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Guidelines

Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition)

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In response to the rapid and wide acceptance and use of endoscopic treatments for early gastric cancer, the Japan Gastroenterological Endoscopy Society, in collaboration with the Japanese Gastric Cancer Association, produced "Guidelines for Endoscopic Submucosal Dissection and Endoscopic Mucosal Resection for Early Gastric Cancer" in 2014, as a set of basic guidelines in accordance with the principles of evidence-based medicine. At the time, a number of statements had to be established by consensus (the lowest evidence level), as evidence levels remained low for many specific areas in this field. However, in recent years, the number of well-designed clinical studies has been increasing. Based on new findings, we have issued the revised second edition of the above guidelines that cover the present state of knowledge. These guidelines are divided into the following seven categories: indications, preoperative diagnosis, techniques, evaluation of curability, complications, long-term postoperative surveillance, and histology.

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

INTRODUCTION

JAPAN HAS PLAYED a central role in the development and advancement of endoscopic treatments for early gastric cancer (EGC). In particular, endoscopic submucosal dissection (ESD), a technique developed in Japan in the 1990s, has been applied widely to the treatment of EGC, for which surgical resection was the standard treatment. The use of this procedure has rapidly expanded from Japan to China, South Korea, and other Asian countries, and is now being adopted in a number of Western countries. Under these circumstances, the Japan Gastroenterological Endoscopy Society (JGES) issued the Guidelines for ESD and Endoscopic Mucosal Resection (EMR) for EGC in 2014.[1] It is estimated that endoscopic treatments account for more than 60% of all treatments for EGC in Japan,[2] and therefore, the importance of the guidelines continues to increase. In this context, we set about to prepare the Guidelines for ESD and Endoscopic Mucosal Resection for EGC (2nd edition), 5 years after the publication of the first edition.

Clinical practice guidelines are defined as statements that provide recommendations, intended to assist patients and practitioners in making decisions about optimal healthcare of high clinical importance, based on a systematic review of evidence, its integral evaluation, and assessment of the benefits and harms of healthcare options.[3] This edition of the Guidelines is a set of EBM-based guidelines developed following the Minds Handbook for Clinical Practice Guideline Development 2017 (Table 1). High-level evidence in this field was lacking, and therefore, we had to rely on consensus opinions of experts, just as we did in the development of the first edition. However, the number of high quality studies has increased in recent years, and findings from such studies are reflected in this edition of the Guidelines.

For detailed procedures, equipment, devices of endoscopic treatments, and the types and usage of drugs, readers are referred to the Gastroenterological Endoscopy Handbook (revised 2nd edition)[4] compiled by the JGES. Instead, the present Guidelines are intended to serve as a basic guidance. The Histology section, however, describes

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Table 1 Grade of recommendation and level of evidence

Grade of recommendation
1: Strongly recommended
2: Weakly recommended (proposed)
None: Definite recommendation cannot be made, or strength of recommendation cannot be determined
Level of evidence
A (High): Strong confidence in the estimation of efficacy (based on strong evidence)
B (Moderate): Moderate confidence in the estimation of efficacy (based on moderate evidence)
C (Low): Limited confidence in the estimation of efficacy (based on weak evidence)
D (Very low): Almost no confidence in the estimation of efficacy (based on very weak evidence)

specific procedures for the processing of resected specimens and measurement of lesions. Because a systematic description of how to handle specimens has not been fully described in other documents, this section of the guidelines aims to aid overseas pathologists as well as pathologists not specialized in gastrointestinal pathology. Because statements in the Histology section were mostly based on consensus opinion of experts and hardly allowed determinations based on evidence, the level of evidence was not specified for these statements. When preparing these Guidelines, we gave due consideration to compatibility with the existing Gastric Cancer Treatment Guidelines (for medical practitioners; ver. 5) issued by the Japanese Gastric Cancer Association (JGCA).[5] The Guidelines for ESD and EMR for EGC, which cover the minimum essential information required for the endoscopic treatment of EGC in everyday clinical situations, is expected to be used comprehensively.

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

Committee members

A TOTAL OF six specialists comprising five gastrointestinal endoscopists and one gastrointestinal pathologist were entrusted with the development of these Guidelines as members of the Guideline Working Committee. A further eight specialists comprising four gastrointestinal endoscopists and one gastrointestinal pathologist appointed to the Evaluation Committee, and one gastric surgeon, one clinical oncologist, and one radiologist appointed to the External Evaluation Committee evaluated the Guidelines (Table 2).

Grade of recommendation, level of evidence, short statement, and clinical question

The Working Committee established the following seven categories: Indications, Preoperative diagnosis, Techniques, Evaluation of curability, Complications, Long-term postoperative surveillance, and Histology. For each category, they drafted a short statement; for example, "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*." The grade of recommendation and level of evidence were determined for each statement (Table 1). In addition, clinical questions (CQs) were set up for key clinical issues, and commentaries were prepared.

