



American Society for Gastrointestinal Endoscopy guideline on endoscopic submucosal dissection for the management of early esophageal and gastric cancers: summary and recommendations

Prepared by:

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This clinical practice guideline from the American Society for Gastrointestinal Endoscopy (ASGE) provides an evidence-based summary and recommendations regarding the role of endoscopic submucosal dissection (ESD) in the management of early esophageal and gastric cancers. It is accompanied by the document subtitled “Methodology and Review of Evidence,” which provides a detailed account of the methodology used for the evidence review. This guideline was developed using the Grading of Recommendations, Assessment, Development and Evaluation framework and specifically addresses the role of ESD versus endoscopic mucosal resection (EMR) and/or surgery, where applicable, for the management of early esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), and gastric adenocarcinoma (GAC) and their corresponding precursor lesions. For ESCC, the ASGE suggests ESD over EMR for patients with early-stage, well-differentiated, nonulcerated cancer >15 mm, whereas in patients with similar lesions ≤15 mm, the ASGE suggests either ESD or EMR. The ASGE suggests against surgery for such patients with ESCC, whenever possible. For EAC, the ASGE suggests ESD over EMR for patients with early-stage, well-differentiated, nonulcerated cancer >20 mm, whereas in patients with similar lesions measuring ≤20 mm, the ASGE suggests either ESD or EMR. For GAC, the ASGE suggests ESD over EMR for patients with early-stage, well- or moderately differentiated, nonulcerated intestinal type cancer measuring 20 to 30 mm, whereas for patients with similar lesions <20 mm, the ASGE suggests either ESD or EMR. The ASGE suggests against surgery for patients with such lesions measuring ≤30 mm, whereas for lesions that are poorly differentiated, regardless of size, we suggest surgical evaluation over endoscopic approaches. (Gastrointest Endosc 2023;■:1-14.)

This guideline document was prepared by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy using the best available scientific evidence and considering a multitude of variables including but not limited to adverse events, patient values, and cost implications. The purpose of these guidelines is to provide the best practice recommendations that may help standardize patient care, improve patient outcomes, and reduce variability in practice.

We recognize that clinical decision-making is complex. Guidelines, therefore, are not a substitute for a clinician's judgment. Such judgements may, at times, seem contradictory to our guidance because of many factors that are impossible to fully consider by guideline developers. Any clinical decisions should be based on the clinician's experience, local expertise, resource availability, and patient values and preferences.

This document is not a rule and should not be construed as establishing a legal standard of care or as encouraging,

advocating for, mandating, or discouraging any particular treatment. Our guidelines should not be used in support of medical complaints, legal proceedings, and/or litigation, as they were not designed for this purpose.

Endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) are mainstays of endoscopic resection. Both ESD and EMR have been shown to be safe and effective and, as such, have replaced surgery as the first-line option in the management of early-stage esophageal and gastric neoplasia in many regions. Even with an optimal EMR technique, en-bloc resection is limited by maximum snare diameter. As such, larger lesions usually require a piecemeal EMR. This limits the use of EMR in early-stage cancers because of the inability to accurately judge an R0 resection (defined as a disease-free resection margin). ESD, which uses electrosurgical knives rather than snares, circumvents the size limitation of snares and permits en-bloc resections of much larger lesions, which is critical to achieving a low recurrence rate.¹ However, ESD is a newer technique relative to EMR and is often available only in tertiary or quaternary referral centers.

For these reasons and others, the decision regarding whether to perform EMR versus ESD for smaller, noninvasive, early-stage cancers can be difficult. Additionally, for larger, early-stage, upper GI cancers or those with invasion of the submucosa, it can be equally difficult deciding which to remove by ESD versus surgery, with each approach associated with its own unique advantages, limitations, and risks of adverse events.² Therefore, formal guidance is required on the appropriate selection of patients for ESD for early-stage upper GI cancers. The aim of this American Society for Gastrointestinal Endoscopy (ASGE) guideline is to provide evidence-based recommendations on the appropriate positioning of ESD in the management of early-stage esophageal and gastric cancers.

METHODS

Terms and definitions used throughout this guideline can be found in [Table 1](#). This guideline was prepared by the ASGE Standards of Practice Committee and used the Grading of Recommendations, Assessment, Development and Evaluation approach throughout its inception.³ For all early upper GI cancers, all evidence comparing ESD with EMR and comparing ESD with surgery was considered, where available. For esophageal adenocarcinoma (EAC), no comparative evidence was available between ESD and surgery; hence, our recommendations focus only on ESD versus EMR for EAC.

The recommendations in this summary document were crafted and informed by contemporary meta-analyses of available evidence for each question. Evidence profiles were created by an independent team of evidence synthe-

sis experts for each question and reviewed at a Grading of Recommendations, Assessment, Development and Evaluation panel that was held virtually on March 29, 2022, where recommendations were generated. When developing our recommendations, we took into consideration multiple factors, including the overall certainty of the evidence, potential benefits and harms of varying approaches, feasibility of implementation, patient values and preferences, direct costs, cost-effectiveness, and impact on health equity. The final wording of our recommendations was approved by all members of the panel and the ASGE governing board. Stronger recommendations are represented using statements such as “we recommend...,” whereas weaker recommendations are represented by statements such as “we suggest...” This document, subtitled “Summary and Recommendations,” provides our final recommendations as well as a high-level summary of the evidence-based guideline process that was followed by the ASGE in preparing this document.

This guideline synthesizes the evidence and makes recommendations on the following 3 clinical questions:

1. In patients with early-stage esophageal squamous cell carcinoma (ESCC), what is the role of ESD compared with (a) EMR and (b) surgery?
2. In patients with early-stage esophageal adenocarcinoma (EAC), what is the role of ESD compared with EMR?
3. In patients with early-stage gastric adenocarcinoma (GAC), what is the role of ESD compared with (a) EMR and (b) surgery?

When considering studies that assessed EMR, we included all variations of EMR techniques (cap, band ligation assisted, or freehand technique) but excluded those with circumferential cut EMR because of technique overlap with ESD. Similarly, snare-assisted ESD cases were excluded.

Further details on methodology and evidence synthesis process are provided in the accompanying article subtitled “Methodology and Review of Evidence.” We note that data were notably lacking on surveillance tools and intervals after ESD. Hence, recommendations presented throughout this document relied heavily on the expert opinion of the panel.

