Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE American Society for Gastrointestinal Endoscopy

American Society for Gastrointestinal Endoscopy guideline on endoscopic submucosal dissection for the management of early esophageal and gastric cancers: methodology and review of evidence

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

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This document from the American Society for Gastrointestinal Endoscopy (ASGE) provides a full description of the methodology used in the review of the evidence used to inform the final guidance outlined in the accompanying Summary and Recommendations document regarding the role of endoscopic submucosal dissection (ESD) in the management of early esophageal and gastric cancers. This guideline used the Grading of Recommendations, Assessment, Development and Evaluation framework and specifically addresses the role of ESD versus 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, the ASGE suggests surgical evaluation over endosic approaches. (Gastrointest Endosc 2023;98:285-305.)

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 resection is a safe, effective, and minimally invasive treatment for various GI neoplastic lesions. Endoscopic resection encompasses endoscopic submucosal dissection (ESD) and EMR, both of which have replaced surgery as first-line therapies in the management of several preneoplastic lesions and early stage cancers of the GI tract. Endoscopic resection can be highly effective in eradicating early malignant lesions when performed for appropriate indications by expert endoscopists.

Although several technical modifications of EMR have evolved over time, EMR procedures involve the basic technique of using a snare to resect the mucosa with or without the assistance of bands or caps. Hence, specimens that can be removed en bloc by EMR generally measure under 2 cm, whereas larger lesions require several distinct resections (piecemeal resection). This limitation in en-bloc lesion size is likely the most significant factor prohibiting the application of EMR in larger early-stage cancers, because of the inability to determine whether the lateral resection margins are disease-free based on the fragmentation or thermocautery injury of pathology specimens. ESD, which instead relies on cutting knives for dissection, largely mitigates this limitation by allowing en-bloc resection of larger lesions. Achieving a margin-free en-bloc resection has been reliably associated with a lower risk of locoregional tumor recurrence.[1] The basic technique of ESD involves several steps: the initial delineation of lesion margins, followed by submucosal lifting of the lesion using various available solutions, then dissecting the submucosa to lift the lesion away from the muscularis propria, and, finally, cutting the mucosal margins of the lesion and completing the en-bloc resection.[2] To enhance the efficiency of submucosal dissection (which is the most time-consuming part of the procedure), various new techniques have been described such as the pocket technique, the tunneling technique, and the introduction of novel traction devices.[3,4]

Determining the presence of invasive disease in a malignant lesion can be challenging, as mucosal biopsy specimens often do not include sufficient submucosal representation to allow an accurate assessment. Several morphology-based classifications of invasiveness have been developed to assist with this process, including the Kudo pit pattern system,[5] the Paris classification,[6] and various narrow-band imaging–based classifications.[7,8] The decision on whether to perform EMR versus ESD for lesions with no invasive components can be difficult and depends on numerous patient- and lesion-related factors.[9-12] Similarly, although EMR is generally sufficient for small premalignant lesions and malignant lesions with no invasive component (ie, carcinoma in situ), the management of more advanced (but still early-stage) cancers of the upper GI tract is less straightforward. Although it is generally accepted that malignant lesions with invasion of the submucosa should not be removed by EMR, it is unclear which of these lesions are best managed by ESD versus surgery, given that each approach carries its own set of advantages and disadvantages including a unique set of potential adverse events (AEs).[13]

Pioneered in Asia, the application of ESD continues to grow in Europe and North America but remains limited to large referral centers with expertise in third-space endoscopy. This could be related to underlying population risks and to the lack of dedicated screening programs for upper GI cancers in the West (outside of Barrett's esophagus [BE]), reducing the potential opportunity for intervention using endoscopic resection for early-stage malignancies. Furthermore, EMR is generally less technically demanding and time-consuming compared with ESD. These factors make selection of the optimal modality even more difficult for clinicians treating patients with early-stage upper GI malignancies. Therefore, formal guidance is needed on the appropriate selection of patients for ESD (vs EMR or surgery) for early-stage esophageal and gastric cancer.

AIMS AND SCOPE

The aim of this American Society for Gastrointestinal Endoscopy (ASGE) guideline is to provide evidence-based recommendations on the use of ESD in the management of early-stage esophageal and gastric cancers. This document, subtitled "Methodology and Review of Evidence," provides a detailed account of the evidence synthesis process that ultimately led to our recommendations, summarized in the article subtitled "Summary and Recommendations" that accompanies this document.

Throughout these 2 documents, the term "early-stage" refers to malignant tumors with no locoregional or distant spread where the tumor remains confined to the mucosa and submucosa only. 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?

METHODS

Overview

This document was prepared by the Standards of Practice Committee of the ASGE and is a continuation of our society's effort to produce evidence-based clinical guidelines using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[14] GRADE is a standardized and transparent process for assessing and presenting summaries of evidence with the

TABLE 1. GRADE categories of quality of evidence and corresponding meaning and interpretation[15] and implications of the strength of GRADE recommendations on various stakeholders[133]

Quality of evidence	Meaning	Interpretation
High	We are confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate	We are moderately confident in the estimate of the effect; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an impact on our confidence in the estimate of the effect and may change the estimate.
Low	Our confidence in the estimate of the effect is limited; the true effect may be substantially different from the estimate of the effect.	Further research is very likely to have an impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low	We have very little confidence in the estimate of the effect; the true effect is likely to be substantially different from the estimate of the effect.	Any estimate of the effect is very uncertain.
Implications for	**Strong recommendation**	**Conditional recommendation**
Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the test. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Compliance with this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders.

GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

goal of informing evidence-based clinical practice recommendations.[15] For all early upper GI cancers, all evidence comparing ESD with EMR and comparing ESD with surgery was considered, where available. For EAC, comparative evidence between ESD and surgery was not available; hence, our recommendations focus only on ESD versus EMR for EAC.

The recommendations in this guideline document were based on an up-to-date meta-analysis of the available literature for each clinical question. The quality or certainty of evidence and strength of recommendations were based on the GRADE approach and followed the evidence-to-decision framework.[16]

Evidence profiles were created with the help of GRADE methodologists (B.S., R.L.M., and N.F.), and a guideline development panel was held virtually on March 29, 2022 where the evidence was reviewed and recommendations were generated. In developing our recommendations, we took into consideration the certainty of the evidence, benefits and harms of different management options, patient values and preferences, resource utilization including direct costs, cost-effectiveness, health equity, acceptability, and feasibility. The final wording of the recommendations including direction and strength were approved by all members of the panel and the ASGE governing board. Strong recommendations are typically stated as "we recommend…," whereas conditional or more closely balanced recommendations are indicated by the phrase "we suggest…." The meanings and interpretations of various qualities of evidence and the implications of corresponding recommendations are summarized in Table 1.

Formulation of clinical questions

Clinical questions were conceptualized by the authors of the documents and members of the ASGE Standards of Practice Committee and approved by the Governing Board. The questions followed the PICO format: P, population; I, intervention; C, comparator; and O, outcomes of interest.[17]

TABLE 2. Summary of guideline questions according to population, intervention, comparator, and outcomes

Population	Intervention	Comparator	Outcomes and importance
Patients with early-stage ESCC	ESD	EMR	• Clinical success (en-bloc R0 resection): critical • Technical success (gross lesion removal): important • Short-term adverse events (≤30 days), ie, bleeding, perforation, infection, death: critical • Long-term adverse events (>30 days), ie, stricture formation: important • Tumor recurrence (local/distant): critical • Time to recurrence: important • Overall survival: critical • Disease-free survival: critical • Disease-specific mortality: critical • All-cause mortality: critical • Procedural duration: important • Length of hospitalization: important • Adequacy of histologic specimen: important
Patients with early-stage ESCC	ESD	Surgery	(Same as above)
Patients with early-stage esophageal adenocarcinoma	ESD	Surgery	(Same as above)
Patients with early-stage GAC	ESD	EMR	(Same as above)
Patients with early-stage GAC	ESD	Surgery	(Same as above)

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

For all clinical questions, relevant outcomes were identified a priori and rated from not important to critically important for decision-making through a consensus process. A detailed list of PICO questions and outcomes is provided in Table 2. The guideline addresses the differential clinical outcomes in patients treated with EMR or surgery compared with ESD including short- and long-term AEs and survival when available.

Literature search and study selection criteria

To inform the evidence review, comprehensive electronic searches of PubMed, Embase, Web of Science, Ovid, and Cochrane EBM Reviews were designed and carried out by an experienced health research librarian from the inception of each database through the search date of September 17, 2020. In addition, the reference sections of any relevant meta-analyses or articles were manually reviewed, as were 5 years of proceedings (2016-2020) from the following conferences: Digestive Disease Week, American College of Gastroenterology's annual scientific meeting, United European Gastroenterology Week, and Society of American Gastrointestinal and Endoscopic Surgeons. The searches were limited to comparative studies published in the English language. To be considered eligible, studies were required to meet all inclusion criteria (English language, comparative study, 1 or more outcomes of interest assessed) and were excluded if any exclusion criteria were met (case report or review, case series, cohort study with no comparator arm, comparative study with <10 patients included, missing or incomplete data).

The full search strategy is provided in Appendix 1 (available online at www.giejournal.org). Citations were imported into EndNote (Thompson Reuters, Philadelphia, Pa, USA), and duplicates were removed. The library was uploaded into Covidence (Covidence, Melbourne, Victoria, Australia), and 3 reviewers (M.A.A., S.E.E., and N.F.) screened titles and abstracts for eligibility, with the first 2 independent assessments used to determine inclusion or exclusion in the next stage and with disagreements resolved by consensus. Full-text screening then took place in a similar fashion, with disagreements again resolved by consensus.

Data extraction and statistical analysis

Data were abstracted using a pilot-tested and standardized form. To avoid overinclusion of patients with low-grade and nondysplastic pathology, only studies with fewer than 25% of lesions with low-grade dysplasia (LGD) or nondysplastic neoplasia were included in the final analyses. When appropriate, for each outcome, measures of effect comparing ESD (the interventional group) and EMR or surgery (the comparator groups) were summarized using forest plots.

Relative risks (RRs) were reported for dichotomous outcomes, and weighted mean differences were reported for continuous outcomes, with each presented along with their associated 95% confidence intervals (CIs). Meta-analysis was carried out with DerSimonian and Laird random-effects models. In the primary analyses, the Yates correction was used wherein a value of .5 was inputted to all cells in outcomes with no events in any of the treatment arms.[18] Studies with no events in both arms were excluded. A sensitivity analysis was used where instead of the Yates correction, a Sweeting correction was used for single-zero studies (the reciprocal of the opposite group arm size was inputted).[19] The Cochrane I^2 statistic was used to measure

TABLE 3. 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
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. There is well (G1) or moderate (G2) differentiation 3. There is no lymphovascular invasion 4. There is 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

and report statistical heterogeneity.[20] Publication bias was assessed visually using funnel plots for all outcomes with 10 or more studies.[21] Risk of bias assessment, using the Newcastle-Ottawa scale,[21] was performed by 3 independent authors (M.A.A., S.E.E., and N.F.). Statistical analyses were performed using RStudio version 1.2.1335 (Integrated Development Environment for R, Boston, Mass, USA).

Certainty of evidence (quality of evidence)

The certainty of evidence was assessed using the GRADE approach. Randomized controlled trials (RCTs) start at an initial certainty level of *high* and nonrandomized studies at an initial certainty level of *low*. Reviewers assessed methodologic limitations (risk of bias), inconsistency, indirectness, imprecision, and publication bias and, for nonrandomized studies, potential large-study effects, dose–response gradients, and plausible confounding.[22] The final certainty of evidence ranges from *very low* to *high* (Table 1). When the results of meta-analyses and the assessments above were used, a GRADE evidence profile was prepared for each clinical study using the GRADEpro GDT application (http://gdt.guidelinedevelopment.org/app). 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.

Panel composition and conflict of interest management

The entire body of evidence was presented at a guideline development panel that took place virtually on March 29, 2022 and included the Standards of Practice Committee members, an oncologist (I.S.), a GI surgeon (E.P.C.), a GI pathologist (M.M.F.), ESD content experts (P.V.D. and M.O.O.), an expert on reimbursement (V.K.), a GRADE methodologist (N.F.), and a patient representative (Dr Katia Gugucheva). All members were asked to disclose their respective conflicts of interests based on the relevant ASGE policies (available at https://www.asge.org/forms/conflict-of-interest-disclosure and https://www.asge.org/docs/ default-source/about-asge/mission-and-governance/asge-conflict-of-interest-and-disclosure-policy.pdf).

Definitions and pathologic considerations

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. Terms and definitions used throughout this guideline can be found in Table 3.

In the esophagus, squamous cell neoplasia encompasses various grades of neoplasia, including LGD, high-grade dysplasia (HGD), carcinoma in situ, and invasive ESCC. Depth of mucosal extent of invasive carcinomas is subdivided into M1 (carcinoma in situ), M2 (microinvasive carcinoma into the lamina propria), and M3 (invasion into the muscularis mucosa). Depth of submucosal invasion is classified as invasion into the upper third (SM1), middle third (SM2), or lower third (SM3). The exact depth of invasion can be difficult to assess on ESD specimens. Therefore, the maximum depth of submucosal invasion (in μm) can be measured instead. In the esophagus, SM1 depth of invasion is $\leq$200 μm. In this document, "early-stage ESCC" encompasses all mucosal tumors and those extending to the submucosa with no lymphadenopathy or distant metastasis on pre-endoscopic resection staging.

TABLE 4. Summary of clinical recommendations

Clinical question/population	American Society for Gastrointestinal Endoscopy recommendation	Strength of recommendation, quality of evidence
Patients with • Esophageal 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
Patients with • Esophageal 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
Patients with • Esophageal dysplasia or early, well-differentiated, nonulcerated ESCC without submucosal invasion	We suggest against surgery	Conditional recommendation, low quality of evidence
Patients with • 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
Patients with • Early-stage EAC (T1) or Barrett's nodular dysplasia • Well differentiated, nonulcerated • Measuring ≤20 mms	We do not make a recommendation for or against either ESD or EMR	Conditional recommendation, low quality of evidence
Patients with • 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
Patients with • 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 ≤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

Please also refer to the algorithms in Figures 1-3.

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

Barrett's neoplasia is also subdivided into LGD, HGD, and carcinoma. Invasive carcinoma that extends into the submucosal layer should be further qualified into thirds (SM1-SM3). When the maximum depth of submucosal invasion is measured, the limit for SM1 in Barrett's carcinoma is ≤500 μm.[23] In this document, "early-stage EAC" encompasses all mucosal tumors and those extending to the submucosa with no lymph node or distant metastasis on pre-endoscopic resection staging.

In the stomach, neoplasms can be classified into LGD, HGD, and carcinoma. Carcinoma is subdivided into mucosal carcinoma (M-type, staged as T1M) and submucosal carcinoma (SM1toSM3 type, staged as T1SM). SM1 tumors involves a depth of invasion ≤500 μm. The types of carcinomas are classified according to the World Health Organization classification and to the Lauren classification (intestinal type, diffuse type, and mixed).[24,25]

RESULTS

A summary of recommendations for each clinical question is provided in Table 4. In addition to the recommendations provided, we prepared accompanying clinical care algorithms with additional details based on patient and lesion characteristics. These algorithms are provided in Figures 1 to 3 as well as in the "Summary and Recommendations" document. For each recommendation, we discussed important considerations including lesion size and morphology as important determinants of resection technique as well is treatment of recurrence and surveillance protocols.

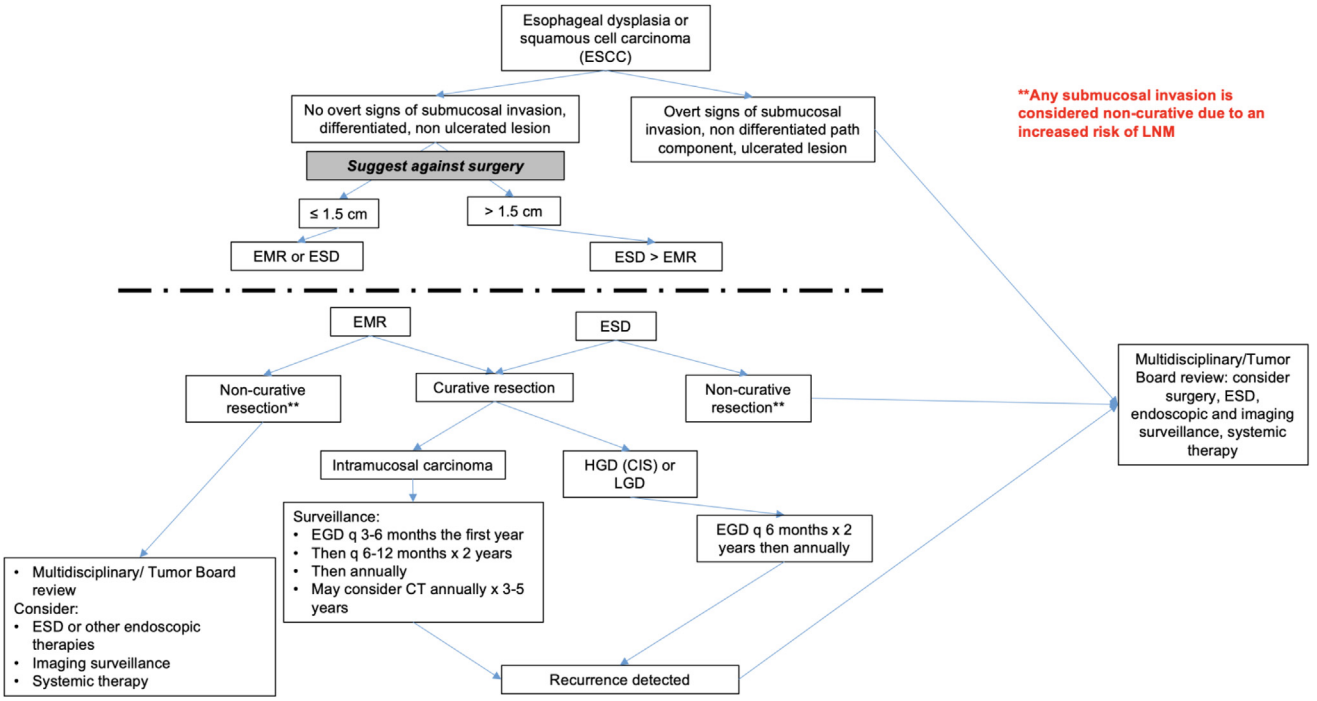


Figure 1. Recommended clinical care algorithm for patients presenting with early-stage ESCC. *ESCC*, Esophageal squamous cell carcinoma; *ESD*, endoscopic submucosal dissection; *LNM*, lymph node metastasis; *HGD*, high-grade dysplasia; *CIS*, carcinoma in situ; *LGD*, low-grade dysplasia.

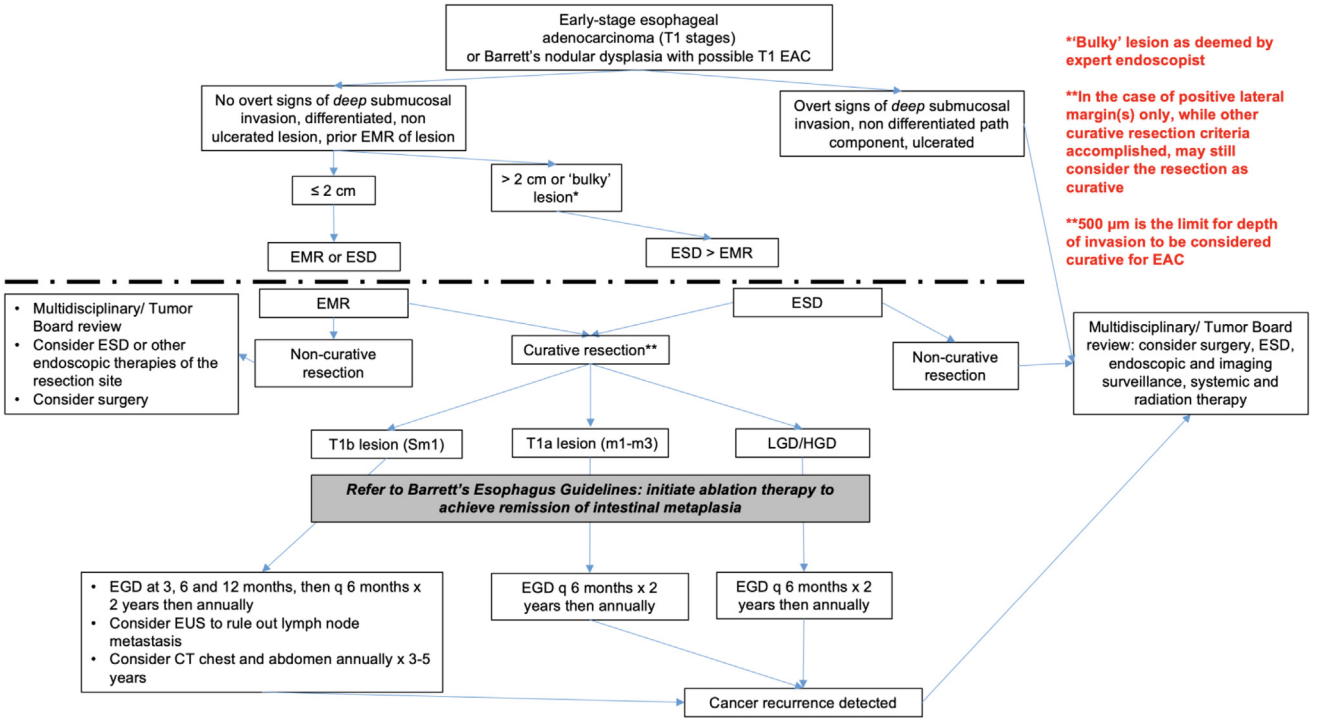


Figure 2. Recommended clinical care algorithm for patients presenting with early-stage EAC. *EAC*, Esophageal adenocarcinoma; *ESD*, endoscopic submucosal dissection; *HGD*, high-grade dysplasia; *LGD*, low-grade dysplasia.

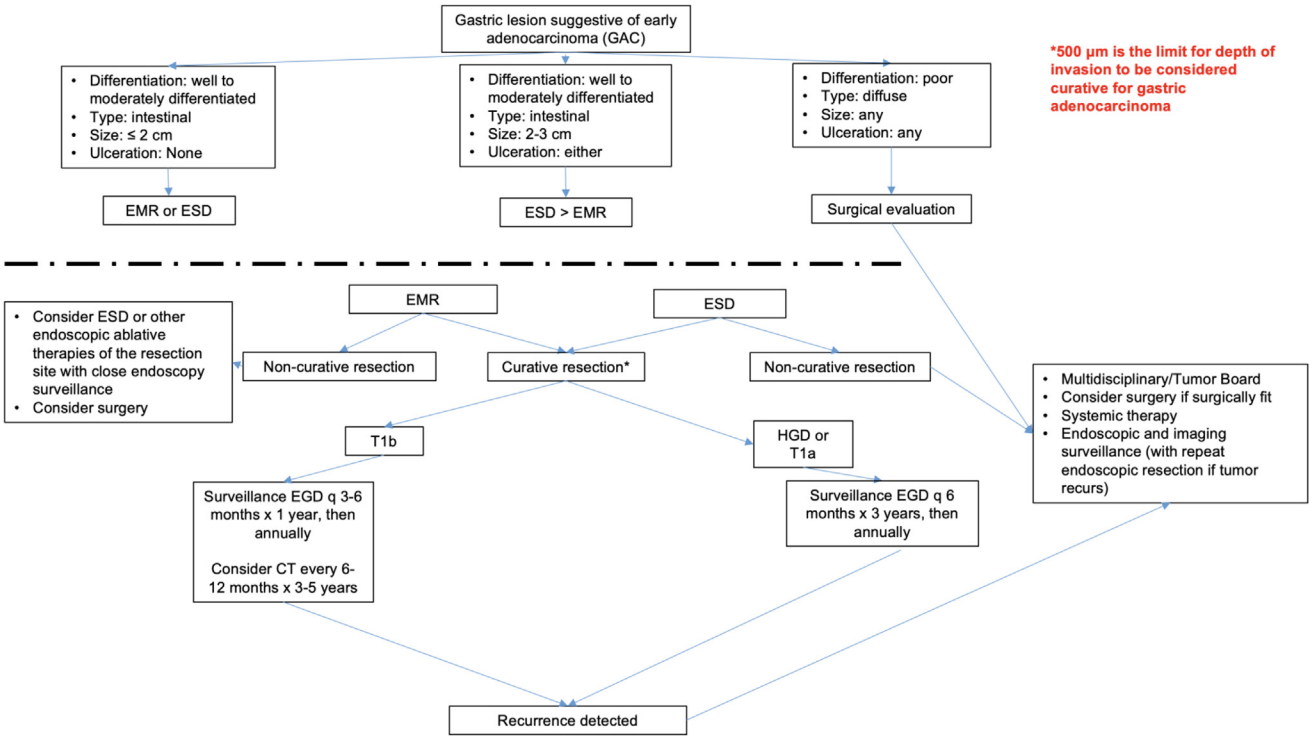


Figure 3. Recommended clinical care algorithm for patients presenting with early-stage GAC. *GAC*, Gastric adenocarcinoma; *ESD*, endoscopic submucosal dissection; *HGD*, high-grade dysplasia.