For each short statement and CQ, a systematic literature search was carried out using PubMed and Ichushi, covering a period from inception to October 2017. Hand searches were also performed in cases of insufficient literature. The retrieved articles were evaluated to sort out those considered to be essential, and commentaries were subsequently prepared. Members of the Working Committee determined the level of evidence for each article as well as the grade of recommendation and level of evidence for each statement in their respective specialty fields, according to the Minds Handbook for Clinical Practice Guideline Development 2017.[3]

Evaluation procedure

A set of guidelines was produced in a review format based on the prepared statements and the commentaries. The final draft statements were voted on by a total of 14 members from the Working Committee and the Evaluation Committee according to a modified Delphi method. The modified Delphi method used the following criteria: a result of 1–3 votes = no consensus; 4–6 = dissatisfaction; and 7–9 = consensus. Statements receiving seven or more votes were adopted. Draft statements that received six or fewer votes and those that required reconsideration according to the committee members' comments were modified, or either the strength of recommendation or the level of evidence or both were amended through discussion. Voting was then repeated until seven votes were obtained. The final draft of the Guidelines for ESD and EMR for EGC were disclosed to JGES members to allow them to voice their opinions in the form of public comments, and these Guidelines were subsequently completed through discussion and modification based on the public comments.

Table 2 Members of the Gastric Cancer ESD and EMR Guidelines Committee

JGES Guidelines Committee	
President	Haruhiro Inoue (Digestive Disease Center, Showa University Koto Toyosu Hospital)
Director	Kazuma Fujimoto (School of Medicine, International University of Health and Welfare)
Chairperson	Kazuma Fujimoto (School of Medicine, International University of Health and Welfare)
Guidelines for ESD and EMR for EGC Working Committee	
Chairperson	Hiroyuki Ono (Endoscopy Division, Shizuoka Cancer Center)
Working Committee Chairperson	Hiroyuki Ono (Endoscopy Division, Shizuoka Cancer Center)
Working Committee Members	Kenshi Yao (Department of Endoscopy, Fukuoka University Chikushi Hospital) Mitsuhiro Fujishiro (Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine) Ichiro Oda (Endoscopy Division, National Cancer Center Hospital) Noriya Uedo (Department of Gastrointestinal Oncology, Osaka International Cancer Institute) Satoshi Nimura (Department of Pathology, Fukuoka University Chikushi Hospital)
Evaluation Committee Chairperson	Naohisa Yahagi (Keio University Hospital Tumor Center)
Evaluation Committee Members	Hiroyasu Iishi (Itami City Hospital) Masashi Oka (Department of Gastroenterology and Hepatology, Saitama Medical Center, Saitama Medical University) Kazuma Fujimoto (School of Medicine, International University of Health and Welfare) Yoichi Ajioka (Department of Clinical Pathology, Niigata University)
External Evaluation Committee Members	Takeshi Sano (Department of Gastroenterological Surgery, Cancer Institute Hospital Ariake: JGCA) Narikazu Boku (Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital: Japanese Society of Medical Oncology) Tsutomu Ishikawa (Department of Radiology, Dokkyo Medical University: Japan Radiological Society)

Authors' conflicts of interest in the context of the article

We asked the members of the Guidelines Working Committee and Evaluation Committee to declare any possible conflicts of interest as follows. With regard to companies or organizations from which each committee member independently received any remuneration, the following information was acquired: payments (≥\1M), shares (≥\1M, or ≥5%), patent royalty (≥\1M), speaking fees (≥\0.5M), manuscript fees (≥\0.5M), research expenses or grants (≥\1M), scholarship (encouragement) endowment (≥\1M), donated fund laboratory provided by a company (≥\1M), and offerings unrelated to research (≥\50,000).

Kenshi Yao (speaking fees: Olympus Corporation; scholarship endowment: Eli Lilly Japan K.K.), Mitsuhiro Fujishiro (speaking fees: Takeda Pharmaceutical Company Limited, EA Pharma Co., Ltd., Nihon Pharmaceutical Co., Ltd.; research expenses/grants: HOYA CORPORATION; scholarship endowment: EA Pharma Co., Ltd.), Ichiro Oda (research expenses/grants: Kaigen Pharma Co., Ltd., CellSeed Inc.), Masashi Oka (speaking fees: Mylan EPD G.K.), Kazuma Fujimoto (speaking fees: Tsumura & Co., EA Pharma Co., Ltd., AstraZeneca K.K., Daiichi Sankyo Co., Ltd.; scholarship endowment: AstraZeneca K.K., Daiichi Sankyo Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., EA Pharma Co., Ltd., Asahi Kasei Medical Co., Ltd.). Ichiro Oda is an Associate Editor of *Digestive Endoscopy*.

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INDICATIONS

Basic approach

Once EGC has been diagnosed, endoscopic or surgical treatment is recommended. (evidence level B, grade of recommendation 1)

No studies have so far 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% confidence interval [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.[6,7]

In general, endoscopic resection should be carried out when the likelihood of lymph node metastasis is extremely low, and when lesion size and site are amenable to resection en bloc. (evidence level B, grade of recommendation 1)

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 performed for lesions where the likelihood of cure is high.[8] 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 relative indications (Fig. 1).