SUMMARY OF RECOMMENDATIONS

A summary of recommendations for each question is provided in [Table 2](#). To accompany and support these recommendations, algorithms were prepared with additional details to guide clinical decisions based on relevant patient and lesion characteristics. These algorithms are provided in [Figures 1 to 3](#). For each recommendation, we discussed important considerations including lesion size and morphology as important determinants of resection technique as well as treatment of recurrence and surveillance protocols.

TABLE 1. Terms and definitions used throughout this guideline

Term	Definition
Early-stage cancer	A malignant tumor that is confined to the mucosa and/or submucosa, with no deeper involvement and no locoregional or distant spread
En-bloc resection	A resection whereby the entirety of neoplastic, dysplastic, and/or cancerous tissue is removed in 1 piece rather than in multiple pieces
R0 resection	Resection margins are disease-free
Clinical success/curative resection	Where the following criteria are fulfilled on histology of the resected specimen: 1. Lateral and deep margins are microscopically free of malignant cells (R0 resection) 2. Well (G1) or moderate (G2) differentiation 3. No lymphovascular invasion 4. No deep invasion beyond the submucosa For the purposes of this document, clinical success was considered equivalent to curative resection
Cancer recurrence	Pathologically demonstrated recurrence at the site of previous resection or surgery or lymph node metastasis
Depth of invasion	M1: intraepithelial noninvasive carcinoma, carcinoma in situ M2: microinvasive carcinoma into the lamina propria M3: microinvasive carcinoma into the muscularis mucosa SM1: microinvasive carcinoma into the upper third of the submucosa SM2: microinvasive carcinoma into the middle third of the submucosa SM3: microinvasive carcinoma into the lower third of the submucosa
Absolute criteria for endoscopic submucosal dissection appropriateness for gastric cancer resection	Mucosal adenocarcinoma (and lesions with high-grade dysplasia): 0 = G1 differentiation 1 = G2 differentiation Must be intestinal type measuring ≤ 2 cm for the absolute indications
Expanded criteria for endoscopic submucosal dissection appropriateness for gastric cancer resection	Mucosal adenocarcinoma (and lesions with high-grade dysplasia): 0 = G1 1 = G2 2 = G1 and or G2 3 = adenocarcinoma intestinal type, G1 or G2, any size, without ulceration 4 = adenocarcinoma, intestinal type, G1 or G2 differentiation, submucosally invasive (< 500 mm) 5 = adenocarcinoma, intestinal type, G1 or G2 differentiation, ≤ 3 cm, with ulceration 6 = adenocarcinoma, diffuse type, G3 or G4 differentiation, ≤ 2 cm, without ulceration 7 = en-bloc resection for lesions at risk for submucosally invasive cancer

Question 1a: In patients with esophageal squamous dysplasia or early, well-differentiated, nonulcerated ESCC, should EMR or ESD performed?

Recommendations: *In patients with esophageal squamous cell dysplasia or early, well-differentiated, nonulcerated squamous cell carcinoma, the ASGE suggests selection of resection strategy based on lesion size:*

- Lesion size > 15 mm: suggest ESD over EMR
- Lesion size ≤ 15 mm: suggest either ESD or EMR
- See [Figure 1](#) algorithm for all considerations (Conditional recommendation, low quality of evidence)

Summary of evidence

Our meta-analysis identified 8 observational studies that included 821 patients who underwent ESD and 1306 patients who underwent EMR.⁴⁻¹¹ In 6 studies that included

1067 patients, ESD was associated with higher rates of clinical success of 93.3% versus 72.1% (relative risk [RR], 1.33; 95% confidence interval [CI], 1.02-1.74; $I^2 = 97.3\%$). In 8 observational studies, ESD was also associated with lower local recurrence rates: .5% versus 5.2% (RR, .19; 95% CI, .07-.48; $I^2 = .0\%$). There were no differences in distant recurrence rates based on 3 observational studies.

Low rates of adverse events were associated with both ESD and EMR. No differences were found between ESD and EMR in bleeding (RR, 1.55; 95% CI, .60-4.03; $I^2 = 31.8\%$) or stricture formation (9.2% vs 7.4%; RR, 1.2; 95% CI, .68-2.11; $I^2 = 36.5\%$). However, ESD was associated with more perforations: 5.7% of ESD patients and .8% of EMR patients (RR, 4.30; 95% CI, 1.22-15.12; $I^2 = 61.3\%$). Over 90% of cases of perforation were managed endoscopically.^{12,13} Procedural time was significantly longer with ESD compared with EMR in 6 studies (weighted mean difference, 46.77 minutes longer; 95% CI, 33.4-60.14; $I^2 = 92.3\%$). No direct data were available regarding cost-effectiveness in this population or on patient values on

TABLE 2. Summary of clinical recommendations

Clinical question/patient population	American Society for Gastrointestinal Endoscopy recommendation	Strength of recommendation, quality of evidence
- Esophageal squamous dysplasia or early-stage ESCC - Well differentiated, nonulcerated - Without submucosal invasion - Measuring over 15 mm	We suggest ESD over EMR	Conditional recommendation, low quality of evidence
- Esophageal squamous dysplasia or early-stage ESCC - Well differentiated, nonulcerated - Without submucosal invasion - Measuring ≤ 15 mm	We do not make a recommendation for or against either ESD or EMR	Conditional recommendation, low quality of evidence
Esophageal squamous dysplasia or early, well-differentiated, nonulcerated ESCC without submucosal invasion	We suggest against surgery	Conditional recommendation, low quality of evidence
- Early-stage EAC (T1) or Barrett's nodular dysplasia - Well differentiated, nonulcerated - Measuring over 20 mm	We suggest ESD over EMR	Conditional recommendation, low quality of evidence
- Early-stage EAC (T1) or Barrett's nodular dysplasia - Well differentiated, nonulcerated - Measuring ≤ 20 mm	We do not make a recommendation for or against either ESD or EMR	Conditional recommendation, low quality of evidence
- Well- or moderately differentiated early-stage GAC - Nonulcerated, intestinal type - Measuring under 20 mm	We do not make a recommendation for or against either ESD or EMR	Conditional recommendation, low quality of evidence
- Well- or moderately differentiated early-stage GAC - Nonulcerated, intestinal type - Measuring 20-30 mm	We suggest ESD over EMR	Conditional recommendation, low quality of evidence
Patients with - Well- or moderately differentiated early-stage GAC - Intestinal type - Measuring under 30 mm	We suggest against surgery	Conditional recommendation, low quality of evidence
Patients with Poorly differentiated early-stage GAC (any size)	We suggest surgical evaluation over endoscopic approaches	Conditional recommendation, low quality of evidence

Also refer to the algorithms in [Figures 1 to 3](#).

