Guideline

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

Hiroyuki Ono,1,2 Kenshi Yao,1,2 Mitsuhiro Fujishiro1,2 Ichiro Oda,1,2 Satoshi Nimura,2 Naohisa Yahagi,1,2 Hiroyasu Iishi,1,2 Masashi Oka,1,2 Yoichi Ajioka,2 and Masao Ichinose1

1Japan Gastroenterological Endoscopy Society, Tokyo, and 2Japanese 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.

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.

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).

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in 2014, 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. 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.

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

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**Table 1** Classification of evidence levels

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

**Table 2** Minds’ grades of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong scientific evidence exists, strongly recommended to do</td>
</tr>
<tr>
<td>B</td>
<td>Scientific evidence exists, recommended to do</td>
</tr>
<tr>
<td>C1</td>
<td>No scientific evidence, but recommended to do</td>
</tr>
<tr>
<td>C2</td>
<td>No scientific evidence, recommended not to do</td>
</tr>
<tr>
<td>D</td>
<td>Scientific evidence that it is ineffective or harmful, recommended not to do</td>
</tr>
</tbody>
</table>
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).

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.

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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%). 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.

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.

However, as shown by observational studies that aimed to elucidate the natural history of EGC, 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.

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 (b, 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). 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. 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.\textsuperscript{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,\textsuperscript{21–23} with additional indigo carmine dye spraying being recommended.\textsuperscript{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.\textsuperscript{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.\textsuperscript{33,34}

Margin delineation can be difficult in undifferentiated EGC as well as in certain differentiated lesions.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{47} It has also been reported that for tumor sizes >1 cm, en bloc resection rates are significantly lower for EMR than for ESD.\textsuperscript{48–50}

Physicians should refer to textbooks\textsuperscript{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.”\textsuperscript{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, is $<2$ 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 \( \geq 2 \) 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(+) or predominantly differentiated, even if undifferentiated components are present, as the risk of metastasis is considered to be less than 1%24 (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% (278) 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 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). 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
should be applied to remnant vessels on the post-resection ulcer surface (evidence level V, grade of recommendation C). 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 C).

Management of perforation
When perforation occurs during ESD or EMR, endoscopic clip closure should first be attempted (evidence level V, grade of recommendation C). 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), 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, and the cumulative 3-year risk is approximately 5.9%. Even when histopathological examination indicates curative resection, follow up with endoscopic examination is desirable, with the main aim of detecting metachronous gastric cancers (evidence level VI, grade of recommendation C). The JGCA Japanese Gastric Cancer Treatment Guidelines 2010 ver. 3 (for medical practitioners) recommends follow-up endoscopic examination once or twice per year following curative resection; 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.

Local recurrence has been reported in cases of positive horizontal margins or piecemeal resection. When histopathological examination indicates expanded indication curative resection, follow up with endoscopic examination is desirable at intervals of 6-12 months (evidence level VI, grade of recommendation C).

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

### Table 4 Reported complications

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

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.
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 (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.

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 \( \mu m \)) from the lower margin of the muscularis mucosa to the deepest part of the invading cancer. If this measurement depth is <500 \( \mu m \), we assess and record it as SM1 (or T1b1), and if it is \( \geq 500 \mu m \), 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 antibodies to desmin 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).


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