Absolute indication lesions

Lesions are considered absolute indications for endoscopic therapy if they are presupposed to have a <1% risk of lymph node metastasis and long-term outcomes similar to those with surgical gastrectomy. ***Absolute indications for EMR/ESD are "clinically intramucosal (cT1a) differentiated-type carcinomas with a long diameter measuring 2 cm or less with UL0." Absolute indications for ESD are "(i) UL0 cT1a differentiated-type carcinomas with a long diameter greater than 2 cm; (ii) UL1 cT1a differentiated-type carcinomas with a long diameter measuring 3 cm or less; and (iii) UL0 cT1a undifferentiated-type carcinomas with a long diameter 2 cm or less" (evidence level B, grade of recommendation 1)***.[9–11] The lesions dealt with as expanded indications for ESD (excluding local recurrence) in the Guidelines for ESD and EMR for EGC (first edition)[1] have been integrated into absolute indications for ESD in this set of Guidelines, based on the results of multicenter prospective studies (JCOG0607 and JCOG1009/1010).[10,11]

Expanded indication lesions

As stated above, lesions categorized as expanded indications according to tumor-related factors in the Guidelines for ESD and EMR for EGC (first edition) have been integrated into absolute indications in this set of Guidelines. However, assuming that studies that aim for further expanded indications will be carried out in the future, expanded indication lesions are defined as lesions that are presumed to have a <1% risk of lymph node metastasis, which is not confirmed by a prospective confirmatory trial with 5 year survival as the primary endpoint. As ESD techniques become increasingly stable, the safety and usefulness of repeated ESD continues to increase. Therefore, only in cases of differentiated-type carcinomas, ***lesions can be regarded as expanded indications for ESD, provided that the absolute indication lesions locally recur as intramucosal cancer after initial ESD/EMR with a C-1 grade of endoscopic curability (eCura) (evidence level C, grade of recommendation 2)***.[12,13]

Relative indication lesions

Some cases of EGC, for which surgical gastrectomy is the standard treatment, may be curable by endoscopic treatment although the cure expectancy is lower. The unreliability of preoperative diagnosis is covered in detail in Preoperative diagnosis. In particular, the preoperative diagnosis accuracy rate is unsatisfactory for lesions that are diagnosed histopathologically as submucosal invasion (pT1b).[14] Thus, endoscopic treatments would be indicated for EGCs that do not meet the requirements for absolute indications or expanded indications for endoscopic treatment, in order to take into account the patient's condition where surgery cannot be recommended or establish an accurate histopathological diagnosis of the whole lesions before surgery.

PREOPERATIVE DIAGNOSIS

THE PREOPERATIVE ENDOSCOPIC diagnosis of gastric cancers required for ESD/EMR can be broadly divided into: "(i) Information to assist the determination of the indication for endoscopic treatment" and "(ii) 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 D, grade of recommendation 1)

First, the histopathological type (differentiated type vs. undifferentiated type) is usually determined by histopathological examination of a biopsy specimen. Although it has been reported that the histopathological type can be

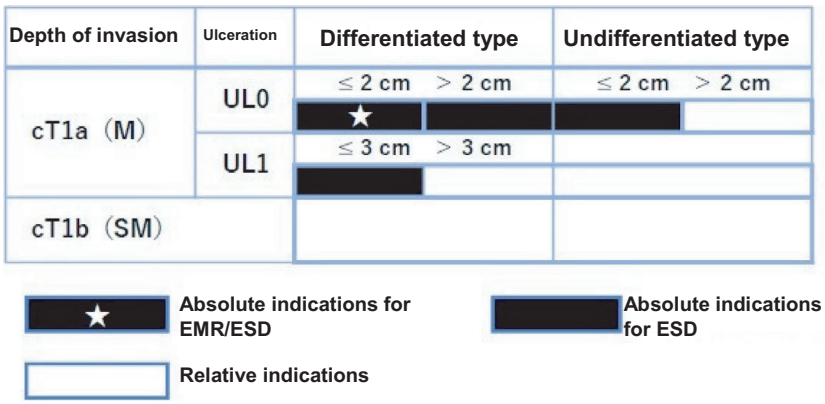

Figure 1 Classification of indications according to tumor-related factors. cT1a (M), intramucosal cancer (preoperative diagnosis), cT1b (SM), submucosally invasive cancer (preoperative diagnosis). UL, finding of ulceration (or ulcer scar); UL0, absence of ulceration or ulcer scar; UL1, presence of ulceration or ulcer scar.

endoscopically predicted to a certain extent, adequate evidence is lacking.[15–20] 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.[21–23] Accurate preoperative determination of lesion size is difficult; therefore, investigations and treatments are conducted with a view to 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 the adherent white exudate and excludes superficial erosions. Furthermore, ulcers in the healing or scarring stage, with 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,[24–27] with additional indigo carmine dye spraying being recommended.[26] When difficulties are encountered in determining the depth of invasion using conventional endoscopy alone, endoscopic ultrasonography may be useful as an additional diagnostic modality.[28–35]

Information to assist the determination of horizontal resection margins

In general, conventional endoscopy with dye spraying or equipment-based image-enhanced endoscopy using a magnifying endoscope is used to determine the horizontal resection margins. (evidence level B, grade of recommendation 1)

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 (HMs) of cancer extent. It has been reported that when this method is used to examine EGC that is possibly indicated for ESD, the extent of the HMs can be delineated in approximately 80% of lesions.[36,37]

It has been reported that, 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.[37] More recently, results of randomized controlled trials of conventional endoscopy with dye spraying vs. IEE using a magnifying endoscope have been reported. In a single-center randomized controlled trial in patients who underwent ESD alone, IEE using a magnifying endoscope showed a better diagnostic accuracy rate than conventional endoscopy with dye spraying (89.4% vs. 75.9%, $P = 0.007$).[38] However, in a multicenter randomized trial in patients who underwent ESD or surgical resection, there was no significant difference in the diagnostic accuracy rate between the two methods (88.0% vs. 85.7%, $P = 0.63$).[39]

Margin delineation by endoscopy can be difficult in undifferentiated-type EGC as well as in certain differentiated lesions.[37] In these cases, biopsies should be taken from the lesion's surroundings and examined histopathologically.

