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GUIDELINES

AGA Clinical Practice Guideline on Endoscopic Eradication Therapy of Barrett's Esophagus and Related Neoplasia

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BACKGROUND & AIMS: Barrett's esophagus (BE) is the precursor to esophageal adenocarcinoma (EAC). Endoscopic eradication therapy (EET) can be effective in eradicating BE and related neoplasia and has greater risk of harms and resource use than surveillance endoscopy. This clinical practice guideline aims to inform clinicians and patients by providing evidence-based practice recommendations for the use of EET in BE and related neoplasia. **METHODS:** The Grading of Recommendations Assessment, Development and Evaluation framework was used to assess evidence and make recommendations. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients, conducted an evidence review, and used the Evidence-to-Decision Framework to develop recommendations regarding the use of EET in patients with BE under the following scenarios: presence of (1) high-grade dysplasia, (2) low-grade dysplasia, (3) no dysplasia, and (4) choice of stepwise endoscopic mucosal resection (EMR) or focal EMR plus ablation, and (5) endoscopic submucosal dissection vs EMR. Clinical recommendations were based on the balance between desirable and undesirable effects, patient values, costs, and health equity considerations. **RESULTS:** The panel agreed on 5 recommendations for the use of EET in BE and related neoplasia. Based on the available evidence, the panel made a strong recommendation in favor of EET in patients with BE high-grade dysplasia and conditional recommendation against EET in BE without dysplasia. The panel made a conditional recommendation in favor of EET in BE low-grade dysplasia; patients with BE low-grade dysplasia who place a higher value on the potential harms and lower value on the benefits (which are uncertain) regarding reduction of esophageal cancer mortality could reasonably select surveillance endoscopy. In patients with visible lesions, a conditional recommendation was made in favor of focal EMR plus ablation over stepwise EMR. In patients with visible neoplastic lesions undergoing resection, the use of either endoscopic mucosal resection or endoscopic submucosal dissection was suggested based on lesion characteristics. **CONCLUSIONS:** This document provides a comprehensive outline of the indications for EET in the management of BE and related neoplasia. Guidance is also provided regarding the considerations surrounding implementation of EET. Providers should engage in shared decision making based on patient preferences. Limitations and gaps in the evidence are highlighted to guide future research opportunities.

Keywords: Barrett's Esophagus; Cryosurgery; Endoscopic Mucosal Resection; Esophageal Neoplasms; Radiofrequency Ablation.

***Authors share co-first authorship.**

Abbreviations used in this paper: **AGA, American Gastroenterological Association; BE, Barrett's esophagus; CEIM, complete eradication of intestinal metaplasia; CEN, complete eradication of neoplasia; EAC, esophageal adenocarcinoma; EET, endoscopic eradication therapy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; fEMR, focal endoscopic mucosal resection; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; PICO, population, intervention, comparison, outcome; PPI, proton pump inhibitor; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; sEMR, stepwise endoscopic mucosal resection.**

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Executive Summary

The advent of endoscopic eradication therapy (EET) for treatment of dysplasia and early-stage cancer has revolutionized the management of Barrett's esophagus (BE), reducing the morbidity and mortality related to esophagectomy and ultimately preventing esophageal adenocarcinoma (EAC) mortality. This evidence-based guideline from the American Gastroenterological Association (AGA) aims to provide recommendations for the use of EET in patients with BE and related neoplasia. The panel agreed on 5 recommendations for the use of EET in BE and related neoplasia and provided multiple additional implementation considerations.

How to Read These Guidelines

Table 1 provides an overview of each guideline recommendation along with the associated strength of recommendation and certainty of evidence. Additional information about the background, methods, evidence reviews, and detailed justifications for each recommendation are provided in the remainder of the document. Corresponding forest plots for each intervention and evidence profiles provide a synthesis of the evidence, as well as Evidence to Decision framework tables that summarize the panel's detailed judgments supporting each recommendation are provided in the tables. Each recommendation is accompanied by clinical practice considerations (based on the collective experience of the panel members) that are meant to help guideline users implement the recommendations. The term *recommend* was used to indicate strong recommendations, and the term *suggest* was used to indicate conditional recommendations. The interpretation of certainty of evidence and implications of strong and conditional recommendations for health care providers, patients, and policy makers are presented in Tables 2 and 3, respectively.

Description of the Health Problem

The incidence of EAC rose 5-fold from the 1970s to the 2010s, and adenocarcinoma now represents the most common form of esophageal cancer in the United States.[1] Survival from all but the earliest stage of EAC remains poor.[2] BE is the only known associated precursor of EAC.[3,4] BE is believed to pass through steps of low-grade dysplasia (LGD), then high-grade dysplasia (HGD), before developing into adenocarcinoma. The advent of EET for treatment of dysplasia and early-stage cancer has revolutionized the management of BE, reducing the morbidity and mortality related to esophagectomy and ultimately preventing EAC mortality.[5–7]

Objective of the Review and Guideline

The AGA developed this systematic review and clinical guideline to provide evidence-based recommendations for the EET of BE and related neoplasia. EET includes resection techniques (endoscopic mucosal resection [EMR] and endoscopic submucosal dissection [ESD]), as well as ablation (including radiofrequency ablation [RFA], cryoablation, and other techniques). Future guidelines from the AGA will address screening and surveillance.

Table 1. Summary of Recommendations and Implementation Considerations

Recommendation 1: In individuals with BE with HGD, the AGA recommends EET over surveillance. *(Strong recommendation, moderate certainty of evidence)*

Implementation Considerations:
- After completion of EET, surveillance should be performed at 3, 6, and 12 mo, then annually.
- Surveillance endoscopies after EET should obtain targeted tissue sampling of visible lesions and random biopsies of the cardia and distal 2 cm of the tubular esophagus.

Recommendation 2: In individuals with BE with LGD, the AGA suggests for EET over surveillance. Patients who place a higher value on the well-defined harms and lower value on the benefits (which are uncertain) regarding reduction of esophageal cancer mortality would reasonably select surveillance endoscopy. *(Conditional recommendation, low certainty of evidence)*

Implementation Considerations:
- After completion of EET, surveillance should be performed at years 1 and 3 after CEIM, then revert to surveillance intervals used in NDBE.
- The tissue sampling protocol during surveillance should be performed the same as in surveillance after EET for HGD.

Recommendation 3: In individuals with NDBE, the AGA suggests against the routine use of EET. *(Conditional recommendation, very low certainty of evidence)*

Recommendation 4: In patients undergoing EET, the AGA suggests resection of visible lesions followed by ablation of the remaining BE segment over resection of the entire BE segment. *(Conditional recommendation, very low certainty of evidence)*

Implementation Considerations:
- In patients with only a small area of BE beyond the visible lesion, completion endoscopic resection in the same setting is acceptable and may be preferred over repeated procedures to perform ablation.
- RFA is the preferred ablative modality.

Recommendation 5: In individuals with BE with visible neoplastic lesions that are undergoing endoscopic resection, the AGA suggests the use of either EMR or ESD based on lesion characteristics. *(Conditional recommendation, very low certainty of evidence)*

Implementation Considerations:
- Patients suspected of having T1 EAC should be referred for consideration of EET.
- Endoscopic resection is the test of choice over endoscopic ultrasound for distinguishing EAC from HGD and for staging depth of invasion in early cancer.
- The vast majority of neoplastic lesions may be managed with EMR rather than ESD.
- Patients with large bulky neoplastic lesions or lesions highly suspicious of at least T1b invasion (for instance those with depressed, Paris IIc, or IIa+c lesions) and deemed candidates for endoscopic resection might benefit from ESD over EMR.
- Patients with previously failed EMR might benefit from ESD.

Table 2. Interpretation of the Certainty of Effects Using the Grading of Recommendations Assessment, Development and Evaluation Framework

Certainty of evidence	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident that the true effect lies close to that of the estimate of the effect. There is a possibility that it is substantially different.
Low	Our confidence that the true effect lies close to that of the estimate of the effect is low. The true effect may be substantially different from the estimate of the effect.
Very low	Our confidence that the true effect lies close to that of the estimate of the effect is very low. The true effect is likely substantially different from the estimate of the effect.

Target Audience

The target audience for these guidelines includes primary care, internal medicine, family medicine, gastroenterology, oncology, and surgery health care providers; patients; and policy makers. The recommendations in this document are not intended to be used as the standard of care. Instead, they can be used to guide the management of patients with BE and related neoplasia. Although no single recommendation can encompass every individual circumstance and context, it can be used to address the benefits and harms of treatments and support the processes of shared decision making so that patients are treated based on their values and preferences.

Methods

Overview

This document represents the official recommendations of the AGA. These recommendations were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Organization and Panel Composition

The guideline panel members were selected based on their clinical and methodological expertise. Each member underwent a vetting process that required disclosing all conflicts of interest. The panel included a total of 14 guideline committee members, either with clinical/research expertise in the content or specialized in methodology. Panel members comprising the evidence review team included gastroenterologists with expertise in BE, 1 senior methodologist, and 3 junior methodologists. The senior methodologist supervised the evidence synthesis for all the interventions across the subcommittees. Members of the guideline committee helped review all of the synthesized evidence, contributed to discussion, and helped develop the clinical decision support tool. A librarian assisted with designing and executing the relevant literature searches.

Management of Conflict of Interest and Guideline Funding

Panel members disclosed all potential conflicts of interest. Conflicts were managed according to AGA policies, the National Academy of Medicine, and Guidelines International Network

Table 3. Interpretation of a Strong and Conditional Recommendation

Implication	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

standards.[8–10] Development of this guideline was wholly funded by the AGA with no support from the industry.

Scope

The guideline panel and evidence review team formulated clinically relevant questions on endoscopic therapies for BE and related neoplasia. The most recent comprehensive position paper by the AGA on BE was published in 2011, and included guidance on screening, surveillance, biomarkers, and endoscopic therapy.[11] Since then, the AGA has published Clinical Practice Updates on the management of BE with LGD,[12] ESD (including outside of the setting of BE),[13] endoscopic treatment of neoplastic BE,[14] and screening and surveillance.[15] The current guideline panel undertook a comprehensive review following the GRADE approach, the results of which add to and update the prior documents. Given the breadth of the review, the guideline panel split the publication of the recommendations into this document on endoscopic treatment and forthcoming guidance on screening and surveillance.

Formulation of Clinical Questions and Determining Outcomes of Interest

Through an iterative process, the guideline panel developed focused clinical questions deemed relevant for clinical practice that the guideline would address, related to the endoscopic treatment of BE and related neoplasia. From these focused questions, well-defined statements in terms of patients, intervention, comparator, and outcome (PICO) were defined, and these formed the framework for formulating the study inclusion and exclusion criteria and guided the literature search. The AGA Governing Board approved the final set of questions and statements (Table 4).

Search Strategy

A protocol guided the systematic review process. For the first 4 PICO questions, we identified recently published systematic reviews and meta-analyses that used a comprehensive search strategy (PubMed, Embase, and Cochrane Library), then updated the search to January 2023, with the help of a medical librarian. Details were included under evidence summaries for each PICO question. For PICO question 5, there was no systematic review or meta-analysis meeting our inclusion criteria. Thus, a separate comprehensive search was conducted on the following databases: Embase, MEDLINE, Cochrane, and PubMed. The search terms used and the final strategy can be found in the Supplementary Material (Supplementary Tables 1–3). References from included references and prior guidelines were searched to identify any missing relevant studies. Furthermore, content experts aided in the identification of any ongoing studies.

Study Selection, Data Collection, and Analysis

Searches from all the databases were combined in Rayyan bibliographic software,[16] and duplicates were removed. One content expert and 1 methodologist screened each title and conducted a full-text review of the eligible studies, and a consensus was reached on inclusion (see Supplementary Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram).[17] In summary, we included randomized controlled trials (RCTs). When RCT data were not available or were sparse, we also considered observational studies, giving preference to observational studies with control arms over uncontrolled observations. Any conflicts were resolved with adjudication by the senior methodologist. Data were extracted from each study, including study characteristics, such as year of publication, study site, study population, intervention, comparison group, outcomes, and methods for risk-of-bias assessment. Meta-analyses were conducted when more than 1 study contributed data for the same intervention and outcome. We combined the dichotomous outcomes to obtain a relative risk (RR) and 95% CI. For the meta-analyses, we used the generic inverse-variance method of weighting and applied the random-effects model; unless 3 or fewer studies were present, we used a fixed-effects model due to the instability of between-study variance. We assessed the statistical heterogeneity using the I^2 index. We used Review Manager RevMan software, version 5.3 (The Nordic Cochrane Centre. Copenhagen, Denmark: The Cochrane Collaboration, 2014) for the comparative studies and OpenMeta analyst for statistical analyses of single-arm studies (OpenMetaAnalyst: Wallace, Byron C, Issa J. Dahabreh, Thomas A. Trikalinos, Joseph Lau, Paul Trow, and Christopher H). We used the Cochrane Risk-of-Bias tool to assess the risk of bias in the included studies incorporated in RevMan. This tool assesses the risk of bias in the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases.

Certainty of the Evidence

We used the GRADE approach to assess the certainty of evidence for the effect of the intervention on each outcome using the GradePro Guideline Development Tool software (https://gradepro.org). The GRADE approach considers factors such as study design, population studied, risk of bias, inconsistency, indirectness, imprecision, and risk of publication bias to rate the certainty of evidence as high, moderate, low, or very low (Table 2).[18] The results of certainty assessment are reported in evidence profiles available in Tables 5–9 for all the interventions included in this review.

Development of Recommendations

The process of translation of evidence into guideline recommendations followed the GRADE Evidence to Decision framework and was achieved by means of discussion during virtual meetings of the guideline committee.[19] The Evidence to Decision framework considers the certainty of evidence, balance of benefits and harm, patient values and preferences, feasibility, acceptability, equity, and resource use.[19] All Evidence to Decision tables are presented in Tables 5–9. Consensus was reached for all the recommendations among the group. The interpretation of strength of recommendations is summarized in Table 3. In situations when the recommendation is only supported with very low certainty for the benefits and very low certainty for the harm outcomes, the guideline panel put a higher value on risk avoidance.

Document Review

The guideline underwent external peer review and invited public comments. The guideline document was revised to address pertinent comments.

