dedicated endoscopic ultrasound-guided biliary drainage stent, specifically designed to prevent migration.[1] At present, all plastic stents remain uncovered by insurance. The puncture needle EZ Shot 3 (Olympus) has received regulatory approval in February 2023, and the balloon catheter REN (Kaneka Medix) has been also approved in April 2023.

3. Indications and Contraindications

The indications for endoscopic ultrasound-guided biliary drainage include biliary stricture in which transpapillary drainage is difficult or unsuccessful. At present, it is positioned as a rescue operation for cases where ERCP is challenging. In cases of duodenal obstruction or surgically altered anatomy, an approach via the duodenum is difficult, and these conditions make EUS-HGS a favorable option via the gastric cavity. A strategy has also been proposed in which EUS-BD is undertaken as the primary intervention, without prior ERCP, in order to reduce the risk of post-ERCP pancreatitis.[2-5] The indications are not necessarily limited to malignant cases, and the procedure may also be applied for benign biliary strictures, benign anastomotic strictures, and bile duct stones if EUS-BD is deemed effective. However, in resectable obstructions, endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) requires careful consideration, since it tends to induce inflammation and adhesions to potentially complicate surgical resection process.

The absolute contraindications for EUS-BD are the same as those for transpapillary drainage and other endoscopic procedures such as endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). In the presence of ascites, there is a risk of infectious peritonitis caused by biliary leakage, and the indication should be assessed with particular caution.[6] When EUS-BD is required, placement of an ascitic drainage catheter before the procedure and continued drainage perioperatively may reduce the risk of infectious peritonitis. However, issues such as fluid management and the risk of inadequate opening formation with



a | b

Figure 2 Prior to EUS-HGS.

a: A clip is placed at the esophagogastric junction.
b: Under fluoroscopic guidance, the clip (arrow) allows confirmation that the scope is positioned on the distal side of the stomach, beyond the esophagogastric junction.

ascitic drainage should be carefully assessed, and the procedure should not be performed without sufficient consideration. In general, antegrade stenting or rendezvous technique is preferred for ascites to minimize the risk of biliary leakage.

4. Practical Procedures and Advice for Basic Technique

(1) EUS guided hepatico-gastrostomy

Before the procedure

Endoscopic ultrasound-guided hepatico-gastrostomy (EUS-HGS) carries the potential risk of serious adverse events such as mediastinitis and pneumothorax when performed via the transesophageal approach.[7] It is critical to employ preventive measures against mispuncture during the EUS-HGS procedure. Because the echoendoscope is pressed against the gastrointestinal wall, direct endoscopic visualization of the puncture site is not possible. To assist fluoroscopic identification of the esophagogastric junction, clip placement at the site by upper gastrointestinal endoscopy prior to EUS-HGS is recommended (**Figure 2**).

1) Visualization of the bile ducts

A curvilinear array echoendoscope is advanced into the stomach to visualize the intrahepatic bile ducts. Routine endoscopic ultrasound screening is important for developing familiarity with the anatomy of the extrahepatic region. The target bile duct should be restricted to either the B2 or B3 branch, with B2 typically located below the portal vein and B3 above it.

2) Needle puncture

(I) Selecting bile duct

In selecting the puncture site, the B2 branch is generally preferred due to its relatively straight course, facilitating the guidewire manipulation and device insertion.[8] However, in the case of B2 puncture, this requires transesophageal puncture with a high risk, so caution is required for puncturing. Puncture into the B3 branch often causes the guidewire to follow a peripheral path, and its curved course over the portal

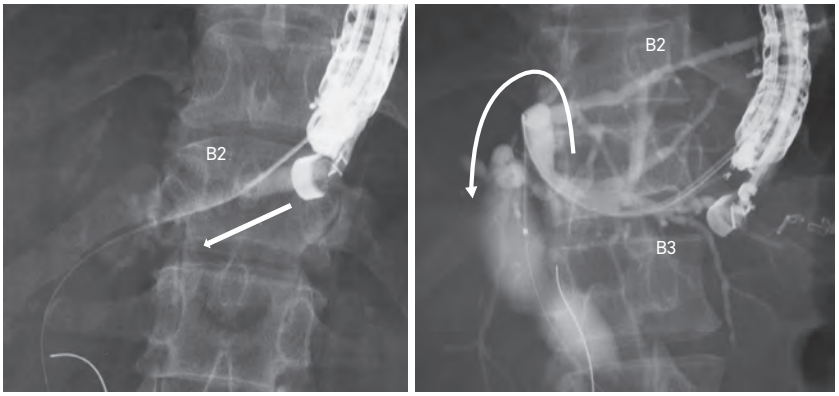


Figure 3 Biliary puncture.

a: In puncturing segment B2, the device insertion angle becomes linear (arrow).
b: In puncturing segment B3, the device should be advanced over the shoulder of the portal vein (arrow), thereby resulting in a more complex trajectory.

vein makes it difficult to advance the guidewire toward the central bile duct. This process potentially complicates device insertion (**Figure 3**). In the puncture stage, when guidewire manipulation is expected to be difficult, it is better to consider another puncture site for successful outcomes, instead of persisting with the undertaking approach.

(II) Needle selection

In selecting an appropriate puncture needle, the 19-gauge needle accommodates a 0.025-inch guidewire, whereas the 22-gauge needle accommodates a 0.018-inch guidewire. The former guidewire is superior in selecting the target bile duct branch and supporting the necessary devices. In contrast, the latter needle is advantageous when the bile duct diameter is small or when puncture should be performed with the forceps elevator raised. The choice of needle should be determined according to the target bile duct branch and its diameter.

3) Tract dilation

During insertion of the dilation device, the guidewire and the device are kept clearly aligned on the endoscopic ultrasound (EUS) screen, as this ensures proper positioning before the device advancement. The punctured route is dilated with electrocautery dilators or mechanically dilated with bougie dilators and balloon catheters. Electrocautery dilators carry a potential risk of bleeding, and current guidelines in Japan recommend their use only when mechanical dilation is difficult.[9] In EUS-HGS, a particular attention is required for dilating due to the potential risk of vascular injury and bleeding involving the portal vein or hepatic artery located within Glisson's sheath in the peribiliary region. Therefore, it is important to avoid the Glisson's sheath as much as possible for selecting the puncture site. Regarding gradual dilation, there are reports suggesting the effectiveness of the ES Dilator (Zeon Medical),[10] which is designed with a ultra-tapered tip to reduce the discrepancy between the guidewire and dilator, and the REN balloon catheter (Kaneka Medix).[11]

These devices require forward pushing during insertion, which generates reactive forces that can displace the endoscope from its intended position. This problem is particularly relevant for operators with limited experience. The Tornus ES (Asahi Intecc) has recently been introduced (**Figure 4**). Unlike conventional dilators, this drill dilator allows tract dilation by simply rotating the proximal grip clockwise, thereby minimizing endoscope displacement. Its main advantage lies in stabilizing the endoscope during EUS-HGS and providing a safer, more straightforward option, especially for less experienced endoscopists.[12,13]

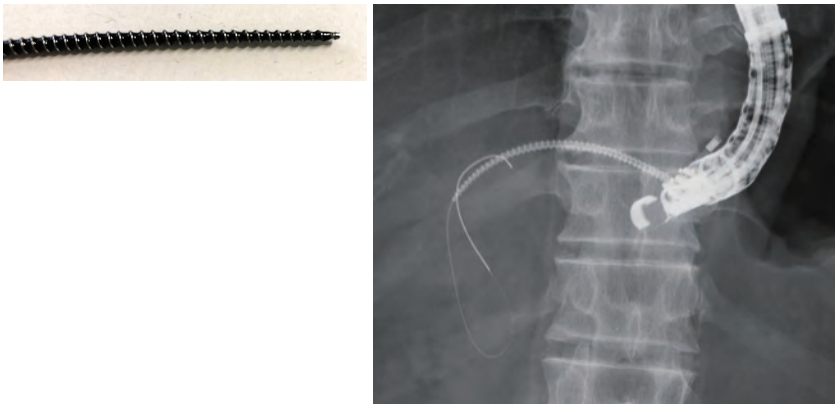


Figure 4 Tornus ES (Asahi Intec Co., Ltd.).

The device features a screw-shaped tip which allows expansion of the puncture route by rotating the handle clockwise. It eliminates the need for strong forward pressure, thereby enabling stable dilation with maintaining the position of the scope.

4) Stent placement

(I) Selecting stents

In selecting a stent, guidelines recommend the use of covered self-expandable metal stents (SEMS) but allow the use of plastic stents (PS) depending on the conditions.[9] Plastic stents offer advantages such as ease of placement and a lower risk of migration into the peritoneal cavity. In EUS-HGS, it is beneficial to use the Through & Pass TYPE IT stent (Gadelius Medical).[14] However, plastic stents carry the potential risk of biliary leakage leading to peritonitis. One of the advantages of a covered self-expandable metal stent (SEMS) is its ability to seal the puncture site and dilation tract, thereby reducing the risk of bile leakage that could result in peritonitis or bleeding. However, its placement demands a certain level of expertise. These stents are categorized as fully covered (FCSEMS) or partially covered (PCSEMS), and fully covered self-expandable metal stents offer good removability and permit subsequent reintervention. The Spring Stopper Stent, specifically designed for endoscopic ultrasound-guided biliary drainage (EUS-BD), includes an anti-migration feature and is available in an 8.5-Fr size. Additionally, the HANAROSTENT® Biliary Full Cover Benefit™ (Boston Scientific) is now available with a 5.9-Fr low-profile delivery system, which enables stent placement without the need for tract dilation. It is essential to understand the characteristics, advantages, and limitations of each stent for appropriate selection.

(II) Stenting method

During placement of self-expandable metal stents, the primary concern is migration into the peritoneal cavity.[15] A stent of 10 cm or more in length is recommended to prevent inward stent migration. Use of a stent that is sufficiently long, typically 10 cm or more, helps ensure a stable connection between the stomach and bile duct. During stent placement, the guidewire and stent should both be visualized on the endoscopic ultrasound (EUS) image and aligned along the same axis before advancing the stent. If insertion remains difficult despite proper alignment, additional dilation is recommended rather than applying excessive force. The hepatic side of the stent should be gently adjusted according to the puncture site, with deployment carried out in careful coordination between the endoscopist and the assistant. The stent is deployed slowly, first from the bile duct, then through the liver tissue, and finally into the gastric wall. Once 2 to 3 cm of the stent has expanded within the endoscope, the delivery system is advanced and

released. At the same time, the endoscope is gradually angulated downward to complete full expansion. This technique maintains firm contact between the liver and gastric wall, thereby preventing excessive separation and reducing the risk of intraperitoneal migration. Stent placement also requires expansion techniques, whose effectiveness has been demonstrated with the Spring Stopper Stent and with ClipFlap anchoring, both designed to prevent intraperitoneal migration.[16)]

(2) Antegrade stenting

Endoscopic ultrasound-guided antegrade stenting (EUS-AGS) was initially reported as a technique for placing a stent across a biliary stricture. However, concerns regarding biliary leakage from the puncture site and the need for reintervention due to stent dysfunction have prompted the development of a combined approach using EUS-AGS with EUS-HGS.[17)] The addition of antegrade stenting to EUS-HGS has potential advantages, such as creating an additional anterograde drainage route to reduce the risk of biliary leakage-induced peritonitis and elongate the stent patency. However, increased procedure time raises the risk of adverse events, and placement of a stent across the major duodenal papilla carries the potential risk of pancreatitis. An alternative staged approach has been proposed, in which EUS-HGS is first performed to establish a stable opening, with antegrade stenting added later when deemed necessary.[16)]

5. EUS Guided-Choledochoduodenostomy

(1) Selecting treatment devices

An echoendoscope used for endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) is either an oblique-viewing curvilinear array echoendoscope or a forward-viewing curvilinear array echoendoscope. The forward-viewing type has been reported to potentially reduce the risk of double penetration of the gastrointestinal mucosa,[2)] however, the standard oblique-viewing type is also feasible for this procedure. The choice of puncture needles, guidewires, dilators, and stents varies according to the endoscopist's preferences. Moreover, the devices normally used for endoscopic retrograde cholangiopancreatography (ERCP) are also used for this procedure. Standardization of these techniques remains an ongoing challenge. Reports from overseas have demonstrated the utility of lumen-apposing metal stents (LAMSs) in endoscopic ultrasound-guided biliary drainage.[18,19)] As of 2023, these stents are not covered by insurance for this indication in Japan and conventional tubular metal stents are therefore used. Although plastic stents may be employed, caution is required as their use have been associated with a higher risk of bile peritonitis and other adverse events.[20)]

(2) Inserting echoendoscope

Screening esophagogastroduodenoscopy (EGD) is routinely performed before the procedure to rule out lesions in the stomach and duodenum. The procedure is often performed with the patient in the prone position, because it facilitates fluoroscopic recognition of the endoscope shape and biliary anatomy. However, this position is not a requirement. The echoendoscope is advanced to the duodenal bulb to obtain a longitudinal view of the extrahepatic bile duct. In cases of obstructive jaundice, the significant

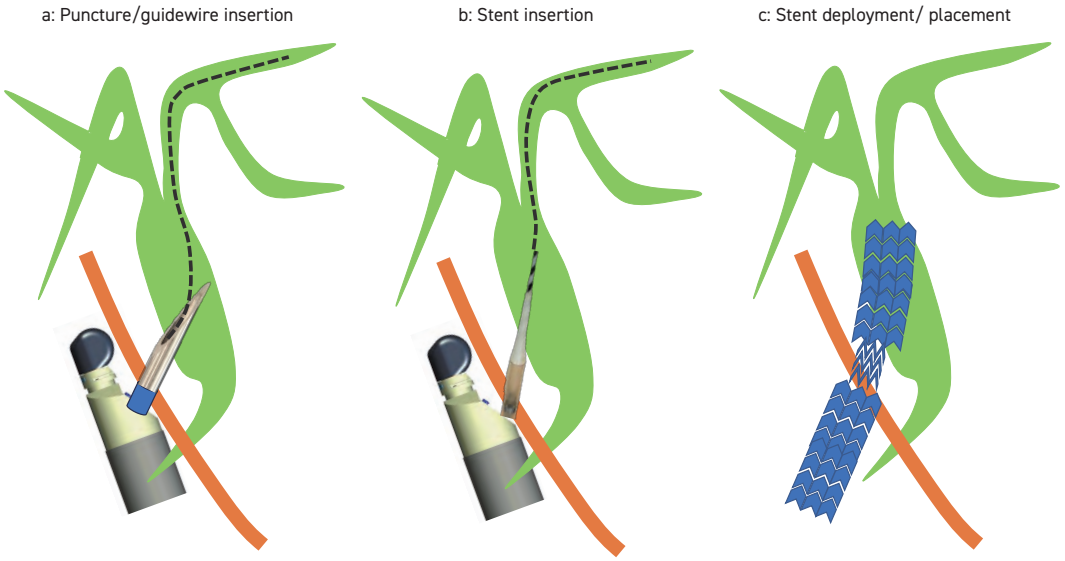


Figure 5 EUS-CDS procedure (Diagram).

a: The extrahepatic bile duct is visualized from the duodenal bulb. A puncture is performed at a site more than 2 cm distal to the hepatic hilum, followed by guidewire insertion.
b: As dilation of the puncture tract is necessary, the delivery system is introduced into the bile duct after dilation.
c: Taking care to avoid the hepatic hilum, approximately 80% of the stent is deployed from the bile duct toward the instrument channel, with the remaining portion deployed within the duodenum for final placement.

cystic duct dilation makes it difficult to distinguish from the extrahepatic bile duct. Therefore, it is important to visualize the bile duct up to the confluence of the right and left hepatic ducts to confirm that the target is the extrahepatic bile duct.

(3) Puncturing bile duct

In biliary puncture, the puncture site should be selected with an adequate distance from the hepatic hilum to ensure the sufficient space for stenting. If a margin of at least 2 cm is secured from the hepatic hilum, stent deployment is possible within the common hepatic duct. During the puncture, it is important to avoid blood vessels located along the intended route. Furthermore, the cystic duct should not be inadvertently punctured (**Figures 5a, 6a, 7a**). In cases of obstructive jaundice, the cystic duct may become markedly dilated, which can make it difficult to distinguish the cystic duct from the extrahepatic bile duct. Additionally, when performing puncture from the duodenal bulb, there is a risk of penetrating the duodenal wall twice. Therefore careful attention is required during the procedure. When the bile duct is insufficiently dilated and lacks adequate tension, puncture with a 19-gauge needle could be difficult. In such situations, a 22-gauge needle or an electrocautery-needle should be used instead. When puncture is performed near the hepatic hilum, there is a risk of resulting in unilateral drainage. To avoid unilateral drainage, the use of a plastic stent is advisable, as its flexibility facilitates appropriate placement and ensures drainage from both hepatic lobes. Otherwise, conversion to endoscopic ultrasound-guided hepatico-gastrostomy should be considered.

a: Puncture/guidewire insertion b: Stent insertion c: Stent deployment/placement

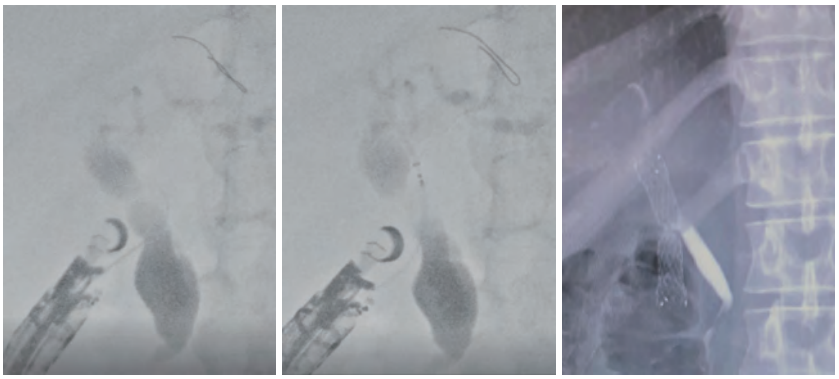


Figure 6 EUS-CDS procedure (Fluoroscopic view).

a: If possible, placing the guidewire into the left hepatic lobe facilitates easier insertion of the stent delivery system.
b: When using a small-caliber stent delivery system, tract dilation is not required.
c: To prevent retrograde cholangitis, the proximal end of the stent should be directed toward the distal duodenum at the completion of the procedure.

a: Puncture/guidewire insertion b: Stent insertion c: Stent deployment/placement



Figure 7 EUS-CDS procedure (Endoscopic ultrasound view).

a: The extrahepatic bile duct is visualized in the longitudinal axis, and puncture should be performed with awareness of the distance to the hepatic hilum.
b: After insertion of the stent delivery system, the guidewire, stent, and other devices should always be kept in view on the EUS image to ensure safe manipulation.
c: Final deployment of the stent should be confirmed to be fully within the bile duct.

(4) Cholangiography and guidewire insertion

Following puncture of the extrahepatic bile duct and bile juice aspiration, contrast medium is injected to confirm the position of the hepatic hilum. If the distance from the puncture site to the hepatic hilum proves shorter than anticipated, it may still be possible to perform a repuncture or to switch to an alternative procedure at that stage. Once the puncture site is confirmed to be appropriate, a guidewire of 0.025 to 0.035 inches is inserted. Thicker guidewires provide greater stiffness, improving device delivery but reducing maneuverability. Therefore selection of the size should be made based on procedural requirements. Insertion of the guidewire into the left lobe provides a more linear trajectory which facilitates easier device insertion (**Figures 5b, 6b, 7b**).

(5) Dilation of puncture route for stent insertion

To minimize adverse events such as hepatorrhea, fistula dilation should be controlled to minimum size. The dilation method varies depending on the type of devices used. If a large-caliber device is introduced,

electrocautery or balloon dilation is required to achieve sufficient dilation. With a low-profile delivery system, stent placement is feasible without dilation. Although an extensive dilation simplifies the procedure, it also increases the risk of adverse events such as hepatorrhea. Therefore, inappropriate dilation should be avoided. Currently, devices used for endoscopic retrograde cholangiopancreatography (ERCP) are also applied for dilation process. When a stent should be inserted after dilation, a metal stent is preferred to reduce the risk of adverse events. For stent insertion, a stent delivery system is first advanced into the bile duct, after that the stent is deployed from just below the hepatic hilum. Once approximately 2 cm of the stent has been deployed, the delivery system is retracted sufficiently, thereby allowing the stent to maintain firm contact with the duct wall. Full deployment within the instrument channel should be avoided, and approximately 1 cm at the distal end of the stent typically remains unexpanded. The echoendoscope is then slightly withdrawn, thereby allowing confirmation of the stent's position within the duodenal lumen. Subsequently, the delivery system is advanced toward the descending portion of the duodenum to complete stent deployment (**Figures 5c, 6c, 7c**). This maneuver helps orient the stent toward the distal side of the duodenum. When the stent is not properly oriented, a practical approach is to advance the echoendoscope into the descending duodenum while maintaining the guidewire within the stent. This technique enables controlled repositioning without the application of excessive force. Alternatively, the same maneuver can be performed by exchanging to a standard upper gastrointestinal endoscope. However, repositioning the stent with a grasper is not recommended, as the technique is technically demanding and carries a high risk of dislocation. At the end of the procedure, the puncture site is examined endoscopically, and the stent position is confirmed under fluoroscopy. The procedure is completed after ensuring that there is no bleeding, perforation, or other adverse events.

6. EUS guided-Antegrade Stenting and Endoscopic Ultrasound-guided Rendezvous Technique

Endoscopic ultrasound-guided antegrade stenting (EUS-AGS) involves a specific process. The intrahepatic bile duct is punctured directly from the gastrointestinal tract, either through the gastric wall or the wall of a reconstructed small intestine. A stent is then placed across the anastomotic site into the obstructed duct, advancing in the forward direction. In contrast, endoscopic ultrasound-guided rendezvous technique (EUS-RV) does not involve anastomosis formation but instead involves placing a guidewire into the bile duct and advancing it across the major duodenal papilla under endoscopic ultrasound guidance. The guidewire is then used to perform selective biliary cannulation with endoscopic retrograde cholangiopancreatography (ERCP).

(1) Visualization of the bile duct

There are mainly two methods. In the first method, the intrahepatic bile duct (B2 or B3) is visualized by ultrasound from the stomach before puncture. In the second method, there are two approaches for puncturing the extrahepatic bile duct under EUS guidance. One involves advancing the echoendoscope to the duodenal bulb in the long position to visualize the extrahepatic bile duct prior to puncture. The other involves positioning the scope in the descending part of the duodenum in the short position to visualize and puncture the extrahepatic bile duct.

Table 2 Comparison of access routes.

	B2	B3
Angle between EUS and needle	Weak	Strong
Angle between needle and bile duct branch	Acute	Obtuse
Guidewire guidance to perihilar bile duct	Gentle	Steep
Intervening liver parenchyma	Short	Long > Short (peripheral side)
Puncture point	Cardia	Gastric body
Device insertion	Easy	Difficult
Re-intervention	Difficult	Easy

(2) Puncture and guidewire placement

In the transgastric approach, targeting the B2 branch tends to direct the puncture needle easily toward the perihilar bile duct (Bp) compared with the B3 approach. Consequently, the guidewire is also more likely to advance into the Bp, facilitating access to the central bile duct (**Table 2**). In the transduodenal approach, when puncturing the extrahepatic bile duct, the puncture needle often tends to point toward the perihilar side (Bp). Consequently, guidewire advancement is sometimes difficult. To facilitate guidewire passage, the puncture should be performed either with the needle oriented perpendicular to the bile duct axis or by adopting a strong push position with the ultrasound transducer directed toward the papilla. This orientation helps improve the stability of the puncture and facilitates smooth guidewire advancement. When puncturing from the descending part of the duodenum, the needle is more easily directed toward the papilla. In cases where the guidewire passage through the papilla proves difficult in the transgastric approach, it is often helpful to convert to endoscopic ultrasound-guided hepatico-gastrostomy.

(3) Guidewire placement and echoendoscope removal (EUS-RV only)

Once the guidewire has passed through the papilla, it should be advanced sufficiently into the duodenum to stabilize its position before echoendoscope withdrawal. Because guidewire dislocation may occur during subsequent endoscopic retrograde cholangiopancreatography, the guidewire should be secured together with a catheter to minimize the risk of displacement.

(4) Biliary cannulation (EUS-RV only)

Selective biliary cannulation can be introduced using either the alongside-the-guidewire method, in which the endoscopic retrograde cholangiopancreatography (ERCP) catheter is advanced parallel to the guidewire, or the over-the-guidewire method, in which the catheter is threaded directly over the guidewire. In the latter approach, the guidewire emerging from the papilla is grasped with a snare or biopsy forceps and withdrawn from the patient through the instrument channel of the ERCP scope. Once the guidewire is secured externally, an ERCP catheter is advanced over it to facilitate subsequent procedures.

7. Procedure and Advice for Challenging EUS-BD Cases

In patients with liver dysfunction but without jaundice, bile duct dilation is often insufficient. When standard puncture is difficult, a 22-gauge needle is preferred because it provides better puncture performance than a 19-gauge needle. In such cases, a 0.018-inch guidewire is selected. The use of drill dilators compatible with 0.018-inch guidewires allows safe fistula dilation. Difficulty in guidewire advancement following intrahepatic bile duct access is frequently encountered. In such situations, the use of a double-lumen catheter is often effective for directing the guidewire into the targeted biliary branch. When guidewire manipulation remains difficult, repuncture of the bile duct should be considered. The B3 approach often requires greater angulation, a steeper puncture trajectory, and a longer puncture distance, making B2 puncture the more favorable option. However, the B2 approach carries a potential risk of mediastinal emphysema and mediastinitis because it requires transesophageal puncture. To reduce this risk, placement of a clip at the esophagogastric junction is useful for confirming the puncture site and avoiding inadvertent transesophageal puncture. Moreover, clipping to prevent transesophageal puncture can also be applied in the B3 approach. However, its efficacy has not been established in patients with large sliding- or mixed-type hiatal hernias. In cases where peribiliary varices, ascites, or other atypical conditions are present, conversion to percutaneous transhepatic biliary drainage (PTBD) or alternative techniques is recommended rather than proceeding with endoscopic ultrasound-guided biliary drainage.

8. Adverse Events and Postprocedure Management

When stent migration into the peritoneal cavity occurs after EUS-guided hepaticogastrostomy, prompt additional intervention is required. Surgical management is generally regarded as the most effective and reliable approach. Although additional stent placement has been proposed as a potential alternative, the supporting evidence remains insufficient.

In EUS-guided choledochoduodenostomy, cases of multiple penetrations of the gastrointestinal mucosa have been reported as a complication. The use of a forward-viewing echoendoscope has been proposed as a means of reducing this risk. Unlike EUS-guided hepaticogastrostomy, early adverse events such as stent migration or dislocation are rare in EUS-guided choledochoduodenostomy. Localized peritonitis and hepatorrhea following EUS- guided biliary drainage (EUS-BD) are observed as adverse events and could often be managed conservatively when drainage is effective. However, if drainage is inadequate, additional endoscopic or percutaneous intervention should be considered. Percutaneous intervention is highly effective for managing adverse events and should be undertaken without delay when necessary. After EUS-guided hepaticogastrostomy or choledochoduodenostomy with metallic stent placement, postoperative management includes blood tests and imaging (X-ray or CT) on the following day to assess for adverse events before initiating oral intake. If the patient's condition remains stable, hospital discharge is possible as early as the second day after the procedure. Cases involving plastic stents or ascites are associated with a higher incidence of adverse events, necessitating more cautious postoperative management. Although the use of antibiotics in EUS-guided hepaticogastrostomy remains a matter of debate, obstruction of the peripheral bile duct likely increases the risk of segmental cholangitis. Therefore, short-term antibiotic administration for several days is commonly practiced to help prevent infection.

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7 Pancreatic Duct Drainage (Including Stone Removal)

1. Indications and Contraindications[1)]

Pancreatic duct drainage is a therapeutic procedure in which a catheter or stent is inserted and placed in the main pancreatic duct via the papilla to facilitate drainage of pancreatic juice. In some cases, pancreatic stone removal is also useful to improve pancreatic juice outflow.

Indications

(i) Stricture of the main pancreatic duct or the presence of pancreatic stones with dilatated distal pancreatic duct, accompanied by symptoms such as abdominal pain or episodes of pancreatitis
(ii) Prevention of pancreatitis exacerbation due to impacted stone fragments during extracorporeal shock wave lithotripsy (ESWL)
(iii) Pancreatic juice leakage caused by disruption of the pancreatic duct
(iv) Prevention of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP)
(v) Continuous pancreatic juice cytology for the diagnosis of pancreatic carcinoma

Contraindications

(i) Diffuse intraductal pancreatic stones
(ii) Main pancreatic duct stricture between the body and tail, with upstream stones
(iii) Severe duodenal stricture

As indications for preventing post-ERCP pancreatitis and conducting pancreatic juice cytology are explained later, this section focuses on the first three indications.