TECHNIQUES

Because the risk of incomplete resection is high when EMR is used for lesions with absolute or expanded

indications for ESD, ESD should be carried out instead of EMR for these lesions. (evidence level B, grade of recommendation 1)

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.[40–42] ESD is a method whereby the mucosa surrounding the lesion is excised using a high-frequency diathermy device, followed by dissection of the submucosa beneath the lesion.[8,43–51] 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, meta-analyses found that, in general, better *en bloc* resection rates are achieved with ESD than with EMR.[52–55] It has been reported that for tumor sizes >1 cm in long diameter, *en bloc* resection rates are significantly lower for EMR than for ESD.[56–58]

Physicians should refer to the Gastroenterological Endoscopy Handbook (revised 2nd edition)[4] compiled by the JGES and other relevant JGES guidelines for accurate information concerning perioperative management for ESD and EMR procedures.[59–61]

EVALUATION OF CURABILITY

Evaluation of endoscopic curability is based on local factors and risk factors for lymph node metastasis. (evidence level B, grade of recommendation 1)

Endoscopic curability A: curative resection

Endoscopic resection is shown to be equal or superior to surgical resection in terms of long-term outcomes.[10,11] When the lesion is resected *en bloc*, the following conditions: (i) predominantly differentiated type, pT1a, UL0, HM0 VM0, Ly0, V0, regardless of size; (ii) long diameter ≤2 cm, predominantly undifferentiated type, pT1a, UL0, HM0, VM0, Ly0, V0; or (iii) long diameter ≤3 cm, predominantly differentiated type, pT1a, UL1, HM0, VM0, Ly0, V0, are considered for endoscopic curability A (eCuraA).[62,63] However, evidence is lacking for cases of differentiated-type cancers with undifferentiated components. The above-mentioned type (1) lesions with the undifferentiated components measuring >2 cm in long diameter are defined as endoscopic curability C (eCuraC)-2 (see the measuring method in Fig. 6).

Endoscopic curability B

Although no sufficient long-term results have yet been obtained, curability can be expected. When the lesion is resected *en bloc*, is ≤3 cm in long diameter, predominantly of the differentiated type, and satisfies the following criteria: pT1b1(SM1) (within <500 μm from the muscularis mucosae), HM0, VM0, Ly0, and V0, it is considered endoscopic curability B (eCuraB).[64] However, the lesion is considered eCuraC-2 (see the measuring method in Fig. 6) if undifferentiated components are present in the submucosally invasive part of the lesion.

Endoscopic curability C

This level of curability corresponds to the concept of non-curative resection described in the Guidelines for ESD and EMR for EGC (first edition).[1] When a lesion meets neither of the above-mentioned eCuraA and B conditions, it is considered eCuraC, which has a likelihood of remnant tumor. When eCuraC lesions are differentiated-type lesions and fulfill other criteria to be classified into either eCuraA or eCuraB but was either not resected *en bloc* or had positive HM, they are considered eCuraC-1. All other eCuraC lesions are considered eCuraC-2.

The risk of metastasis is low in eCuraC-1 lesions. In addition to surgical resection, repeat ESD, diathermy, and follow-up without treatment are possible options, with the patient's informed consent, according to the policy of the treating institution. However, in general, open or laparoscopic surgical resection is indicated in the following cases: (i) long diameter ≤3 cm, predominantly differentiated type, pT1a, and UL1; or (ii) long diameter ≤3 cm, predominantly differentiated type, and pT1ba (SM1) lesions, if the combined size of 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 and 3).

In general, open or laparoscopic surgical resection should be performed in cases of eCuraC-2, in view of the risk of metastasis and recurrence (evidence level C, grade of recommendation 1). If, for any reason, open or laparoscopic surgical resection is not performed, curability should be evaluated with reference to the following reports on the frequencies of lymph node metastasis. The patient's informed consent should be obtained after explaining to them that the likelihood of cure is low in cases of recurrence. Table 3 shows the reported rates of lymph node metastasis in cases of lesions without lymphovascular infiltration.[5,62,63] It has been reported from the analysis of 1101 cases of gastric ESD followed by open or laparoscopic surgical

resection that the risk of lymph node metastasis can be stratified through a scoring system that adds a score of 1 for each lesion >3 cm in long diameter, positive deep margins, positive venous infiltration, and pT1b2 (SM2) or deeper, and a score of 3 for positive lymphatic infiltration (Table 4).[65]

COMPLICATIONS

MAJOR COMPLICATIONS ARE bleeding and perforation. According to a multicenter prospective study covering approximately 10,000 cases, the complications found were postoperative bleeding (4.4%), transfusion (0.7%), intraoperative perforation (2.3%), delayed perforation (0.4%), and emergency surgery to a complication (0.2%).[66] Other reported complications that are worthy of note, although their incidences are low, include stricture, pneumonia, and air embolism.[67–72] 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 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. In particular, in cases of ESD, coagulation of bleeding vessels using hemostatic forceps, which does not interfere with subsequent resection, is the first-choice technique.[73] Depending on the circumstances, clips and injections may also be used.

Prevention of postoperative bleeding

Appropriate preventive measures should be applied to visible remnant vessels on the post-resection ulcer surface (evidence level C, grade of recommendation 1). It has been reported that the use of hemostatic forceps or other instruments to coagulate visible remnant vessels on the post-resection ulcer surface reduced the rate of bleeding following ESD from 7.1% to 3.1%.[74] However, caution is required, as excessive vessel coagulation may increase the risk of delayed perforation.

