Communication from the ASGE Standards of Practice Committee

GUIDELINE

Endoscopic eradication therapy for patients with Barrett's esophagus–associated dysplasia and intramucosal cancer

Prepared by: STANDARDS OF PRACTICE COMMITTEE

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Barrett's esophagus (BE) is defined by the replacement of the normal squamous epithelium of the distal esophagus with metaplastic intestinal-type columnar epithelium.[1-3] BE is an adverse event of chronic GERD and the only identifiable premalignant condition for esophageal adenocarcinoma (EAC), a cancer that continues to increase in incidence. In 2014 there were approximately 18,170 incident cases of esophageal cancer in the United States, nearly 60% of which were EAC.[4-6] Although uncommon, EAC is a highly lethal cancer associated with a poor 5-year survival rate of 15% to 20% and an overall median survival of <1 year in cases with advanced disease.[5-7] It is estimated that BE is present in 1% to 2% of the general adult population.[8,9] The stepwise and hypothesized progression of BE to invasive EAC is believed to occur through the histopathologic stages of intestinal metaplasia to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to intramucosal EAC and finally to invasive EAC.[3,10-13]

Endoscopic eradication therapy (EET) has significantly changed the management of patients with BE-related neoplasia and allows a minimally invasive treatment approach that avoids the morbidity and mortality associated with esophagectomy. Contemporary EET, supported by published literature, entails endoscopic mucosal resection (EMR) of visible lesions within the Barrett's segment and ablative techniques that include radiofrequency ablation (RFA) and cryotherapy. Several studies, including randomized controlled trials (RCTs), large observational studies, and population-based studies, have demonstrated the efficacy, effectiveness, and safety of EET to achieve complete eradication of intestinal metaplasia (CE-IM) and neoplasia while maintaining disease remission.[14-22] In addition, population-based studies report comparable outcomes between esophagectomy and EET in the management of BE-related HGD and mucosal EAC.[23] Available data suggest that EET is being performed not only at academic and tertiary care centers but also among community practices.[14,18]

AIMS/SCOPE

The aim of this document is to offer evidence-based recommendations and clinical guidelines addressing key issues related to EET in the management of BE-related neoplasia. This document addresses the following clinical questions:

1. What is the role of confirmation of diagnosis by an expert GI pathologist or by a panel of pathologists in BE patients with dysplasia or intramucosal EAC referred for EET?
2. Comparing EET with surveillance, what is the optimal management strategy in BE patients with dysplasia (HGD and LGD) and intramucosal EAC?
3. Comparing EET with esophagectomy, what is the optimal management strategy in BE patients with HGD and intramucosal EAC?
4. What is the role of EMR in BE patients with a visible lesion detected during screening or surveillance?
5. What is the role of ablation of the remaining BE segment after EMR of all visible lesions in BE patients referred for EET?
6. Comparing EMR of visible lesions followed by ablation of remaining BE segment with EMR of entire BE segment, what is the optimal EET approach in BE patients with dysplasia or intramucosal EAC referred for EET?
7. After achieving CE-IM, what is the role of surveillance endoscopy?

This document was approved by the American Society for Gastrointestinal Endoscopy (ASGE) Governing Board and represents the official recommendations of the ASGE.

METHODS

Overview

This document was prepared by a working group of the Standards of Practice Committee of the ASGE in

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conjunction with a Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologist. It includes a systematic review of available literature along with guidelines for EET in the management of BE-related dysplasia and intramucosal EAC patients, developed using the GRADE framework.[24] After evidence synthesis, recommendations were drafted by the full panel during a face-to-face meeting on March 23, 2017 and approved by the Standards of Practice committee members and the ASGE Governing Board.

Panel composition and conflict of interest management

The panel consisted of 2 content experts with expertise in systematic reviews and meta-analysis (S.W., B.Q.), a GRADE methodologist (S.S.), oncologic surgeon, committee chair (J.D.), patient representative, and other committee members. All panel members were required to disclose potential financial and intellectual conflicts of interest, which were addressed according to ASGE policies (https://www.asge.org/forms/conflict-of-interest-disclosure and https://www.asge.org/docs/default-source/about-asge/mission-and-governance/asge-conflict-of-interest-and-disclosure-policy.pdf).

Formulation of clinical questions

A total of 7 clinical questions were developed and then approved by the ASGE Governing Board (Table 1). For each PICO question we identified the population (P), intervention (I), comparator (C), and outcomes of interest (O). For all clinical questions potentially relevant patient-important outcomes were identified a priori and rated from not important to critical through a consensus process. Relevant clinical outcomes included progression to cancer, cancer-specific and all-cause mortality, adverse events, and recurrence rates. EET in this document refers to EMR and RFA (based on the vast body of literature) unless explicitly stated otherwise.

Literature search and study selection criteria

For each of the PICO questions a literature search for existing systematic reviews and meta-analyses was performed. If none was identified, a full systematic review and meta-analysis (when possible) was conducted using the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria.[25] Details of the search strategy are reported in Supplementary Text 1 (available online at www.giejournal.org). A medical librarian (B.H.) performed a comprehensive literature search of Ovid Medline (Ovid MEDLINE in-process and other non-indexed citations, Ovid MEDLINE) Daily and Ovid MEDLINE 1946 to present), Embase (via Embase.com), and the Cochrane Database of Systematic Reviews/Cochrane Register of controlled trials (via Wiley Online Library). All searches ended on March 11, 2016. Inclusion and exclusion criteria were developed for each PICO question (Supplementary Text 2, available online at www.giejournal.org).

Citations were imported into EndNote (Thompson Reuters, Philadelphia, Pa), and duplicates were removed. The EndNote library was then uploaded into Covidence (www.covidence.org). Two reviewers were assigned to each search for each PICO question. Studies were first screened by title and abstract and then by full text, and all conflicts were resolved by consensus. If existing systematic reviews and meta-analyses were available, inclusion and exclusion criteria were reviewed, and methodological quality of the study was assessed using the Measurement Tool to Assess Systematic Reviews (AMSTAR) tool (https://amstar.ca/Amstar_Checklist.php).[26] Only systematic reviews and meta-analysis meeting the quality thresholds were used for data synthesis. For this guideline an arbitrary threshold (meeting 8 or more of the 11 criteria) was used. When applicable, available systematic reviews and meta-analyses were updated based on literature review as described above.