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 dysplasia or early, well-differentiated, nonulcerated squamous cell carcinoma, the ASGE suggests that the resection strategy be 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 recommendations, low quality of evidence)

Evidence. We identified 8 comparative studies meeting eligibility criteria that reported on any relevant outcome(s) in 821 patients receiving ESD and 1306 patients receiving EMR.[26-33] A Preferred Reporting Items for Systematic Reviews and Meta-analyses diagram detailing study screening and inclusion is provided in Figure 4, which outlines the search and screening process for all review questions in this guideline. All 8 studies were observational. In 6 observational studies including 473 ESD patients and 594 EMR patients, a higher clinical success rate of 93.3% was observed in the ESD cohort compared with 72.1% in the EMR cohort (RR, 1.33; 95% CI, 1.02-1.74; very low certainty of evidence). In 8 observational studies totaling 776 patients treated with ESD and 1289 patients treated with EMR, local recurrence rates were lower with ESD, at .5% and 5.2% respectively (RR, .19; 95% CI, .07-.48; I^2 = .0%). No differences were observed in the rates of distant recurrence between the 2 cohorts (1.9% vs 1.1% for ESD and EMR, respectively), with an RR of 1.35 (95% CI, .50-3.65; I^2 = 0.0%). based on 3 observational studies.

AEs associated with endoscopic resections were generally low. In 5 observational studies, bleeding was observed in 2.2% versus 1.7% of patients with ESD versus EMR, respectively (RR, 1.55; 95% CI, .60-4.03; I^2 = 31.8%). The risk of perforation was significantly higher with ESD in 8 observational studies (5.7% vs .8%; RR, 4.30; 95% CI, 1.22-15.12; I^2 = 61.3%). The perforation rates in esophageal ESD were mostly amenable to endoscopic management, with 32 of 34 perforations (94.1%) successfully treated with endoscopic clipping, whereas 2 of 34 perforations (5.9%) required surgical management. The rates of stricture formation in 5 observational studies were similar between ESD and EMR (9.2% vs 7.4%; RR, 1.2; 95% CI, .68-2.11; I^2 = 36.5%). 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%). Forest plots for these findings are presented in Supplementary Figures 1-7, available online at www.giejournal.org. No direct data were available regarding cost-effectiveness in this population. The panel discussed the importance of averting the high costs of surgery where possible, which justified the increased time required to perform ESD. No data were no available on patient values on EMR versus ESD in this clinical

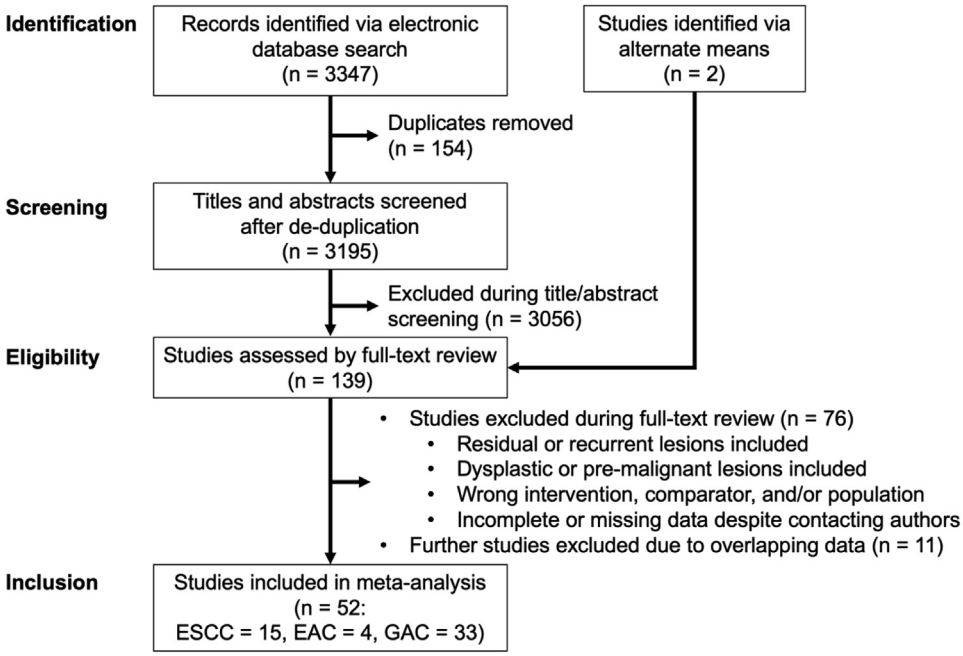


Figure 4. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram outlining search and screening results. *ESCC*, Esophageal squamous cell carcinoma; *EAC*, esophageal adenocarcinoma; *GAC*, gastric adenocarcinoma.

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.

Certainty in the evidence. There were significant sources of potential bias, particularly related to the degree of selection and comparability of patients managed by EMR versus ESD. We also rated down for inconsistency for clinical success given the high I^2 values exceeding 90%. There were no major concerns relating to the studies included in assessing local recurrence but were concerns with inconsistency (I^2 values exceeding 90%) in the studies reporting on procedural time. There were no issues with indirectness with any of the included studies. A full evidence profile for this question is provided in Supplementary Table 1 (available online at www.giejournal.org), with a full description of outcomes and studies included for Questions 1a and 1b provided in Supplementary Tables 2 and 3, respectively (available online at www.giejournal.org).

Discussion. *Lesion size.* In ESCC, lesion size continues to strongly impact the choice of endoscopic resection modality because of the necessity of en-bloc resection to provide cure or as staging to guide further treatment decisions. Additional factors that weigh in on the choice of resection approach include depth of invasion, histopathologic type, and presence of ulceration. ESD is preferred not only in lesions with suspected invasion of the muscularis mucosa with no lymph node metastasis (LNM), but also in those that exceed 1.5 cm in size. However, in 1 study, the risk of LNM and local recurrence was increased in lesions >5 cm,[34] no limit on size has been determined, and ESD continues to be offered to patients with large and circumferential lesions that are confined to the mucosa.

Our analyses found no direct comparative data on lesion size in ESD versus EMR. Recurrence rates for piecemeal EMR of ESCC were reported to be up to 25%.[35,36] Based on the mean lesion size removed by EMR in our analyses, the panel chose a cutoff of 15 mm. Lesions >15 mm should preferably not be resected with cap-assisted EMR but rather with ESD. Although size-stratified meta-analyses would have been optimal, these were not possible given the input data. Furthermore, the panel wished to re-emphasize the conditional recommendation in support of a 15 mm cutoff but that this should not be considered a strict cutoff, and the decision to proceed with ESD should be based on several other considerations, such as local availability and expertise, endoscopist's discretion, and patient preferences. No upper limit on lesion size 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 LNM. However, determining the depth of invasion before endoscopic resection remains challenging. The risk of LNM increases to up to 18% for lesions invading the muscularis mucosae (M3), up to 50% for lesions invading the submucosal layer to ≤200 μm (SM1), and up to 54% for deeper lesions (SM2-SM3).[37,38] 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, whereas

the relative indication was defined as M3 to SM1 lesions and where endoscopic resection would leave a mucosal defect of circumferential extent exceeding 75%.[37-39] Tumors with T1 stages of M1 (intraepithelial) or M2 (invading the lamina propria) are typically associated with negligible-risk LNM.

EUS remains the standard tool for T staging with positive predictive values previously reported to be as high as 75% to 100%. EUS remains superior to CT in assessing T and N staging[40]; however, its utility in accurately predicting the depth of submucosal invasion remains limited. Selection bias could reduce the impact of these data. In Japan, Lugol chromoendoscopy and narrow-band imaging have been adopted and are increasingly replacing EUS with promising accuracy for prediction of depth of invasion by enhancing and characterizing the boundaries and the microvascular pattern of the lesion.[41-44] Besides the depth of invasion, the incidence of LNM correlates closely to tumor histology and differentiation (G1-G2 vs G3). Endoscopic resection should be limited to well-differentiated lesions.

Management of recurrent lesions. Our analyses demonstrated that local recurrence rates were lower with ESD, at .5% compared with 5.2% in lesions treated by EMR. 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 in many of these lesions, particularly if a patient is not fit for surgery. However, data to inform on the comparative effectiveness of various strategies to manage recurrence are limited. Forest plots for these findings are presented in Supplementary Figures 8-14, available online at www.giejournal.org.

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 to be performed every 3 to 6 months for the first year, then every 6 to 12 for the following 2 years, and then annually. However, patients with only HGD or LGD can undergo post–endoscopic resection endoscopic surveillance every 6 months for the first 2 years and then annually thereafter (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 dysplasia or early, well-differentiated, nonulcerated ESCC, without overt signs of submucosal invasion, the ASGE suggests against surgical resection.*

(*Conditional recommendation, low quality of evidence*)

Evidence. We identified 5 observational comparative studies meeting eligibility criteria that reported on 463 patients treated with ESD and 495 patients treated with surgery.[45-49] In 3 observational studies that included 463 ESD and 495 surgery patients, a lower clinical success rate of 87.5% was observed in the ESD cohort compared with 98.2% in the surgery cohort (RR, .85; 95% CI, .74-.98; I^2 = 84.6%). Local recurrence was assessed in 2 observational studies of 190 patients treated with ESD and 351 patients treated with surgery, with no differences in local recurrence rates between ESD and surgery (4.7% vs 6.8%; RR, 1.14; 95% CI, .60-2.17; I^2 = 0.0%). There was no difference in distant recurrence with surgery compared with ESD (9.0% vs 3.6%; RR, .48; 95% CI, .14-1.64; I^2 = 27.8%). 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%). Of note, no mortality was reported beyond 30 days in the ESD group. However, there was no difference in periprocedural bleeding or long-term stricture formation. No difference in 5-year overall survival was observed in our analysis based on 2 observational studies.

No direct comparisons of costs were available in this population, but 1 study assessing patients with EAC largely favored endoscopic resection to surgery given a shorter hospitalization, even after accounting for the need for future endoscopic surveillance.[50] 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.

Certainty in the evidence. No significant issues with bias were found except in 1 study[46] assessing the 5-year overall survival as determined using the Newcastle-Ottawa tool. There were no concerns with imprecision with the outcomes of local recurrence, distant recurrence, bleeding, stricture formation, and 5-year overall survival because of the small number of events. However, we rated down for inconsistency for clinical success (I^2 = 84.6%). There were no issues with indirectness with any included study. A full evidence profile for this question is provided in Supplementary Table 4 (available online at www.giejournal.org).

Discussion. Esophagectomy has traditionally been the criterion standard for early-stage ESCC; however, it is associated with 30-day mortality rates of 4% to 10%.[51] The long-term outcomes of ESD in comparison with esophagectomy remain less understood, especially in lesions invading SM1, where the risk of LNM is slightly increased. When compared with other esophageal cancers like those arising from BE, the propensity for LNM is higher with ESCC; hence, accurate lesion staging and pathologic assessment of the resected specimen are very important.

Decision-making for primary esophagectomy is complex. Systemic therapy (including radiation, chemotherapy, and immunotherapy) offers a reasonable and effective

treatment option for those with metastatic and locally advanced disease who are not surgical candidates.[52] Therefore, the potential for curability with endoscopic resection for ESCC and the opportunity for staging are both achievable with an en-bloc histologic specimen. Unlike BE, no screening programs are endorsed for ESCC in the West. In Japan, a national screening program yields more early-stage ESCC compared with the West, where patients might present with more advanced stages of disease not amenable to endoscopic resection.

It is important to note that previous ESD does not preclude patients from receiving additional future therapies (surgery or systemic therapy). The risks associated with AEs related to ESD such as perforation and possible delays in providing definitive therapy like surgery should be considered but overall remain nonprohibitive of staging endoscopic resection.

The panel considered additional evidence on cost-effectiveness analyses, patient values, patient preferences, and harm. None of the studies included in our analyses compared direct costs of care between endoscopic and surgical techniques. Comparative cost-effectiveness analysis in the ESCC literature is lacking, but direct cost analysis in EAC favors endoscopic resections compared with surgery largely because of the shorter hospital stay, despite the need for repeated endoscopic sessions for primary treatment and surveillance.[50] The panel weighed heavily on the views expressed by the patient representative on the panel strongly supporting endoscopic resection in lesions amenable to EMR or ESD and low value on any burden or harms associated with esophageal surgery. None of the studies included in our analyses, or any others found by a search of the literature, compared patient preferences specific for ESCC treatments.

Lesion size. As per the algorithm in Figure 1 and our recommendations, we suggest against surgery for ESCC in the absence of overt signs of submucosal invasion (Paris classification types 0-I, 0-IIc, and 0-III), ulceration, or poor differentiation, regardless of size. However, we acknowledge the practical and technical limitations to performing ESD beyond a certain size range. Therefore, particularly very large lesions (>5 cm) should likely 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 availability and expertise, endoscopist discretion, and patient values.

Morphology and/or invasion. ESD remains the preferred method for resecting potentially curative lesions (mucosal stage up to M3 in all patients and up to SM3 in patients with higher surgical risk). Because of the lower risk of short-term mortality associated with ESD, the panel recommended ESD be considered for nonulcerated, well-differentiated lesions with low risk of submucosal invasion (see Fig. 1 agorithm). Patients presenting with lesions with ulceration, suspected submucosa invasion, or with poorly differentiated pathology are recommended to be referred 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 preference. Given the 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, particularly those with high risk for surgery and those with multiple comorbidities.

Management of recurrent lesions. As above, 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. From limited numbers of observational studies, there were no significant differences between ESD and surgery in terms of local or distant recurrence. Definitive systemic therapy may be considered as a treatment in those with local recurrence who are not candidates for endoscopic or surgical options. Again, data to inform clinicians on the comparative effectiveness of different strategies to manage recurrence are limited.

Surveillance. Data to inform clinicians on the comparative effectiveness of different surveillance strategies are limited. 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. For T1a lesions, we propose surveillance endoscopy to be performed every 3 to 6 months for the first year, then every 6 to 12 for the following 2 years, and then annually. However, lesions with only HGD or LGD can be surveyed by performing endoscopy every 6 months for the first 2 years and then annually (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 that the resection strategy should be based on lesion size:*

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

(Conditional recommendations, low quality of evidence)

Evidence. Our search identified 4 studies meeting eligibility criteria that reported on 247 patients treated with ESD and 761 patients treated with EMR.[53-56] Three studies were observational and 1 was an RCT.[53] Clinical success rates were similar in the ESD group (76.1%) compared with the EMR group (64.6%; RR, 1.38; 95% CI, .83-2.29; I^2 =

93.9%). Local recurrence rates were 3.2% for ESD versus 26.1% for EMR (RR, .19; 95% CI, .04-.98; I^2 = 52.8%). Bleeding was significantly lower with ESD compared with EMR (2.2% vs 10.5%; RR, .32; 95% CI, .13-.78; I^2 = 1.0%). The risks of perforation or stricture formation were not different. Two studies reported on post-ESD treatment of perforations,[53,56] with all 3 patients treated with endoscopic clipping (including the use of an over-the-scope clip in 1 patient). No studies reported on the treatment of post-EMR bleeding or perforation. In EAC, none of the studies classified recurrences based on margin status, depth of invasion, or lymphovascular invasion (LVI). Data on recurrence treatment were available on 1 ESD patient only,[53] who was successfully treated with EMR. No data were available on any EMR recurrences Forest plots for these findings are presented in Supplementary Figures 15-19, available online at www.giejournal.org.

Certainty in the evidence. No significant issues with bias were found except in 1 study[56] when assessing the curative resection outcomes, where concerns about selection bias and comparability domains emerged. This study carried 45% of the weight in a pooled analysis that resulted in imprecision and inconsistency across several outcomes. Also, concerns with inconsistency arose in the 3 included studies in regards to assessing the local recurrence outcome, where point estimates varied, the CIs of some of the studies did not overlap, and the magnitude of statistical heterogeneity was considerable, with I^2 = 52.8%. There were no issues with indirectness overall. A full evidence profile for this question is provided in Supplementary Table 5 (available online at www.giejournal.org), with a full description of outcomes and studies included for Question 2 provided in Supplementary Tables 6 and 7, respectively (available online at www.giejournal.org).

Discussion. Endoscopic resection is recommended for the removal of all visible abnormalities arising from BE.[57,58] The adoption of endoscopic therapy for Barrett's neoplasia was built on the evidence that HGD and T1m carcinoma are associated with a low rate of LMN, reported to be up to 10% in endoscopic and surgical series, whereas submucosal invasion, when present, carries a higher risk up to 46%.[59,60] Because of the inaccuracies of detecting the full extent of pathology in nodular lesions noted within BE, the ASGE recommends endoscopic resection, which has been shown to upgrade the pathology previously obtained by mucosal biopsy sampling by up to 40%.[61,62] Therefore, all lesions suspected to harbor cancer should be removed en bloc when possible, including those with Paris type I and IIa+c lesions. EMR of visible nodular lesions followed by eradication of residual BE reduces the risk of metachronous neoplasia and is widely accepted by Western endoscopists as the standard of care for early-stage Barrett's adenocarcinoma.[58,62]

Given the relative infrequency of BE in Asian countries, the data on ESD in BE remain very limited. Several studies and a meta-analysis established the safety and efficacy of ESD in BE.[63-65] Clinical success in endoscopic resection is judged by the ability to produce 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 confined to the superficial submucosa (<500 μm).[59,66] Lesions that do not fit these criteria are considered at higher risk for LNM. Similar 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.[63,67]

Because of length of the procedure and the technical complexity associated with ESD, AEs are higher in ESD compared with EMR. Our analysis does not reveal any significant differences between EMR and ESD in terms of risk of perforation or stricture formation, but the number of patients assessed was limited. The risk of bleeding, however, was higher in EMR, with reasons for this remaining unclear. We hypothesize that this may be related to the reduced ability to manage intraprocedural bleeding in EMR compared with ESD, where the operators are well versed in methods of hemostasis, as expected from those performing third-space endoscopy, and have access to the needed tools (needle-knives, coagulation forceps).

Our analysis reported lower curative rates of ESD in early-stage EAC compared with ESCC. The small number of studies and patients included (4 studies with 155 patients for this outcome) may have contributed to this. Terheggen et al[53] reported on 17 patients (10.9% of the weight of this outcome and the only RCT included) with only a 58.8% curative resection rate in a cohort of patients with Barrett's adenocarcinoma.

The panel considered additional evidence on cost-effectiveness, patient values, patient preferences, and harm. None of the studies included in our analyses compared direct costs of care between endoscopic and surgical techniques. A comparative cost-effectiveness analysis in the EAC literature is lacking, but very limited direct-costs analysis in EAC favors endoscopic resections compared with surgery. The reduced total costs of care in endoscopically managed EAC are largely because of the shorter hospital stay compared with esophagectomy, despite the need for repeated endoscopic sessions for primary treatment and surveillance.[50] The panel again relied heavily on the patient representative's views supporting endoscopic resection in lesions amenable to EMR or ESD and a low value on burden or harm associated with esophageal surgery. None of the studies included in our analyses, or any others found by search of the literature, compared patient preferences specific for esophageal surgical versus endoscopic adenocarcinoma treatments.

Lesion size. Both EMR and ESD can be used for early-stage EAC, but EMR remains the first-line therapy for BE, particularly in lesions measuring ≤20 mm. The panel deliberated on additional scenarios where ESD should prioritized

TABLE 5. Absolute, expanded, and relative resection criteria for endoscopic resection of early gastric cancer

Criteria	Recommendation
Absolute	For EMR or ESD: Differentiated-type T1a adenocarcinoma *without* ulceration measuring <20 mm For ESD: Differentiated-type T1a adenocarcinoma *without* ulceration measuring >20 mm OR Differentiated-type T1a adenocarcinoma *with* ulceration measuring ≤30 mm
Expanded	Undifferentiated-type T1a adenocarcinoma *without* ulceration measuring ≤20 mm
Relative	Lesions not fulfilling absolute *or* expanded criteria

ESD, Endoscopic submucosal dissection.
Adapted from Japanese gastric cancer treatment guidelines.[94]

over EMR in EAC and BE with nodular dysplasia. The panel deliberated 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. The benefit of ESD over EMR is less established for EAC and raised focal lesions in BE because of scant literature. 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 ligation-assisted EMR system.

Morphology and/or invasion. Although lesion morphology may predict the extent of submucosal invasion in early-stage EAC, it is widely accepted that the most accurate local staging remains pathology of endoscopically resected nodular lesion. Paris types 0-Is and 0-IIc lesions, where the depth of submucosal invasion can be estimated to exceed 500 μm, 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. Additionally, the panel deliberated on the 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, but this needs to be confirmed at repeat endoscopy. 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 BE ablation therapy after endoscopic resection to achieve eradication of remaining intestinal metaplasia.[58]

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. The feasibility of ESD in treating post-EMR recurrences can be extrapolated to post-ESD local recurrences, which is likely feasible in a proportion of these lesions. Other options include surgery (in appropriate patients), endoscopic ablative therapies, or systemic therapy.

Surveillance. We encountered no studies that assessed post-EMR or ESD surveillance systematically. We propose a risk-based approach derived from known risk factors for tumor recurrence and recommend endoscopy, EUS, and cross-sectional imaging studies for lesions with evident submucosal invasion but negative deep margins (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 mm.*
- *The ASGE suggests ESD over EMR in well- or moderatelydifferentiated lesions measuring 20 to 30 mm, with or without ulceration, intestinal type early GAC.*
- *See Figure 3 algorithm for all considerations.*

(*Conditional recommendations, low quality of evidence*)

Evidence. Our search identified 13 studies that met eligibility criteria and reported on 3232 patients treated with ESD and 3154 patients treated with EMR.[68-80] All studies identified were observational, except for 1 RCT[81] that compared outcomes of ESD-treated patients with cancer with a control group of EMR patients. ESD resulted in higher rates of clinical success in comparison with EMR (86.5% vs 54.4%; RR, 1.79; 95% CI, 1.40-2.30; I^2 = 98.2%). Similarly, the rates of local recurrence were significantly lower in the ESD group compared with the EMR group (1.7% vs 7.2%; RR, .16; 95% CI, .08-.33; I^2 = 74.7%). Reports on AEs demonstrated no difference between ESD and EMR in bleeding risk, but ESD was associated with higher perforation rates (3.7% vs 1.9%; RR, 2.23; 95% CI, 1.19-4.19; I^2 = 64.7%).

Disease-free survival data at 1, 3, and 5 years were mixed, with no clear trends in favor of 1 modality over another, although only 2 studies were available for each survival interval. Finally, in the 6 studies that reported on procedural time, the duration of ESD was longer than the duration of EMR (weighted mean difference, 48.93 minutes; 95% CI, 22.45-75.42; $I^2 = 97.9\%$). Only 1 GAC study reported on post-EMR recurrence based on margin status[69] whereby 30 of 39 recurrences (76.9%) occurred in lesions with positive deep margins. The same study was the only study that reported on post-EMR recurrences based on absolute or expanded criteria (Table 5), with 10 of 39 recurrences (25.6%; or 10/387, 2.6% of the entire cohort) occurring in the absolute criteria cohort and 29 of 39 recurrences (74.4%; or 29/387, 7.5% of the overall cohort) occurring in the expanded criteria cohort. Recurrence treatment was detailed in only 4 EMR studies with 85 local recurrences.[69,73,77,82] Repeat EMR was successful in 11 patients, whereas a mixed endoscopic approach was reported in 37 patients (EMR and ESD), and 37 patients with post-EMR recurrences were referred to surgery. No studies reported on metachronous lesions in the EMR cohort.