Administration of a gastric acid secretion inhibitor following ESD or EMR (evidence level B, grade of recommendation 1) is required.[75–87] A randomized controlled trial study has reported that proton pump inhibitors are more effective than H2-receptor antagonists in the prevention of postoperative bleeding,[79] and a meta-analysis also showed similar results.[88] From the viewpoint of prevention of postoperative bleeding, ***second-look endoscopy following ESD or EMR is not necessary (evidence level B, grade of recommendation 1)***. A randomized controlled trial showed non-inferiority of the non-implementing second-look endoscopy, compared with the

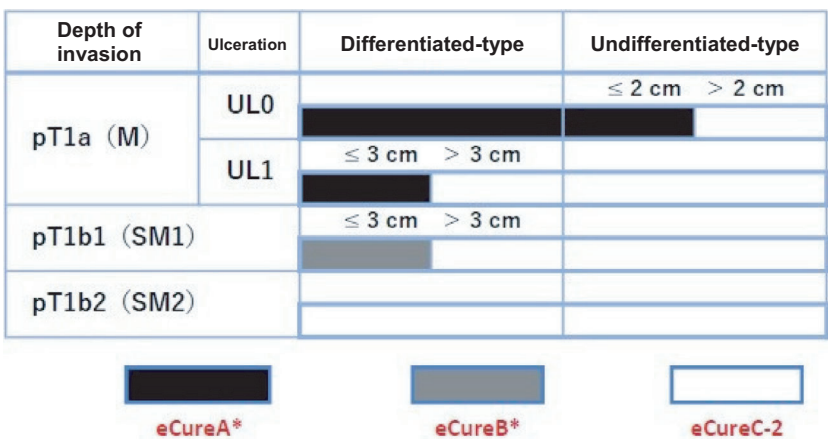

Figure 2 Evaluation of curability according to tumor-related factors. *, Confined to *en bloc* resection and HM0, VM0, Ly0, and V0. pT1a (M), intramucosal cancer (histopathological diagnosis); pT1b (SM), submucosally invasive cancer (histopathological diagnosis). UL, finding of ulceration (or ulcer scar); UL0, absence of ulceration or ulcer scar; UL1, presence of ulceration or ulcer scar.

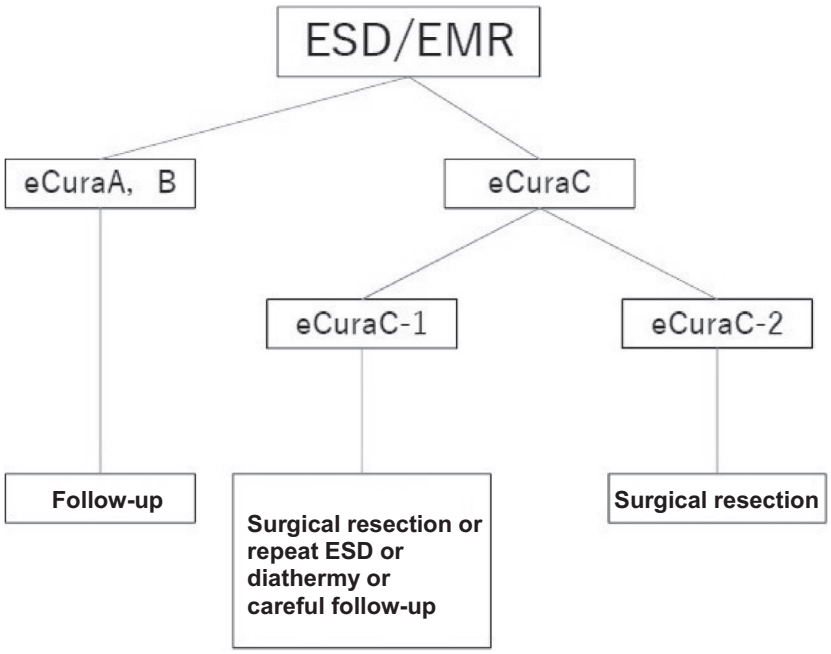

Figure 3 Therapeutic flowchart following endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR).

Table 3 Rates of lymph node metastasis in case of lesions without lymphovascular infiltration (based on data from references [5,62,63])

	Category	Rate of lymph node metastasis	No. of cases
1)	>3 cm in long diameter, differentiated type, pT1a, UL1	3.0% (95% CI: 1.2–6.2%)	7/230
2)	>3 cm, differentiated type, pT1b1 (SM1)	2.6% (95% CI: 0.3–9.0%)	2/78
3)	>2 cm, undifferentiated type, pT1a, UL0	2.8% (95% CI: 1.0–6.0%)	6/214
4)	≤2 cm, undifferentiated type, pT1a, UL1	2.9% (95% CI: 1.2–5.7%)	8/271
5)	>2 cm, undifferentiated type, pT1a, UL1	5.9% (95% CI: 4.3–7.9%)	44/743
6)	Undifferentiated type, pT1b1 (SM1)	10.6% (95% CI: 5.0–19.2%)	9/85

Table 4 Rates of lymph node metastasis (adapted from Table 3 in reference [65])

Total score	Rate of lymph node metastasis	No. of cases
0	1.6% (95% CI: 0.3–8.6%)	1/62
1	2.6% (95% CI: 1.4–4.9%)	9/341
2	4.9% (95% CI: 2.6–9.0%)	9/185
3	7.4% (95% CI: 4.2–12.8%)	11/148
4	8.3% (95% CI: 4.7–14.3%)	11/132
5	19.9% (95% CI: 14.1–27.2%)	28/141
6	27.3% (95% CI: 18.6–38.1%)	21/77
7	26.7% (95% CI: 10.9–52.0%)	4/15

95% CI was calculated using the Wilson score method without continuity correction.

implementing-group, in average risk patients without antithrombotic use.[89] Similar results have also been reported by a meta-analysis.[90]

Management of perforation

When perforation occurs during ESD or EMR, endoscopic closure should first be considered (evidence level B, grade of recommendation 1). 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 are often successful,[49,91-106] surgical

management should be considered if the perforation cannot be closed or if peritonitis is suspected despite apparent closure.

