Digestive Endoscopy 2016; **28**: 3–15 doi: 10.1111/den.12518

Guideline

Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer*

Hiroyuki Ono,[1,2] Kenshi Yao,[1,2] Mitsuhiro Fujishiro,[1,2] Ichiro Oda,[1,2] Satoshi Nimura,[2] Naohisa Yahagi,[1,2] Hiroyasu Iishi,[1,2] Masashi Oka,[1,2] Yoichi Ajioka,[2] Masao Ichinose[1] and Toshiyuki Matsui[1]

[1]*Japan Gastroenterological Endoscopy Society, Tokyo, and* [2]*Japanese Gastric Cancer Association, Kyoto, Japan*

In response to the rapid and wide acceptance and use of endoscopic treatments for early gastric cancer, the Japan Gastroenterological Endoscopy Society (JGES), in collaboration with the Japanese Gastric Cancer Association (JGCA), has produced 'Guidelines for ESD and EMR for Early Gastric Cancer', as a set of basic guidelines in accordance with the principles of evidence-based medicine. These Guidelines cover the present state of knowledge and are divided into the following seven categories: Indications, Preoperative diagnosis, Techniques, Evaluation of curability, Complications, Long-term postoperative surveillance, and Histology. Twenty-three statements were finally accepted as guidelines, and the majority of these were obtained from descriptive studies with lower evidence levels. A number of statements had to be created by consensus (the lowest evidence level), as evidence levels remain low for many specific areas in this field.

Key words: early gastric cancer, endoscopic mucosal resection, endoscopic submucosal dissection, evidence based guideline

NEED FOR GUIDELINES FOR GASTRIC ENDOSCOPIC SUBMUCOSAL DISSECTION AND ENDOSCOPIC MUCOSAL RESECTION

THE ENDOSCOPIC TREATMENTS of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been widely accepted and used for the treatment of early gastric cancers (EGC) with negligible risk of lymph node metastasis. In Japan, detection of an increasing proportion of EGC among all gastric cancers has been achieved owing to the nationwide screening program and advances in endoscopic knowledge and technologies. Endoscopic treatment is considered to be preferable to open or laparoscopic surgery if similar efficacy is obtained in terms of oncological aspects.[1,2]

In order to achieve good results in EMR and ESD for EGC, however, excellent skills and knowledge regarding the diagnosis, indications, actual procedures, evaluation of curability, complications, long-term postoperative surveillance, and histopathology are essential. As EMR and ESD become more widely used and more complex in nature, standardization has been sought in these therapies for optimal patient care. Additionally, while these skills and knowledge are well known among gastroenterological endoscopists in Japan, we speculate that such knowledge may remain limited in other countries. From these backgrounds, the Japan Gastroenterological Endoscopy Society (JGES) in collaboration with the Japanese Gastric Cancer Association (JGCA) has created guidelines for ESD and EMR for the treatment of EGC.

Corresponding: Hiroyuki Ono, Japan Gastroenterological Endoscopy Society, 4th Floor, Shin-Ochanomizu Urban Trinity Building, 3-2-1 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan. Email: h.ono@scchr.jp

**These guidelines have already been published in Japanese (reference no. [114]).*

Received 3 August 2014; accepted 29 July 2015.

BASIC PRINCIPLES OF CREATING THE JGES GUIDELINES

SINCE 1992, JGES has produced three editions of guidelines for ESD and EMR for EGC.[3] However, thus far, the guidelines have focused on technical aspects through discussion between several specialists; they were not strictly founded on evidence-based medicine (EBM). Accordingly, in January 2010, the JGES set up a Guidelines Committee in order to design therapeutic guidelines under the aegis of the Society in accordance with the principles of EBM. The Committee decided to first deal with relatively urgent topics, including gastric ESD and EMR, esophageal ESD and EMR, endoscopic procedures in patients undergoing antithrombotic treatment, and anesthesia and sedation for endoscopic procedures. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment were published as an English version

in 2014,[4] and the creation of the next set of guidelines for ESD and EMR for EGC was then started.

The basic principles that were followed in producing the Guidelines of JGES are as follows.

1. They are based on scientific evidence.
2. Where there is a gap in the evidence concerning endoscopic techniques or other areas, it will be filled through consensus.
3. Recommendations are practical, therapeutic choices are clear, and important recommendations can be easily identified. Furthermore, levels of evidence and grades of recommendation will be given.
4. The parameters of literature searches will vary with the topic, so each working committee will make their own decisions, and clearly note the methodology, parameters, and selection criteria for their references.
5. In general, reference sources in both English and Japanese will be used.
6. The form of these Guidelines will be a review format.

When we refer to a consensus, this indicates the committee reaching an agreement through application of the scientific method, used to determine recommendations when the level of evidence is low. These Guidelines were produced with input from working and evaluation committees comprising specialists in each area, with further contributions from external members. For the sake of thoroughness, we also sought the opinions of Society members in the form of public comments.

The basic production process for these Guidelines followed the Japanese Medical Information Service (Minds) guide for the production of therapeutic guidelines.[5,6] We then assessed the Guidelines using the AGREE tool for the assessment of practice guidelines in a process that endeavored to meet societal demands. We set the grades of recommendation for each short statement by synthesizing the best available evidence in the literature and by consensus from our specialist subcommittees (Tables 1,2). We naturally gave due consideration to compatibility with relevant guidelines from a variety of sources. As a result of the time taken to produce these Guidelines, there were limitations on the range of evidence that could be used. Accordingly, we set out a production process for each short statement. Considering the rapidly changing nature of this field, extensive, ongoing changes in endoscopic therapy will likely necessitate revisions to these Guidelines every few years.

Table 1 Classification of evidence levels

I	Systematic review/meta-analysis of randomized controlled trial
II	At least one randomized controlled trial
III	Non-randomized controlled trial
IVa	Analytical epidemiological study (cohort study)
IVb	Analytical epidemiological study (case–control study, cross-sectional study)
V	Case series, case report
VI	Not based on patient data, or based on opinions from a specialist committee or individual specialists

Table 2 'Minds' grades of recommendation

A	Strong scientific evidence exists, strongly recommended to do
B	Scientific evidence exists, recommended to do
C1	No scientific evidence, but recommended to do
C2	No scientific evidence, recommended not to do
D	Scientific evidence that it is ineffective or harmful, recommended not to do

The Guidelines Committee takes responsibility for the content of these guidelines, which are produced with the general aim of assisting with decision-making in clinical practice. Accordingly, these Guidelines will be most useful when they are used in everyday clinical situations. However, their content is not to be used as evidence in medical malpractice suits. In other words, the individual medical practitioner bears the responsibility for the actual results of medical procedures that they carry out.

Toshiyuki Matsui
Chairman, Guidelines Committee
Japan Gastroenterological Endoscopy Society

PROCEDURE FOR THE PRODUCTION OF GUIDELINES FOR ESD AND EMR FOR EGC

Committee members

A TOTAL OF FIVE specialists comprising four gastrointestinal endoscopists and one gastrointestinal pathologist were entrusted with the production of these Guidelines as members of the Guidelines Working Committee. A further eight specialists comprising one gastrointestinal endoscopist, three gastroenterologists, one clinical oncologist, one gastrointestinal surgeon, one radiologist, and one gastrointestinal pathologist were appointed to the Evaluation Committee and External Evaluation Committee (Table 3).