Table 4. PICO Questions

Focused question	Patients	Intervention	Comparator	Outcomes
1. Should patients with BE with HGD undergo EET?	Adult patients with BE and HGD	EET	Endoscopic surveillance	Benefits: 1. Prevent progression to EAC (critical outcome) 2. CEN 3. CEIM Harms: 1. Bleeding 2. Perforation 3. Stricture 4. Serious adverse events
2. Should patients with BE with LGD undergo EET?	Adult patients with BE and LGD	EET	Endoscopic surveillance	Benefits: 1. Prevent progression to HGD or EAC (critical outcome) 2. Progression to EAC 3. Progression to cancer requiring esophagectomy, chemotherapy, or radiation Harms: 1. Bleeding 2. Perforation 3. Stricture 4. Serious adverse events
3. Should patients with BE without dysplasia undergo EET?	Adult patients with NDBE	EET	No EET	Benefits: 1. Prevent progression to dysplasia and EAC (critical outcome) 2. All-cause mortality (critical outcome) 3. Progression to HGD or EAC Harms: 1. Bleeding 2. Perforation 3. Stricture 4. Pain
4. In patients undergoing EET, should patients undergo resection of the entire BE segment vs resection of visible lesions followed by ablation of the remaining BE segment?	Adult patients with dysplastic BE (LGD/HGD) or T1a EAC who are undergoing EET	Endoscopic resection alone (of the entire BE segment)	Endoscopic resection followed by ablation	Benefits: 1. EAC at 1- to 2-y follow-up (critical outcome) 2. CEN 3. Avoid need for esophagectomy and/or adjuvant therapy Harms: 1. Bleeding 2. Perforation 3. Stricture
5. In patients undergoing endoscopic resection of a visible lesion, should patients undergo primary ESD vs EMR?	Adult patients with neoplastic BE who are undergoing endoscopic resection	ESD	EMR	Benefits: 1. EAC at 1- to 2-y follow-up (critical outcome) 2. R0 resection 3. CEN 4. CEIM Harms: 1. Bleeding 2. Perforation 3. Stricture

Recommendations

A summary of all recommendations is provided in Table 1.

General Implementation Considerations:

- In patients with BE, counsel tobacco cessation and weight loss if overweight.
- Refer patients with dysplastic BE to high-volume endoscopists with expertise in EET, pathologists with expertise in BE neoplasia, with access to multidisciplinary care.
- Histologic diagnosis of BE dysplasia or early cancer should be confirmed by an expert pathologist.
- In patients undergoing management of dysplastic BE, optimize reflux control with medication, lifestyle modifications, and assessing adherence.
- Before embarking on EET, discuss risks and benefits of EET, need for adherence with reflux management, expected outcomes, need for continued surveillance after completion of EET, with adequate time to assess patient values and preferences.
- The goal of EET should be complete eradication of intestinal metaplasia and neoplasia.
- Failure to achieve complete eradication of intestinal metaplasia should prompt reassessment and optimization of reflux control.
- Endoscopists and practices performing EET are encouraged to monitor key outcomes and quality metrics, including complete eradication of intestinal metaplasia and neoplasia and adverse events.

Importance of Tobacco Cessation and Weight Loss

Tobacco use and obesity are risks factor for EAC,[20–22] and the most common causes of death in patients with BE undergoing EET is cardiovascular disease and other cancers, for which tobacco use and obesity are also major risk factors.[23–25] In addition, tobacco use is associated with stricture formation after EMR.[26] Therefore, patients with BE who use tobacco or are overweight, and in particular those undergoing EET, should be counseled to abstain from tobacco use and lose weight. The prospect of progression to cancer in patients with dysplastic BE often holds greater valence than prior counseling attempts, and patients may re-commit to such efforts after consultation for EET.

Referral to Experts

Patients found to have dysplastic BE should be referred to high-volume endoscopists, including in its endoscopic examination and resection, and pathologists with expertise in its interpretation. There is substantial disagreement among pathologists for interpreting dysplastic BE, particularly for LGD.[27] Community pathologists tend to be overly sensitive in their interpretation at the detriment of specificity for risk of progression, and expert pathologists may tend to be more specific, but at the detriment to sensitivity.[28] In a meta-analysis, expert pathologists downgraded 31% of LGD diagnoses referred from community settings, but also upgraded 10% to HGD or cancer.[29] A working definition of an expert pathologist is one with a special interest in BE-related neoplasia who is recognized as an expert in the field by peers, in part related to sufficient volume of cases.

Up to 63% of patients with dysplastic BE, including 27% in BE LGD, without a documented visible lesion referred from community settings to expert EET endoscopists are in fact found to have a visible lesion by the expert endoscopist, which requires endoscopic resection rather than ablation.[29] Endoscopic resection permits more accurate histologic assessment than biopsy. In one expert center, 55% of patients referred for BE with HGD without a visible lesion at the community site were found to have a visible lesion with invasive adenocarcinoma upon endoscopic resection.[30] And 26% of patients thought to have BE LGD were upgraded by the expert endoscopist's tissue sampling, including adenocarcinoma in 7%–11% and even some with advanced adenocarcinomas not amenable to EET.[29–32] EET performed at higher-volume centers and by higher-volume endoscopists has been associated with favorable outcomes, including complete eradication of intestinal metaplasia (CEIM), reduced risk of recurrence, and reduced risk of complications.[33–36] However, how to define expert endoscopists is uncertain. For instance, a threshold of 20 RFA procedures has been associated with improved CEIM, but at least 40 may be required to minimize recurrence after RFA. The specific number of procedures may also vary by type of EET. A working definition of an expert BE endoscopist is one who is recognized as an expert in the field by peers, in part related to sufficient volume of cases, in addition to training in advanced imaging, selection of patients for EET, technical skills to perform both resection and ablation, and management of adverse events.

Reflux Management

Patients with BE have greater reflux than other patients with gastroesophageal reflux disease, frequently have severe nocturnal reflux, which may persist with once-daily proton pump inhibitor (PPI), and often asymptomatic reflux events complicating the ability of the provider to manage reflux based on symptoms alone.[37–40] In the RCTs of EET for BE, patients were prescribed twice-daily PPI. Patients with incomplete response to EET are more likely to have uncontrolled reflux.[41,42] Therefore, patients should be prescribed twice-daily dosing of PPI with appropriate timing 30–45 minutes before meals before initiating EET. They should also be advised to avoid eating 4 hours before lying down, and to raise the head of their bed to minimize nocturnal reflux.

Table 5. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 1: Comparing EET With Surveillance in Individuals With BE and HGD

Certainty assessment							No. of patients[a] (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EET	Surveillance	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Progression of HGD to EAC (evidence from RCTs), follow-up time was between 1 and 4 y												
2	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	20/210 (9.5)	35/124 (28.2)	RR 0.40 (0.23–0.69)	169 fewer per 1000 (from 217 fewer to 88 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Progression of HGD to EAC (evidence from NRS)												
19	NRS	Serious[c]	Not serious	Not serious	Not serious	None	67/9023	69/1241	Rate ratio 0.28 (0.22–0.32)	40 fewer per 1000 patient-years (from 43 fewer to 38 fewer)[d]	⨁◯◯◯ Very low	IMPORTANT
Serious adverse events (evidence from RCT)												
2	Randomized trials	Not serious	Not serious	Not serious	Very serious[e]	None	7/222 (3.2)	1/113 (0.9)	RR 2.56 (0.45–14.54)	14 more per 1000 (from 5 fewer to 120 more)	⨁⨁◯◯ Low	IMPORTANT
Stricture, with EMR and RFA (evidence from NRS)												
40	NRS	Not serious	Not serious	Not serious	Not serious	Strong association	558/12,790 (4.4)	1/10,000 (0.0)	Not estimable	56 more per 1000 (from 46 more to 67 more)[f]	⨁⨁⨁◯ Moderate	CRITICAL
Bleeding with EMR + RFA (evidence from NRS)												
20	NRS	Not serious	Not serious	Not serious	Not serious[g]	Strong association	53/5902 (0.9)	1/10,000 (0.0)	Not estimable	6 more per 1000 (from 4 more to 9 more)[h]	⨁⨁⨁◯ Moderate	CRITICAL

Table 5. Continued

Certainty assessment								No. of patients[a] (%)		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		EET	Surveillance	Relative (95% CI)	Absolute (95% CI)		
Perforation with EMR + RFA (evidence from NRS)													
28	NRS	Not serious	Not serious	Not serious	Not serious[g]	Strong association		16/5799 (0.3)	1/10,000 (0.0)	Not estimable	2 more per 1000 (from 1 more to 4 more)[i]	⨁⨁◯ Moderate	CRITICAL

NRS, non-randomized studies.
[a]These are not weighted proportions, for weighted proportions please refer to forest plots.
[b]Low event number.
[c]All studies are single-arm cohort and lacking comparison.
[d]Rate ratio calculated between 2 separately pooled incidence rates.
[e]Very few events.
[f]Stricture events in surveillance group with esophageal biopsy are very low.
[g]Although low events were observed, given the extremally low baseline risk and large total number of patients, we did not rate down for imprecision.
[h]Major bleeding events in the surveillance group with esophageal biopsy are very low.
[i]Perforation events in the surveillance group with esophageal biopsy are very low in studies, usually referenced between 1/2500 and 1/11,000.

In patients failing to achieve CEIM, the mainstay of management is centered on controlling reflux adequately. In a single-center study, failure to achieve CEIM was most commonly associated with poorly controlled reflux, and 41% of those were due to nonadherence to twice-daily PPI dosing with appropriate timing.[43] After optimization of reflux control with re-education, change to a more potent PPI, or fundoplication, 94% of those initially failing CEIM ultimately achieved CEIM. Potassium competitive acid blockers might also have a role in patients who are not responding adequately to EET and its role needs to be assessed in future studies. Ambulatory reflux monitoring can help guide such decisions, including whether to refer for fundoplication before resuming EET. Similarly, patients who have ulceration found at the time of planned repeat EET should have EET delayed until reflux control is optimized. Whether changing the method of EET (either dosimetry or equipment) adds additional benefit beyond optimization of reflux control is not certain.

Goals of Endoscopic Eradication Therapy

The goal of EET should be CEIM and complete eradication of neoplasia (CEN). Among patients with BE with HGD or early cancer who underwent endoscopic resection of the visible lesion, 40% of patients randomized to surveillance had recurrent HGD or cancer within 3 years compared with 3% among those randomized to ablation of the remaining BE.[44] Similarly, in a retrospective observational study of patients undergoing endoscopic resection of HGD or cancer, those who did not undergo ablation after complete resection of the neoplasia had a relative risk of 2.5 for recurrent neoplasia over a median follow-up of 63 months.[45] In the US RFA Registry, patients who achieved CEIM were less likely to progress to death (odds ratio, 0.4).[25] Repeat EET sessions are typically performed every 2–3 months to allow adequate healing between sessions. Persistent or recurrent nondysplastic IM limited to the gastric cardia is common, but typically evanescent, and appears to have a very low risk of neoplastic progression.[46,47] Therefore, although ablation sessions should include treatment of the gastric cardia circumferentially, nondysplastic IM limited to the gastric cardia found after CEIM of the tubular esophagus does not warrant continued EET. Persistent or recurrent IM in the tubular esophagus without dysplasia can be an indication for repeat EET, depending on age, comorbidities, baseline histology, and prior course of EET attempts.

Monitoring of Quality Metrics

A number of quality metrics in EET have been proposed, with varying levels of validation and specification.[48] Although measurement errors related to small numbers of procedures can limit the accuracy in estimation of rare outcomes among individual practices, and particularly among individual endoscopists, monitoring and reporting key outcome measures can provide assurance to referring providers and patients regarding the quality of the EET provided. Key metrics to report include the proportion achieving CEIM (suggested minimum threshold, 70%) and

Table 6. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 2: Comparing Endoscopic Eradication Therapy With Surveillance in Individuals with Barrett's Esophagus and Low-Grade Dysplasia

Certainty assessment							No. of patients (%)[a]		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EET	Surveillance	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Progression to HGD and/or EAC (evidence from RCT), follow-up time between 1 and 3 y												
3	Randomized trials	Not serious	Serious[b]	Not serious[b]	Serious[c]	None	8/150 (5.3)	32/132 (24.2)	RR 0.25 (0.07–0.93)	182 fewer per 1000 (from 225 fewer to 17 fewer)	⨁⨁◯◯ Low	CRITICAL
Progression to EAC (evidence from RCT), follow-up time between 1 and 3 y												
3	Randomized trials	Not serious	Not serious[d]	Not serious	Very serious[d,e]	None	3/150 (2.0)	7/132 (5.3)	RR 0.44 (0.12–1.64)	30 fewer per 1000 (from 47 fewer to 34 more)	⨁⨁◯◯ Low	IMPORTANT
Progression to EAC (evidence from NRS)												
10	NRS	Serious[f]	Not serious	Not serious	Not serious	None	26/6139	119/16,672	Rate ratio 0.55 (0.52–0.61)	3 fewer per 1000 patient-years (from 4 fewer to 2 fewer)[g]	⨁◯◯◯ Very low	IMPORTANT
Progression to HGD and/or EAC (evidence from NRS)												
12	NRS	Serious[f]	Not serious	Not serious	Not serious	None	43/5001	(1.7)	Rate ratio 0.34 (0.24–0.40)	11 fewer per 1000 patient-years (from 13 fewer to 10 fewer)	⨁◯◯◯ Very low	IMPORTANT
Stricture, with EMR and RFA (evidence from NRS)												
40	NRS	Not serious	Not serious	Not serious	Not serious	Strong association	558/12790 (4.4)	1/10,000 (0.0)	Not estimable	56 more per 1000 (from 46 more to 67 more)[h]	⨁⨁⨁◯ Moderate	CRITICAL
Bleeding with EMR + RFA (evidence from NRS)												
20	NRS	Not serious	Not serious	Not serious	Not serious[i]	Strong association	53/5902 (0.9)	1/10,000 (0.0)	Not estimable	6 more per 1000 (from 4 more to 9 more)[j]	⨁⨁⨁◯ Moderate	CRITICAL

Table 6. Continued

Certainty assessment							No. of patients (%)[a]		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EET	Surveillance	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Perforation with EMR + RFA (evidence from NRS)												
28	NRS	Not serious	Not serious	Not serious	Not serious[i]	Strong association	15/5799 (0.3)	1/10,000 (0.0)	Not estimable	2 more per 1000 (from 1 more to 4 more)[k]	⨁⨁⨁◯ Moderate	CRITICAL

NRS, non-randomized studies.
[a]These are not weighted proportions, for weighted proportions please refer to forest plots.
[b]Although there is some inconsistency in between the studies with I^2 of 55%, it was felt to be due to indirectness of outcome because this is a composite outcome of HGD and EAC; thus, because of the correlation between inconsistency and indirectness we decided to rate down once only.
[c]There were few events.
[d]Although there is some inconsistency in between the studies with I^2 of 60%, it was felt to be due to very serious imprecision; thus, we decided to rate down twice for imprecision and not for inconsistency.
[e]Very few events.
[f]All studies are single-arm cohort and no comparison group.
[g]Rate ratio was used between 2 separately pooled incidence rates.
[h]Stricture events in the surveillance group with esophageal biopsy are very low.
[i]Although low events were observed, given the extremally low baseline risk and large total number of patients we did not rate down for imprecision.
[j]Major bleeding events in the surveillance group with esophageal biopsy are very low.
[k]Perforation events in the surveillance group with esophageal biopsy are very low in studies, usually referenced between 1/2500 and 1/11,000.