One study reported on endoscopic treatment of the 2 post-EMR bleeding cases.[30] Data available on post-EMR perforations from 3 studies included 7 perforations, of which 6 (85.7%) were treated with clipping and 1 (14.3%) required surgery. Data were available on treatment of post-ESD perforations in 6 studies, and among the 37 perforations, 31 (84%) were treated with conservative management and endoscopic closure (clipping) and 6 (16%) required surgery.

Only 1 ESD study reported on local recurrence stratified based on margin status. In that study, all 23 recurrences (100%) were associated with a positive deep margin.[69] Four studies classified recurrences after ESD based on absolute versus expanded criteria: 7 recurrences occurred in the absolute criteria group out of 1024 patients (.68%), whereas 22 recurrences occurred in the expanded criteria group out of 611 patients (3.6%).[69,77,83,84] Eight studies (including 2701 ESDs) evaluated for the detection of metachronous lesions[13,80,84-89] and reported a total of 149 metachronous lesions within 1 year (5.5%). Finally, data on local recurrence treatment of GAC were available in 13 ESD studies including 4450 patients with 69 local recurrences[13,69,71,75-77,80,84-90] that were successfully treated with EMR in 9 cases, repeat ESD in 29, surgery in 28, and argon plasma coagulation in 3. Forest plots for these findings are presented in Supplementary Figures 20-25, available online at www.giejournal.org.

The reviewed studies showed no definite pattern for endoscopic and imaging surveillance after endoscopic resection. Surveillance was initiated as early as 3 months or as late as 12 months in most studies. In the EMR cohort, 7 studies reported on postresection endoscopic surveillance using a combination of endoscopy from 3 to 12 months after resection and then annually. In the ESD cohort, 25 studies reported on the postresection surveillance using endoscopy from 3 to 12 months and then annually after resection, with a trend toward earlier and more frequent endoscopy in cases of noncurative resection. In the same cohort, 14 studies reported on postresection imaging surveillance with CTs 6 to 12 months after resection. Overall, no protocols tailored to depth of invasion, margin status, LVI, or tumor grade were noted in any of the studies included.

We found no direct comparisons of the cost of ESD versus EMR for GAC. Nevertheless, data from colorectal ESD versus EMR pointed to a lack of cumulative difference in total costs, with a small trend toward higher costs in EMR because of a higher number of surveillance endoscopies.[91] No data were available on patient values on EMR versus ESD in this setting, and the patient representative on the panel reemphasized the importance of presenting comparative data to patients in a clear but simplified form.

Certainty in the evidence. The 2 most critical outcomes (curative resection and local recurrence) both had problems with inconsistency. In the case of curative resection, the direction of the effect was not consistent between the included studies, and the magnitude of statistical heterogeneity was considerable, leading to rating this outcome down ($I^2 = 99.2\%$).

In the case of local recurrence, point estimates vary considerably, and CIs of most studies do not overlap. The direction of the effect was not consistent between the included studies, and the magnitude of statistical heterogeneity was considerable, leading to rating this outcome down ($I^2 = 74.7\%$). All disease-free survival outcomes (1, 3, and 5 years) had problems with inconsistency and were rated down because of a considerable degree of statistical heterogeneity ($I^2 = 96\%$, 81.8%, and 89.3%, respectively). A full evidence profile for this question is provided in Supplementary Table 8 (available online at www.giejournal.org), with a full description of outcomes and studies included for Questions 3a and 3b provided in Supplementary Tables 9 and 10, respectively (available online at www.giejournal.org).

Discussion. Gastric ESD is the most well-studied endoscopic resection technique for early neoplasia among the 3 main conditions discussed in this document. Gastric ESD is backed by a robust and expanding body of evidence from the East and emerging data from the West supporting its use for early-stage gastric lesions.[92,93] Although our analyses demonstrated no difference in disease-free survival between ESD and EMR in GAC, the number of studies that reported on this outcome were limited. Our analysis confirms the resource-intensive nature of gastric ESD as evidenced by its longer procedural time and higher risk of perforation. Nevertheless, ESD-related AEs are increasingly being managed with endoscopy alone with high rates of success.

We found no direct comparisons of the cost of ESD versus EMR for GAC. Nevertheless, data from colorectal ESD versus EMR pointed to a lack of cumulative difference in total costs, with a small trend toward higher costs in EMR because of higher number of surveillance endoscopies.[91] The panel expressed the importance of considering issues

of access to institutions with well-trained individuals who have the ability to safely and proficiently perform ESD.

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 5).[94] These suggest that differentiated-type T1a lesions without ulceration measuring up to 20 mm can be removed by EMR or ESD. In our review, mean GAC lesion size resected by EMR was 15.36 mm compared with 20.30 mm for ESD. This, in addition to the data showing lower risk of recurrence with ESD, led the panel to suggest ESD preferentially over EMR in this scenario, although this decision should be made based on patient preferences and availability of local endoscopy expertise.

Morphology and/or invasion. Lesion selection remains of upmost importance to reduce the risk of including lesions with LNM not suitable for ESD. Cross-sectional imaging rarely contributes to the staging process of early GAC because of an overall low risk of LNM. Endoscopic features associated with submucosal invasive disease include irregular surface, marginal elevation of 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.[95,96]

The Japanese guidelines have defined a number of criteria to reduce the probability of endoscopic resection of lesions with deep invasive components, commonly referred to as the absolute versus expanded criteria (Table 5). According to the Japanese Gastric Cancer Association, absolute indications for ESD include noninvasive neoplasia (irrespective of size); all differentiated, nonulcerated adenocarcinomas limited to the mucosa (T1m); and size of $\leq$2 cm. After the assessment of additional lesion-related criteria in a large Japanese study of over 5200 patients, additional criteria were considered suitable for ESD because of low risk of LNM (expanded criteria, Table 5).[94] Meta-analyses have confirmed the presence of acceptably low-risk 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.[97] Several studies showed comparable outcomes between the absolute and expanded indications.[69,98]

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. Concerns about overstaging (and hence committing lesions to surgery that would otherwise be suitable to ESD) and inferior staging performance compared with enhanced optical and digital chromoendoscopy–based staging led to reduced use of EUS for early-stage GAC staging in Asian countries.[99]

The panel deliberated on the implications of positive margins, submucosal tumor infiltration >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. In the studies included in our analysis, we observed variable approaches to handling lesions with such a profile, ranging from empirically repeating ESD of the resection site to close endoscopic surveillance every 3 to 6 months to referral to surgery and systemic therapy. Studies where ESD was performed for local recurrences after endoscopic resection indicated that this approach is both safe and feasible and is associated with lower rates of AEs in select patients.[71,100] The long-term management strategy in the case of a positive lateral margin as the only noncurative criterion remains to be answered. However, evidence is mounting that additional endoscopic therapy within 3 to 6 months after ESD can be sufficient in lieu of surgery and is associated with long-term tumor-free remission.[101,102]

Management of recurrence. Comparative data on the optimal strategy for management of recurrence after endoscopic resection of early GAC are scarce. Although outside the scope of our review, we identified a small number of studies assessing ESD versus surgery for metachronous and/or recurrent early GAC after endoscopic resection. One study demonstrated a higher chance of complete resection with ESD versus surgery in this scenario,[101] whereas others demonstrated strong trends toward incomplete resection with ESD.[103,104] However, these studies did not clearly differentiate between true recurrences and incomplete resections, among other issues, and therefore no conclusions can be made regarding surgery versus ESD for recurrence. Data on recurrence rates with the subsequent management strategy are also similarly limited in comparing surgery with ESD for recurrence. Studies assessing EMR versus ESD for recurrent disease, although fraught with the same limitations, are clearly in favor of ESD.[100] Although a systematic review of available comparative studies in this area is needed, we suggest for the time being that a multidisciplinary meeting should inform decision-making in this scenario but that EMR should likely not be attempted for recurrent disease.

Surveillance. In GAC, endoscopic surveillance is recommended to detect local recurrences and metachronous lesions. All lesions with a T1b pathologic stage but with negative margins should undergo endoscopic surveillance with consideration for cross-sectional imaging and/or EUS and earlier start of surveillance. Endoscopy under 3 months after resection is unlikely to be helpful in surveillance. We propose the first endoscopy should be in 3 to 6 months and then annually because most recurrences happen in the first year.[105,106] The value of biopsy sampling in the absence of clear endoscopic recurrence has not been established. Nevertheless, given the higher risk of recurrence after piecemeal resection and/or positive margin findings, we believe that in this context biopsy sampling should be performed.

Long-term surveillance is warranted given the 10% to 20% risk of synchronous and metachronous cancers.[107,108]

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 recommendations, low quality of evidence)

Evidence. Our search identified 21 studies meeting eligibility criteria that reported on 2947 patients treated with ESD and 3484 patients treated with surgery.[13,80-87,89,109-119,133] All studies identified were observational except for 1 clinical trial (Chiu et al,[81] in abstract form) that compared outcomes of ESD-treated patients with cancers with a control group of patients who underwent gastrectomy. The performance of ESD was associated with lower rates of clinical success compared with surgery (91.7% vs 99.5%; RR, .92; 95% CI, .89-.95; I^2 = 88.1%). Similarly, the rates of local recurrence were significantly higher in the ESD group compared with the surgery group (2.1% vs .6%; RR, 4.27; 95% CI, 2.36-7.73; I^2 = 9.4%). Reports on AEs demonstrated no difference between ESD and surgery regarding bleeding risk, but ESD was associated with significantly lower rates of postoperative infections (.3% vs 7.7%; RR, .12; 95% CI, .02-.71; I^2 = 67.1%). Mortality within 30 days was not statistically different (.1% vs .4%; RR, .34; 95% CI, .05-2.54; I^2 = 78.3%); similarly, long-term death rates were no different between the 2 cohorts. No difference in the rates of stricture formation was found between the 2 groups. Four- and 5-year overall survival as well as 4- and 5-year disease-free survival were not different between the ESD and surgery cohorts (Supplementary Materials). Finally, in the 8 studies that reported on procedural time, ESD was associated with shorter procedures compared with surgery (median difference, 129.8 minutes less; 95% CI, 89.0-170.6; I^2 = 99.1%). Forest plots and funnel plots for these findings are presented in Supplementary Figures 26-37, available online at www.giejournal.org.

We found no direct comparisons of the cost of ESD versus surgery in the United States. However, 1 study showed lower overall hospital costs associated with ESD compared with surgery, mainly because of a shorter hospital stay.[120] The patient representative on the panel indicated the preference for ESD in appropriate cases of GAC because of early introduction of 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.[118,121,122]

Certainty in the evidence. For clinical success, there were concerns with inconsistency, where point estimates varied and CIs of some of the studies did not overlap. The direction of the effect was not consistent between the included studies, and the magnitude of statistical heterogeneity was high, leading to rating this outcome down (I^2 = 88.1%). The local recurrence outcome had problems with imprecision because of the presence of a large effect with wide 95% CIs based on small number of events.

Estimates of bleeding and infection risks were inconsistent, with non-overlapping CIs in some of the studies. The direction of the effect was not consistent between the included studies, and the magnitude of statistical heterogeneity was high, leading to rating down in both with I^2 = 77.6% and 67.1%, respectively.

Overall survival data showed no issues with bias particularly related to the degree of selection and comparability of ESD and surgery, but issues of bias were found when considering the 4- and 5-year disease-free survival, respectively. Disease-free survival outcomes (4 and 5 years) had problems with inconsistency and were rated down because of a considerable degree of statistical heterogeneity (I^2 = 96%, 81.8%, and 89.3%, respectively). No issues were found of indirectness in any outcome assessed. A full evidence profile for this question is provided in Supplementary Table 11 (available online at www.giejournal.org), with full assessments of study quality for all review questions provided in Supplementary Table 12 (available online at www.giejournal.org).

Discussion. Our data clearly demonstrate that surgery was associated with higher postprocedure morbidity than ESD, particularly risk of infections. Five patients (.38%) died within 30 days of surgery compared with 1 (.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. Our data also supported longer operative time, although data on open versus laparoscopic surgery were not available in most included studies. Postoperative AEs might prolong the hospital stay, leading to increased total medical cost. As ESD continues to evolve as a mainly outpatient surgery (or 1 with very limited hospital stay), we expect this cost differential to be more evident in future analyses.

Lesion 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 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.[123,124] 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 lesion size (see Fig. 3 algorithm).

Management of recurrent lesions. ESD is associated with higher rates of local recurrence compared with surgery. Despite the generally high rates of curative resections in ESD, other theories could explain this difference in recurrence. ESD only allows the removal of the primary tumor along with the submucosal layer. However, the surrounding mucosa still might carry the risk of developing cancer because of ongoing atrophic gastritis, intestinal metaplasia, and *Helicobacter pylori*. In fact, eradication of *H pylori* could lower the risk of recurrent and metachronous cancers.[125] On the other hand, surgical resection commonly involves removal of the gastric body and antrum, which removes the entire high-risk portion of the stomach because fewer cancers develop in the proximal third of the stomach.

Management of residual GAC after noncurative ESD remains controversial. Two meta-analyses suggested gastrectomy with lymph node dissection for patients undergoing noncurative endoscopic resection because of survival benefits.[126,127] 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 al[128] 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 a candidate for surgical resection.

Surveillance. The viability of endoscopic follow-up after noncurative endoscopic resection has been assessed in 2 studies in patients with increased comorbidities and might be a reasonable option in R0 but otherwise noncurative resections.[129,130] In addition, studies have demonstrated that surgery outcomes are not compromised by prior ESD.[131,132] For lesions with a T1b pathologic stage, 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 HGD, 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. RCTs 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 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 have summarized the best available evidence to support recommendations regarding endoscopic resection in the management of upper GI malignancies. ESD plays a crucial role in the management of esophageal and gastric cancer, but its 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: AE, adverse event; ASGE, American Society for Gastrointestinal Endoscopy; BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; ESD, endoscopic submucosal dissection; GAC, gastric adenocarcinoma; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HGD, high-grade dysplasia; LGD, low-grade dysplasia; LNM, lymph node metastasis; LVI, lymphovascular invasion; RCT, randomized controlled trial; RR, relative risk.

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APPENDIX 1

Final electronic search strategy

Search date: September 17, 2020

Databases searched: MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 16, 2020; EBM Reviews - Cochrane Central Register of Controlled Trials August 2020, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to September 10, 2020

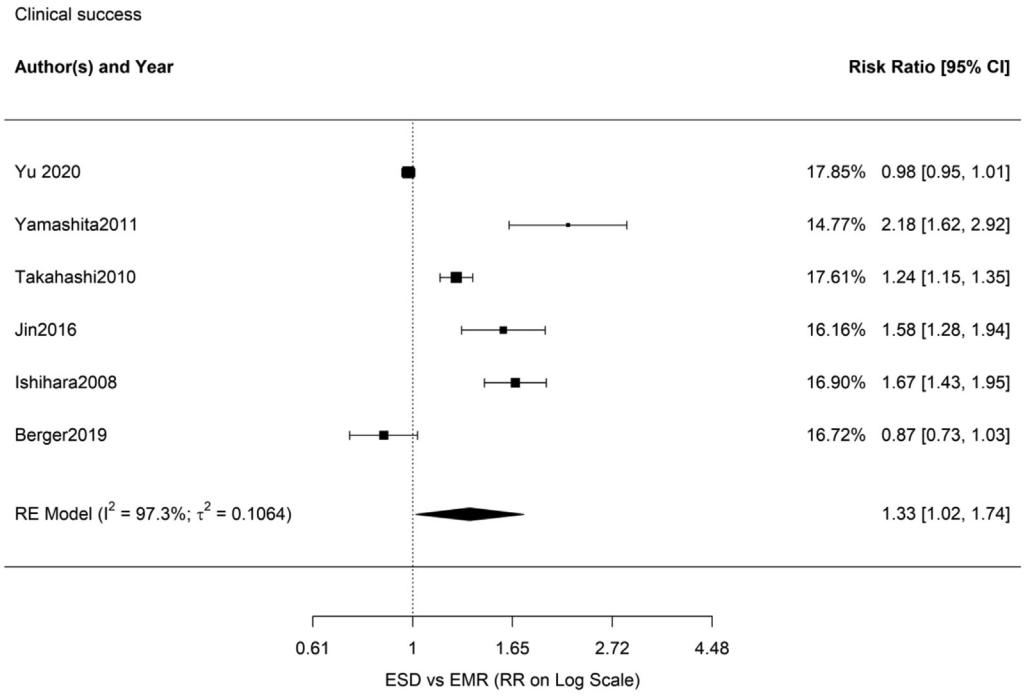
Limits: English, 2005 onward

Excluded: Case reports, editorials, letters, comments, conference abstracts published before 2018

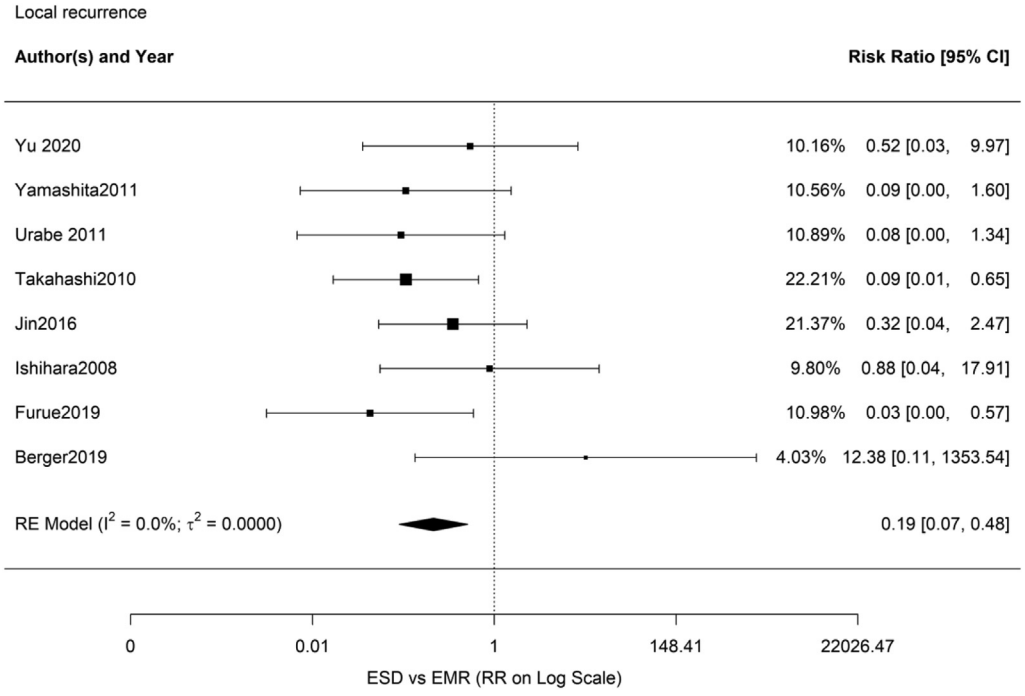
Embase, Ovid MEDLINE(R)

Number	Searches	Results
1	exp *esophageal ESCC/	10,837
2	((Esophag* or oesophag*) adj2 (dysplas* or metaplas* or adenocarcinoma* or carcinoma* or cancer* or neoplas* or tumor* or tumour* or preneoplas* or pre-neoplas*)).ti,kw.	62,132
3	exp *Barrett Esophagus/ use ppez	6541
4	exp *barrett esophagus/ use oemezd	9928
5	Barrett*.ti,kw.	18,733
6	exp *Stomach Neoplasms/ use ppez	82,609
7	exp *Stomach Cancer/ use oemezd	80,298
8	((Gastric or stomach) adj2 (dysplas* or metaplas* or adenocarcinoma* or carcinoma* or cancer* or neoplas* or tumor* or tumour* or preneoplas* or pre-neoplas*)).ti,kw.	145,452
9	or/1-8	275,958
10	exp Endoscopic Mucosal Resection/	8337
11	(Endoscop* adj2 (mucosal or submucosal) adj2 (Resection or Dissection)).ti,kw.	12,748
12	(ESD or EMR).ti,kw.	6247
13	or/10-12	21,673
14	9 and 13	7043
15	limit 14 to english language	6543
16	limit 15 to yr="2005 -Current"	6248
17	limit 16 to (editorial or letter or case reports or comment) [Limit not valid in Embase; records were retained]	538
18	exp Case Report/	4,642,961
19	16 not (17 or 18)	5270
20	limit 19 to (conference abstract or congress) [Limit not valid in Embase, Ovid MEDLINE(R), Ovid MEDLINE(R) Daily Update, Ovid MEDLINE(R) In-Process, Ovid MEDLINE(R) Publisher; records were retained]	1697
21	limit 20 to yr="1860 - 2017"	1389
22	19 not 21	3881
23	remove duplicates from 22	2849

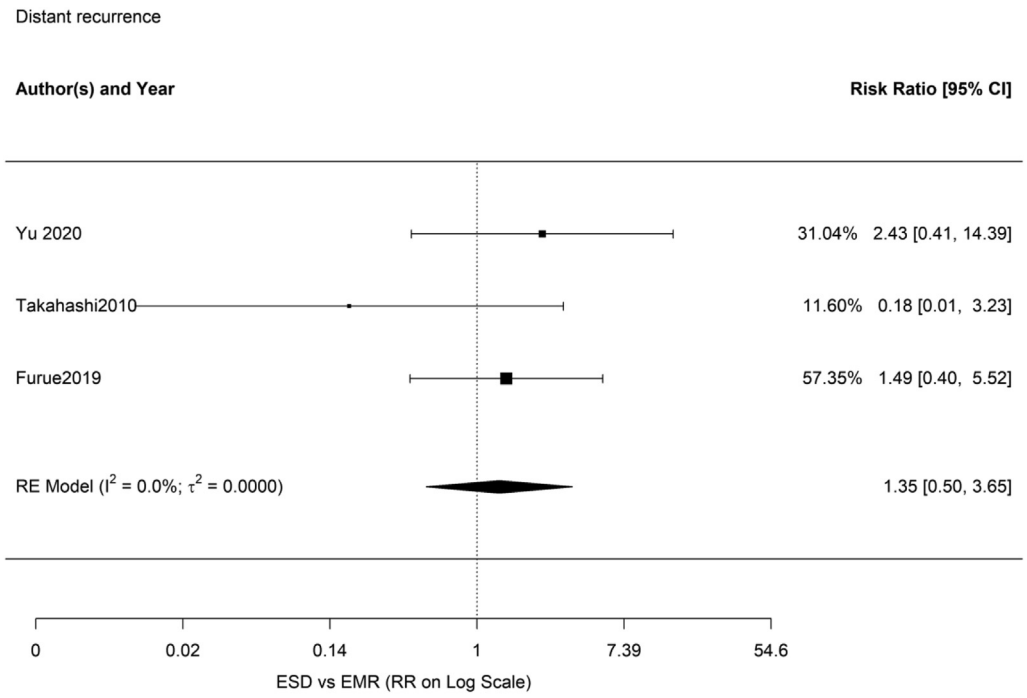
Cochrane EBM reviews. ((esophageal ESCC or ((Esophag* or oesophag*) adj2 (dysplas* or metaplas* or adenocarcinoma* or carcinoma* or cancer* or neoplas* or tumor* or tumour* or preneoplas* or pre-neoplas*)) or Barrett Esophagus or Barrett* or Stomach Neoplasms or ((Gastric or stomach) adj2 (dysplas* or metaplas* or adenocarcinoma* or carcinoma* or cancer* or neoplas* or tumor* or tumour* or preneoplas* or pre-neoplas*))) and (Endoscopic Mucosal Resection or (Endoscop* adj2 (mucosal or submucosal) adj2 (Resection or Dissection))) or (ESD or EMR))).hw,kw,sh,ti. 498