Evidence levels, grades of recommendation, and short statements

The Working Committee established the following seven categories: Indications, Preoperative diagnosis, Techniques, Evaluation of curability, Complications, Long-term postoperative surveillance, and Histopathology. For each category, they drafted a short statement; for example, 'In general, endoscopic

Table 3 Members of the Gastric Cancer ESD and EMR Guidelines Committee

Japan Gastroenterological Endoscopy Society Guidelines Committee	
Director	Masao Ichinose (JGES: Second Department of Internal Medicine, Wakayama Medical University)
Chairperson	Toshiyuki Matsui (JGES: Department of Gastroenterology, Fukuoka University Chikushi Hospital)
Guidelines Working Committee	
Working Committee Chairperson	Hiroyuki Ono (JGES: Endoscopy Division, Shizuoka Cancer Center)
Working Committee Members	Kenshi Yao (JGES: Department of Endoscopy, Fukuoka University Chikushi Hospital)
	Mitsuhiro Fujishiro (JGES: Department of Endoscopy and Endoscopic Surgery, The University of Tokyo)
	Ichiro Oda (JGES: Endoscopy Division, National Cancer Center Hospital)
	Satoshi Nimura (JGCA: Department of Pathology, Fukuoka University School of Medicine)
Guidelines Evaluation Committee	
Evaluation Committee Chairperson	Naohisa Yahagi (JGES: Keio University Hospital Tumor Center)
Evaluation Committee Members	Toshiyuki Matsui (JGES: Department of Gastroenterology, Fukuoka University Chikushi Hospital)
	Hiroyasu Iishi (JGES: Department of Gastroenterology, Osaka Medical Center for Cancer and Cardiovascular Diseases)
	Masashi Oka (JGES: Department of Hepatology, Saitama Medical University Hospital)
	Yoichi Ajioka (JGCA: Department of Pathology, Niigata University)
External Evaluation Committee Members	Takeshi Sano (JGCA: Department of Surgery, Cancer Institute Hospital)
	Narikazu Boku (Department of Oncology, St Marianna University School of Medicine)
	Tsutomu Ishikawa (Japan Radiological Society: Department of Radiology, Dokkyo Medical University)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; JGCA, Japanese Gastric Cancer Association; JGES, Japan Gastroenterological Endoscopy Society.

resection should be carried out when the likelihood of lymph node metastasis is extremely low, and lesion size and site are amenable to en bloc resection.' For each statement, we carried out a systematic literature search for the period from 1985 to 2012 using the PubMed (English) and Ichushi (Japanese) databases. The levels of evidence and grades of recommendation were determined in accordance with the above-mentioned 'Minds' system (Tables 1,2). Furthermore, we produced these Guidelines with full consideration of compatibility with the Japanese Gastric Cancer Association *Japanese Gastric Cancer Treatment Guidelines 2010* (ver. 3).[7]

Evaluation procedure

We produced a total of 58 short statements. These were evaluated by the Evaluation Committee using three grades of 'Accepted', 'Reevaluate', and 'Not accepted'. Of the 58 statements, 10 were accepted unanimously, with the remaining 48 evaluated as either 'Not accepted' or 'Reevaluate'. The Working Committee then worked on revisions for the statements graded as 'Reevaluate', and both the accepted and revised statements were presented to the 82nd Congress of JGES held on 22 October 2011 (President, T. Matsui). Members attending the Congress were asked to evaluate the statements again using the three grades of 'Accepted', 'Reevaluate', and 'Not accepted', on an answer pad. The Evaluation Committee assessed the levels of evidence and grades of recommendation, and recorded their findings on these Guidelines.

After this process, we accepted 32 short final draft statements, and a set of guidelines were produced based on these statements in a review format. The final draft statements were then voted on by mail, by the Working Committee, the Evaluation Committee, and by the JGES Director, totaling 14 committee members in all. In accordance with the modified Delphi method, the following criteria were used: a result of 1–3 votes = no consensus; 4–6 = dissatisfaction; and 7–9 = consensus; statements receiving seven or more votes were adopted. Finally, 23 statements that received seven or more votes from all voting members were accepted for the Guidelines. The draft manuscript of the final version of the Guidelines for ESD and EMR for EGC was created following a period of public comments, and these Guidelines were then completed.

Target

The target subjects of these Guidelines are patients who undergo EMR or ESD for EGC. The users of these Guidelines will be clinicians who carry out EMR or ESD and their supervisors. The Guidelines can only ever be a standard guide, and careful consideration should be given to each individual patient in terms of their age, concurrent disease, social situation, and other factors before choosing the treatment.

Indications

Basic approach

Once EGC has been diagnosed, endoscopic or surgical treatment is recommended (evidence level IVa, grade of recommendation B).

No studies have clearly demonstrated an improved prognosis or quality of life (QOL) with endoscopic therapy for gastric cancer or a difference in prognosis or QOL between endoscopic and open surgical treatment.

However, in a non-concurrent, long-term, follow-up study conducted in 71 patients who were diagnosed endoscopically with EGC but in whom surgical resection was not done or was delayed by more than 6 months after diagnosis, the cumulative 5-year risk for progressing to the advanced stage was 63.0% (95% CI: 48–78%).[8] Various studies, including this study, have shown that patients with EGC would still benefit even when surgery is delayed by more than 6 months after diagnosis.[8,9]

In general, endoscopic resection should be carried out when the likelihood of lymph node metastasis is extremely low, and lesion size and site are amenable to resection en bloc (evidence level V, grade of recommendation C1).

As endoscopic therapy is a stomach-preserving technique, without formal testing we can assume that QOL is better with endoscopic treatment than with surgical treatment. Endoscopic treatment should therefore be done for lesions where the likelihood of cure is high.[10]

However, as shown by observational studies that aimed to elucidate the natural history of EGC,[8,9] we do not expect that unresected EGC would cause mortality in all patients.

In addition to the preoperative diagnosis, the selection of treatment should be based on a risk-benefit analysis and consideration of each patient's condition. Indications for tumor-related factors are classified as absolute indications, expanded indications, and out of indications (Fig. 1).

As a result of the present lack of adequate evidence regarding prognosis after ESD, the standard treatment for expanded indication lesions is still surgery, and prospective studies are ongoing for patients in this category.

In general, informed consent should be obtained from the patient for the endoscopic treatment of gastric cancer.

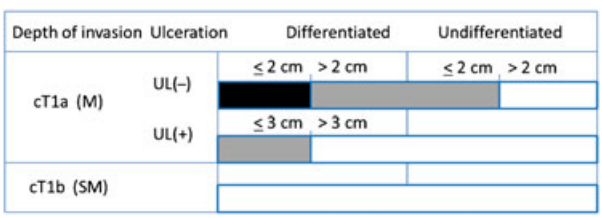

Figure 1 Classification of indications according to tumor-related factors. ■, absolute indication lesion; ■ expanded indication lesion; □, out of indication lesion. cT1a (M), intramucosal cancer (preoperative diagnosis); cT1b (SM), submucosally invasive cancer (preoperative diagnosis); UL, finding of ulceration (scar).

Indicated lesions

Endoscopic therapy is absolutely indicated in 'macroscopically intramucosal (cT1a) differentiated carcinomas measuring less than 2 cm in diameter. The macroscopic type does not matter, but there must be no finding of ulceration (scar); i.e. UL(–).' The expanded indications are: '1. UL(–) cT1a differentiated carcinomas greater than 2 cm in diameter; 2. UL(+) cT1a differentiated carcinomas less than 3 cm in diameter; and 3. UL(–) cT1a undifferentiated carcinomas less than 2 cm in diameter.' When vascular infiltration (ly, v) is absent together with the above-mentioned criteria, the risk of lymph node metastasis is extremely low, and it may be reasonable to expand the indications. If a lesion falls within the indication criteria at the initial ESD or EMR, subsequent locally recurrent intramucosal cancers may be dealt with under expanded indications (evidence level V, grade of recommendation C1).

Out of indication lesions

The unreliability of preoperative diagnoses is covered in detail below in 'Preoperative diagnosis'. In particular, the preoperative diagnostic accuracy rate is unsatisfactory for lesions that are diagnosed histopathologically as submucosal invasion (pT1b).[11] ***Thus, the indications for treatment are sometimes decided with a view to establishing an accurate histopathological diagnosis (evidence level V, grade of recommendation C1).***

Preoperative diagnosis

The preoperative endoscopic diagnosis of gastric cancers required for ESD/EMR can be broadly divided into '1. Information to assist the determination of the indication for endoscopic treatment' and '2. Information to assist the determination of horizontal resection margins'.

Information to assist the determination of the indication for endoscopic treatment

In order to determine whether ESD or EMR is indicated, it is necessary to determine: (1) histopathological type; (2) size; (3) depth of invasion; and (4) whether ulceration is present (evidence level VI, grade of recommendation C1).

First, the histopathological type is usually determined by histopathological examination of a biopsy specimen. Although it has been reported that the histopathological type can be endoscopically predicted to a certain extent, adequate evidence is lacking.[12–17] In general, the histopathological type

of a gastric cancer is determined through histopathological examination of a biopsy specimen taken using endoscopic forceps.