EAC, Esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; ESD, endoscopic submucosal dissection; GAC, gastric adenocarcinoma.

EMR versus ESD in this clinical setting. The patient representative on the panel stressed that dedicated educational efforts aimed toward patients and primary care providers are critical to inform them about these procedures and their associated outcomes. The panel discussed that lesion size strongly impacts the choice between ESD and EMR, given the need for en-bloc resection to be considered curative and for staging accuracy.

Discussion

In ESCC, lesion size, depth of invasion, histopathologic grade, and presence of ulceration are all important factors when deciding on resection modality. Management of recurrence and surveillance after resection are also both important considerations.

Lesion size. The panel considered it necessary to achieve en-bloc resection in ESCC to provide cure or to accurately stage the disease and guide further treatment decisions. Our analyses found no direct comparative data on size of lesions in ESD versus EMR. Based on the mean lesion size removed by EMR in our analyses, the panel

chose a cutoff of 15 mm to inform the decision between ESD and EMR; however, this should not be considered a strict cutoff, and the decision to proceed with ESD should be based on several other considerations, including local expertise, availability, endoscopist's discretion, and patient preferences. No upper limit on lesion size for ESD was established.

Morphology and/or invasion. The panel discussed the issue of lesion morphology as a predictor of depth of invasion in detail. The depth of invasion is a major predictor of lymph node metastasis (LNM). However, determining the depth of invasion before resection remains challenging. The Japan Esophageal Society published guidelines for treatment of esophageal cancer, with the absolute indication for endoscopic resection defined as flat lesions (Paris 0-II), with M1 to M2 invasion, and circumferential extent of no more than two-thirds and the relative indication defined as M3 to SM1 lesions and where endoscopic resection would leave a mucosal defect of circumferential extent exceeding 75%.¹⁴⁻¹⁶

EUS remains the standard modality for T staging and is superior to CT in assessing T and N staging; however, its

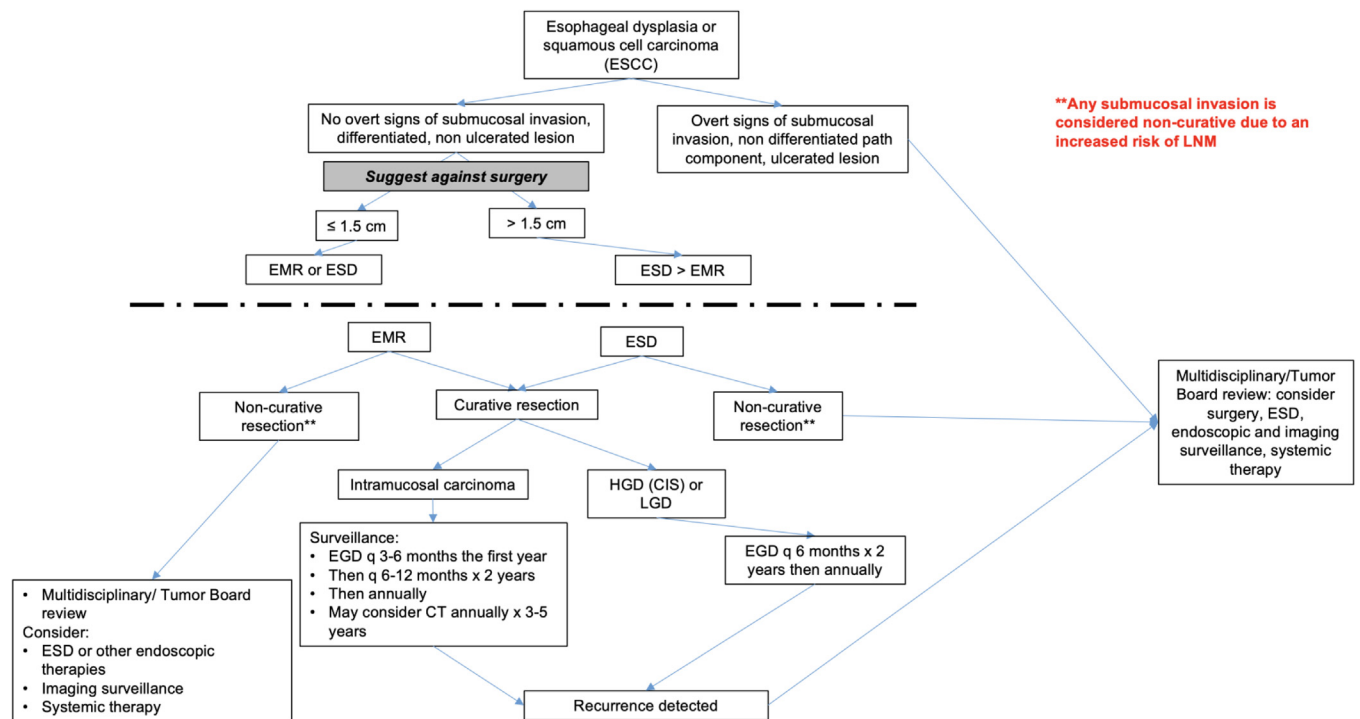


Figure 1. Recommended clinical care algorithm for patients presenting with early-stage ESCC. *ESCC*, Esophageal squamous cell carcinoma; *ESD*, endoscopic submucosal dissection; *LNM*, lymph node metastasis; *HGD*, high-grade dysplasia; *CIS*, carcinoma in situ; *LGD*, low-grade dysplasia.