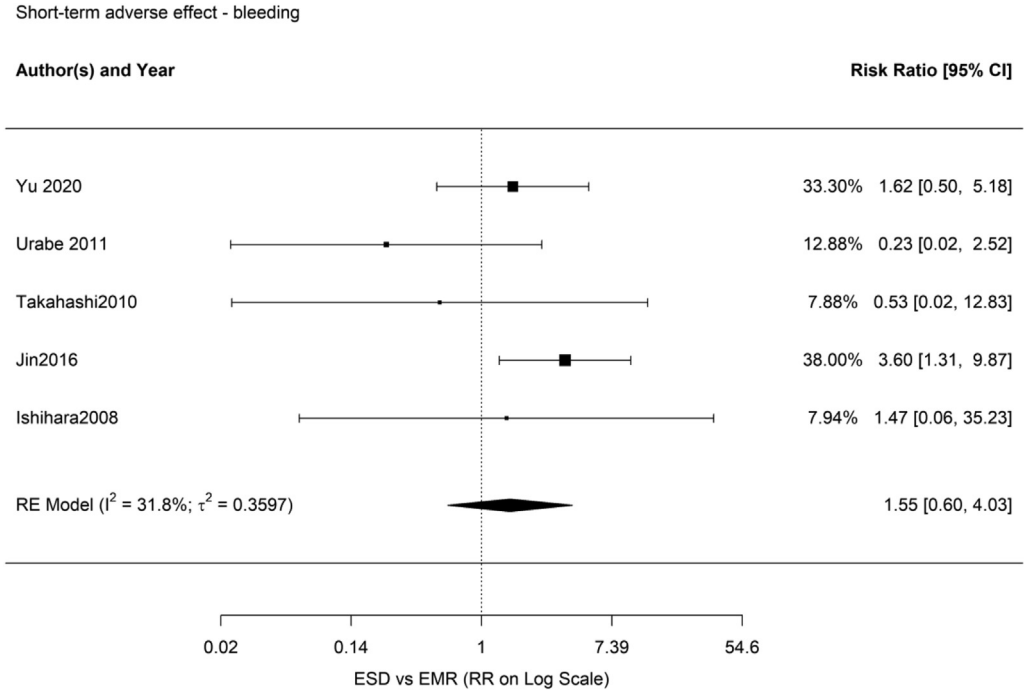
Supplementary Figure 1. Forest plot for question 1a: ESD versus EMR for esophageal squamous cell carcinoma—clinical success outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



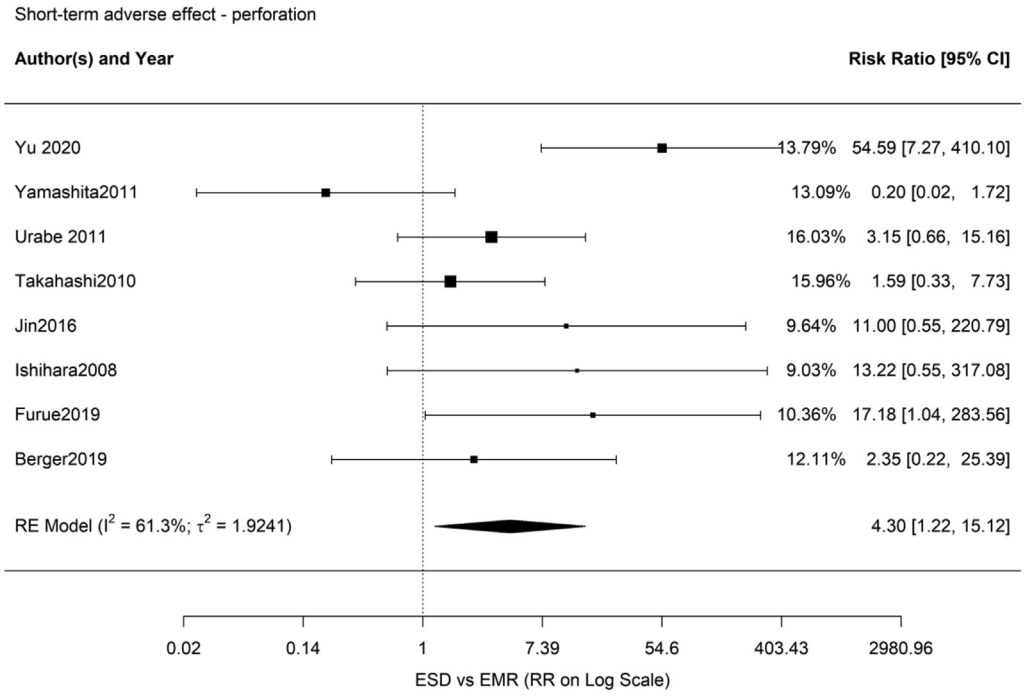
Supplementary Figure 2. Forest plot for question 1a: ESD versus EMR for esophageal squamous cell carcinoma—local recurrence outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



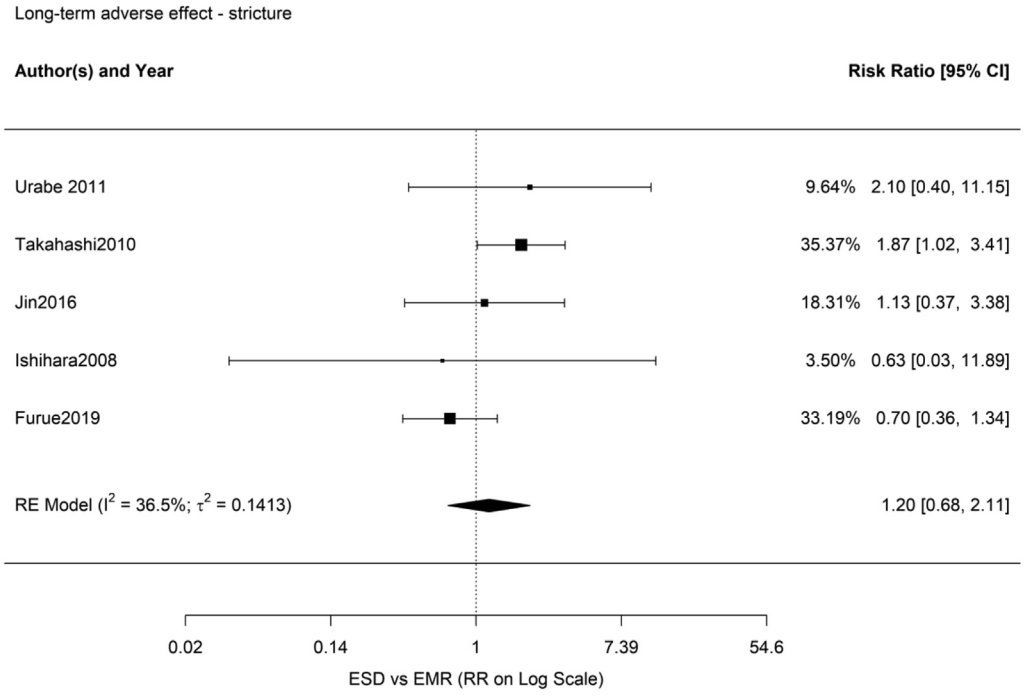
Supplementary Figure 3. Forest plot for question 1a: ESD versus EMR for esophageal squamous cell carcinoma—distant recurrence outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



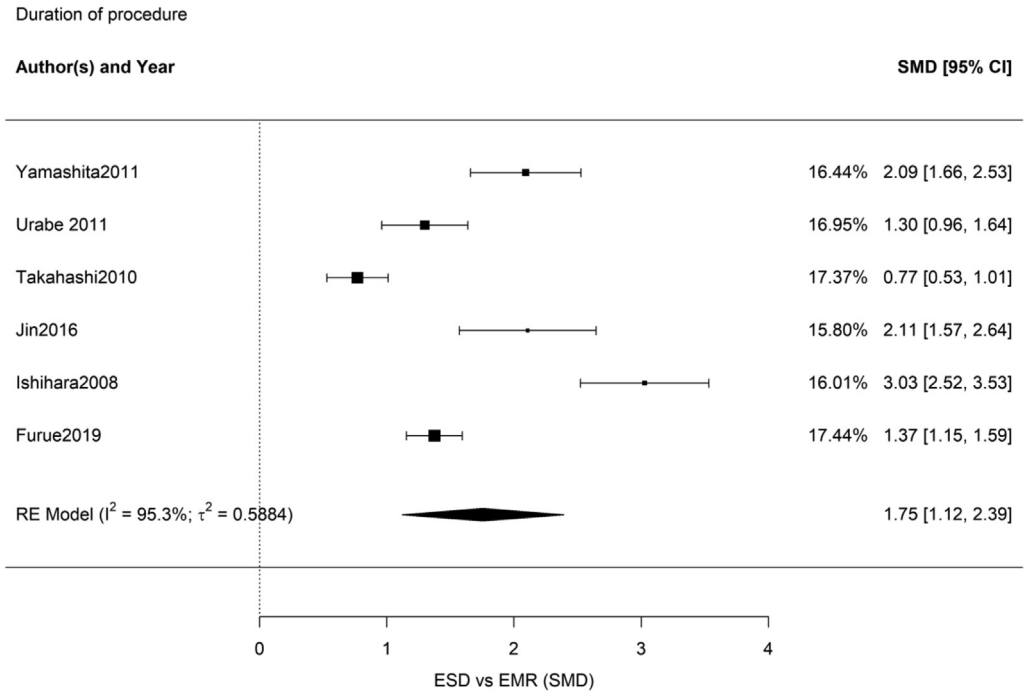
Supplementary Figure 4. Forest plot for question 1a: ESD versus EMR for esophageal squamous cell carcinoma—short-term bleeding outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



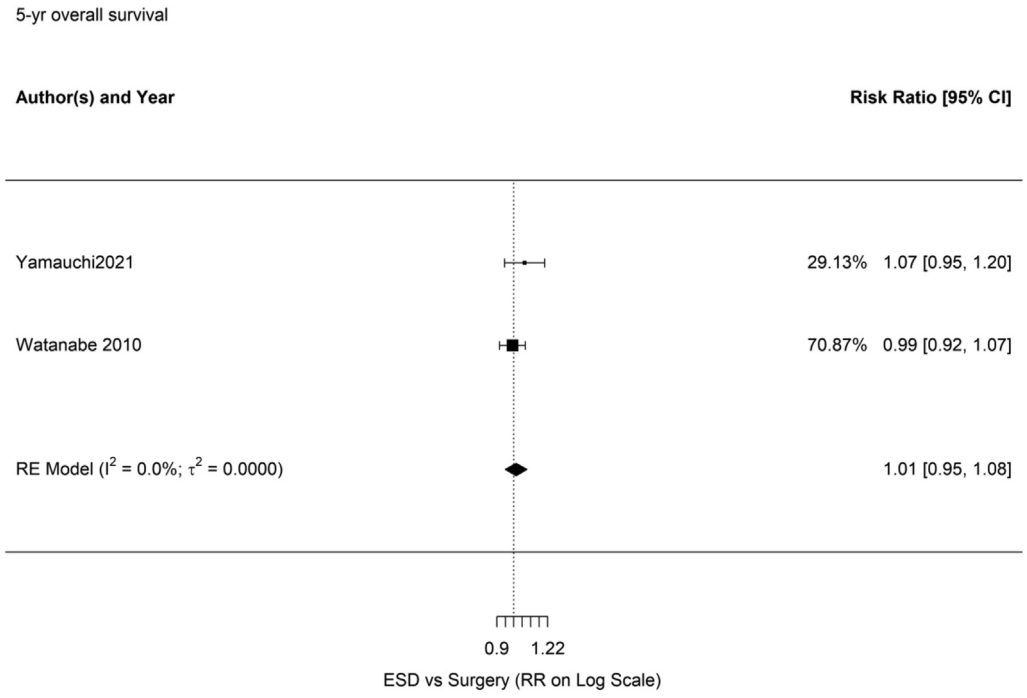
Supplementary Figure 5. Forest plot for question 1a: ESD versus EMR for esophageal squamous cell carcinoma—short-term perforation outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



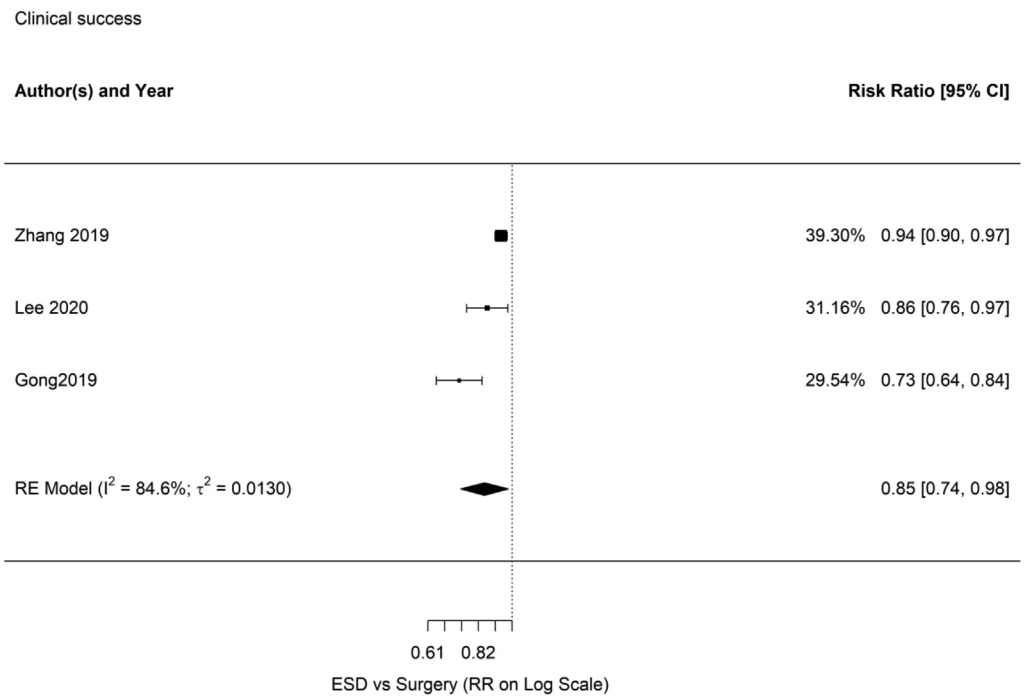
Supplementary Figure 6. Forest plot for question 1a: ESD versus EMR for esophageal squamous cell carcinoma—long-term stricture formation outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



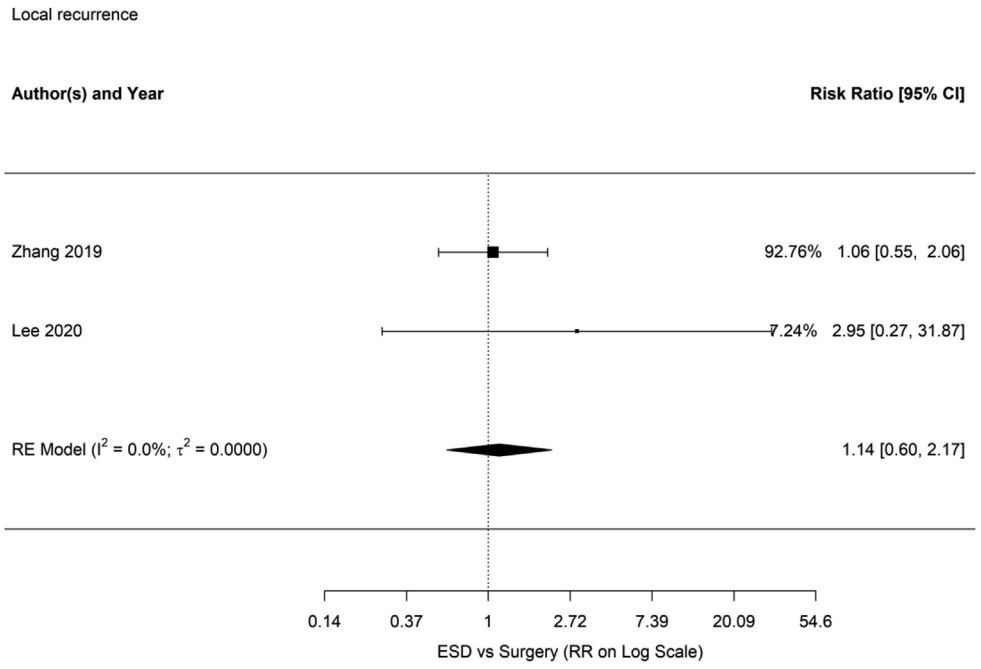
Supplementary Figure 7. Forest plot for question 1a: ESD versus EMR for esophageal squamous cell carcinoma—procedure time outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *SMD*, standardized mean difference.



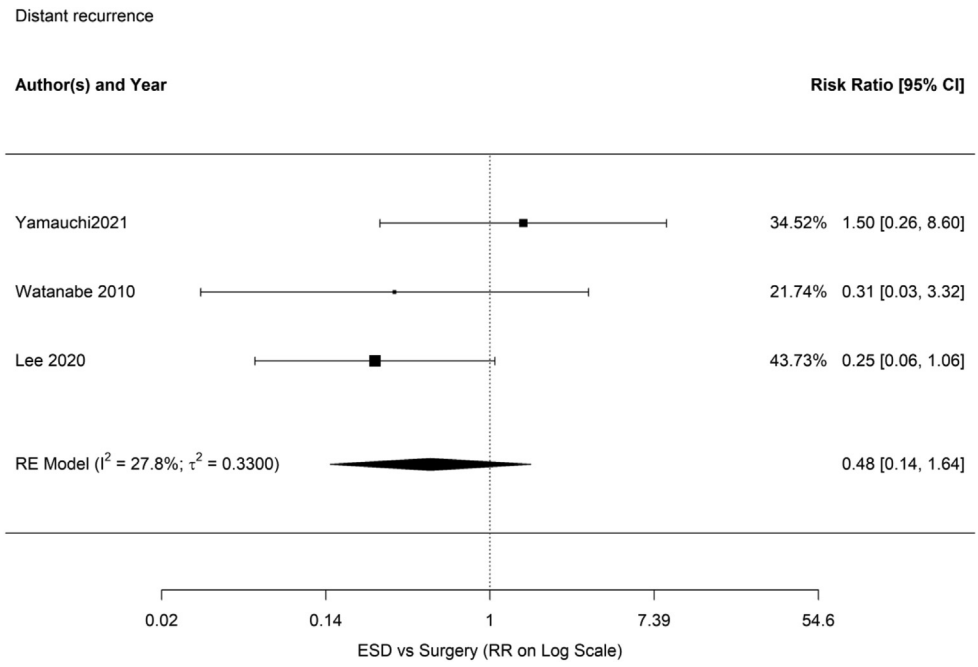
Supplementary Figure 8. Forest plot for question 1b: ESD versus surgery for esophageal squamous cell carcinoma—5-year overall survival outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



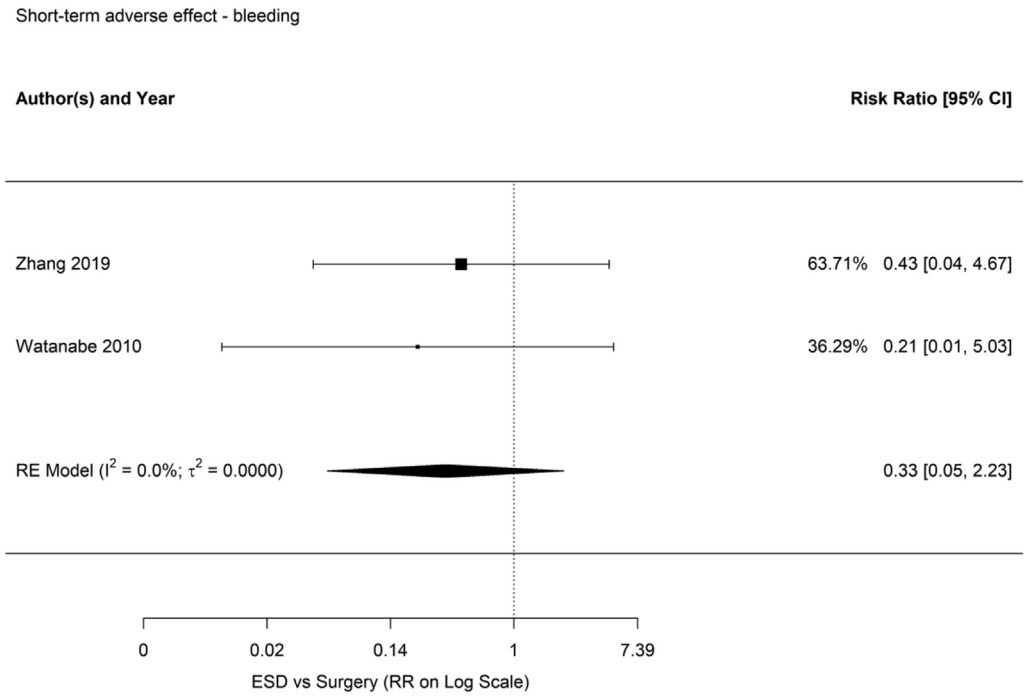
Supplementary Figure 9. Forest plot for question 1b: ESD versus surgery for esophageal squamous cell carcinoma—clinical success outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



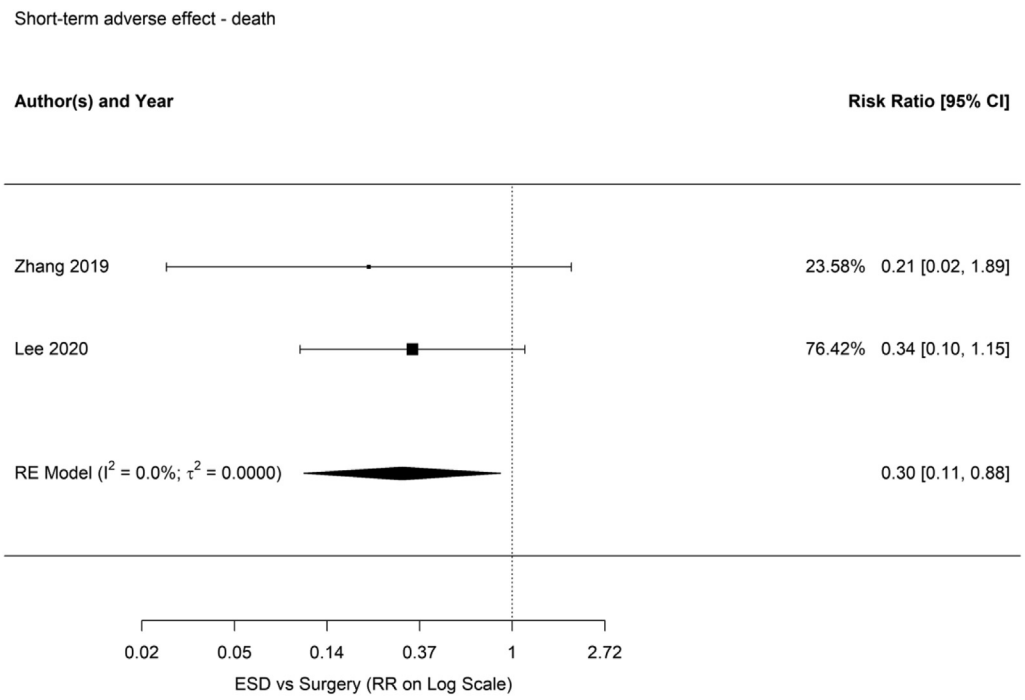
Supplementary Figure 10. Forest plot for question 1b: ESD versus surgery for esophageal squamous cell carcinoma—local recurrence outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



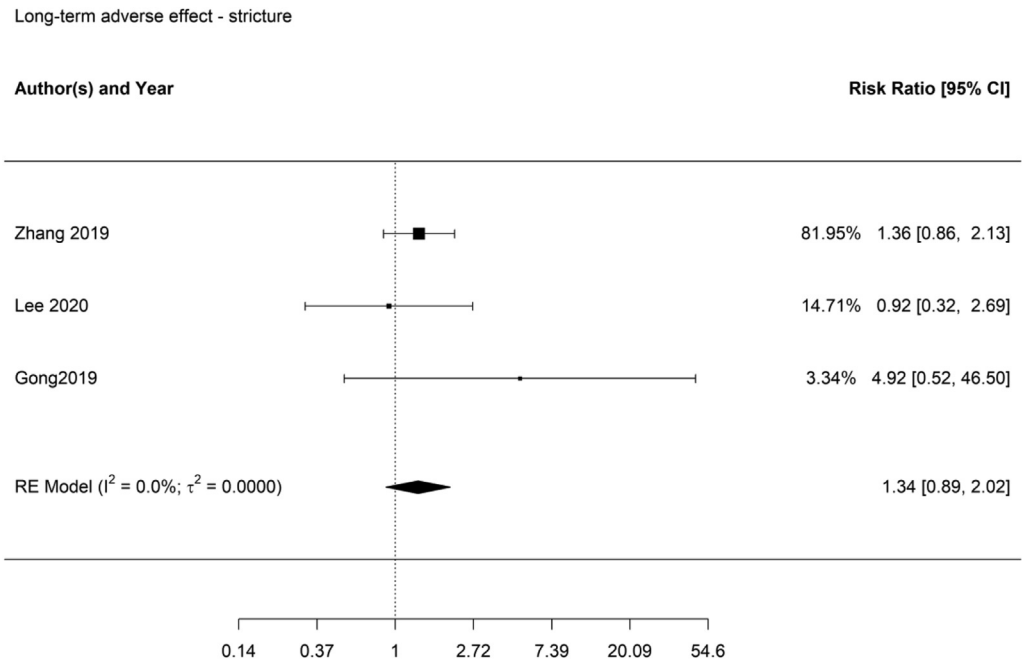
Supplementary Figure 11. Forest plot for question 1b: ESD versus surgery for esophageal squamous cell carcinoma—distant recurrence outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