Data extraction and statistical analysis

If data extraction was needed for a meta-analysis, data were extracted by 2 independent reviewers using Microsoft Excel (Microsoft Corporation, Redmond, Wash). The primary estimate of effect was based on the outcomes of interest in the PICO question and included relative risk (RR), odds ratio (OR), or proportions (change in diagnosis, cumulative rate of disease progression, among others). For outcomes with limited or no available direct comparisons, indirect comparisons were used to estimate the magnitude and direction of effect. Heterogeneity was assessed using the I^2 and Q statistic. Significant heterogeneity was defined at $I^2 > 50\%$ and significant P value (<.05) on the Q statistic. Random-effects models were used if significant heterogeneity was detected. Otherwise, fixed-effects models were used. Studies were weighted based on their size. A priori sources of heterogeneity for each outcome were hypothesized and addressed in sensitivity analyses when applicable. Publication bias was assessed using funnel plots and the classic-fail-safe. Statistical analyses were performed using Comprehensive Meta Analysis V_3 (Biostat Inc, Englewood, NJ).

Certainty in evidence (quality of evidence)

The certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest, following the GRADE approach based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of dose–effect relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high (Table 2). With this approach direct evidence from RCTs starts at

TABLE 1. List of clinical questions and questions in PICO (Population, Intervention, Comparator, and Outcomes) format

Focused question	Population	Intervention	Comparator	Outcomes
1. What is the role of confirmation of diagnosis by an expert GI pathologist or by a panel of pathologists in BE patients with dysplasia or intramucosal EAC referred for EET?	BE patients with dysplasia/neoplasia referred for EET	Review of pathology by ≥1 expert GI pathologist	No expert review of pathology	• Difference in progression rates to cancer (critical) • Proportion of cases with change in dysplasia/neoplasia grade (important)
2. Comparing EET to surveillance, what is the optimal management strategy in BE patients with dysplasia (HGD and LGD)?	BE patients with dysplasia/IMC referred for EET This PICO was explored in the context of 2 subgroups: (1) HGD and (2) LGD	EET	Surveillance	• Progression to cancer (critical) • Cancer-specific mortality (critical) • All-cause mortality (critical) • Morbidity and adverse event rates (critical)
3. Comparing EET with esophagectomy, what is the optimal management strategy in BE patients with HGD and IMC?	BE patients with dysplasia/IMC referred for EET	EET	Esophagectomy	• Progression to cancer (important) • Cancer-specific mortality (critical) • All-cause mortality (critical) • Morbidity and adverse event rates (critical)
4. What is the role of endoscopic resection in BE patients with a visible lesion detected during screening or surveillance?	BE patients with a visible lesion detected during screening or surveillance	Endoscopic resection of all visible lesions	No endoscopic resection	• Difference in progression rates to cancer (critical) • Proportion of cases with change in dysplasia/neoplasia grade (important) • Proportion of cases with change in management plan (critical) • Adverse events (critical)
5. What is the role of ablation of the remaining BE segment after EMR of all visible lesions in BE patients referred for EET?	BE patients undergoing EET	Ablation of remaining flat BE (with or without dysplasia) after endoscopic resection of all visible lesions	No ablation	• Progression to cancer (critical) • Progression to HGD/cancer (important) • Recurrence rates (critical)
6. Comparing endoscopic resection of visible lesions followed by ablation of remaining BE segment to endoscopic resection of entire BE segment What is the optimal EET approach in BE patients with dysplasia or IMC referred for EET?	BE patients undergoing EET	Endoscopic resection of visible lesions followed by ablation of the remaining flat BE (with or without dysplasia)	EMR of entire BE	• Progression to cancer • Progression to HGD/cancer • Adverse events
7. After achieving complete eradication of dysplasia and intestinal metaplasia, what is the role of surveillance endoscopy?	BE patients after eradication of dysplasia and intestinal metaplasia	Enrolled in endoscopic surveillance programs	No surveillance	• Progression to cancer (important) • Report recurrence rates (important) • Cancer-specific and all-cause mortality (critical)

EET, Endoscopic eradication therapy; *BE*, Barrett's Endoscopy; *LGD*, low-grade dysplasia; *HGD*, high-grade dysplasia; *IMC*, intramucosal cancer.

high quality and is then rated down based on assessment of the above variables. On the other hand, evidence from observational studies starts at low quality and then is potentially downgraded based on the above variables or upgraded in case of the dose–response relationship and large magnitude of effect. For each PICO an evidence profile or summary of findings table was created using the GDTpro application (http://gdt.guidelinedevelopment.org/app).

Considerations in the development of recommendations

During an in-person meeting, the panel developed recommendations based on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, the assumptions about the values and preferences associated with the decision along with available data on resource utilization, and cost-effectiveness. The final wording of the

TABLE 2. GRADE categories of quality of evidence

GRADE quality of evidence	Meaning	Interpretation
High	We are confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate	We are moderately confident in the estimate of the effect; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an impact on our confidence in the estimate of the effect and may change the estimate.
Low	Our confidence in the estimate of the effect is limited; the true effect may be substantially different from the estimate of the effect.	Further research is very likely to have an impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low	We have very little confidence in the estimate of the effect; the true effect is likely to be substantially different from the estimate of the effect.	Any estimate of the effect is very uncertain.

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

TABLE 3. Interpretation of definitions of strength of recommendation using GRADE framework

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders.

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

recommendations (including direction and strength), remarks, and qualifications were decided by consensus and were approved by all members of the panel. The recommendations are labeled as either "strong" or "conditional" according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations and "suggests" for conditional recommendations. Table 3 provides the suggested interpretation of strong and conditional recommendations by patients, clinicians, and healthcare policymakers.

Patient values and preferences. Limited data address patient preferences with regards to management of BE with and without dysplasia. Three studies shed light on this important subject.[27-29] In a prospective study Yachimski et al[27] showed that patients with nondysplastic BE (NDBE) preferred endoscopic ablation over chemoprevention (aspirin) to prevent progression of BE to EAC. Rosmolen and colleagues[29] assessed the influence of EET and surgery on quality of life and fear of cancer recurrence. In this study that included 66 patients treated with EET and 29 patients undergoing esophagectomy, patients in the surgery group reported more eating problems (OR, 18.3; 95% CI, 4.1-81.5) and reflux symptoms (OR, 3.4; 95% CI, 1-10.5), whereas endoscopy patients reported greater fear of recurrence. These results highlight the need for proper patient education with a specific focus on cancer recurrence in patients undergoing EET. There are no recent studies of patient preferences for management of BE-related neoplasia using contemporary endoscopic therapies (EMR, RFA, cryotherapy), surgical esophagectomy, and surveillance.