2. Drainage Methods

In cases of chronic pancreatitis, fibrosis of the major papilla due to chronic inflammation can be observed. For removing pancreatic stones with a basket catheter, endoscopic pancreatic sphincterotomy (EPST) is beneficial. The treatment strategy for managing pancreatic stones follows *the Japanese Clinical Guidelines for Endoscopic Treatment of Pancreatolithiasis 2014* (**Figure 1**).[2)]

Pancreatic duct drainage is classified into endoscopic nasopancreatic drainage (ENPD) which involves the temporary placement of an external catheter in the pancreatic duct, and endoscopic pancreatic stenting (EPS) which is intended for medium- to long-term drainage. In cases of chronic pancreatitis with severe strictures of the main pancreatic duct that hinder passage of a contrast catheter, ENPD should be performed as the initial approach. This process facilitates the subsequent placement of pancreatic duct

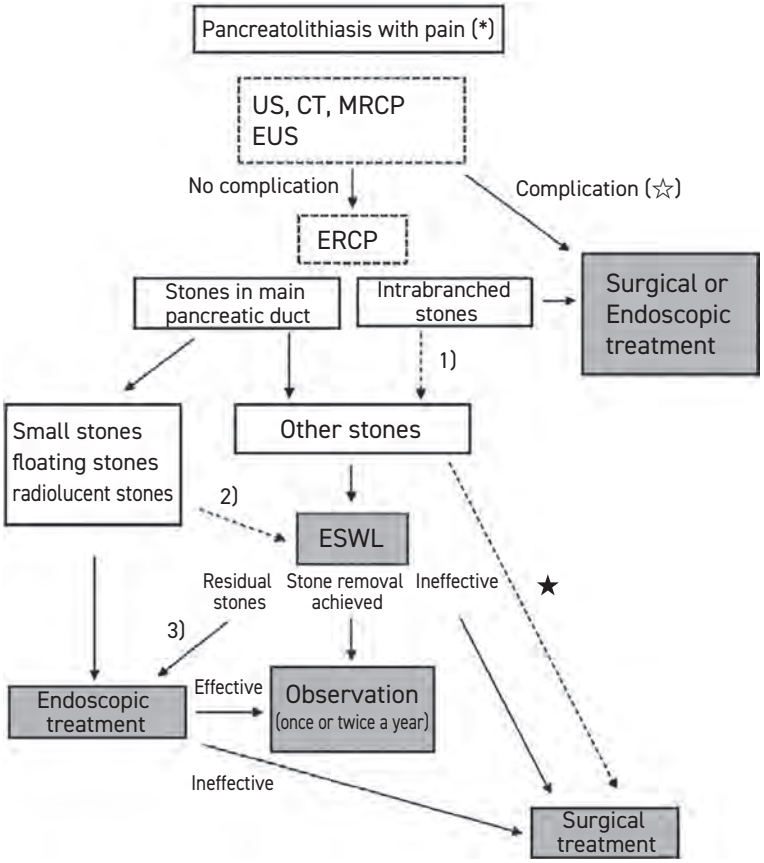


Figure 1 **Therapeutic flow of pancreatic stones.**

*: In cases without pain, observation or traditional conservative medical management is applied. However, even in the absence of pain, if pancreatic stones are impacted within the main pancreatic duct without pancreatic parenchymal atrophy, treatment should be performed to improve pancreatic function.

☆: Duodenal stricture, severe biliary stricture, or pancreatic cancer

★: Surgical treatment is considered when there are impacted stones or when stones are located only in the pancreatic tail and endoscopic stone extraction is predicted to be ineffective.

1) Stones located in branch ducts are also suitable for extracorporeal shock wave lithotripsy (ESWL) if accompanied by stones in the main pancreatic duct.

2) Endoscopic treatment is effective for small stones measuring 5 or 6 mm or less, floating or radiolucent pancreatic stones. When pancreatography using an endoscopic nasopancreatic drainage catheter is achievable, lithotripsy with ESWL is considered.

3) When duodenal papillary or main pancreatic duct strictures are present, concurrent endoscopic dilation therapy is used to facilitate stone clearance.

(Cited from Literature 2)

stents. When transpapillary drainage is not feasible, endoscopic ultrasonography (EUS) -guided pancreatic duct drainage (EUS-PDD) is also useful.

In addition to transpapillary endoscopic nasopancreatic drainage (ENPD) or transpapillary endoscopic pancreatic stenting (EPS), EUS-guided pancreatic pseudocyst drainage (EUS-PCD) is also a treatment option when direct drainage of the fluid collection is required. When infection is complicated, direct drainage should be selected. However, ENPD or EPS is expected to be effective only if the ruptured part of the pancreatic duct is clear on CT or other images before treatment. Even after performing EUS-PCD, confirmation of pancreatic duct disruption is important, and after improving the infection, endoscopic

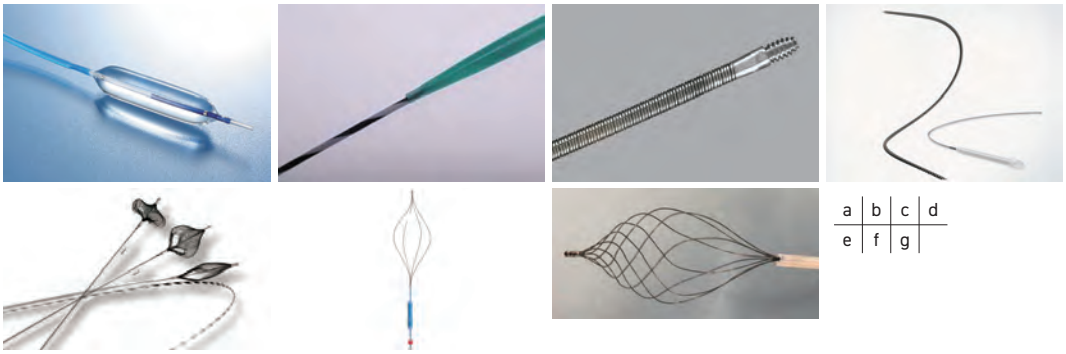


Figure 2 **Devices for pancreatic duct drainage.**

a to d: Dilation instruments
a: Kaneka biliary dilation balloon REN (Kaneka Medix)
b: ES Dilator (Zeon Medical)
c: COOK Soehendra® Stent Retriever (Cook Medical)
d: Endoscopic dilator (Tornus ES) (Olympus)
Balloon catheter is generally useful with a 2 or 3 cm balloon length and a 3 to 6 mm dilation diameter and is inflated for 1 minute at 4 to 8 atm, 1 or 2 times. The REN balloon catheter has a tapered tip that enables superior passage through strictures. When balloon catheter advancement is difficult, blunt dilation with ES Dilator or Soehendra® Stent Retriever has traditionally been used. Recently, Tornus ES has gained attention as it enables dilation by lightly pressing the tip against the stricture and rotating the device clockwise, while a stable endoscope position is maintained.
e-g: Basket catheters
e: Nitinol basket catheter (Reforma) (PIOLAX)
f: MTW disposable stone retrieval basket catheter (Mini Catch) (ABIS)
g: Kaneka stone retrieval basket RASEN2 (Kaneka Medix)
*Including products used off-label.
Due to the tortuous anatomy of the pancreatic duct, guidewire-assisted catheters are used for safe intubation. Caution is required as even small stones could cause basket impaction when multiple stones are grasped simultaneously. Nitinol basket catheters are advantageous for maintaining shape within narrow pancreatic ducts. Reforma catheter, with a 72-wire design, is effective in removing small fragments after ESWL. RASEN2 is a helical basket with an asymmetrical structure to facilitate release of grasped stones.

retrograde pancreatography (ERP) is performed. In cases where pancreatic duct disruption is observed, EPS should be subsequently performed.

These ERCP-related procedures are also applied to patients who have undergone pancreaticojejunal anastomosis following pancreatoduodenectomy by utilizing balloon-assisted endoscopy. In such cases, several procedural considerations arise, including the more distal location of the pancreaticojejunal anastomosis than that of the hepaticojejunal anastomosis, its tangential alignment, and the clear, colorless nature of pancreatic juice. These features make it particularly difficult to identify the anastomotic site in cases of anastomotic stricture. Due to the technical difficulty, such ERCP-related procedures should be conducted by specialists experienced in balloon-assisted biliary interventions.

The primary instruments used for pancreatic duct drainage, including pancreatic stents, are illustrated in **Figures 2 and 3** and listed in **Table 1**. Understanding of the characteristics of each device is crucial for ensuring safe and successful procedures.

3. Practical Procedure and Advice

Pancreatic duct drainage is performed in various combinations depending on the underlying conditions. Compared with biliary drainage, the procedure is technically difficult and should be completed by an experienced endoscopist with expertise in biliary interventions, along with a skilled assistant.



Figure 3 **Pancreatic duct stents.**

a-e: Stents for main pancreatic duct treatment
a: Geenen® Pancreatic Stent Sets (Cook Medical)
b: S-type pancreatic duct stent (Olympus)
c: AdvanixTM Pancreatic Stent (Boston Scientific)
d: Harmo Ray endoscopic pancreatic duct stent (Hanaco Medical)
e: Zimmon® Pancreatic Stent Sets (Cook Medical)
The straight stent with bilateral flaps (a) and the s-shaped stent (b) conforming to the pancreatic duct anatomy are designed to reduce the risks of migration and mucosal injury. Advanix™ stent (c), although straight, is made of an extremely soft material that minimizes discomfort. Harmo Ray stent (d) accommodates a guiding catheter (inner catheter) even at 5 Fr, and the locking system between the stent and the pushing catheter allows repositioning. Caution is needed as stent length definitions differ by manufacturer (Table 1). To prevent migration, some pancreatic duct stents are designed with a pig tail shape on the intestinal side (e). Selection of the appropriate device and stent length should be based on the stricture site and the pancreatic duct course to prevent the stent tip from contacting the duct wall.
f-h: Pancreatic duct stents for other purposes
f: Geenen® Pancreatic Stent Set with No Internal Flap (Cook Medical)
g: Pit-stentTM for pancreatic duct (Gadelius Medical)
h: Through & Pass® TYPE ITTM stent (Gadelius Medical)
Stents used for the prevention of post-ERCP pancreatitis often have a structure without flaps on the pancreatic duct side (f). Because there is no flap, it often falls out naturally with intestinal peristalsis, and is also called a self-detaching type. Generally, a small-diameter stent of 3 to 5 Fr and 2 to 4 cm length is used, but because the flap is small and migration could occur, a semi-pigtail type is also used (g). For EUS-guided pancreatic duct drainage, the TYPE IT stent is useful which has a straight type with a flap on the pancreatic side and a unilateral pigtail type on the gastric side to prevent migration (h).

Table 1 **Type of pancreatic stents ((Only Double-Flap Types).**

Stent	Manufacturer	Shape	Measurement of length	Retrieval mechanism	Diameter	Guiding catheter
Stype	Olympus	S-shaped	Between flaps	None	7 Fr 8.5 Fr 10 Fr	None Yes Yes
Geenen	Cook Medical	Curved	Flap to tip	None	5 Fr 7 Fr 10 Fr	None None Yes
Advanix	Boston Scientific	Straight	Flap to tip	None	5 Fr 7 Fr 10 Fr	None Yes Yes
Harmo Ray	HANACO Medical.	Curved	Between flaps	Required	5 Fr 7 Fr	Yes Yes

(1) Endoscopic retrograde pancreatography (ERP)

1) Pancreatic cannulation

The pancreatic duct is typically located in the 1 to 2 o'clock orientation at the papilla. In chronic pancreatitis, a narrowing, bending or meandering duct tends to be present just above the papilla. To understand the pancreatic duct anatomy, contrast injection should be performed at an early stage, even with shallow cannulation. Compared with the biliary cannulation where contrast injection is minimized, pancreatic duct cannulation does not always require the use of a guidewire. When the guidewire does not advance into the deeper duct, early contrast injection is helpful for delineating the pancreatic duct course. Notably, pancreatic stones could be detectable only in the initial phase of imaging, thus the early assessment is crucial. In pancreatography, pancreatic stones and their positional relationship with the main pancreatic duct are clarified readily. Even a small amount of contrast offers important diagnostic insights. In cases of pancreatic juice leakage, identifying the precise leakage fistula is crucial for determining the appropriate treatment.

2) Guidewire placement

The guidewire used for pancreatic duct interventions should demonstrate excellent penetrability into strictures with smooth tractability. A 0.025-inch guidewire with excellent tip control is initially selected, as the balloon dilation catheter used subsequently is designed to be compatible with this guidewire size. In placing a guidewire, a successful stricture passage depends on the proper endoscopic axial alignment and the coordinated manipulation of the catheter. As the guidewire successfully passes the stricture, the followability of catheter should be confirmed. When the catheter succeeds in advancing beyond the stricture, balloon dilation is performed to enable the placement of a 7 Fr stent. Otherwise, initial placement of a 5 Fr stent is a safer option for endoscopic nasopancreatic drainage (ENPD), depending on the notch formation in the balloon dilation process.

(2) Endoscopic pancreatic sphincterotomy

In endoscopic pancreatic sphincterotomy (EPST), a papillotome is selectively inserted into the pancreatic duct and incised in the 12 to 1 o'clock orientation (**Figure 4**).[3,4] The incision should not extend beyond the superior border of papilla to avoid perforation or bleeding. In cases where pancreatic duct intubation is difficult because of pancreatic stones impacted just above the papilla or due to concomitant biliary stricture, endoscopic sphincterotomy (EST) may be performed first to facilitate subsequent treatment. In cases of recurrent pancreatitis associated with pancreatic divisum, minor papilla sphincterotomy may be indicated,[5] but the incision should be limited to the superior border.

(3) Balloon dilation to pancreatic duct stricture

In cases of significant pancreatic duct strictures, a dilation balloon is introduced into the narrowing site for expanding the lumen (**Figure 5**). A 0.025-inch guidewire is compatible with the REN dilation balloon from Kaneka Medix, enabling smooth passage of the catheter to minimize friction. The balloon diameter is selected based on the upstream and downstream pancreatic duct calibers, typically around 6 mm. As balloon dilation causes substantial pain, not only should analgesics be administered but measures should also be in place to manage patient movement. Because dilation devices are not specifically approved for

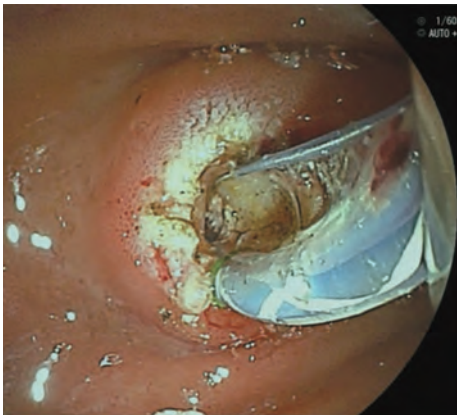
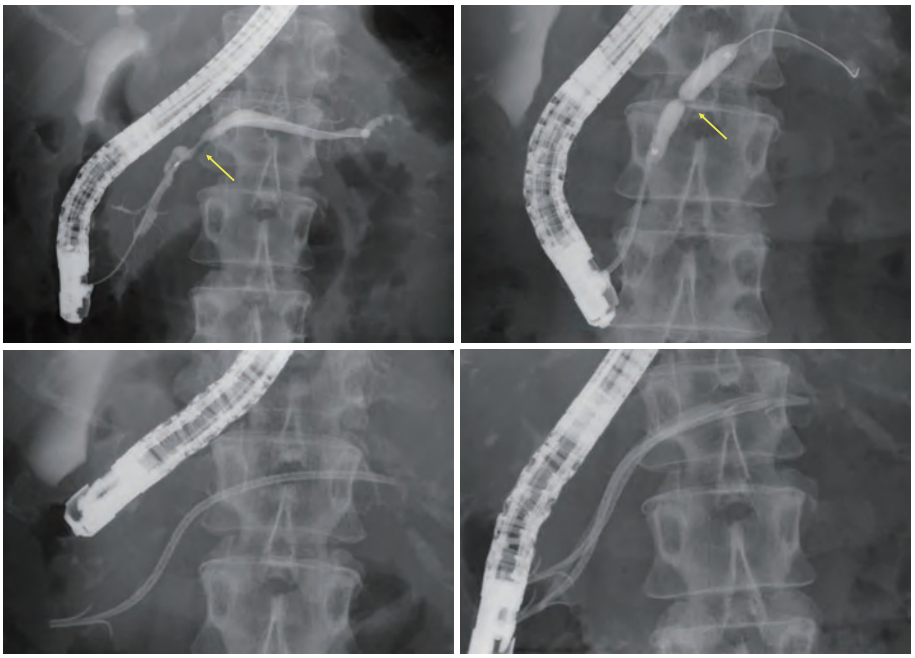


Figure 4 Endoscopic pancreatic sphincterotomy.

Incision was directed towards the 12 to 1 o'clock orientation, with the incision length not exceeding beyond the superior border of papilla.

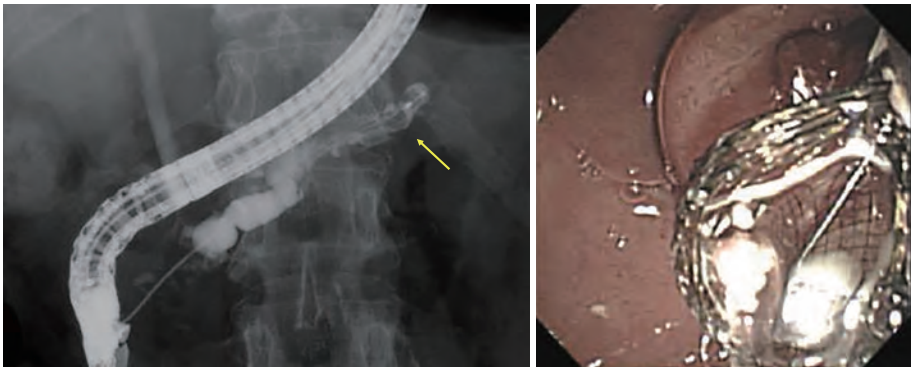


a | b
c | d

Figure 5 Pancreatic duct stenting.

a: A stricture was observed in the head of the main pancreatic duct (arrow).
b: The stricture was dilated with a balloon catheter, forming a notch at the site (arrow).
c: A 7 Fr s-shaped pancreatic duct stent was placed across the stricture.
d: Three months later, two 7 Fr stents were placed, and after another three months, a third 5 Fr stent was added for a total of three stents.

treating pancreatic duct strictures, their use should be guided by the protocols and policies established at each medical institution.



a | b

Figure 6 Pancreatic stone extraction.

a: ERP revealed a radiolucent lesion under 5 mm in the pancreatic duct (arrow).
b: Reforma basket catheter was used to extract small fragments.

(4) Pancreatic stone removal

1) Managing small, floating, or radiolucent stones

For pancreatic stones smaller than 5 mm, floating stones, or radiolucent stones in the absence of downstream strictures, removal with a basket forceps alone is possible (**Figure 6**).[3,4,6] Nitinol spiral-type baskets designed for pancreatic lithiasis maintain their shape within the narrow pancreatic duct and are particularly effective.[7,8] For stones near the papilla, direct grasping with forceps is also useful.[4] In order to minimize the risk of basket impaction, excessive force should be avoided, and that stones should be removed sequentially from the papillary side. Balloon catheters may also be used for stone extraction, but stones sometimes migrate into the accessory pancreatic duct and their retrieval often becomes difficult.

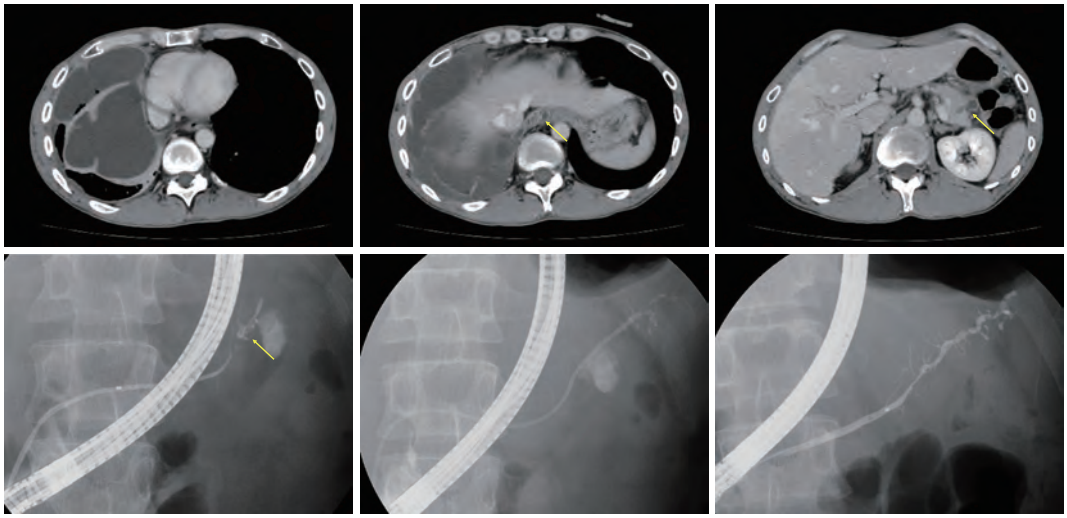
2) Managing large or impacted stones

Extracorporeal shock wave lithotripsy (ESWL) is the common first-line treatment for stones larger than 5 mm or impacted stones.[9] Endoscopic nasal pancreatic drainage (ENPD) or pancreatic duct stenting facilitates targeting of stones during ESWL and prevents stone fragment impaction. Once sufficient fragmentation is achieved, the fragments should be removed with the aforementioned methods. In cases where a pancreatoscope reaches the stone, electrohydraulic lithotripsy (EHL) is also available. However, eligible cases are limited, and EHL for pancreatic stones is currently not covered by national health insurance in Japan.[10]

(5) Pancreatic duct drainage

1) Endoscopic nasopancreatic drainage

The placement point of the tip position of the endoscopic nasopancreatic drainage (ENPD) catheter is determined based on the location and morphology of the pancreatic duct stricture.[1,6,11] In cases of pancreatic duct disruption, the catheter should ideally extend beyond the disruption site into the distal main pancreatic duct (**Figure 7**).[12] ENPD catheters with multiple side holes are usually selected, but care should be taken to ensure that proximal side holes do not reside in the duodenum. To minimize the risk of dislocation, the proximal side holes should be placed at least 3 cm beyond the papilla. If the catheter tip extends too deeply, it should be trimmed to an appropriate length.



a b c
d e f

Figure 7 **ENPD for pancreatic juice leakage in pancreatic duct disruption.**

a: Pancreatic pleural effusion was present.
b: A tract from the peritoneal to pleural cavity was observed (arrow).
c: The disrupted spot of the pancreatic duct was identified (arrow).
d: ERP confirmed disruption of the pancreatic duct (arrow).
e: An ENPD catheter was placed across the disrupted spot.
f: Later ERP showed resolution of pancreatic juice leakage.

2) Endoscopic pancreatic stenting (EPS)

Same as selecting ENPD, the shape, length, and diameter of the pancreatic stent are determined based on the location and shape of the pancreatic duct stricture (**Figure 5**). In addition to straight stents, s-type stents are also available.[13] When selecting an appropriate stent, it is important to consider the course of the pancreatic duct from the head to the body. Additionally, the potential contact between the stent tip and the main pancreatic duct in the body should be carefully evaluated to ensure proper stent placement and function. The choice of stent length, presence or absence of a guiding catheter (inner catheter), and whether a retrieval mechanism is incorporated varies by stent type and diameter. An initial stent size of 7 Fr or smaller is generally recommended. In challenging cases of stent placement, particularly when using stents that lack a retrieval mechanism, the procedure often involves releasing the stent, retrieving it, and then making another attempt to intubate the pancreatic duct. To avoid this process, care should be taken not to extend the stent too far from the endoscope, as increasing the distance between the endoscope and the papilla makes the procedure more challenging. During the final stent release, endoscopists should carefully withdraw the guiding catheter together with guidewire while pressing the proximal flap against the papilla. Rapid removal causes to migrate the flap with the catheter into the pancreatic duct.

3) Pancreatic stent exchange and removal

Pancreatic stents should generally be exchanged every three months.[14] When the stricture persists at the time of scheduled stent replacement, placement of multiple stents is beneficial (**Figure 5**).[15] For benign conditions, the ultimate goal of stent therapy is to achieve a stent-free state. When the planned removal could not be completed, alternative strategies should be employed including surgical intervention.[16]

4. Procedure and Advice for Difficult Cases

(1) Selective pancreatic duct cannulation

Pancreatic duct cannulation is generally easy and successful compared with biliary cannulation. In chronic pancreatitis, the pancreatic duct orifice at the papilla is frequently narrowed due to fibrosis. In such situations, careful probing of the pancreatic orifice is required using a fine-tipped contrast catheter. When the distal pancreatic duct is displaced caudally, the endoscope should be slightly withdrawn while gradually increasing left angulation to achieve axial alignment. This adjustment improves the chances of successful intubation while keeping the endoscope stable. When selective cannulation remains unsuccessful, endoscopic sphincterotomy (EST) or precut techniques is preferred to facilitate further intervention, and endoscopic pancreatic sphincterotomy (EPST) is also required.

(2) Guidewire advancement into deep pancreatic duct

Guidewire performance varies depending on its positioning relative to the catheter. When the catheter is pulled back and more of the guidewire tip is exposed, this enables better control over its rotation or torque. Conversely, when the catheter is advanced close to the stricture with only a short guidewire tip exposed, the force applied to the tip increases. These characteristics should be selectively utilized depending on the situation. For example, extensive probing with torque performance is important for the cases with tortuosity, whereas careful manipulation with tip force is required for bypassing an impacted stone. When there is crab claw shaped obstruction due to impacted stones, inducing the guidewire from both claw-tips of the obstruction could increase the chances of success. If the guidewire advances into a branch duct, applying gentle pressure allows the soft tip to form a J-turn and subsequently redirect into the main pancreatic duct. Excessive force should be avoided to prevent pancreatic duct injury. Generally, endoscopists should be attentive to any resistance at the catheter tip, while their assistant should be mindful of changes in resistance during guidewire manipulation.

(3) Dilation of pancreatic duct stricture

Pancreatic duct strictures should be dilated by either a balloon or a bougie. While a bougie could only be expanded to the diameter of catheter, a balloon could be inflated to a predetermined diameter, making it the preferred method for dilation. In cases where a dilation balloon fails to traverse the stricture or the tightest segment remains unexpanded despite balloon inflation, the use of a bougie is helpful. Previously, ES Dilator (Zeon Medical) with a tapered tip and Soehendra® Stent Retriever (Cook Medical) with a screw tip were commonly used.[17] Recently, the commercially available drill dilator Tornus ES (Olympus) has been reported to be effective in overcoming various strictures and could be also beneficial for pancreatic duct strictures.[18]

(4) Basket impaction

It is important not to pull the catheter forcibly. In cases of basket impaction, the proximal catheter portion should be cut to leave only the sheath and wire within the pancreatic duct. The endoscope is then

withdrawn and the catheter should come out of the mouth. Following this, the catheter is repositioned through the nasal route, similar to the approach used in endoscopic nasopancreatic drainage (ENPD).[4] In some cases, impaction resolves within one to two days, resulting in spontaneous catheter removal. When the impaction is not resolved, extracorporeal shock wave lithotripsy (ESWL) should be performed at a facility where it is available. Fragmenting the impacted stone with ESWL allows the stone removal under direct endoscopic visualization. Otherwise, surgical intervention should be considered.

(5) Passing through a stricture with pancreatic duct stent

Overextension of the stent from the endoscope should be avoided to prevent loss of control. Various methods could be used to generate insertion force, including elevating the forceps elevator, up-angulating the endoscope, rotating the endoscope leftward, or withdrawing the endoscope. When these maneuvers are coordinated with the tension of the guidewire, applying pressure to advance the entire tube may be beneficial. Additionally, twisting motions by gently swinging the endoscope tip left and right could further aid in successful insertion. If the stent and delivery system are not integrated into a retrievable unit and its insertion remains unsuccessful, the stent should be released proximal to the stricture or within the duodenum. This requires a complete reattempt from the beginning. When the difficulty is anticipated, initial placement of a 5 Fr should be considered for endoscopic nasopancreatic drainage (ENPD).

(6) Removing a pancreatic duct stent

When a stent migrates into the pancreatic duct, its retrieval is performed with a snare, basket forceps, or alligator forceps. If a guidewire can be advanced through the stent, a stent retriever is useful for removal. However, care should be taken as excessive force could inadvertently push the stent further into the pancreatic duct.

5. Adverse Events and Postprocedural Management

The primary aim of drainage treatment is to reduce intraductal pressure in the pancreatic duct, thereby alleviating pain in pancreatitis or decreasing fluid collection. Monitoring the improvement of subjective symptoms in the patients is essential, along with serial imaging to assess pancreatic duct caliber reduction and laboratory evaluations of pancreatic enzyme levels, white blood cell count, and inflammatory markers. Severe postprocedural adverse events require close monitoring such as bleeding and perforation. If such adverse events of occur, prompt intervention should be considered, including surgical management. If the long-term follow-up indicates that the endoscopic drainage does not achieve sufficient therapeutic effect, surgical treatment should be planned as an alternative.

(1) Hemorrhage

Bleeding associated with endoscopic pancreatic sphincterotomy (EPST) should be managed similarly to that following endoscopic sphincterotomy (EST). Hemostasis could be achieved by spraying epinephrine-saline solution or thrombin. Recent reports have highlighted the efficacy of self-assembling peptide hydrogel (PuraStat®) as an absorbable topical hemostatic agent in managing post-EST bleeding, and

similar benefits are expected for EPST.[19] When access to the pancreatic duct is maintained, hemostasis could also be achieved using a SureClip which is widely utilized with duodenoscopy.[4]

(2) Perforation

Perforation may occur following endoscopic pancreatic sphincterotomy (EPST) or when a large pancreatic stone is extracted forcefully through a small papilla. After EPST, fluoroscopic imaging should be temporarily expanded to cover the entire upper abdomen to check for the presence of extraluminal free air, and images should be acquired for documentation. When perforation is suspected, computed tomography (CT) should be performed. In cases where the patient is clinically stable and free air is confined to the peripancreatic region, conservative management is an option. However, pancreatic juice, bile, and gastric or duodenal contents all have the potential to leak. Based on the ERCP findings, the minimal necessary intervention should be determined to divert the relevant fluid via a nasogastric, nasobiliary, or nasopancreatic drainage catheter. At the same time, the surgical team should be notified, while preparations should be made in case the patient's condition deteriorates.

(3) Pancreatic duct injury

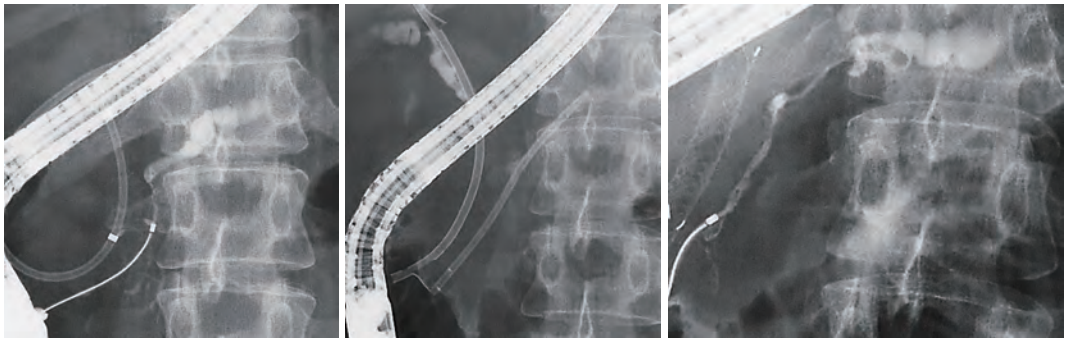
Pancreatic duct injury caused by guidewires or endoscopic instruments results in the same pathological conditions as pancreatic duct disruption. In cases of minor injury, introduction of an endoscopic nasopancreatic drainage (ENPD) catheter or endoscopic pancreatic stent (EPS) beyond the site of injury is generally sufficient for management. If peripancreatic fluid collection becomes difficult to control, EUS-guided drainage or surgical intervention should be implemented.