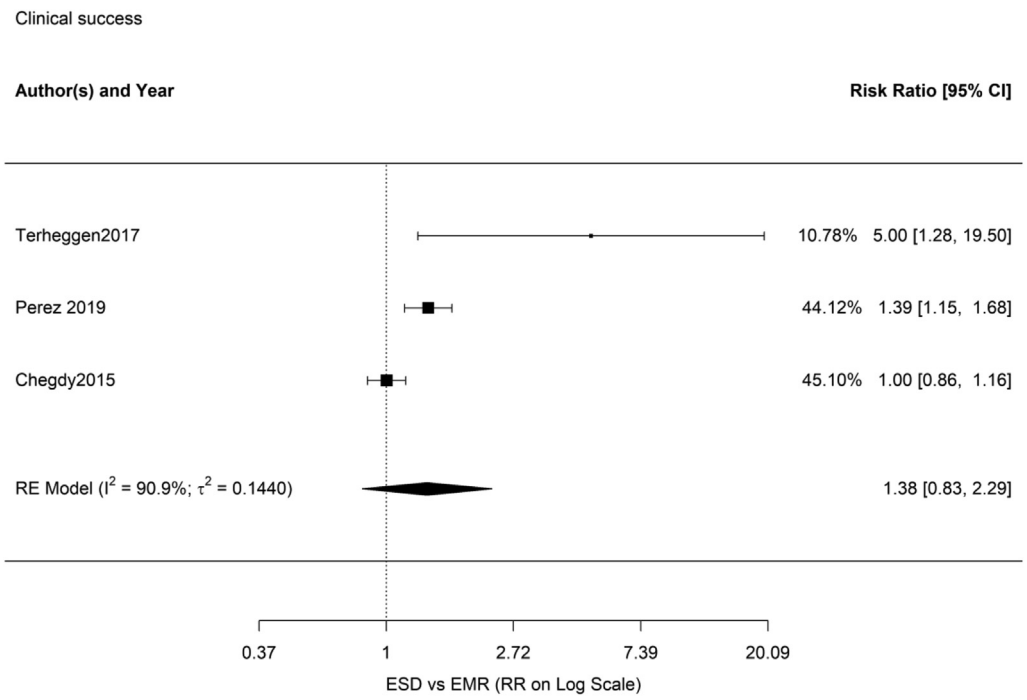
Supplementary Figure 12. Forest plot for question 1b: ESD versus surgery for esophageal squamous cell carcinoma—short-term bleeding outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



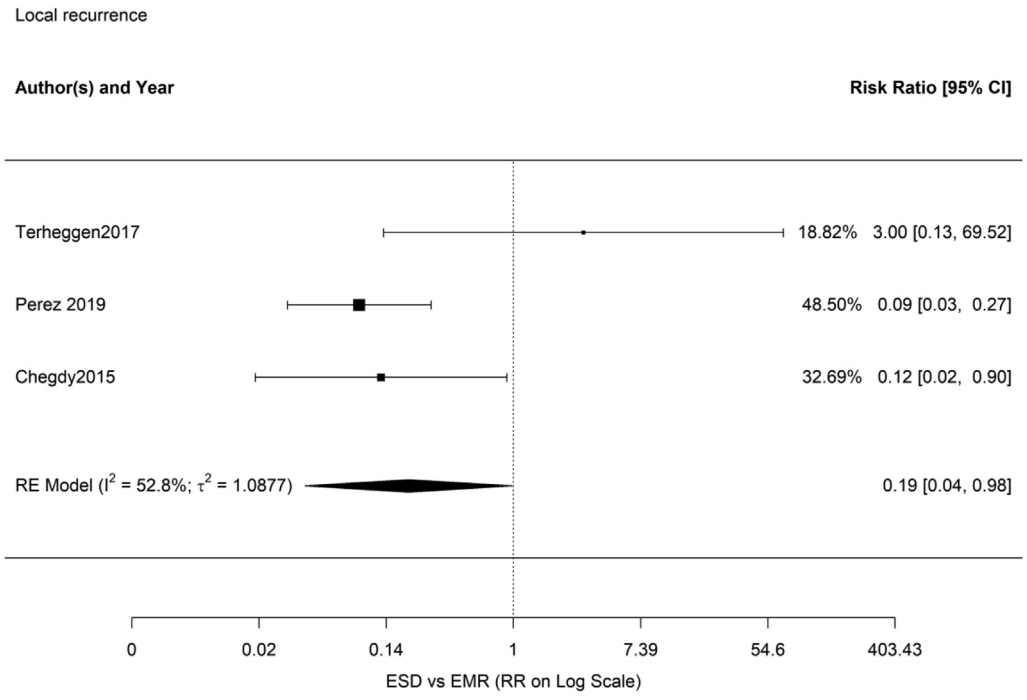
Supplementary Figure 13. Forest plot for question 1b: ESD versus surgery for esophageal squamous cell carcinoma—short-term mortality outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



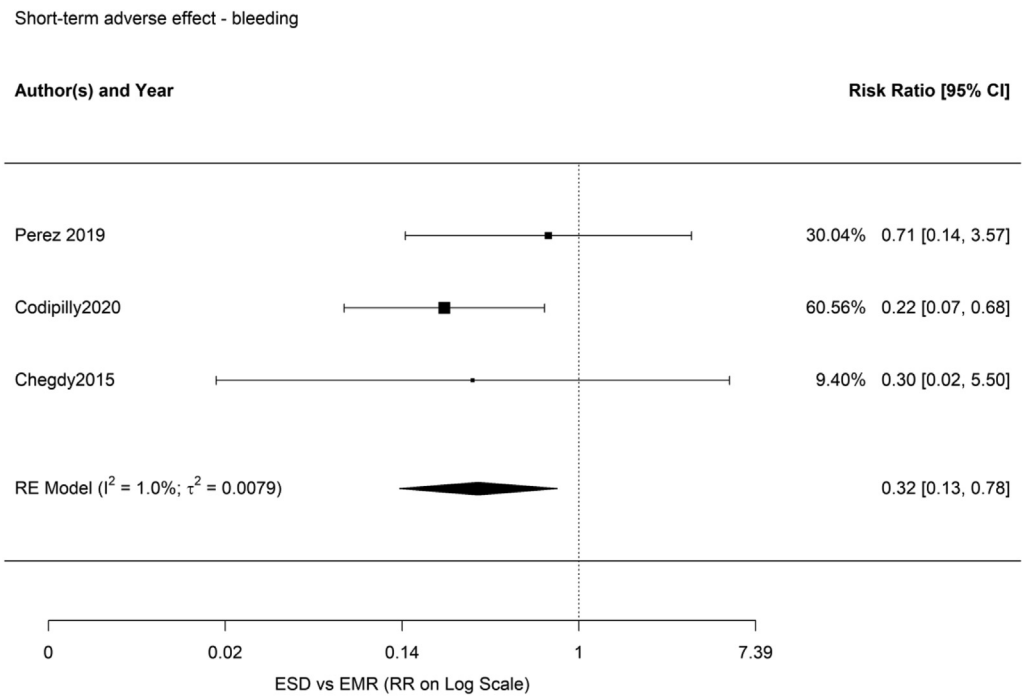
Supplementary Figure 14. Forest plot for question 1b: ESD versus surgery for esophageal squamous cell carcinoma—long-term stricture formation outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



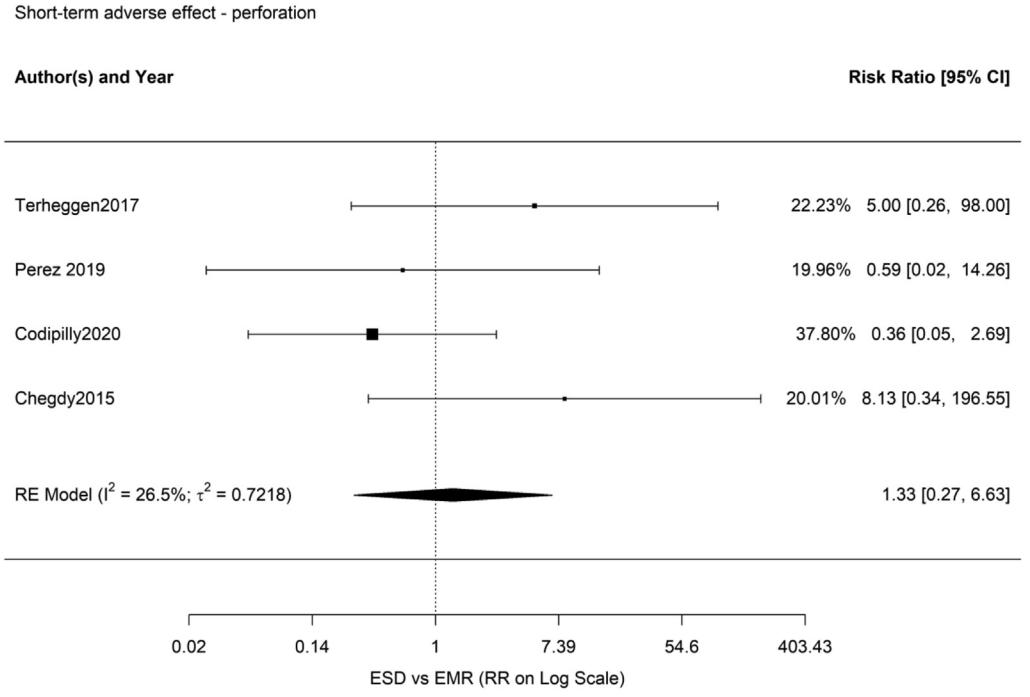
Supplementary Figure 15. Forest plot for question 2: ESD versus EMR for esophageal adenocarcinoma—clinical success outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



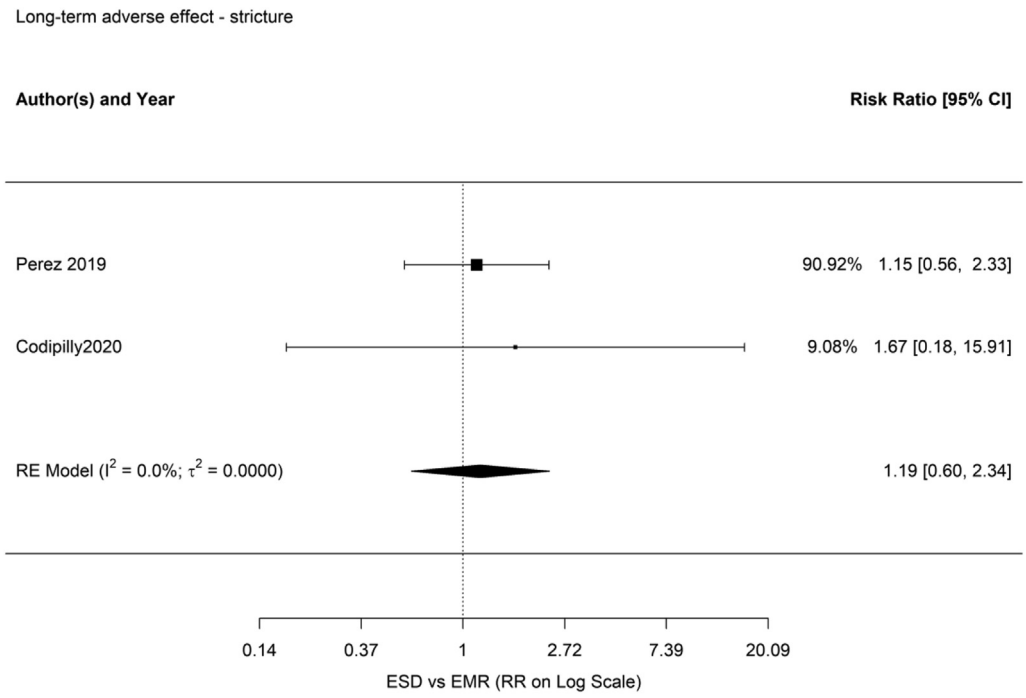
Supplementary Figure 16. Forest plot for question 2: ESD versus EMR for esophageal adenocarcinoma—local recurrence outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



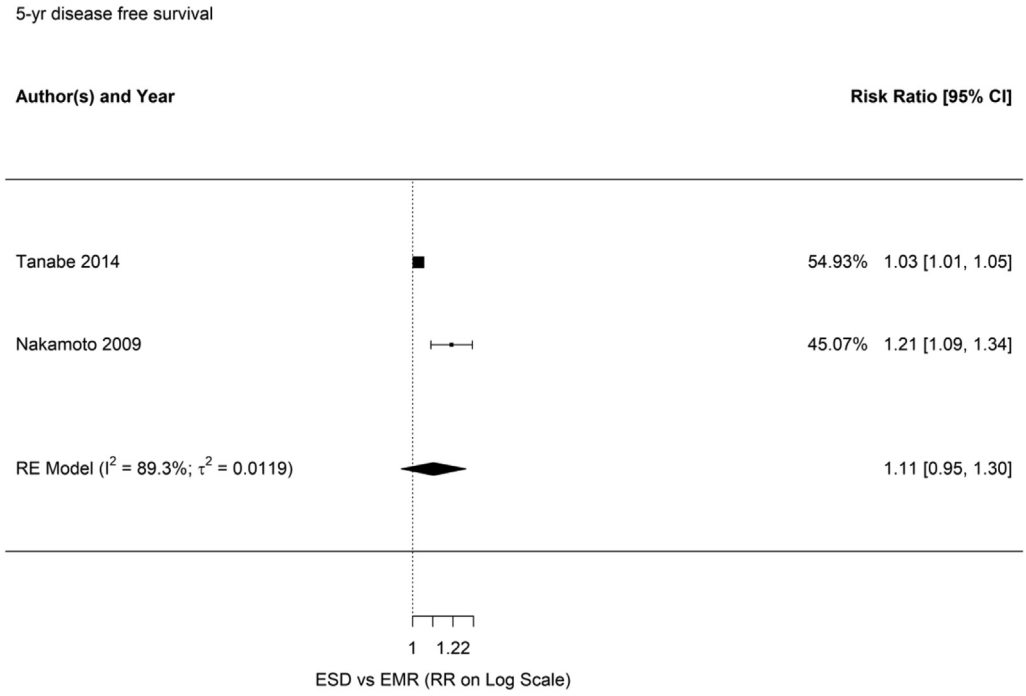
Supplementary Figure 17. Forest plot for question 2: ESD versus EMR for esophageal adenocarcinoma—short-term bleeding outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



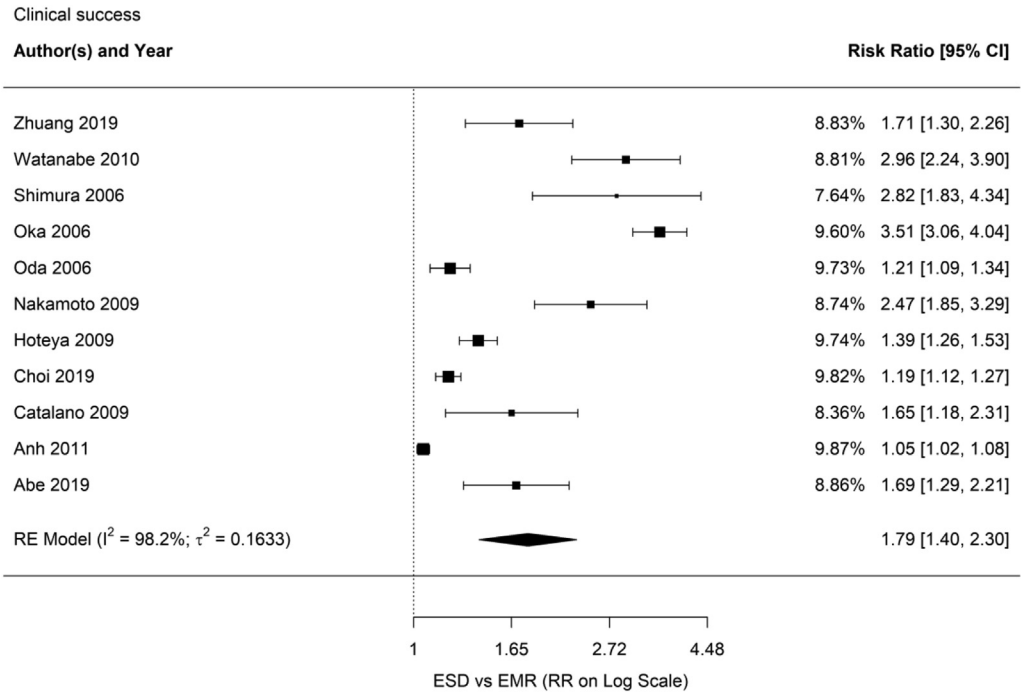
Supplementary Figure 18. Forest plot for question 2: ESD versus EMR for esophageal adenocarcinoma—short-term perforation outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



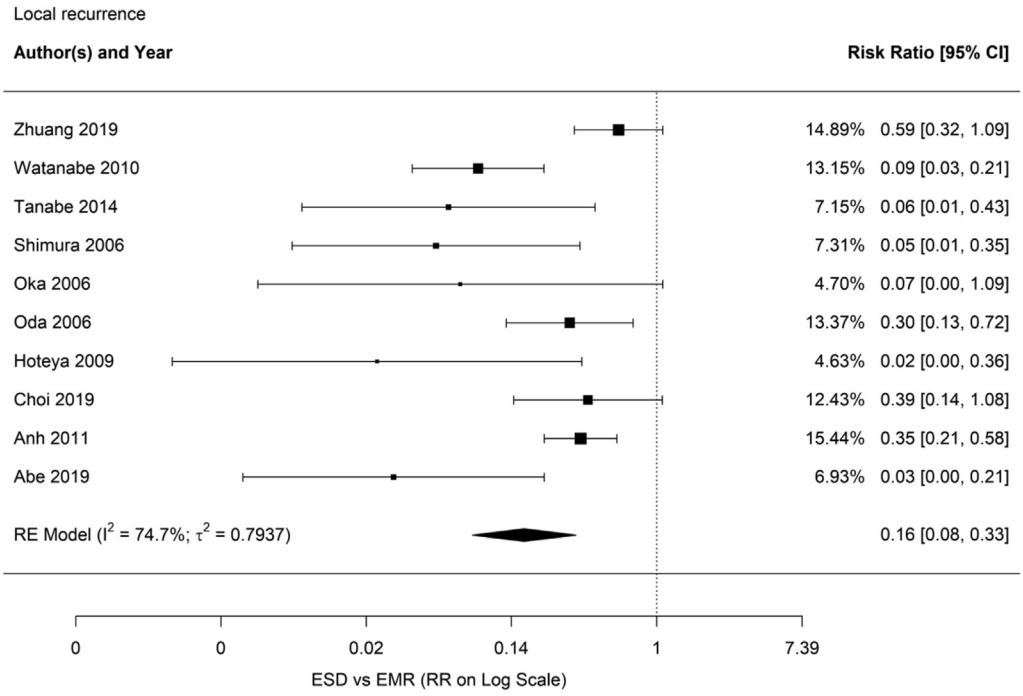
Supplementary Figure 19. Forest plot for question 2: ESD versus EMR for esophageal adenocarcinoma—long-term stricture formation outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



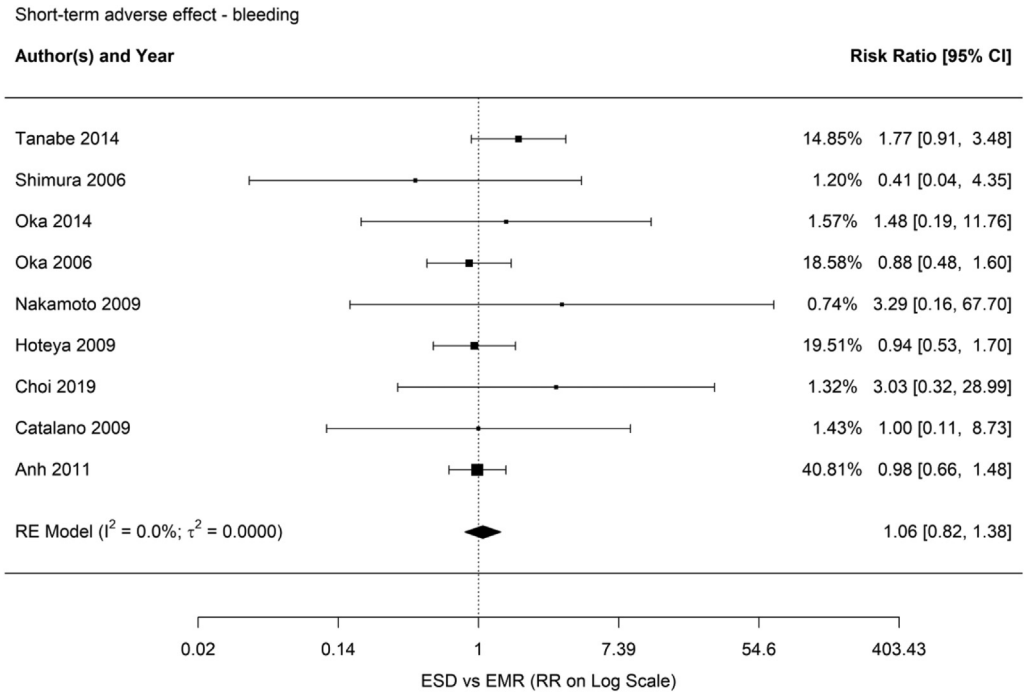
Supplementary Figure 20. Forest plot for question 3a: ESD versus EMR for gastric adenocarcinoma—5-year disease-free survival outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



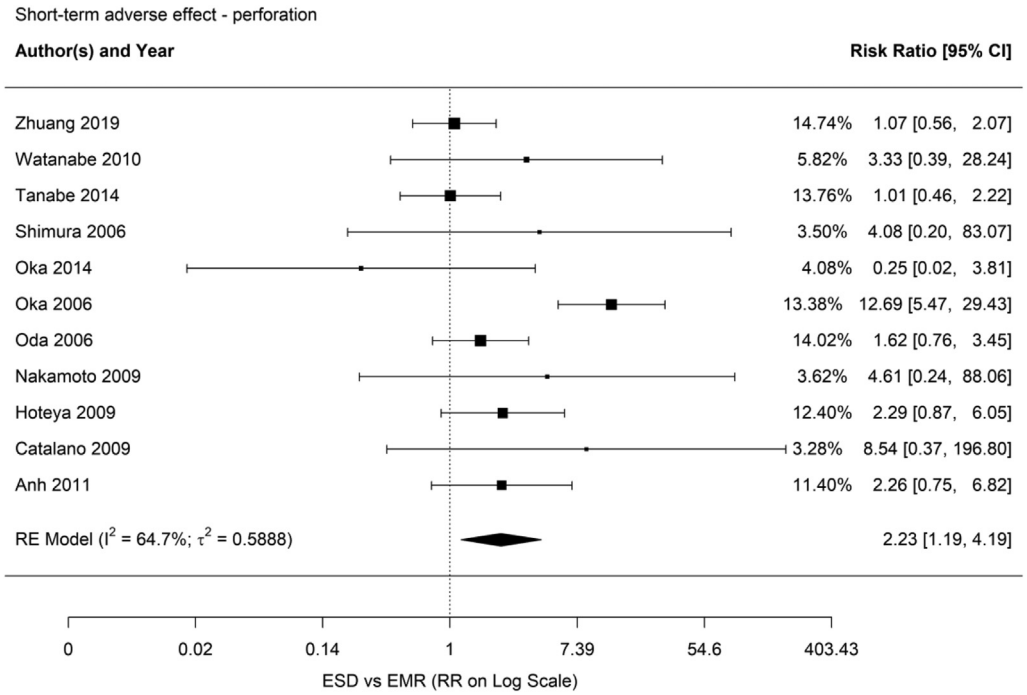
Supplementary Figure 21. Forest plot for question 3a: ESD versus EMR for gastric adenocarcinoma—clinical success outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