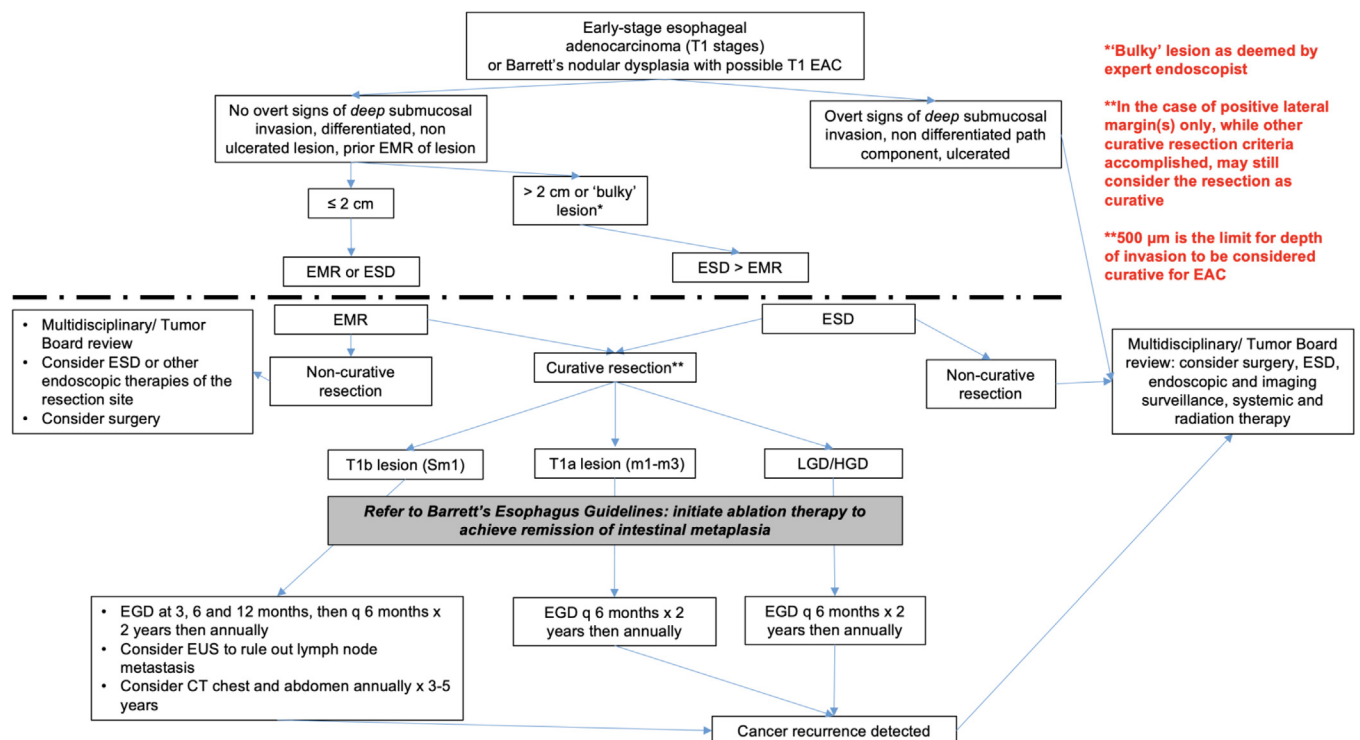


Figure 2. Recommended clinical care algorithm for patients presenting with early-stage EAC. *EAC*, Esophageal adenocarcinoma; *ESD*, endoscopic submucosal dissection; *HGD*, high-grade dysplasia; *LGD*, low-grade dysplasia.

utility in accurately predicting depth of submucosal invasion remains limited.¹⁷ Lugol-based chromoendoscopy and narrow-band imaging have been adopted and are

increasingly replacing EUS with promising accuracy.¹⁸⁻²¹ Ulcerations indicate a high likelihood of invasion into the submucosa, and thus ulcerated lesions should not be

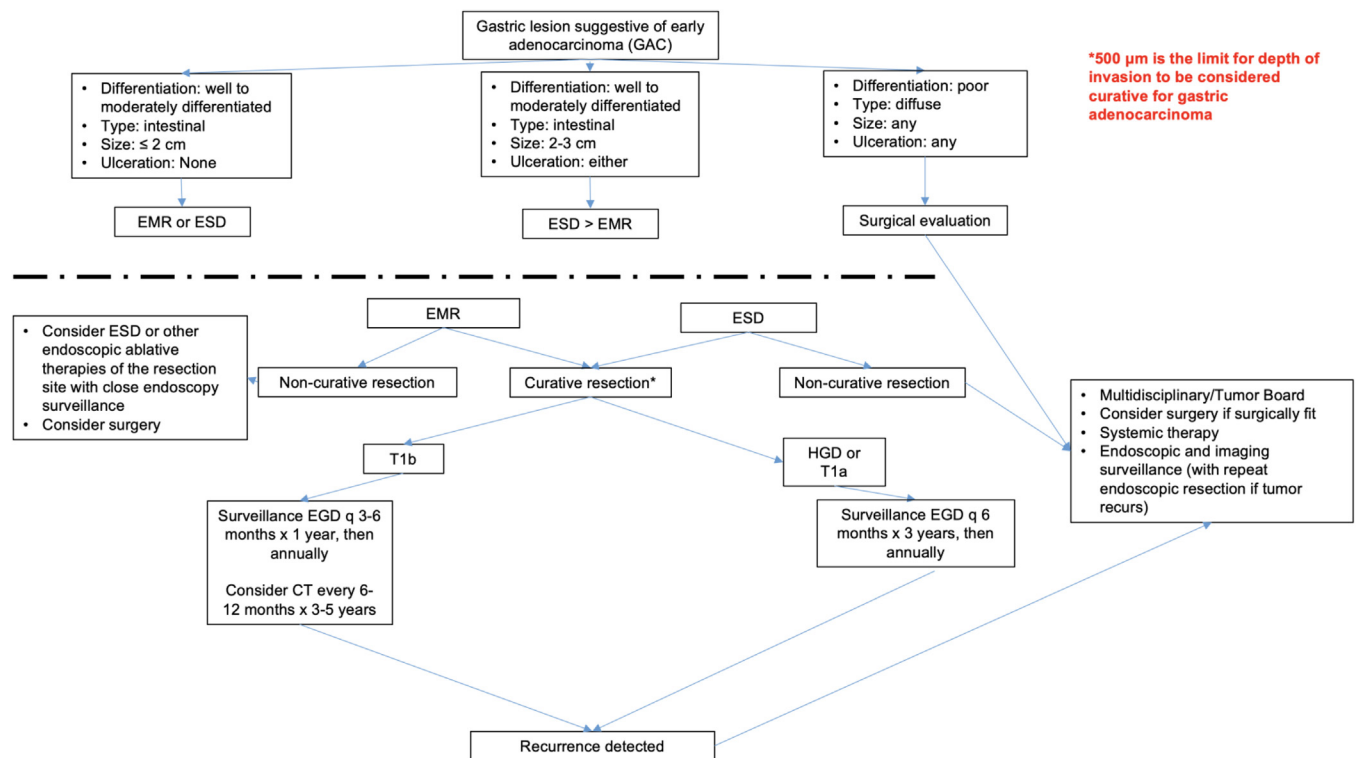


Figure 3. Recommended clinical care algorithm for patients presenting with early-stage GAC. GAC, Gastric adenocarcinoma; ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia.