It has been pointed out that measurements of lesion size using conventional endoscopic methods are prone to error.[18–20] Accurate preoperative determination of lesion size is difficult; therefore, investigations and treatments are conducted with a view to making the final measurements after histopathological examination of the resected specimen.

To determine whether ulceration is present, a lesion is examined for the presence of either active ulceration or an ulcer scar. Histopathologically, an ulcer is defined as a mucosal defect at least UL-II in depth (which is deeper than the muscularis mucosae). At preoperative endoscopy, active ulceration refers to open ulcers with adherent white exudate and excludes superficial erosions. Furthermore, ulcers in the healing or scarring stage, with the mucosal folds or rugae converging on one point, are also defined as ulceration.

Determination of the depth of invasion by EGC is generally carried out using conventional endoscopy,[21–23] with additional indigocarmine dye spraying being recommended.[24] When difficulties are encountered in determining the depth of invasion using conventional endoscopy alone, endoscopic ultrasonography may be useful as an additional diagnostic modality.[25–32]

Information to assist the determination of horizontal resection margins

In general, conventional endoscopy with dye spraying is used to determine the horizontal resection margins (evidence level V, grade of recommendation C1).

In general, conventional endoscopy with dye spraying, a simple method that is also the most widely carried out, is used to determine the horizontal margins of cancer extent. It has been reported that when this method is used to examine EGC possibly indicated for ESD, the extent of the horizontal margins can be delineated in approximately 80% of lesions.[33,34]

Margin delineation can be difficult in undifferentiated EGC as well as in certain differentiated lesions.[34] In these cases, biopsies should be taken from the lesion's surroundings and examined histopathologically.

When the determination of horizontal resection margins is difficult using conventional endoscopy alone, equipment-based image-enhanced endoscopy (IEE) using a magnifying endoscope is useful as an additional diagnostic modality.[34]

Techniques

The risk of incomplete resection is high when using EMR for lesions with expanded indications, so ESD should be carried out instead of EMR for these lesions (evidence level V, grade of recommendation C1).

The optimal endoscopic treatment method should be selected after consideration of the patient's condition, characteristics of the lesion, therapeutic environment at the treating institution, and experience of the endoscopist.

EMR is a method whereby the lesion is elevated, placed in a metal wire snare, and resected using high-frequency diathermy.[35–37]

ESD is a method whereby the mucosa surrounding the lesion is excised using a high-frequency diathermy knife, followed by dissection of the submucosa beneath the lesion.[10,38–46]

There have been no randomized controlled trials examining the therapeutic results between EMR and ESD or among EMR or ESD procedures in the stomach. However, a meta-analysis found that, in general, better en bloc resection rates are achieved with ESD than with EMR.[47] It has also been reported that for tumor sizes >1 cm, en bloc resection rates are significantly lower for EMR than for ESD.[48–50]

Physicians should refer to textbooks[1,51] and other relevant JGES guidelines for accurate information concerning perioperative management for ESD and EMR procedures. For example, in January 2014, JGES published 'Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment'.[4]

Evaluation of curability

Evaluation of curability is based on local factors and risk factors for lymph node metastasis (evidence level V, grade of recommendation C1).

Curative resection

If the risk of lymph node metastasis is less than 1% and 3% in pT1a and pT1b cancers, respectively, we assume that similar outcomes can be achieved with ESD and EMR as with open surgical resection.

When the lesion is resected en bloc, is <2 cm in diameter, predominantly differentiated type, pT1a, UL(–), ly(–), v(–), and with negative surgical margins, it is considered curative resection.

When a lesion is resected en bloc and is: (1) ≥2 cm in diameter, predominantly differentiated type, pT1a, and UL(–); (2) <3 cm, predominantly differentiated type, pT1a, and UL(+); (3) <2 cm, predominantly undifferentiated type, and pT1a, UL(–); or (4) <3 cm, predominantly differentiated type, pT1b (SM1); and ly(–), v(–), and with negative surgical margins, it is considered curative resection for expanded indications.

However, evidence is lacking concerning cases of differentiated cancers with undifferentiated components, and the expanded indications need to be worked out in further detail. For instance, a non-curative resection that requires further surgical resection is defined for the above-mentioned type (1) lesions that are ≥2 cm, pT1a, UL(–), and predominantly differentiated, if the undifferentiated components exceed 2 cm at the greatest diameter, as well as for type (4) lesions that are 3 cm, pT1b (SM1), and predominantly differentiated, if undifferentiated components are present in the submucosally invasive part of the lesion.[7,52,53] ***Curative resection for expanded indications applies for the above-mentioned type (2) lesions that are <3 cm, pT1a, UL(+), and predominantly differentiated, even if undifferentiated components are present, as the risk of metastasis is considered to be less than 1%[54] (evidence level V, grade of recommendation C1).***

Non-curative resection

When a lesion meets none of the absolute or expanded indications for curative resection, it is considered non-curative resection.

Open or laparoscopic surgical resection is indicated in most cases of non-curative resection, because of the clear risk of lymph node metastasis (evidence level V, grade of recommendation C1). When there is no evidence of vascular infiltration, the reported rates of lymph node metastasis are as follows: (1) 3.0% (7/230) for >3 cm, predominantly differentiated type, pT1a, and UL(+) lesions; (2) 2.6% (2/78) for >3 cm, predominantly differentiated, and pT1b (SM1); (3) 2.8% (6/214) for >2 cm, predominantly undifferentiated, pT1a, and UL(–); (4) 5.1% (52/1014) for predominantly undifferentiated, pT1a, and UL(+); and (5) 10.6% (9/85) for predominantly undifferentiated, and pT1b (SM1). The risk of lymph node metastasis and recurrence is thus high for lesions that undergo non-curative resection.[7,52,53]

In general, open or laparoscopic surgical resection should be done in cases of non-curative resection.

However, in some cases of non-curative resection of predominantly differentiated-type lesions, when the only non-curative factor is piecemeal resection or resection en bloc with positive horizontal margins, open surgical resection is not the only option. According to the policy of the treating institution, repeat ESD, diathermy, and no treatment are all possible choices, with the patient's informed consent, although careful follow up is required. Open or laparoscopic surgical resection is indicated in the following cases: (1) <3 cm, predominantly differentiated type, pT1a, and UL(+); or (2) <3 cm, predominantly differentiated type, and pT1b (SM1) lesions, if the combined size of the endoscopically determined remnant lesion plus the lesion in the resected specimen exceeds 3 cm, or if the submucosally invasive part of a lesion is either resected piecemeal or has positive margins (Figs 2,3).

Complications

Reported rates of the most common complications of ESD and EMR, bleeding and perforation, are given in Table 4;[44,55–84] some of the differences between studies can be attributed to different definitions. Other reported complications that are worthy of note, although their incidences are low, include stricture, pneumonia, and air embolism (Table 4). The risk of complications should be kept in mind at all times when carrying out ESD or EMR for gastric cancers.

Management of intraoperative bleeding

Bleeding during ESD and EMR procedures is almost inevitable, particularly during ESD, if we include the slight bleeding that is seen during ESD. However, if the response to this bleeding is inappropriate, it can affect the patient's hemodynamic status, leading to further complications requiring transfusion, interventional radiology (IVR), or surgery. Accordingly, the appropriate management of bleeding during the procedure is extremely important for the safe performance of ESD and EMR of gastric cancers. ***Use of hemostatic forceps is recommended to coagulate bleeding vessels during ESD, as they do not interfere with resection once hemostasis has been obtained (evidence level VI, grade of recommendation C1).***[85] Depending on the circumstances, clips and injections may also be used.