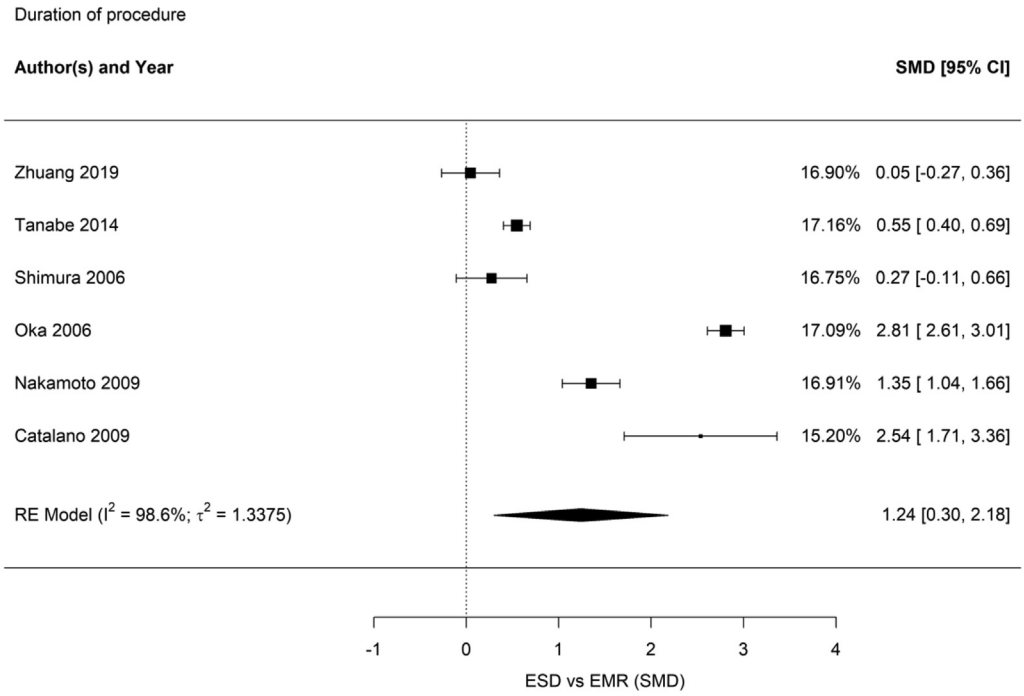
Supplementary Figure 22. Forest plot for question 3a: ESD versus EMR for gastric adenocarcinoma—local recurrence outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



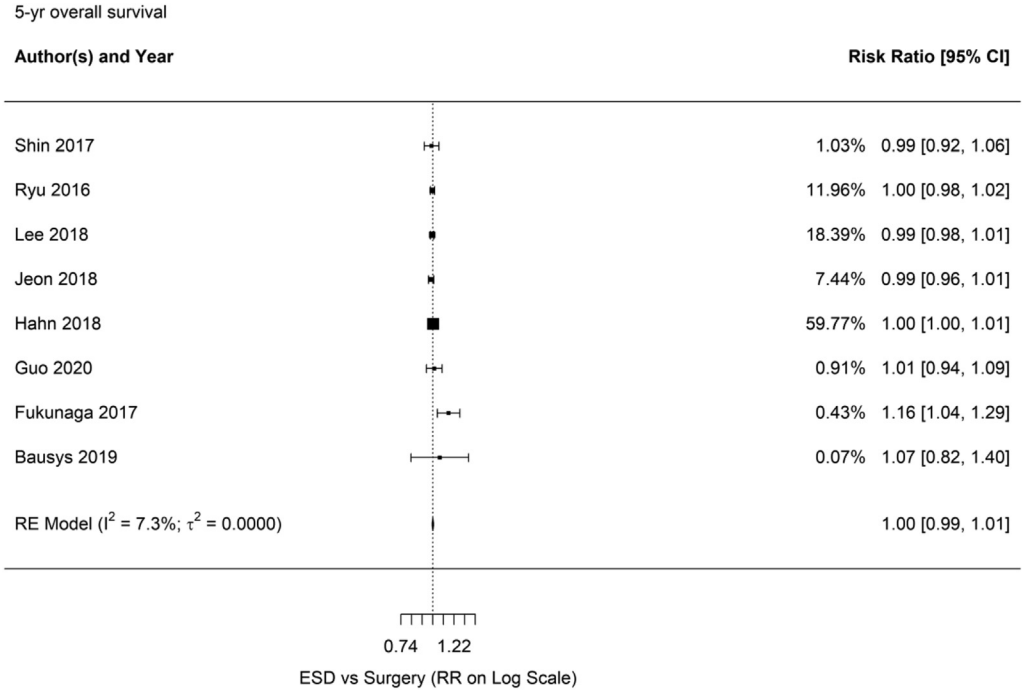
Supplementary Figure 23. Forest plot for question 3a: ESD versus EMR for gastric adenocarcinoma—short-term bleeding outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



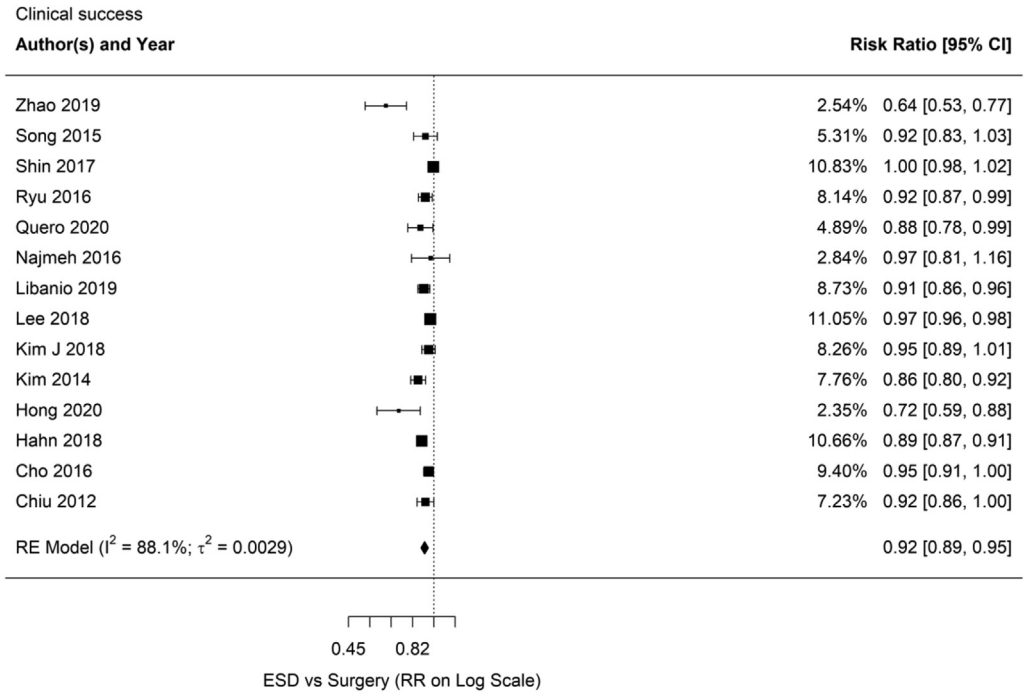
Supplementary Figure 24. Forest plot for question 3a: ESD versus EMR for gastric adenocarcinoma—short-term perforation outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



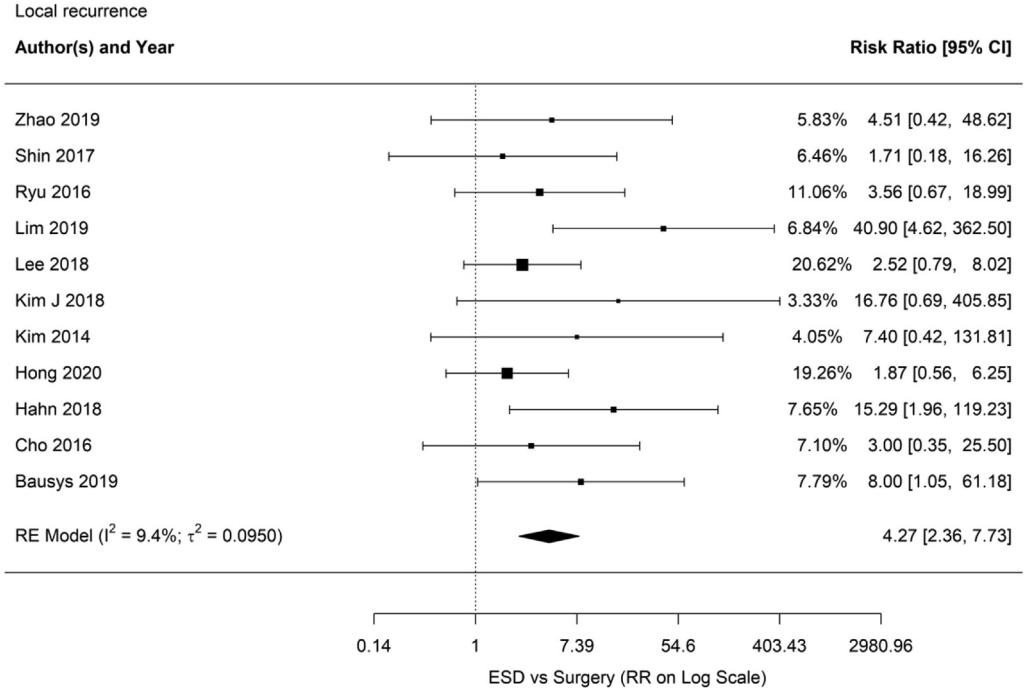
Supplementary Figure 25. Forest plot for question 3a: ESD versus EMR for gastric adenocarcinoma—procedure time outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *SMD*, standardized mean difference.



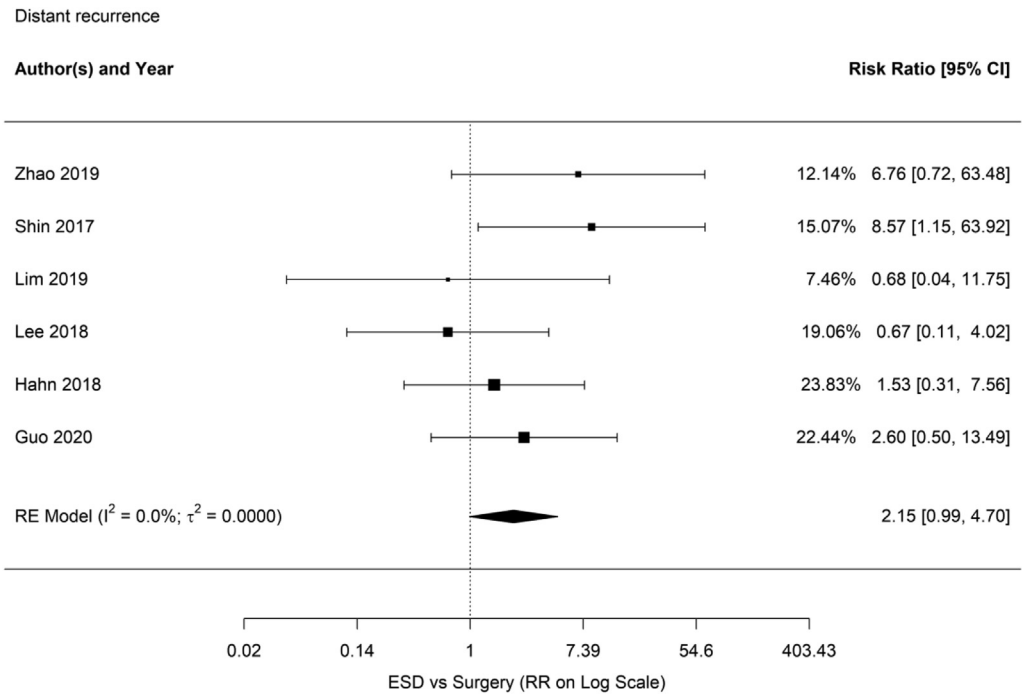
Supplementary Figure 26. Forest plot for question 3b: ESD versus surgery for gastric adenocarcinoma—5-year overall survival outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



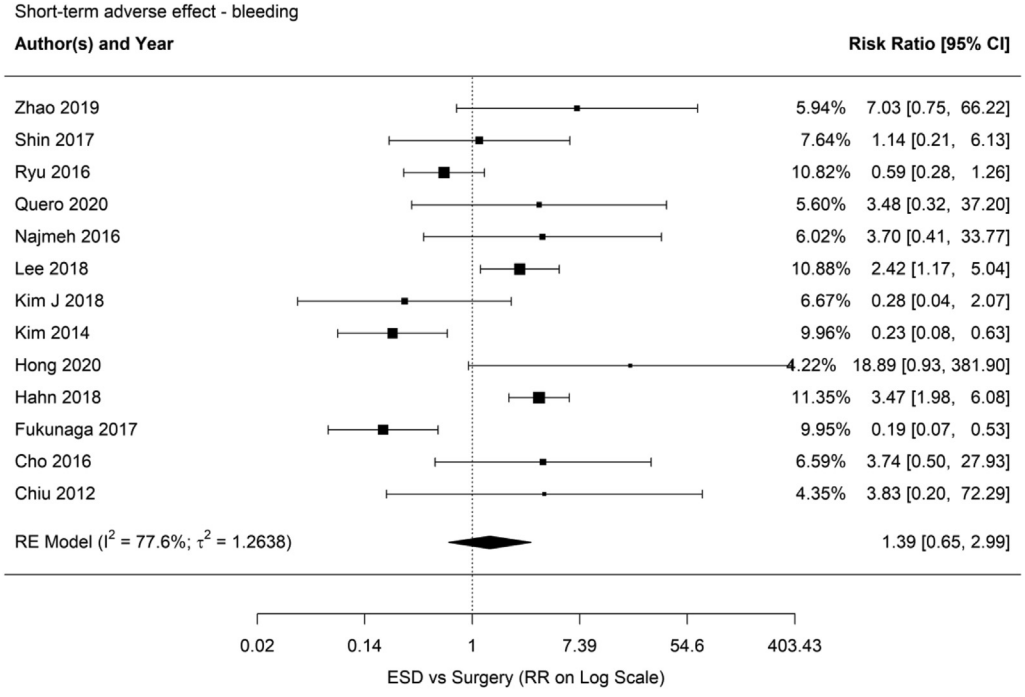
Supplementary Figure 27. Forest plot for question 3b: ESD versus surgery for gastric adenocarcinoma—clinical success outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



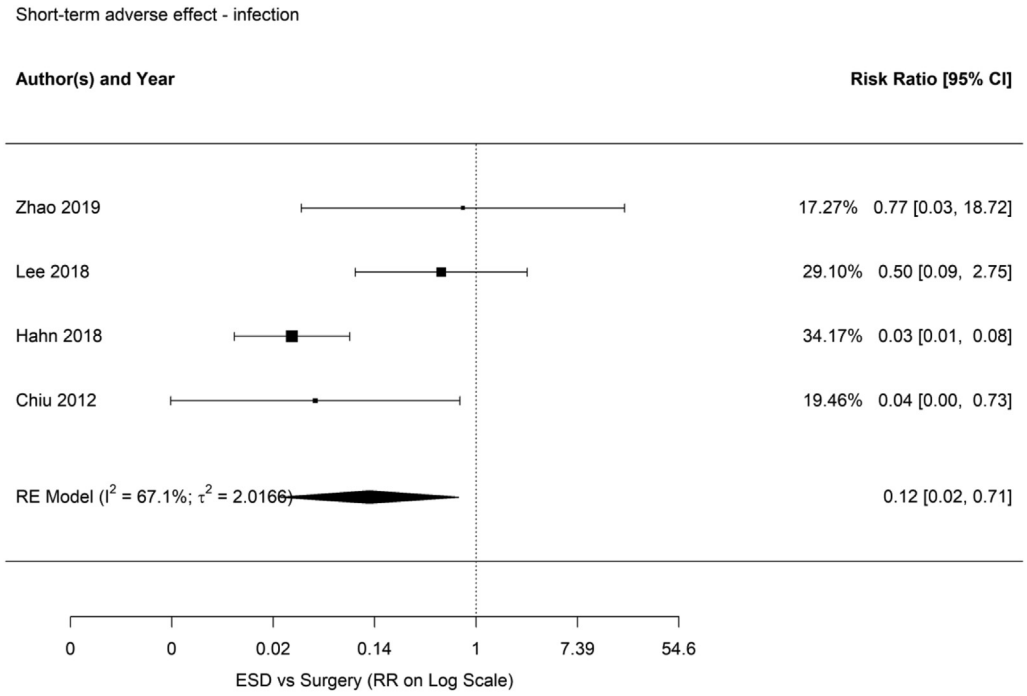
Supplementary Figure 28. Forest plot for question 3b: ESD versus surgery for gastric adenocarcinoma—local recurrence outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



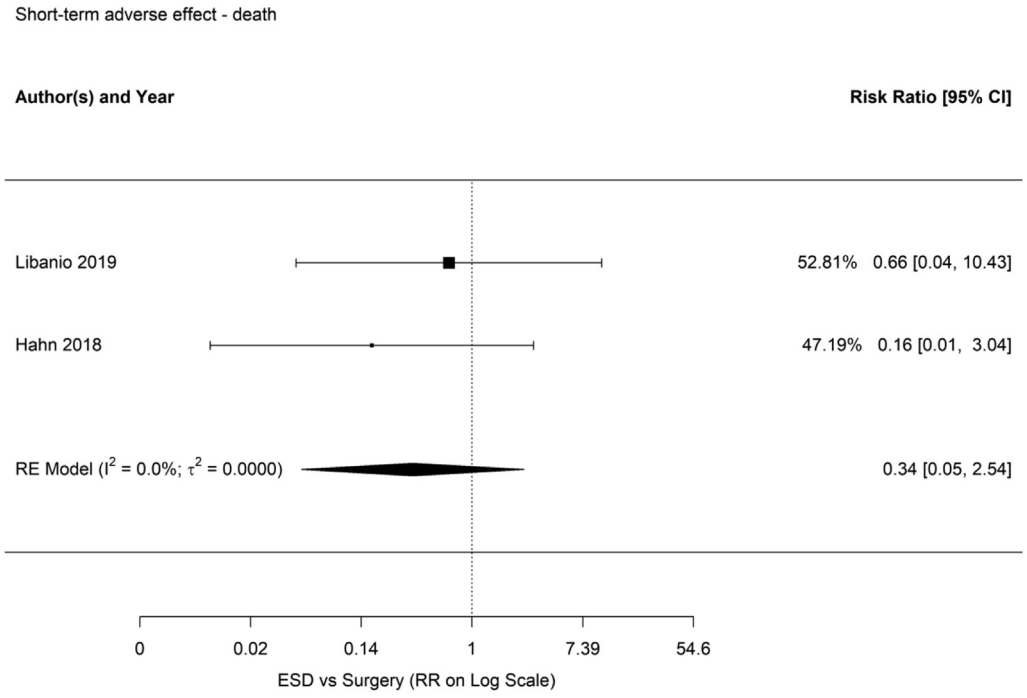
Supplementary Figure 29. Forest plot for question 3b: ESD versus surgery for gastric adenocarcinoma—distant recurrence outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



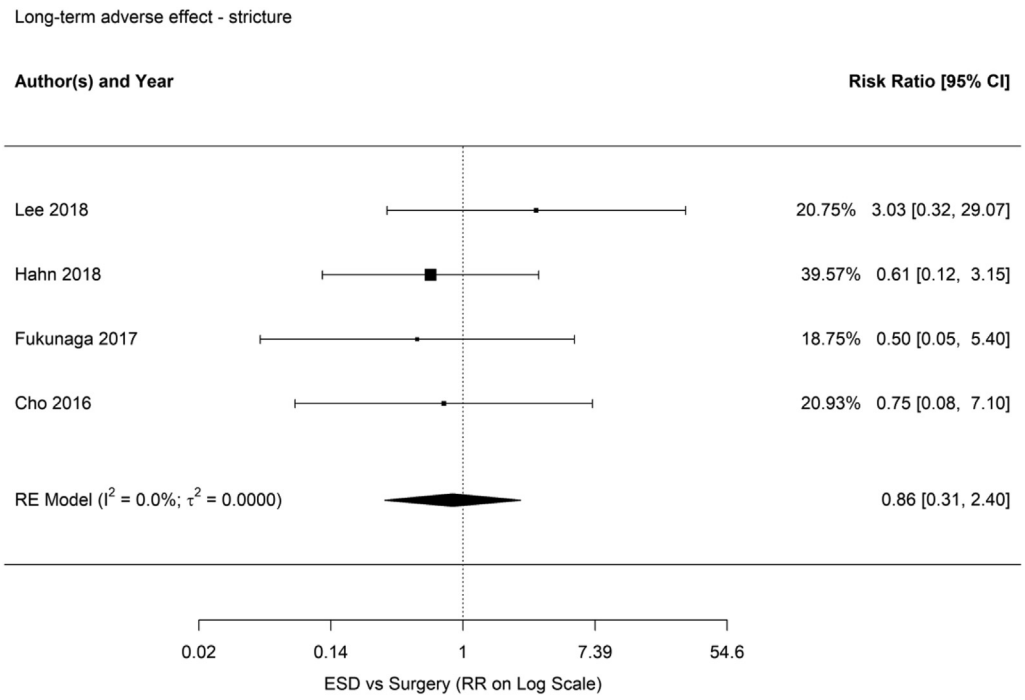
Supplementary Figure 30. Forest plot for question 3b: ESD versus surgery for gastric adenocarcinoma—short-term bleeding outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



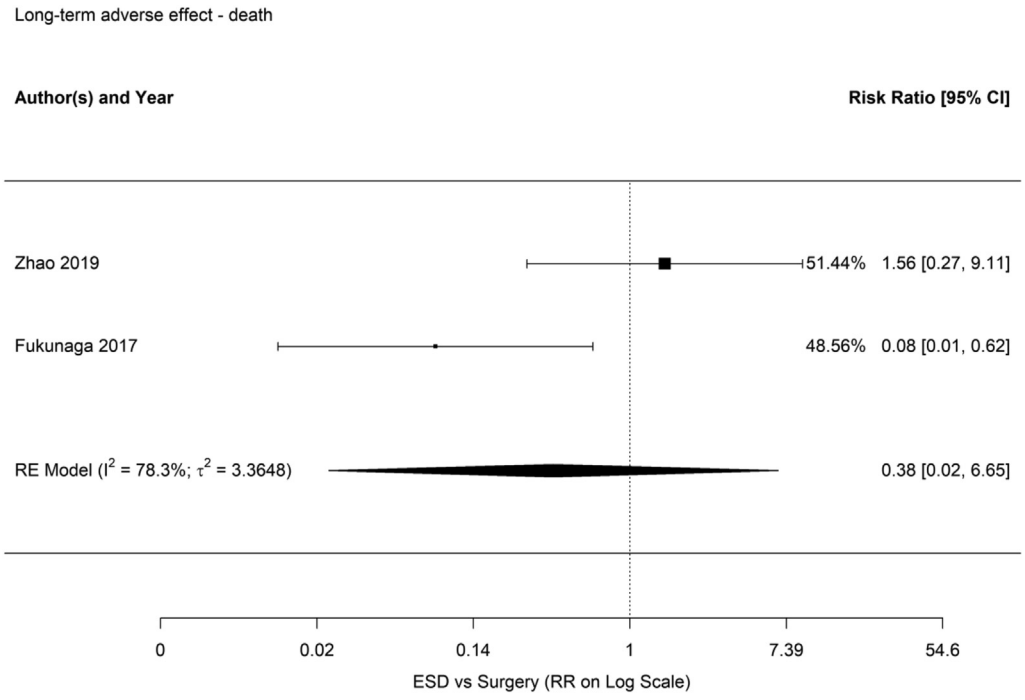
Supplementary Figure 31. Forest plot for question 3b: ESD versus surgery for gastric adenocarcinoma—short-term infection outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