(4) Acute pancreatitis

The incidence of postprocedural pancreatitis varies depending on baseline pancreatic function and procedural factors. Since initial pancreatic duct drainage carries a potential risk of inducing pancreatitis, appropriate preventive measures should be performed. These include minimizing contrast injection pressure to avoid acinarization, ensuring precise guidewire and instrument manipulation to prevent pancreatic duct injury, and securing effective pancreatic duct drainage. In cases where pancreatitis occurred after prior drainage or intervention, rectal administration of nonsteroidal anti-inflammatory drugs (NSAIDs) should be actively considered for preventing the recurrence. In chronic pancreatitis, serum amylase levels may not rise even when pancreatitis occurs. Therefore, using only the standard criteria for ERCP-related pancreatitis is not sufficient for accurate assessment. When pancreatitis is suspected based on clinical symptoms, contrast-enhanced CT should be performed to assess inflammatory changes, and appropriate treatment should be initiated promptly.

(5) Acute cholangitis

Biliary stricture is frequently observed in patients with chronic pancreatitis, and cholangitis could develop following pancreatic duct drainage. In some cases, EST alone could prevent cholangitis. However, biliary drainage should also be performed, if necessary.



a | b | c

Figure 8 Stent induced ductal change.

a: Localized stricture was observed in the pancreatic head.
b: A 7 Fr plastic stent was placed across the main pancreatic duct stricture.
c: On stent removal, the range of stricture was expanded.

(6) Stent occlusion and acute obstructive suppurative pancreatic ductitis

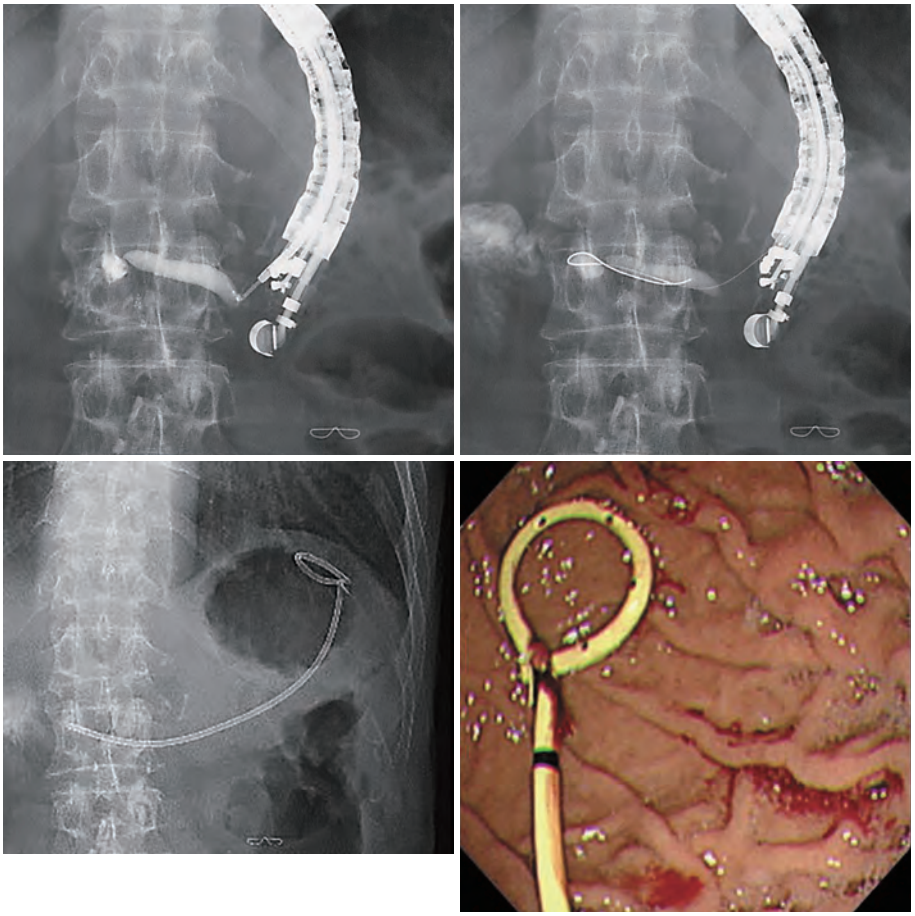
Pancreatic stent occlusion could lead to a severe condition similar to acute obstructive suppurative cholangitis.[20] In such cases, pancreatic enzyme levels often remain within normal limits, and only high fever and elevated white blood cell count or C-reactive protein (CRP) may be observed. To prevent delayed diagnosis and allow timely treatment, it is necessary for all clinicians and endoscopists involved in ERCP to share information, including those handling emergency cases on call. Emergency ERCP should be performed, and upon removal of the pancreatic stent, an evacuation of grayish thick pus from the pancreatic duct is typically observed. The prognosis is favorable if ENPD and antibiotic therapy are administered in a timely manner.

(7) Stent-induced pancreatic duct changes

Stent-induced ductal changes refer to the development of secondary strictures near the tip of an indwelling pancreatic duct stent (**Figure 8**).[21] When this complication occurs, a longer stent is required for adequate coverage. However, removal of the existing stent and placement of a new one may result in additional strictures. The use of softer stents or those designed to conform to the natural curvature of the pancreatic duct can reduce the risk of this complication. Placement of multiple stents of varying lengths can help achieve a more even distribution of pressure along the duct. This might lower the risk of developing a localized stricture. In some cases, spontaneous resolution occurs after stent removal. Therefore, it is important to delay intervention and evaluate whether the condition improves spontaneously before proceeding with additional treatment.

6. EUS Guided Pancreatic Duct Drainage

When pancreatic duct drainage is not feasible via endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound-guided pancreatic duct drainage (EUS-PD) has been an option as an alternative approach (**Figure 9**).[22] EUS-PD involves two main approaches. One method entails puncturing the dilated pancreatic duct under EUS guidance and placing a stent between the gastrointestinal tract, primarily the stomach, and the pancreatic duct by employing a technique similar to EUS-guided



a b
c d

Figure 9 **EUS-guided pancreatic duct drainage.**

a: Following puncture of the pancreatic duct, pancreatography confirmed the stricture at the pancreatojejunal anastomosis.
b: A 0.025-inch guidewire was inserted into the pancreatic duct.
c: A 7 Fr plastic stent was placed between the pancreatic duct and the stomach.
d: The plastic stent was visualized within the stomach.

hepaticogastrostomy (EUS-HGS). Another approach involves advancing a guidewire from the punctured gastrointestinal tract to the pancreatic duct stricture tract toward the papilla and a stent is place between the duodenum and the upstream of the dilated pancreatic duct. This approach is also applied for surgically altered anatomy, where a stent is placed between the duodenum and the upstream dilated pancreatic duct. The second approach is further categorized into antegrade pancreatic duct stenting, where a stent is placed directly in the pancreatic duct, and retrograde pancreatic duct stenting or rendezvous technique, where the EUS scope is exchanged for a duodenoscope. This exchange allows the guidewire to be retrieved through the papilla for stenting transpapillary. At present, most reports involve a limited number of cases, with procedural success rates ranging from 44% to 100% and adverse event rates varying widely from 0% to 42.9%.[23] In EUS-PD, ensuring that the scope remains in close contact with the gastrointestinal wall while performing fistula dilation is a critical technical factor, and the usefulness of drill dilators has been reported.[24] Due to the technical complexity and relatively high risk of adverse events associated with EUS-PD, this technique is not yet considered a standard treatment and should only be performed at highly specialized centers.

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Takafumi Mie and Naoki Sasahira

8 Drainage of Pancreatic Pseudocyst and Walled-off Necrosis

Pancreatic pseudocyst (PPC) and walled-off necrosis (WON) are late complications of acute pancreatitis, collectively referred to as pancreatic fluid collections (PFCs). According to the revised Atlanta classification, PFCs are categorized into four distinct conditions based on the time elapsed since onset and the presence or absence of necrotic material (**Figure 1**).[1] PPC and WON typically develop after approximately four weeks, when the collection becomes encapsulated. A fluid collection without necrotic tissue is classified as PPC, whereas a fluid collection containing necrotic tissue is classified as WON.

Since PPC and WON differ in their pathogenesis and disease characteristics, it is important to distinguish between them. PPC results from pancreatic duct disruption caused by pancreatitis or trauma, leading to the accumulation of leaked pancreatic juice. WON develops in severe acute pancreatitis, where the pancreas and surrounding fat tissue undergo necrosis, and the necrotic debris becomes encapsulated. PPC and WON that cause clinical symptoms such as abdominal pain and become complicated with infection necessitate drainage treatment.

Conventionally, drainage procedures have included surgical debridement and percutaneous drainage. However, these approaches involve significant invasiveness and a high incidence of treatment-related adverse events. Advances in endoscopic technology and devices have led to the establishment of endoscopic drainage as the first-line treatment due to its minimally invasive nature. This consists of endoscopic ultrasound (EUS)-guided drainage of pancreatic fluid collection (EUS-PFD) combined with DEN to remove necrotic debris, when necessary.[2-4] For PPC associated with pancreatic duct disruption, transpapillary drainage via ERCP is incorporated into the treatment strategy.[5]

Table 1 **Revised Atlanta classification**

Peripancreatic fluid collections (PFCs) are classified into four types based on the duration from the onset of acute pancreatitis (less than 4 weeks / 4 weeks or more) and the presence or absence of necrotic material.

	Less than 4 weeks from onset	4 weeks or more from onset
No necrotic material	Acute peripancreatic fluid collection (APFC)	Pancreatic pseudocyst (PPC)
Necrotic material present	Acute necrotic collection (ANC)	Walled-off necrosis (WON)

(Created from Literature 1)

1. Indications and Contraindications

PPC and WON complicated with infection are absolute indications for drainage. However, because acute pancreatitis itself often presents with fever and elevated inflammatory markers, distinguishing between infected and non-infected PFCs is sometimes difficult. Persistent bacteremia, elevated biomarker levels such as procalcitonin,[6,7] and imaging findings suggestive of infection, like the presence of gas within the collection, suggest the presence of infection. Previously, puncture aspiration and culture of PFC contents were performed to confirm infection, but recent practice increasingly relies on clinical signs for decision-making.

Even in the absence of infection, drainage of PFCs is generally indicated when specific clinical findings are present, such as:

- Abdominal pain, nausea, vomiting, or insufficient oral intake
- Gastrointestinal obstruction
- Biliary obstruction
- Recurrent acute pancreatitis
- Rupture of PFCs resulting in pancreatic leakage

Although the size of a PFC (e.g., over 6 cm) was previously regarded as an indication for treatment, drainage is now less commonly performed based on size alone.

Endoscopic drainage is contraindicated in the following situations:

- Pseudoaneurysmal bleeding into the PFC
- Gastrointestinal perforation
- Uncontrolled bleeding tendency
- Poor systemic condition rendering the patient unsuitable for endoscopic intervention

When pseudoaneurysmal bleeding is present, hemostasis should be secured by transcatheter arterial embolization before any drainage procedure. Although endoscopic drainage is considered unfeasible in such cases, prompt consultation with relevant specialties is required to assess the appropriateness of percutaneous or surgical drainage.

2. Selecting Drainage Methods

(1) EUS-guided drainage of pancreatic fluid collection

EUS-PFD is performed by puncturing a PFC through the gastrointestinal wall and placing a stent or drainage tube. WON following severe acute pancreatitis commonly develops around the pancreas, particularly within the omental bursa between the stomach and pancreas, and is adherent to the stomach and/or duodenal wall. It is a favorable indication for EUS-PFD as EUS enables clear visualization and subsequent puncture of the target collection. In cases of PPC without communication with the main pancreatic duct, EUS-PFD is generally preferred over transpapillary drainage.

Before the EUS-PFD procedure, it is necessary to confirm encapsulation of the PFCs. As described in the revised Atlanta classification, encapsulation is typically present in most cases approximately four weeks after the onset of acute pancreatitis. On the other hand, drainage is sometimes required within four weeks in clinical practice. Several reports have shown that EUS-guided drainage of pancreatic fluid collections within four weeks is associated with higher rates of adverse events and mortality, suggesting that it should be avoided whenever possible.[8,9] In such cases, it is essential to confirm encapsulation of

PFCs by imaging studies, such as contrast-enhanced computed tomography (CT). Prospective data on the optimal timing of drainage remain insufficient, and further accumulation of evidence is warranted.[10)]
Stents used for EUS-PFD include plastic stents and metal stents. Double pigtail plastic stents are commonly selected to prevent migration or misplacement. Among metal stents, the lumen-apposing metal stent (LAMS) that has been developed for cystic drainage is widely used.[11)] The Hot system is particularly useful because the cautery-tipped delivery system enables one-step LAMS placement.
The drainage strategy differs between PPC and WON. A PPC that is predominantly fluid-filled and has a simple, monocular structure is often managed with the placement of a single stent to achieve adequate drainage. In such cases, the efficacy of plastic stents and LAMSs is generally comparable.[12,13)] In contrast, because WON contains more necrotic components than PPC, LAMSs are commonly employed not only to facilitate effective drainage but also to provide an access route for subsequent DEN.[14)] For collections with a complex, multilocular structure, multiple stents should be placed through a single tract, known as the single transluminal gateway transcystic multiple drainage (SGTMD) technique, or multiple stents through multiple access routes, referred to as the multiple transluminal gateway technique (MTGT).[15)]
Although there is no consensus on the placement of an additional external drainage tube, nasocystic drainage is frequently used in Japan to enhance drainage efficiency. Saline irrigation through a nasocystic tube is reported to be beneficial for patients with WON,[16)] which can be a treatment option before step-up to DEN.

(2) Direct endoscopic necrosectomy

When PFCs do not resolve with EUS-PFD alone, drainage should be escalated employing an endoscopic step-up approach.[17,18)] If initial EUS-PFD fails to achieve sufficient improvement, the second step involves either placing additional stents in inadequately drained areas and/or performing irrigation via a nasocystic drainage tube. If this step also fails, DEN is performed to remove residual necrotic material within the PFC. DEN is mainly indicated for WON, with reports showing that approximately 10 to 50% of WON cases require this intervention.
DEN is an intervention using a forward-viewing endoscope advanced into the PFC to remove necrotic tissue. The endoscope is introduced through the drainage tract established during EUS-PFD. When a LAMS is in place, insertion can be readily performed through the stent lumen. In contrast, when a plastic stent has been placed, balloon dilation of the tract is often required, making the procedure slightly more complex. Once the endoscope is advanced into the PFC, necrotic debris is removed from inadequately drained areas with reference to preoperative imaging findings. Currently, devices specifically designed for DEN are available in some countries,[19)] otherwise, biopsy forceps, snares, and retrieval baskets are used for the treatment.
Close attention should be paid to adverse events during the procedure, particularly bleeding, perforation, penetration into the gastrointestinal tract, and air embolism.[20)] In cases of severe adverse events, transcatheter arterial embolization or surgical intervention is necessary in collaboration with interventional radiology and surgery units. Since DEN is an invasive procedure usually performed in critically ill patients, it should be undertaken only at high-volume centers.
There is currently no established consensus on the optimal timing for termination of DEN. In most cases, DEN is usually concluded once the majority of necrotic debris has been removed and clinical symptoms, together with laboratory parameters, have improved.

(3) Transpapillary pancreatic duct drainage

In cases of PFCs associated with pancreatic duct disruption, transpapillary pancreatic duct drainage becomes necessary during the course of treatment. When pancreatic duct disruption is evident in PPC, endoscopic retrograde cholangiopancreatography (ERCP) can be selected as the initial drainage method. For PFCs with confirmed infection, particularly WON, endoscopic ultrasound-guided drainage of pancreatic fluid collection is performed as the first-line approach. Thereafter, transpapillary pancreatic duct stenting via ERCP should be considered in such cases because available data indicate that recurrence is frequent after EUS-guided drainage in PFCs with disconnected pancreatic duct syndrome (DPDS).[21,22]

When performing stent placement, bridging the disconnected pancreatic duct to the upstream pancreatic duct is ideal, as this could facilitate healing of the disruption. However, in cases of complete disconnection, cannulation into the upstream pancreatic duct is often technically challenging. For drainage of the upstream pancreatic duct, endoscopic ultrasound-guided pancreatic duct drainage (EUS-PDD) represents an alternative approach.[23] In patients with chronic pancreatitis, pancreatic duct strictures and/or pancreatic stones are often present downstream to the site of disruption, necessitating thorough preoperative imaging evaluation.

Since most cases involve severe acute pancreatitis, particular caution should be taken to prevent post-ERCP pancreatitis. Considering the complexity of the procedure, it should be performed by experienced endoscopists with skilled assistants. Special attention should be given to avoid excessive contrast injection and ensure careful manipulation of the guidewire.

(4) Percutaneous drainage

When PFCs are located far from the stomach or duodenum and endoscopic drainage is technically demanding, percutaneous drainage should be employed as an alternative. Patients in poor general condition who are unsuitable for endoscopic intervention are also indicated. Percutaneous drainage is performed under ultrasound or CT guidance, which is selected depending on the location of the lesion. Percutaneous endoscopic necrosectomy can subsequently be conducted by inserting an endoscope directly through the adequately dilated percutaneous tract.[24]

(5) Surgical drainage

When neither endoscopic nor percutaneous drainage provides sufficient improvement, surgical drainage becomes a treatment option. Minimally invasive approaches, such as videoscopic-assisted retroperitoneal debridement (VARD) and laparoscopic debridement, are generally considered first; however, in some cases, open surgical debridement remains necessary.[18]

3. Practical Procedures and Tips for Endoscopic Drainage Technique

(1) EUS-guided drainage of pancreatic fluid collection (EUS-PFD)

EUS-PFD is performed using a convex-type endoscopic ultrasonography (EUS), in combination with an

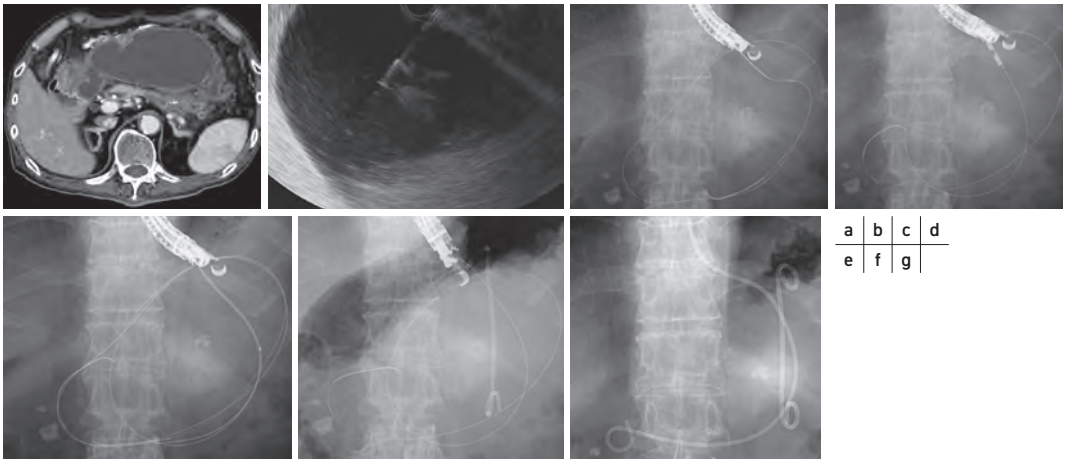


Figure 1 **EUS-PFD (Plastic stent placement).**

(a) A CT image reveals a PPC with a homogenous internal fluid density, encapsulated circumferentially.
(b) Endoscopic ultrasound (EUS) shows the cyst with fluid contents, which was punctured with a 19-gauge FNA needle.
(c) The PPC was punctured under EUS guidance, and a 0.025-inch guidewire was coiled inside the cyst cavity.
(d) The fistula tract was dilated using a 4 mm dilation balloon.
(e) A double-lumen catheter was inserted into the PPC, and a second guidewire was placed.
(f) A 7 Fr double pigtail plastic stent was placed into the PPC.
(g) Using the second guidewire, a 7 Fr pigtail nasocystic drainage tube was inserted into the deeper portion of the PPC.

ultrasound imaging platform. Stent placement for PFCs includes two approaches: (i) puncture with a fine needle aspiration (FNA) needle, guidewire insertion, and subsequent stent deployment; or (ii) direct single-step puncture and stent placement with an electrocautery LAMS.

1) Placing plastic stents (Figure 1)

(i) The PFC is first visualized by EUS to identify the puncture site (*1). Doppler mode is then applied to confirm the absence of blood vessels along the puncture route.

(ii) Puncture the PFC with an FNA needle, with the stylet removed in advance and a syringe attached for aspiration. Once the needle tip is confirmed within the PFC under EUS guidance, fluid content is aspirated and submitted for culture and biochemical analysis.

(iii) Contrast injection confirms that the needle is within the PFC. A guidewire is inserted through the needle and coiled within the collection space. The combination of a 19-gauge needle and a 0.025-inch guidewire is commonly used.

(iv) Dilate the puncture tract with dilators. Non-cautery dilators, such as balloon dilators,[25] bougie dilators,[26] or drill dilators,[27] are recommended to provide safe dilation (*2). The extent of tract dilation depends on both the diameter and the number of stents to be placed.

(v) When external drainage is planned in addition to internal stent placement, a second guidewire is inserted using a double-lumen catheter. The placement of two guidewires provides a safety wire in case the first wire fails, while also stabilizing the endoscope position and facilitating subsequent procedures.[28]

(vi) A plastic stent is deployed. A double pigtail PS is commonly selected to prevent migration or misplacement. If feasible, a delivery system that permits repositioning should be used.

(vii) When placing an external drainage tube, the second guidewire is used. Because the endoscope often shifts away from the puncture site after deployment of the first stent, it is essential to realign the

endoscope to the original puncture position under endoscopic, EUS, and fluoroscopic guidance. If insertion of the second drainage is difficult, additional dilation of the puncture tract is required.

2) Placing LAMS with electrocautery puncture (Figure 2)

(i) The PFC is first visualized by EUS to identify the puncture site. Doppler mode is then applied to confirm the absence of blood vessels along the puncture route.
(ii) The delivery system is inserted into a PFC using a high-frequency electrocautery and advanced deep enough before the distal flange deployment.
(iii) The distal flange of LAMS is deployed.
(iv) The entire delivery system is pulled back until the distal flange positioned contiguously to the PFC wall.
(v) The proximal flange is then deployed, which is performed either under direct endoscopic visualization or by the intra-channel release technique, in which the flange is released within the working channel and pushed out subsequently.[29)]
(vi) For specimen collection and/or placement of a nasocystic drainage tube, an ERCP catheter with a guidewire is inserted through the LAMS into the PFC.

*1: Several factors should be considered when selecting the puncture site:

(i) Sufficient space should be available for guidewire placement and device insertion.

(ii) Select the area with abundant fluid components.

(iii) If subsequent DEN is anticipated, the puncture site should be chosen with consideration of puncture direction and angle to facilitate endoscope insertion and necrosectomy.

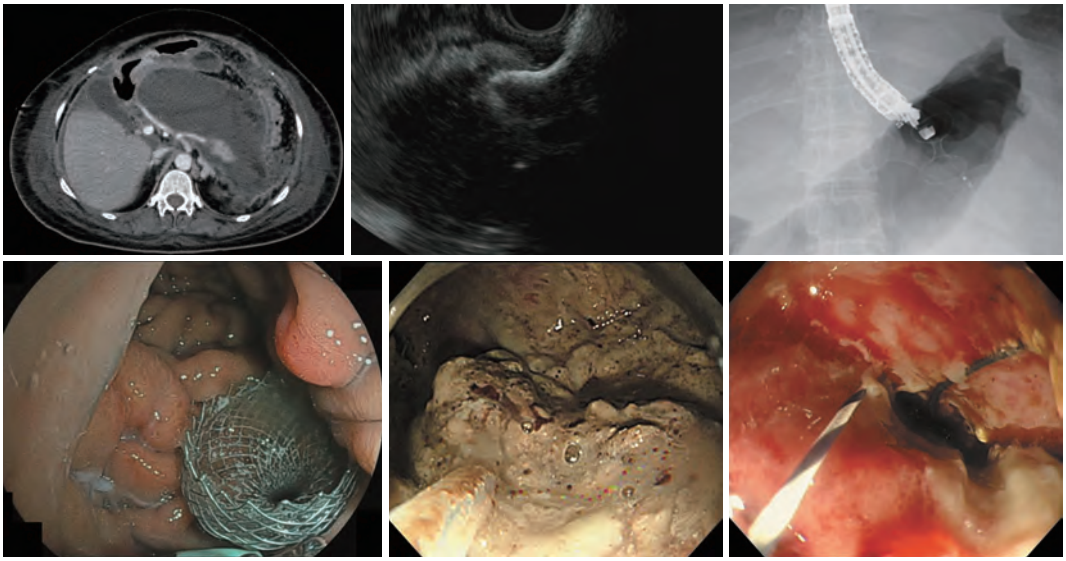
*2: Electrocautery dilators have been used; however, because of the high risk of adverse events such as bleeding and perforation, their use is now limited for cases in which tract dilation is difficult with other devices.[30)]

(2) Direct endoscopic necrosectomy (Figure 2)

In DEN, a forward-viewing upper gastrointestinal endoscope is used. If available, selecting an endoscope with an irrigation function is desirable. An overtube should be used because the procedure involves repeated endoscopic insertion and withdrawal. The overtube also helps prevent aspiration pneumonia. To minimize the risk of air embolism, carbon dioxide insufflation should be used.

(i)When a plastic stent is present, the stent is first removed, and a guidewire is advanced into the WON using an ERCP catheter. The tract is then dilated with a balloon dilator of 15 to 20 mm in diameter as appropriate. After adequate dilation, the endoscope is directly advanced into the WON (*1).

When a LAMS is present, further dilation is usually unnecessary if the stent is adequately expanded. The LAMS allows direct advancement of the endoscope into the WON through its lumen.
(ii) Under direct visualization, necrotic tissue is removed. Devices, including biopsy forceps, alligator forceps, snares, and retrieval baskets, are used. The selection of instruments depends on factors such as the consistency of necrotic debris, the size of the walled-off necrosis cavities, the risk of bleeding, and the endoscopist's preference to optimize procedural efficiency.



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d e f

Figure 2 **EUS-PFD (LAMS placement) and endoscopic necrosectomy.**

(a) CT imaging reveals a WON with heterogeneous attenuation suggestive of necrotic tissue. The WON appears encapsulated circumferentially.
(b) EUS image shows deployment of the distal flange of an LAMS, with the cyst wall being apposed.
(c) Fluoroscopic image during LAMS deployment demonstrates a one-step procedure from electrocautery-assisted puncture to stent deployment without guidewire placement.
(d) Endoscopic image immediately after LAMS placement shows the proximal flange deployed on the posterior wall of the gastric body near the greater curvature.
(e) During DEN, a large amount of necrotic debris within the WON was removed using a polypectomy snare.
(f) After multiple necrosectomy sessions, most of the necrotic debris was cleared from the WON cavity, and the pink cyst wall became visible endoscopically.

(iii) Before performing DEN, imaging studies such as CT should be reviewed to identify the target areas for treatment. Fluoroscopy-guided advancement of the guidewire with contrast injection assists in delineating the extent of the lesion that may not be evident on endoscopic imaging.

(iv) The procedure typically lasts around one hour in most institutions. To reduce the risk of aspiration pneumonia and other adverse events, prolonged procedures should be avoided. After completion of DEN, the previously removed plastic stent is reinserted into the tract to maintain the access route. In cases requiring saline irrigation, a nasocystic drainage tube is placed as deeply as possible within the lesion.

*1: When endoscope insertion is difficult, the combination use of balloon dilation is sometimes helpful. With the balloon inflated within the tract, the endoscopist gently advances the endoscope forward, pushing the balloon into the WON cavity. Collaboratively, the assistant gradually deflates the balloon, thereby enabling secure advancement of the endoscope into the targeted cavity.

(3) Transpapillary pancreatic duct drainage (Figure 3)

In transpapillary pancreatic duct drainage, standard ERCP devices are used. Because many cases

involve pancreatic duct disruption, adequate contrast injection is essential to delineate the pancreatic duct, and a highly selective guidewire should be employed.

(i) A side-viewing endoscope is inserted, and cannulation of the pancreatic duct is performed through the major duodenal papilla.

(ii) Pancreatography is then performed to identify the site of pancreatic duct disruption. In cases of chronic pancreatitis, strictures or stones may be present proximal to the disruption site, necessitating careful assessment of contrast findings. Guidewire manipulation should be performed with caution to traverse these strictures or stones, thereby enabling catheter advancement (*1).

(iii) In a symptomatic PPC with pancreatic duct disruption, the initial ERCP focuses on draining the PPC. A guidewire is advanced through the disruption site into the PPC, and a nasocystic external drainage tube is placed.

(iv) After resolution of the PPC, a second ERCP is performed. A guidewire is then advanced through the disrupted site into the upstream pancreatic duct, allowing for the placement of a pancreatic duct stent that bridges the site of disruption (*2).

(v) A follow-up ERCP is performed approximately three months later, and pancreatography is used to confirm whether the leakage improves before stent removal (“stent-free”). Additional intervention is planned for pancreatic duct strictures and/or stones that caused pancreatic duct disruption and PPC.

*1: Guidewires with high torque control are preferred.

*2: When the disruption is extensive or located at the stricture site, cannulating the upstream pancreatic duct is highly challenging. In cases requiring upstream pancreatic duct drainage, endoscopic ultrasound-guided pancreatic duct drainage (EUS-PDD) is a viable option.