Prevention of postoperative bleeding

The use of hemostatic forceps or other instruments to coagulate remnant vessels on the post-resection ulcer surface has been reported to reduce the rate of bleeding following ESD from 7.4% to 3.2%.[62] ***Appropriate preventive measures***

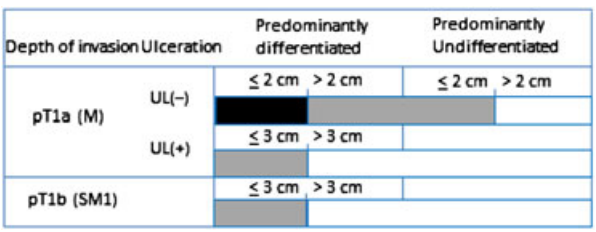

Figure 2 Evaluation of curability according to tumor-related factors. ■, curative resection†; ■, expanded indication, curative resection†,‡; □, non-curative resection. †confined to en bloc resection and HM0, VM0, ly(–), v(–); ‡with some exceptions. pT1a (M), intramucosal cancer (histopathological diagnosis); pT1b (SM), submucosally invasive cancer (histopathological diagnosis); SM is classified as SM1 and SM2. SM1 is defined as cancer invasion <500 μm from the muscularis mucosae, whereas SM2 is defined as invasion to 500 μm or deeper. UL, finding of ulceration (scar).

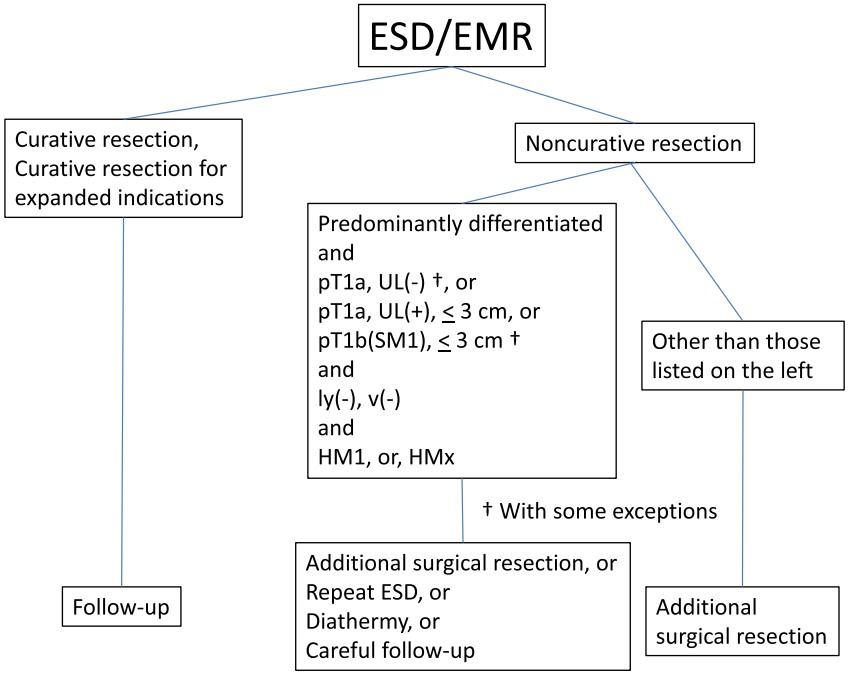

Figure 3 Therapeutic flowchart following endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR). †with some exceptions. pT1a (M), intramucosal cancer (histopathological diagnosis); pT1b (SM), submucosally invasive cancer (histopathological diagnosis); SM is classified as SM1 and SM2. SM1 is defined as cancer invasion <500 μm from the muscularis mucosae, whereas SM2 is defined as invasion to 500 μm or deeper. UL, finding of ulceration (scar).

should be applied to remnant vessels on the post-resection ulcer surface (evidence level V, grade of recommendation C1). However, caution is required, as excessive vessel coagulation may increase the risk of delayed perforation.

Furthermore, ***a proton pump inhibitor (PPI) or histamine H2-receptor antagonist should be given following ESD or EMR, similar to peptic ulcer therapy (evidence level V, grade of recommendation C1).***[86–93]

Management of perforation

When perforation occurs during ESD or EMR, endoscopic clip closure should first be attempted (evidence level V, grade of recommendation C1). If endoscopic clip closure is successful, the patient can be managed conservatively, with fasting and a nasogastric tube *in situ* along with antimicrobial therapy. Although conservative management and careful follow up is often successful (Table 4),[94] if the perforation cannot be closed or if peritonitis is suspected despite apparent closure, a surgeon should be consulted on the need for surgical management.

Long-term postoperative surveillance

As described in 'Evaluation of curability', evaluation of the degree of likelihood of cure after ESD or EMR is carried out through histopathological examination of the resected specimen, on the basis of which subsequent treatment is decided. When the procedure is considered likely to have been curative, the patient should be carefully observed, keeping in mind the possibility of residual or recurrent tumor and the development of a metachronous cancer. A risk of metachronous gastric cancer exists following ESD or EMR,[95,96] and the cumulative 3-year risk is approximately 5.9%.[96] ***Even when histopathological examination indicates curative resection, follow up with esophagogastroduodenoscopy at intervals of 6–12 months is desirable, with the main aim of detecting metachronous gastric cancers (evidence level VI, grade of recommendation C1).*** The JGCA *Japanese Gastric Cancer Treatment Guidelines 2010* ver. 3 (for medical practitioners) recommends follow-up esophagogastroduodenoscopy once or twice per year following curative resection[7]; however, there have been no reports of comparisons between endoscopic follow-up examinations at 6- and 12-month intervals. One study reported that annual endoscopic follow up enabled ESD or EMR treatment of more than 95% of metachronous gastric cancers.[96]

When histopathological examination indicates expanded indication curative resection, follow up with esophagogastroduodenoscopy, as well as ultrasonography or computed tomography (CT) scanning for the detection of metastases, is desirable at intervals of 6–12 months (evidence level VI, grade of recommendation C1).

Local recurrence has been reported in cases of positive horizontal margins or piecemeal resection.[38,97,98] ***When histopathological assessment indicates non-curative resection not requiring surgical resection (See Evaluation of curability, Non-curative resection), and observation without further***

Table 4 Reported complications

Author	Year published	Method of resection	No. lesions	Postoperative bleeding, % (*n*)	Perforation, % (*n*)	Delayed Perforation, % (*n*)	Pneumonia, % (*n*)	Stricture, % (*n*)	Air embolism, *n*
Okano *et al.*[55]	2003	EMR	504	5.3% (25)	–	–	–	–	–
Oda *et al.*[56]	2005	ESD	1033	5.7% (59)	3.4% (35)	–	–	–	–
Minami *et al.*[57]	2006	EMR	566	–	5.3% (30)	–	–	–	–
		ESD	1894	–	4.8% (91)	–	–	–	–
Oda *et al.*[58]	2006	EMR	411	0.1% (1)	1.2% (5)	–	–	–	–
		ESD	303	0% (0)	3.6% (11)	–	–	–	–
Oka *et al.*[59]	2006	EMR	825	3.9% (32)	0.5 (4)	–	–	–	–
Jung *et al.*[60]	2007	ESD	552	7.6% (42)	2.7% (15)	–	–	–	–
Takenaka *et al.*[61]	2008	ESD	306	0.7% (2)	5.2% (16)	–	–	–	–
Ono *et al.*[44]	2008	ESD	314	8.3% (26)	4.5% (14)	–	–	–	–
Tsunada *et al.*[62]	2008	ESD	532	–	–	–	–	0.9% (5)	–
Takizawa *et al.*[63]	2008	ESD	1083	5.8% (63)	–	–	–	–	–
Hoteya *et al.*[64]	2009	EMR	328	5.2% (17)	1.5% (5)	–	–	–	–
		ESD	572	4.9% (28)	3.5% (20)	–	–	–	–
Isomoto *et al.*[65]	2009	ESD	589	1.7% (10)	4.2% (25)	–	–	–	–
Chung *et al.*[66]	2009	ESD	1000	15.6% (156)	1.2% (12)	–	–	–	–
Coda *et al.*[67]	2009	ESD	2011	–	–	–	–	0.7% (15)	–
Kawahara *et al.*[68]	2009	ESD	–	–	–	–	–	–	2
Hotta *et al.*[69]	2010	ESD	703	0.3% (2)	4.1% (29)	–	–	–	–
Mannen *et al.*[70]	2010	ESD	478	8.9% (39)	3.9% (17)	–	–	–	–
Goto *et al.*[71]	2010	ESD	454	5.7% (26)	–	–	–	–	–
Tsuji *et al.*[72]	2010	ESD	398	5.8% (23)	–	–	–	–	–
Jeon *et al.*[73]	2010	ESD	1711	–	2.3% (39)	–	–	–	–
Hanaoka *et al.*[74]	2010	ESD	1329	–	–	0.5% (6)	–	–	–
Isomoto *et al.*[75]	2010	ESD	713	–	–	–	0.8% (6)	–	–
Iizuka *et al.*[76]	2010	ESD	308	–	–	–	–	1.9% (6)	–
Ahn *et al.*[77]	2011	EMR	537	5.2% (28)	0.7% (4)	–	–	–	–
		ESD	833	5.3% (44)	1.7% (14)	–	–	–	–
Akasaka *et al.*[78]	2011	ESD	1188	3.1% (37)	4.1% (49)	–	1.6% (19)	–	–
Toyokawa *et al.*[79]	2012	ESD	1123	5.0% (56)	2.4% (27)	–	–	–	–
Lee *et al.*[80]	2011	ESD	806	4.2% (34)	3.5% (28)	–	–	–	–
Higashiyama *et al.*[81]	2011	ESD	924	3.0% (28)	–	–	–	–	–
Okada *et al.*[82]	2011	ESD	647	4.3% (28)	–	–	–	–	–
Sugimoto *et al.*[83]	2012	ESD	485	3.7% (18)	3.9% (19)	–	–	–	–
Goto *et al.*[84]	2012	ESD	1814	5.5% (100)	–	–	–	–	–