Cost-effectiveness. Several studies have demonstrated the cost-effectiveness of contemporary EET in the management of BE-related neoplasia. Hur et al[30] analyzed the cost-effectiveness of RFA for management of BE using a decision analytic Markov model, and separate analyses of hypothetical cohorts of BE with dysplasia (HGD and LGD) and NDBE were conducted. In HGD patients treatment strategies compared were (1) endoscopic surveillance with esophagectomy when cancer was detected and (2) initial RFA followed by endoscopic surveillance. Treatment options for confirmed and stable LGD patients included (1) endoscopic surveillance with surgery when cancer

TABLE 4. Summary of recommendations with strength of recommendation and quality of evidence

Statement	Strength of recommendation	Quality of evidence
1. **In BE patients with LGD and HGD being considered for EET, we suggest confirmation of diagnosis by at least 1 expert GI pathologist or panel of pathologists compared with review by a single pathologist.**	Conditional	Low
2a. **In BE patients with LGD, we suggest EET compared with surveillance; however, patients who place a high value on avoiding adverse events related to EET may choose surveillance as the preferred option.**	Conditional	Moderate
2b. **In BE patients with confirmed HGD, we recommend EET compared with surveillance.**	Strong	Moderate
3. **In BE patients with HGD/IMC, we recommend against surgery compared with EET.**	Strong	Very low quality evidence
4. **In BE patients referred for EET, we recommend endoscopic resection of all visible lesions compared with no endoscopic resection of visible lesions.**	Strong	Moderate
5. **In BE patients with visible lesions who undergo endoscopic resection, we suggest ablation of the remaining Barrett's segment compared with no ablation.**	Conditional	Low
6. **In BE patients with dysplasia and IMC referred for EET, we recommend against routine complete endoscopic resection of entire Barrett's segment compared with endoscopic resection of visible lesion followed by ablation of remaining Barrett's segment.**	Strong	Very low
7. **In BE patients with dysplasia and IMC who have achieved CE-IM after EET, we suggest surveillance endoscopy versus no surveillance.**	Conditional	Very low

BE, Barrett's esophagus; *EET*, endoscopic eradication therapy; *HGD*, high-grade dysplasia; *LGD*, low-grade dysplasia; *IMC*, intramucosal cancer; *CE-IM*, complete eradication of intestinal metaplasia.

was detected, (2) endoscopic surveillance with RFA when diagnosed with HGD, and (3) initial RFA at LGD stage followed by endoscopic surveillance. In patients with HGD this analysis showed that RFA was more effective and less costly than surveillance followed by esophagectomy at the detection of EAC (.704 more quality-adjusted life years and costing $25,609). Initial RFA was also cost-effective for confirmed and stable LGD and not cost-effective in NDBE patients. Data from a recent RCT showed that ablation with RFA for patients with confirmed LGD is more effective and more expensive than surveillance in reducing the risk of progression to the endpoint of HGD/EAC.[31] Similarly, a decision analysis that compared cost-effectiveness of esophagectomy and EET in the treatment of early EAC showed that EET was more effective and less expensive than esophagectomy.[32] EET was also a cost-effective alternative in patients with submucosal cancer, especially in patients with high operative risk.

RESULTS

The recommendations, quality of evidence, and strength of recommendations are summarized in Table 4.

The panel members recommend that before embarking on EET, patients have a clear understanding of the risks, benefits, and alternatives to EET.

The panel members agreed that before EET, clinicians should obtain informed consent that includes discussions of the natural history of BE including progression rates to EAC, appropriate surveillance and treatment options, risks and benefits of each approach, and the frequency of EET sessions and duration of follow-up.[14,15] Patient preferences and assessment of patient comorbidities and life expectancy should be considered in the management algorithm of these patients.

Question 1: What is the role of confirmation of diagnosis by an expert GI pathologist or by a panel of pathologists in BE patients with dysplasia or intramucosal EAC referred for EET?

Recommendation: In BE patients with HGD and LGD being considered for EET, we suggest confirmation of diagnosis by at least 1 expert GI pathologist or a panel of pathologists compared with review by a single pathologist (conditional recommendation, low quality of evidence).

Summary of the Evidence: The patient important outcomes for this clinical question were the differences in progression rates to cancer among patients with confirmed dysplasia (critical outcome) and proportion of patients with a change in diagnosis in grade of dysplasia based on an expert pathology review or review by a panel of pathologists (important outcome). No RCTs addressed these outcomes, and hence indirect comparisons from observational studies were used to inform this recommendation. The evidence profile for this clinical question is summarized in Table 5.

Progression rates to EAC or a composite endpoint of HGD/EAC based on expert pathology review have been

TABLE 5. GRADE evidence profile for Question 1: What is the role of confirmation of diagnosis by an expert GI pathologist or by a panel of pathologists in BE patients with dysplasia or intramucosal EAC referred for EET?

Quality assessment						
No. of participants (studies) follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
Rates of progression to HGD/EAC in BE-LGD—critical						
2746 (19 observational studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕◯◯ LOW
Change in dysplasia diagnosis—important						
2354 (8 observational studies)	Not serious	Serious*	Not serious	Not serious	Publication bias suspected	⊕◯◯◯ VERY LOW

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *BE*, Barrett's esophagus; *EAC*, esophageal adenocarcinoma; *EET*, endoscopic eradication therapy; *CI*, confidence interval; *HGD*, high-grade dysplasia; *LGD*, low-grade dysplasia.
*The I^2 was high ($I^2 = 98\%$), suggesting significant heterogeneity.

studied predominantly in BE patients with LGD. A recent meta-analysis by Qumseya et al[33] compared progression rates in LGD patients based on review by an expert pathologist or a panel of pathologists. In this analysis 17 studies were included and subdivided based on review by an expert pathologist (10/17 studies) or a panel of pathologists. The cumulative rate of progression from LGD to HGD/EAC was significantly higher among studies where expert GI pathologist/panel of pathologists confirmed the diagnosis of LGD compared with those studies that did not report such a measure (15.7% [95% CI, 12.7%-19.3%] vs 8.1% [95% CI, 5.3%-12%], $P = .004$). The cumulative rate was defined as the rate of progression over the study period. The reported study duration was variable (ranged from 4 to 84 months), and to account for this variation the authors also reported the incidence rate of disease progression that controls for follow-up in person-years. Expert pathologist/panel review was associated with a higher incidence rate of progression (.031 [95% CI, .022-.041] vs .012 [95% CI, .008-.016)] (Supplementary Fig. 1, available online at www.giejournal.org). These results demonstrate that LGD, as confirmed by expert pathologist/panel of pathologists, was associated with a higher rate of disease progression to HGD/EAC.