LONG-TERM POSTOPERATIVE SURVEILLANCE

Post-treatment follow-up

AS DESCRIBED IN the Evaluation of curability section, evaluation of the degree of likelihood of cure after ESD or EMR is carried out through histological examination of the resected specimen, on the basis of which subsequent treatment is decided. A risk of metachronous gastric cancer exists after ESD or EMR.[107-110] ***Even when histological examination indicates endoscopic curability A (eCuraA), esophagogastroduodenoscopy should be performed with the primary aim of detecting metachronous gastric cancers (evidence level B, grade of recommendation 1)***. The JGCA Japanese Gastric Cancer Treatment Guidelines ver. 5 recommends follow-up esophagogastroduodenoscopy performed once or twice per year following eCuraA resection.[5] 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.[108] With regard to the termination of follow-up, a report of 234 patients followed up after endoscopic treatment (median 5 years) suggested that the risk of metachronous gastric cancer is decreased after more than 10 years.[111] However, in a study of long-term follow-up of a greater number of patients (median follow-up period, 6.8 years), the incidence of metachronous gastric cancer continued to increase, with several cases of death from metachronous gastric cancer being reported.[110] Although endoscopic examination to evaluate the presence or absence of local recurrence is not necessary in cases of curative resection, endoscopic follow-up about once a year is required in consideration of the risk of metachronous gastric cancer.

When histological examination indicates resection of endoscopic curability B (eCuraB), follow-up with esophagogastroduodenoscopy, as well as ultrasonography or computed tomography (CT) scanning for the detection of metastases, is desirable.(evidence level C, grade of recommendation 2)

Local recurrence may occur in cases of positive HMs or piecemeal resection.[43,112,113] In particular, the risk of local recurrence is high when the positive HM is ≥6 mm,[114] and when the tumor is ≥2 cm in long diameter.[115] ***When histological examination indicates resection of endoscopic curability C-1 (eCuraC-1) not requiring additional surgery, and observation without further treatment is selected for further management, careful follow-up with esophagogastroduodenoscopy should be performed (evidence level C, grade of recommendation 2).***

Helicobacter pylori (H. pylori) eradication

Three randomized controlled trials,[116-118] meta-analyses of these studies,[118-122] and other meta-analyses[123,124] including observational studies have shown that *H. pylori* eradication significantly reduced the incidence of metachronous gastric cancer in patients who underwent endoscopic treatment of EGC. Therefore, ***eradication therapy is recommended in H. pylori-positive patients (evidence level A, grade of recommendation 2)***. However, because the results of a number of randomized controlled trials and meta-analyses revealed that metachronous gastric cancer would still occur after eradication therapy, resulting in prolonged risk of such cancers, periodic esophagogastroduodenoscopy for possible metachronous gastric cancer is required after eradication therapy.

HISTOLOGY

Processing of resected specimens and recording of histological findings are in accordance with the Japanese classification of gastric carcinoma (3rd English edition).[125] (grade of recommendation 1)

Processing of resected specimens

For accurate histopathological diagnosis, it is important to appropriately implement the processing of specimens. Processing includes the following steps.

Stretching and attaching the fresh specimen onto a plate

The fresh specimen should be stretched and fixed on a plate (foam polystyrene, rubber plate, or corkboard) with the mucosal surface facing upward, using mounting pins, to obtain the tumor size consistent with endoscopic observation (Fig. 4).

Fixation in formalin

The region where the fresh specimen is attached should be promptly immersed in a 10% neutral buffered formalin solution for fixation at room temperature for about 24-48 h. The formalin solution should be renewed for each specimen.[126]

Sectioning of the fixed specimen

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. Further incisions are then made parallel to the first incision at intervals of 2.0–3.0 mm (grade of recommendation 1) (Fig. 5a,b).

Photography

For reconstructing (mapping) the extent and depth of invasion of the tumor and the portions comprising mixed undifferentiated components, it is desirable to take macroscopic photographs of the fixed specimen along with the incisions (grade of recommendation 2) (Fig. 5c).[127-134] When taking the photographs, a ruler with clear markings should be placed adjacent to the specimen. The photographs after making incisions are used for reconstruction of the tumor spread.