The above data were taken from English language reports of studies of more than 300 gastric cancers that listed complication rates as well as clarified the endoscopic resection method (ESD or EMR), with the exception of cases of air embolism, which were taken from Japanese case reports. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

treatment is selected for further management, careful follow up with twice yearly esophagogastroduodenoscopy is desirable (evidence level VI, grade of recommendation C1).

Helicobacter pylori eradication

A randomized controlled trial of *Helicobacter pylori* eradication found that eradication therapy reduced the annual incidence of metachronous gastric cancer from 2–3% to approximately 1%.[99] In contrast, cohort and retrospective studies have found that *Helicobacter pylori* eradication did not affect the development of metachronous gastric cancer.[100–102] ***Eradication therapy is recommended in* Helicobacter pylori*-positive patients (evidence level II, grade of recommendation B), although the possibility of the development of metachronous gastric cancer should still be considered following successful eradication (evidence level IVa, grade of recommendation B).***

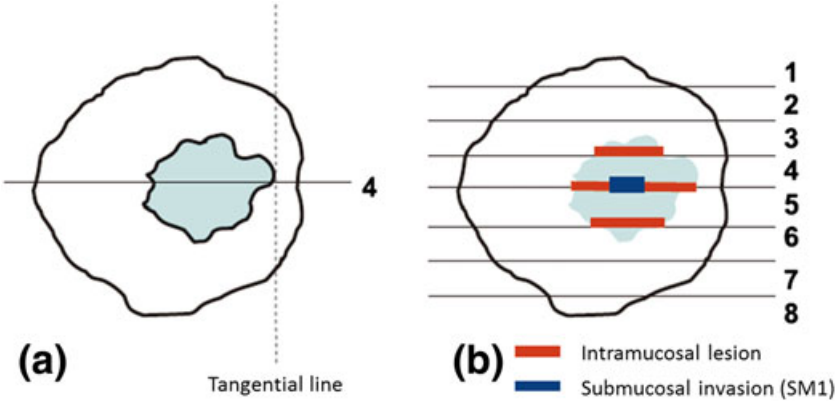

Figure 4 Processing of a fixed specimen and reconstruction of tumor spread (actual case). (a) Imagine a line tangential to the margin of the lesion where it is closest to the horizontal margin (lateral edge) of the specimen, and make the first incision perpendicular to this tangential line (section 4). Then, make further incisions parallel to the first at intervals of 2.0–3.0 mm. (b) With a macroscopic photograph of the fixed specimen with the incisions made, we can reconstruct the extent of intramucosal spread and depth of invasion by the tumor.

Histology

Processing of resected specimens

We obtain a histopathological diagnosis through processing of the resected specimen. This processing includes stretching of the fresh specimen, fixation in formalin, sectioning of the fixed specimen, and macroscopic photography before and after sectioning.

The fresh specimen is stretched upon a plate, and immediately fixed through immersion in 10% formalin solution. As a general rule, the immersion time should be 24–48 h at room temperature.

The first incision is made to allow histopathological examination of the part of the lesion with the minimum distance between the margin of the lesion and the lateral edge of the specimen. Then, further incisions are made parallel to the first at intervals of 2.0–3.0 mm (evidence level VI, grade of recommendation C1) (Fig. 4).

As shown in Figure 4a, imagine a line tangential to the margin of the lesion where it is closest to the horizontal margin of the specimen (mucosal dissection margin), and make the first incision perpendicular to this tangential line.[103–109]

For reconstructing the extent of intramucosal spread and depth of invasion by the tumor, it is desirable to take macroscopic photographs of the fixed specimen with the incisions made (evidence level VI, grade of recommendation C1).[103–109]

Recording of histopathological findings

Tumor histopathological types are classified in accordance with the Japanese classification of gastric carcinoma: 3rd English edition.[110] Well- or moderately differentiated tubular and papillary adenocarcinomas are classified as differentiated cancers, whereas signet-ring cell carcinomas and poorly differentiated adenocarcinomas are classified as undifferentiated cancers. Furthermore, ***when multiple histopathological types coexist, each histopathological type should be recorded, in descending order of relative surface area within the lesion (e.g. tub1 > pap > por) (evidence level VI, grade of recommendation C1).***

The depth of invasion is recorded as the deepest layer that the cancer has infiltrated. Furthermore, for cancers invading the submucosa, we measure the distance (in μm) from the lower margin of the muscularis mucosa to the deepest part of the invading cancer. If this measurement depth is <500 μm, we assess and record it as SM1 (or T1b1), and if it is ≥500 μm, it is classified as SM2 (or T1b2).

The above-mentioned vertical infiltration distance is measured using a microscope with an eyepiece micrometer. If the muscularis mucosa cannot be identified because of ulceration or an ulcer scar within the lesion, we draw an imaginary line continuous with the intact muscularis mucosa in the adjacent mucosa, from which we measure the vertical depth of invasion.[108] Immunohistochemical staining with anti-desmin antibodies is also useful in identifying the muscularis mucosa.

Determination of whether ulceration or an ulcer scar is present within the lesion is necessary when evaluating whether a resection has been curative. Intralesional ulceration is defined as 'histopathological appearance resembling a benign gastric ulcer or scar, with scanty or no cancerous tissue at the ulcer base'. This does not include shallow and narrow biopsy ulcers.[111,112]

Assessment of vascular infiltration should be carried out using specific staining (evidence level VI, grade of recommendation C1).

Immunohistochemical staining with elastic fiber stains (Elastica van Gieson or Victoria blue-hematoxylin and eosin) is useful for identifying veins, and anti-lymphatic endothelial antibodies (D2-40) for lymphatic vessels.[113]

CONFLICTS OF INTEREST

WE ASKED THE members of the Guidelines Working Committee, Evaluation Committee, and Review Committee to declare any possible conflicts of interest as follows.

1. Any companies or organizations (in alphabetical order) from which the committee member, or any dependents living with them, received any form of payment in connection with these Gastric Cancer ESD and EMR Guidelines.

The disclosure criteria were as follows: directorship or consultancy (≥¥1M), shares (≥¥1M), patent royalties (≥¥1M), speaking fees (≥¥1M), manuscript fees (≥¥1M), research expenses (≥¥2M in an individual's name), or other payments (≥¥1M). Eisai Co., Ltd

2. Any companies or organizations engaged in physician-industry cooperation with a committee member's affiliated department (excluding clinical trials), in connection with these Gastric Cancer ESD and EMR Guidelines.

The disclosure criteria were as follows: financial endowment (≥¥2M), collaborative research or trust fund (≥¥2M), transfer of license agreement or rights (≥¥2M), or scholarship endowment (≥¥2M).

Bristol Myers Squibb Co.; Chugai Pharmaceutical Co., Ltd; FY 2013 Ministry of Health, Labour and Welfare Cancer Research Grant; Janssen Pharmaceutical K.K.; Ministry of Health, Labour and Welfare Grants-in-Aid for Scientific Research; MSD K.K.; Shinnihonseiyaku Co., Ltd.; Toray Medical Co. Ltd.