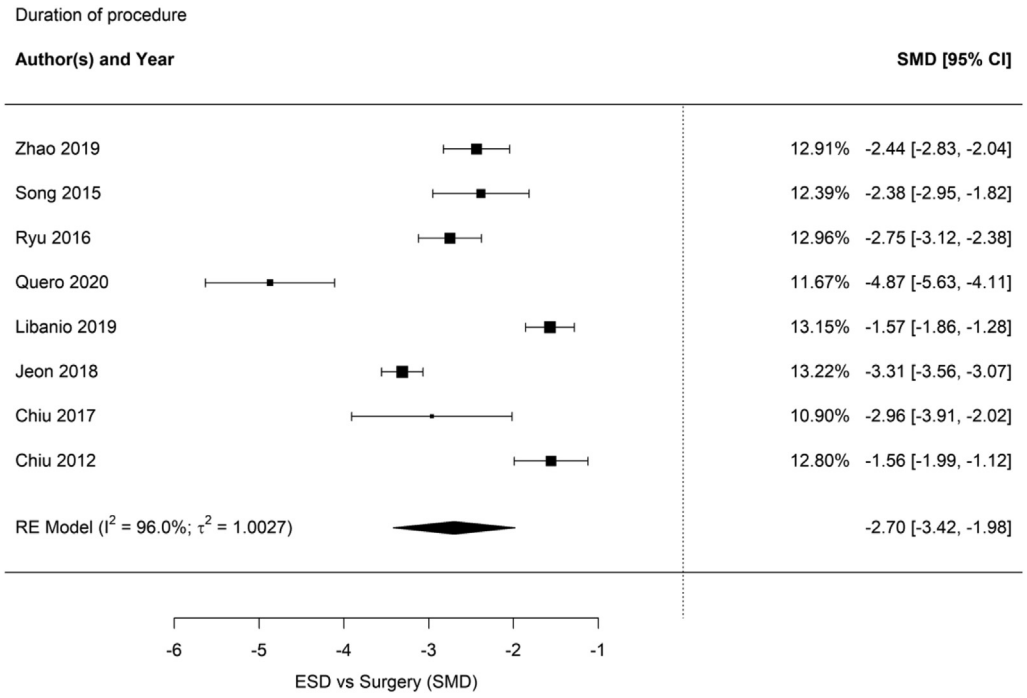
Supplementary Figure 32. Forest plot for question 3b: ESD versus surgery for gastric adenocarcinoma—short-term mortality outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



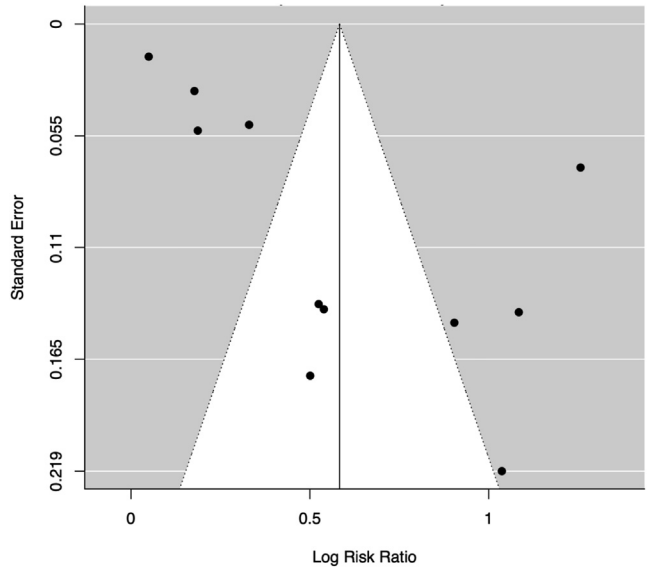
Supplementary Figure 33. Forest plot for question 3b: ESD versus surgery for gastric adenocarcinoma—long-term stricture outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



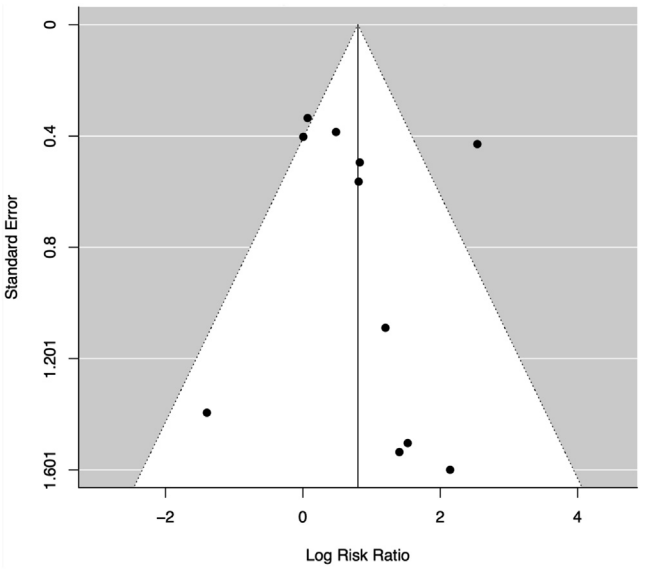
Supplementary Figure 34. Forest plot for question 3b: ESD versus surgery for gastric adenocarcinoma—long-term mortality outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *RR*, risk ratio.



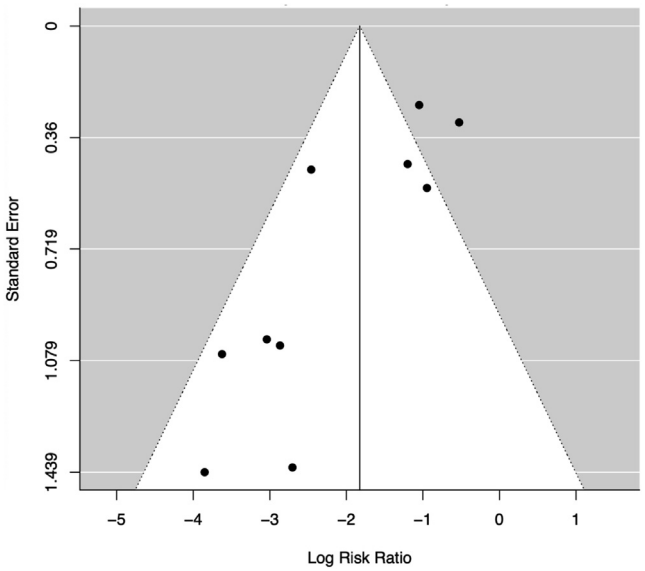
Supplementary Figure 35. Forest plot for question 3b: ESD versus surgery for gastric adenocarcinoma—procedure time outcome. *ESD*, Endoscopic submucosal dissection; *CI*, confidence interval; *RE*, random effects; *SMD*, standardized mean difference.



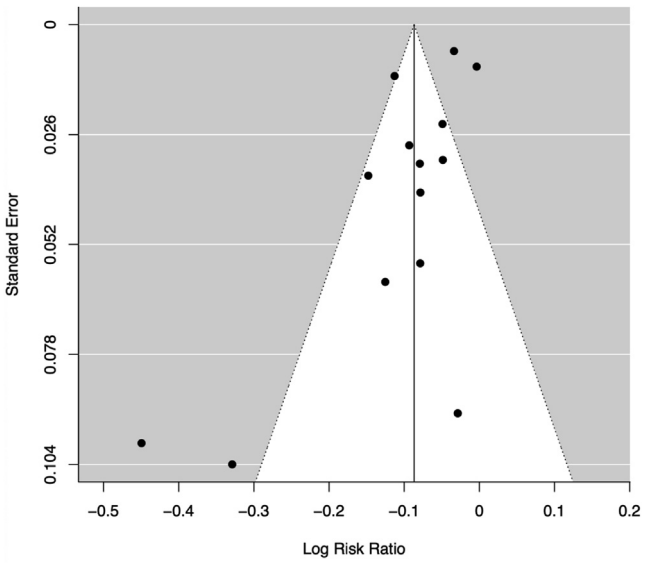
Supplementary Figure 36. Funnel plot for question 3a: endoscopic submucosal dissection versus EMR for gastric adenocarcinoma—clinical success outcome.



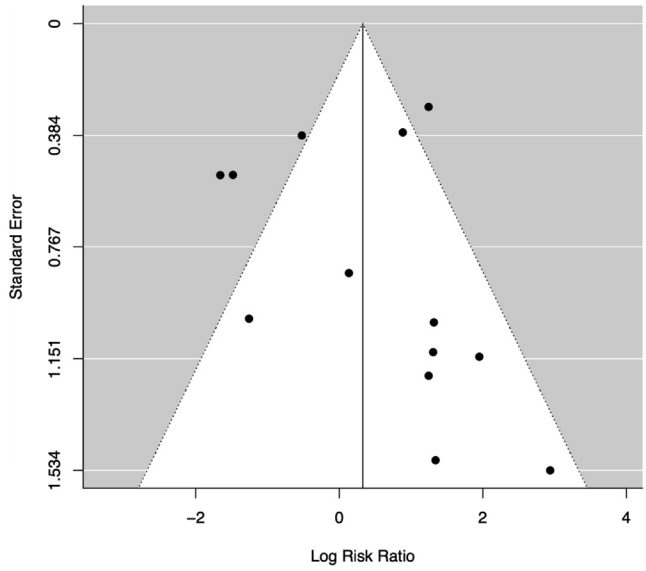
Supplementary Figure 37. Funnel plot for question 3a: endoscopic submucosal dissection versus EMR for gastric adenocarcinoma—short-term perforation outcome.



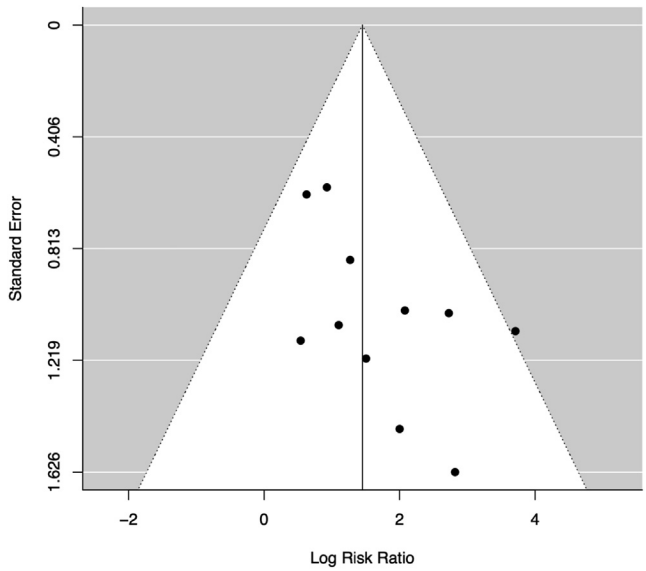
Supplementary Figure 38. Funnel plot for question 3a: endoscopic submucosal dissection versus EMR for gastric adenocarcinoma—local recurrence outcome.



Supplementary Figure 39. Funnel plot for question 3b: endoscopic submucosal dissection versus surgery for gastric adenocarcinoma—clinical success outcome.



Supplementary Figure 40. Funnel plot for question 3b: endoscopic submucosal dissection versus surgery for gastric adenocarcinoma—short-term bleeding outcome.



Supplementary Figure 41. Funnel plot for question 3b: endoscopic submucosal dissection versus surgery for gastric adenocarcinoma—local recurrence outcome.

SUPPLEMENTARY TABLE 1. Evidence profile for clinical question 1a: ESD vs EMR for early-stage esophageal squamous cell carcinoma

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Clinical success						
6	Observational studies	Not serious*	Serious†	Not serious	Not serious‡	None
Local recurrence						
8	Observational studies	Not serious§	Not serious‖	Not serious¶	Not serious**	None
Distant recurrence						
3	Observational studies	Not serious††	Not serious	Not serious	Serious‡‡	None
Short-term AE: bleeding						
5	Observational studies	Serious§§	Not serious‖‖	Not serious	Serious‡‡	None
Short-term AE: perforation						
8	Observational studies	Not serious§	Not serious¶¶	Not serious	Serious‡‡	None
Long-term AE: stricture						
5	Observational studies	Not serious***	Not serious†††	Not serious	Serious‡‡‡	None
Procedure time (min)						
6	Observational studies	Not serious§§§	Serious†	Not serious	Not serious‡	None

ESD, Endoscopic submucosal dissection; *AE*, adverse event; *CI*, confidence interval; *RR*, risk ratio; —, not applicable.

*Three studies had problems with selection bias, comparability, and outcome/comparison domains; however, most of the weight was from studies with minimal problems with quality.

†The magnitude of statistical heterogeneity was high, $I^2 > 90\%$, and the confidence interval of some studies did not overlap with those of most included studies/the point estimate of some of the included studies.

‡Decided not to rate down further because inconsistency (high heterogeneity and not overlapping 95% CIs of primary studies because of precise estimation of effect) and use of random-effects model caused the wide 95% CIs for the pooled effect.

§Three studies had problems with selection bias domain and 4 studies had problems with comparability. Decision for not rating down further was based on considerable overlap of studies effect estimates and their 95% CIs.

‖$I^2 = .0\%$ and most studies point estimates and 95% CIs overlap.

¶Only 1 study (Yu et al[33]) was judged to have serious indirectness with 10% of the weight and considerable overlap of effect estimates with most studies included in the analysis

**Large effect based on small number of events.

††One study (Yu et al[33]) was judged to have serious indirectness and problems with selection bias and outcome/comparison domain with 31% of the weight. Decision for not rating down further was based on considerable overlap of effect estimates and their 95% CIs.

‡‡Wide CIs, based on small number of events.

§§Three studies had problems with selection bias, comparability, and outcome/comparison domains with more than 70% of weight.

‖‖$I^2 = 31.8\%$, but seems to be driven by the risk of bias.

¶¶$I^2 = 61.3\%$, but seems to be driven by risk of bias and indirectness from Yu et al.[33]

***Two studies had problems with selection bias and comparability domains, 1 study had problems with comparability and outcome/comparison domains, but most studies had minimal or no concerns for risk of bias.

†††$I^2 = 36.5\%$, point estimates from 2 studies with wide 95% CIs had different direction of effect.

‡‡‡Small number of events with wide 95% CIs for pooled effect. Inconsistency and random-effects model may be the reason for wide 95% CIs and therefore not double penalized for inconsistency and imprecision.

§§§Most weight for the pooled effect estimate comes from studies with minimal risk of bias concerns.

SUPPLEMENTARY TABLE 1. Continued

No. of patients		Effect			
ESD	EMR	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
444/473 (93.9%)	428/594 (72.1%)	RR 1.33 (1.02-1.74)	238 more per 1000 (from 14 more to 533 more)	⨁◯◯◯ Very low	CRITICAL
4/776 (.5%)	67/1289 (5.2%)	RR .19 (.07-.48)	42 fewer per 1000 (from 48 fewer to 27 fewer)	⨁⨁◯◯ Low	CRITICAL
10/514 (1.9%)	10/893 (1.1%)	RR 1.35 (.50-3.65)	4 more per 1000 (from 6 fewer to 30 more)	⨁◯◯◯ Very low	CRITICAL
13/579 (2.2%)	18/1036 (1.7%)	RR 1.55 (.60-4.03)	10 more per 1000 (from 7 fewer to 53 more)	⨁◯◯◯ Very low	CRITICAL
47/821 (5.7%)	11/1306 (.8%)	RR 4.30 (1.22-15.12)	28 more per 1000 (from 2 more to 119 more)	⨁◯◯◯ Very low	CRITICAL
48/524 (9.2%)	44/595 (7.4%)	RR 1.20 (.68-2.11)	15 more per 1000 (from 24 fewer to 82 more)	⨁◯◯◯ Very low	IMPORTANT
539	610	—	Mean difference 46.77 min more (33.4 more to 60.14 more)	⨁◯◯◯ Very low	IMPORTANT

SUPPLEMENTARY TABLE 2. Outcomes for esophageal squamous cell carcinoma

Outcome	Relative risk (95% confidence interval)	I^2 statistic	No. of studies	No. of patients (ESD)	No. of patients (EMR)
Comparison: ESD vs EMR					
Complete gross resection	1.22 (1.00-1.49)	99.2	6	571/597	561/698
Clinical success	1.33 (1.02-1.74)	97.3	6	444/473	428/594
Local recurrence	.19 (.07-.48)	.0	8	4/776	67/1289
Distant recurrence	1.35 (.50-3.65)	.0	3	10/514	10/893
Adequacy of specimen	1.00 (.99-1.01)	.0	4	240/240	466/466
Procedure time	SMD 1.75 (1.12-2.39)	95.3	6	539	610
Short-term adverse effect: bleeding	1.55 (.60-4.03)	31.8	5	13/579	18/1036
Short-term adverse effect: perforation	4.30 (1.22-15.12)	61.3	8	47/821	11/1306
Long-term adverse effect: stricture	1.20 (.68-2.11)	36.5	5	48/524	44/595
Outcome	Relative risk (95% confidence interval)	I^2 statistic	No. of studies	No. of patients (ESD)	No. of patients (surg)
Comparison: ESD vs surgery					
Clinical success	.85 (.74-.98)	84.6	3	405/463	486/495
Local recurrence	1.14 (.60-2.17)	.0	2	14/190	24/351
Distant recurrence	.48 (.14-1.64)	27.8	3	6/169	16/178
Short-term adverse effect: bleeding	.33 (.05-2.23)	.0	2	1/378	3/309
Short-term adverse effect: death	.30 (.11-.88)	.0	2	4/385	17/367
Long-term adverse effect: stricture	1.34 (.89-2.02)	.0	3	51/463	36/495
5-y overall survival	1.01 (.95-1.08)	.0	2	96/106	74/85

ESD, Endoscopic submucosal dissection; *SMD*, standardized mean difference.

SUPPLEMENTARY TABLE 3. Study matrix with outcomes reported for esophageal squamous cell carcinoma

	Study														
Outcome	Lee 2020[45]	Urabe 2011[30]	Yamauchi 2017[49]	Yu 2020[33]	Zhang 2019[47]	Watanabe 2010[46]	Berger 2019[26]	Jin 2016[28]	Takahashi 2010[29]	Ishihara 2008[32]	Furue 2019[27]	Gong 2019[48]	Min 2018	Yamashita 2011[31]	Yamauchi 2021[49]
Comparison: ESD vs EMR															
Complete gross resection		X					X	X	X	X	X				
Clinical success				X			X	X	X	X				X	
Local recurrence		X		X			X	X	X	X	X			X	
Distant recurrence				X					X		X				
Adequacy of specimen							X	X	X	X					
Procedure time		X						X	X	X	X			X	
Short-term AE: bleeding		X		X				X	X	X					
Short-term AE: perforation		X		X			X	X	X	X	X			X	
Long-term AE: stricture		X						X	X	X	X				
Comparison: ESD vs surgery															
Clinical success	X				X							X			
Local recurrence	X				X										
Distant recurrence	X					X									X
Short-term AE: bleeding					X	X									
Short-term AE: death	X				X										
Long-term AE: stricture	X				X							X			
5-y overall survival						X									X

ESD, Endoscopic submucosal dissection; *AE*, adverse event.

SUPPLEMENTARY TABLE 4. Evidence profile for clinical question 1b: ESD vs surgery for early-stage esophageal squamous cell carcinoma

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
5-y overall survival (patients surviving at 5 y)						
2	Observational studies	Serious*	Not serious†	Not serious	Serious‡	None
Clinical success						
3	Observational studies	Not serious	Serious§	Not serious	Not serious‖	None
Local recurrence						
2	Observational studies	Not serious	Not serious	Not serious	Serious‡	None
Distant recurrence						
3	Observational studies	Not serious¶	Not serious**	Not serious	Serious‡	None
Short-term AE: bleeding						
2	Observational studies	Not serious††	Not serious†	Not serious	serious‡	None
Short-term AE: death						
2	Observational studies	Not serious	Not serious†	Not serious	Not serious‡‡	None
Long-term AE: stricture						
3	Observational studies	Not serious	Not serious†	Not serious	Serious‡	None
Length of stay (days)						
3	Observational studies	Not serious	Serious§§	Not serious	Not serious	None

ESD, Endoscopic submucosal dissection; *AE*, adverse event; *CI*, confidence interval; *RR*, risk ratio; —, not applicable.
*One study (Watanabe et al[46]) with 70% of weight had problems with selection bias, comparability, and outcome/comparison domains.
†$I^2 = .0\%$ and considerable overlap of studies point estimates and 95% CIs.
‡Wide CIs, based on small number of events.
§Point estimates vary, and the CIs of the studies do not overlap. The magnitude of statistical heterogeneity was high, with $I^2 = 84.6\%$.
‖Inconsistency and random-effects model may be the reason for wide 95% CIs and therefore not double penalized for inconsistency and imprecision.
¶One study (Watanabe et al[46]) with ~22% of weight had problems with selection bias, comparability, and outcome comparison domains.
**Statistical heterogeneity was low ($I^2 = 27.8\%$) with considerable overlap of effect estimates and their 95% CIs.
††One study (Watanabe et al[46]) with 36% of weight had problems with selection bias, comparability, and outcome/comparison domains.
‡‡95% CIs for pooled effect does not include null value, and given the importance of the outcome (death) it was decided not to rate down despite small number of events.
§§The magnitude of statistical heterogeneity is high at 83.3%.

SUPPLEMENTARY TABLE 4. Continued

No. of patients		Effect			
ESD	Surgery	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
96/106 (90.6%)	74/85 (87.1%)	RR 1.01 (.95-1.08)	9 more per 1000 (from 44 fewer to 70 more)	⨁◯◯◯ Very low	IMPORTANT
405/463 (87.5%)	486/495 (98.2%)	RR .85 (.74-.98)	147 fewer per 1000 (from 255 fewer to 20 fewer)	⨁◯◯◯ Very low	CRITICAL
14/190 (7.4%)	24/351 (6.8%)	RR 1.14 (.60-2.17)	10 more per 1000 (from 27 fewer to 80 more)	⨁◯◯◯ Very low	CRITICAL
6/169 (3.6%)	16/178 (9.0%)	RR .48 (.14-1.64)	47 fewer per 1000 (from 77 fewer to 58 more)	⨁◯◯◯ Very low	CRITICAL
1/378 (.3%)	3/309 (1.0%)	RR .33 (.05-2.23)	7 fewer per 1000 (from 9 fewer to 12 more)	⨁◯◯◯ Very low	CRITICAL
4/385 (1.0%)	17/367 (4.6%)	RR .30 (.11-.88)	32 fewer per 1000 (from 41 fewer to 6 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
51/463 (11.0%)	36/495 (7.3%)	RR 1.34 (.89-2.02)	25 more per 1000 (from 8 fewer to 74 more)	⨁◯◯◯ Very low	CRITICAL
483	495	—	Mean difference 11.62 days lower (15.86 lower to 7.38 lower)	⨁◯◯◯ Very low	CRITICAL

SUPPLEMENTARY TABLE 5. Evidence profile for clinical question 2: ESD vs EMR for early-stage esophageal adenocarcinoma

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Clinical success						
3	Observational studies	Serious*	Not serious†	Not serious	Not serious‡	None
Local recurrence						
3	Observational studies	Not serious§	Serious‖	Not serious	Not serious‡	None
Short-term AE: bleeding						
3	Observational studies	Not serious§	Not serious¶	Not serious	Not serious**	None
Short-term AE: perforation						
4	Observational studies	Not serious§	Not serious††	Not serious	Serious‡‡	None
Long-term AE: stricture						
2	Observational studies	Not serious	Not serious§§	Not serious	Serious‡‡	None

ESD, Endoscopic submucosal dissection; *AE*, adverse event; *CI*, confidence interval; *RR*, risk ratio.

*One study (Chedgy et al[56]) had some problems with selection bias and comparability domains. This study with 45% of weight seems to be the cause of imprecision and inconsistency.

†Statistical heterogeneity was considerable (I^2 = 91%) but mainly because of non-overlapping point estimate and 95% CIs from Chedgy et al[56] with risk of bias concerns.

‡Inconsistency and random-effects model may be the reason for wide 95% CIs and therefore not double penalized for inconsistency and imprecision.

§One study (Chedgy et al[56]) had some issues with selection bias and comparability domains. However, this study only contributes 20% of the weight to the analysis and point estimate and 95% CIs overlap with the other studies.

‖Point estimates vary, and CI of some of the studies do not overlap. The direction of the effect was not consistent between the included studies, and the magnitude of statistical heterogeneity was considerable, with I^2 = 52.8%.

¶I^2 = 1.0% and considerable overlap of studies point estimates and 95% CIs.

**Large effect based on small number of events.

††Statistical heterogeneity was low (I^2 = 26.5%). Point estimates and 95% CIs had considerable overlap.

‡‡Wide 95% CI, based on small number of events with 95% CIs including considerable benefit and important harms.

§§I^2 0.0% and considerable overlap of studies point estimates and 95% CIs.