Recording of histopathological findings

The items to be recorded in the histopathological report include tumor site, macroscopic type, size, histological type, distribution of undifferentiated-type carcinoma, depth of invasion, presence/absence of ulceration within the lesion, presence/absence of vascular infiltration, and evaluation of resection margins.[125]

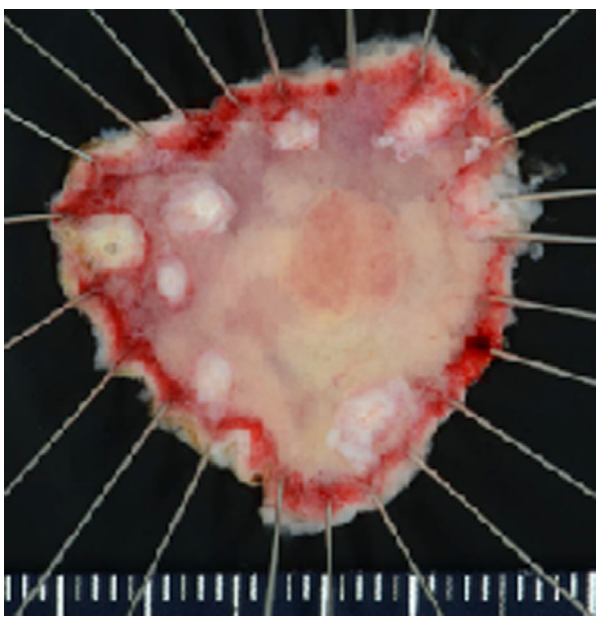

Figure 4 Stretching of the resected specimen. Using mounting pins, the fresh resected specimen should be stretched adequately on a plate, and attached promptly onto the plate with the mucosal surface facing upward.

1. Recording of the tumor site and macroscopic type are in accordance with the Japanese classification of gastric carcinoma (3rd English edition).[125]
2. Tumor size corresponds to "the maximum diameter (long diameter) of the tumor on the reconstructed figure and the short diameter perpendicular to the long diameter."
3. Tumor histopathological types are classified in accordance with the Japanese classification of gastric carcinoma (3rd English edition).[125] ***When multiple histopathological types coexist in the tumor lesion, each histopathological type should be recorded, in descending order of relative surface area within the lesion (e.g., tub1 > pap > por) (grade of recommendation 1)***. In these Guidelines, gastric cancers that predominantly include well-differentiated or moderately differentiated tubular adenocarcinomas and papillary adenocarcinomas are classified as differentiated-type cancers, whereas gastric cancers that predominantly include poorly-differentiated adenocarcinomas, signet ring cell carcinomas, or mucinous adenocarcinomas are classified as undifferentiated-type cancers.
4. Heterogeneity of histological types

In cases where a differentiated-type carcinoma coexists with an undifferentiated-type carcinoma within the respective demarcated area, the extent of the undifferentiated-type carcinoma should also be reconstructed to measure and record the long diameter of the area (Fig. 6a).[134-136] If undifferentiated-type carcinoma is present in several areas in the tumor lesion, the long diameter of each area should be measured and the sum of the values should be recorded (Fig. 6b).[135] However, if the area of the undifferentiated-type carcinoma is too small to allow measurement of its long diameter on the reconstructed figure, this should be specified accordingly. Differentiated and undifferentiated-type carcinomas may either be mixed to varying degrees, or differentiated-type carcinoma may be predominant in the surface layer with the deep layer being composed of undifferentiated-type carcinoma. In such cases, the entire area in question is considered to be an undifferentiated-type carcinoma, and its long diameter is measured and recorded.[135]

Assessment of the depth of invasion

The depth of invasion is assessed as the deepest layer that the cancer has infiltrated[125] and recorded by T classification. In these Guidelines, Tis is expressed as pT1a (M). Even if

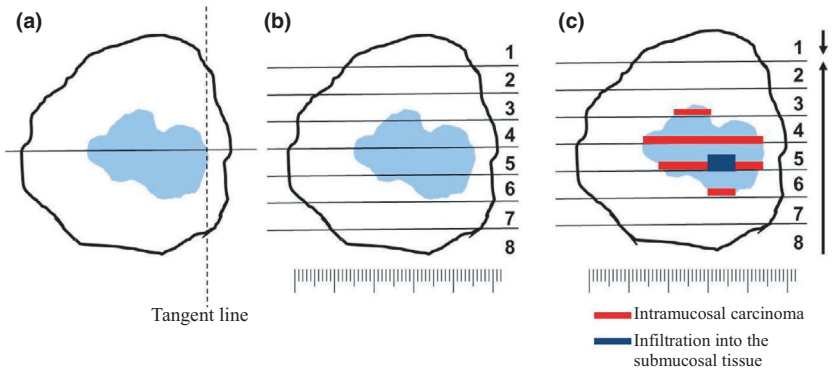

Figure 5 Sectioning of the fixed specimen and reconstruction of the tumor spread (example). (a) Imagine a line tangential to the margin of the lesion where it is closest to the horizontal margin of the specimen (broken line in the figure), and make the first incision perpendicular to this tangential line. (b) Make additional incisions parallel to the first at intervals of 2.0–3.0 mm. Take macroscopic photographs of the fixed specimen with the incisions, with a scale placed adjacent to the specimen. Number each section. (c) Document the mixed, undifferentiated components as well as the extent and depth of invasion of the tumor in the macroscopic photograph of the fixed specimen, including the incisions (reconstructing or mapping). Measure the long diameter using the reconstructed figure. The arrows in the figure show the directions of sectioning. Section 1 is sliced in the direction opposite to those in sections 2–8.

the cancer grows into the submucosal tissue by replacing the submucosal ectopic gastric gland, all lesions without evident interstitial infiltration are recorded as pT1a (M).[125] When vascular infiltration is found in areas deeper than the deepest part of the tissue with continuous infiltration of the tumor lesion, the layer in which vascular infiltration is present is recorded as the depth of invasion.[125] For instance, even if the deepest part with continuous infiltration is the muscularis mucosae, the depth of invasion is recorded as pT1b (SM) if evident lymphatic infiltration is found in a certain part of the submucosa.