FUNDING

ALL FUNDING FOR the production of these Guidelines was provided by the Japan Gastroenterological Endoscopy Society.

REFERENCES

1 Ono H, Seewald S, Soehendra N. *Endoscopic resection, ablation, and dissection*. In: Classen M, Tytgat GNJ, Lightdale CJ (eds). Gastroenterological Endoscopy, 2nd edn. Stuttgart-New York: Thieme, 2010; pp. 331–41.
2 Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; **10**: 1–11.
3 Postgraduate Education Committee of the Japan Gastroenterological Endoscopy Society (eds). *Guidelines for Gastroenterological Endoscopy*, 3rd edn. Tokyo, Japan: Igaku Shoin Ltd, 2006 (in Japanese).
4 Fujimoto K, Fujishiro M, Kato M *et al.* Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig. Endosc.* 2014; **26**: 1–14.
5 Fukui T, Yoshida M, Yamaguchi N. In: Shoin I (ed.). *Minds: A Guide to the Production of Therapeutic Guidelines 2007, procedure of guidelines making*. Tokyo, Igaku Shoin, 2007. (in Japanese).
6 Committee to Advise the Public Health Service on Clinical Practice Guidelines; Institute of Medicine. Field MJ, Lohr KN (eds). *Clinical Practice Guidelines: Directions for a New Program*. Washington, DC: National Academy Press, 1990.
7 Japanese Gastric Cancer Association. *Japanese Gastric Cancer Treatment Guidelines 2010 (ver. 3)*, vol. **14**. Gastric Cancer, 2011; 113–23.
8 Tsukuma H, Oshima A, Narahara H, Morii T. Natural history of early gastric cancer: A nonconcurrent, long term, follow up study. *Gut* 2000; **47**: 618–21.
9 Matsui T, Nagahama T, Chounan A *et al*. Growth rates of early gastric cancers – a retrospective nationwide survey. *Stom. Intest.* 2008; **43**: 1798–809. (in Japanese).
10 Ono H, Kondo H, Gotoda T *et al*. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225–9.
11 Ono H, Yoshida S. Determination of the depth of invasion of gastric cancers: Determining the depth of invasion from the endoscopic appearance. *Stom. Intest.* 2001; **36**: 334–40 (in Japanese).
12 Honmyo U, Misumi A, Murakami A *et al*. Mechanisms producing color change in flat early gastric cancers. *Endoscopy* 1997; **29**: 366–71.
13 Yao K, Yao T, Matsui T, Iwashita A, Oishi T. Hemoglobin content in intramucosal gastric carcinoma as a marker of histologic differentiation: A clinical application of quantitative electronic endoscopy. *Gastrointest. Endosc.* 2000; **52**: 241–5.
14 Yao K, Oishi T, Matsui T, Yao T, Iwashita A. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. *Gastrointest. Endosc.* 2002; **56**: 279–84.
15 Otsuka Y, Niwa Y, Ohmiya N *et al*. Usefulness of magnifying endoscopy in the diagnosis of early gastric cancer. *Endoscopy* 2004; **36**: 165–9.
16 Nakayoshi T, Tajiri H, Matsuda K, Kaise M, Ikegami M, Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: Correlation of vascular pattern with histopathology. *Endoscopy* 2004; **36**: 1080–4.
17 Yokoyama A, Inoue H, Minami H *et al*. Novel narrow-band imaging magnifying endoscopic classification for early gastric cancer. *Dig. Liver Dis.* 2010; **42**: 704–8.
18 Okabe H, Ohida M, Okada N *et al*. A new disk method for the endoscopic determination of gastric ulcer area. *Gastrointest. Endosc.* 1986; **32**: 20–4.
19 Vakil N, Smith W, Bourgeois K, Everbach EC, Knyrim K. Endoscopic measurement of lesion size: Improved accuracy with image processing. *Gastrointest. Endosc.* 1994; **40**: 178–83.
20 Yao K, Matsui T, Furukawa H, Yao T, Sakurai T, Mitsuyasu T. A new stereoscopic endoscopy system: Accurate 3-dimensional measurement in vitro and in vivo with distortion-correction function. *Gastrointest. Endosc.* 2002; **55**: 412–20.
21 Sano T, Okuyama Y, Kobori O, Shimizu T, Morioka Y. Early gastric cancer. Endoscopic diagnosis of depth of invasion. *Dig. Dis. Sci.* 1990; **35**: 1340–4.

22 Yao T, Tanabe H, Nagahama T *et al*. Findings of depressed SM gastric cancers in comparison to the histological findings. *Stom. Intest.* 2008; **43**: 1109–25. (in Japanese).
23 Choi J, Kim SG, Im JP, Kim JS, Jung HC, Song IS. Endoscopic prediction of tumor invasion depth in early gastric cancer. *Gastrointest. Endosc.* 2011; **73**: 917–27.
24 Abe S, Oda I, Shimazu T *et al*. Depth-predicting score for differentiated early gastric cancer. *Gastric Cancer* 2011; **14**: 35–40.
25 Yanai H, Tada M, Karita M, Okita K. Diagnostic utility of 20-megahertz linear endoscopic ultrasonography in early gastric cancer. *Gastrointest. Endosc.* 1996; **44**: 29–33.
26 Yanai H, Noguchi T, Mizumachi S *et al*. A blind comparison of the effectiveness of endoscopic ultrasonography and endoscopy in staging early gastric cancer. *Gut* 1999; **44**: 361–5.
27 Yoshida S, Tanaka S, Kunihiro K *et al*. Diagnostic ability of high-frequency ultrasound probe sonography in staging early gastric cancer, especially for submucosal invasion. *Abdom. Imaging* 2005; **30**: 518–23.
28 Ichikawa T, Kudo M, Matsui S, Okada M, Kitano M. Endoscopic ultrasonography with three miniature probes of different frequency is an accurate diagnostic tool for endoscopic submucosal dissection. *Hepatogastroenterology* 2007; **54**: 325–8.
29 Akashi K, Yanai H, Nishikawa J *et al*. Ulcerous change decreases the accuracy of endoscopic ultrasonography diagnosis for the invasive depth of early gastric cancer. *Int. J. Gastrointest. Cancer* 2006; **37**: 133–8.
30 Kim GH, Park do Y, Kida M *et al*. Accuracy of high-frequency catheter-based endoscopic ultrasonography according to the indications for endoscopic treatment of early gastric cancer. *J. Gastroenterol. Hepatol.* 2010; **25**: 506–11.
31 Choi J, Kim SG, Im JP, Kim JS, Jung HC, Song IS. Is endoscopic ultrasonography indispensable in patients with early gastric cancer prior to endoscopic resection? *Surg. Endosc.* 2010; **24**: 3177–85.
32 Okada K, Fujisaki J, Kasuga A *et al*. Endoscopic ultrasonography is valuable for identifying early gastric cancers meeting expanded-indication criteria for endoscopic submucosal dissection. *Surg. Endosc.* 2011; **25**: 841–8.
33 Yoshinaga S, Gotoda T, Oda I *et al*. 5. Diagnostic imaging of early gastric cancer 3) Detailed examination for margin delineation (2) Conventional endoscopy. *Stom. Intest.* 2009; **44**: 650–62. (in Japanese).
34 Nagahama T, Yao K, Maki S *et al*. Usefulness of magnifying endoscopy with narrow-band imaging for determining the horizontal extent of early gastric cancer when there is an unclear margin by chromoendoscopy (with video). *Gastrointest. Endosc.* 2011; **74**: 1259–67.
35 Inoue H. Endoscopic mucosal resection using a cap-fitted endoscope (EMRC) in the treatment of early esophageal and gastric cancers. *Endoscopia Digestiva* 1992; **4**: 1801–5. (in Japanese).
36 Masuda K, Fujisaki J, Suzuki H *et al*. Endoscopic mucosal resection using a ligating device (EMRL). *Endoscopia Digestiva* 1993; **5**: 1215–19.
37 Tada M, Murata M, Murakami F. Development of strip-off biopsy. *Gastroenterol. Endosc.* 1984; **26**: 833–9 (in Japanese).
38 Hirao M, Masuda K, Asanuma T *et al*. Endoscopic resection of early gastric cancer and other tumors with local injection of hypertonic saline-epinephrine. *Gastrointest. Endosc.* 1988; **34**: 264–9.
39 Yamamoto H, Kawata H, Sunada K *et al*. Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small caliber-tip transparent hood. *Endoscopy* 2003; **35**: 690–4.
40 Oyama T, Kikuchi Y. Aggressive endoscopic mucosal resection in the upper GI tract–hook knife EMR method. *Minim. Invasive Ther. Allied Technol.* 2002; **11**: 291–5.
41 Yahagi N, Uraoka T, Ida Y *et al*. Endoscopic submucosal dissection using the flex and the dual knife. *Tech. Gastrointest. Endosc.* 2011; **13**: 74–8.
42 Inoue H, Sato Y, Kazawa T *et al*. Resection and dissection using a triangle tipped knife. *Stom. Intest.* 2004; **39**: 53–6. (in Japanese).
43 Fujishiro M, Yahagi N, Kashimura K *et al*. Comparison of various submucosal injection solutions for maintaining mucosal elevation during endoscopic mucosal resection. *Endoscopy* 2004; **36**: 579–83.
44 Ono H, Hasuike N, Inui T *et al*. Usefulness of a novel electrosurgical knife, the insulation-tipped diathermic knife-2, for endoscopic submucosal dissection of early gastric cancer. *Gastric Cancer* 2008; **11**: 47–52.
45 Akahoshi K, Honda K, Motomura Y *et al*. Endoscopic submucosal dissection using a grasping-type scissors forceps for early gastric cancers and adenomas. *Dig. Endosc.* 2011; **23**: 24–9.
46 Kakushima N, Fujishiro M. Endoscopic submucosal dissection for gastrointestinal neoplasms. *World J. Gastroenterol.* 2008; **14**: 2962–7.
47 Park YM, Cho E, Kang HY *et al*. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. *Surg. Endosc.* 2011; **25**: 2666–77.
48 Nakamoto S, Sakai Y, Kasanuki J *et al*. Indications for the use of endoscopic mucosal resection for early gastric cancer in Japan: A comparative study with endoscopic submucosal dissection. *Endoscopy* 2009; **41**: 746–50.
49 Shimura T, Sasaki M, Kataoka H *et al*. Advantages of endoscopic submucosal dissection over conventional endoscopic mucosal resection. *J. Gastroenterol. Hepatol.* 2007; **22**: 821–6.
50 Watanabe K, Ogata S, Kawazoe S *et al*. Clinical outcomes of EMR for gastric tumors: Historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. *Gastrointest. Endosc.* 2006; **63**: 776–82.
51 Fukami N (ed.). *Endoscopic Submucosal Dissection: Principles and Practice*. New York: Springer, 2015.
52 Gotoda T, Yanagisawa A, Sasako M *et al*. Incidence of lymph node metastasis from early gastric cancer: Estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219–25.
53 Hirasawa T, Gotoda T, Miyata S *et al*. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer* 2009; **12**: 148–52.
54 Takizawa K, Kawata N, Tanaka M *et al*. Clinicopathological characteristics of mixed histological type intramucosal gastric