Table 7. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 3: Comparing Endoscopic Eradication Therapy With Surveillance in Individuals With Nondysplastic Barrett's Esophagus

Certainty assessment							No. of patients (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EET	No treatment	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Disease progression and mortality												
6	NRS	Serious[a]	Not serious	Not serious	Serious[b]	None	No comparative evidence from RCT or cohort studies. Population-based studies and single-arm cohort studies with consecutive patients: Progression to EAC (incidence): The US RFA Patient Registry[25]: incidence of EAC in patients with NDBE was 0.47 per 1000 PY. US large database-TriNetX[102]: incidence of EAC was 3.34 per 1000 PY (95% CI, 0.75–7.04). Progression to LGD and HGD (incidence): US RFA Registry[33] incidence of LGD and HGD was 1.2 per 1000 PY and 3.12 per 1000 PY, respectively. Small cohort study[103]: 53 patients followed for 11.5 y post RFA of NDBE for incidence of LGD of 1.64 per 1000 PY. Single-arm cohort study[104]: 123 patients followed for 7 y, incidence of LGD and HGD 3.48 and 1.16 per 1000 PY, respectively. Single-arm cohort study[92]: 61 patients, 3.3 y of follow-up, no progression to progress to HGD or adenocarcinoma.				⨁◯◯◯ Very low	CRITICAL
Stricture												
10	NRS	Not serious	Not serious	Not serious	Serious[c]	Strong association	75/1489 (5.0)	1/10,000 (0.0)	Not estimable	38 more per 1000 (from 28 more to 48 more)[d]	⨁⨁◯◯ Low	CRITICAL
Bleeding												
9	NRS	Not serious	Not serious	Not serious	Very serious[b]	None	12/1439 (0.8)	1/10,000 (0.0)	Not estimable	9 more per 1000 (from 4 more to 14 more)[e]	⨁◯◯◯ Very low	CRITICAL

Table 7. Continued

No. of studies	Study design	Certainty assessment: Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients (%): EET	No. of patients (%): No treatment	Effect: Relative (95% CI)	Effect: Absolute (95% CI)	Certainty	Importance
Pain												
8	NRS	Not serious	Not serious	Not serious	Very serious[b]	None	11/370 (3.0)	1/10,000 (0.0)	Not estimable	21 more per 1000 (from 1 more to 42 more)[f]	⨁◯◯◯ Very low	IMPORTANT

NRS, non-randomized studies; PY, patient-year.
[a]No comparison group, poorly defined intervention (mostly combining 2 different endoscopic methods). Also some studies limited the cohort to responders to endoscopic treatment only. Furthermore, major confounders, such as PPI use and smoking, were not adjusted for in most of the studies.
[b]Very low event numbers.
[c]Low events were observed.
[d]Stricture events in the surveillance group with esophageal biopsy were very low.
[e]Major bleeding events in the surveillance group with esophageal biopsy were very low.
[f]Severe pain post upper endoscopy with biopsy is very rare.

CEN (suggested minimum threshold, 80%) 18 months after initiating EET; number of EET procedures required to achieve CEIM and CEN; recurrence of neoplasia after EET; and adverse event rates, including bleeding events, perforation, and stricture.

Recommendation 1: In individuals with BE with HGD, the AGA recommends EET over surveillance. (*Strong recommendation, moderate certainty of evidence*)

Implementation Considerations:

- Following completion of EET, surveillance should be performed at 3, 6, and 12 months, then annually.
- Surveillance endoscopies after EET should obtain targeted tissue sampling of visible lesions and random biopsies of the cardia and distal 2 cm of the tubular esophagus.

Summary of the Evidence

Evidence informing the recommendation for the management of BE with HGD was derived from both RCTs and observational cohort studies. Data from observational cohort studies were used as supplemental evidence for rate of progression to EAC due to limited follow-up time from the RCTs. Evidence from a published well-done systematic review and a meta-analysis was used.[49] To update this systematic review, we identified new studies using similar search terms and a start date of January 1, 2016 (Supplementary Table 1).

Two RCTs were included in the previous meta-analysis, which reported progression from HGD to EAC between EET vs surveillance in patients with HGD.[50,51] No additional RCTs were identified in the updated search. Shaheen et al[51] compared RFA with surveillance in patients with BE with HGD and Overholt et al[50] compared photodynamic therapy with surveillance. The 2 RCTs had similar baseline characteristics: mean age was 66 years and studies included White men predominantly. Mean length of BE was 5.3 cm in Shaheen et al[51] and >50% of patients had BE >6 cm in Overholt et al. Shaheen et al followed patients up to 1 year, and Overholt et al followed patients up to 3.6 years. Patients in the Overholt et al trial had a surveillance endoscopy every 3 months until 4 consecutive quarterly biopsies were negative for HGD, then every 6 months thereafter. Patients in the Shaheen et al trial underwent RFA at 3, 6, 9, and 12 months.

Benefits

The critical outcome for this question was progression rate to cancer among patients with HGD who were treated with EET compared with endoscopic surveillance alone. Pooled analysis of 2 RCTs using fixed-effects models with a total of 180 participants in the EET group vs 91 participants in the endoscopic surveillance group demonstrated decrease in progression to EAC when EET was used

Table 8. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 4: Comparing Resection of Visible Lesions Followed by Ablation of the Remaining Barrett's Esophagus Segment With Resection of the Entire Barrett's Esophagus Segment

Certainty assessment							No. of patients (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	sEMR	fEMR + RFA	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
EAC at 1–2 y (only 3 studies had follow-up of more than 3 y); single-arm comparison: sEMR (11 observational studies) vs fEMR + RFA (9 observational studies)												
20[a]	Observational studies	Serious[b]	Not serious	Not serious	Very serious[c]	Publication bias strongly suspected[d]	10/701 (1.4)	12/702 (1.7)	RR 0.83 (0.36–1.92)	3 fewer per 1000 (from 11 fewer to 16 more)	⨁◯◯◯ Very low	CRITICAL
CEN at 1–2 y (only 3 studies had follow-up of more than 3 y) indirect comparison: sEMR (11 observational studies) vs fEMR + RFA (9 observational studies)												
20[a]	Observational studies	Serious[b]	Not serious	Serious[e]	Not serious	Publication bias strongly suspected[d]	717/774 (92.6)	699/747 (93.6)	OR 1.33 (0.56–3.15)	15 more per 1000 (from 45 fewer to 43 more)	⨁◯◯◯ Very low	CRITICAL
Stricture												
52[f]	Observational studies	Serious[g]	Not serious[h]	Not serious	Not serious	None	269/840 (32.0)	585/13882 (4.2)	RR 7.33 (6.46–8.31)	267 more per 1000 (from 230 more to 308 more)	⨁◯◯◯ Very low	CRITICAL
Bleeding												
32[i]	Observational studies	Serious[b]	Not serious[h]	Not serious	Serious[j]	None	59/840 (7.0)	53/5902 (0.9)	RR 7.82 (5.44–11.25)	61 more per 1000 (from 40 more to 92 more)	⨁◯◯◯ Very low	CRITICAL
Perforation												
40[k]	Observational studies	Serious[b]	Not serious	Not serious	Serious[j]	None	13/840 (1.5)	16/5799 (0.3)	RR 5.62 (2.72–11.65)	13 more per 1000 (from 5 more to 29 more)	⨁◯◯◯ Very low	CRITICAL

[a]sEMR (11 observational studies) vs fEMR + RFA (9 observational studies).
[b]Comparison of independent single-arm studies with no time concurrent controls.
[c]Very small event number in both treatment groups.
[d]Publication bias was noted by Desai et al[118] using Eggers regression test for the sEMR studies.
[e]Indirectness suspected because the outcome is eradication of dysplasia and not recurrence of cancer or mortality from cancer.
[f]sEMR (12 observational studies) vs fEMR + RFA (40 observational studies).
[g]Comparison of independent single-arm studies with no time concurrent controls. In addition, the sEMR intervention was not standardized and differed between studies; some studies had fewer resections per procedure and used steroid, and other studies had more resections per procedure.
[h]Cannot assess for inconsistency because 2 treatment interventions are pooled from single-arm studies, but there was heterogeneity observed when the pooled estimate was calculated for each intervention separately.
[i]sEMR (12 observational studies) vs fEMR + RFA (20 observational studies).
[j]Low event number.
[k]sEMR (12 observational studies) vs fEMR + RFA (28 observational studies).

Table 9. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile for PICO Question 5: Comparing Endoscopic Mucosal Resection With Endoscopic Submucosal Dissection in Individuals With Barrett's Esophagus and Visible Neoplastic Lesions

Certainty assessment							No. of patients[a] (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EMR	ESD	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
EAC at 1–2 y of follow-up												
5	1 RCT and 4 NRS	Serious[b]	Not serious	Not serious	Very serious[c]	None	24/391 (6.1)	17/164 (10.4)	RR 0.93 (0.50–1.72)	7 fewer per 1000 (from 52 fewer to 75 more)	⨁◯◯◯ Very low	CRITICAL
R0 resection, margins of resection are free of cancer or HGD												
7	1 RCT and 6 NRS	Not serious	Serious[d]	Serious[e]	Not serious	None	221/746 (29.6)	478/601 (79.5)	RR 0.43 (0.29–0.64)	453 fewer per 1000 (from 565 fewer to 286 fewer)	⨁◯◯◯ Very low	IMPORTANT
CEN												
3	NRS	Not serious	Not serious	Serious[e]	Serious[f]	None	472/599 (78.8)	153/186 (82.3)	RR 0.93 (0.87–1.00)	58 fewer per 1000 (from 107 fewer to 0 fewer)	⨁◯◯◯ Very low	IMPORTANT
CEIM												
4	1 RCT and 3 NRS	Not serious	Not serious	Serious[e]	Serious[f]	None	408/619 (65.9)	131/206 (63.6)	RR 1.06 (0.95–1.19)	38 more per 1000 (from 32 fewer to 121 more)	⨁◯◯◯ Very low	IMPORTANT
Strictures: single proportion comparison: EMR (27 observational studies) vs ESD (38 observational studies)												
65[g]	NRS	Serious[h]	Not serious	Not serious	Not serious	None	408/3729 (10.9)	361/2731 (13.2)	RR 0.83 (0.72–0.95)	22 fewer per 1000 (from 37 fewer to 7 fewer)	⨁◯◯◯ Very low	CRITICAL
Bleeding: single proportion comparison: EMR (20 observational studies) vs ESD (32 observational studies)												
52[i]	NRS	Serious[h]	Not serious	Not serious	Serious[i]	None	39/2061 (1.9)	64/2589 (2.5)	RR 0.77 (0.52–1.14)	6 fewer per 1000 (from 12 fewer to 3 more)	⨁◯◯◯ Very low	CRITICAL

Table 9. Continued

Certainty assessment							No. of patients[a] (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EMR	ESD	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Perforation single proportion comparison: EMR (27 observational studies) vs ESD (33 observational studies)												
60[k]	NRS	Not serious[h]	Not serious	Not serious	Serious[j]	None	17/2845 (0.6)	46/2693 (1.8)	RR 0.34 (0.20–0.60)	11 fewer per 1000 (from 14 fewer to 7 fewer)	⨁◯◯◯ Very low	CRITICAL

NRS, non-randomized studies.
[a]These are not weighted proportions, for weighted proportions please refer to forest plots.
[b]Suspected residual confounding because of lesion size. ESD lesions were usually larger and could have underestimated the results.
[c]Low event number and the effect is from small benefit with EMR to small benefit with ESD, minimal important difference for cancer recurrence is 5%, thus the CI involves 2 thresholds.
[d]$I^2 = 83\%$.
[e]Indirect outcome.
[f]Pooled estimate is imprecise because the CIs involves benefit from both interventions EMR and ESD.
[g]EMR (27 observational studies) vs ESD (34 observational studies).
[h]Comparison of independent single-arm studies with no time concurrent controls.
[i]EMR (20 observational studies) vs ESD (32 observational studies).
[j]Low event number.
[k]Single-arm comparison: EMR (27 observational studies) vs ESD (33 observational studies).

compared with surveillance (RR, 0.40; 95% CI, 0.23–0.69) (Table 5 and Supplementary Figure 2).

These results were supported by the indirect evidence from observational studies that reported disease progression rates in patients treated with EET compared with those undergoing surveillance. The previous meta-analysis was updated with an additional 8 studies.[49] A total of 19 studies were included for the indirect comparison, including 3155 patients. A total of 234 patients progressed to EAC over 13,595 person-years. Incidence rate for progression to EAC was pooled using inverse variance. The incidence rate of disease progression in the EET group was 1.9 per 100 person-years (95% CI, 1.1–2.7) (Supplementary Figure 3). The incidence rate of disease progression in the surveillance group was 6.6 per 100 patient-years (95% CI 5.0–8.2).[52]

Harms

The patient-important outcomes that informed the harms for this PICO question were: (1) strictures, (2) major bleeding, (3) perforation, and (4) serious adverse events. Stricture was defined as any symptomatic dysphagia post treatment that required endoscopic dilation. Bleeding was defined as major bleeding (ie, requiring blood transfusion, repeat esophagogastroduodenoscopy, or hospitalization). Perforation was defined as any full-thickness defect that required endoscopic or surgical intervention. Due to very sparse events occurring in the RCTs (total of 8 events: 7 in the EET and 1 in the surveillance), we used single-arm retrospective cohort studies to determine the proportions of patients experiencing strictures, bleeding, and perforation. We used a published systematic review from 2016 and updated it with newly published studies.[53] Because of the same treatment approach of EET with RFA with or without EMR, both population groups with BE and LGD and/or HGD were included in the analysis. The original systematic review had 28 published articles and 9 meeting abstracts. In addition to those, we identified 21 studies,[35,43,47,54–71] including some with the full text of the prior abstracts. The proportion of stricture formation was reported in 40 studies. There were 704 strictures in 12,790 patients undergoing EET at a pooled proportion of 6.3% (95% CI, 5.0%–7.6%) (Supplementary Figure 4.1). To calculate the difference between EET and surveillance groups, a very low event rate was used for stricture formation in the surveillance group with esophageal biopsies (1/10,000). The absolute effect was calculated to be 56 more strictures per 1000 patients undergoing RFA with or without EMR, with a 95% CI of 46 more to 67 more strictures per 1000 (Table 5).

Major bleeding events were reported in a total of 20 studies. Fifty-three events out of 5902 patients were identified for a pooled proportion of 0.6% (95% CI, 0.4%–0.9%) (Supplementary Figure 4.2). Similar to using the stricture outcome to calculate the difference between EET and surveillance groups, a very low event rate was used for the major bleeding in the surveillance group with esophageal biopsies (1/10,000). The absolute effect was calculated to be 6 more major bleeding events per 1000 patients undergoing RFA with or without EMR, with a 95% confidence limit of 4 more to 9 more bleeding events per 1000 (Table 5). Lastly, for the outcome of perforation, we used 28 studies and there were a total of 16 perforations reported in 5799 patients for a pool proportion of 0.2% (95% CI, 0.1%, 0.4%) (Supplementary Figure 4.3). As for the other harms, perforations in the surveillance group with esophageal biopsy is very low, and is usually referenced between 1/2,500 and 1/11,000.[72] Thus, the difference between groups in absolute effect were 2 more perforations per 1000 patients undergoing EET, from 1 more to 4 more per 1000 (Table 5).