A systematic review and meta-analysis was conducted to address the question of change in diagnosis (grade/presence of dysplasia) based on expert pathology review. Of the 682 screened studies, 43 were reviewed in full text format and 8 were included in the final analysis and included a total of 2354 patients. Using a random-effects model, expert pathology review resulted in a change in the pathologic diagnosis (upgrading or downgrading) in 55% (95% CI, 31%-77%) of all patients. In most studies this change was associated with downgrading to a lower pathologic diagnosis (36% [95% CI, 18%-59%]) (Fig. 1). One additional study by Duits et al[34] provides further evidence to support these findings. This European study retrospectively evaluated 255 patients with a primary diagnosis of LGD (78% men; mean age, 63 years) who participated in an RCT of surveillance versus RFA. Patients were examined by a median of 4 endoscopies (interquartile range, 3-6 endoscopies), and 3 expert pathologists independently reviewed baseline and subsequent LGD specimens. Of 255 patients, 45 (18%) developed HGD or EAC during a median 42-month follow-up period (interquartile range, 25-61 months). The number of pathologists confirming LGD was strongly associated with progression to neoplasia (suggesting a dose–response effect), and risk for progression increased greatly when all 3 pathologists agreed on LGD (OR, 47.14; 95% CI, 13.10-169.70).

Certainty in the Evidence: For the critical outcome of disease progression, the quality of evidence was low based on the use of observational studies. There was no serious risk of bias, inconsistency, indirectness, imprecision, or publication bias. For change in dysplasia diagnosis (important outcome), the quality of evidence was rated down for inconsistency given the high I^2, suggesting significant heterogeneity. Hence, the quality of evidence for this outcome was very low. The overall body of evidence across all outcomes was deemed low quality.

Considerations: One potential downside is increased cost associated with expert pathology review because of limited local expertise. Given the important potential impact on patient management and that coverage is usually provided by medical insurance providers, the costs associated with this intervention did not impact the recommendation provided.

Discussion: Despite recent advances in genetic and molecular markers, the degree of dysplasia is still the best biomarker to predict progression to EAC and guide further management.[3] The revised Vienna classification for GI mucosal neoplasia and the World Health

TABLE 5. Continued

Summary of findings				
Study event rates (%)			Anticipated absolute effects	
With pathology review by 1 pathologist	With pathology review performed by >1 expert GI pathologist	Relative effect (95% CI)	Risk with pathology review by 1 pathologist	Risk difference with pathology review performed by >1 expert GI pathologist
Cumulative rate of disease progression when expert >1 (or panel) of GI pathologists confirmed the diagnosis of LGD compared with those studies that did not was 15.7% (95% CI, 12.7%-19.3%) vs 8.1% (95% CI, 5.3%-12%)				
Change in dysplasia diagnosis when >1 expert GI pathologist confirmed the diagnosis (pooled event rate across 8 studies) was 55% (range, 31%-77%), with most cases being downgraded.				

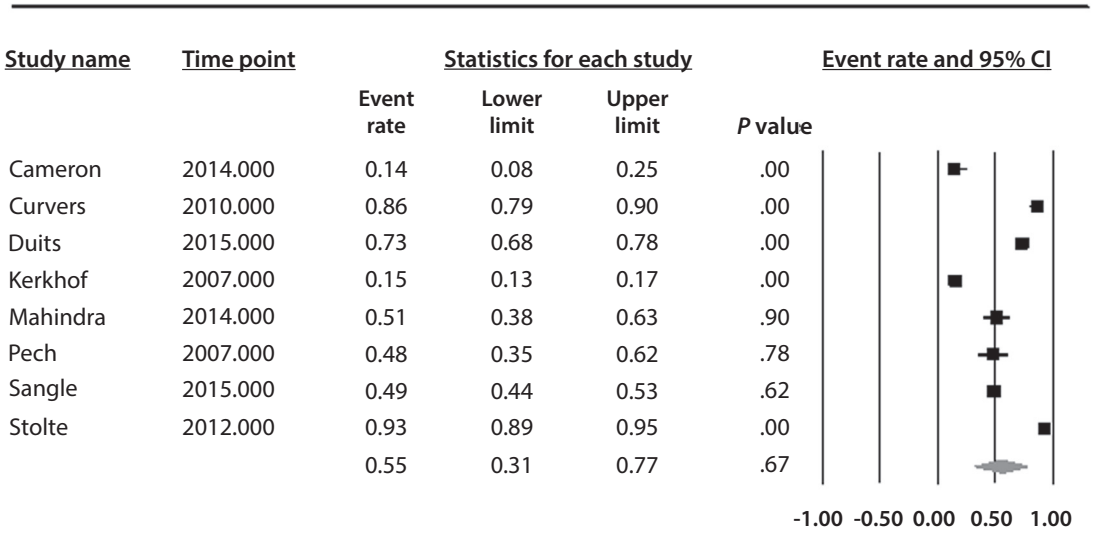

Figure 1. Forest plot of the proportion of cases in which pathologic review resulted in a change in the diagnosis among patients with Barrett's esophagus. *CI*, Confidence interval.

Organization classification of GI tumors are the grading systems used to categorize the grade of dysplasia in BE patients.[35,36] Significant interobserver and intraobserver variability has been well described among community and expert pathologists, especially regarding the diagnosis of LGD.[11,37-40] Results from a U.S. multicenter cohort study showed that the interobserver agreement among 2 expert central GI pathologists for the diagnosis of LGD was slight (κ value = .14).[11] A recent study that included 7 expert pathologists from the United States and Europe showed that the κ value for NDBE was .22 (95% CI, .11-.29), LGD .11 (95% CI, .004-.15), and HGD .43 (95% CI, .36-.46), reaffirming the high interobserver variability even among expert pathologists.

As described above, there is evidence across multiple studies and various outcomes that review by an expert pathologist or panel of pathologists affects outcomes in patients with BE, especially in BE patients with LGD. The exact definition of an expert pathologist is debatable. A recent expert review from the Clinical Practice Updates Committee of the American Gastroenterological Association defined an expert pathologist as one with a special interest in BE-related neoplasia and recognized as an expert in this field by his or her peers.[3] It is beyond the scope of this clinical guideline to define the detailed criteria that should be used in practice by pathologists and how they should arrive at a consensus diagnosis.

Finally, this recommendation is consistent with other published guidelines and supports the idea of confirmation of dysplasia by at least 1 expert GI pathologist or a panel of pathologists.[2] This is what practitioners should be doing in clinical practice. Given the low quality of evidence

TABLE 6. GRADE evidence profile for Question 2a; comparing EET with surveillance, what is the optimal management strategy in BE patients with LGD?