SUPPLEMENTARY TABLE 5. Continued

No. of patients		Effect		Certainty	Importance
ESD	EMR	Relative (95% CI)	Absolute (95% CI)		
118/155 (76.1%)	201/311 (64.6%)	RR 1.38 (.83-2.29)	246 more per 1000 (from 110 fewer to 834 more)	⨁◯◯◯ Very low	CRITICAL
5/158 (3.2%)	82/314 (26.1%)	RR .19 (.04-.98)	212 fewer per 1000 (from 251 fewer to 5 fewer)	⨁◯◯◯ Very low	CRITICAL
5/227 (2.2%)	78/741 (10.5%)	RR .32 (.13-.78)	72 fewer per 1000 (from 92 fewer to 23 fewer)	⨁⨁◯◯ Low	CRITICAL
4/247 (1.6%)	15/761 (2.0%)	RR 1.33 (.27-6.63)	7 more per 1000 (from 14 fewer to 111 more)	⨁◯◯◯ Very low	CRITICAL
12/176 (6.8%)	20/601 (3.3%)	RR 1.19 (.60-2.34)	6 more per 1000 (from 13 fewer to 45 more)	⨁◯◯◯ Very low	IMPORTANT

SUPPLEMENTARY TABLE 6. Outcomes for esophageal adenocarcinoma

Outcome	Relative risk (95% confidence interval)	I^2 statistic	No. of studies	No. of patients (ESD)	No. of patients (EMR)
Comparison: ESD vs EMR					
Complete gross resection	3.52 (1.92-6.44)	48.1	2	104/107	54/174
Clinical success	1.38 (.83-2.29)	93.9	3	118/155	201/311
Local recurrence	.19 (.04-.98)	52.8	3	5/158	82/314
Short-term adverse effect: bleeding	.32 (.13-.78)	1.0	3	5/227	78/741
Short-term adverse effect: perforation	1.33 (.27-6.63)	26.5	4	4/247	15/761
Long-term adverse effect: stricture	1.19 (.60-2.34)	.0	2	12/176	20/601

ESD, Endoscopic submucosal dissection.

SUPPLEMENTARY TABLE 7. Study matrix with outcomes reported for esophageal adenocarcinoma

	Study			
Outcome	Perez 2019	Chedgy 2015	Codipilli 2020	Terheggen 2017
Comparison: ESD vs EMR				
Complete gross resection	X			X
Clinical success	X	X		X
Local recurrence	X	X		X
Short-term adverse effect: bleeding	X	X	X	
Short-term adverse effect: perforation	X	X	X	X
Long-term adverse effect: stricture	X		X	

All studies are observational, except Terheggen 2017 is a randomized controlled trial.

SUPPLEMENTARY TABLE 8. Evidence profile for clinical question 3a: ESD vs EMR for early-stage gastric adenocarcinoma

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
5-y disease-free survival (patients survived)						
2	Observational studies	Not serious*	Serious†	Not serious	Not serious‡	None
Clinical success						
11	Observational studies	Not serious§	Serious‖	Not serious	Not serious‡	None
Local recurrence						
10	Observational studies	Not serious¶	Serious**	Not serious	Not serious††	None
Short-term AE: bleeding						
9	Observational studies	Serious‡‡	Not serious§§	Not serious	Serious‖‖	None
Short-term AE: perforation						
11	Observational studies	Not serious¶¶	Not serious***	Not serious	Serious†††	None
Procedure time						
6	Observational studies	Serious‡‡‡	Serious§§§	Not serious	Not serious‡	None

ESD, Endoscopic submucosal dissection; *AE*, adverse event; *CI*, confidence interval; *RR*, risk ratio; —, not applicable.

*One study had some problems with comparability domain and the other study had some problems with outcome/comparison domain. Risk of bias concerns did not seem to cause variability in effect estimates.

†Despite minimal variability in studies point estimates, the CIs of the studies do not overlap. The magnitude of statistical heterogeneity was high, with $I^2 = 89.3\%$.

‡Inconsistency and random-effects model may be the reason for wide 95% CIs and therefore not double penalized for inconsistency and imprecision.

§Three studies had some problems with selection bias domain; more than half of studies had some problems with comparability domain, and 5 studies had some problems with outcome/comparison domains; however, risk of bias does not seem to explain the observed variability in the effect estimates.

‖Point estimates vary considerably, and CIs of most studies do not overlap. The magnitude of statistical heterogeneity was considerable, with $I^2 = 98.2\%$.

¶Three studies had some problems with selection bias domain, more than half of studies had some problems with comparability domain, and 3 studies had some problems with outcome/comparison domains; however, risk of bias does not seem to explain the observed variability in the effect estimates.

**Point estimates vary considerably, and CIs of most studies do not overlap. The direction of the effect was not consistent between the included studies, and the magnitude of statistical heterogeneity was considerable, with $I^2 = 74.7\%$.

††Pooled estimate had wide 95% CIs informed by small number of events. Inconsistency and random-effects model may be the reasons for wide 95% CIs and therefore not double penalized for inconsistency and imprecision.

‡‡Only 1 study was without risk of bias concern in all domains; 1 study had some problems with comparability domain, and the remainder of studies had some problems with 2 of the 3 domains.

§§$I^2 = .0\%$ and there was a considerable overlap of studies point estimates and 95% CIs.

‖‖Wide 95% CIs, based on small number of events.

¶¶Four studies had some problems with selection bias domain, more than half of studies had some problems with comparability domain, and 6 studies had some problems with outcome/comparison domains; however, risk of bias does not seem to explain the observed variability in direction or magnitude of the effect estimates.

***Statistical heterogeneity was moderate ($I^2 = 64.7\%$) with noticeable overlap of effect estimates and their 95% CIs. It was decided not to rate further down because inconsistency and random-effects model may be the reasons for wide 95% CIs and therefore not double penalized for inconsistency and imprecision.

†††Wide 95% CIs, based on small number of events. It was decided not rate down for both inconsistency and imprecision, and some of the observed imprecision can be because of inconsistency.

‡‡‡All studies had some problems with at least 1 domain; 5 studies had some problems with comparability domain, and half the studies had some problems with outcome/comparison domain.

§§§Point estimates vary considerably, and CIs of most studies do not overlap. The direction of the effect was not consistent between the included studies, and the magnitude of statistical heterogeneity was considerable, with $I^2 = 98\%$.

SUPPLEMENTARY TABLE 8. Continued

No. of patients		Effect			
ESD	EMR	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
525/527 (99.6%)	413/439 (94.1%)	RR 1.11 (.95-1.30)	103 more per 1000 (from 47 fewer to 282 more)	⨁◯◯◯ Very low	CRITICAL
2741/3169 (86.5%)	1630/2998 (54.4%)	RR 1.79 (1.40-2.30)	430 more per 1000 (from 217 more to 707 more)	⨁◯◯◯ Very low	CRITICAL
55/3226 (1.7%)	223/3092 (7.2%)	RR .16 (.08-.33)	61 fewer per 1000 (from 66 fewer to 48 fewer)	⨁◯◯◯ Very low	CRITICAL
133/2742 (4.9%)	130/2675 (4.9%)	RR 1.06 (.82-1.38)	3 more per 1000 (from 9 fewer to 18 more)	⨁◯◯◯ Very low	CRITICAL
106/2887 (3.7%)	59/3154 (1.9%)	RR 2.23 (1.19-4.19)	23 more per 1000 (from 4 more to 60 more)	⨁◯◯◯ Very low	CRITICAL
975	1001	—	Mean difference 48.93 min more (22.45 more to 75.42 more)	⨁◯◯◯ Very low	IMPORTANT

SUPPLEMENTARY TABLE 9. Outcomes for gastric adenocarcinoma

Outcome	Relative risk (95% confidence interval)	I^2 statistic	No. of studies	No. of patients (ESD)	No. of patients (EMR)
Comparison: ESD vs EMR					
Complete gross resection	1.26 (1.10-1.46)	99.8	12	3095/3232	2377/2928
Clinical success	1.79 (1.40-2.30)	98.2	11	2741/3169	1630/2998
Local recurrence	.16 (.08-.33)	74.7	10	55/3226	223/3092
Adequacy of specimen	1.00 (1.00-1.00)	15.7	7	1776/1776	1714/1722
Procedure time	SMD 1.24 (.30-2.18)	98.6	6	975	1001
Short-term adverse effect: bleeding	1.06 (.82-1.38)	.0	9	133/2742	130/2675
Short-term adverse effect: perforation	2.23 (1.19-4.19)	64.7	11	106/2887	59/3154
1-y disease-free survival	1.14 (.90-1.44)	95.9	2	665/674	557/605
3-y disease-free survival	1.03 (.99-1.08)	81.8	2	715/724	733/770
5-y disease-free survival	1.11 (.95-1.30)	89.3	2	525/527	413/439
Outcome	Relative risk (95% confidence interval)	I^2 statistic	No. of studies	No. of patients (ESD)	No. of patients (surgery)
Comparison: ESD vs surgery					
Complete gross resection	.99 (.98-1.00)	.1	9	870/900	1092/1101
Clinical success	.92 (.89-.95)	88.1	14	2703/2947	3466/3484
Local recurrence	4.27 (2.36-7.73)	9.4	11	56/2624	18/3191
Distant recurrence	2.15 (.99-4.70)	.0	6	27/2061	17/2428
Adequacy of specimen	1.00 (.99-1.01)	.0	5	383/383	640/640
Procedure time	SMD −2.70 (−3.42 to −1.98)	96.0	8	819	846
Short-term adverse effect: bleeding	1.39 (.65-2.99)	77.6	13	114/2829	109/3270
Short-term adverse effect: infection	.12 (.02-.71)	67.1	4	5/1856	178/2298
Short-term adverse effect: death	.34 (.05-2.54) .34 (.05-2.54)	78.3	2	1/970	5/1307
Long-term adverse effect: stricture	.86 (.31-2.40)	.0	4	9/2120	9/2280
Long-term adverse effect: death	.38 (.02-6.65)	.0	2	3/132	15/210
4-y overall survival	1.02 (.93-1.12)	50.0	2	75/77	144/150
5-y overall survival	1.00 (.99-1.01)	7.3	8	2378/2447	2855/2981
4-y disease-free survival	.96 (.88-1.05)	.0	2	52/58	99/106
5-y disease-free survival	.91 (.86-.98)	82.1	5	1265/1291	1838/1891

ESD, Endoscopic submucosal dissection; *SMD*, standardized mean difference.

SUPPLEMENTARY TABLE 10. Study matrix with outcomes for gastric adenocarcinoma

	Study															
Outcome	**Chiu 2017[81]**	**Cho 2016[85]**	**Song 2015[109]**	**Shin 2017[88]**	**Quero 2021[110]**	**Bausys 2019**	**Guo 2020[86]**	**Hoteya 2009[72]**	**Jeon 2018[84]**	**Lim 2019[111]**	**Nakamoto 2009[73]**	**Oda 2006[74]**	**Oka 2014[79]**	**Zhao 2019[112]**	**Abe 2019[68]**	**Oka 2006[75]**	**Hong 2020[83]**
Comparison: ESD vs EMR																	
Complete gross resection								X			X	X	X		X	X	
Clinical success								X			X	X			X	X	
Local recurrence								X				X			X	X	
Adequacy of specimen															X	X	
Procedure time											X					X	
Short-term AE: bleeding								X			X		X			X	
Short-term AE: perforation								X			X	X	X			X	
1-y disease-free survival																	
3-y disease-free survival												X					
5-y disease-free survival											X						
Comparison: ESD vs surgery																	
Complete gross resection		X			X	X								X			X
Clinical success		X	X	X	X									X			X
Local recurrence		X		X		X				X				X			X
Distant recurrence				X			X			X				X			
Adequacy of specimen																	X
Procedure time	X				X				X					X			
Short-term AE: bleeding		X		X	X									X			X
Short-term AE: infection														X			
Short-term AE: death																	
Long-term AE: stricture		X															
Long-term AE: death														X			
4-y overall survival														X			
5-y overall survival				X		X	X		X								

(*continued on the next page*)

SUPPLEMENTARY TABLE 10. Continued

	Study															
Outcome	**Chiu 2017**[81]	**Cho 2016**[85]	**Song 2015**[109]	**Shin 2017**[88]	**Quero 2021**[110]	**Bausys 2019**	**Guo 2020**[86]	**Hoteya 2009**[72]	**Jeon 2018**[84]	**Lim 2019**[111]	**Nakamoto 2009**[73]	**Oda 2006**[74]	**Oka 2014**[79]	**Zhao 2019**[112]	**Abe 2019**[68]	**Oka 2006**[75]	**Hong 2020**[83]
4-y disease-free survival														X			
5-y disease-free survival						X	X		X								

	Study																	
Outcome	**Choi 2019**[71]	**Anh 2011**	**Zhuang 2019**	**Wata-nabe 2010**[46]	**Chiu 2012**[113]	**Kim 2014**[114]	**Ryu 2016**[87]	**Shimura 2006**	**Kim 2018**[123]	**Cata-lano 2009**[70]	**Fuku-naga 2017**[117]	**Hahn 2018**[89]	**Lee 2018**	**Libanio 2019**[118]	**Najmeh 2016**[119]	**Tanabe 2014**[77]	**Outcome**
Comparison: ESD vs EMR																	
Complete gross resection		X	X	X				X		X						X	
Clinical success	X	X	X	X				X		X							
Local recurrence	X	X	X	X				X								X	
Adequacy of specimen		X	X	X				X		X							
Procedure time			X					X		X						X	
Short-term AE: bleeding	X	X						X		X						X	
Short-term AE: perforation		X	X	X				X		X						X	
1-y disease-free survival	X			X													
3-y disease-free survival																X	
5-y disease-free survival																X	
Comparison: ESD vs surgery																	
Complete gross resection					X	X	X		X								
Clinical success					X	X	X		X			X	X	X	X		
Local recurrence						X	X		X			X	X				
Distant recurrence												X	X				
Adequacy of specimen					X	X	X		X								
Procedure time					X		X							X			
Short-term AE: bleeding					X	X	X		X		X	X	X		X		
Short-term AE: infection					X							X	X				
Short-term AE: death												X		X			
Long-term AE: stricture											X	X	X				
Long-term AE: death											X						
4-y overall survival															X		
5-y overall survival							X				X	X	X				

(*continued on the next page*)

SUPPLEMENTARY TABLE 10. Continued

	Study																
Outcome	Choi 2019[71]	Anh 2011	Zhuang 2019	Watanabe 2010[46]	Chiu 2012[113]	Kim 2014[114]	Ryu 2016[87]	Shimura 2006	Kim 2018[123]	Catalano 2009[70]	Fukunaga 2017[117]	Hahn 2018[89]	Lee 2018	Libanio 2019[118]	Najmeh 2016[119]	Tanabe 2014[77]	Outcome
4-y disease-free survival															X		
5-y disease-free survival							X					X					

ESD, Endoscopic submucosal dissection; *AE*, adverse event.

SUPPLEMENTARY TABLE 11. Evidence profile for clinical question 3b: ESD vs surgery for early-stage gastric adenocarcinoma

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
5-y overall survival (patients surviving at 5 y)						
8	Observational studies	Not serious*	Not serious†	Not serious	Not serious	None
Clinical success						
14	Observational studies	Not serious‡	Serious§	Not serious	Not serious	None
Local recurrence						
11	Observational studies	Not serious‖	Not serious¶	Not serious	Serious**	None
Distant recurrence						
6	Observational studies	Not serious††	Not serious‡‡	Not serious	Serious§§	None
Short-term AE: bleeding						
13	Observational studies	Not serious‖‖	Serious¶¶	Not serious	Serious§§	None
Short-term AE: infection						
4	Observational studies	Not serious***	Serious†††	Not serious	Not serious‡‡‡	None
Short-term AE: death						
2	Observational studies	Not serious§§§	Not serious‖‖‖	Not serious	Serious§§	None
Long-term AE: stricture						
4	Observational studies	Not serious¶¶¶	Not serious‡‡	Not serious	Serious§§	None
Long-term: death						
2	Observational studies	Not serious	Serious‖‖‖	Not serious	Serious§§	None
Procedure time (min)						
8	Observational studies	Not serious****	Serious††††	Not serious	Not serious	None
Length of hospital stay (days)						
14	Observational studies	Not serious	Serious‡‡‡‡	Not serious	Not serious	None

ESD, Endoscopic submucosal dissection; *AE*, adverse event; *CI*, confidence interval; *RR*, risk ratio; —, not applicable.

*One study had some problems with all domains, and 2 studies had some problems with selection bias and outcome/comparison domains with <10% of weight.

†I^2 = 7.3% and considerable overlap of studies point estimates and 95% CIs.

‡Five studies with majority of the weight had no problems with all domains; only 1 study with ~2% of the weight had some problems with all domain; the remaining studies has some problems with at least 1 domain.

§Point estimates vary, and CIs of some of the studies do not overlap. The direction of the effect was not consistent between the included studies, and the magnitude of statistical heterogeneity was high, with I^2 = 88.1%.

‖Only 1 study had issues with all domains; 2 studies had some problems with outcome/comparison domain, and 1 study had problems with selection bias domain with majority of weight (>60%) for the pooled-effect estimate coming from studies with no concern in all domains.

¶I^2 = 9.4% and considerable overlap of studies point estimates and 95% CIs.

**Large effect with wide 95% CIs, based on small number of events.

††Four studies had no issues in all domains, and 2 studies had issues with outcome/comparison domain.

‡‡I^2 = 0% and considerable overlap of studies point estimates and 95% CIs.

§§Wide 95% CIs, based on small number of events.

‖‖One study had some problems with all domains; 7 studies had no concern in all domains with majority of the weight (>60%); the remaining studies had some problems with at least 1 domain.

¶¶Point estimates vary, and CIs of some of the studies do not overlap. The direction of the effect was not consistent between the included studies, and the magnitude of statistical heterogeneity was high, with I^2 = 77.6%.

***One study had some problems with selection bias and comparability domain. The remaining 3 studies had no risk of bias concerns.

†††Point estimates vary widely, and the CIs of some of the studies do not overlap with those of most included studies or the point estimate of some of the included studies. The magnitude of statistical heterogeneity was high, with I^2 = 67.1%.

‡‡‡A small number of events with wide 95% CIs for pooled effect. Inconsistency and random-effects models may be the reason for wide 95% CIs and therefore not double penalized for inconsistency and imprecision.

§§§One study had some problems with comparability and outcome/comparison domains. It did not seem to have biased the study effect estimate.

‖‖‖Point estimates vary with minimal overlap of their CIs. The direction of the effect was not consistent between the included studies, and the magnitude of statistical heterogeneity was high, with I^2 = 78.3%.

¶¶¶All studies had no concern in all domains, except 1 study with some problems with outcome/comparison domain.

****One study had some problems with all domains, 2 studies had some problems with comparability and outcome/comparison domains, and 1 study had some problems with selection bias and comparability domain with ~45% of weight.

††††Point estimates vary considerably, and CIs of most of the studies do not overlap. The magnitude of statistical heterogeneity was high, with I^2 = 99%.

‡‡‡‡High degree of statistical heterogeneity at 97.8%.

SUPPLEMENTARY TABLE 11. Continued

No. of patients		Effect		Certainty	Importance
ESD	Surgery	Relative (95% CI)	Absolute (95% CI)		
2378/2447 (97.2%)	2855/2891 (98.8%)	RR 1.00 (.99-1.01)	0 fewer per 1000 (from 10 fewer to 10 more)	⨁⨁◯◯ Low	IMPORTANT
2703/2947 (91.7%)	3466/3484 (99.5%)	RR .92 (.89-.95)	80 fewer per 1000 (from 109 fewer to 50 fewer)	⨁◯◯◯ Very low	CRITICAL
56/2624 (2.1%)	18/3191 (.6%)	RR 4.27 (2.36-7.73)	18 more per 1000 (from 8 more to 38 more)	⨁◯◯◯ Very low	CRITICAL
27/2061 (1.3%)	17/2428 (.7%)	RR 2.15 (.99-4.70)	8 more per 1000 (from 0 fewer to 26 more)	⨁◯◯◯ Very low	CRITICAL
114/2829 (4.0%)	109/3270 (3.3%)	RR 1.39 (.65-2.99)	13 more per 1000 (from 12 fewer to 66 more)	⨁◯◯◯ Very low	CRITICAL
5/1856 (.3%)	178/2298 (7.7%)	RR .12 (.02-.71)	68 fewer per 1000 (from 76 fewer to 22 fewer)	⨁◯◯◯ Very low	IMPORTANT
1/970 (.1%)	5/1307 (.4%)	RR .34 (.05-2.54)	3 fewer per 1000 (from 4 fewer to 6 more)	⨁◯◯◯ Very low	CRITICAL
9/2120 (.4%)	9/2280 (.4%)	RR .86 (.31-2.40)	1 fewer per 1000 (from 3 fewer to 6 more)	⨁◯◯◯ Very low	IMPORTANT
3/132 (2.3%)	15/210 (7.1%)	RR .38 (.02-6.65)	44 fewer per 1000 (from 70 fewer to 404 more)	⨁◯◯◯ Very low	CRITICAL
819	846	—	Mean difference 129.82 minutes fewer (89.01 fewer to 170.62 fewer)	⨁◯◯◯ Very low	IMPORTANT
2517	1969	—	Mean difference 6.45 days lower (7.84 lower to 5.07 lower)	⨁◯◯◯ Very low	CRITICAL

SUPPLEMENTARY TABLE 12. Summaries of study quality (according to NOS) and estimated indirectness

First author and year	NOS selection domain /4	NOS comparability domain /2	NOS outcome/comparator domain /3	Estimated indirectness
Studies assessing esophageal squamous cell carcinoma				
Lee 2020[45]	3	2	3	Low (nonserious)
Urabe 2011[30]	3	1	2	Low
Yamauchi 2017[49]	3	2	2	Low
Yu 2020[33]	2	2	2	Serious
Zhang 2019[47]	3	2	3	Low
Watanabe 2010[46]	2	1	2	Low
Berger 2019[26]	3	1	3	Low
Jin 2016[28]	2	1	2	Low
Takahashi 2010[29]	3	2	3	Low
Ishihara 2008[32]	2	1	3	Low
Furue 2019[27]	3	2	2	Low
Gong 2019[48]	3	2	2	Low
Min 2018	3	2	3	Low
Yamashita 2011[31]	3	2	2	Low
Yamauchi 2021[49]	3	2	3	Low
Studies assessing esophageal adenocarcinoma				
Perez 2019[54]	N/A	N/A	N/A	Low
Chedgy 2015[56]	2	1	3	Low
Codipilly 2020[55]	3	2	3	Low
Terheggen 2017[53]	N/A	N/A	N/A	Low
Studies assessing gastric adenocarcinoma				
Chiu 2017[81]	N/A	N/A	N/A	Low
Cho 2016[85]	3	2	2	Low
Song 2015[109]	3	1	2	Low
Shin 2017[88]	3	2	3	Low
Quero 2021[110]	2	2	3	Low
Bausys 2019	2	2	2	Low
Guo 2020[86]	3	2	2	Low
Hoteya 2009[72]	2	1	2	Low
Jeon 2018[84]	2	1	2	Low
Lim 2019[111]	3	2	2	Low
Nakamoto 2009[73]	3	2	2	Low
Oda 2006[74]	3	2	3	Low
Oka 2014[79]	2	2	2	Low
Zhao 2019[112]	3	2	3	Low
Abe 2019[68]	3	2	3	Low
Oka 2006[75]	3	1	2	Low
Hong 2020[83]	2	1	2	Low
Choi 2019[71]	3	2	3	Low
Anh 2011	2	1	2	Low
Zhuang 2019	3	1	3	Low
Watanabe 2010[46]	3	2	3	Low
Chiu 2012[113]	2	1	3	Low

(*continued on the next page*)

SUPPLEMENTARY TABLE 12. Continued

First author and year	NOS selection domain /4	NOS comparability domain /2	NOS outcome/comparator domain /3	Estimated indirectness
Kim 2014[114]	3	1	3	Low
Ryu 2016[87]	3	2	3	Low
Shimura 2007[76]	2	1	3	Low
Kim J 2018[80]	N/A	N/A	N/A	Low
Catalano 2009[70]	3	1	2	Low
Fukunaga 2017[117]	3	2	3	Low
Hahn 2018[89]	3	2	3	Low
Lee 2018[13]	3	2	3	Low
Libanio 2019[118]	3	1	2	Low
Najmeh 2016[119]	3	1	2	Low
Tanabe 2014[77]	3	1	3	Low

NOS, Newcastle-Ottawa Scale; *N/A*, not applicable.