4. Adverse Events and Postprocedural Management

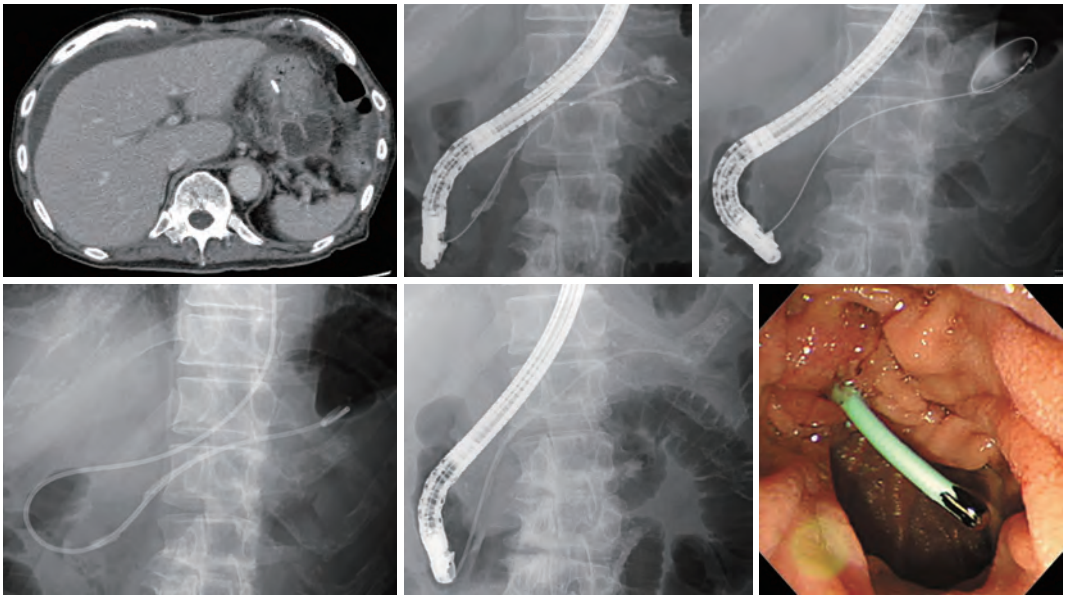
(1) EUS-guided drainage of pancreatic fluid collection

In EUS-guided drainage of pancreatic fluid collection (EUS-PFD), specific adverse events could occur at various steps of the procedure. To enable early detection and management of adverse events, it is important to monitor vital signs and clinical symptoms after treatment as well as to perform a CT scan on the day following the procedure.

1) Hemorrhage

Bleeding may occur if blood vessels are present along the puncture route. Doppler mode should be used to evaluate for arterial vessels in the gastric wall. Excessive pressure with the ultrasound probe could temporarily obscure blood flow and lead to misinterpretation. Therefore, gentle compression is required for accurate assessment. In cases of severe acute pancreatitis complicated by portal vein occlusion, particular caution is warranted because collateral vessels around the gastrointestinal tract may be present.

Although most cases improve with conservative management, including blood transfusion, endoscopic hemostasis, transcatheter arterial embolization, or surgical intervention may be required in selected cases.



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Figure 3 **Transpapillary pancreatic duct drainage for a disrupted pancreatic duct.**

(a) A CT image reveals a PPC due to disruption of the main pancreatic duct. A multilocular cystic lesion continuous with the main pancreatic duct is observed in the pancreatic tail.
(b) Pancreatography by ERCP demonstrates disruption of the main pancreatic duct, confirmed with contrast leakage in the tail region.
(c) A guidewire was advanced through the disruption site and coiled within the cyst cavity.
(d) As the initial drainage procedure, a 5 Fr pigtail nasocystic drainage tube was placed into the PPC.
(e) After confirming the shrinkage of the PPC, a second ERCP was performed. A 5 Fr pancreatic duct stent was placed from the upstream pancreatic duct to the duodenum, bridging the site of ductal disruption.
(f) Endoscopic view of the pancreatic stent.

2) Perforation and peritonitis

Gastrointestinal perforation occurs most often during tract dilation. To avoid overexpansion, balloon dilation should generally be limited to a diameter of 4 to 6 mm. Electrocautery dilators may also cause perforation due to thermal injury and should be reserved for cases in which tract dilation with other devices is difficult. It is also important to select a puncture site based on preoperative imaging findings where the gastrointestinal tract and the pancreatic fluid collection are in direct contact.

In cases of incomplete encapsulation of PFCs, particular caution should be paid to the possibility that perforation of the PFC wall may occur during the insertion of a guidewire or catheter. A rapid decrease in the size of the PFC on EUS, accompanied by a sudden increase in echo-free space within the abdominal cavity, should raise suspicion of perforation.

On postprocedural CT, the presence of free air and/or new-onset ascites should be evaluated. If conservative management is inadequate, peritoneal drainage or surgical intervention may be required.

3) Aspiration pneumonia

When a LAMS is placed for a PFC with liquid components, a large volume of fluid may rapidly flow into the stomach immediately after stent deployment, leading to esophageal reflux and aspiration pneumonia. Immediate suctioning through the endoscope just after stent placement is necessary to minimize this risk.

Elderly patients and those with prolonged fasting generally have impaired swallowing function, which makes them more susceptible to aspiration during endoscopic procedures. Frequent oral suctioning and other preventive measures are recommended.

4) Stent-related adverse events

Stent migration and misplacement immediately after deployment are among the most serious adverse events. To prevent displacement, double pigtail plastic stents are often selected, and an appropriate length stent should be used to avoid migration into the PFC. Postprocedural CT should be performed to thoroughly confirm the stent position. If stent migration or misplacement is detected, the feasibility of endoscopic intervention should be assessed, while surgical backup should be arranged.

Prolonged placement of a LAMS for several months may lead to bleeding due to tissue contact or embedment into the surrounding tissue, making removal difficult ("buried stent syndrome").[31] It is generally recommended that LAMS be removed within approximately 60 days.

After removal of a LAMS, a plastic stent may be left in place for an extended period to prevent recurrence of the PFC. The optimal duration of additional PS placement has not been established. In cases without recurrence risk factors, such as disconnected pancreatic duct syndrome (DPDS), stent removal is typically considered within 3 to 6 months. During the period of plastic stent placement, adverse events such as stent occlusion with recurrent PFC, stent-induced perforation, and penetration into adjacent organs may occur. Regular follow-up with clinical symptoms, blood tests, and imaging studies is therefore required.

(2) Direct endoscopic necrosectomy

Direct endoscopic necrosectomy (DEN) is an invasive procedure associated with the potential for severe adverse events. Careful procedural maneuvers and post-treatment follow-up tailored to anticipated adverse events are essential.

1) Hemorrhage

Blood vessels are often present within WON, but they are difficult to distinguish from necrotic tissue during endoscopy. When a pulsating, strand-like structure suggestive of a blood vessel is observed, intervention in the surrounding area should be avoided. Preoperative CT is recommended to identify vessels within the WON and to assess for the presence of inflammatory pseudoaneurysms. If a pseudoaneurysm is detected, transcatheter arterial embolization should be performed before DEN.

When bleeding occurs during DEN, the first step is to identify the bleeding point and assess the feasibility of endoscopic hemostasis, such as balloon tamponade or clipping. If massive bleeding obscures the endoscopic field, a request for transcatheter arterial embolization should be made to interventional radiology.

2) Perforation

Perforation and peritonitis often result from inadvertent injury to the wall of the WON during removal of necrotic tissue. Areas with incomplete encapsulation are particularly vulnerable to perforation. The risk is increased when excessive pressure is applied to the wall in an attempt to remove a large volume of necrotic debris at once, or when blind maneuvers are performed in areas not directly visualized. Secure visualization and controlled techniques should therefore be maintained throughout the

procedure.

If perforation occurs, DEN should be discontinued, and a nasocystic external drainage tube should be placed near the perforation site to minimize intra-abdominal fluid leakage. Postprocedural CT should be performed to assess the presence of free air and the distribution of ascites. The need for peritoneal drainage or surgical intervention should also be considered. Once perforation has occurred, repeating DEN for the same necrotic site becomes challenging. Therefore, meticulous attention to perforation prevention is essential.

3) Gastrointestinal fistula

In cases where WON is in direct contact with the gastrointestinal tract, inflammation may lead to fistula formation into the gastrointestinal lumen. Fistula formation is also recognized as an adverse event of DEN, typically identified by the leakage of contrast medium from the WON cavity into the gastrointestinal tract. When fistula into the colon occurs, the retrograde flow of intestinal contents often spreads infection within the WON, making control with endoscopic drainage difficult. Once gastrointestinal fistula is confirmed, consultation with surgical teams is necessary to evaluate the need for ileostomy.

4) Air embolism

Blood vessels of various sizes traverse the cavities of WON, and vascular disruption may occur during the removal of necrotic tissue. During DEN, insufflation can introduce air into exposed blood vessels, resulting in air embolism, a life-threatening adverse event.[32] To prevent this fatal complication, carbon dioxide (CO_2) insufflation should always be used during DEN.

5) Aspiration pneumonia

In cases with extensive necrotic debris, DEN procedures tend to be prolonged. Prolonged procedure time increases the risk of aspiration pneumonia, necessitating close postprocedural monitoring of respiratory status.

(3) Transpapillary pancreatic duct drainage

Adverse events associated with transpapillary pancreatic duct drainage are generally similar to those of ERCP. Especially in the context of transpapillary drainage of PPCs, particular attention should be given to post-ERCP pancreatitis and infection.

1) Post-ERCP pancreatitis

Endoscopic retrograde cholangiopancreatography (ERCP) for PPC requires adequate pancreatography to assess strictures or disruption of the main pancreatic duct. In addition, guidewire manipulation is necessary to traverse obstructive narrowings or a disconnected pancreatic duct, which increases the risk of post-ERCP pancreatitis. Because many of these patients have a history of pancreatitis, particular caution is warranted. ERCP for PPC should therefore be performed by experienced endoscopists, with precise contrast injection and careful guidewire handling. Rectally administered nonsteroidal antiinflammatory drugs (NSAIDs) immediately after ERCP are effective for prophylaxis.[33]

2) Infection of pancreatic pseudocyst

Transpapillary pancreatic duct drainage sometimes causes infection within a PPC. When a bridging stent is placed while the PPC remains intact, inadequate drainage of the PPC may result in a secondary infection. The initial ERCP should therefore focus on draining the PPC itself, for example, by placing a nasocystic external drainage tube within the cyst. Bridging of the disruption site could then be planned in subsequent ERCP sessions to minimize the risk of infection.

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9 Pathological sampling in the pancreas and biliary tract

Transpapillary cytology and biopsy of the pancreatic and bile ducts employing endoscopic retrograde cholangiopancreatography (ERCP) play a crucial role in diagnosing pancreatic and biliary diseases. It has been reported that 5–10% of cases suspected to be carcinoma of the pancreas based on imaging and subsequently resected were actually benign conditions. Given the significant invasiveness of surgery, a preoperative pathological diagnosis is recommended whenever possible.[1)] Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is the primary method for tissue sampling in pancreatic tumorous lesions, but in cases of main pancreatic duct stenosis without an identifiable mass, transpapillary approaches are selected for pancreatic juice cytology and brush cytology. Recent studies have highlighted the usefulness of serial pancreatic-juice aspiration cytologic examination (SPACE) for the early detection of pancreatic carcinoma.[2)] In biliary diseases, histological assessment plays an essential role not only in distinguishing between benign and malignant conditions but also in preoperative assessment of the extent of biliary malignancy.

However, transpapillary cytology and biopsy carry a risk of severe adverse events, including pancreatitis, bleeding, and perforation. Therefore, a thorough understanding of the indications, contraindications, procedural techniques, and device selection is essential before performing these procedures.

1. Pathological sampling in the pancreas

(1) Indications and contraindications

Indications for pancreatic duct cytology and biopsy using ERCP include cases with stenosis, obstruction, irregularity of the duct, or an intraductal lesion suspicious for malignancy. These procedures are also performed when malignancy needs to be excluded. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is commonly used for mass-forming lesions. However, when a mass is absent or the puncture route is interrupted by the pancreatic duct, cysts, or blood vessels, EUS-FNA should be avoided. In such cases, a transpapillary approach is indicated. The *Clinical Practice Guidelines for Pancreatic Cancer 2025* recommend performing pancreatic juice cytology via ERCP when abnormal pancreatic duct findings are present despite the absence of a detectable mass.[1)]

Recent reports have described needle tract seeding, in which tumor cells spread along the gastric wall after transgastric EUS-FNA of pancreatic body and tail tumors.[3)] This complication raises serious concerns about the potential dissemination of cancer cells during diagnosis.

Contraindications include not only the general contraindications for ERCP but also biopsy-specific limitations; use of large biopsy forceps should be avoided in sharply angulated strictures because of the risk of pancreatic duct injury. Furthermore, ERCP and pancreatic juice sampling for intraductal papillary mucinous neoplasms (IPMNs) should be limited to clinical research and are not recommended in routine clinical practice.[4] In particular, fluoroscopic biopsy within branch-type IPMNs should be avoided because of the risk of perforation.

(2) Transpapillary biopsy and cytology

The procedure begins with pancreatography to evaluate the main pancreatic duct and its branches. During contrast injection, it is important to avoid excessive increase in intraductal pressure while assessing the location, severity, and extent of the stricture. A guidewire is then inserted and carefully advanced through the stenotic or obstructed segment. To minimize the risk of pancreatic duct injury, a soft-tipped guidewire is preferable. For cell collection, a conventional catheter, brushing catheter, biopsy forceps, or an endoscopic nasopancreatic drainage (ENPD) tube should be advanced to the target stricture. In most cases, pancreatic sphincterotomy is not required.

(3) Sampling methods

1) Biopsy

Under fluoroscopic guidance, small-caliber biopsy forceps are inserted to obtain tissue samples from the pancreatic duct epithelium. Using the guidewire as a landmark, the forceps are carefully advanced under fluoroscopic visualization, with particular attention to avoiding injury to the pancreatic duct. Pancreatic duct biopsy is technically demanding, and obtaining specimens from the target site is often challenging. Therefore, indications should be carefully considered. Moreover, because the sensitivity of biopsy alone is limited, it is preferable to combine biopsy with cytology.[5]

EUS-FNA is standard approach for mass-forming lesions in many institutions.

2) Pancreatic-juice aspiration cytology

Catheters with side holes facilitate pancreatic juice aspiration. To improve the diagnostic accuracy in pancreatic fluid analysis, several innovative techniques have been developed. One approach employs a double-lumen catheter to lavage the pancreatic duct with saline before collecting the fluid; this method often incorporates the cell block technique to obtain higher-quality specimens for examination.[6] Another technique involves gently scraping the pancreatic duct stricture with a guidewire to collect fluid.[7] Both methods aim to obtain more comprehensive samples for improved diagnostic yield. Aspiration is generally most effective when performed following biopsy.

3) Brush cytology

A brush catheter is advanced over a guidewire to the target stricture, and epithelial cells are obtained by scraping the ductal epithelium. The brush is moved back and forth approximately ten times across the stricture, from distal to proximal, with care taken to avoid inadvertent entry into pancreatic duct branches. Specimens are prone to degeneration and should be submitted for pathological analysis promptly. To prevent obstructive pancreatitis at the stricture site, ENPD or pancreatic duct stenting is recommended.

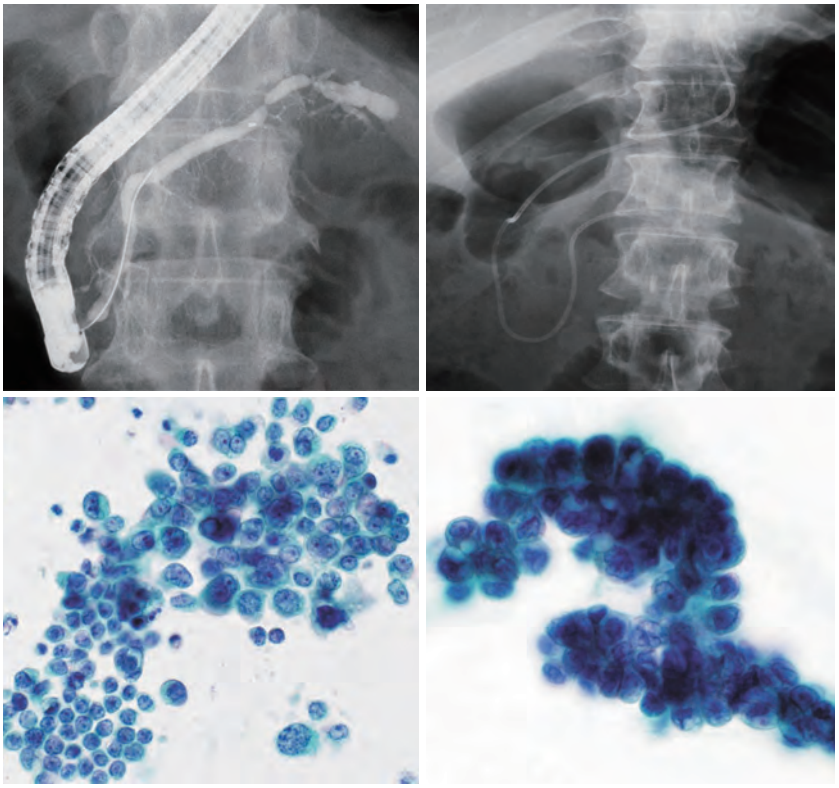


Figure 1 SPACE findings in pancreatic carcinoma *in situ.*

(a) Pancreatography showing a stricture of the main pancreatic duct in the pancreatic body.
(b) An endoscopic nasopancreatic drainage (ENPD) tube was placed, and pancreatic juice was repeatedly aspirated through the tube for cytological analysis.
(c) Cytology (first specimen): a few atypical cells with mild nuclear enlargement and slightly increased chromatin, classified as atypical/indeterminate.
(d) Cytology (third specimen): cellular clusters with high density and irregular overlapping; nuclear irregularity and prominent nucleoli observed, diagnosed as malignant (adenocarcinoma).

4) Serial pancreatic-juice aspiration cytologic examination (SPACE)

Figure 1 illustrates the serial pancreatic-juice aspiration cytologic examination (SPACE) performed after endoscopic nasopancreatic drainage (ENPD) placement.

In cases where imaging examinations demonstrate focal stenosis of the main pancreatic duct without an identifiable mass, SPACE using an ENPD tube has been reported as an effective method for diagnosing small pancreatic carcinoma, including carcinoma in situ (high-grade PanIN). Reported sensitivity ranges from 75% to 82.4%, specificity is 100%, and overall diagnostic accuracy is 88% to 94.9%,[8-10] with higher sensitivity observed in smaller tumors.[11]

For this procedure, a 4- or 5-Fr ENPD tube is used, and fresh pancreatic juice is submitted for pathological analysis at intervals of several hours after tube placement. Because prolonged storage causes cellular degeneration due to digestive enzymes, pancreatic juice accumulated in a collection bag should not be used for cytological diagnosis. Compared with single-session pancreatic juice cytology, SPACE provides a superior diagnostic yield, and collection of at least six samples is recommended.[12]

(4) Adverse events

After SPACE for pancreatic duct stenosis without a mass, the frequency of pancreatitis has been reported as 6.8%.[12] When pancreatic juice outflow is poor, tube occlusion may occur. In such cases, the tube should be removed promptly.

2. Pathological sampling in the Bile Duct

(1) Indications and contraindications

Indications for cytology and biopsy of the bile duct using ERCP include biliary stricture or obstruction, as well as the presence of intraductal protruding lesions to differentiate between benign and malignant conditions. In cholangiocarcinoma, horizontal extension is common, and in surgical candidates, stepwise biopsy is recommended to assess tumor extent.

Recent advances in genetic panel testing have expanded treatment options for biliary tract cancer, necessitating the collection of sufficient tumor tissue for DNA analysis. EUS-FNA may be performed for lesions suspected to be puncturable biliary tract tumors or lymph node metastases. In principle, it should be limited to cases in which puncture can be performed without traversing the biliary tract lumen, given the risks of tumor seeding and bile leakage.[13]

(2) Transpapillary biopsy and cytology

Cholangiography is performed to identify the site of stricture or obstruction. A guidewire is then advanced across the stenotic or obstructed segment, followed by the insertion of a conventional catheter, brushing catheter, or biopsy forceps to the target site for sampling.

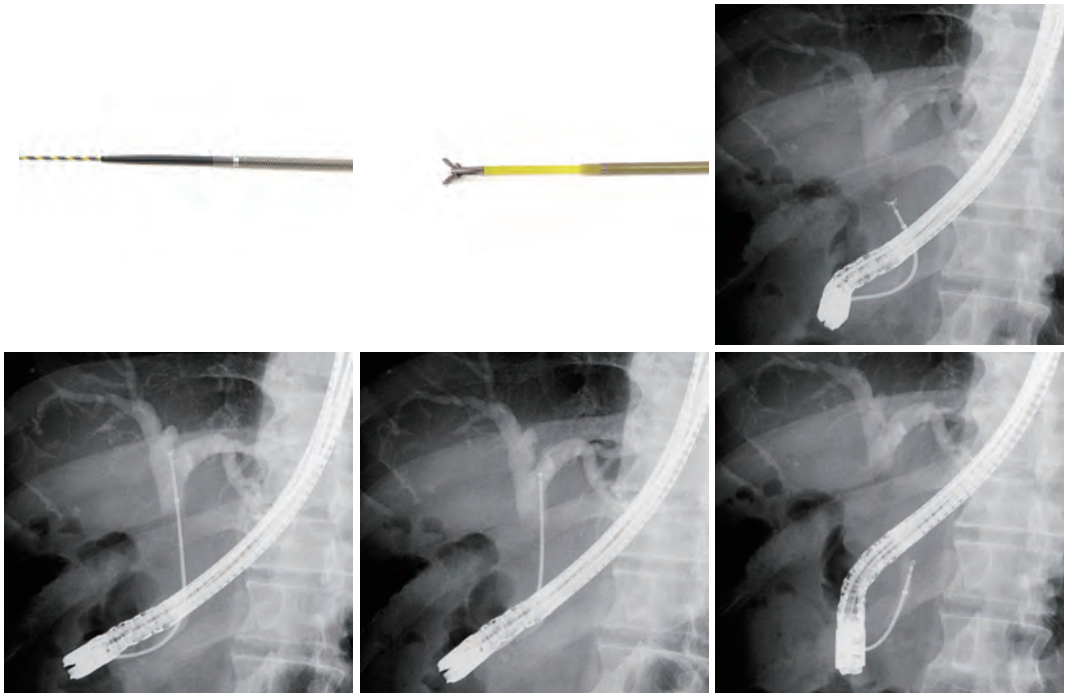
(3) Sampling methods

1) Bile juice cytology and brush cytology

Cells present in bile are often detached for prolonged periods and may undergo degeneration due to continuous exposure to bile. As a result, morphological evaluation is difficult and diagnostic sensitivity is generally low. In contrast, brush cytology provides fresher cellular material, which makes morphological assessment more reliable. Under fluoroscopic guidance with guidewire assistance, the brushing catheter is advanced, and approximately ten to-and-fro movements are performed along the narrowed segment. After brushing, the brush tip is cut off and immersed in saline, and the material within the sheath is aspirated for analysis. In addition, bile containing exfoliated cells is collected and submitted for cytological examination.

2) Fluoroscopy-guided bile duct biopsy

Biopsy forceps have a rigid metallic tip and emerge in a straight line from the endoscopic channel, requiring careful manipulation during insertion into the bile duct. The forceps are advanced along the upper left side of the guidewire. To align them with the axis of the bile duct, the duodenoscope is gently pushed forward to create an upward orientation, and fluoroscopy is used to confirm proper alignment



a b c
d e f

Figure 2 **Biopsy using endoscopic introducer.**

(a) An endoscopic introducer with outer and inner sheaths was inserted along the guidewire. (b) The guidewire and inner sheath were removed, and biopsy forceps were inserted through the outer sheath.
(c) Biopsy at the site of the stricture
(d–f) For evaluation of superficial extension, additional biopsies were taken from the right hepatic duct (d), left hepatic duct (e), and intrapancreatic bile duct (f).

before insertion. After reaching the target site, the forceps jaws are opened. With the jaws kept open, the elevator is gradually released so that the forceps are pressed as perpendicular as possible against the ductal wall. The jaws are then gently closed to obtain a specimen. If the forceps are closed too quickly, they may straighten and slip, resulting in inadequate sampling. For evaluation of tumor extension in cholangiocarcinoma, biopsies should be performed stepwise from the hepatic side of the lesion toward the target area. The use of an endoscopic introducer helps guide the forceps accurately to the target, facilitating insertion and reducing the risk of contamination (**Figure 2**).

3) Peroral cholangioscopy-guided biopsy

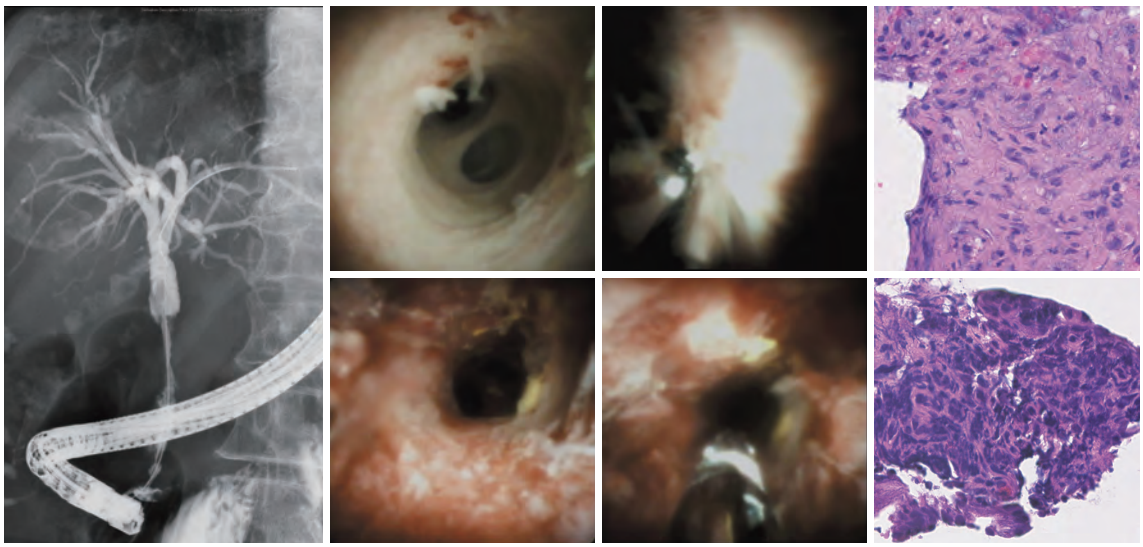
Peroral cholangioscopy (EUS)-guided biopsy is primarily performed preoperatively to evaluate the superficial extension of cholangiocarcinoma. Superficial spread is particularly common in protruding-type cholangiocarcinomas. After endoscopic evaluation, stepwise biopsy is performed. The CHF-B290 video cholangioscope (Olympus) provides high-resolution imaging, allowing detailed evaluation of mucosal surface morphology and fine vessel patterns (**Figure 3**). The disposable SpyGlass DSII system (Boston Scientific) enables four-way tip deflection, enhancing targeting precision during biopsy and facilitating assessment of tumor extent (**Figure 4**). Small-caliber biopsy forceps are used for cholangioscopy-guided biopsy.



a | b | c

Figure 3 **Intraductal images of the bile ducts obtained with CHF-B290 biliary videoscope.**

(Olympus)
(a) Normal bile duct.
(b) Close-up view of the normal bile duct showing a network of fine blood vessels.
(c) Cholangiocarcinoma with dilated tumor vessels within an area of granular mucosa.



a | b | c | d
e | f | g

Figure 4 **Cystic duct carcinoma localized by biopsy using the SpyGlass DS system.**

(a) Cholangiography showing irregular strictures of the distal bile duct.
(b–d) In POCS using the SpyGlass DS system, no redness or irregular stricture was observed at the hepatic hilum (b), and biopsy from this site (c) showed no malignant features (d).

(e–g) A widespread tumorous lesion was observed extending from the cystic duct to the common bile duct (e), and biopsy from this site (f) confirmed adenocarcinoma (g).

3. Specimen Processing

Rapid processing is essential for bile and pancreatic juice cytology, as these specimens are highly susceptible to degeneration. To minimize deterioration, methods such as suspension in tissue culture medium or the addition of gelatin solution have been introduced, and favorable results have been reported.[14,15)]

4. Cytology and Histopathology Reports

(1) Cytology

Cytology reports assess whether the collected specimen is adequate for diagnostic evaluation. If adequate, the report classifies the specimen as benign or malignant and provides cytological findings along with the suspected lesion type. Pancreaticobiliary lesions encompass a wide spectrum of tumors with diverse biological behaviors, ranging from benign tumors to low- to high-grade malignancies. Simply reporting the diagnostic category (e.g., “indeterminate” or “malignant”) often fails to convey the underlying rationale. Therefore, close communication between clinicians and pathologists is essential for accurate interpretation and appropriate patient management. For pancreatic lesions, it is recommended to follow the classification system shown below.[16,17)]

Cytology reporting format in the pancreatic region
1.Cytological classification
  Inadequate sample
  Adequate sample
  Negative/benign
  Atypical/indeterminate
    Findings suggesting benign disease (favor benign)
    Findings suggesting malignant disease (favor malignant)
    Others
  Suspicious for malignancy / at least low-grade malignancy
  Positive / malignant
2.Record findings (e.g., grade of atypia), or presumptive diagnosis

(2) Pathological Report of Pancreatic Biopsy

In 2010, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) biopsy was included in Japan’s national healthcare insurance system. Since then, biopsies have been performed more often for pancreatic lesions. Therefore, the reporting format is recommended for pathological diagnosis as follows:

Reporting format for histopathological diagnosis of pancreatic biopsy
[1] Inadequate sample
[2] Adequate sample
  [2-1] No neoplastic lesion
  [2-2] Definite diagnosis of neoplasm is difficult.
  [2-3] Neoplastic lesion
    [2-3-1] Ductal carcinoma
    [2-3-2] Non-ductal neoplasm
    [2-3-3] Unclassifiable neoplasm

In 2022, through the collaboration of the International Academy of Cytology (IAC) and the International Agency for Research on Cancer (IARC), the Papanicolaou Society of Cytopathology (PSC) Guideline was revised, and published as the WHO Reporting System for Pancreatobiliary Cytopathology (WHO system)[18]. Since this WHO system is expected to become the international standard in the future, its classification is also described herein.