resected endoscopically. Besides depth of invasion, LNM incidence correlates well with tumor histology and differentiation (G1-G2 vs G3). Endoscopic resection should be limited to histologically well- to moderately differentiated lesions (G1 or G2) identified on previous biopsy samples.

Management of recurrence. The panel discussed various treatment options for local recurrence of ESCC after endoscopic resection and recommended a multidisciplinary review and individualized approach based on a case-by-case discussion. ESD remains a feasible option for many of these lesions, particularly if a patient is unfit for surgery. However, data to inform the comparative effectiveness of various strategies to manage recurrent lesions are limited.

Surveillance. We did not identify any comparative studies assessing various surveillance methods or intervals. The panel used existing protocols from published studies to guide our recommendation on this issue. Based on our review, the panel suggested that all lesions with T1a pathologic stage should undergo endoscopic surveillance with consideration of cross-sectional imaging after endoscopic resection. For T1a lesions, we propose surveillance endoscopy should be performed every 3 to 6 months for the first year, then every 6 to 12 months for the following 2 years, and then annually. However, lesions with only high-grade dysplasia or low-grade dysplasia can be surveyed by performing endoscopy every 6 months for the

first 2 years and then annually (see Fig. 1 algorithm).

Question 1b: In patients with esophageal squamous dysplasia or early, well-differentiated, nonulcerated ESCC without overt signs of submucosal invasion, should surgery or ESD be considered?

Recommendation: *In patients with esophageal squamous dysplasia or early, well-differentiated, non-ulcerated ESCC, without overt signs of submucosal invasion, the ASGE suggests against surgical resection. (Conditional recommendation, low quality of evidence)*

Summary of evidence

We identified 5 observational, comparative studies including 463 patients receiving ESD and 495 patients undergoing surgery.^{12,13,22-24} Thirty-day mortality was lower in the ESD group compared with the surgery group (1.0% vs 4.6%; RR, .30; 95% CI, .11-.88; $I^2 = .0\%$). However, clinical success was lower in the ESD group compared with the surgery group: 87.5% of ESD patients versus 98.2% of surgical patients (RR, .85; 95% CI, .74-.98; $I^2 = 84.6\%$). There were no differences in 5-year overall survival, local recurrence (4.7% ESD vs 6.8% surgery; RR, 1.14; 95% CI, .60-2.17; $I^2 = .0\%$), rates of metastatic recurrence (3.6% surgery vs 9.0% ESD; RR, .48; 95% CI, .14-1.64; $I^2 = 27.8\%$), periprocedural bleeding, or long-term stricture formation.

No direct comparisons of costs were available for this population, but 1 study assessing patients with EAC largely favored endoscopic resection over surgery given a shorter hospitalization, even accounting for the need for future endoscopic surveillance.²⁵ No data were identified on patient values and preferences. However, the panel's patient representative strongly favored endoscopic resection where possible given the lower periprocedural risk.

Discussion

Esophagectomy has traditionally been the criterion standard for early-stage ESCC; however, it is associated with a high 30-day mortality of up to 10%.²⁶ The long-term outcomes of ESD compared with esophagectomy remain poorly understood, especially for lesions invading the superficial submucosal layer (SM1), where the risk of LNM is increased. When compared with other esophageal cancers (like those arising from Barrett's esophagus), the propensity of ESCC for LNM is higher, and hence accurate lesion staging of resected specimens is very important. The panel noted that ESD performed for staging purposes does not preclude patients from receiving adjunctive therapies (surgery or systemic therapy). In fact, endoscopic resection has not been shown to carry any adverse events in patients who undergo subsequent definitive surgery.²⁷

Size. We suggest against surgery for ESCC in the absence of overt signs of submucosal invasion, ulceration, or poor differentiation. Very large lesions (>5 cm) and those involving two-thirds or more of the circumference should be discussed on a multidisciplinary level and could still end up requiring surgery as the safest and most practical option. This again could depend on local expertise, availability, endoscopist's discretion, and patient preferences.

Morphology and/or invasion. ESD remains the preferred method for potentially curative resections (mucosal stage up to M3 in all patients and up to SM3 in patients with higher surgical risk as a noncurative alternative management option). Because of the lower risk of short-term mortality associated with ESD, the panel recommended ESD should be considered for nonulcerated, well-differentiated lesions with a low risk of submucosal invasion (see Fig. 1 algorithm). Patients presenting with lesions with ulceration, suspected submucosal invasion, or with poorly differentiated pathology are recommended for referral for multidisciplinary review, regardless of the lesion size. However, many of these patients may still be candidates for ESD after considering risks of surgery, locally available expertise, and patient wishes. Given the estimated 5% risk of LNM in lesions that extend to the superficial submucosa (SM1) and the highly morbid nature of the surgical alternative, ESD should be considered in patients with this stage (if known), particularly those with high risk for surgery and those with multiple comorbidities.

Management of recurrent lesions. Data are limited to inform clinicians on the comparative effectiveness of different strategies to manage recurrence. The panel sug-

gests a multidisciplinary review and individualized approach for each case.

Surveillance. Data are limited to inform clinicians on the comparative effectiveness of different surveillance strategies. In ESCC, endoscopic surveillance is recommended to detect local recurrences and metachronous lesions. All lesions with a T1a pathologic stage should undergo endoscopic surveillance with consideration for cross-sectional imaging (see Fig. 1 algorithm).

Question 2: In patients with early, well-differentiated, nonulcerated EAC (T1 stage) or nodular Barrett's dysplasia, should EMR or ESD performed?