Certainty in Evidence of Effects

The overall certainty in the evidence across the critical outcomes and considering both benefits and harms was moderate. See Table 5 for the full evidence profile. Our certainty in the critical desirable outcomes of disease progression to EAC was moderate. The major concern regarding the effect of EET on progression to EAC was imprecision, given the low number of events. Data on benefits from non-randomized studies was used to complement the RCT data and those outcomes were considered important, although very low in certainty. The observational data are at serious risk of bias due to comparison of independent, single-arm studies without time-concurrent controls; however, this did not impact the overall certainty of evidence because the baseline stricture event number is extremely low. For the outcome of adverse events, the certainty of evidence was moderate. Stricture formation was considered as the most common harm. Despite no studies with concurrent controls, we are certain that the baseline stricture rate in surveillance upper endoscopies with biopsy is very rare. In addition, we rated up, given the large difference between groups, thus the certainty in harms was judged to be moderate.

Discussion

In the setting of BE with HGD, EET results in a large decrease in progression to cancer with moderate certainty of evidence. The harms associated with EET were considered small, although not trivial. Bleeding and perforation are rare. Strictures are not uncommon, but are usually easily treatable with appropriate acid suppression and endoscopic dilation. Patients frequently have chest pain after EET,[61,73–75] but this is a short-term effect. The costs of EET were considered moderate, and cost-effectiveness analyses favored EET over surveillance.[76] There is probably no important uncertainty or variability in how much patients value the main benefits and harms unless they have life-threatening comorbidities. Patients generally find EET for HGD acceptable and implementing it has been largely feasible, except for challenges related to less access to EET among rural residents. Finally, given the relatively small number of

individuals with HGD and the large impact on cancer progression, a strategy of EET in this setting probably does not have a substantial negative impact on equity. On balance, the authors believed that EET is favored over surveillance for BE with HGD.

Implementation Considerations

After completion of EET, there is a risk of recurrent neoplasia and intestinal metaplasia, although typically at the same degree or less severe than at initiation of EET.[77,78] EET performed at higher-volume centers is associated with lower risk of early recurrence, suggesting that recurrences may actually be progression of prevalent microscopic foci of persistent BE to macroscopic lesions rather than de novo development of new BE.[35] In the US national registry of RFA for BE with HGD or early adenocarcinoma, the cumulative incidence of adenocarcinoma was 6.3% at 5 years after CEIM.[79] In some studies, the risk appeared greatest within the first year after completion of EET, but cancers continued to be identified long after that. Based on the registry data, a suggestion has been made of performing surveillance at 3, 6, and 12 months after CEIM for HGD or T1a adenocarcinoma, then annually, which seems reasonable until more definitive studies are conducted accounting for the risks and benefits of continued surveillance and repeated EET.[77] Surveillance should continue until patients have life-limiting comorbidities or wish to discontinue surveillance based on their values and preferences.

When performing surveillance post EET, the esophagus and cardia should be examined under white light and virtual chromoendoscopy with near focus, particularly using a clear cap. Targeted tissue sampling should be performed of visible lesions, including islands or tongues of columnar mucosa, nodules (including subsquamous), altered crypt pattern, or erosions. Nodules, including subsquamous nodules, are best assessed by means of endoscopic resection. Most but not all neoplastic recurrences are found at the esophagogastric junction.[47,80,81] Among expert endoscopists, <1% of patients will be found to have dysplasia in biopsies from normal-appearing squamous mucosa.[80,81] And the vast majority of those are found within the 2 cm proximal to the esophagogastric junction, although this may be a function of the small prevalence of very long BE segments undergoing EET. In contrast, up to 50% of dysplastic recurrences in the gastric cardia are found only on random biopsies of normal-appearing columnar mucosa; the absolute yield is still low, albeit greater than in normal-appearing squamous mucosa.[47,80,81] Therefore, during surveillance, random biopsies should be obtained from the gastric cardia immediately distal to the squamocolumnar junction, and of the distal 2 cm of the neosquamous epithelium in the tubular esophagus. Recurrent lesions are typically small and treatable with repeat EET, but prior scarring may make endoscopic resection more challenging. Additional research is warranted to make more firm recommendations on biopsy protocols during surveillance.

Recommendation 2: In individuals with BE with LGD, the AGA suggests EET over surveillance. (*Conditional recommendation, low certainty of evidence*)

Comment: Patients who place a higher value on the well-defined harms, and lower value on the uncertain benefits regarding reduction of esophageal cancer mortality would reasonably select surveillance.

Implementation Considerations:

- Following completion of EET, surveillance should be performed at years 1 and 3 after CEIM, then revert to surveillance intervals used in nondysplastic BE.
- The tissue sampling protocol during surveillance should be performed the same as in surveillance after EET for HGD.

Summary of the Evidence

Evidence informing the recommendation for the management of BE with LGD was derived from both RCTs and observational cohort studies. Data from observational cohort studies were explored to supplement the evidence for progression to EAC due to limited follow-up in the RCTs. There was a previously published, well-done, systematic review that assessed the risk of progression to EAC among patients with BE with LGD treated with RFA.[82] The authors analyzed data from 2 RCTs[51,83] and 3 observational cohort studies[25,84,85]; their systematic search ended on December 31, 2015. To update this systematic review, we identified new studies using similar search criteria using a start date of January 1, 2016. One additional RCT[86] and 9 observational cohort studies[57,68,70,86–92] were identified and analyzed together with the studies from the existing systematic review.[86] The historical incidence rate for natural progression of BE with LGD from a previously published systematic review was used.[93] The 3 RCTs had similar demographic and baseline characteristics of their populations.[51,83,86] Mean age ranged from 63 through 67 years and the populations were male and White predominantly. Mean length of BE was similar between the studies and ranged from 2 to 4 cm circumferential and from 5 to 7 cm in the longest extent. The follow-up period was 3 years for 2 RCTs and 1 year for 1 RCT. All patients in the ablation group had surveillance endoscopy 6 months after treatment was completed, then annually. Patients in the surveillance group had follow-up endoscopy every 12 months. The 2 largest cohort studies were conducted using national registries.[25,70] One was from the United Kingdom with 10-year follow-up and the other was from the United States with 2.4 years of follow-up.[25,70] The other 11 studies were either multicenter or single-center, retrospective, single-arm, cohort studies with a follow-up period between 1 and 6 years. These had very similar demographic characteristics compared with the RCTs; mean age was between 60 and 70 years, most were male and White, with BE length of 4–6 cm.

Benefits

The patient-important outcomes that informed the benefits for this PICO question were: (1) progression to cancer, (2) disease progression defined as a composite outcome of progression to HGD and/or EAC, and (3) progression to advanced cancer requiring esophagectomy and/or radiation/chemotherapy. The pooled analysis of 3 RCTs with a total of 150 participants in the EET group vs 132 participants in the endoscopic surveillance group demonstrated no significant difference in progression to EAC when EET was compared with surveillance (RR, 0.44; 95% CI, 0.12–1.64) (Figure 1.1), with an absolute decrease of 30 cancers per 1000 patients (95% CI, 47 fewer to 34 more). For the combined outcome of HGD/EAC, EET was associated with a reduced risk of progression compared with surveillance (RR, 0.25; 95% CI, 0.07–0.93) (Figure 1.2) and absolute decrease of 182 per 1000 patients (95% CI, 225 fewer to 17 fewer).

In addition, we explored observational data from 10 single-arm studies that retrospectively analyzed patients with BE and LGD treated with RFA. The incidence rate for progression to EAC was 0.3 per 100 patient-years (95% CI, 0.2–0.4) (Figure 1.3) calculated by pooling using inverse variance from 10 studies with a total of 26 EAC outcomes in 6129 patient-years. In a previously published systematic review and meta-analysis, the pooled annual rate of progression from LGD to EAC was reported to be 0.54 per 100 patient-years (95% CI, 0.33–0.76).[93] The rate ratio for RFA compared with surveillance in these observational studies showed a decrease in progression to EAC of 0.55 (95% CI, 0.52–0.61). For the composite outcome of disease progression to HGD and/or EAC, similarly, we pooled rates from 12 single-arm cohort studies with 43 events in a total of 4992 patient-years, for an incidence rate of 0.6 per 100 patient-years (95% CI, 0.3–0.8) (Figure 1.4). The previously reported natural disease progression from LGD to HGD and/or EAC was reported to be 1.7 per 100 patient-years (95% CI, 1.0–2.5).[94] The calculated rate ratio for RFA compared with surveillance in these observational studies for progression to HGD and/or EAC was 0.34 (95% CI, 0.24–0.40) (Table 6).

When assessing for progression to advanced cancer requiring esophagectomy and/or radiation/chemotherapy in the 3 RCTs,[51,83,86] we identified only 1 event of esophagectomy in the surveillance group,[83] with all other reported cancers amendable to EET. There was no cancer-related mortality reported. Observational studies were lacking robust data on advanced cancer and mortality specific for the LGD population. In the US registry, there were no deaths or advanced cancers in the LGD group.[25] Similarly, no advanced cancer requiring surgery or increased cancer mortality was reported in 2 other studies.[68,92]

Harms

The patient-important outcomes that informed the harms for this PICO question were: (1) strictures; (2) major bleeding either requiring blood transfusion, intervention, or hospitalization; (3) perforation; and (4) serious adverse events. In the 3 RCTs,[51,83,86] there were only 7 such serious adverse events, all in the EET groups, and none reported in the surveillance groups. Due to sparse events, the aforementioned systematic review of observational studies was used to estimate the risk of adverse events in LGD, as both LGD and HGD used similar treatment approaches with EET (see the Harm section under HGD, Supplementary Figures 4.1–4.3).

Certainty of the Evidence

The overall certainty in the evidence across the critical outcomes with consideration of both benefits and harms was low. See Table 6 for the full evidence profile. Our certainty in the critical desirable outcomes, such as progression to EAC and progression to the composite outcome of HGD and/or EAC from RCTs was low. The major concern for progression to EAC was imprecision, as there were very few events. In addition, there was some inconsistency between the studies with I^2 of 60%, which was believed to be due to imprecision in the individual studies, so the certainty of evidence was rated down twice for imprecision rather than for heterogeneity of results. Similarly, for the composite outcome of HGD and/or EAC, there was concern for serious imprecision due to low events for which we rated down once. Also, there was a concern for inconsistency between the studies with I^2 of 55%, but it was felt to be due to indirectness of outcome because this is a composite outcome of HGD and/or EAC; thus, because of the correlation between inconsistency and indirectness, we decided to rate down once only. Data from non-randomized studies were very low in certainty due to serious risk of bias

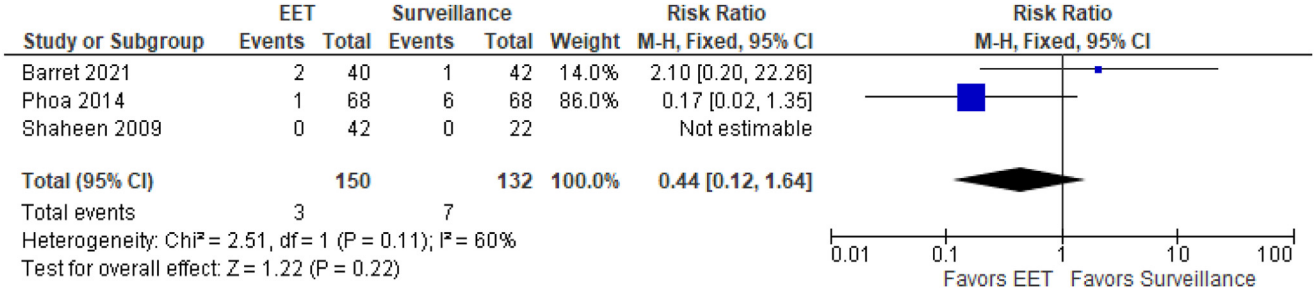

Figure 1.1. Forest plot RCTs comparing progression to EAC among patients with LGD who were treated with EET compared with endoscopic surveillance alone. M-H, Mantel-Haenszel.

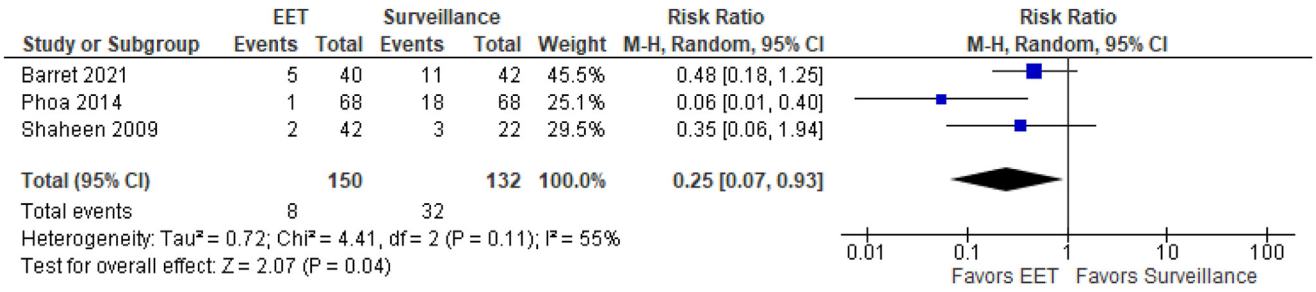

Figure 1.2. Forest plot of RCTs comparing progression to HGD or EAC among patients with LGD who were treated with EET compared with endoscopic surveillance alone. M-H, Mantel-Haenszel.

resulting from comparison of independent single-arm studies without concurrent controls. The overall certainty for harms was moderate. Stricture formation was the most common adverse event. Despite no concurrent controls, we are certain that the baseline stricture rate in surveillance upper endoscopies with biopsy is very low. We rated up for certainty, given the large difference between groups. However, due to low certainty in benefits, the overall certainty across all outcomes was low.