WHO Reporting System for Pancreatobiliary Cytopathology (WHO system)[19]
Insufficient/Inadequate/Non-diagnostic
Benign/Negative for Malignancy
  Benign non-neoplastic processes
  Benign neoplastic processes
Atypical
Pancreatobiliary neoplasm: low-risk/grade (PaN-low)
Pancreatobiliary neoplasm: high-risk/grade (PaN-high)
Suspicious for malignancy
Malignant

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10 Endoscopic Papillectomy

Endoscopic papillectomy (EP) has become widely performed, particularly at high-volume centers, and a guideline has been established in Japan.[1] However, it has not yet been fully covered by insurance, and concerns remain regarding the occurrence of severe adverse events such as pancreatitis. Given these potential risks, this procedure should be performed with careful consideration. It is essential that it should be carried out by specialists with extensive experience or under their supervision. This section provides practical and educational guidance relevant to the routine clinical practice.

1. Indications and Contraindications

(1) Indications

EP is indicated for papillary adenomas that do not extend into the pancreatic or bile duct. In papillary carcinomas, EP is an option for well-differentiated adenocarcinomas that are confined to the mucosa and do not invade the sphincter of Oddi. Lymph node metastasis is rarely observed in such cases, and EP is a potentially acceptable treatment approach.[2-5] However, even with detailed preoperative evaluation using endoscopic ultrasound (EUS) and intraductal ultrasound (IDUS), accurate judgement on tumor invasion into the sphincter of Oddi remains challenging. Current imaging modalities have limitations in detecting such invasion associated with a potential risk of lymph node metastasis. Studies have also been made to histologically determine the presence of invasion through immunohistochemical staining of biopsy specimens,[6,7] but a standardized method has not yet to be established. Due to these uncertainties, a consensus on EP for cancerous lesions has not been reached. Moreover, for adenomatous lesions with intraductal extension into the pancreatic or bile duct, or large lesions where a clear visual field is difficult to maintain and stable snaring is not feasible, surgical resection should be considered.

(2) Contraindications

EP is contraindicated in patients with a bleeding tendency or acute pancreatitis. Once these conditions improve, it should be considered. In patients taking antithrombotic agents, EP is classified as a high-risk procedure for bleeding in the *Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment*. Therefore, the risk of thromboembolism should be assessed, and the procedure should generally be performed in accordance with these guidelines.[8,9] For patients with a

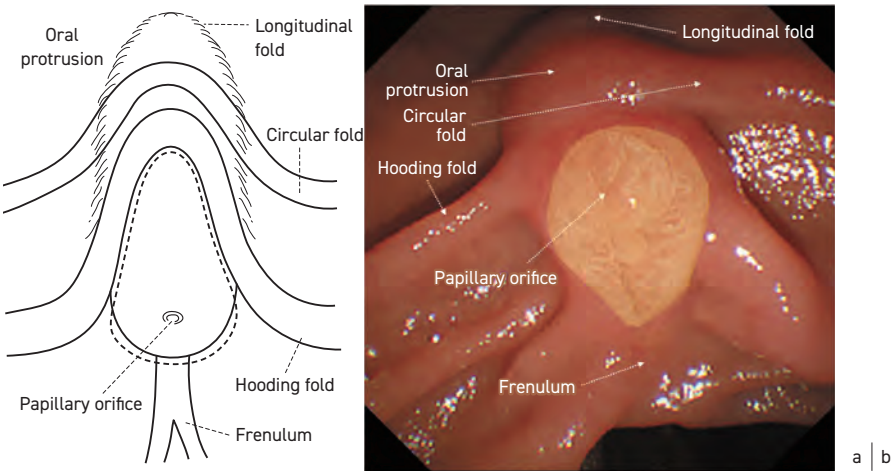


Figure 1

a: Schematic diagram of the papilla (frontal view). The area within the dashed line is the papilla.
b: Actual papilla (duodenoscope observation). The yellow-highlighted region is the papilla.
(Cited from Literature 10)

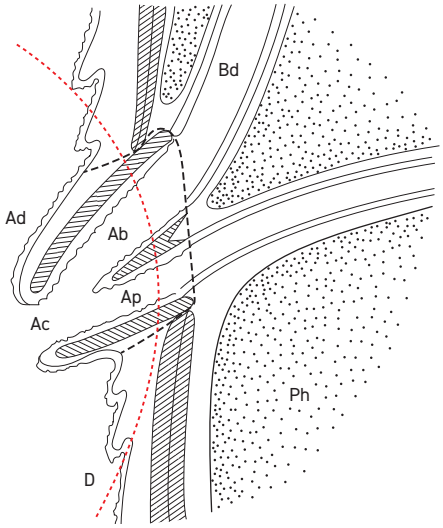
pacemaker or an implantable cardioverter-defibrillator, caution is required for concomitantly using high frequency generators and X-ray fluoroscopic diagnostic devices, since these are categorized as medical equipment requiring careful concomitant use. It is important to consult with cardiovascular specialists, and the procedure should be performed in the presence of clinical engineers.

2. Anatomy of Papillary Region and Morphology of papillary Tumor

Various tumors may develop in the ampulla of Vater, originating from either the small intestine or the biliary system. In addition to adenomas and adenocarcinomas, which are the primary focus, neuroendocrine neoplasms and paragangliomas is also likely to arise in this region. Understanding of the anatomy of the papilla is essential for accurately diagnosing papillary tumors. The ampulla of Vater is the site where the bile duct and pancreatic duct open into the duodenum, as indicated by the dashed line in **Figure 1a** and the yellow-highlighted area in **Figure 1b**. The longitudinal folds of the duodenum are ridges formed by the sphincter of Oddi muscle running within the submucosa. Along with the annular folds, hooding folds, and frenulum, these structures are not considered part of the ampulla of Vater but are classified as part of the duodenum.

The ampulla of Vater is divided into major duodenal papilla (Ad), common channel (Ac), bile duct of the papillary region (Ab), and pancreatic duct of the papillary region (Ap), as outlined within the black dashed line in **Figure 2a**.[10] The area that can be resected by EP includes not only Ad and Ac but also parts of Ab and Ap, as shown within the red dashed line in **Figure 2a**.

When tumors arise from the surface region of Ad, they present as exposed-type. In endoscopic findings, adenomas in this region typically appear as white mucosa extending toward the surrounding duodenal mucosa. In contrast, carcinomas are characterized by reddening mucosa with irregular surface and friability, as seen in **Figure 3**. Tumors originating from deeper structures such as Ac, Ab, and Ap are classified as non-exposed type. This type shows enlarged proximal protrusion, as shown in **Figure 4**. Understanding of the site of tumor development is therefore critical for accurate diagnosis and treatment planning.

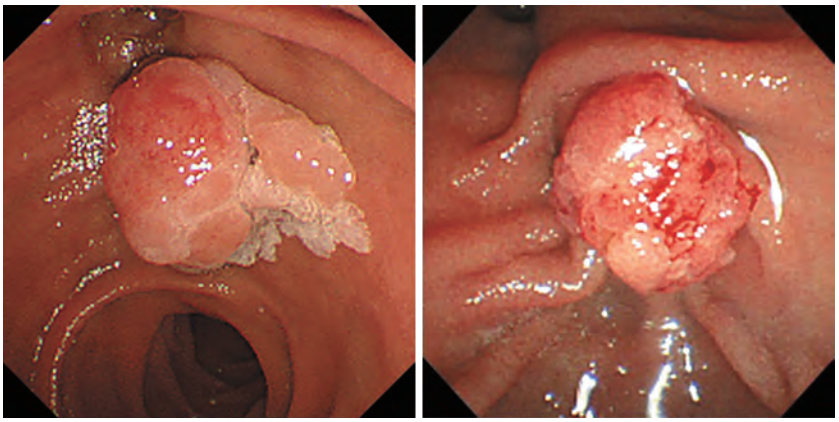




a | b

Figure 2

a: Schematic diagram of the papilla (cross-section). The area within the black dashed line is the papilla, and the red dashed line is the limit of resection by EP.
b: Actual cross-section of the papilla (EP specimen). Major duodenal papilla (Ad), common channel (Ac), bile duct of the papillary region (Ab), pancreatic duct of the papillary region (Ap).
(Cited from Literature 10)



a | b

Figure 3

a: Papillary adenoma. White mucosa extending to the surrounding duodenal mucosa.
b: Papillary carcinoma. It presents with reddening, friable, irregular mucosa.

3. Preparation

As with routine upper gastrointestinal endoscopy, pharyngeal anesthesia is administered before the procedure. For antispasmodic premedication, butylscopolamine bromide (Buscopan®) is used. In patients with ischemic heart disease, glaucoma, prostatic hypertrophy, or advanced age, glucagon is preferred instead. Intravenous access is secured, and continuous fluid infusion is maintained. Intraoperative fluid administration helps compensate for circulating blood volume loss due to bleeding.

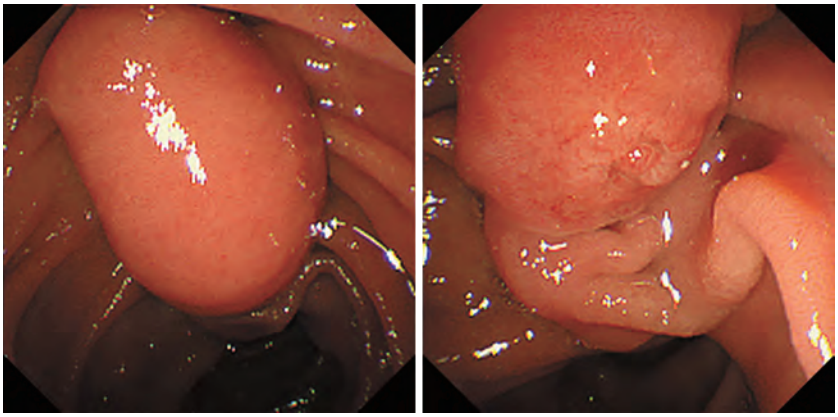


Figure 4 Non-exposed papillary adenoma.

The lesion is visualized as an enlarged oral protrusion, interpreted as an expanded papilla.

Ringer's solution or similar fluids are preferred unless there is concern about cardiac overload. Once intravenous access is established, sedation is induced using either a sedative or an analgesic, or both. Midazolam (Dormicum®), diazepam (Horizon®, Cercine®), and flunitrazepam (Silece®) are commonly used sedatives in Japan. When a prolonged procedure is anticipated, dexmedetomidine (Precedex®) is also useful. Propofol (Diprivan®) provides stable sedation, but its use should comply with institutional regulations and safety protocols. As analgesics, pethidine hydrochloride (Pethidine Hydrochloride Injection) and pentazocine hydrochloride (Sosegon®) are commonly administered.

During the procedure, respiratory depression and hypotension is likely to occur. To mitigate these risks, a nasal cannula is placed before the examination, and continuous monitoring is carried out using an ECG monitor, pulse oximeter, and continuous blood pressure monitor. As antagonists for respiratory depression, flumazenil (Anexate®) and naloxone hydrochloride are prepared in advance.

4. Preprocedural Examination

(1) Endoscopic observation and tissue sampling

Duodenoscopy allows to obtain the frontal view of the ampulla of Vater, enabling evaluation on its overall appearance. In addition to conventional white-light imaging, narrow-band imaging (NBI) has been reported to be useful in delineating the boundary between normal duodenal mucosa and lesions.[11] The concordance rate between preoperative biopsy and postoperative histopathological diagnosis has been reported to range from 39.7% to 70%, whereas the false-negative rate for adenocarcinoma has been between 16% and 60%.[1] It is difficult to obtain a definitive histopathological diagnosis preoperatively, as in endoscopic imaging diagnosis. Findings such as ulceration, increased friability, and firmness have been reported as indicators suggestive of malignancy.[12] It has also been noted that tumors originating from deeper layers of the papilla tend to have a higher degree of invasive malignancy.[13] Given the risk of post-biopsy pancreatitis, targeted biopsy should focus on areas with a high suspicion of malignancy based on endoscopic findings.

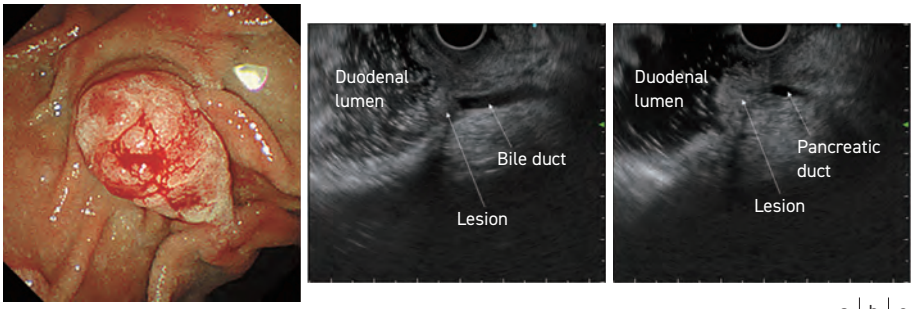


Figure 5

a: Endoscopic image showed duodenal papillary adenoma (high-grade dysplasia)
b: EUS image revealed no extension into the bile duct of the papillary region
c: EUS image revealed no extension into the pancreatic duct of the papillary region

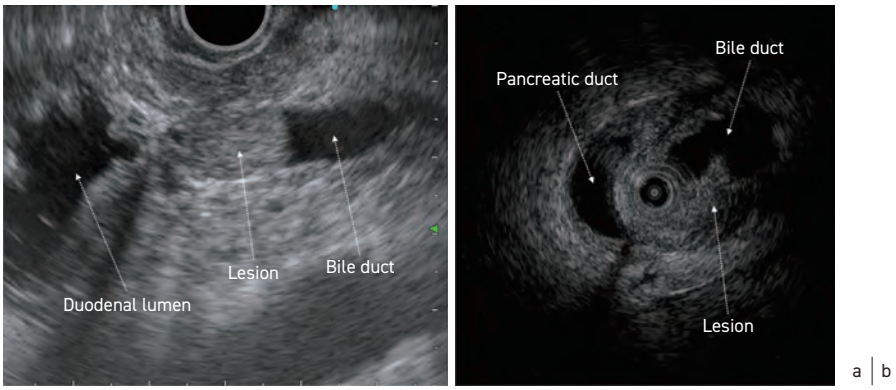


Figure 6

a: EUS image revealed extension into the bile duct of the papillary region.
b: IDUS image by intraductal scanning revealed extension into the bile duct of the papillary region.

(2) Assessment of tumor extent

The objective of preoperative assessment for EP is not only to confirm whether the lesion remains localized to the papilla, corresponding to T1 stage, but also to evaluate the intraductal extension into the pancreatic and bile ducts. This assessment is performed using EUS or IDUS as shown in **Figure 5**.

Regarding determining EP indication, the sensitivity and specificity of EUS for T1 stage cancer were 77% and 78%, respectively, according to a meta-analysis.[14] And the T1 stage diagnostic rate of IDUS was reportedly as high as 80–100%.[15-17]

In assessment on the intraductal extension of tumor, the diagnostic accuracy of EUS has been reported to be 86% to 90% for the biliary duct and 77% to 92% for the pancreatic duct.[15,16,18] IDUS has demonstrated a higher diagnostic accuracy of 90% to 95% for the biliary duct and 88% to 100% for the pancreatic duct (**Figure 6**).[15,16,18]

While IDUS offers the superior diagnostic precision compared with EUS, caution is required because of the risk of post-procedural pancreatitis. It is also important to recognize that neither EUS nor IDUS can differentiate T1 stage papillary carcinomas based on the presence or absence of their invasion into the sphincter of Oddi.

5. Practical Procedure and Advice

(1) Snaring the tumor

The snare used for EP should be designed to press firmly against the mucosa while minimizing slippage. A rigid monofilament snare or a spiral-shaped snare is commonly available. The diameter of a snare wire plays a significant role in how efficiently it can cut. Therefore, selecting appropriate snares requires practical knowledge of how these variations impact cutting performance.[19)]

(2) High frequency electrosurgical unit

High frequency electrosurgical units available include the ICC and VIO series from ERBE and the ESG series from Olympus. Their incision modes include autoCUT® and PureCut, which offer simple cut resection, and endoCUT® and PulseCut, which alternate between cutting and coagulating. There is currently no definitive evidence to determine the optimal incision mode for EP, and their usages are largely decided based on institutional preferences. A multicenter randomized controlled trial comparing endoCUT® mode and autoCUT® mode in EP found no significant difference in the incidents of bleeding (13.3% vs. 16.7%, P = 1.00) or pancreatitis (27% vs. 30%, P = 0.77).[20)]

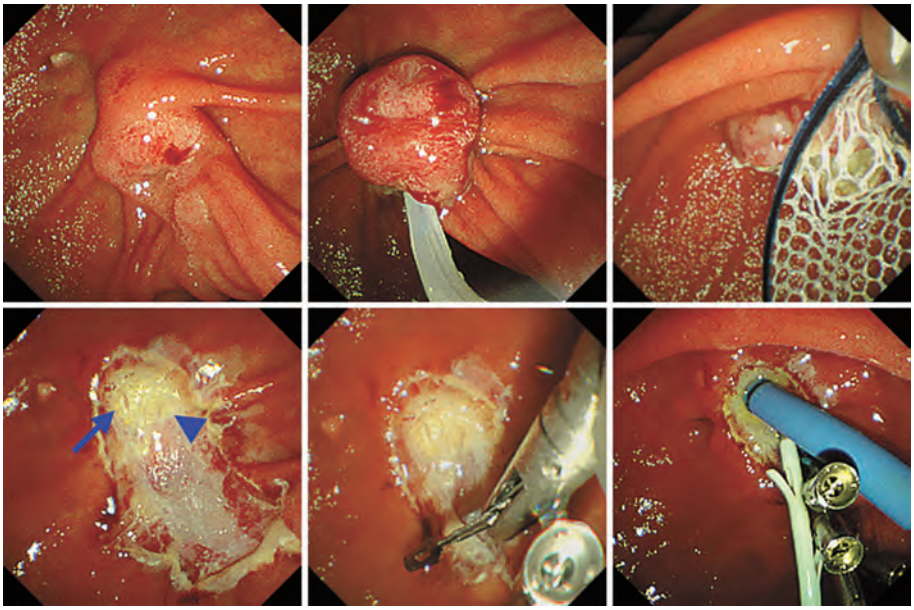
However, pathological findings from excised specimens indicated that endoCUT® mode resulted in a significantly higher rate of tissue damage (27% vs. 3.3%, P = 0.03). A basic study investigating the optimal electrosurgical unit (ESU) settings for EP suggested that strong cutting ability with adequate coagulating effect was achieved by endoCUT® mode I with high duration, lowest coagulation (Setting 1), and low interval settings.[19)] Further clinical studies are needed to validate treatment outcomes in actual practice.

(3) Stenting

In papillary adenomas, the bile and pancreatic ducts are typically normal, without stenosis or dilatation. Therefore, the most commonly used stents are plastic stents ranging from 7 to 10 Fr for the bile duct and 3 to 5 Fr for the pancreatic duct. To prevent migration, a stent with an appropriate shape should be selected.

(4) Clipping

To prevent bleeding and perforation, clips are used to suture the resected surface area, primarily on the anal side. Clipping under duodenoscopy presents technical challenges, because the movement of the clip forceps is limited by the elevator mechanism, making the procedure demanding in terms of technical proficiency. In recent years, a novel clip has been introduced that allows the tip to bend up to 90 degrees when the forceps elevator is raised. It has good rotation and can grasp the target site repeatedly with no difficulty. This is a reliable device to suture a resected surface without stress.



a b c
d e f

Figure 7 Endoscopic papillectomy.

a: A case of duodenal papillary adenoma was observed.
b: The lesion was snared and resected using a high frequency electrosurgical unit.
c: The resected lesion was immediately retrieved with net forceps.
d: After resection, the papillary region revealed the bile duct orifice (arrow) and the pancreatic duct orifice (arrowhead).
e: The distal side of the resection site was closed with clips.
f: Under guidewire assistance, stents were placed in both the bile duct and the pancreatic duct.

6. Procedure of Endoscopic Papillectomy

EP is a procedure requiring the proficiency in both endoscopic resection techniques and ERCP-related procedures. It involves snaring and electrosurgically resecting a lesion, retrieving the specimen, closing the resected surface site with clips, and performing drainage of the pancreatic and bile ducts (**Figure 7**). The following describes the procedure and key points.

(1) Lesion snaring

The snaring process typically starts by placing the tip of the snare on the proximal side of the hooding fold, aligning it with the 12 to 2 o'clock orientation relative to the lesion. With this position serving as a support point, the snare is opened and leaned downward toward the distal side to wrap around the lesion. In order to ensure subsequent bile and pancreatic duct cannulations, a deep and sufficiently large snare capture is performed at the upper margin of papillary roof or the proximal side of the hooding fold. Aspiration is applied to draw the lesion into the snare without leaving residual tumor. The extent of the snaring is confirmed under endoscopic visualization to ensure complete resection, including the distal side margin of the lesion.

(2) Electrocautery cutting

Following confirmation of complete snaring, the loop is tightened to constrict the blood flow, causing congestion of the papilla within a few seconds. The high-frequency electrosurgical unit is activated by pressing the foot pedal.The lesion is resected while being drawn toward the endoscope tip with electrocautery.

(3) Specimen retrieval

After resection, the specimen is immediately grasped by a net retriever or grasper to prevent it from moving to the distal side where it could not be retrieved. The specimen is secured and removed together with the endoscope.

(4) Clip closure after papillectomy

For closure of the resection site, the first clip is applied distally to the normal mucosa to serve as an anchor, and clips are applied to grasp the normal mucosa surrounding the edge of the resection site, allowing the area to be closed. Careful attention is paid to avoid clipping the pancreatic duct orifice. Prior to clipping, thorough observation of the resection site is crucial to prevent entrapment of any residual lesion.

(5) Pancreatic and bile duct stenting

Stent placement after EP is intended to prevent cholangitis and pancreatitis which result from impaired drainage of bile and pancreatic juice due to edema at the resection site. In addition, it contributes to reducing the risk of papillary stenosis in the process of ulcer scarring.

1) Pancreatic stenting

Detailed observation of the resection site is performed to identify the orifices of the bile and pancreatic ducts. The orifices (openings) generally appear in different ways, either as concentric openings or slit-like structures, depending on the depth of the resection and how the sphincter of Oddi is positioned. Forceful or misdirected cannulation and contrast injection pose risks of pancreatitis and perforation. The catheter tip is gently placed at the orifice, contrast injection is performed with caution to delineate the pancreatic duct course, and the stent is inserted over a guidewire. Preoperative imaging, such as MRCP, is not only used to assess the pancreatic orifice diameter and duct course, but to select appropriate stent size, length, and shape.

2) Biliary stenting

There is no established evidence favoring either stent placement or additional endoscopic sphincterotomy (EST), and it depends on the preference of the endoscopist. In EP, the additional EST takes place in a setting where the papillary region including the sphincter of Oddi has already been resected. The incision should be made carefully, or there is an increased risk of bleeding and perforation. When a stent is placed after EP, it offers the advantage of making clip hemostasis easier to perform if bleeding occurs.

7. Specimen Handling

Proper handling of resected specimens is essential for accurate pathological evaluation, particularly for assessing horizontal and vertical tumor extension. To facilitate this assessment, a specimen is carefully stretched and affixed onto a rubber or cork board with tweezers before being fixed in formalin. Unlike resected specimens from other gastrointestinal tumors, those obtained from EP require precise evaluation of tumor extension toward the bile and pancreatic ducts. To support this evaluation, a catheter sheath, such as that from an intravenous indwelling needles, is inserted into the bile or pancreatic duct. During resection, the mucosa and surrounding tissue at the ductal orifices are usually included in the specimen, and formalin is introduced through the sheath to ensure proper fixation. Preoperative endoscopic images are useful to identify the proximal and distal margins of the specimen and document the location of the bile and pancreatic duct orifices so that this information is accurately conveyed to the pathologist.

8. Definition of Complete Resection and remnant/recurrence

The complete resection rate of EP is reported to range from 47% to 93%. Although no standardized definition of complete resection exists, many studies define it based on the absence of tumor cells at the resection margin on pathological examination.[1)] The criteria for remnant/recurrence following EP vary across studies. Various reports define remnant when tumor cells are detected at the resection margin on pathological evaluation or when a histopathological diagnosis of remnant is made within three to six months after the initial endoscopic treatment. Recurrence is generally defined as a diagnosis made during follow-up beyond this period.[1)] The classification of recurrence could include situations in which adenomas that were initially too small or obscured to be clinically detected later become visible or diagnosable.

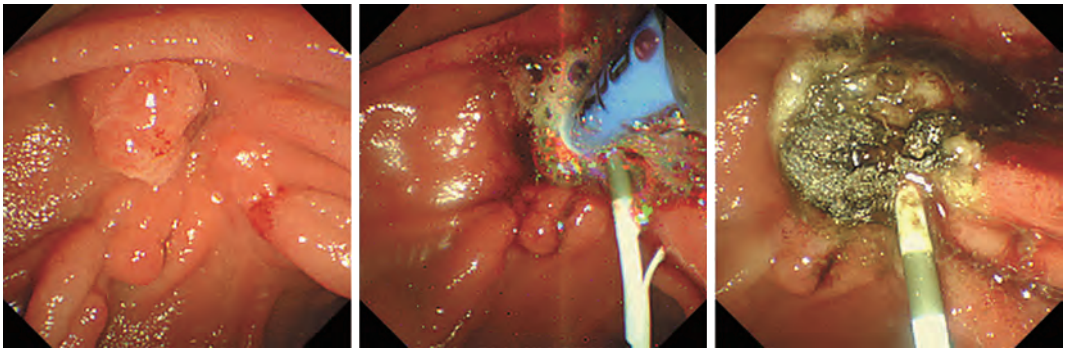
9. Management of Residual/Recurrent Lesions

For residual or recurrent adenomas, additional resection using a snare or ablative therapy with argon plasma coagulation (APC) is implemented (**Figure 8**). While surgical resection remains the standard approach for cases with adenomatous involvement extending into the bile or pancreatic duct lumen, recent reports suggest the potential utility of endoscopic intraductal radiofrequency ablation (RFA).[21,22)] Although long-term outcomes and safety data remain insufficient, EP combined with RFA is expected to become a viable treatment option for papillary adenomas with intraductal extension.

For residual or recurrent adenocarcinomas, pancreaticoduodenectomy or other surgical resection is prioritized as the primary treatment approach.

10. Management of Papillary Carcinoma Diagnosed After Resection

The concordance rate between preoperative biopsy and postoperative diagnosis of papillary tumors is not sufficient. A lesion initially diagnosed as an adenoma is often later found to contain adenocarcinoma after EP. There is no established consensus on the appropriate treatment strategy when adenocarcinoma is diagnosed after EP. The rate of lymph node metastasis in T1 cancer is reported to



a | b | c

Figure 8 **Argon plasma coagulation (APC) ablation for residual adenomatous lesions after EP.**

a: Following endoscopic papillectomy for a papillary adenoma, endoscopic follow-up at two months revealed residual adenomatous tissue.
b, c: APC ablation was performed after placing a pancreatic duct stent.

range from 10% to 22%.[23,24] On the other hand, EP could be acceptable because well-differentiated adenocarcinomas limited to the ampulla of Vater are associated with minimal lymph node metastasis. Histological subtype also plays a crucial role in treatment decisions.[2-5] Intestinal-type adenocarcinomas are reported to have lower rates of local infiltration and better prognoses than those of pancreatobiliary-type adenocarcinomas.[7,25,26]

Therefore, additional surgical resection is suitable for cases of papillary carcinoma diagnosed as a lesion invaded into the sphincter of Oddi or positive for lymphovascular invasion. In other cases, management should be carefully determined based on individual patient factors.

11. Follow-up

Postoperative follow-up requires endoscopic evaluation of the resection site through duodenoscopy. When remnant or recurrence is suspected, biopsy should be performed for histopathological confirmation. In practice, additional imaging assessments such as CT, US, or EUS is employed based on endoscopic piecemeal resection, pathological presence of carcinoma, and positive resection margin in the resected specimen. However, there is no established consensus on the optimal imaging approach. As for surveillance intervals, the ASGE guidelines recommend an initial evaluation between one and six months after EP, followed by surveillance every three to twelve months for at least two years.[27]

12. Adverse Events and Its Management

The incidence of early adverse events within one month following EP is reported to range from 6.1% to 58.3%. The major adverse events include acute pancreatitis (0–23.1%), bleeding (0–21.6%), perforation (0–8.3%), and cholangitis (0–7.3%).1) Late adverse events occurring more than one month after EP other than recurrence have been reported in 2% to 17% of cases. These events include papillary stenosis and bile duct stones.[1]

(1) Hemorrhage

Post-EP bleeding may occur intraoperatively or as delayed bleeding a few days after the procedure. Intraoperative bleeding typically results from mucosal tears due to excessive insufflation or manipulation at the bile and pancreatic duct orifices. It is generally managed with epinephrine solution or hemostatic agents, local application of absorbable hemostatic materials, or clip closure. Delayed bleeding is more commonly associated with ulcer formation at the resection site due to electrocautery effects, which lead to bleeding from the exposed vessels. Identification of the hemorrhagic source through thorough irrigation with saline is essential before hemostatic intervention. When an exposed vessel is identified, hemostasis could be achieved using clips or argon plasma coagulation (APC). In cases of larger vessel bleeding or pulsatile hemorrhage, clip placement or APC alone is insufficient, and local injection of hypertonic saline epinephrine (HSE) should be added.

(2) Pancreatitis

Post-EP pancreatitis requires immediate assessment based on the severity criteria outlined in *the Guidelines for the Management of Acute Pancreatitis: JPN Guidelines 2021* for implementing appropriate treatment.[28] Post-EP pancreatitis is also likely to occur due to pancreatic duct stent occlusion caused by intraductal clot formation. When bleeding is suspected, endoscopic evaluation of the resection site should be considered.

(3) Perforation

Perforation is diagnosed intraoperatively by direct endoscopic visualization or fluoroscopic findings such as contrast leakage or abnormal free air around the liver and kidneys. When perforation is identified during the procedure, clip closure of the perforation site is performed. Placement of nasobiliary and nasopancreatic drainage tubes is helpful for preventing exposure of bile and pancreatic juice to the peritoneal cavity.

(4) Cholangitis

Cholangitis should be managed according to the *Clinical Guidelines for Acute Cholangitis and Cholecystitis*,[29] with endoscopic transpapillary biliary drainage as the first-line approach.

(5) Papillary stenosis

Papillary stenosis is often managed with endoscopic interventions such as EST/EPST, stent placement, balloon dilation, and a combination of these procedures.