Recommendations: In patients with early, well-differentiated, nonulcerated EAC (T1 stage) or nodular Barrett's dysplasia, the ASGE suggests the resection strategy should be based on lesion size:

1. Lesion size >20 mm: suggest ESD over EMR
2. Lesion size ≤20 mm: suggest either ESD or EMR
3. See Figure 2 algorithm for all considerations

(Conditional recommendation, low quality of evidence)

Summary of evidence

We identified 4 comparative studies (3 observational, 1 randomized) including 247 patients receiving ESD and 761 patients receiving EMR.²⁸⁻³¹ Our meta-analyses of available data showed a mean lesion size resected by EMR of 11.9 mm versus a mean lesion size of 35.22 mm for ESD. ESD was associated with higher rates of clinical success (76.1% vs 64.6%; RR, 1.38; 95% CI, .83-2.29; $I^2 = 93.9\%$) and lower rates of local recurrence (3.2% for ESD vs 26.1% for EMR; RR, .19; 95% CI, .04-.98; $I^2 = 52.8\%$). EMR was associated with higher rates of bleeding compared with ESD (10.5% vs 2.2%; RR, .32; 95% CI, .13-.78; $I^2 = 1.0\%$). The risk of perforation or stricture formation was no different between ESD and EMR, with rates of 1% to 2% and 3% to 7%, respectively. All perforations were treated endoscopically.^{28,31}

No studies reported on the treatment of post-EMR bleeding or perforation or classified recurrences based on margin status, depth of invasion, or lymphovascular invasion (LVI). Data on recurrence treatment were available on 1 ESD patient, and this patient was successfully treated with EMR. No data were available on any recurrences after EMR.²⁸ No direct evidence on cost-effectiveness or patient values were available in this population. None of the studies included in our analyses compared direct costs of care between endoscopic and surgical techniques.

Discussion

Endoscopic resection is recommended for the removal of all visible abnormalities arising from Barrett's esophagus.^{32,33} The adoption of endoscopic therapy for Barrett's

neoplasia was built on the evidence that high-grade dysplasia and T1m adenocarcinoma are associated with a low rate of LNM, reported to be up to 10% in endoscopic and surgical series, whereas submucosal invasion, when present, carries a higher risk of up to 46%.³⁴⁻³⁶ Because of the inaccuracies of detecting the full extent of pathology in nodular lesions noted within Barrett's esophagus, the ASGE recommended endoscopic resection, which has been shown to upgrade the pathology previously obtained by mucosal biopsy samples by up to 40%.^{37,38} Therefore, all lesions suspected to harbor cancer should be removed en bloc, when possible, including those with Paris type I and Paris IIa+c lesions. EMR of visible nodularity followed by eradication of residual Barrett's esophagus reduces the risk of metachronous neoplasia and is widely accepted by Western endoscopists as the standard of care for early-stage Barrett's adenocarcinoma.^{33,38}

Clinical success in endoscopic resection is judged by the ability to achieve negative lateral and deep resection margins (ie, curative resection). Additional criteria identified for "curative" resection include well- to moderately differentiated histology, lack of LVI, and submucosal invasion, if present, confined to the superficial submucosa ($<500\text{ }\mu\text{m}$).^{34,39} Lesions that do not fit these criteria are considered at higher risk for LNM. Similarly to ESCC, the ability of white-light endoscopy, image-enhanced endoscopy, digital chromoendoscopy, and EUS in accurately predicting the depth of invasion remains suboptimal with inaccuracies observed in as many as 60% of reported cases.^{40,41}

Size. Both EMR and ESD can be used in Barrett's dysplasia, but EMR remains the first-line therapy in lesions measuring $\leq 20\text{ mm}$. The panel deliberated on additional scenarios where ESD should be prioritized over EMR in EAC and Barrett's esophagus with nodular dysplasia. The panel reflected at length about the size cutoff to consider ESD versus EMR. Our analyses demonstrated that the mean lesion size resected by EMR was 11.9 mm compared with a mean lesion size of 35.22 mm for ESD. Because of scant literature, the benefit of ESD over EMR is less established for EAC and Barrett's visible lesions. The panel agreed that adopting a 20-mm size cutoff highlights the maximal ability of EMR to resect nodular dysplasia en bloc based on the various available devices including the most widely used band ligation-assisted EMR system.

Morphology and/or invasion. Although lesion morphology can predict the extent of submucosal invasion in early-stage EAC, it is widely accepted that the most-effective local staging remains pathology of endoscopically resected nodular lesions. Paris type 0 to Is and 0 to IIc lesions, where the depth of submucosal invasion can be estimated to exceed $500\text{ }\mu\text{m}$, are best triaged to ESD. Additional scenarios were discussed in depth. For example, ESD, when

available, remains the best-suited endoscopic therapy in lesions previously removed by EMR and found to have positive deep margins, poorly lifting tumors, and lesions at risk for submucosal invasion and locally recurrent neoplasia after prior EMR. However, the success of ESD in this scenario could also be limited by prior scarring. Additionally, the panel deliberated on the clinical impact of a positive lateral margin in a lesion removed with piecemeal EMR when other curative resection criteria were fulfilled. The consensus of the panel was that in this case, the resection can still be considered as curative as long as the highest-grade lesion in the field was curatively resected. The panel recommended a multidisciplinary review for all other lesions that fall outside of the recommended resection criteria (see Fig. 2 algorithm) and emphasized the importance of the early initiation of ablation therapy after ESD to eradicate any remaining Barrett's esophagus.³³

Management of recurrence. Treatment of local recurrence after ESD in EAC remains largely under-reported in the literature compared with ESCC and GAC. The panel discussed various treatment options and recommended a multidisciplinary review and case-by-case determination. Data informing specific modalities used after an initial failed resection are poor, with these including ESD, EMR, surgery (in fit patients), local endoscopic ablative therapies, or systemic therapy.

Surveillance. Regarding post-EMR or post-ESD surveillance, we encountered no studies that assessed this systematically. We propose a risk-based approach derived from known risk factors for tumor recurrence, recommending endoscopy, EUS, and cross-sectional imaging studies for lesions with evident submucosal invasion (see Fig. 2 algorithm).

Question 3a: In patients with early-stage GAC, should EMR or ESD be performed?