Quality assessment						
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
Progression to HGD/EAC comparing EET with surveillance: indirect estimates among cohorts (cumulative rate of progression) follow up: 4-84 months—critical						
2746 (22 observational studies)	Not serious	Serious*	Not serious	Not serious	None	⊕◯◯◯ VERY LOW
Progression to HGD/EAC: from RCT studies (cumulative rate of progression) follow-up 12-36 months—critical						
199 (2 RCTs)	Not serious	Not serious	Not serious	Serious†	None	⊕⊕⊕◯ MODERATE
Major adverse events including perforation, strictures, bleeding, pain, hospitalization—critical						
9200 (37 studies)	Not serious	Not serious‡	Not serious	Not serious	None	⊕⊕◯◯ LOW

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *EET*, endoscopic eradication therapy; *BE*, Barrett's esophagus; *LGD*, low-grade dysplasia; *CI*, confidence interval; *HGD*, high-grade dysplasia; *EAC*, esophageal adenocarcinoma; *RR*, relative risk; *RCT*, randomized control trial; *RFA*, radiofrequency ablation.
*The I^2 was high (I^2 = 83%), suggesting significant heterogeneity.
†There were few events and serious imprecision.
‡The I^2 was high (I^2 = 89%), suggesting significant heterogeneity.

supporting this recommendation, there is an opportunity for more and better evidence to inform this recommendation. This recommendation was also recently included as 1 of the ASGE and American College of Gastroenterology endorsed quality indicators for EET in BE.[14,41]

Question 2a: Comparing EET with surveillance, what is the optimal management strategy in BE patients with LGD?

Recommendation: In BE patients with LGD, we suggest EET compared with surveillance (conditional recommendation, moderate quality evidence); however, patients who place a high value on avoiding adverse events related to EET may choose surveillance as the preferred option.

Summary of the Evidence: The patient-important outcomes of interest for this clinical question were differences in progression rates to cancer, cancer-specific mortality, all-cause mortality, and adverse events. The evidence for these outcomes was informed by 2 recent systematic reviews (see Table 6).[22,33] Qumseya et al[33] conducted a systematic review and meta-analysis comparing the risk of progression to HGD/EAC among BE patients with LGD treated with RFA compared with surveillance endoscopy using data from 22 studies of over 2500 patients. Three head-to-head studies (2 RCTs[16,17] and 1 retrospective[42]) assessed the primary outcome of the RR of disease progression among patients treated with RFA compared with surveillance. For the purposes of this guideline the RR was calculated using data from the 2 RCTs only. When fixed-effects models are used, the RR of disease progression in BE patients with LGD treated with RFA compared with surveillance was .16 (95% CI, .04-.57; P = .001) (Fig. 2).

Considering the entire body of evidence by incorporating observational studies, a total of 22 studies including the above RCTs (2746 patients) reported similar results (RR = .14 of disease progression in patients treated with RFA compared with surveillance) (Fig. 3). The cumulative rate of disease progression (follow-up up to 84 months) among patients who underwent surveillance was 12.6% (95% CI, 9.8%-15.9%) and for patients who received RFA was significantly lower at 1.7% (95% CI, 1.1%-2.6%). The magnitude and direction of this estimate was very similar to the results of the 2 RCTs. This analysis also demonstrated that the incidence rate of progression among patients undergoing surveillance was significantly higher than those treated with RFA (.022 [95% CI, .015-.03] vs .005 [95% CI, .002-.007]). The outcome of serious adverse events for patients undergoing RFA was also addressed using a recent systematic review and meta-analysis.[22] This analysis included 37 studies with 9200 patients and reported a pooled rate of serious adverse events of 8.8% (95% CI, 6.5%-11.9%) related to RFA with

TABLE 6. Continued

Summary of findings				
Study event rates (%)			**Anticipated absolute effects**	
With surveillance	**With EET**	**Relative effect (95% CI)**	**Risk with surveillance**	**Risk difference with EET**
183/1521 (12.0%)	19/1225 (1.6%)	RR .14	Study population	
			12 per 100	10 fewer per 100
			High risk: confirmed, persistent LGD on biopsy	
			25 per 100	22 fewer per 100
21/89 (23.6%)	3/110 (2.7%)	RR .16 (.04-.57)	Study population	
			24 per 100	20 fewer per 100 (10 fewer to 23 fewer)
			High risk: confirmed, persistent LGD on biopsy sampling	
			25 per 100	21 fewer per 100 (11 fewer to 24 fewer)
Overall adverse event rate across 37 studies was 8.8% (95% CI, 6.5%-11.9%). Treatment modality EET included RFA ± EMR. Stricture post-treatment most common adverse event 5.6% (95% CI, 4.2%-7.4%).			0 per 100 (rare)	9 more per 100 (7 more to 12 more)

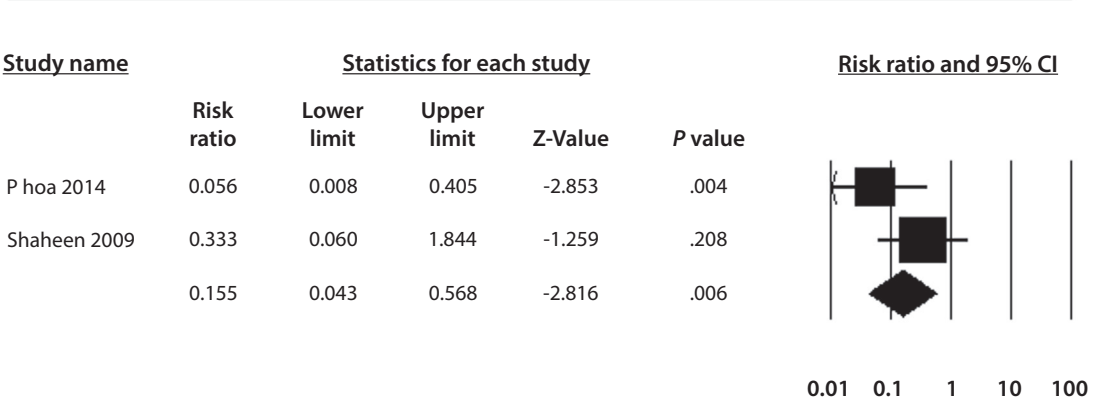

Figure 2. Forest plot with 2 randomized controlled trials comparing radiofrequency ablation with surveillance with pooled relative risk of disease progression in Barrett's esophagus patients with low-grade dysplasia. *CI*, Confidence interval.

or without EMR. Esophageal stricture formation was the most common adverse event (5.6% [95% CI, 4.2%-7.4%]). Bleeding (1% [95% CI, .8%-1.3%]) and perforation (.6% [95% CI, .4%-.9%]) were less common adverse events (Supplementary Fig. 2, available online at www.giejournal.org). None of the published studies compared the outcomes of all-cause and cancer-related mortality. A recent study reported the EAC-specific and all-cause mortality in BE patients undergoing RFA (n = 4982).[18] Among LGD patients (n = 1020), the adjusted all-cause mortality rate was 6.8 per 1000 person-years (95% CI, 3.4-10.1), and none of the patients died from EAC.