13. Postoperative Patient Management

There is no clear consensus on the role of second-look endoscopy following EP. After EP, not only clinical monitoring is necessary for changes in vital signs such as decreased blood pressure and

tachycardia, but also attention is paid to signs of bleeding such as hematemesis and progression of anemia. When bleeding is suspected, an emergency endoscopy should be performed.

The optimal timing for stent removal and initiation of oral intake after EP remains undefined. Since EP is performed in patients with normal pancreatic anatomy, prolonged stent placement in a non-dilated pancreatic duct may increase the risk of pancreatic duct stenosis. Early removal is generally preferred, typically within a few days to four weeks. Early initiation of oral intake is also important to promote ulcer healing. Once major adverse events such as bleeding, pancreatitis, and perforation have been ruled out, oral intake should resume as soon as possible.

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Kenjirou Yamamoto and Hiroki Kawashima

Handling and Curability Assessment of Endoscopically Resected Specimens

I Pharyngeal and Esophageal Cancer

1. Handling of Endoscopically Resected Specimens

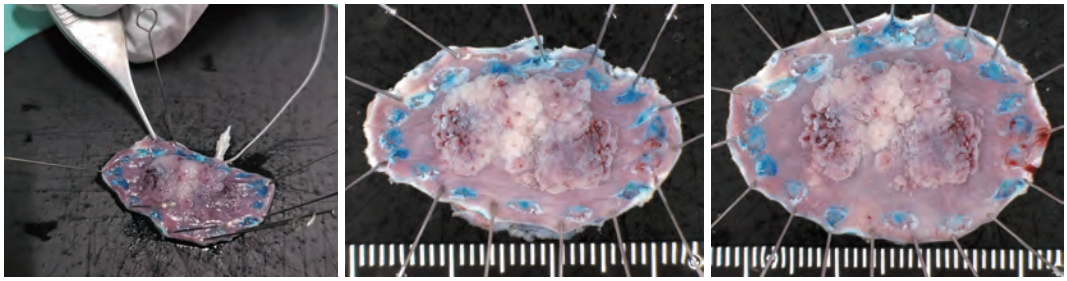
Endoscopic mucosal resection (EMR) has been used since approximately 1990 and has become a standard treatment for esophageal cancer. With the development of advanced techniques for the en bloc resection of larger lesions, such as endoscopic submucosal dissection (ESD) and endoscopic laryngopharyngeal surgery (ELPS) for pharyngeal lesions, superficial cancer is now often treated endoscopically. In either method, careful specimen handling, record-keeping, and specimen cutting are required for precise curability assessment. Except for some institutions where pathologists process unfixed specimens, clinicians are often responsible for specimen processing and, in some situations, sectioning. Therefore, clinicians need to fully understand how to handle specimens.

(1) Immediately after resection: pinning, photographing, and fixing the specimen

The specimen is pinned onto a rubber or cork sheet immediately after resection. It is spread flat so that no creases remain, and the surrounding mucosa, including the muscularis mucosae, does not fold underneath (**Figure 1**). Thin pins are used to minimize artifacts in the specimen. When the specimen is obtained by piecemeal resection, the pieces are arranged and pinned in a way that restores their original spatial relationships. The orientation of the specimen, such as the oral side, is marked. Before being photographed, the pinned specimen is placed in formalin solution (10% neutral buffered formalin solution is recommended[1]) for 1 to 2 minutes to achieve fixation. Images captured with an endoscope are not ideal because of "fisheye lens effects" (**Figure 2**).[2] A platform for specimen photography or a stereoscopic microscope is preferable when images are taken. Pharyngeal or esophageal specimens are photographed both before and after iodine staining, allowing the shape and size of iodine-unstained areas to guide the placement of incision lines and to enable comparison with pre-resection endoscopic findings. Following photography, the specimen is placed in formalin solution[1] for at least 12 hours but no longer than one to two days, in order to prevent over-fixation.

(2) After formalin fixation: photographing, macroscopic observation, and cutting of the specimen

After sufficient formalin fixation, the specimen will be photographed, macroscopically observed, and cut. The specimen is first removed from the formalin solution, and the pins are carefully taken out without tearing the mucosa or causing the tissue to crumble. One hand holds the specimen gently while



a | b | c

Figure 1 **Flattening and pinning out resected specimens.**

The specimen was flattened so that the surrounding mucosa, including the muscularis mucosa, does not go underneath (a). A specimen with inadequate vertical flattening, resulting in creases on the mucosa (b). A specimen with adequate flattening (c). The mucosa, flattened evenly, looks smooth without creasing.

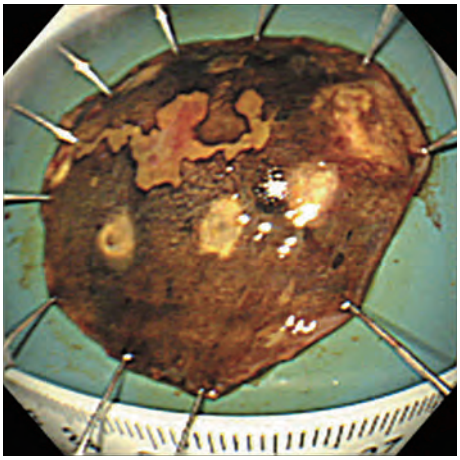


Figure 2 **A resected specimen stained with iodine immediately after resection and captured with an endoscope.**

The specimen is well-stained with iodine. Endoscopic images, when not obtained from directly above, may look different from the original specimen due to the "fisheye lens effects."

the other removes the pins. The specimen is then rinsed thoroughly under running water. For optimal iodine staining, rinsing is carried out for at least 30 minutes and extended to one hour or more when possible. [1] The specimen is photographed both before and after iodine staining (**Figure 3**), begining with the unstained state. Close-up images are taken so that the specimen fills the frame, and a ruler is included for scale.

The specimen is then stained with iodine. A diluted iodine solution, at a concentration of approximately 0.1 to 0.5%, is applied, and sufficient time is allowed for staining. This produces a high-contrast image that clearly distinguishes cancerous from non-cancerous areas (**Figures 3b & d**). A high concentration of iodine solution results in a low-contrast image, with unintentional staining of areas that should be unstained or weakly stained (**Figure 4**).[2] Fixed specimens react more slowly with iodine solution than fresh, unfixed specimens, necessitating longer immersion to achieve adequate staining during observation. To prevent halation in photographs (**Figure 5**),[2] excess water is wiped from the surface of

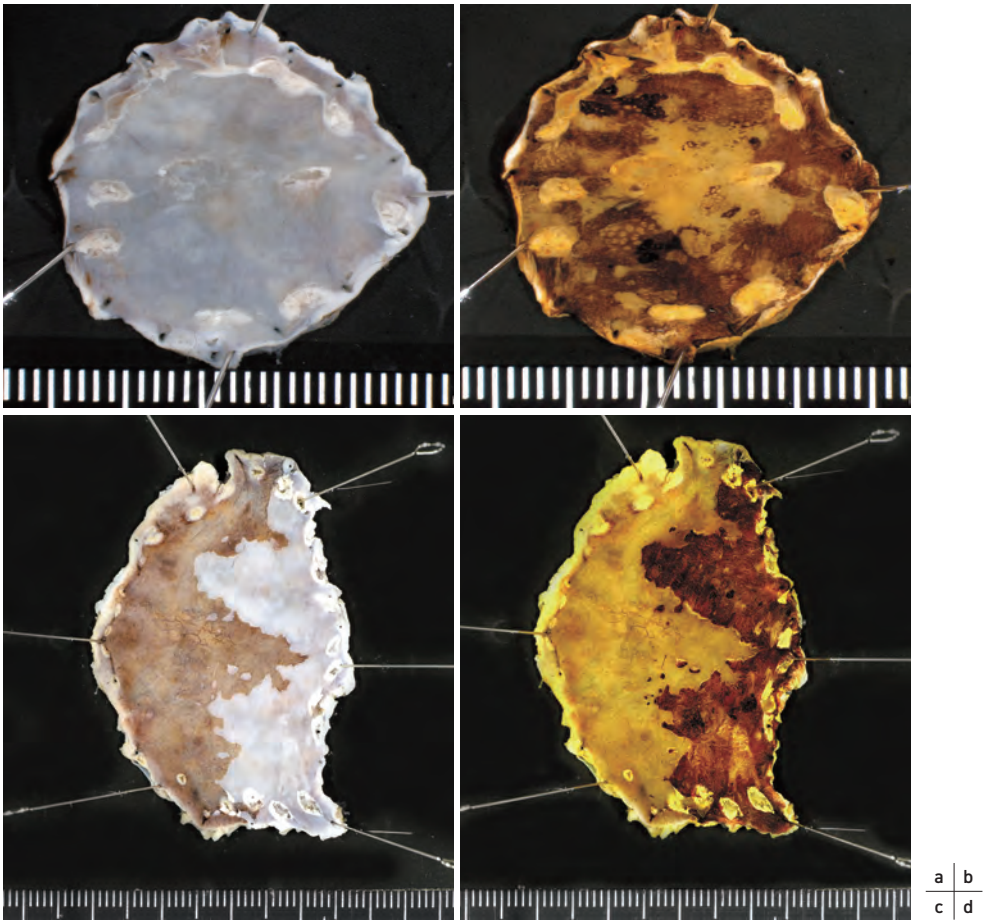


Figure 3 **Macroscopic images of esophageal ESD specimens (before and after iodine staining).**

ESD specimens of esophageal squamous cell carcinoma (a, b) and Barrett's esophageal adenocarcinoma (c, d). Images before iodine staining (a, c) and those after thorough rinsing under running water and full immersion in an optimal concentration of iodine solution (b, d). Esophageal squamous cell carcinoma lesions are recognized as demarcated, iodine-unstained areas (b). Iodine staining identifies the squamocolumnar junction and squamous islands in Barrett's esophagus (d). To avoid halation, all images were obtained while the specimens were soaked in water.
ESD: endoscopic submucosal dissection.

the specimen, or the specimen is photographed while immersed in water (**Figure 3**), with the latter method generally preferred. The specimen is photographed in a way that later allows the iodine-unstained areas to be compared directly with images obtained by endoscopy (**Figure 6**). Iodine staining is also valuable in Barrett's esophageal adenocarcinoma and esophagogastric junction carcinoma, as it enables macroscopic visualization of the squamocolumnar junction (**Figures 3c & d**)[2] The specimen is positioned appropriately and photographed while macroscopic features are assessed, including tumor diameter, macroscopic tumor type, depth of invasion, and the distance between the lesion and the resection margin.

After photography and macroscopic observation, the specimen proceeds to the cutting process. The first step involves slicing the entire specimen into strips that include the lesion. In the case of squamous cell carcinoma, incision lines are positioned to obtain a slice in which the distance between the iodine-

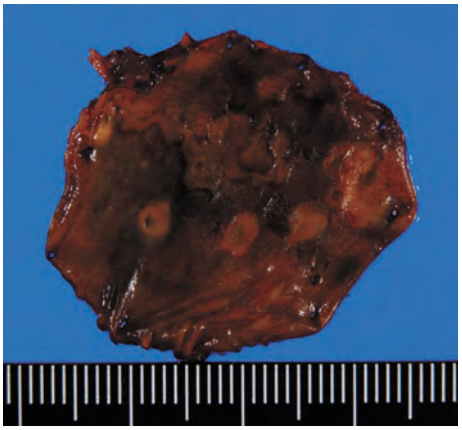


Figure 4 **Macroscopic image of a resected specimen stained with a high concentration of iodine solution.**

A high concentration of iodine solution results in a low-contrast image, with unintentional staining of areas that should be unstained or weakly stained.

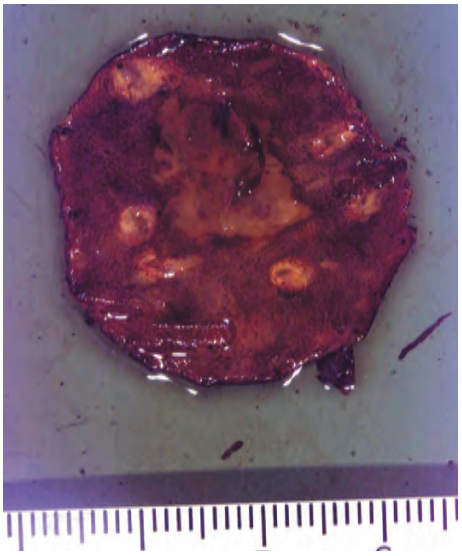


Figure 5 **Macroscopic image of a resected specimen with excessive remaining water.**

Excessive remaining water on the resected specimen results in an unclear image with halation.

unstained area and the resection margin is shortest (**Figure 7a**). For esophagogastric junction carcinoma or Barrett's esophageal adenocarcinoma, incision lines are generally placed along the longitudinal axis of the digestive tract, enabling demonstration of the squamocolumnar junction in tissue sections. This approach supports histological assessment of the esophagogastric junction (**Figure 7b**). The specimen, with incision lines visible, is photographed by assembling the completely or partially cut pieces. This method later allows side-by-side comparison between endoscopic and histological findings (**Figures 6 & 8**). Incision lines drawn on a photo or a diagram of the intact specimen may not accurately represent the actual incision lines. The recommended thickness of each slice is approximately 2 to 3 mm.[1)] The thicker the slices are, the lower the accuracy of pathological diagnosis due to a higher likelihood of overlooking details. In pathological diagnosis, to assess the curability and the necessity of additional treatment, it is necessary to cut the specimen into thin enough slices to ensure diagnostic accuracy. When an area of interest, such as one suspected of deeper tumor invasion, has already been identified in the specimen, an incision line is positioned approximately 0.5 mm from that area. This ensures that the intended cut surface appears in the tissue sections while accounting for tissue loss during trimming. In specimens obtained by piecemeal resection, incision lines are applied to each fragment so that the true resection margin is represented in the tissue sections (**Figure 9**).[2)]

(3) Selection of staining methods

Hematoxylin and eosin (H&E) staining is the primary method for pathological diagnosis, often used along with other supplemental staining methods. Periodic acid-Schiff (PAS) stains cells containing glycogen granules. In esophageal squamous cell carcinoma, macroscopic iodine-unstained areas typically correspond to areas that are PAS-negative in tissue sections. Therefore, PAS staining provides

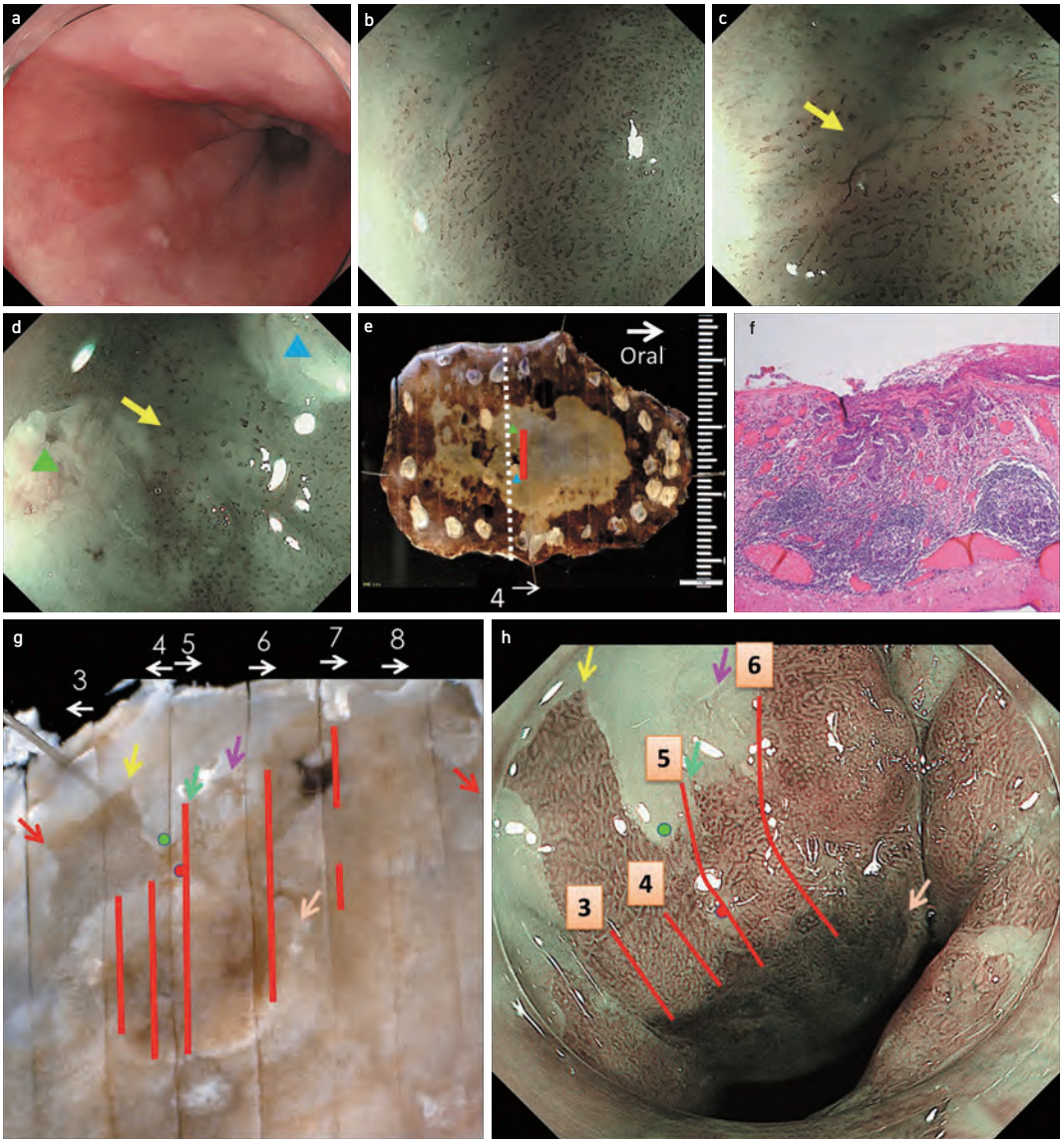


Figure 6 **Comparison of endoscopic, macroscopic, and histological findings.**

A case of esophageal squamous cell carcinoma (a-f). A flat red area in the left wall of the middle thoracic esophagus (a). ME-NBI identifies B1 vessels (b). There is an area containing non-loop, B2 vessels (c, arrow), next to which two markers are placed (d, blue and green arrow heads). A photo of a fixed and iodine-stained specimen (e), with an incision line next to a line connecting the two markers. Histopathological assessment of a lesion between the two markers reveals squamous cell carcinoma invading the lamina propria mucosae (f). Appropriate incision lines enable the histological assessment of an area identified by an endoscope.
A case of Barrett's esophageal adenocarcinoma (g, h). Red lines on a resected specimen represent the area of the lesion identified by histological assessment (g). Red lines copied on an endoscopic image, along with landmarks (arrows and dots), represent the area of the lesion identified by histological assessment (h).
ME-NBI: magnifying endoscopy with narrow band imaging.

valuable histological information that can supplement iodine staining (**Figure 10**).[2] However, it is well recognized that iodine-unstained areas may sometimes lack neoplastic epithelial cells, and weakly stained areas can occasionally harbor them. PAS staining is also useful in assessing pharyngeal lesions, but the staining of normal epithelial cells is weaker than that in esophagus. Elastic fiber staining, such as elastica van Gieson (EVG) staining and Victoria blue (VB) staining, should be used for assessing

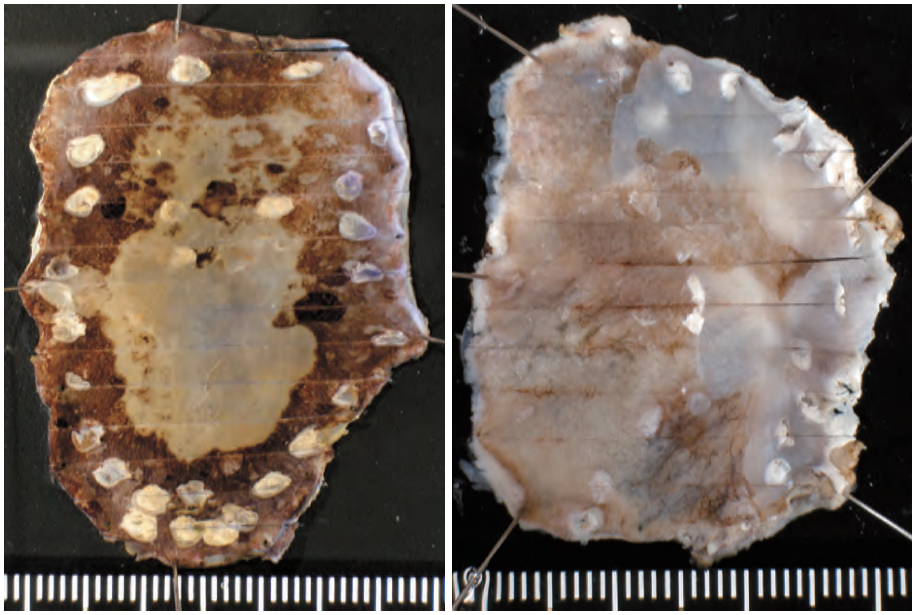


Figure 7 **Macroscopic images of a resected specimen with incision lines.**

Images of a specimen with incision lines offer accurate positional information for preparing tissue sections. ESD specimens of esophageal squamous cell carcinoma (a) and Barrett's esophageal adenocarcinoma (b).
ESD: endoscopic submucosal dissection.

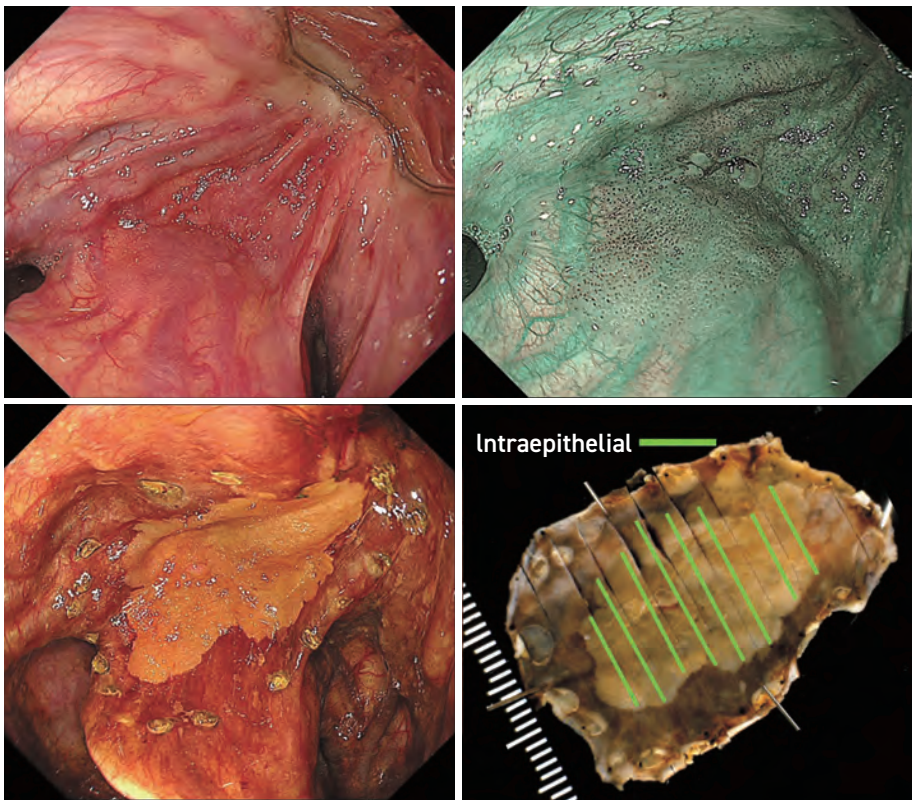


Figure 8 **Superficial pharyngeal carcinoma resected by ESD.**

WLI identifies a flat, pale red area with an obscure vascular pattern on the lingual surface of the epiglottis (a). NBI identifies a pale brownish area with B1 vessels (b). Iodine staining identifies an irregular unstained area (c). A photo of a fixed resected specimen with incision lines (d). Green lines indicate the location of carcinoma *in situ*/high-grade dysplasia. The shape of the iodine-unstained area is useful to compare the specimen with endoscopic images.
NBI, narrow band imaging; WLI, white light imaging.

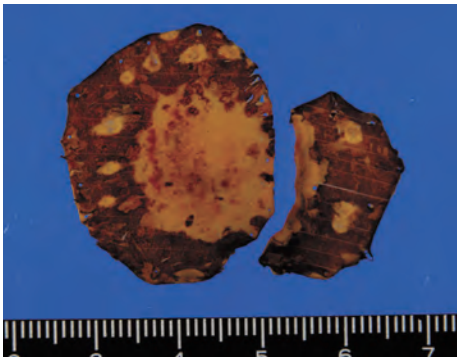


Figure 9 **Macroscopic image of a specimen resected into two pieces.**

Incision lines should be placed considering the location of the true resection margin.

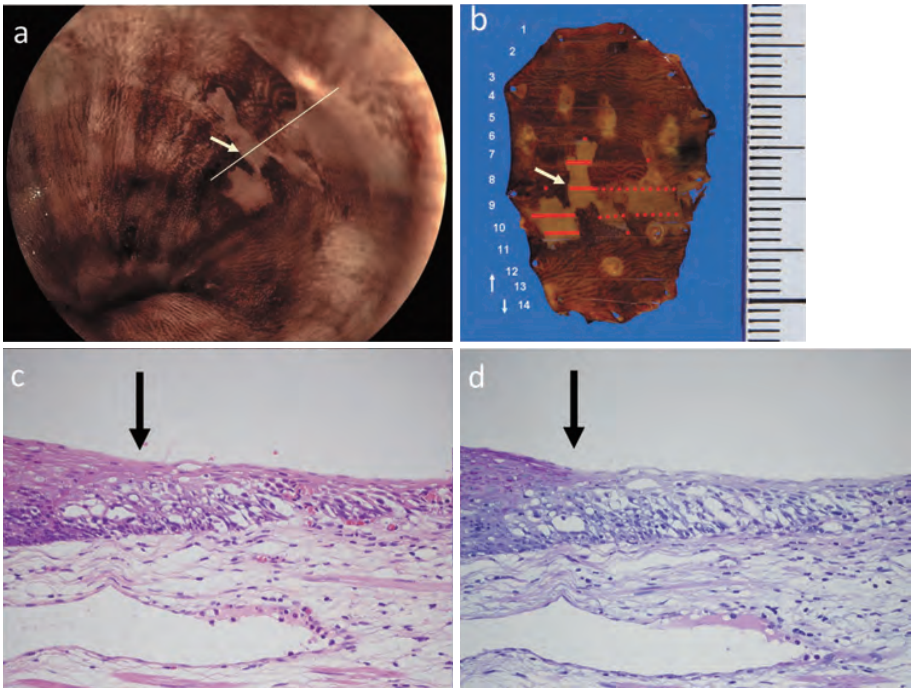
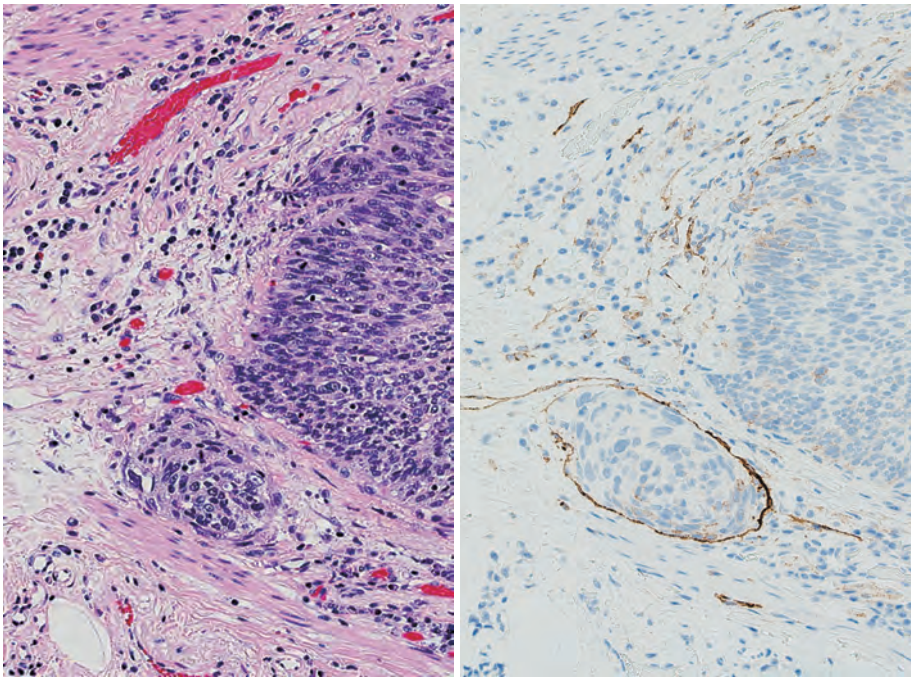


Figure 10 **Usefulness of PAS staining.**

An endoscopic image of a lesion (a). A fixed, iodine-stained specimen with incision lines and markers (b). The point indicated by a white arrow (a, b) represents the tumor border indicated by a black arrow in tissue sections (c, d). The tumor border is more clearly demonstrated with a poorly stained lesion in a PAS-stained section (d) than in an HE-stained section (c).
HE, hematoxylin and eosin; PAS, periodic acid-Schiff.

venous invasion, and immunohistochemistry (IHC) for lymphatic endothelial cells, such as D2-40, should be used for assessing lymphatic invasion (**Figure 11**).[2)]



a | b

Figure 11 Lymphatic invasion.

In cases where hematoxylin–eosin staining (a) does not allow reliable identification, lymphatic invasion can be demonstrated by immunohistochemical staining (b, D2-40).

2. Pathological Diagnosis of Endoscopically Resected Specimens and Its Clinical Utility

Pathological assessment of endoscopically resected specimens determines follow-up policies and the necessity of additional treatment. Pathological assessment consists of the evaluation of (1) resection margin and (2) risk factors for lymph node metastasis. Specimens need to provide sufficient information for such an evaluation.