cancers with different patterns. *Stom. Intest.* 2013; **48**: 1567–79. (in Japanese).
55 Okano A, Hajiro K, Takakuwa H, Nishio A, Matsushita M. Predictors of bleeding after endoscopic mucosal resection of gastric tumors. *Gastrointest. Endosc.* 2003; **57**: 687–90.
56 Oda I, Gotoda T, Hamanaka H *et al*. Endoscopic submucosal dissection for early gastric cancer: Technical feasibility, operation time and complications from a large consecutive series. *Dig. Endosc.* 2005; **17**: 54–8.
57 Minami S, Gotoda T, Ono H, Oda I, Hamanaka H. Complete endoscopic closure of gastric perforation induced by endoscopic resection of early gastric cancer using endoclips can prevent surgery. *Gastrointest. Endosc.* 2006; **63**: 596–601.
58 Oda I, Saito D, Tada M *et al*. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262–70.
59 Oka S, Tanaka S, Kaneko I *et al*. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest. Endosc.* 2006; **64**: 877–83.
60 Jung HY, Choi KD, Song HJ, Lee GH, Kim JH. Risk management in endoscopic submucosal dissection using needle knife in Korea. *Dig. Endosc.* 2007; **19** (Suppl 1): S5–8.
61 Takenaka R, Kawahara Y, Okada H *et al*. Risk factors associated with local recurrence of early gastric cancers after endoscopic submucosal dissection. *Gastrointest. Endosc.* 2008; **68**: 887–94.
62 Tsunada S, Ogata S, Mannen K *et al*. Case series of endoscopic balloon dilation to treat a stricture caused by circumferential resection of the gastric antrum by endoscopic submucosal dissection. *Gastrointest. Endosc.* 2008; **67**: 979–83.
63 Takizawa K, Oda I, Gotoda T *et al*. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection – an analysis of risk factors. *Endoscopy* 2008; **40**: 179–83.
64 Hoteya S, Iizuka T, Kikuchi D, Yahagi N. Benefits of endoscopic submucosal dissection according to size and location of gastric neoplasm, compared with conventional mucosal resection. *J.?Gastroenterol. Hepatol.* 2009; **24**: 1102–6.
65 Isomoto H, Shikuwa S, Yamaguchi N *et al*. Endoscopic submucosal dissection for early gastric cancer: A large-scale feasibility study. *Gut* 2009; **58**: 331–6.
66 Chung IK, Lee JH, Lee SH *et al*. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. *Gastrointest. Endosc.* 2009; **69**: 1228–35.
67 Coda S, Oda I, Gotoda T, Yokoi C, Kikuchi T, Ono H. Risk factors for cardiac and pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment. *Endoscopy* 2009; **41**: 421–6.
68 Kawahara Y, Okada H, Yamamoto K. Prevention and management of ESD complications: Two cases of air embolism during ESD procedures. *Gastroenterol. Endosc.* 2009; **51** (Suppl 2): 2086 (in Japanese).
69 Hotta K, Oyama T, Akamatsu T *et al*. A comparison of outcomes of endoscopic submucosal dissection (ESD) for early gastric neoplasms between high-volume and low-volume centers: Multi-center retrospective questionnaire study conducted by the Nagano ESD Study Group. *Intern. Med.* 2010; **49**: 253–9.
70 Mannen K, Tsunada S, Hara M *et al*. Risk factors for complications of endoscopic submucosal dissection in gastric tumors: Analysis of 478 lesions. *J.?Gastroenterol.* 2010; **45**: 30–6.
71 Goto O, Fujishiro M, Kodashima S *et al*. A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: A retrospective analysis of postendoscopic submucosal dissection bleeding. *Gastrointest. Endosc.* 2010; **71**: 241–8.
72 Tsuji Y, Ohata K, Ito T *et al*. Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. *World J. Gastroenterol.* 2010; **16**: 2913–17.
73 Jeon SW, Jung MK, Kim SK *et al*. Clinical outcomes for perforations during endoscopic submucosal dissection in patients with gastric lesions. *Surg. Endosc.* 2010; **24**: 911–16.
74 Hanaoka N, Uedo N, Ishihara R *et al*. Clinical features and outcomes of delayed perforation after endoscopic submucosal dissection for early gastric cancer. *Endoscopy* 2010; **42**: 1112–15.
75 Isomoto H, Ohnita K, Yamaguchi N *et al*. Clinical outcomes of endoscopic submucosal dissection in elderly patients with early gastric cancer. *Eur. J. Gastroenterol. Hepatol.* 2010; **22**: 311–17.
76 Iizuka H, Kakizaki S, Sohara N *et al*. Stricture after endoscopic submucosal dissection for early gastric cancers and adenomas. *Dig. Endosc.* 2010; **22**: 282–8.
77 Ahn JY, Jung HY, Choi KD *et al*. Endoscopic and oncologic outcomes after endoscopic resection for early gastric cancer: 1370 cases of absolute and extended indications. *Gastrointest. Endosc.* 2011; **74**: 485–93.
78 Akasaka T, Nishida T, Tsutsui S *et al*. Short-term outcomes of endoscopic submucosal dissection (ESD) for early gastric neoplasm: multicenter survey by Osaka University ESD study group. *Dig. Endosc.* 2011; **23**: 73–7.
79 Toyokawa T, Inaba T, Omote S *et al*. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for early gastric neoplasms; analysis of 1123 lesions. *J.?Gastroenterol. Hepatol.* 2012; **27**: 907–12.
80 Lee H, Yun WK, Min BH *et al*. A feasibility study on the expanded indication for endoscopic submucosal dissection of early gastric cancer. *Surg. Endosc.* 2011; **25**: 1985–93.
81 Higashiyama M, Oka S, Tanaka S *et al*. Risk factors for bleeding after endoscopic submucosal dissection of gastric epithelial neoplasm. *Dig. Endosc.* 2011; **23**: 290–5.
82 Okada K, Yamamoto Y, Kasuga A *et al*. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg. Endosc.* 2011; **25**: 98–107.
83 Sugimoto T, Okamoto M, Mitsuno Y *et al*. Endoscopic submucosal dissection is an effective and safe therapy for early gastric neoplasms: A multicenter feasible study. *J.?Clin. Gastroenterol.* 2012; **46**: 124–9.
84 Goto O, Fujishiro M, Oda I *et al*. A multicenter survey of the management after gastric endoscopic submucosal dissection related to postoperative bleeding. *Dig. Dis. Sci.* 2012; **57**: 435–9.
85 Muraki Y, Enomoto S, Iguchi M, Fujishiro M, Yahagi N, Ichinose M. Management of bleeding and artificial gastric