Recommendations: *The choice of ESD or EMR in patients with early-stage GAC depends on 4 factors: differentiation (well or moderate vs poor), morphology (ulcerated vs nonulcerated), type of cancer (intestinal vs diffuse), and size.*

- The ASGE suggests either ESD or EMR in well- or moderately differentiated, nonulcerated, intestinal type early GAC measuring $<20\text{ mm}$
 - The ASGE suggests ESD over EMR in well- or moderately differentiated lesions measuring 20 to 30 mm, with or without ulceration, intestinal type early GAC
 - See Figure 3 algorithm for all considerations
- (Conditional recommendation, low quality of evidence)

Summary of evidence

We identified 13 comparative studies (12 observational, 1 randomized controlled trial) on 3232 patients treated with ESD and 3154 patients treated with EMR.⁴²⁻⁵⁴ Based on meta-analyses, ESD was associated with higher rates of clinical success (86.5% vs 54.4%; RR, 1.79; 95% CI, 1.40-2.30; $I^2 = 98.2\%$) and lower rates of local recurrence (1.7% vs 7.2%; RR, .16; 95% CI, .08-.33; $I^2 = 74.7\%$). However, ESD was associated with higher rates of perforation (3.7% vs 1.9%; RR, 2.23; 95% CI, 1.19-4.19; $I^2 = 64.7\%$) and longer procedure times (weighted mean difference, 48.93 minutes; 95% CI, 22.45-75.42; $I^2 = 97.9\%$). We found no difference between ESD and EMR in disease-free survival or periprocedural bleeding.

Only 1 study assessed EMR recurrence based on margin status,⁴³ and 30 of 39 recurrences (76.9%) occurred in lesions with positive deep margins. Similarly, 1 study assessed recurrence by margin status after ESD, and 100% of recurrences were associated with positive deep margins.^{43,51,55,56} In 13 studies of 4450 patients having received ESD, there were 69 local recurrences^{2,43,45,49-51,54,56-62}; 9 patients were treated with EMR, 29 patients with repeat ESD, 28 patients with surgery, and 3 with argon plasma coagulation. Of the 8 studies assessing the rate of detection of metachronous cancer in 2701 patients,^{2,54,56-59,61,62} 149 metachronous lesions (5.5%) were detected within 12 months.

Postresection surveillance was variable in included studies and occurred at as early as 3 months or as late as 12 months. Most studies used a program of endoscopic surveillance that began with endoscopy at between 3 and 12 months after resection, followed annually, with earlier and more frequent surveillance generally used in cases of noncurative resection. Postresection cross-sectional imaging with CT was generally performed at 6 to 12 months after resection.

We found no direct comparisons of the cost of ESD versus EMR for GAC. There were no available data on patient values on EMR versus ESD in this setting, but the patient representative on the panel emphasized the importance of presenting comparative data to patients in a clear but simplified form.

Discussion

ESD has a well-established body of evidence supporting its use in early-stage gastric lesions.^{63,64} The following are specific considerations discussed by the panel.

Size. The panel agreed that our guidelines should largely support the absolute and expanded resection criteria proposed in the existing Japanese gastric cancer treatment guidelines (Table 1).⁶⁵ These suggest that differentiated type T1a lesions without ulceration measuring up to 20 mm can be removed by EMR or ESD. In our results, mean GAC lesion size resected by EMR was 15.36 mm compared with 20.3 mm for ESD. This, in addition to our data showing lower risk of recurrence with ESD, led the

panel to suggest ESD preferentially over EMR for lesions over 20 mm in size.

Morphology and/or invasion. Lesion selection remains of upmost importance to reduce the risk of including lesions with LNM not suitable for ESD. Endoscopic features associated with submucosal invasive disease include irregular surface, marginal elevation of the lesion, and abrupt cutting or fusion of converging folds. Endoscopy with optical magnification and with dye or digital chromoendoscopy enhances diagnostic accuracy and staging, improves the ability to delineate the tumor margins, and helps in assessing feasibility of achieving an en-bloc resection.^{66,67} Meta-analyses have confirmed the presence of an acceptably low risk of LNM in patients with early-stage GAC treated according to the absolute criteria (.2%) and those treated according to the expanded criteria (.7%), which remain practically acceptable risks (Table 1).⁶⁸ Several studies showed comparable outcomes between the absolute and expanded indications.^{43,69}

The role of EUS in staging of early-stage GAC remains controversial and is driven by the presence of local expertise and is generally more valued in the West. The panel deliberated on the implications of either positive lateral or deep margins, submucosal tumor infiltration more than 500 μm , poorly or undifferentiated pathology, ulcerated tumors >3 cm size, and those with LVI, all of which become only evident on pathology analysis after ESD. Although referral to surgery is very appropriate in these cases, the panel emphasized the importance of a multidisciplinary review given the risks associated with gastrectomy. The long-term management strategy in the case of a positive lateral margin as the only noncurative criterion remains to be answered. However, there is mounting evidence that additional endoscopic therapy within 3 to 6 months after ESD can be sufficient in lieu of surgery and is associated with long-term remission.^{70,71}

Management of recurrence. We identified a small number of studies assessing ESD versus surgery for metachronous and/or recurrent early gastric cancer after endoscopic resection.^{70,72,73} However, these studies did not clearly differentiate between true recurrences and incomplete resections, and therefore no conclusions can confidently be made regarding surgery versus ESD for recurrent lesions. Studies assessing EMR versus ESD for recurrent disease, although similarly limited, clearly favor ESD.⁷⁴ We suggest that a multidisciplinary meeting should inform decision-making in this scenario.

Surveillance. All lesions with a T1b pathologic stage with negative deep margins should undergo endoscopic surveillance with consideration for CT and/or EUS and an earlier start of surveillance. We propose the first endoscopy should be in 3 to 6 months and then annually.^{75,76} Nevertheless, given the higher risk of recurrence after piecemeal resection and/or positive margin findings, we believe that in these contexts, biopsy sampling should be performed. Long-term surveillance is warranted given the

10% to 20% risk of synchronous and metachronous cancers.^{77,78}

Question 3b: In patients with early-stage GAC, should surgery or ESD be performed?