(1) Pathological assessment of resection margin and its clinical utility

a. Horizontal margin

The specimen is considered to have a positive horizontal margin when tumor (e.g., carcinoma *in situ*/high-grade dysplasia or intramucosal carcinoma) invades the lateral mucosal edge. Additional resection or local treatment, such as argon plasma coagulation, will be considered for the residual tumor (most commonly carcinoma *in situ*/high-grade dysplasia or intramucosal carcinoma). When the residual tumor is not visible on endoscopy, it can be observed without additional treatment.

b. Vertical margin

The specimen is considered to have a positive vertical margin when cancer invades its bottom edge. A positive vertical margin is caused by either invasive tumor (specifically tumor invading below the submucosa) or ductal spread of non-invasive tumor. For ESD resected specimens, a positive vertical margin can also be caused by a shallow-angled cut when peeling off the specimen, which results in

revealing a tumor in the superficial mucosa on the bottom surface of the specimen. Even in cases with a positive vertical margin, the tumor might have been resected just at the margin, leaving no residual tumor. However, if the tumor resides in the deep submucosa or below, the risk of lymph node metastasis is high, and additional surgery or chemoradiotherapy should be considered. Local recurrence may occur if surgery is not performed.

(2) Pathological assessment of risk factors for lymph node metastasis and its clinical utility

known risk factors for lymph node metastasis include histological type and differentiation grade, depth of tumor invasion, lymphovascular invasion, and infiltrative growth pattern.

a. Histological type and differentiation grade

In Japan, squamous cell carcinoma is the most common histological type of esophageal cancer. This carcinoma is categorized into three grades of differentiation according to the extent of keratinization and stratification: well-differentiated, showing prominent keratinization and stratification; moderately-differentiated, showing moderate levels; and poorly-differentiated, showing little or no keratinization and stratification. Other rare "special" histological types of esophageal cancer include basaloid squamous cell carcinoma, neuroendocrine carcinoma, carcinosarcoma (sarcomatoid squamous cell carcinoma), and melanoma. Accurate pathological diagnosis is crucial for neuroendocrine carcinoma and melanoma, as both have poor prognoses and need specific treatment. Pathological diagnosis is made based on characteristic histological findings in combination with useful IHC methods. The most common histological type of cancer that develops from Barrett's esophagus is adenocarcinoma. This carcinoma is classified into three grades of differentiation according to the extent of gland formation: well-differentiated, showing prominent gland formation; moderately-differentiated, showing a moderate degree of gland formation; and poorly-differentiated, showing little or no gland formation.

b. Depth of tumor invasion

In esophageal cancer, a tumor remaining in the mucosa is classified as pTis (carcinoma *in situ*/high-grade dysplasia, pT1a-EP), a tumor reaching the lamina propria mucosae as pT1a-LPM, a tumor reaching or invading the muscularis mucosae as pT1a-MM, and a tumor reaching the submucosa as pT1b-SM. For endoscopically resected specimens, squamous cell carcinoma of pT1b-SM is further classified into two types based on the depth of tumor invasion: pT1b-SM1 (≤ 200 μm from the muscularis mucosae) and pT1b-SM2 (> 200 μm from the muscularis mucosae). It should be noted that the classification of endoscopically resected specimens differs from that of surgically resected specimens. In surgically resected specimens, pT1b-SM is subdivided into three types according to the depth of tumor invasion: pT1b-SM1, involving the upper third of the submucosa; pT1b-SM2, involving the middle third; and pT1b-SM3, involving the lower third. In Barrett's esophageal adenocarcinoma confined to the mucosa, the presence of a newly developed muscularis mucosae above the original layer provides additional subclassification. Tumor invasion reaching this superficial muscularis mucosae is designated pT1a-SMM, invasion reaching the original deep muscularis mucosae is designated pT1a-DMM, and invasion into the stroma between the two muscularis mucosae is designated pT1a-LPM.[1] For Barrett's esophageal adenocarcinoma and esophagogastric junction carcinoma, the cutoff point distinguishing pT1b-SM1 from pT1b-SM2 is set at 500 μm, in contrast to the 200 μm threshold used for squamous cell carcinoma.[1)]

Because the pharynx lacks muscularis mucosae, the classification of tumor invasion depth in pharyngeal cancer differs from that in esophageal cancer. A specific system has been established for evaluating invasion depth and the associated risk of lymph node metastasis. The current recommendation is to measure tumor thickness—the distance from the tumor surface to the point of deepest invasion—and to use this value as an index of invasion depth.[3,4] When the histological diagnosis is carcinoma *in situ*/high-grade dysplasia, it is categorized as pTis, and measurement of tumor thickness is not required. For tumors with subepithelial invasion, the diagnosis is described as carcinoma invading the subepithelial layer, with the measured tumor thickness. In the present UICC TNM classification system for head and neck cancer, where the T factor is determined by tumor diameter, carcinoma *in situ*/high-grade dysplasia or carcinoma limited to the superficial subepithelial layer can be classified as T2 if the tumor diameter exceeds 2 cm.[5] This limitation should be considered when applying the current UICC TNM classification system.

c. Lymphovascular invasion

Lymphovascular invasion consists of lymphatic invasion (Ly) and venous invasion (V), which should be assessed separately. For EMR/ESD resected specimens, a positive-negative dichotomy is used for the pathological diagnosis of lymphovascular invasion: Ly0/Ly1 (negative versus positive lymphatic invasion) and V0/V1 (negative versus positive venous invasion). Ly/V (+) should be used when lymphovascular invasion cannot be clearly classified as venous or lymphatic.[1]

Some cases of lymphovascular invasion are evident on H&E-stained sections, but other cases require elastic fiber staining (e.g., EVG or VB staining) and IHC using D2-40, CD31, and CD34 for their diagnosis (**Figure 11**).[2]

d. Infiltrative growth pattern

According to the *Japanese Classification of Esophageal Cancer*, the infiltrative growth pattern of tumors (INF) is categorized into three types: INFa, the expansive type, characterized by a solid growth pattern with a well-defined border from the surrounding normal tissue; INFb, the intermediate type, showing an infiltrative pattern that falls between INFa and INFc; and INFc, the infiltrative type, defined by growth as small nests or single cells with an ill-defined border from the normal tissue.[1] In addition to the INF classification, descriptive terms such as "droplet infiltration[6]" and "tumor budding[7]" are also used to characterize patterns of tumor infiltration.

3. Curability Assessment and Treatment Strategy Based on Pathological Diagnosis

Table 1 presents the probability of lymph node metastasis in superficial esophageal squamous cell carcinoma, stratified by the depth of tumor invasion.[8] Esophageal cancer of pTis or pT1-LPM is unlikely to have lymph node metastasis; therefore, endoscopic treatment is indicated for non-circumferential tumors or whole-circumferential tumors ≤ 5 cm in length.[9] On the other hand, approximately 10% of cases classified as pT1a-MM are associated with lymph node metastasis. When resected specimens are positive for lymphovascular invasion, additional treatment with surgery or chemoradiotherapy is generally recommended. In such cases, pathological evaluation of endoscopically resected specimens provides important information for assessing the risk of lymph node metastasis. Endoscopic treatment is not indicated for esophageal cancer classified as pT1b-SM.[9] The probability of lymph node metastasis in pT1b-SM1 is similar to that in pT1a-MM,[10] whereas the risk rises to 40% or

Table 1 Relationship between depth of invasion, vessel invasion and lymph node metastasis in superficial carcinoma (surgically resrcted cases).

Depth	No. of cases	Vessel invasion (%)	Lymph node metastasis (%)
pT1a-EP (pTis)	54	0 (-)	0 (-)
pT1a-LPM	42	2 (5)	0 (-)
pT1a-MM	37	13 (35)	3 (8)
pT1b-SM1	24	13 (54)	4 (17)
pT1b-SM2	58	42 (72)	16 (28)
pT1b-SM3	75	68 (91)	37 (49)

(Modified from Literature 8)

higher in pT1b-SM2 and more deeply invasive tumors.[11] Beyond the depth of invasion, additional factors such as poor differentiation, positive lymphovascular invasion, and infiltrative growth patterns are also regarded as risk factors for lymph node metastasis, and the likelihood increases when multiple risk factors are present.[10)] In pharyngeal cancer, tumor thickness—used as an index of invasion depth—is another important predictor, with a measurement of 1,000 μm or greater representing a significant risk for lymph node metastasis.[4)]

Additional treatment is generally recommended when endoscopically resected specimens demonstrate risk factors for lymph node metastasis. Treatment decisions consider the patient's overall background, with close collaboration among endoscopists, diagnostic pathologists, esophageal surgeons, otolaryngologists, and head and neck surgeons regarded as essential.

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Esophageal cancer

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II Gastric and Duodenal Cancer

1. Handling of Endoscopically Resected Specimens

With the development of novel endoscopy devices, the techniques for endoscopic treatment have advanced considerably. Among them, endoscopic mucosal resection (EMR) offers the benefit of obtaining histological findings without the need for surgical resection and achieving curability comparable to that of surgical resection. At the same time, recurrence of residual disease may occur in some EMR cases. Cases of piecemeal resection are prone to insufficient pathological assessment and require careful follow-up. The development of endoscopic submucosal dissection (ESD) has enabled the en bloc resection of larger lesions with the surrounding normal tissue. With the emergence of a discussion on the expansion of endoscopic treatment indications,[1)] careful handling of endoscopically resected specimens and accurate pathological diagnosis have become more important than ever.
The following text outlines the process for resected specimens, including how they should be pinned out, fixed with formalin, observed under a stereoscopic microscope, and pathologically diagnosed.

(1) Immediately after resection: pinning, photographing, and fixing the specimen

After resection, the fresh specimen is rinsed to remove blood and mucus from the mucosal surface. The specimen is then pinned onto a cork or rubber sheet with sufficient pins, with only minimal extension, so that the tumor diameter remains close to the size observed endoscopically. Once the oral and anal sides of the lesion are marked, the specimen is fixed in formalin solution—commonly 10% neutral buffered formalin—for approximately 6 to 72 hours, as is standard practice for gastric specimens.

(2) After formalin fixation: photographing, macroscopic observation, and cutting of the specimen

Before the cutting process, the fixed specimen can be examined under a stereoscopic microscope when available. For visualizing both normal and tumor vessels, fresh specimens often provide clearer images than fixed specimens. Observation at different magnifications allows three-dimensional assessment of the specimen.
When mucus is firmly adherent to the mucosal surface, a mucolytic solution is applied to remove it. One example is thorough washing with a mixture of 1 g of sodium bicarbonate, one packet of a mucolytic agent (GASZYME®), and 200 mL of tap water. Formalin-fixed specimens are rinsed thoroughly with water prior to observation.
Resected specimens may be stained with dyes such as 3% cresyl violet, crystal violet (pyoktanin blue), or Carrazzi's hematoxylin. The staining time varies depending on the specimen, with reaction periods ranging from several tens of seconds to a few minutes, until optimal staining is achieved.
Clear photographs can be obtained by soaking the specimen in water to reduce light reflection or by adjusting the illumination from different angles to highlight the uneven surface structure of the lesion. Figure 1 shows the stereoscopic microscope images of a type 0-IIc tumor in the lesser curvature of the gastric antrum resected by ESD, illuminated from various angles. When illuminated from one side, the uneven surface structure is clearly demonstrated in specimens not soaked in water (**Figures 1 c - e**), but not so much in specimens soaked in water (**Figures 1 f - h**).

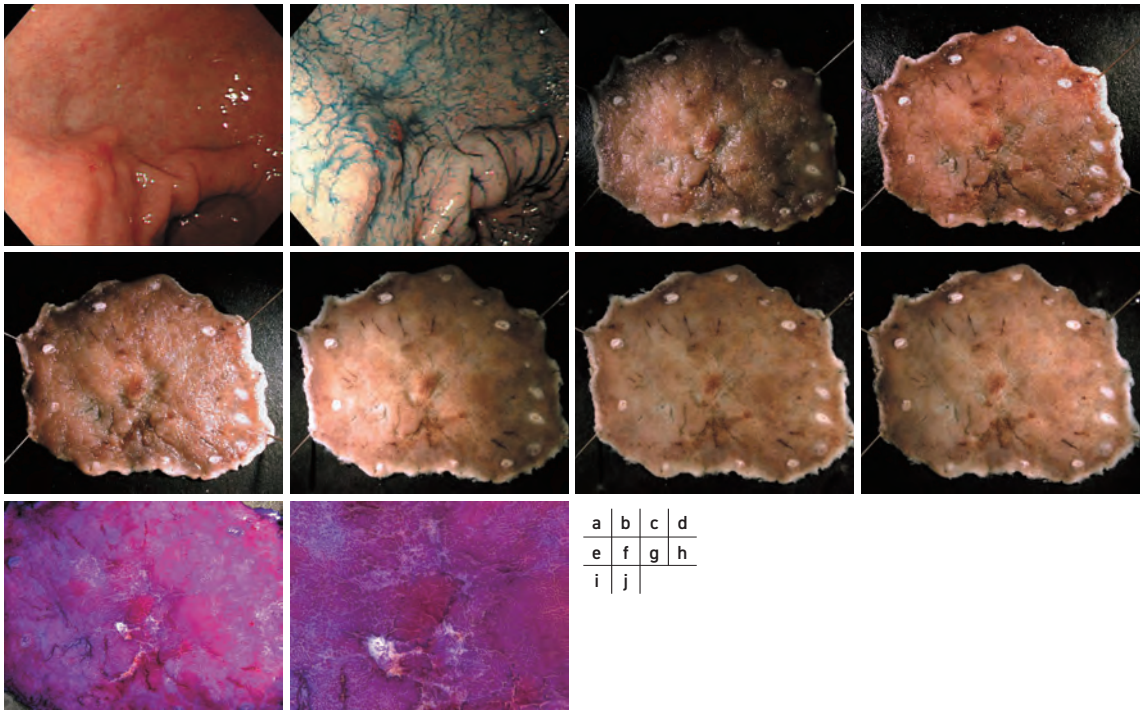


Figure 1 **Stereoscopic microscope images.**

A type 0-IIc tumor in the lesser curvature of the gastric antrum (a, WLI; b, chromoendoscopy). Stereoscopic microscope images of a specimen (c, illuminated from the left; d, illuminated from above; e, illuminated from the right). Stereoscopic microscope images of a specimen soaked in water (e, illuminated from the left; f, illuminated from above; g, illuminated from the right). Highly magnified stereoscopic microscope images of specimens stained with cresyl violet and soaked in water (i, j).
WLI, white light imaging.

A detailed mucosal pattern is demonstrated in highly magnified images of specimens stained with cresyl violet and soaked in water (**Figures 1 i, j**). A stereoscopic microscope can assess the horizontal margin of the specimen if the lesion demonstrates clear elevation and depression or has a different surface structure from the normal tissue.

When the specimen is cut, the tangent line at the tumor boundary nearest to the horizontal margin is taken as a reference. A shallow incision is made at a right angle to this tangent line, and the specimen is then sliced into sections 2 to 3 mm thick in parallel with the initial incision (**Figure 2**). Complete transection is avoided, as cutting through the entire specimen makes subsequent photography of the whole specimen difficult.

After the entire specimen has been photographed, each slice is separated and one of the cut surfaces is marked with black or red ink. The slice is then embedded in paraffin, and sectioning is initiated from the unmarked surface to prepare tissue sections.

When tissue sections from slice #1 reveal tumor lesions, additional sections are prepared. If these additional sections show no tumor involvement, the mucosal margin of the specimen is regarded as negative (**Figure 3**).

Record the following information on a cutting diagram.

- Size of resected specimen: $X \times Y$ mm

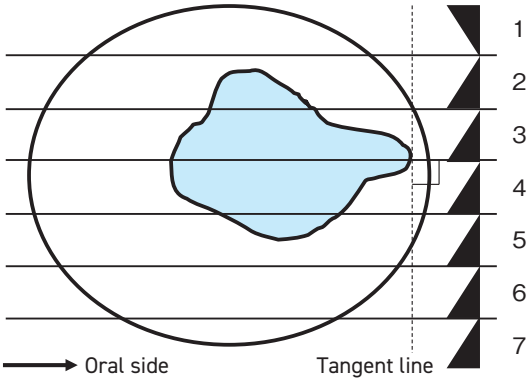


Figure 2 **Specimen cutting procedure.**

For each slice, ink is applied to one of the cut surfaces (indicated by the base of a triangle). Sectioning starts from the surface with no ink and tissue sections are prepared. The oral and anal sides of a specimen are specified in a cutting diagram.

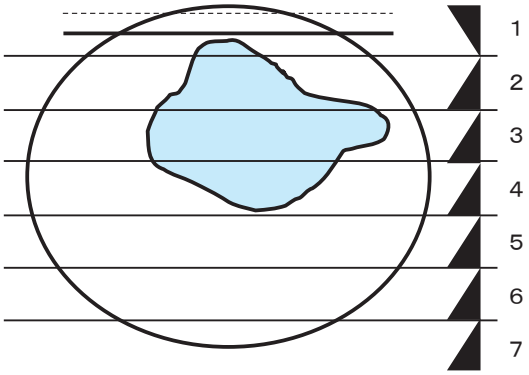


Figure 3 **Additional sectioning for the assessment of horizontal margin.**

If tissue sections from slice #1 contain tumor lesions, additional sectioning is performed. If the additional sections contain no lesion, the specimen is considered to have a negative mucosal margin (dotted line).

- Size of tumor lesion: $A \times B$ mm
- Macroscopic type
- Orientation of tumor lesion (oral and anal sides)
- Number of prepared tissue sections

(3) Examples of specimen cutting

Case 1

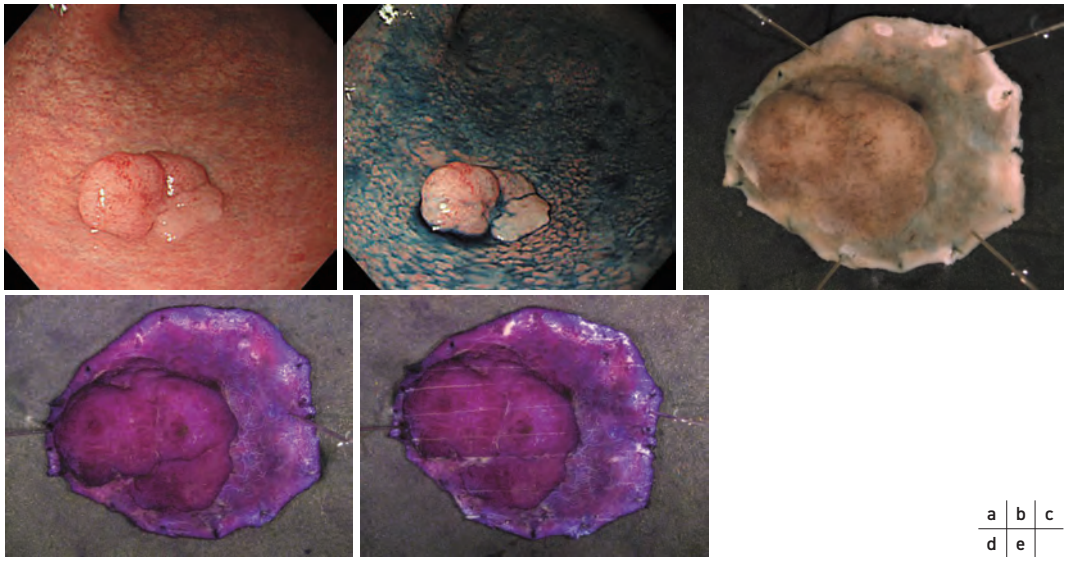
A type 0-IIa tumor was located in the greater curvature of the gastric antrum (**Figure 4**). A shallow incision was placed at right angles to the assumed tangent line at the tumor boundary located closest to the horizontal margin. The specimen was cut into 2 mm slices parallel to the first incision.

Case 2

A type 0-IIa + IIc tumor was located in the posterior wall of the gastric antrum (**Figure 5**). The entire specimen was first photographed, followed by closer observation of the tumor lesion at higher magnifications. The specimen was subsequently stained with cresyl violet, after which both whole-specimen and magnified images were taken. Finally, the entire specimen with partially cut incision lines was photographed.

(4) Endoscopic images of resected specimens

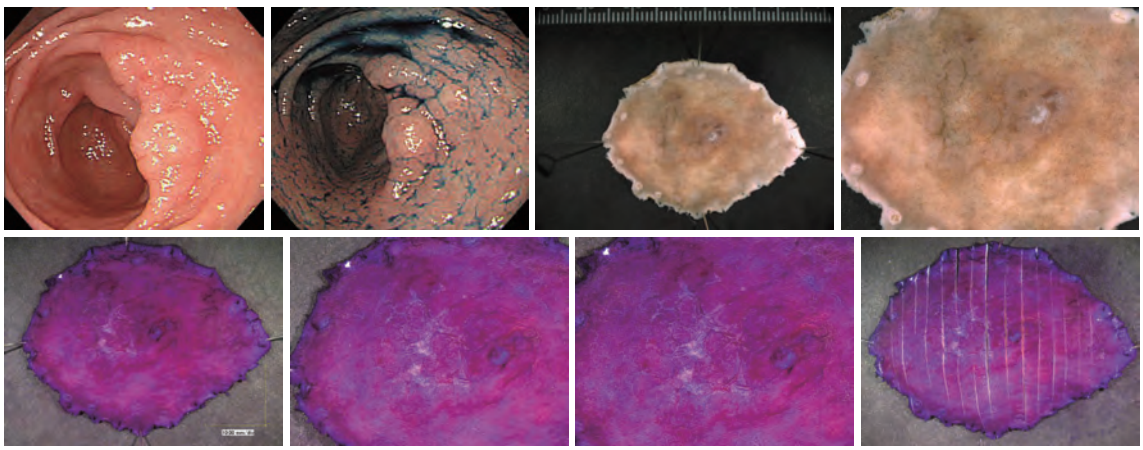
In daily practice, specimens are often pinned out in the endoscopy procedure room and photographed with an endoscope. Taking endoscopic images of the specimen have many advantages: (1) it allows side-by-side comparison with preoperative endoscopic images that are captured with the same endoscope, (2) in addition to white light imaging (WLI), imaging using special light, such as narrow band imaging (NBI), is available, (3) it can shorten the time from acquisition to fixation of the specimen, (4) it does not require special photography equipment or full-time pathologists within the facility. As shown in **Figure 6**, placing additional markers facilitates a side-by-side comparison of the



a	b	c
d	e	

Figure 4 Example of specimen cutting.

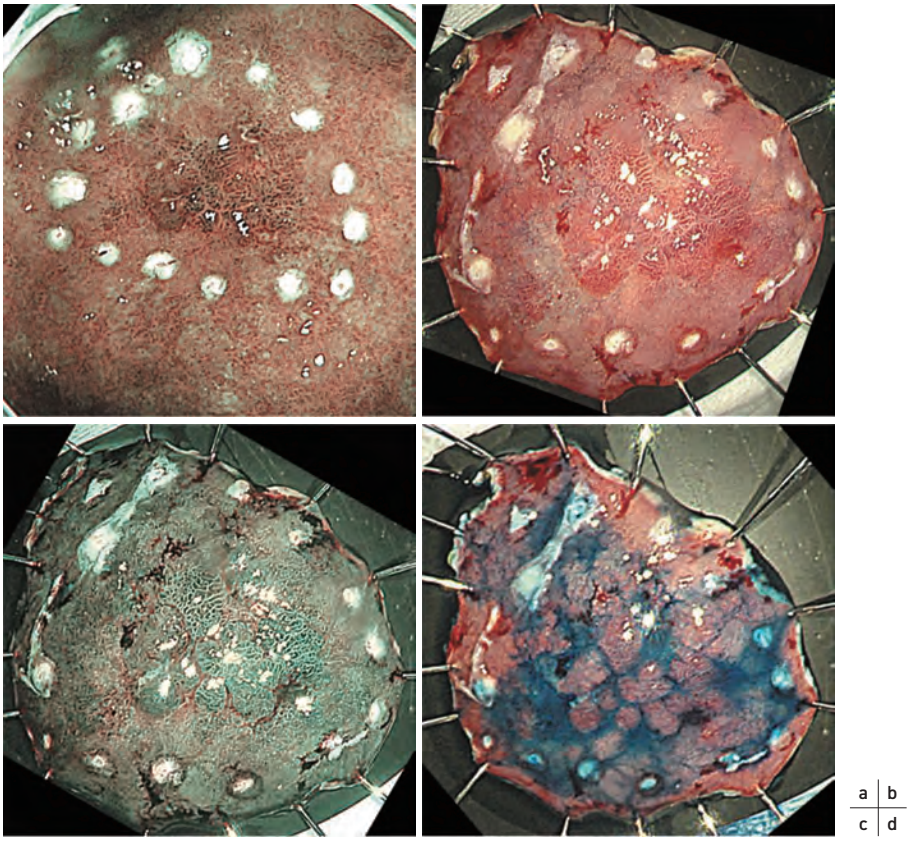
A type 0-IIa tumor in the greater curvature of the gastric antrum (a, WLI; b, chromoendoscopy). Stereoscopic microscope images (c, an entire specimen before staining; d, an entire specimen stained with cresyl violet before cutting; e, an entire specimen with incision lines).
WLI, white light imaging.



a	b	c	d
e	f	g	h

Figure 5 Example of specimen cutting.

A type 0-IIa + IIc tumor in the posterior wall of the gastric antrum (a, WLI; b, chromoendoscopy). Stereoscopic microscope images (c, an entire specimen before staining; d, magnified image of the lesion; e, an entire specimen stained with cresyl violet; f, g, a magnified image of a specimen stained with cresyl violet; h, an entire specimen with incision lines).
WLI, white light imaging.



a b
c d

Figure 6 **Resected gastric specimen captured with an endoscope.**

NBI of a type 0-IIa tumor in the lesser curvature of the lower part of the gastric corpus (a). Before ESD, markers were placed on the perimeter of the lesion, with additional markers on the oral side of the lesion. A resected specimen observed by WLI (b) and NBI (c), and with indigo carmine dye spray (d).
ESD, endoscopic submucosal dissection; NBI, narrow band imaging; WLI, white light imaging.

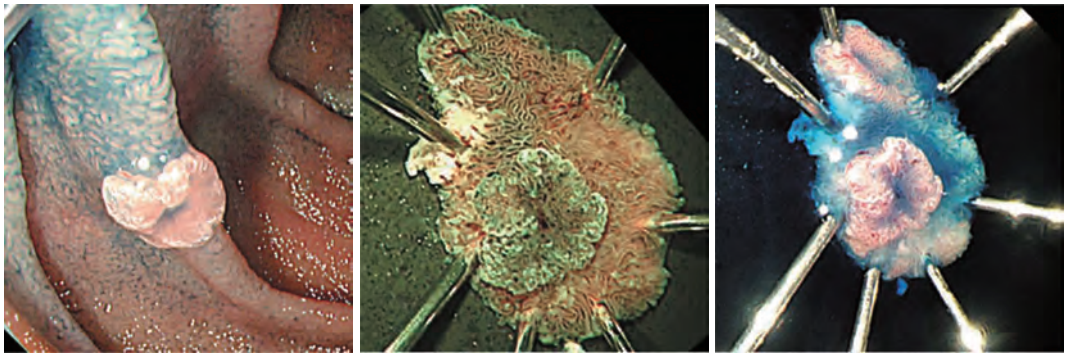
tumor orientation in preoperative endoscopic images and that of the resected specimen. Additional techniques, such as NBI and indigocarmine staining, provide macroscopic images of the resected specimen that are similar to preoperative endoscopic images.

Duodenal lesions are often resected by underwater EMR or cold snare polypectomy. The duodenal mucosa is thin, and suction retrieval can damage resected specimens, affecting pathological diagnosis. Instead, forceps or retrieval nets are used to gently collect the specimens. During photography, the specimen is soaked in water which reduces light reflection and allows the surface structure to be seen more clearly (**Figure 7**).

The goal of photographing the specimen is to obtain enough information for pathological diagnosis. It is essential to provide pathologists with a diagram that shows the tumor location, the horizontal margin located nearest to the tumor, and the depth of tumor invasion. To obtain an accurate pathological diagnosis, effective communication and discussion with pathologists are required.

2. Curability Assessment and Treatment Strategy Based on Pathological Diagnosis

According to the Japanese guidelines for endoscopic submucosal dissection and endoscopic mucosal



a | b | c

Figure 7 **Resected duodenal specimen captured with an endoscope.**

A type IIa tumor in the descending part of the duodenum (a). The specimen containing the lesion, resected en bloc by underwater EMR, was pinned out and observed by underwater NBI (b). WLI of the specimen sprayed with indigocarmine dye (c).
EMR, endoscopic mucosal resection; NBI, narrow band imaging; WLI, white light imaging.

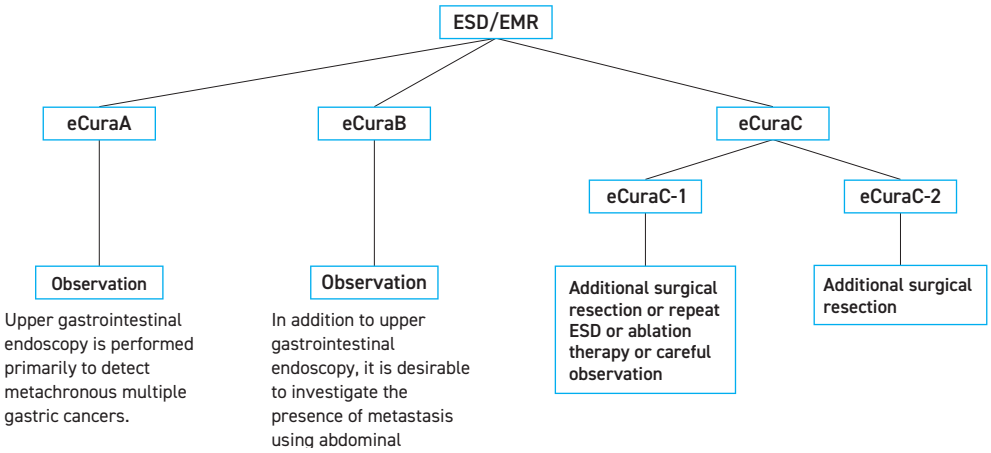


Figure 8 **Treatment flowchart after ESD or EMR.**

(Modified from Literature 2)

resection for early gastric cancer,[2] endoscopic curability, expressed as A, B, and C (C is further divided into C-1 and C-2), determines the necessity of additional treatment. Endoscopic curability A (eCuraA) means a curative resection by ESD/EMR, which consists of the following conditions: the lesion is resected en bloc and (1) any size, predominantly differentiated type, pT1a, UL0, Ly0, V0, pHM0, and pVM0; (2) a long diameter of ≤ 2 cm, predominantly undifferentiated type, pT1a, UL0, Ly0, V0, pHM0, and pVM0; or (3) a long diameter of ≤ 3 cm, predominantly differentiated type, pT1a, UL1, Ly0, V0, pHM0, and pVM0. If the long diameter of undifferentiated components exceeds 2 cm in (1), the lesion is classified as endoscopic curability C-2 (eCuraC-2).