Discussion

For the critical outcome of HGD and combined outcomes of HGD and/or EAC, there were only 3 RCTs[51,83,86] that showed a substantial magnitude of benefit, but with inconsistent and imprecise estimates. The guideline authors had spirited conversations whether progression to EAC alone (not as a combined outcome with HGD) should be included as a critical outcome or just an important outcome, settling on important. Arguing against its being included as a critical outcome is that HGD is a finding that should be an actionable event, triggering EET similar to T1a EAC. Furthermore, conducting prospective studies of EET in LGD aimed at a primary outcome of progression to EAC not amenable to EET would be largely infeasible due to the extremely large number of subjects that would be required. Arguing in favor of using EAC alone as the critical outcome is the fact that individuals do not die from HGD, but rather from advanced cancer; if prospective studies assessing the outcome of cancer are impractical because surveillance of LGD successfully identifies HGD, prompting EET and thereby preventing cancer, then that same success indicates that surveillance could be preferred in clinical practice over EET for LGD. The summary estimate from the 3 RCTs did not demonstrate a statistically significant decrease in EAC burden for EET compared with surveillance, but with very imprecise estimates that could range to as many as 47 fewer EACs per 1000 patients with LGD undergoing EET. Observational studies suggested EET was associated with a significant decrease in EAC, but with a much smaller absolute magnitude of benefit (4 fewer EACs per 1000 patients) than in the RCTs. This may be due to the lower progression rates of LGD without EET reported in the observational studies (0.54% per year) compared with patients enrolled in surveillance in the RCTs with central pathology review, highlighting the importance of expert pathology review before considering EET. The lifetime cumulative incidence for a patient with BE to be diagnosed with LGD is substantial. Cost-effectiveness analyses have indicated that if EET was performed for all LGD diagnoses, 64% of patients with BE would eventually undergo EET.[95] Those analyses found that EET is only cost-effective if LGD is confirmed on repeat

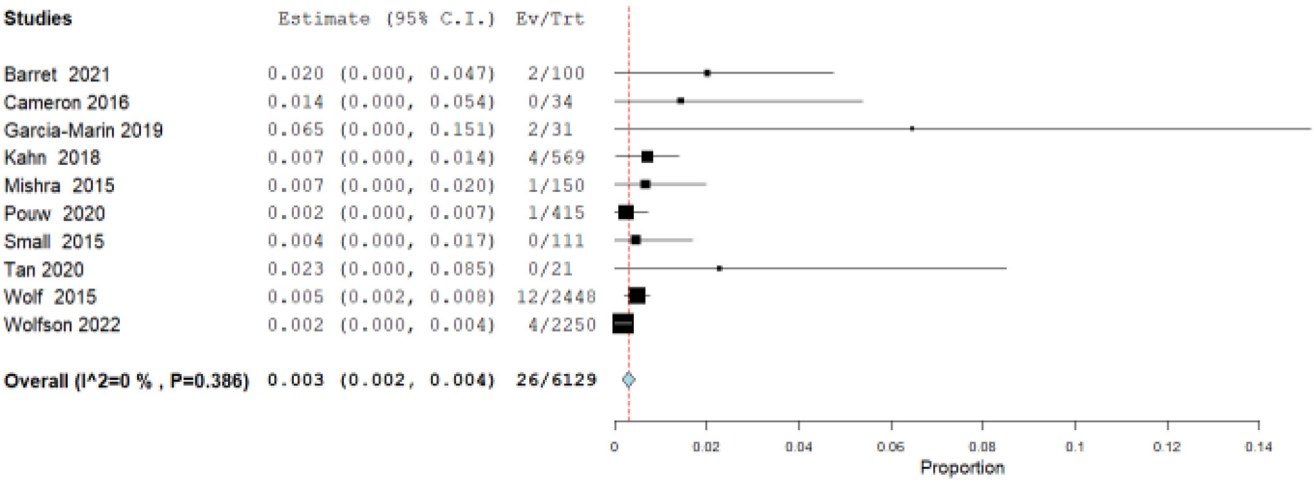

Figure 1.3. Forest plot from observational studies of pooled incidence rate of progression to EAC per patient-year among patients with LGD treated with EET.

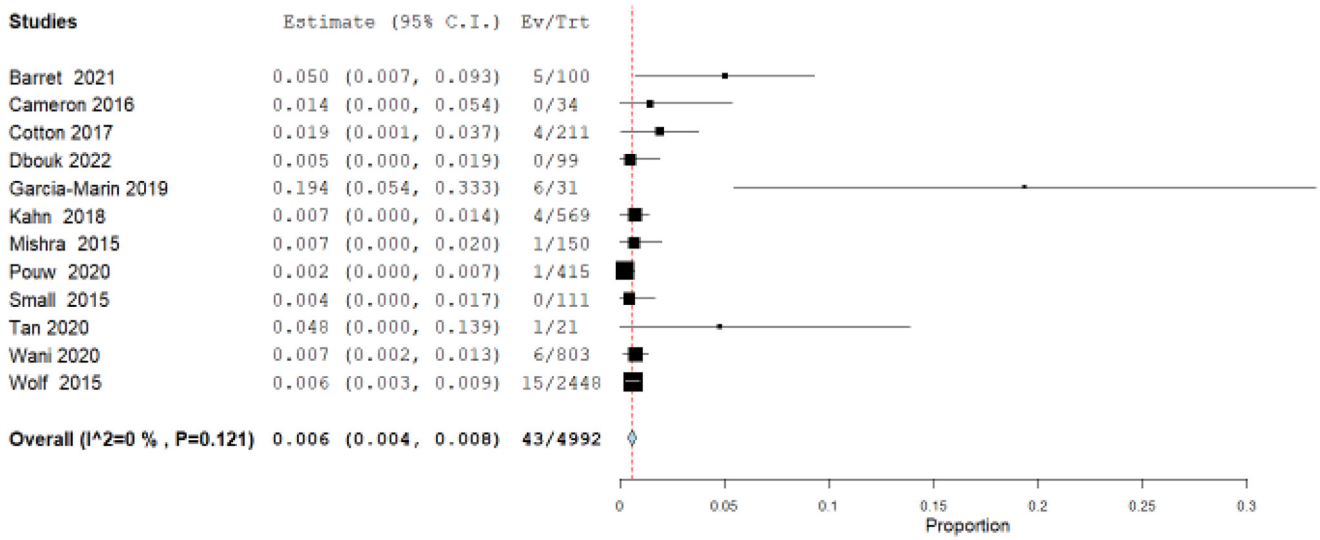

Figure 1.4. Forest plot from observational studies of pooled incidence rate of progression to EAC or HGD per patient-year among patients with LGD treated with EET.

esophagogastroduodenoscopy, which would decrease the proportion of patients with BE eventually undergoing EET to 36%. Overall, the benefits of EET in LGD were considered small to moderate. The harms were judged to be similar to those of EET for HGD (small). Patients without HGD and/or EAC are less likely to undergo concomitant EMR, and so the stricture rate could conceivably be lower, but there were only 3 small studies assessing strictures in patients without HGD and/or EAC undergoing ablation. The costs were expected to be similar to those for EET for HGD (moderate). Cost-effectiveness analyses suggest EET is probably favored over surveillance for BE with LGD, only if LGD is confirmed with repeat endoscopy.[76] A strategy of EET for LGD is largely feasible, but because LGD is commonly found in BE and the benefits of EET are diminished compared with EET for HGD, widespread EET for LGD probably reduces overall health equity. EET for LGD is probably acceptable to most patients, but there is possible important uncertainty and variability in how people value the main outcomes, as discussed above. Overall, the guideline authors felt that the balance of benefits to harms probably favors EET, but the importance of shared decision making with patients with LGD is emphasized. The risks, expected discomfort, need for multiple EET sessions, and need for continued surveillance after completion of EET should be discussed in detail, in addition to detailing the benefits in terms of reduction in progression to HGD and the uncertainty around the potential benefits of prevention of EAC and mortality to help patients decide their preferences.

Implementation Considerations

LGD, even when confirmed by expert pathologists, will regress to nondysplastic BE (NDBE) during surveillance in 28%–66% of patients.[83,96,97] This could be due to multiple reasons, including sampling error during follow-up, false-positive interpretation of LGD, or true regression. One of the reasons for the substantial interobserver variability in the histologic interpretation of LGD is that regenerative changes seen in the esophageal mucosa secondary to inflammatory injury related to uncontrolled reflux can share some of the same histologic features as dysplasia.[98] Assessment with ambulatory reflux monitoring has demonstrated that regression of ostensible LGD is associated with more effective suppression of esophageal reflux, and fundoplication is more closely associated with regression than PPI.[99,100] As discussed above in the general implementation considerations, the most common cause for failure to achieve CEIM is poorly controlled reflux; furthermore, among the 3 RCTs of EET for LGD, the one with the worst rate of CEIM and CEN was the one that did not include a specific PPI regimen in the protocol for patients undergoing EET.[86] Therefore, the concept of optimizing reflux control is particularly emphasized in the management of LGD.

In patients with LGD undergoing EET, the goal should be similar to that in patients with HGD. However, if CEIM is not achieved with the initial set of EET sessions, or if NDBE recurs, the balance of potential benefits to harms of continued EET is attenuated compared with the balance in patients with HGD. As a result, patients might reasonably elect to pursue surveillance of the remaining NDBE and only re-initiate EET if dysplasia is encountered during surveillance.

In the US national registry of RFA for BE with LGD, the cumulative incidence of adenocarcinoma after CEIM was 1.3% at 5 years.[79] Based on the registry data, a suggestion has been made of performing surveillance at 1 and 3 years after CEIM.[77] An initial surveillance at 1 and 3 years seems appropriate, but because the observed incidence of adenocarcinoma appears similar to that observed in patients with NDBE without EET, surveillance intervals after CEIM of LGD might justifiably be even less frequent than every 2 years after that, and can revert to the same intervals used in NDBE undergoing surveillance without any prior EET. Surveillance examinations and tissue sampling

should be performed in the same manner as after EET for HGD.

Recommendation 3: In individuals with NDBE, the AGA suggests against the routine use of EET. (*Conditional recommendation, very low certainty of evidence*)

Summary of the Evidence

We identified a published systematic review and meta-analysis that used a comprehensive search strategy (PubMed and Embase) from inception to August 24, 2012, including EET in NDBE.[101] We updated the systematic review with a search that ended on January 1, 2023 (Supplementary Table 2). Seven studies entered qualitative analysis to inform the benefits. Although the specific PICO was on NDBE, the evidence of harms in this histology group was very sparse. Therefore, we explored evidence on treatment not only in NDBE but in populations with dysplasia.

Benefits

No comparative evidence from RCT or cohort studies was found regarding EET of NDBE with outcomes of progression to EAC or esophageal cancer–related mortality. A previously published systematic review and meta-analysis evaluating the natural history of BE included 57 studies and 11,434 patients with histologically confirmed NDBE, for a total of 58,547 patient-years of follow-up.[101] This systematic review identified 186 incident cases of EAC and calculated a pool incidence of 3.3 per 1000 person-years (95% CI, 2.8–3.8).[101] Population-based studies from large BE RFA registries and single-arm EET cohort studies with consecutive patients were used for comparison. The US RFA Patient Registry was used to collect information on progression of NDBE to EAC post EET. The incidence of EAC in patients with NDBE after EET was 0.47 per 1000 patient-years; 2 of 668 and 5 of 668 patients developed HGD and LGD over 2.4 years of follow-up, respectively.[25] However, a large database study using the TriNetX research network reported an incidence of EAC after EET of NDBE that was 3.34 per 1000 person-years (95% CI, 0.75–7.04), which is numerically similar to the incidence found in the systematic review of natural history of NDBE.[101,102] A small cohort study reported results of 53 patients followed for at least a decade post RFA of NDBE. Only 1 patient developed neoplasia (LGD).[103] Similarly, a cohort study with 123 patients followed for 7 years reported 1 patient progressing to HGD and 3 to LGD.[104] Lastly, a single-arm cohort study followed 61 patients who were treated with RFA and achieved complete eradication of their NDBE. After 3.3 years, 12 of 61 had recurrence of IM, but none progressed to HGD or EAC.[92]

Harms

The patient-important outcomes that informed the harms for this PICO question were: (1) strictures; (2) major bleeding requiring blood transfusion, intervention, or hospitalization; (3) perforation; and (4) post-procedure pain. For these outcomes, we used the same previously published systematic review that informed the decision regarding HGD and LGD.[53]

However, endoscopic resection would be unlikely to be needed in NDBE, so we focused on analyses restricted to the use of RFA, although those studies did include patients with dysplasia. A total of 10 studies (3 from the published systematic review and 7 that we identified) were used to inform the harm outcomes. Stricture formation was reported in all 10 studies. There were 75 strictures out of 1489 patients undergoing RFA at a pooled proportion of 3.8% (95% CI, 2.8%–4.8%) (Table 7, Supplementary Figure 5.1). To calculate the difference between EET and the surveillance group, a very low event rate was used for the stricture formation in the surveillance group with esophageal biopsies (1/10,000). Major bleeding events were reported in a total of 9 studies with 12 events from a total of 1439 patients for a pooled proportion of 0.9% (95% CI, 0.4%–1.4%) (Table 7, Supplementary Figure 5.2). Eight studies reported on perforations, and there were no perforations in 541 patients (Supplementary Figure 5.3). In addition, as an important outcome, we evaluated for post-procedural pain. Pain was reported in 5 studies, including a total of 370 patients. The pooled proportion of pain was 2.1% (95% CI, 0.1%–4.2%) (Supplementary Figure 5.4).

Certainty in the Evidence of Effects

The certainty of evidence was very low across all outcomes, including benefits and harms (Table 7). The key concerns across the outcomes were use of single-arm cohort studies (serious risk of bias due to lack of a comparator), poorly defined interventions (most combining 2 different endoscopic methods), and some studies limiting the cohort to responders to EET only. Also, major confounders, such as PPI use and smoking, were not adjusted for in most of the studies. Furthermore, there was serious imprecision for the outcome of progression to HGD and/or EAC because the data were very sparse. Most studies did not document how pain was assessed, and many of those that were documented were restricted to emergency department visits or hospitalizations for pain.

Discussion

The maximum potential benefit of EET in the setting of NDBE is bound by the small incidence of progression to invasive cancer without EET, which is likely approximately 0.6% per year averaged over 20 years of follow-up, and even smaller for shorter durations of follow-up.[105] The vast majority of patients with NDBE ultimately die from causes other than EAC.[23,24] Therefore, even if large, high-quality RCTs with long-term follow-up were available, the potential magnitude of benefit from EET in the setting of NDBE would be trivial at best.

In the setting of such small potential benefit, the expected harms from EET become relatively magnified. The harms of complications from EET, including bleeding and perforation, are rare but present and greater than with

surveillance endoscopy. Strictures are not uncommon but relatively easy to manage. Importantly, patients undergoing EET experience the inconvenience of the potential need for multiple EET sessions with associated loss of work, changes in diet, time away from other pursuits, and burden for both the patient and their chaperone. Although the evidence review found pain was rare, this seems to be underassessed in those studies, relying on emergency department or hospitalizations for ascertainment. In other studies, when pain symptoms were actively collected, patients nearly universally experienced considerable chest pain for days to weeks after EET, particularly with RFA, for which there is the highest-quality data on effectiveness.[61,73,74] In 1 multicenter study published since completion of the systematic review, 95% of patients undergoing RFA experienced chest pain, including 65% with major chest pain.[75] In individuals with NDBE, the harms may outweigh any small benefit. Finally, there is moderate cost associated with EET, particular as patients continue to undergo surveillance after EET. Compared with strategies of surveillance of NDBE followed by EET for dysplasia, cost-effectiveness analyses indicate that EET for NDBE followed by surveillance for recurrence would either be more expensive than the commonly accepted willingness-to-pay threshold in the United States, or even dominated (meaning EET is both more expensive and leads to fewer quality-adjusted life-years).[76,106–108] There are limited data regarding patient preferences for or against EET in the setting of NDBE.[109] Although EET for NDBE is probably feasible from a health system standpoint, and may be acceptable to patients, it would likely also reduce equity because those diagnosed with NDBE are *ipso facto* those with access to expensive health care resources and undergoing EET would further direct resources away from other individuals. Balancing these potential benefits and harms, the data probably support against EET for NDBE.