Certainty in the Evidence: For the outcome of disease progression, we evaluated the RCT studies separately from the observational studies. The 2 RCTs started as high-quality evidence, but we rated down for imprecision. For the observational studies the overall quality of evidence was very low after we rated down for significant heterogeneity, and even with very low quality of evidence, the magnitude and direction of the effect estimate strongly

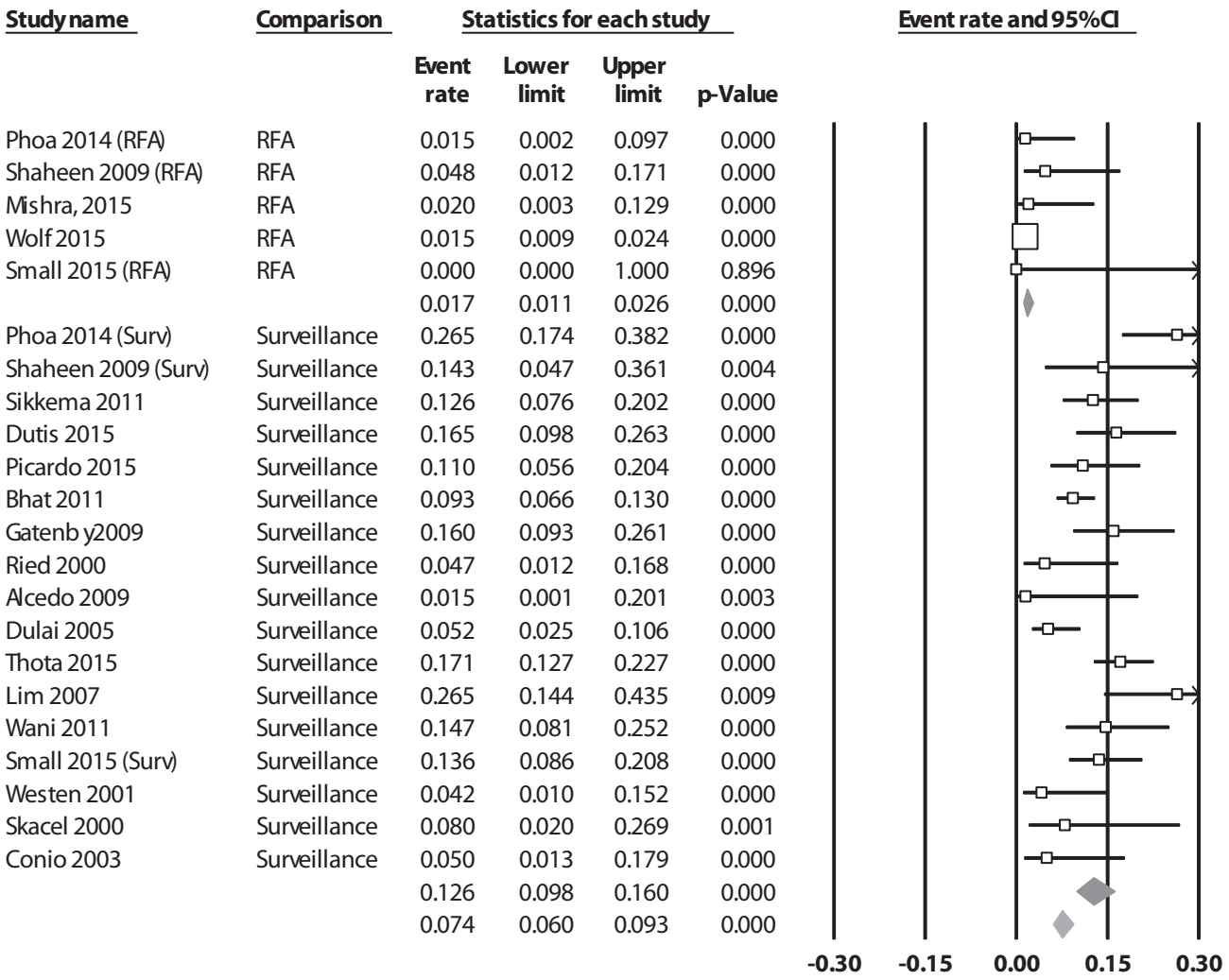

Figure 3. Forest plot highlighting the pooled cumulative rate of disease progression in Barrett's esophagus patients with low-grade dysplasia treated with radiofrequency ablation compared with those undergoing surveillance. *CI*, Confidence interval (Reprinted with permission from: Qumseya BJ, Wani S, Gendy S, et al. Disease progression in Barrett's low-grade dysplasia with radiofrequency ablation compared with surveillance: systematic review and meta-analysis. Am J Gastroenterol 2017;112:849-65).

supports the evidence from the 2 RCTs. For the outcome of adverse events, the quality of evidence was low.

Considerations: In absolute terms the risk of progression to HGD/EAC in BE patients with confirmed LGD (diagnosis confirmed by an expert/panel pathologists) was estimated as 25 per 100 patients in the surveillance arm over a follow-up duration of up to 84 months. Treating 100 patients with EET would lead to 21 fewer patients (95% CI, 11 fewer to 24 fewer) with HGD/EAC and 9 adverse events, mostly strictures that were believed to be treatable. The previously described data on cost-effectiveness also factored into this risk-to-benefit assessment.[30,31] There are limited to no data addressing the issue of patient preferences and burden and inconvenience associated with either of these treatment approaches.