Endoscopic curability B (eCuraB) means that the lesion is resected en bloc, with a long diameter of ≤ 3 cm, predominantly differentiated type, pT1b1 (SM1, < 500 μm from the muscularis mucosa), Ly0, V0, pHM0, and pVM0. If undifferentiated components exist in the submucosa, the lesion is classified as eCuraC-2.

Lesions neither classified as eCuraA nor eCuraB are classified as endoscopic curability C (eCuraC),

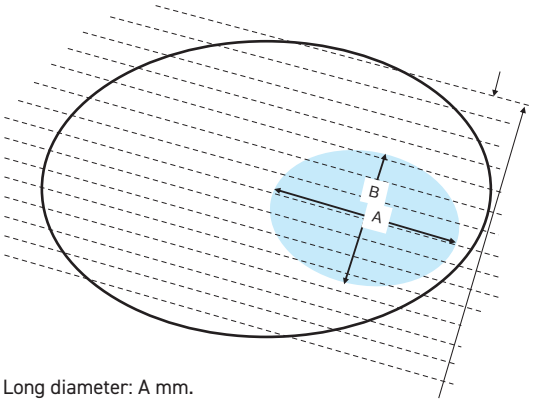


Figure 9 Measurement of tumor diameters in ESD/EMR specimens.

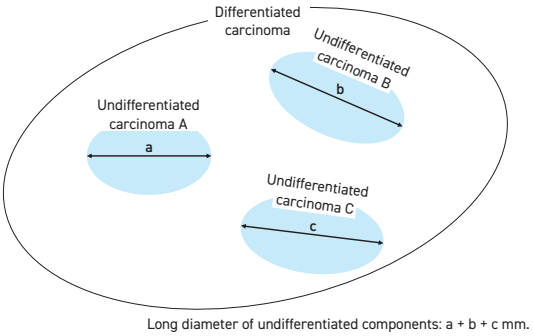


Figure 10 Measurement of the long diameter of undifferentiated components.

which is further divided into endoscopic curability C-1 (eCuraC-1) and eCuraC-2. An eCuraC-1 lesion consists of a differentiated type, but is either resected piecemeal or with a positive horizontal margin. All other eCuraC lesions are classified as eCuraC-2.

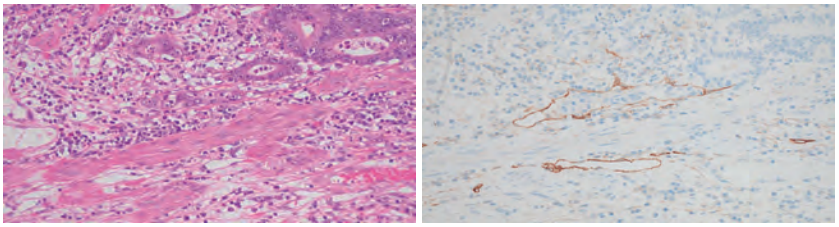
Figure 8 shows a flowchart outlining additional treatment strategy options based on the results of endoscopic curability assessment. Pathological findings necessary for endoscopic curability assessment comprise six items: tumor diameter, histological type, depth of tumor invasion, ulceration (or ulcer scar), lymphovascular invasion, and resection margins. These items are outlined in the following text.

(1) Tumor diameter

Specimens generally shrink after fixation in formalin. To minimize this effect, the fresh specimen is pinned onto a board before immersion in formalin solution. In cutting diagrams, the area of the lesion identified on H&E-stained sections is outlined, and both the long and short diameters are defined at right angles (**Figure 9**). For undifferentiated components, the long diameter is calculated as the sum of the long diameters of each component (**Figure 10**). When the total long diameter of undifferentiated components exceeds 2 cm, the lesion, even if otherwise fulfilling the eCuraA criteria, is classified as eCuraC-2. Lesions in which undifferentiated-type cancer is overlaid by differentiated-type cancer are regarded as undifferentiated components and are included in this measurement.

(2) Histological type

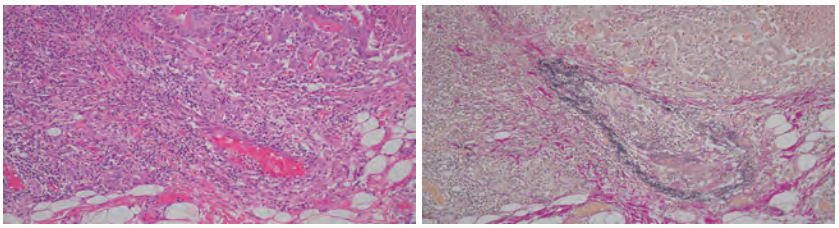
Papillary adenocarcinoma, well differentiated tubular adenocarcinoma, and moderately differentiated tubular adenocarcinoma are considered differentiated types, while poorly differentiated adenocarcinoma and signet-ring cell carcinoma are considered undifferentiated types. Even in predominantly differentiated type lesions, any undifferentiated components affect the results of endoscopic curability assessment. The presence of a special type of carcinoma, such as endocrine cell carcinoma or hepatoid adenocarcinoma, should be mentioned in a pathology report.



a | b

Figure 11 **Lymphatic invasion.**

HE staining (left) and IHC staining using anti-podoplanin antibody (right).
HE, hematoxylin and eosin; IHC, immunohistochemistry.



a | b

Figure 12 **Venous invasion.**

HE staining (left) and EVG staining (right).
EVG, elastica van Gieson; HE, hematoxylin and eosin.

(3) Depth of tumor invasion

The depth of tumor invasion is measured at the point of deepest invasion. When lymphovascular invasion is present below the point of deepest invasion, the point of lymphovascular invasion is considered the depth of tumor invasion. For tumors invading the submucosa, the depth of tumor invasion is classified as pT1b1 (SM1, < 500 μm) and pT1b2 (SM2, ≥ 500 μm), based on the distance between the muscularis mucosae and the point of deepest invasion. IHC staining using an anti-desmin antibody is useful in identifying the vague muscularis mucosae. The depth of tumor invasion is measured using an ocular micrometer of a microscope or digital camera software; the latter provides more accurate measurement.

(4) Ulceration (or ulcer scar)

The lesion free of ulceration or ulcer scars is classified as pUL0, and the lesion containing ulceration or ulcer scars is classified as pUL1. Ulcer scars often accompany the rupture or loss of the muscularis mucosae, as well as intricate fibrosis in the submucosa. IHC staining using an anti-desmin antibody is useful in identifying the muscularis mucosae. Masson's trichrome staining helps identify fibrous nests. For ulcer scars caused by biopsy, fibrotic areas tend to be small and remain just below the muscularis mucosae.

(5) Lymphovascular invasion

The presence of lymphovascular invasion indicates that the lesion is not curatively resected. In invasive tumors, lymphovascular invasion should be thoroughly assessed using IHC or special staining techniques. IHC using an anti-podoplanin antibody (D2-40) is useful for assessing lymphatic invasion (**Figure 11**). It helps identify lymphatic vessels that are not visible in HE-stained sections and distinguish lymphatic vessels within the lamina propria mucosae from capillary vessels. Elastic fiber staining, such as elastica van Gieson (EVG) staining and Victoria blue (VB) with HE staining, is useful for assessing venous invasion (**Figure 12**). Venous invasion is difficult to identify in areas with stromal fibrosis, but the lesion is classified as V1 if the elastic lamina is observed in at least half or more of its circumference. It is vital to be aware that if the resected specimen is cut into a 2 mm slice and then mounted on glass slides as a 5 μm section, only 5/2,000 (1/400) of the entire specimen is observed, indicating that no lymphovascular invasion on a glass slide specimen does not mean lymphovascular invasion does not exist.

(6) Resection margins

The resection margins of endoscopically resected specimens consist of the horizontal margin (pHM) and the vertical margin (pVM). For the assessment of pHM, the specimen should be appropriately sliced to show the surface where the tumor is located nearest to the resection margin. The accurate diagnosis of pHM is difficult in specimens that are not sufficiently flattened before pinning out or those with markers near the resection margin. For the assessment of pVM, the specimen should be sectioned into the appropriate thickness. Histological assessment of coagulated specimens can be challenging, and immunohistochemistry with an anti-cytokeratin antibody may provide useful diagnostic guidance.

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III Colorectal Cancer

1. Handling of Endoscopically Resected Specimens

The curability of endoscopically resected lesions is determined based on the histological findings of resected specimens. The following text outlines the appropriate handling process of resected specimens before proceeding with histological assessment.

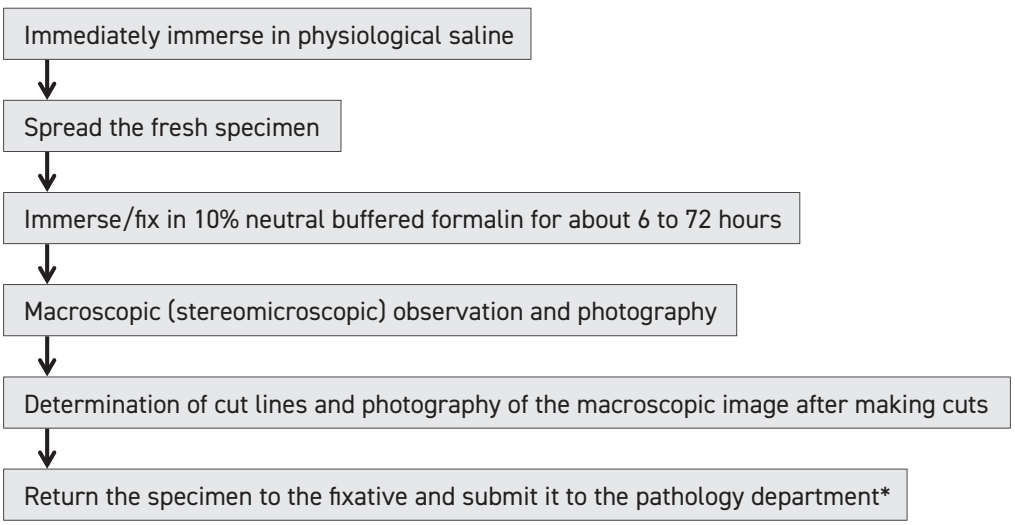
Specimen handling process

Figure 1 shows the handling process of resected specimens. Procedures before formalin fixation should be completed immediately after resection. Therefore, they must be performed by endoscopists. Preferably, procedures after formalin fixation are also performed by endoscopists who understand the endoscopic image of the lesion. If leaving such procedures to pathologists, endoscopists should draw a detailed macroscopic image of the lesion, along with incision lines, in a pathology request form.

When the resected specimen is pinned out, the procedure begins from the resection margin located farthest from the lesion. The specimen is stretched so that the lesion resembles its endoscopic appearance, and the surrounding non-cancerous mucosa lies evenly flattened (**Figure 2**). Only stainless-steel pins are used, as iron pins rust easily in formalin.

During macroscopic observation of the formalin-fixed specimen, the depth and area of tumor invasion are estimated and recorded in a diagram. When needed, the specimen is sprayed with indigo carmine dye and examined under a stereoscopic microscope. The resection margin is then evaluated according to the pit pattern, and photographs are taken of the entire lesion together with magnified views, particularly of areas where submucosal invasion is suspected.

To obtain the intended cut surface in tissue sections, incision lines are placed approximately 0.5 to 1 mm from the target surface and at intervals of 2 to 3 mm, with consideration given to tissue loss during trimming of paraffin-embedded blocks. Incision lines are positioned at two key locations: (1) where



*In some facilities, endoscopists even pack each tissue section into a cassette.

Figure 1 Handling process of endoscopically resected specimens.

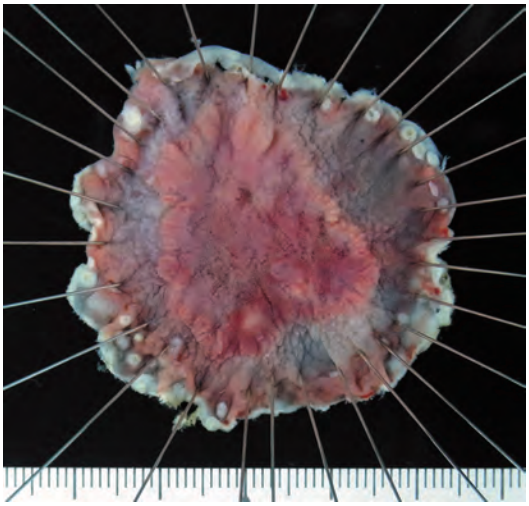


Figure 2 **Spreading and pinning out endoscopically resected specimens.**

A resected specimen was spread so that the surrounding noncancerous mucosa is evenly flattened, and the tumor diameter is nearly equal to that observed endoscopically. The specimen was pinned out with stainless steel pins (not iron nails) and macroscopic images were photographed with a ruler.

tumor invasion is estimated to be the deepest, and (2) where the distance between the tumor and the resection margin is shortest. In principle, all prepared tissue sections are mounted on slides and subjected to histological assessment. [1] After incision lines have been placed, macroscopic images of the entire specimen, taken under a stereoscopic microscope, are photographed.

To obtain the intended cut surface in tissue sections, incision lines are placed approximately 0.5–1 mm from the target surface and at intervals of 2–3 mm, with consideration given to tissue loss during trimming of paraffin-embedded blocks. Incision lines are positioned at two key locations: (1) where tumor invasion is estimated to be the deepest, and (2) where the distance between the tumor and the resection margin is shortest. In principle, all prepared tissue sections are mounted on slides and subjected to histological assessment.[1)] After incision lines have been placed, macroscopic images of the entire specimen, taken under a stereoscopic microscope, are photographed.

Specimens collected by piecemeal resection are immediately assembled and flattened onto a board before subsequent procedures. When this is not feasible, each specimen is attached to filter paper before immersion in saline, allowing the original lesion to be reconstructed later. A hand-drawn diagram is also prepared when possible. If reconstruction of the lesion cannot be achieved, this is specified in the pathology request form.

2. Curability Assessment and Treatment Strategy Based on Pathological Diagnosis

Endoscopically resected lesions are considered curatively treated only if they are “completely resected” and “remain within the specimen”. The former is determined by assessing resection margins, and the latter is determined by the presence (or number) of risk factors for regional lymph node metastasis. In submucosal invasive (pT1) carcinoma, the known risk factors for regional lymph node metastasis are the depth of submucosal invasion, histological type, lymphovascular invasion, and tumor budding. According to the *JSCCR Guidelines 2019 for the Treatment of Colorectal Cancer* (*JSCCR guidelines*),[2)] *completely resected* pT1 tumors are considered curatively treated and therefore can be observed without additional treatment if they meet the following criteria: (1) papillary adenocarcinoma, tubular adenocarcinoma, or medullary carcinoma, (2) pT1a (the depth of submucosal invasion is < 1,000 μm),

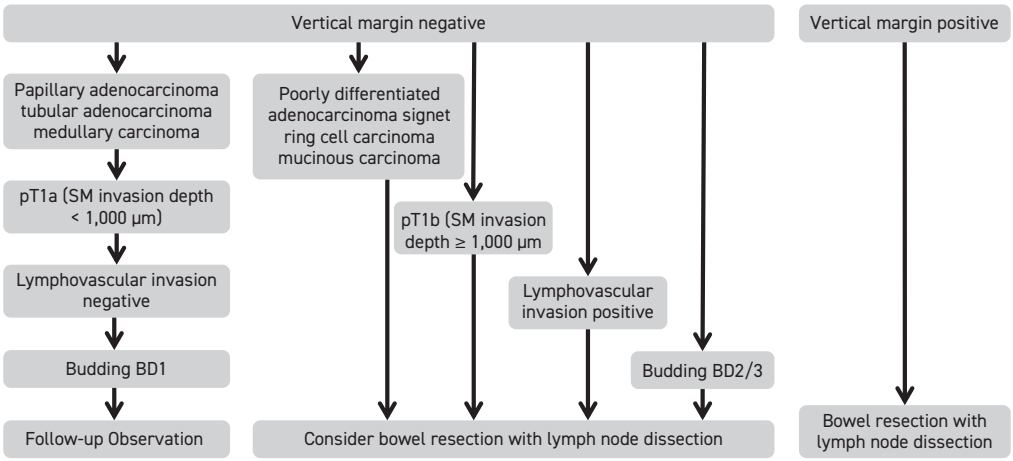


Figure 3 **Treatment strategy for submucosal invasive (pT1) carcinoma after endoscopic resection.**

(Modified from Literature 2)

(3) negative lymphovascular invasion, and (4) budding grade of BD1 (**Figure 3**). Surgery with lymph node dissection is considered for tumors that do not meet any of the above criteria. The following text outlines basic pathological information necessary to apply the *JSCCR guidelines* appropriately.

(1) Assessment of resection margins

The resection margins of a specimen are classified into the horizontal margin (mucosal margin) and the vertical margin (submucosal margin) (**Figure 4**). For intramucosal (pTis) carcinoma, complete resection is defined by a negative horizontal margin alone. In contrast, for pT1 tumors, both horizontal and vertical margins must be negative to be regarded as completely resected.

Endoscopic resection is typically performed using a high-frequency current, which results in a certain degree of tissue degeneration at the resection margin (**Figure 5**). Except for cases treated by cold forceps or snare polypectomy, little or no tissue degeneration at the resection margin indicates that the true resection margin is not included in the section. In that case, perform additional sectioning of the paraffin-embedded block until tissue degeneration appears at the resection margin.

There are two limitations regarding the assessment of resection margins of the endoscopically resected specimen. First, there are no established criteria for diagnosing a negative or positive resection margin in other countries. According to *the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma*,[3] if cancer is not identified at the horizontal margin, it means that the horizontal margin is negative, and the distance between the tumor and the horizontal margin should be recorded. It also states that local recurrence may occur in cases in which the distance between the tumor and the vertical margin is < 500 μm.3 Second, the presence or absence of cancer in resection margins cannot be accurately diagnosed by histological assessment if the non-cancerous mucosa surrounding small lesions is not included in tissue sections. In such a case, the resection margins can be falsely diagnosed as positive.



Figure 4 Resected margins of tissue sections prepared from endoscopically resected specimen.

There are horizontal mucosal margins (solid line) and vertical submucosal margin (dotted line). In this case, the lesion is an intramucosal adenocarcinoma (pTis) coexisting with adenoma, and the horizontal margin is negative, which qualifies as curative resection.

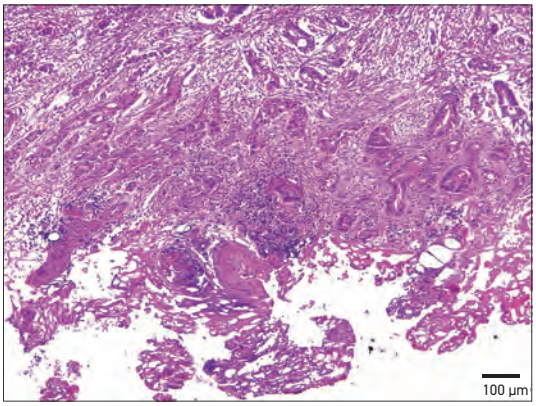


Figure 5 Heat degeneration of tissues in the vertical margin.

Tissue at the vertical margin of the endoscopic resection specimen exhibits degeneration caused by high-frequency current (diathermy burn). When carcinoma invades near the vertical margin, not only the stromal tissue but also tumor cells may show varying degrees of degeneration. On hematoxylin and eosin–stained slides, the vertical margin appears reddish and is identified as a shrunken area.

(2) Assessment of the depth of tumor invasion and submucosal invasion

Colorectal intramucosal (pTis) carcinoma does not metastasize to lymph nodes or other organs, and the curability of pTis tumors (including adenomas) is determined by pathohistological findings of the resection margin, i.e., whether the tumor is completely resected. On the other hand, approximately 10% of pT1 tumors accompany lymph node metastasis, and a histologically complete resection does not assure a curative resection. For pT1 tumors that have little to no risk of lymph node metastasis, the *JSCCR guidelines* state that, if completely resected, they are considered curatively treated and can be observed without additional treatment.[2] JSCCR has reported that tumors with a depth of submucosal invasion of < 1,000 µm (pT1a) have little to no risk for lymph node metastasis, and their guidelines include a depth of SM invasion of < 1,000 µm as one of the endoscopic curability criteria for pT1 tumors (**Figure 3**).[2]

Figure 6 shows the measurement of the depth of submucosal invasion described in *the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma*[3] *and the JSCCR guidelines*.[2] If the location of the muscularis mucosae is identified or can be estimated, the distance between the lower border of the muscularis mucosae and the point of deepest invasion should be measured (**Figure 6a**). Even if the upper part of the lesion is likely to remain in the mucosa, when the muscularis mucosae is fragmented or disarrayed and its location is not easily identified, the depth of submucosal invasion

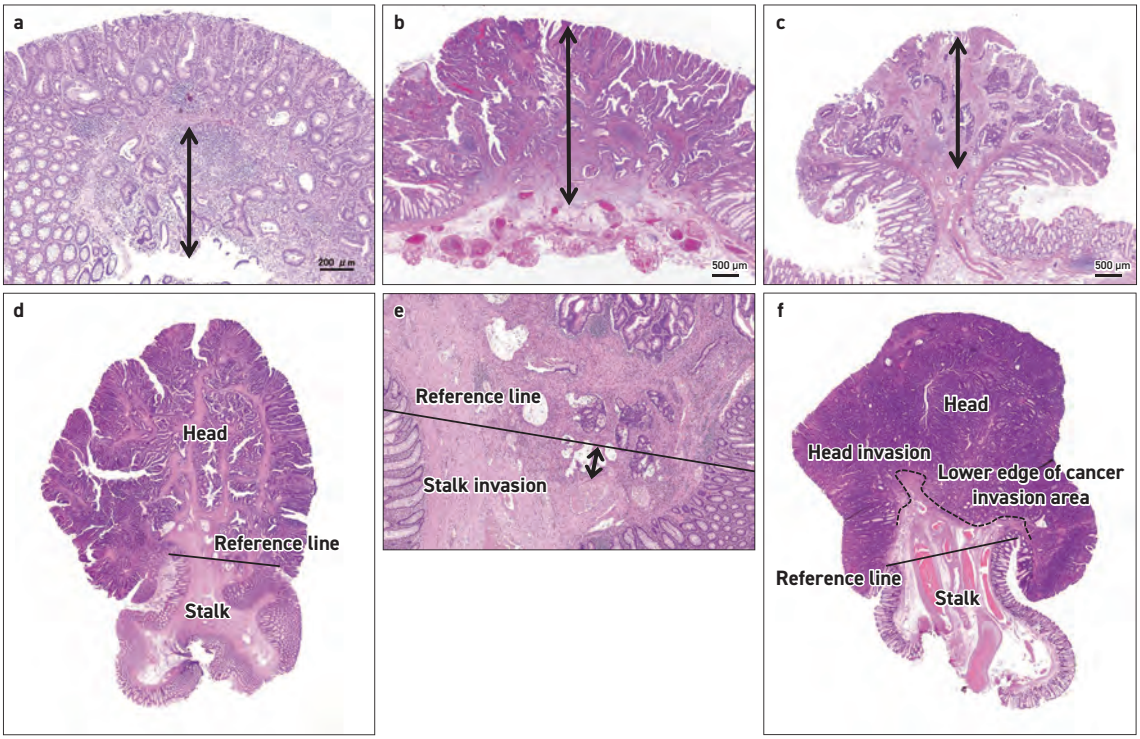


Figure 6 **Measurement of the depth of submucosal invasion of pT1 tumors.**

(a) In sessile pT1 cancer with preserved muscularis mucosae, the invasion depth is measured from the lower edge of the muscularis mucosae to the deepest point of invasion. (b) In sessile pT1 cancer with disrupted or fragmented muscularis mucosae, measurement is performed from the uppermost surface of the lesion to the deepest point of invasion. (c) In pedunculated pT1 cancer with absent muscularis mucosae, the measurement is performed from the surface of the lesion to the deepest point of invasion. Desmoplastic reaction is prominent in the tumor stroma. (d) In pedunculated pT1 cancer with disorganized muscularis mucosae, a reference line (solid line) is drawn at the junction of the head and stalk. (e) When tumor invasion extends beyond the reference line, it is defined as stalk invasion, and the distance is measured from the reference line (solid line) deepest point of invasion. (f) In pedunculated pT1 cancer with disorganized muscularis mucosae, when the lowest edge of tumor invasion (dotted line) remains confined within the head and does not exceed the reference line (solid line), it is defined as head invasion. In such cases, submucosal invasion depth is not measured.In panels a, b, c, and e, the double-headed arrows indicate the vertical distance of tumor invasion.

should be measured from the upper surface of the lesion (pedunculated or sessile) (**Figures 6 b, c**). It is essential to understand that this method is designed to standardize the measurement of submucosal invasion. The measurement based on this method may not reflect the actual depth of submucosal invasion, and the decision on whether the muscularis mucosae is fragmented or disarrayed may vary among pathologists.

For pedunculated pT1 tumors, when the muscularis mucosae is disarrayed and cannot be used as a reference, the depth of submucosal invasion is measured as the distance between the neck (the junction between the head and the stalk) and the point of deepest invasion (**Figures 6 d, e**). The junction between the head and the stalk is defined as the point where the tumor head (with the surrounding reactive mucosal hyperplasia) appears to arise. If there is no clear junction, it is practical to use the boundary between cancerous and non-cancerous lesions within the upper mucosa as a reference.

When tumor invasion is confined to the head, it is classified as head invasion, and measurement of submucosal invasion depth is not required (**Figure 6f**). The distinction between pedunculated and sessile tumors is determined by the endoscopist. Therefore, endoscopists need to write the macroscopic type in the pathology diagnosis request form.

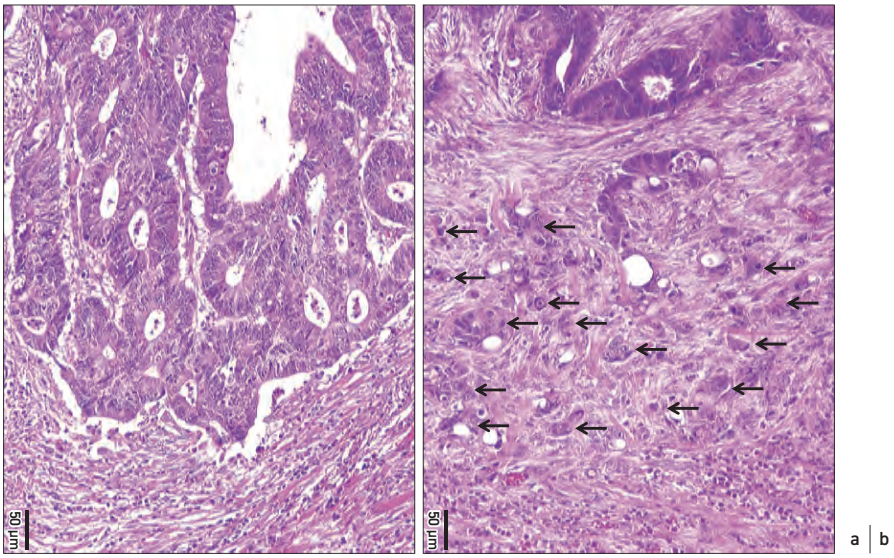


Figure 7 **Assessment of tumor budding at the invasive front of pT1 tumors.**

Tumor budding defined as BD1 is minimal within the stromal tissue at the invasive front of the cancer (a). Prominent tumor budding (arrow) defined as BD3 is observed in the stromal tissue at the invasive front, with more than 10 cancer nests present (b).

The key factor in evaluating the depth of submucosal invasion is whether it is less than 1,000 μm, as the precise numerical value does not influence assessment of endoscopic curability or the risk of lymph node metastasis. A depth of invasion below 1,000 μm, which forms part of the endoscopic curability criteria, requires accurate diagnosis. When the measurement is uncertain, the depth of submucosal invasion is recorded as approximately 1,000 μm in the pathology report and is not used for curability assessment. Treatment strategies are determined with reference to other risk factors for lymph node metastasis.

Finally, in the histological diagnosis of pedunculated tumors, it is important to distinguish so-called pseudo-carcinomatous invasion, defined as the migration of non-malignant adenomatous epithelium into the submucosa,[4] from true pT1 tumors.

(3) Assessment of other risk factors for lymph node metastasis

a. Histological type

Tubular adenocarcinoma is the most common histological type of colorectal cancer that is indicated for endoscopic treatment. Histological assessment of the resected specimen will sometimes identify other histological types coexisting with tubular adenocarcinoma. Poorly differentiated adenocarcinoma, signet-ring cell carcinoma, mucinous adenocarcinoma, and neuroendocrine carcinoma are known risk factors for lymph node metastasis. Therefore, even when tubular adenocarcinoma is predominant in the lesion, the other coexisting histological types should be recorded in a pathology report.

b. Lymphovascular invasion

Lymphovascular invasion is generally assessed on the largest cut area. Non-cancerous areas should also

be assessed carefully, as lymphovascular invasion can occur in the normal mucosa surrounding the lesion. According to *the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma*,[3] the lesion is classified as positive lymphatic invasion if an anti-podoplanin antibody (D2-40) staining identifies endothelial cells in at least half or more of the circumference of tumor nests; the lesion is classified as positive venous invasion if elastic fiber staining, such as elastica van Gieson (EVG) staining and Victoria blue (VB) staining, identifies the elastic lamina in at least half or more of its circumference.

c. Tumor budding at the invasive tumor front

According to *the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma*, a tumor bud is defined as a nest of cancer cells consisting of a single cell or a cluster of fewer than five cells that infiltrates the stroma at the invasive front of the tumor.[3] Tumor budding (BD) is graded in three categories based on the number of buds observed within a single field at 20× magnification in the area showing the most prominent budding (**Figure 7**). The assessment is generally performed on HE-stained sections, with results recorded as BD1 (< 5 buds), BD2 (5 to 9 buds), or BD3 (≥ 10 buds).

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