ulcers associated with endoscopic submucosal dissection. *World J. Gastrointest. Endosc.* 2012; **4**: 1–8.
86 Kakushima N, Yahagi N, Fujishiro M *et al*. The healing process of gastric artificial ulcers after endoscopic submucosal dissection. *Dig. Endosc.* 2004; **16**: 327–31.
87 Lee SY, Kim JJ, Lee JH *et al*. Healing rate of EMR-induced ulcer in relation to the duration of treatment with omeprazole. *Gastrointest. Endosc.* 2004; **60**: 213–17.
88 Niimi K, Fujishiro M, Goto O *et al*. Prospective single-arm trial of 2-week rabeprazole treatment for ulcer healing after gastric endoscopic submucosal dissection. *Dig. Endosc.* 2012; **24**: 110–16.
89 Yamaguchi Y, Katsumi N, Tauchi M *et al*. A prospective randomized trial of either famotidine or omeprazole for the prevention of bleeding after endoscopic mucosal resection and the healing of endoscopic mucosal resection-induced ulceration. *Aliment. Pharmacol. Ther.* 2005; **21**(Suppl 2): 111–15.
90 Uedo N, Takeuchi Y, Yamada T *et al*. Effect of a proton pump inhibitor or an H2-receptor antagonist on prevention of bleeding from ulcer after endoscopic submucosal dissection of early gastric cancer: A prospective randomized controlled trial. *Am. J. Gastroenterol.* 2007; **102**: 1610–16.
91 Asakuma Y, Kudo M, Matsui S *et al*. Comparison of an ecabet sodium and proton pump inhibitor (PPI) combination therapy with PPI alone in the treatment of endoscopic submucosal dissection (ESD)-induced ulcers in early gastric cancer: Prospective randomized study. *Hepatogastroenterology* 2009; **56**: 1270–3.
92 Kato T, Araki H, Onogi F *et al*. Clinical trial: Rebamipide promotes gastric ulcer healing by proton pump inhibitor after endoscopic submucosal dissection – a randomized controlled study. *J. Gastroenterol.* 2010; **45**: 285–90.
93 Fujiwara S, Morita Y, Toyonaga T *et al*. A randomized controlled trial of rebamipide plus rabeprazole for the healing of artificial ulcers after endoscopic submucosal dissection. *J. Gastroenterol.* 2011; **46**: 595–602.
94 Imagawa A, Okada H, Kawahara Y *et al*. Endoscopic submucosal dissection for early gastric cancer: Results and degrees of technical difficulty as well as success. *Endoscopy* 2006; **38**: 987–90.
95 Nasu J, Doi T, Endo H, Nishina T, Hirasaki S, Hyodo I. Characteristics of metachronous multiple early gastric cancers after endoscopic mucosal resection. *Endoscopy* 2005; **37**: 990–3.
96 Nakajima T, Oda I, Gotoda T *et al*. Metachronous gastric cancers after endoscopic resection: How effective is annual endoscopic surveillance? *Gastric Cancer* 2006; **9**: 93–8.
97 Tanabe S, Koizumi W, Mitomi H *et al*. Clinical outcome of endoscopic aspiration mucosectomy for early stage gastric cancer. *Gastrointest. Endosc.* 2002; **56**: 708–13.
98 Eguchi T, Gotoda T, Oda I, Hamanaka H, Hasuike N, Saito D. Is endoscopic one-piece mucosal resection essential for early gastric cancer? *Dig. Endosc.* 2003; **15**: 113–16.
99 Fukase K, Kato M, Kikuchi S *et al*. Japan GAST Study Group. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: An open-label, randomised controlled trial. *Lancet* 2008; **372**: 392–7.
100 Yanaoka K, Oka M, Ohata H *et al*. Eradication of *Helicobacter pylori* prevents cancer development in subjects with mild gastric atrophy identified by serum pepsinogen levels. *Int. J. Cancer* 2009; **125**: 2697–703.
101 Maehata Y, Nakamura S, Fujisawa K *et al*. Long-term effect of *Helicobacter pylori* eradication on the development of metachronous gastric cancer after endoscopic resection of early gastric cancer. *Gastrointest. Endosc.* 2012; **75**: 39–46.
102 Kato M, Nishida T, Yamamoto K *et al*. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: A multicentre retrospective cohort study by Osaka University ESD study group. *Gut* 2013; **62**: 1425–32.
103 Tanaka M, Ashida K, Umegaki E *et al*. Endoscopic resection of early gastric cancers, aiming for cure. *Stom. Intest.* 1993; **28**: 87–98. (in Japanese).
104 Oshiba S, Ashida K, Tanaka M *et al*. Cases of early gastric cancer that underwent open surgical resection following endoscopic mucosal resection. Report by the Endoscopic Therapy Committee of the Gastric Cancer Research Group. *Stom. Intest.* 1994; **29**: 1162–70. (in Japanese).
105 Umegaki E. Stereoscopic microscopic examination of specimens resected from the gastrointestinal tract. *Gastroenterol. Endosc.* 2006; **48**: 70–8. (in Japanese).
106 Takizawa T, Iwasaki Y, Kato H *et al*. Evaluation of endoscopic resection of early gastric cancer. From the histological viewpoint. *Stom. Intest.* 1991; **26**: 389–96. (in Japanese).
107 Koike M, Takizawa T, Fukayama M *et al*. Processing and histological examination of resected specimens of early gastric cancer. *Stom. Intest.* 1993; **28**: 127–38. (in Japanese).
108 Watanabe G, Nishikura K, Kobayashi M *et al*. Processing of resected specimens of early gastric cancer. *Stom. Intest.* 2006; **41**: 451–7. (in Japanese).
109 Nakano K, Yanagisawa A, Kubo K *et al*. Present problems concerning expansion of the indications for endoscopic mucosal resection of early gastric cancer. *Stom. Intest.* 1996; **31**: 1067–72. (in Japanese).
110 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101–12.
111 Nishimaki M, Watanabe H, Muto T. Histopathological analysis of a gastric cancer with peptic ulceration within the lesion. *Jpn. J. Gastroenterol.* 1985; **82**: 2544–53. (in Japanese).
112 Shimoda T, Kushima R, Ono H. Differentiation between peptic ulceration and biopsy scarring in ESD specimens. *Stom. Intest.* 2013; **48**: 16–24. (in Japanese).
113 Tsutsumi Y, Onoda N, Osamura Y. Victoria Blue-Hematoxylin and Eosin staining: A useful routine stain for demonstration of venous invasion by cancer cells. *J. Histotechnol.* 1990; **13**: 271–4.
114 Ono H, Yao K, Fujishiro M *et al*. Guidelines for ESD and EMR for early gastric cancer. *Gastroenterol. Endosc.* 2014; **56**: 310–23. (in Japanese).