Recommendations: *The choice of endoscopic or surgical resection in patients with early-stage GAC depends on 3 factors: differentiation (well or moderate vs poor), type of cancer (intestinal vs diffuse), and size.*

- The ASGE suggests against surgical resection in lesions that meet all the following criteria: well- or moderately differentiated, intestinal type, early GAC measuring ≤ 3 cm
 - The ASGE suggests surgical resection over endoscopic approaches in lesions with poor differentiation measuring any size
 - See [Figure 3](#) algorithm for all considerations
- (Conditional recommendation, low quality of evidence)

Summary of evidence

We identified 20 studies that included 2947 patients having undergone ESD and 3484 patients having undergone surgery. Patients having undergone ESD experienced lower rates of clinical success (91.7% vs 99.5%; RR, .92; 95% CI, .89-.95; $I^2 = 88.1\%$), higher rates of local recurrence (2.1% vs .6%; RR, 4.27; 95% CI, 2.36-7.73; $I^2 = 9.4\%$), and lower rates of periprocedural infections (.3% vs 7.7%; RR, .12; 95% CI, .02-.71; $I^2 = 67.1\%$) compared with those who underwent surgery. The performance of ESD was associated with shorter procedure times compared with surgery (mean difference, 129.8 minutes less; 95% CI, 89.0-170.6; $I^2 = 99.1\%$). There were no differences in 30-day mortality (.1% vs .4%; RR, .34; 95% CI, .05-2.54; $I^2 = 78.3\%$), 4- and 5-year overall and disease-free survival, long-term mortality rates, stricture formation, or bleeding.

We found no direct cost comparisons of ESD versus surgery in the United States. However, 1 Korean study showed lower overall hospital costs associated with ESD compared with surgery.⁷⁹ The patient representative on the panel indicated a preference for ESD in appropriate cases of GAC because of earlier introduction of a diet, shorter hospital stay, and earlier resumption of daily activities. This is further supported by literature highlighting the positive impact on health-related quality of life perspectives associated with ESD when compared with gastrectomy.⁸⁰⁻⁸²

Discussion

A growing body of evidence has compared the performance of ESD with surgery, particularly as it relates to risk associated with the intervention. Our data clearly support that surgery was associated with higher postprocedure morbidity, as evident in the increased risk of

infections. Five patients (.38%) died within 30 days of surgery compared with 1 patient (.1%) in the ESD group. Death beyond 30 days was noted in 3 patients (2%) in the ESD group compared with 15 patients (7.1%) in the surgery group. However, this did not reach statistical significance, likely because of being underpowered.

Size. A decision to proceed with surgical evaluation and/or management over endoscopic resection in GAC should not typically be based on size but rather on the degree of differentiation (if known), diffuse type (over intestinal type), or clear ulceration. Lesions meeting expanded criteria ([Table 1](#)) could also still have potential LNM, which, if present, is not treated by ESD and could contribute to higher recurrence rates.

Morphology and/or invasion. A careful endoscopic examination of lesions with early-stage GAC is essential and can potentially predict the extent of submucosal invasion. Although the use of cross-sectional imaging and EUS for lesions with early-stage GAC remain controversial, a detailed endoscopic evaluation with the use of optical magnification and dye or digital chromoendoscopy remains an important step for assessing the mucosal surface, vascular pattern, and borders of the lesion before selecting the appropriate resection approach.^{83,84} In our review, surgery was associated with higher postprocedure morbidity than ESD. Furthermore, mortality within 30 days of surgery was .38% compared with .1% in the ESD group, and mortality beyond 30 days of surgery was 7.1% compared with 2% in the ESD group. The panel suggests against surgical resection for well- or moderately differentiated, intestinal type early GAC lesions measuring ≤ 3 cm given the relatively low risk of LNM in such lesions and the higher morbidity associated with surgery. However, the panel suggests surgical resection for tumors with poor differentiations regardless of the lesion size (see [Fig. 3](#) algorithm).

Management of recurrence. Management of residual GAC after noncurative ESD remains controversial. In practice, it is very difficult to confirm that all ESD recurrences are at the site of the primary resection or are a new metachronous lesion or previously missed synchronic lesion. Two meta-analyses suggested gastrectomy with lymph node dissection for patients undergoing noncurative endoscopic resection because of survival benefits.^{85,86} Because of the morbidity associated with gastrectomy, additional criteria have been discussed to identify higher-risk patients who may benefit from surgical resection versus those whose can be managed endoscopically. A meta-analysis by Zhao et al⁸⁷ identified LVI, deeper submucosal invasion (SM2 or deeper), and positive deep margins as factors favoring referral for additional surgery. For management of local recurrence, the panel recommended a multidisciplinary review and discussed various treatment options including referral to surgery if the patient is clinically fit and systemic therapy or endoscopic therapies if the patient is not candidate for surgical resection.

Surveillance. For lesions with a T1b pathologic stage but negative lateral and deep margins, the panel recommended endoscopic surveillance every 3 to 6 months for the first year and then annually, with consideration of cross-sectional imaging every 6 to 12 months for 3 to 5 years. However, for T1a lesions or high-grade dysplasia, the panel recommended endoscopic surveillance every 6 months for the first 3 years and then annually.

FUTURE DIRECTIONS

Our systematic review uncovered several gaps that represent priority areas for future research in the field of ESD for upper GI malignancy:

1. Randomized controlled trials to assess differences in outcomes between ESD, EMR, and surgical approaches
2. Studies with longer follow-up periods to assess potentially important differences in long-term survival outcomes
3. Studies assessing potential differences in various surveillance approaches after the initial resection
4. Comparative studies assessing approaches to treat recurrence after the initial (failed) resection including novel full-thickness resection techniques
5. Studies assessing the learning curves associated with each type of procedure studied
6. Cost-effectiveness studies to better gauge the impacts of procedure times, costs, and recovery

SUMMARY AND CONCLUSIONS

These ASGE guidelines summarize the best available evidence regarding the role of ESD versus EMR or surgery in the management of esophageal and gastric neoplasia. Although endoscopic tissue resection plays an increasingly crucial role in the management of esophageal and gastric cancers, safe and efficient performance depends on endoscopist expertise and local availability.

GUIDELINE UPDATE

ASGE guidelines are reviewed for updates approximately every 5 years or in the event that new data may influence a recommendation. Updates follow the same ASGE guideline development process.

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Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GAC, gastric adenocarcinoma; LNM, lymph node metastasis; LVI, lymphovascular invasion; RR, relative risk.

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