Discussion: This recommendation places a high value on the potential benefit of EET on patient-important outcomes and a lower value on potential adverse effects and patient burden or inconvenience (based on feedback from the patient representative). The management of BE patients with LGD continues to generate a great deal of controversy.[3] Although the primary outcome of the evidence was RR of disease progression among BE patients with LGD treated with RFA compared with surveillance, similar beneficial effects were noted while assessing incidence rate of disease progression, progression to HGD only, and progression to EAC only. The panel recognized there were no direct data on the following patient-important outcomes: cancer-specific mortality and all-cause mortality. Additionally, panel members also discussed factors that supported a strategy of continued surveillance such as (1) unclear generalizability of above results as the safety and effectiveness have predominantly been shown at expert centers, (2) lack of clear diagnostic pathologic criteria for LGD and significant inter-observer variability among pathologists regarding the

diagnosis of LGD (though confirmation by an expert or panel of pathologists may mitigate this variability), (3) phenomenon of regression of LGD (inability to demonstrate LGD on subsequent endoscopy), and (4) surveillance of LGD, at least at expert centers, detects progressors at a stage amenable to EET and rarely required esophagectomy.[3] Evidence-based recommendations regarding surveillance intervals are not available. A recent expert review on LGD suggests that in patients with LGD undergoing surveillance rather than EET, surveillance should be performed every 6 months times 2 and then annually unless there is reversion to NDBE and that biopsy sampling should be obtained in 4 quadrants every 1 to 2 cm and of any visible lesions.[3]

Improved risk stratification with reliable predictors of progression has the potential to better define individuals at the highest risk of progression to HGD/EAC and thus most likely to benefit from EET. Given the importance of risk stratification, the panel members reviewed the results of studies assessing predictors of progression in BE patients with LGD.[3] BE patients with confirmed LGD (defined by confirmation of diagnosis by an expert pathologist or a panel of pathologists) are at a higher risk of progression to HGD/EAC. In addition, recent studies have identified persistent LGD (defined by the presence of LGD on 2 consecutive endoscopies) as a risk factor for progression in LGD patients.[3,34,43,44] With the exception of confirmed and persistent LGD, no other variable appears to be reproducibly associated with progression in LGD patients. In addition, although several biomarkers have been studied to improve risk stratification, none is ready for application in clinical practice. Effect estimates were explored based on stratifying patients into a high- or low-risk group based on confirmed and persistent LGD (Table 6). However, given the limited data, the panel decided against providing recommendations based on the risk group but emphasized the importance of confirmation of LGD (see Question 1) and highlighting the need for a shared decision-making approach with specific discussion with the patient about his or her values and preferences for treatment.

Question 2b*: *Comparing EET with surveillance, what is the optimal management strategy in BE patients with HGD?

Recommendation: In BE patients with HGD, we recommend EET compared with surveillance (strong recommendation, moderate quality evidence).

Summary of the Evidence: The primary outcomes of interest for this clinical question were differences in progression rates to cancer, cancer-specific and all-cause mortality, and adverse events (Table 7). A systematic review and meta-analysis was conducted to address this clinical question. A total of 1909 citations were identified, and 20 studies (including 2 RCTs) were included in the final analysis. Progression to EAC was assessed in 2 RCTs; Overholt et al[45] compared photodynamic therapy (PDT) versus surveillance (study follow-up, up to 43 months), and Shaheen et al[16] compared RFA versus surveillance in BE patients with HGD (study follow-up, up to 1 year). When fixed-effects models were used, the RR of disease progression in comparing EET with surveillance was .42 (95% CI, .24-.73; $P = .0002$) (Fig. 4). These results were supported by the body of indirect evidence that compared disease progression rates in patients treated with EET with those undergoing surveillance (2478 patients, number of progressors to EAC = 418). The cumulative risk of disease progression in the surveillance group was 34% (95% CI, 25.5%-43.8%) and in the EET group 7.4% (95% CI, 4.5%-11.7%) with a calculated RR of .22 (Fig. 5). Significant heterogeneity was noted, and funnel plots and the classic fail safe showed low risk of publication bias.

The outcome of adverse events for all patients undergoing RFA with or without EMR was informed by the recent systematic review and meta-analysis by Qumseya et al,[22] which included 37 studies (9200 patients) and reported a pooled rate of adverse events of 8.8% (95% CI, 6.5%-11.9%) related to RFA with or without EMR. Esophageal stricture formation was the most common adverse event (5.6% [95% CI, 4.2%-7.4%]). Bleeding (1% [95% CI, .8%-1.3%]) and perforation (.6% [95% CI, .4%-.9%]) were less common adverse events (Supplementary Fig. 2). A subanalysis addressing adverse events only in BE patients with HGD/intramucosal EAC showed a pooled rate of adverse events (10.6% [95% CI, 5.7%-19.1%]) that was similar to the overall adverse event rate (Fig. 6). Limited data address the outcomes of all-cause and cancer-related mortality. A recent study reported the EAC-specific and all-cause mortality in BE patients undergoing RFA (n = 4982).[18] Among HGD patients (n = 990), the adjusted all-cause mortality rate was 24.8 per 1000 person-years (95% CI, 12.1-37.4) and EAC-related mortality rate 2.0 per 1000 person-years (95% CI, .8-4.5).

Certainty in the Evidence: For the outcome of disease progression to EAC addressed by the 2 RCTs, the quality of evidence was rated down for imprecision given the wide CIs. Although the RCT by Overholt et al[46] compared PDT with surveillance, we did not rate down for indirectness. For the studies that provided indirect comparison in progression rates between patients treated with EET and those undergoing surveillance, the quality of evidence was low given that most were observational studies. The quality of evidence was rated down further for inconsistency. For the outcome of adverse events, the quality of evidence was low.

Considerations: For this recommendation the panel placed a high value on the potential benefit of EET on patient-important outcomes, specifically risk of progression to EAC and a lower value on potential adverse effects. Cost-effectiveness analyses, described earlier, clearly demonstrate that among BE patients with HGD, RFA was more effective and less costly than endoscopic surveillance.[30]

TABLE 7. GRADE evidence profile for Question 2b: comparing EET with surveillance, what is the optimal management strategy in BE patients with HGD and or EAC?

Quality assessment						
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
Progression to EAC comparing EET with surveillance-indirect estimates of rates among cohorts (cumulative rate of progression) follow-up: 4-84 months—critical						
2478 (20 observational studies)	Not serious	Serious*	Not serious	Not serious	None	⊕◯◯◯ VERY LOW
Progression to HGD/EAC: from RCT studies (cumulative rate of progression)—critical						
271 (2 RCTs)	Not serious	Not serious	Not serious	Serious†	None	⊕⊕⊕◯ MODERATE
Major adverse events including perforation, strictures, bleeding, pain, hospitalization—important						
9200 (37 studies)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕◯◯ LOW
7 studies (HGD/IMC)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕◯◯ LOW

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *EET*, endoscopic eradication therapy; *BE*, Barrett's esophagus; *HGD*, high-grade dysplasia; *EAC*, esophageal adenocarcinoma; *CI*, confidence interval; *RR*, relative risk; *LGD*, low-grade dysplasia; *RCT*, randomized control trial; *IMC*, intramucosal cancer; *RFA*, radiofrequency ablation.
*The I^2 was high ($I^2 = 83\%$), suggesting significant heterogeneity.
†There were few events and serious imprecision.