There might be specific populations with NDBE in whom the benefits of EET outweigh the harms. The risk of progression stratified by variables such as first-degree relative with esophageal cancer, young onset at age of BE, and length of BE is not well known. In patients with potentially increased risk for EAC based on these variables, decision to perform EET should be made considering the net benefit for the patient and their values and preferences. Further research is needed to determine the place of such risk factors in guiding EET, but using the Progression in Barrett's Esophagus Score,[110] which relies on length, sex, smoking status, and LGD, even the highest-risk group only had an annual incidence of combined HGD or cancer of 1.5% in a large validation cohort,[111] which is approximately one-eighth that found in patients with confirmed LGD assigned to surveillance in the RCTs of EET for LGD (Table 6). This indicates that it may be difficult to find clinical risk factors beyond confirmed LGD that raise the risk of cancer enough to warrant EET in NDBE. Although some patients with NDBE may express severe anxiety about the risk of neoplastic progression and initially state a preference for EET over surveillance, they should be counseled regarding the considerations outlined above, and the typical practice of continued surveillance even after successful EET. Thus, EET might only lead to a temporary and incomplete decrease in the associated anxiety. The authors acknowledge that individuals who may be at increased risk of progression to cancer might be identified by means of tissue-based biomarkers, particularly aberrant p53 or Tissue Systems Pathology Test-9 alone or in combination with clinical and endoscopic characteristics.[28,112–117] Whether such biomarkers should be used routinely in patients with NDBE and how those results should be used is a topic that is deferred to the forthcoming AGA guideline on surveillance in BE.

Recommendation 4: In patients undergoing EET, the AGA suggests resection of visible lesions followed by ablation of the remaining BE segment over resection of the entire BE segment. (*Conditional recommendation, very low certainty of evidence*)

Implementation Considerations:

- In patients with only a small area of BE beyond the visible lesion, completion endoscopic resection in the same setting is acceptable and may be preferred over repeated procedure to perform ablation.
- RFA is the preferred ablative modality.

Summary of the Evidence

Evidence informing this PICO question comes from a previously published systematic review of single-arm, observational cohort studies.[118] In this systematic review, data from 20 studies were analyzed. There was only 1 RCT directly comparing these 2 strategies.[119] The RCT had enrolled 47 patients and showed no difference in the CEN, but the stenosis rate was significantly higher in stepwise or complete EMR (sEMR) (88%) vs focal EMR (fEMR) + RFA (14%). However, because of the limited sample size, it is not possible to extrapolate these findings on a larger scale; thus, the authors of the systematic review analyzed the results of the RCT with the observational studies. Nine single-arm cohort studies reported on fEMR + RFA and 11 single-arm cohort studies reported on sEMR; both are established strategies for eradication of BE-related HGD and/or EAC. In addition, we identified 1 larger study from the national Dutch database with long-term follow-up reporting on EET for BE neoplasia with fEMR + RFA.[47] We also updated the systematic review for the harms. Thirty-one additional single-arm studies were used to update the harms for fEMR + RFA and 2 studies for the sEMR.

Demographic characteristics between the studies and the 2 interventions were similar. The follow-up period ranged from 12 to 61 months in the fEMR + RFA group and 15 to 54.7 months in the sEMR group. Reported BE length was 2 to 8 cm in the fEMR + RFA group and 2 to 5.5 cm in the s-EMR group. The fEMR + RFA intervention strategy was the same throughout the studies: all studies had initial fEMR for a visible lesion followed by RFA. Serial RFA was done every 3 months until CEN and/or CEIM was achieved. For the sEMR strategy, the protocols were different among

the individual studies in terms of resections per session and the timing between the repeat endoscopies.

Benefits

We considered 2 outcomes informing the benefits: (1) EAC at 1- to 2-year follow-up as a critical outcome, and (2) CEN as an important outcome. In the prior meta-analysis, a total of 701 patients in the sEMR vs 702 patients in the fEMR + RFA group showed no substantial difference in regard to EAC outcomes with a pooled estimate of 0.7% (95% CI, 0.1%–1.4%), and 1.4% (95% CI, 0.2%–2.7%), respectively (RR, 0.83; 95% CI, 0.36–1.92) (Table 8).[118] Similarly, there was no substantial difference in the pooled estimate for CEN, with 94.9% (95% CI, 92.2%–97.5%) for sEMR compared with 93.4% (95% CI, 90.8%–96.1%) for fEMR + RFA with RR of 1.01 (95% CI, 0.98–1.04). The proportion achieving CEIM in the fEMR + RFA group was 73.1% (95% CI, 63.0%–83.1%) and in the sEMR group was 79.6% (95% CI, 75.2%–84.1%). Similar rates for recurrence of EAC were observed in the newer, long-term, follow-up study for fEMR + RFA: a total of 1386 patients were followed over 43 months, with 22 having progression or recurrence of EAC (1.6%; 95% CI, 1.1%–2.4%).[47]

Harms

Three critical outcomes were considered to inform harms: (1) stricture formation, (2) major bleeding, and (3) perforation. A total of 52 studies informed the outcome of stricture formation. There were 269 strictures in 840 patients undergoing sEMR and 585 strictures in 13,382 patients in the fEMR +RFA group, for a pooled estimate of 30.4% (95% CI, 17.2%–43.6%) vs 6.3% (95% CI, 5.0%–7.6%), respectively (Supplementary Figures 4.1 and 6.1). When compared, there was a substantial difference, with sEMR more likely to cause a stricture (RR, 7.33; 95% CI, 6.46–8.31). Furthermore, the pooled estimate for major bleed events in the sEMR was 6.5% (95% CI, 3.5%–9.4%) and in the fEMR + RFA was 0.6% (95% CI, 0.4%–0.9%) (RR, 7.82; 95% CI, 5.44–11.25) (Supplementary Figures 4.2 and 6.2). Lastly, there were 13 perforations out of 840 patients, for a pooled estimate of 1.2% (95% CI, 0.5%–2.0%) in the sEMR group, and 16 out of 5799 patients for a pooled estimate of 0.2% (95% CI, 0.1%–0.4%) in the fEMR + RFA group (RR, 5.62; 95% CI, 2.72–11.65) (Supplementary Figures 4.3 and 6.3).

Certainty of the Evidence

Across all of the critical outcomes, the overall certainty was very low (Table 8). For the outcome of EAC, there were multiple concerns regarding the certainty of evidence: (1) only a single RCT exists; (2) serious risk of bias because the comparison was of independent, single-arm studies with no concurrent controls; (3) very serious imprecision because of few events in both treatment groups; and (4) publication bias as noted by Desai et al,[118] suggesting overestimation of CEN in the published sEMR studies. Furthermore, for the CEN outcome, there was indirectness because the outcome is eradication of neoplasia and not specifically cancer or mortality from cancer. Finally, for the harms, in addition to the imprecision due to low events, serious risk of bias was detected because the sEMR intervention was not standardized and differed between studies in terms of number of resections per procedure and whether prophylactic corticosteroids were used.

Discussion

Compared with fEMR followed by ablation, the effect of sEMR on the critical benefits were trivial to small and the effect on harms were moderate, both with very low certainty of evidence. There is probably no uncertainty or variability in how much patients value the main benefits and harms. Either form of EET is probably feasible and accessible, although some endoscopists who perform fEMR may not be adept at sEMR. There may be a moderate increase in resource utilization with sEMR due to the need for additional procedures for dilation of strictures, but there is very low certainty regarding this. The choice of one form of EET over another is unlikely to impact equity. Finally, there were no cost-effectiveness analyses available to guide the recommendation. On balance, the authors believed that focal resection of visible lesions followed by ablation of remaining BE is favored over sEMR, largely due to the likely greater risk of harms with sEMR.

Implementation Considerations

Regardless of the extent of nodularity, all nodularity should be resected rather than ablated. There was large heterogeneity in stricture rates after sEMR, which might be related to differences in techniques or patient populations. There was agreement that in settings of only a small area of remaining BE beyond the visible lesion resected, completion EMR requiring only one or a few additional resections in the same procedure is acceptable and may be preferred over repeating the procedure to perform ablation later, particularly if the additional resections are longitudinally adjacent to the prior resection bed rather than circumferentially.

Multiple ablation techniques exist, including RFA, cryoablation (including multiple different vendors, cryogenic gases, and tools), hybrid-argon plasma coagulation, and multi-polar electrocoagulation. The comparison and specific dosimetries of these techniques are beyond the scope of this guideline. However, RFA has the highest-quality and most extensive evidence available from RCTs supporting its use for reaching the critical benefits of interest, while the other modalities have primarily been studied in case series or RCTs with only the important outcomes of CEIM and CEN, and often included mixed populations of EET-naïve and those with prior RFA.[51,83,86] Therefore, RFA is the preferred ablative modality. Nonetheless, chest pain appears to be of shorter duration and less severity with cryoablation.[73] Likewise, which specific technique of EMR used is beyond the scope of this document. RCTs comparing various ablation techniques with each other

and additional trials comparing EMR techniques with each other are needed.

Recommendation 5: In individuals with BE with visible neoplastic lesions that are undergoing endoscopic resection, the AGA suggests the use of either EMR or ESD based on lesion characteristics. (*Conditional recommendation, very low certainty of evidence*)

Implementation Considerations:

- Patients suspected of having T1 EAC should be referred for consideration of EET.
- Endoscopic resection is the test of choice over endoscopic ultrasound for distinguishing EAC from HGD and for staging depth of invasion in early cancer.
- The vast majority of neoplastic lesions may be managed with EMR rather than ESD.
- Patients with large bulky neoplastic lesions or lesions highly suspicious of at least T1b invasion (for instance, those with depressed, Paris IIc or IIa + c lesions) and deemed candidates for endoscopic resection might benefit from ESD over EMR.
- Patients with previously failed EMR might benefit from ESD.

Summary of the Evidence

Evidence informing the recommendation for ESD vs EMR was derived from 1 RCT and observational cohort studies. No prior systematic review or meta-analysis was identified in our systematic search to answer this question. Thus, we conducted a new systematic review and a meta-analysis. We selected studies that included patients who underwent EET for a visible lesion with ESD or EMR, followed by ablative therapy if needed. Once they achieved CEN or CEIM, patients were enrolled in surveillance. Studies that classified outcomes of patients before completion of sEMR or did not provide granular data were excluded. R0 resection was defined as absence of the highest-grade histology (HGD or EAC) at the lateral and deep margin on the initial procedure.

One RCT[120] and 4 comparative observational cohort studies[121–124] were included in the meta-analysis comparing EMR with ESD. The RCT[120] included a total of 40 patients randomized to either ESD (20 patients) or EMR (20 patients). The mean age of patients was 64.5 years and they were male predominantly. The mean size of the ESD lesion was significantly larger than the EMR (29 mm vs 18 mm). Mean follow-up was 1.9 years. The 4 observational studies were 2 articles[121,122] and 2 conference abstracts from 2022–2023.[123,124] We contacted the authors of 1 of the abstracts to obtain more robust data. Mean age was 68–69 years with male predominance in 85%–87%. The initial pathology varied between studies including only EAC (1 study),[122] HGD and EAC (2 studies),[123,124] and all degrees of dysplasia (1 study).[121] Younis et al[124] had significantly more EAC in the ESD group 85.2% compared with the EMR group (57.4%). Follow-up in these studies ranged between 2.3 years and 3.7 years. The EMR group follow-up was 2.8–3.7 years, whereas the ESD group follow-up was 1.4–2.3 years.

One RCT[120] and 6 observational comparative cohort studies[121,122,124–127] were included in the direct comparison for harm. Given the low number of events and very serious imprecision, we decided to explore data from single-arm studies. A total of 42 ESD studies[120–122,124–161] and 32 EMR studies were included in the analysis for harm.

Benefits

The critical outcome for this question was EAC at 1–2 years after EET. The pooled analysis of 1 RCT[120] and 4 observational comparative studies[121–124] using random-effects models with a total of 391 participants in the EMR group vs 164 participants in the ESD group demonstrated no difference in EAC (RR, 0.93; 95% CI, 0.50–1.72) (Figure 2.1).

R0 resection was considered an important but not a critical outcome. Seven studies[120–122,125,127,162,163] (1 RCT and 6 observational studies) were included in the direct comparison; 221 of 746 achieved R0 resection in the EMR group compared with 478 of 601 in the ESD group (RR, 0.43; 95% CI, 0.29–0.78) (Figure 2.2). For the outcome of CEN, 3 comparative cohort studies report on CEN, with a total of 472 subjects achieving CEN out of 599 subjects in the EMR group and 153 of 186 subjects in the ESD group, resulting in a pooled RR of 0.93 (95% CI, 0.87–1.00)

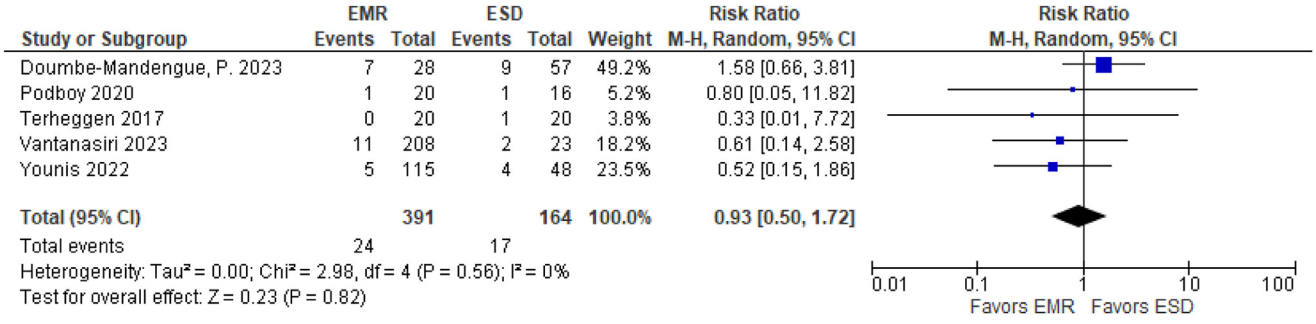

Figure 2.1. Forest plot of comparative studies comparing EAC at 1–2 years follow-up for patients treated with EMR vs ESD. M-H, Mantel-Haenszel.