For cancers invading the submucosa, the distance (in μm) from the lower margin of the muscularis mucosae to the deepest part of the invading cancer should be measured. If the measured depth is <500 μm, the lesion is assessed and recoded as pT1b1 (SM1). If the measured depth is ≥500 μm, the lesion is classified as pT1b2 (SM2).[125]

The above-mentioned distance is measured using a microscope with an eyepiece micrometer. If the muscularis mucosae is torn or eliminated by cancer infiltration, the distance from the most superficial layer to the deepest part should be measured. Even if the muscularis mucosae cannot be identified because of ulcer scar within the lesion, the lesion is classified as pT1a (M), provided that the cancer is localized within the regenerative mucosa covering the ulcer scar and that there is no evident infiltration into the submucosal tissue. On the other hand, if the cancer infiltrates into the submucosal tissue in an ulcer scar, an imaginary line continuous with the intact muscularis mucosae in the adjacent mucosa is drawn, and the distance from this line to the vertical depth of invasion is used to determine whether the lesion is pT1b1 (SM1) or pT1b2 (SM2). Immunohistochemical staining with anti-desmin antibodies is also useful in identifying the muscularis mucosae.

Assessment of ulceration or ulcer scar within the lesion

This is an essential factor for evaluation of curability. If ulceration or ulcer scar is found within the lesion, the lesion is classified as pUL1, whereas it is classified as pUL0 when there is no ulceration or ulcer scar.[125] In general, most pUL1 cases have a U1-II ulcer scar accompanied by fibrosis involving the full thickness of the submucosal tissue and a broadening towards the end, beginning from the torn part of the muscularis mucosae. On the other hand, biopsy-derived scars can be identified as a fibrotic focus localized within a small area just under the muscularis mucosae.[137] However, in U1-II scars in which fibrosis has disappeared, it may be difficult to distinguish ulcer scars from biopsy-derived scars. In such cases, the lesion is classified as pUL1.[5]

Assessment of vascular infiltration

The presence or absence of vascular infiltration determined by histopathological examination of endoscopically resected specimens serves as a criterion for assessing the necessity of

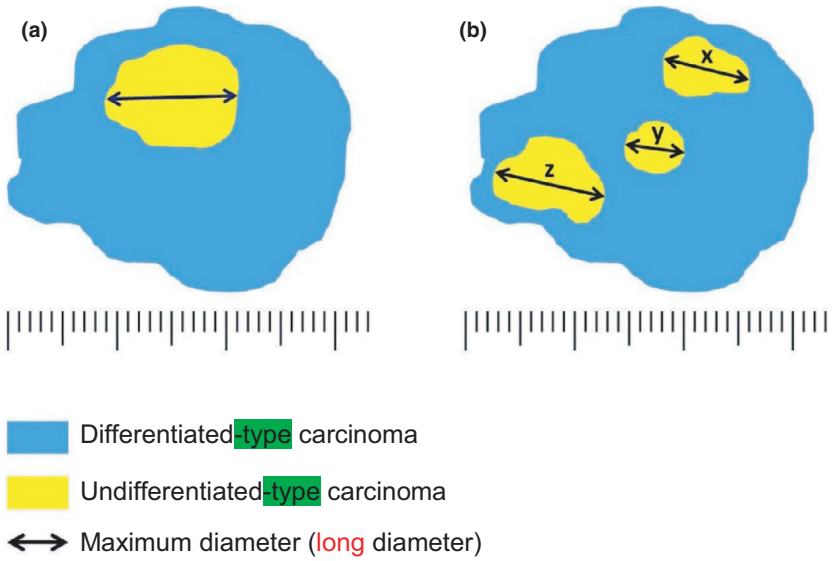

Figure 6 Measurement of the size of the coexisting undifferentiated-type carcinoma. (a) Reconstruct the area of the undifferentiated-type carcinoma, and measure the long diameter of that area. (b) If undifferentiated-type carcinoma is present in more than one area, measure the long diameters (*x*, *y*, *z*) of all these areas and record the sum of these values.

further surgical resection. Therefore, ***assessment of vascular infiltration should be carried out using specific staining strategies (grade of recommendation 2)***. Immunohistochemical staining with anti-lymphatic endothelial antibodies (D2-40) is useful for identifying lymphatic vessels, whereas elastic fiber stains (Elastica van Gieson or Victoria blue/hematoxylin-eosin) are effective for identifying veins.[125,138] Even in cases of intramucosal carcinoma, it is preferable to perform these specific staining procedures if vascular infiltration is suspected (particularly when there is coexisting undifferentiated-type carcinoma). Lymphatic infiltration is expressed as Ly1 when positive and Ly0 when negative, and venous infiltration is expressed as V1 when positive and V0 when negative.

Evaluation of resection margins

Surgical margins are classified as HM and vertical margins (VM). If tumor tissue is present in these resection margins, positive HM and VM are expressed as pHM1 and pVM1, respectively. If no tumor tissue is present, they are expressed as pHM0 and pVM0, respectively. In general, tissue in resection margins is injured to various degrees by high-frequency electricity and diathermy during resection. When injured severely, the existing mucosal epithelial cells may be confused with tumor cells, and may, therefore, require caution. If the exposure of tumor tissue in resection margins cannot be evaluated, they are expressed as pHMX and pVMX, respectively.

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