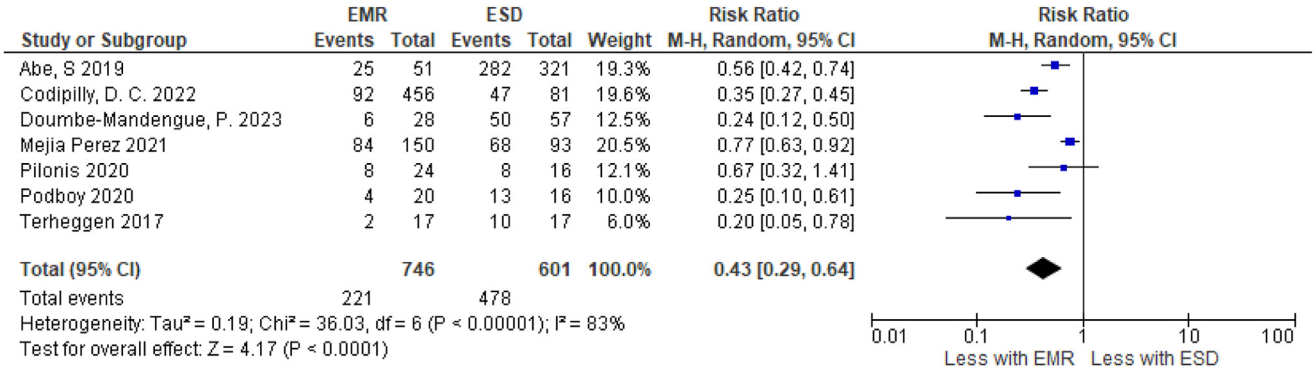

Figure 2.2. Forest plot of comparative studies comparing R0 resection among patients treated with EMR vs ESD. M-H, Mantel-Haenszel.

(Figure 2.3). For the outcome of CEIM, 1 RCT and 3 comparative cohort studies were identified with a total of 408 of 619 subjects in the EMR group achieving CEIM compared with 131 of 206 subjects in the ESD group (RR, 1.06; 95% CI, 0.87–1.00) (Figure 2.4).

Harms

The patient-important outcomes that informed the harms for this PICO question were: (1) strictures; (2) major bleeding either requiring blood transfusion, intervention, or hospitalization; and (3) perforation. A systematic review and meta-analyses were performed to estimate the risk of adverse events for ESD and EMR.

We included 38 studies in the meta-analysis reporting stricture formation after ESD. Three hundred sixty-one of 2731 patients developed a stricture post–esophageal ESD. The pooled proportion of stricture formation with ESD from single-arm studies was 12.4% (95% CI, 9.6%–15.2%) (Figure 3.1). Twenty-seven studies were included in the EMR single-arm analysis. Of 3,729 patients, 408 developed stricture post EMR. The pooled proportion of stricture formation with EMR was 9.1% (95% CI, 6.4%–11.7%) (Supplementary Figure 7.1). In the indirect comparison, EMR was associated with fewer strictures compared with ESD (RR, 0.83; 95% CI, 0.72–0.95). Furthermore, there was 1 RCT[120] and 6 observational comparative studies[121,122,124–127] in the direct comparison of stricture formation after ESD and EMR. Fifty-eight of 966 developed stricture post EMR compared with 65 of 580 in the post-ESD group (RR, 0.66; 95% CI, 0.42–1.05) (Figure 3.2).

We included 32 studies in the single-arm analysis of significant bleeding post ESD. Significant bleeding was found in 64 of 2589 patients after ESD with pooled proportion of 1.8% (95% CI, 1.3%–2.3%) (Figure 4.1). We included 20 studies in the single-arm analysis of significant bleeding post EMR. Significant bleeding was found in 39 of 2061 patients after EMR with pooled proportion of 1.5% (95% CI, 0.8%–2.1%) (Supplementary Figure 7.2). In the indirect comparison, there was no significant difference in bleeding events (EMR vs ESD RR, 0.77; 95% CI, 0.52–1.14). There were 5 studies in the direct comparison (1 RCT[120] and 4 observational studies[122,124,125,127]); there was no significant difference in bleeding with 17 of 769 in the EMR group and 9 of 299 in the ESD (RR, 0.87; 95% CI, 0.38–2.00) (Figure 4.2).

We included 33 single-arm studies assessing perforation post ESD: 46 of 2644 patients developed perforation post ESD with pooled proportion of 1.1% (95% CI, 0.7%–1.5%) (Figure 5.1). We included 27 single-arm studies assessing perforation after EMR: 16 of 5799 patients developed perforation post EMR (pooled proportion, 0.34%; 95% CI, 0.19%–0.58%) (Supplementary Figure 7.3). In the indirect comparison, EMR was associated with fewer perforations than ESD (RR, 0.34; 95% CI, 0.20–0.60). In addition, there was 1 RCT[120] and 5 observational[121,122,124,125,127] studies in the direct comparison analysis. Seven of 800 patients developed perforation with EMR compared with 5 of 319 patients in the ESD (RR, 0.93; 95% CI, 0.16–5.41) (Figure 5.2).

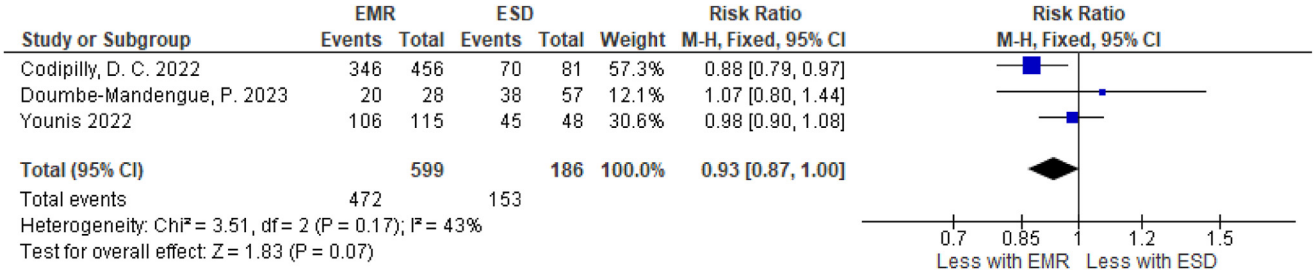

Figure 2.3. Forest plot of comparative studies comparing CEN among patients treated with EMR vs ESD. M-H, Mantel-Haenszel.

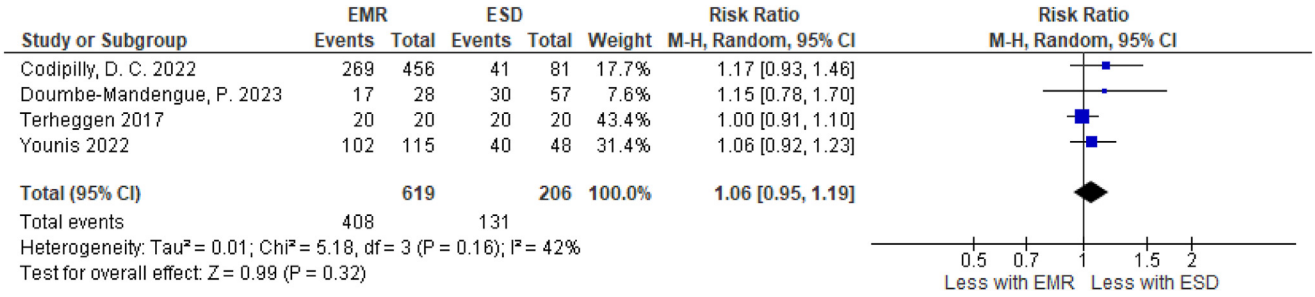

Figure 2.4. Forest plot of comparative studies comparing CEIM among patients treated with EMR vs ESD. M-H, Mantel-Haenszel.

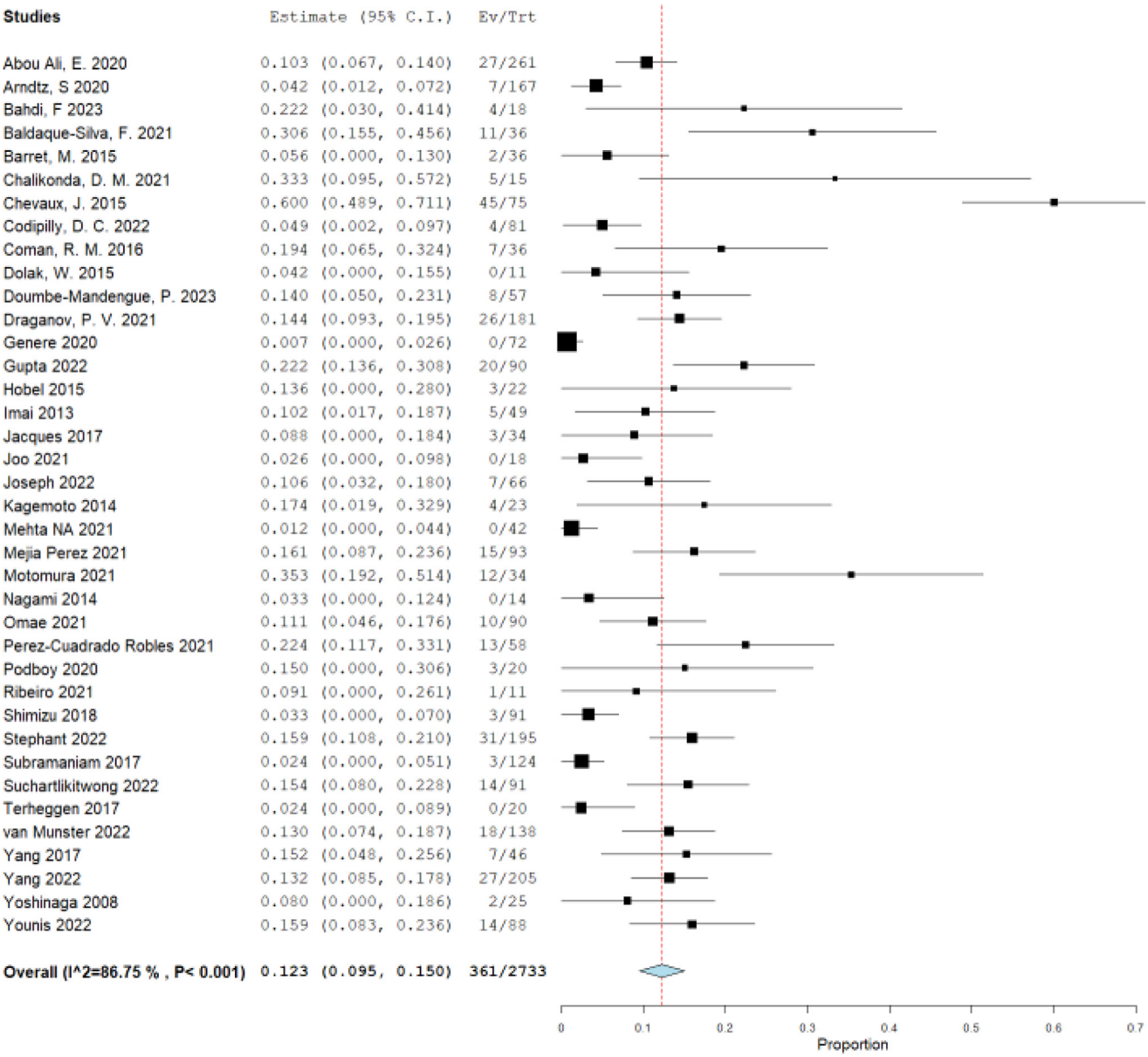

Figure 3.1. Forest plot of pooled proportion of stricture formation among patients with BE and visible lesion treated with ESD.

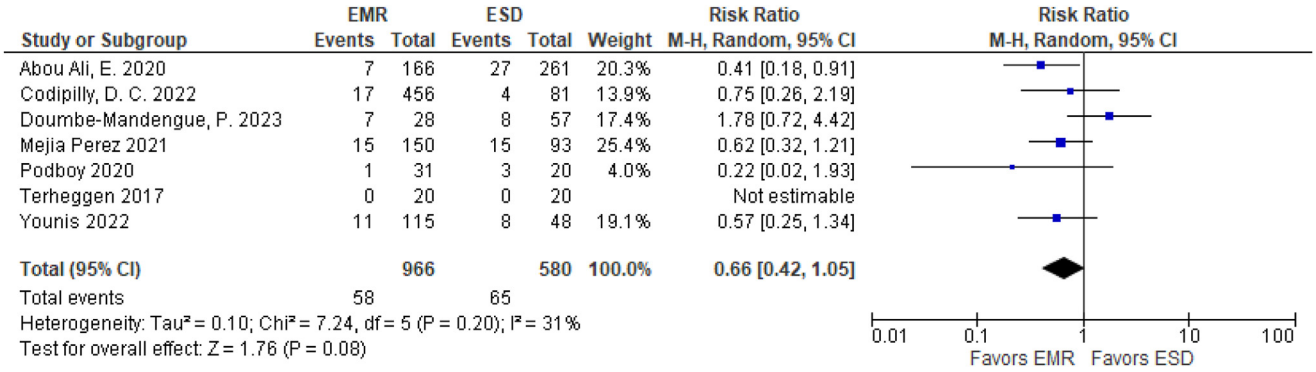

Figure 3.2. Forest plot of direct comparative studies comparing stricture formation in patients with BE and visible lesion treated with EMR vs ESD. M-H, Mantel-Haenszel.

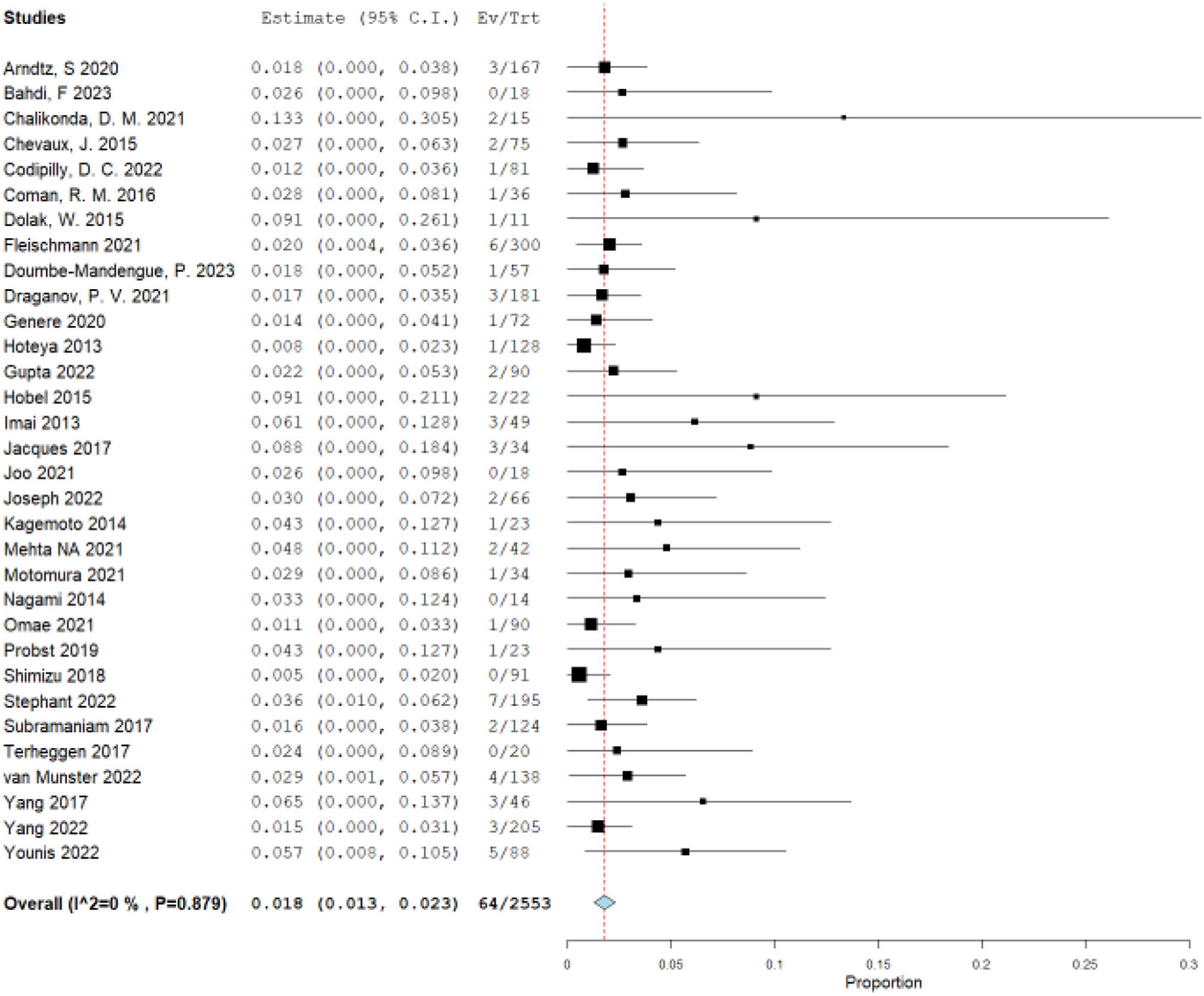

Figure 4.1. Forest plot of pooled proportion of major bleeding events among patients with BE and visible lesion treated with ESD.

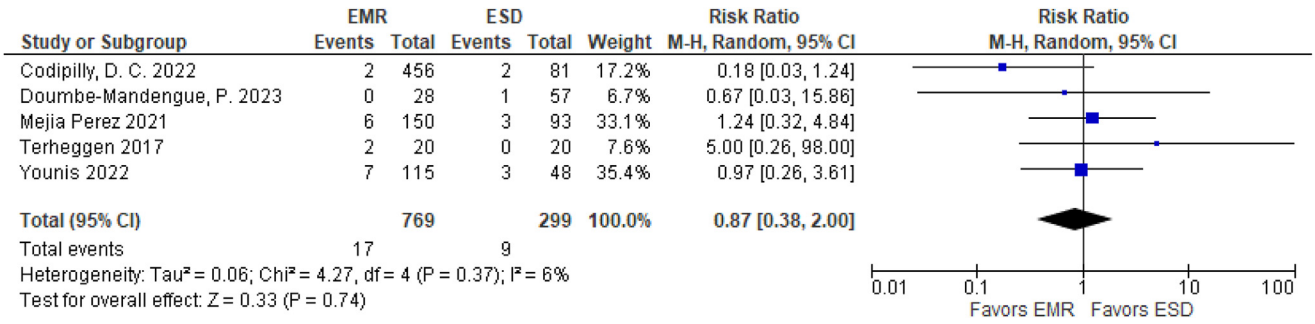

Figure 4.2. Forest plot of direct comparative studies comparing major bleeding in patients with BE and visible lesion treated with EMR vs ESD. M-H, Mantel-Haenszel.

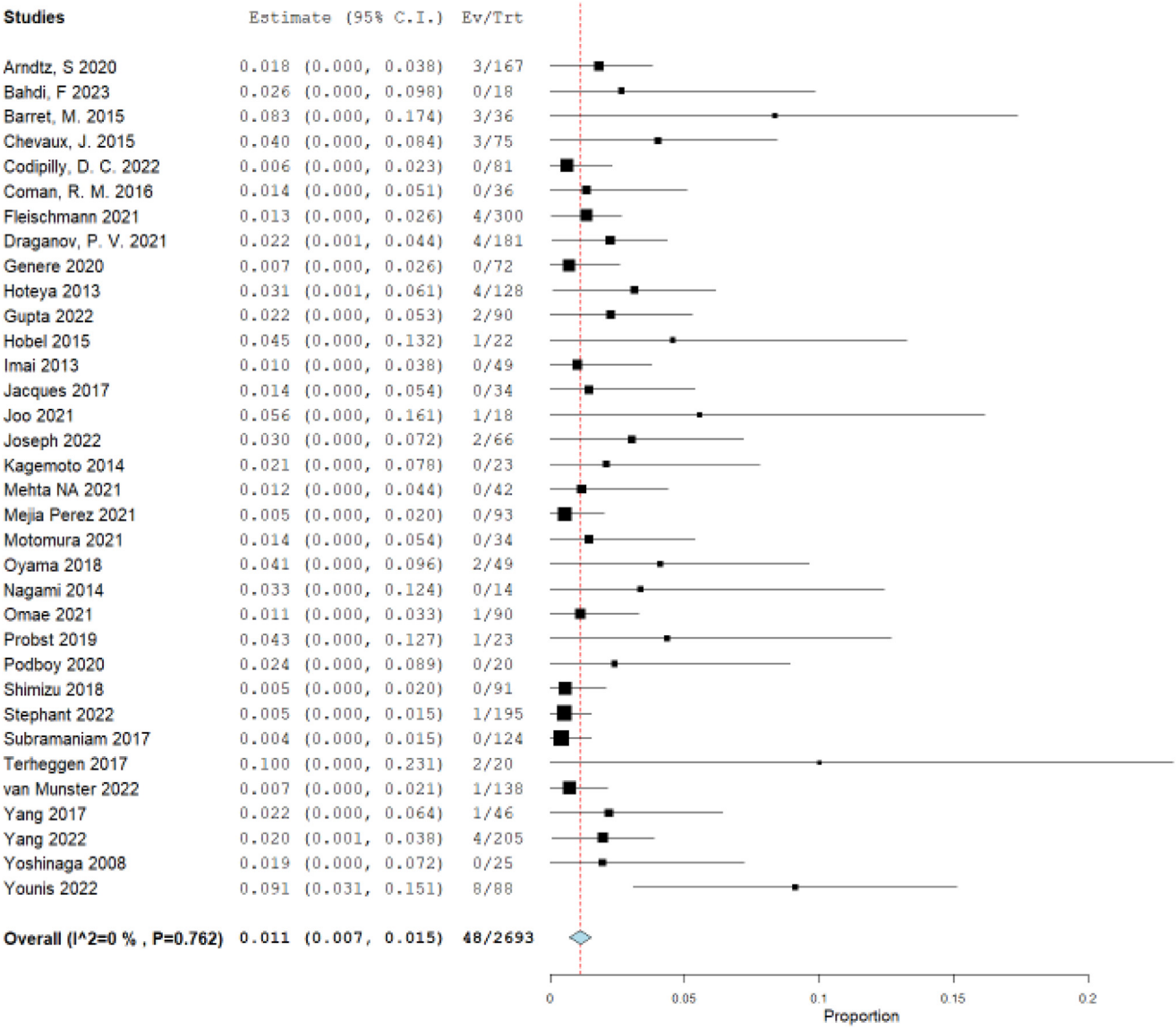

Figure 5.1. Forest plot of pooled proportion of perforation among patients with BE and visible lesion treated with ESD.

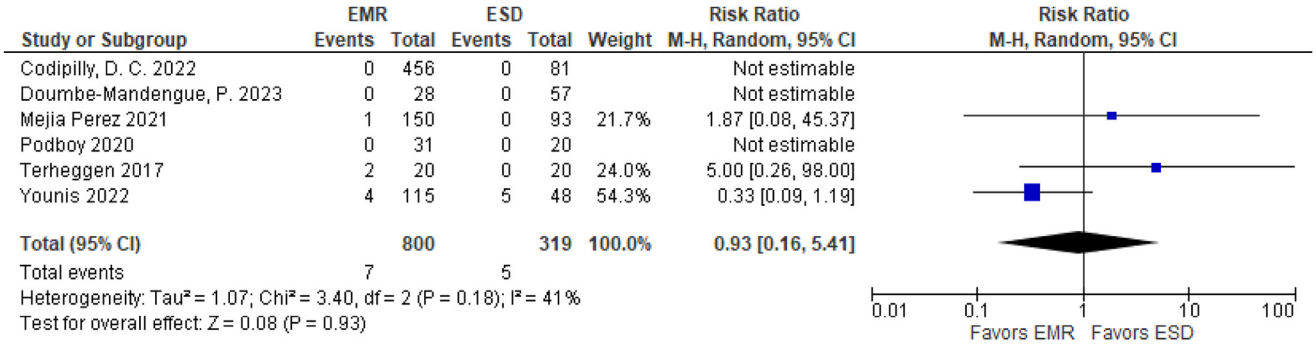

Figure 5.2. Forest plot of direct comparative studies comparing perforation in patients with BE and visible lesion treated with EMR vs ESD. M-H, Mantel-Haenszel.

Certainty in Evidence of Effects

The overall certainty in the evidence across the critical outcomes with consideration of both benefits and harms was very low (Table 9). Our certainty in the critical outcome of EAC was very low. The major concern for the EAC outcome when treated with EET was imprecision, given the low number of events. There was also concern about the risk of bias in observational studies. For the outcome of adverse events, the certainty of evidence was also very low. Data from non-randomized studies was very low in certainty due to serious risk of bias in observational studies due to a comparison of independent single-arm studies with no time-concurrent controls. Stricture formation was considered the most common harm. There was significant heterogeneity in reported stricture formation in the single-arm studies (I^2 = 86.57% in the ESD studies and 88.25% in the EMR studies).

Discussion

There was considerable discussion among the panel regarding the evidence to support this recommendation. For the critical outcome of EAC, there was no difference. For the important outcome of CEN, only observational studies were available. The results of the meta-analysis were heavily influenced by the largest study, which was a single-center retrospective study reporting overall greater CEN in ESD than in EMR, but also reported improvement in CEN with EMR over time, and those authors found no difference in CEN in sub-analyses comparing ESD with EMR performed during the later time period.[125] The other 2 studies in the CEN meta-analysis had point estimates near the null. For the important outcome of CEIM, there was no difference between EMR and ESD, including in the 1 available RCT. R0 resection was achieved to a greater degree with ESD compared with EMR. Harms were deemed moderately greater with ESD compared with EMR. There is possibly important variability in how patients may value the relative importance of the various outcomes. ESD is expected to be associated with increased resource utilization because many patients currently are hospitalized after ESD. ESD also requires longer procedure duration and utilization of more devices than EMR. To our knowledge, there are no cost-effectiveness analyses comparing these strategies. Because few providers are trained to competently perform ESD and the learning curve is steep, particularly in the esophagus, and potentially appropriate cases are relatively uncommon, widespread implementation of ESD faces substantial barriers to being feasible[13] and would likely exacerbate health care inequalities. Although ESD is probably acceptable to patients, the relative acceptability compared with EMR has not been well studied. Similar to the comparison of sEMR with fEMR followed by ablation, the authors believed that EMR can be used in most patients with visible neoplastic lesions and decision to perform ESD may be made based on characteristics of visible neoplastic lesions.

Implementation Considerations

Patients found to have T1 EAC, particularly T1a, may be cured with endoscopic resection if EET is completed to CEN/CEIM and endoscopic surveillance continues. Of note, endoscopic ultrasound is inaccurate for distinguishing T1a from T1b, and to a lesser degree from T2 cancers, so patients suspected endoscopically of T1 cancer should undergo endoscopic resection for tumor depth staging.[164] Obstructive or ulcerated lesions are unlikely to represent T1 disease and can forego endoscopic resection. Factors on endoscopic resection associated with favorable prognosis with EET alone include negative deep margin, T1a depth, moderate or well differentiation, and lack of lymphovascular invasion.[165–168] Patients not meeting any of those criteria, or those with endosonographic or cross-sectional imaging evidence suggestive of metastases should undergo multidisciplinary consultation to consider esophagectomy, chemotherapy, and/or radiation depending on stage and functional status.

There was substantial uncertainty with regard to the potential benefit of ESD compared with EMR. Guidelines from some other societies have suggested or recommended ESD, particularly in individuals with large lesions.[169] The studies assessing EAC outcomes after EET had relatively short durations of follow-up. The patients undergoing ESD in the observational studies tended to have larger lesions, which may have greater risk of technical failure with EMR or progression, but there was insufficient data to perform analyses stratified by lesion size. Because the large difference in R0 rates did not translate to improvements in CEIM or EAC after EET, the R0 resection appears to be of minor

importance. Patients undergoing EMR requiring more than 1 resection during the procedure can have technically successful resections of overlapping, contiguous pieces. Histologically, this will necessarily result in a positive lateral margin on each neighboring piece. Much more important is the deep margin. ESD may hold advantages over EMR for ensuring negative deep margins, but the studies included did not address this. EMR should be sufficient for T1a lesions, and ESD may be more effective for T1b lesions, but one does not know the depth of penetration until after the resection. Certain endoscopic features, including larger size, but more importantly depressed lesions (Paris IIc or IIa+c), may be suggestive of a more deeply invasive lesion, and hence might be preferentially referred for ESD.[170] Some prior guidelines have suggested a size threshold above which ESD should be favored over EMR, but this appears to be based on the technical limits of R0 lateral margins with EMR rather than for longitudinal cancer control outcomes. The guideline authors attempted to perform analyses stratified by size of lesions, but the available published data were not presented in a manner that allowed for such analyses. In addition, bulky sessile lesions, even if T1a, may be technically difficult to resect with EMR due to limitations of the cap size. Future RCTs are needed to demonstrate whether ESD has improved outcomes in such populations (aside from R0 resection) that are worth the added harms and barriers to implementation.[131]

Knowledge Gaps

These evidence reviews identified several important knowledge gaps that future research should address. These are detailed in the discussions of the individual recommendations. In summary, regarding patient selection for EET, further research is needed to understand the balance of risks and benefits in patients with BE and LGD and identifying whether there are populations with NDBE whose risks of EAC warrant EET. RCTs are needed comparing ESD and EMR in higher-risk populations assessing outcomes of critical importance, including long-term cancer control. For management of patients during EET, research is needed to identify optimal control of post-EET pain, stricture prevention, and management of resistant/recurrent disease beyond reflux control. For management of patients after EET, better data are needed to identify optimal surveillance intervals and biopsy protocols, and under what circumstances to discontinue endoscopic surveillance after completion of EET, which would likely depend on index histology, age, and comorbidities.

Plans for Updating

Considerable resources are expended for the development of guidelines, and keeping guidelines up to date is a challenging process. Future updates of this guideline will depend on the availability of new evidence on the existing interventions and new intervention. We hope to incorporate the advances in the technological platforms and models of guideline development in the future updates without duplication or reproduction of the current guideline document.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2024.03.019.

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