Discussion: Available evidence supports a strong recommendation for EET in the management of BE patients with HGD/intramucosal EAC compared with surveillance.

Question 3: Comparing EET with esophagectomy, what is the optimal management strategy in BE patients with HGD and intramucosal EAC?

Recommendation: In BE patients with HGD/intramucosal EAC, we recommend against surgery compared with EET (strong recommendation, very low-quality evidence).

Summary of the Evidence: The patient-important outcomes for this clinical question were differences in complete eradication rates of dysplasia/intramucosal EAC, recurrence rates, overall survival, EAC-related mortality, and adverse events. An existing systematic review and meta-analysis by Wu et al[46] was updated (794 studies were screened and 13 full-text articles were reviewed) to inform this question (Table 8).[23,47] Two studies were added to the final analysis for the 5-year survival data. There was no difference between the 2 treatment modalities for the endpoint of complete eradication of HGD/intramucosal EAC (RR, .96; 95% CI, .91-1.01). Recurrence rate of neoplasia was higher in the EET group (RR, 9.5; 95% CI, 3.26-27.75). There was no difference between the 2 groups with regard to overall survival (1-, 3-, and 5-year survival) and EAC-related mortality. For the important outcome of 5-year survival, there was no difference between the 2 groups, with an RR of .88 (95% CI, .74-1.04; Fig. 7). Patients undergoing EET had significantly lower rates of adverse events compared with esophagectomy (RR, .38; 95% CI, .20-.73).

Certainty in the Evidence: The evidence supporting this recommendation was provided by observational studies (retrospective single-institutional or population-based studies using the Surveillance, Epidemiology and End Results database) starting out as low quality of evidence. However, the quality of evidence was rated up to moderate for the endpoints of complete eradication, overall survival at 1 and 3 years, and major adverse events given the selection bias in the included studies where patients with multiple comorbid illnesses were more likely to undergo EET compared with esophagectomy and that accounting for all plausible confounding would actually reduce the demonstrated effect. The quality of evidence was very low for recurrence rates after EET and esophagectomy (rated down for imprecision because only 1 recurrence was seen in the surgery group) and overall survival at 5 years (rated down for inconsistency). Similarly, the quality of evidence for EAC-related mortality was rated down to very low given the sparse events in both groups.

Considerations: This recommendation places a high value on the potential adverse effects associated with esophagectomy as compared with EET. Adverse events related to esophagectomy include bleeding, anastomotic leakage, stenosis, prolonged hospitalization, and death. This analysis demonstrated a lower risk of major adverse events associated with EET (16 fewer per 100 adverse events compared with the esophagectomy). The adverse events related to EET were mostly bleeding, perforation, and stricture formation, as discussed above. The

TABLE 7. Continued

Summary of findings				
Study event rates (%)			**Anticipated absolute effects**	
With EET	**With surveillance**	**Relative effect (95% CI)**	**Risk with surveillance**	**Risk difference with EET**
182/1854 (9.8%)	236/624 (37.8%)	RR .22	Study population	
			10 per 100	8 fewer per 100
19/180 (10.6%)	24/91(26.4%)	RR .42 (.24-.73)	Study population	
			26 per 100	15 fewer per 100 (7 fewer to 20 fewer)
Overall adverse event rate across 37 studies was 8.8% (95% CI, 6.5%-11.9%). Treatment modality EET included RFA ± EMR. Stricture post-treatment most common adverse event 5.6% (95% CI, 4.2%-7.4%). Overall adverse event rate across 7 studies was 10.6% (95% CI, 5.7%-19.1%). Treatment modality EET included RFA ± EMR.			0 per 100 (rare) 0 per 100 (rare)	9 more per 100 (7 more to 12 more) 11 more per 100 (7 more to 12 more)

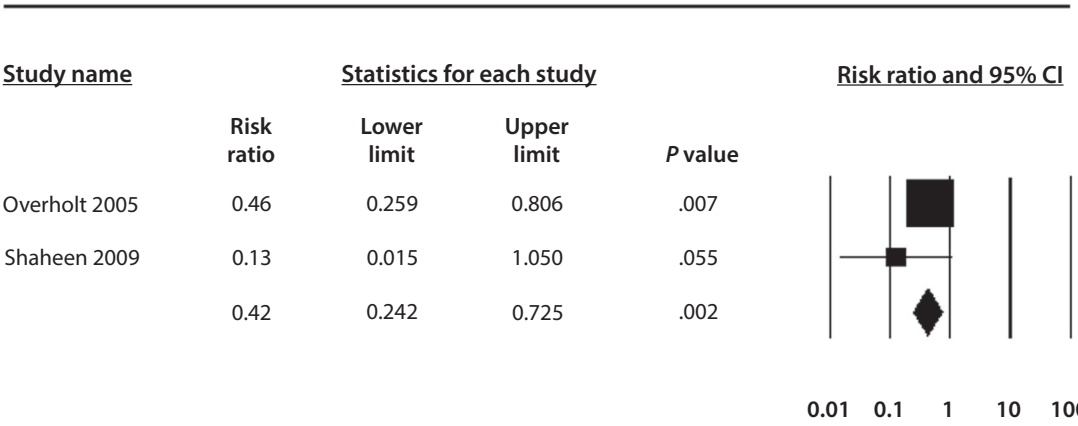

Figure 4. Forest plot with 2 randomized controlled trials comparing endoscopic eradication therapies (radiofrequency ablation and photodynamic therapy) with surveillance with the pooled relative risk of disease progression in Barrett's esophagus patients with high-grade dysplasia. *CI*, Confidence interval.

absolute risk of recurrence of neoplasia was minimally higher in the EET group with 2 more recurrences of neoplasia per 100 patients compared with the esophagectomy group. Limited data address the issue of patient values, preferences, and burden associated with either of these treatment approaches. As highlighted earlier, a study assessing the influence of EET and esophagectomy on quality of life showed that patients undergoing EET reported a greater fear of recurrence.[29]

Discussion: Given the high tumor-free survival rates, esophagectomy was the standard treatment for BE patients with HGD and intramucosal EAC, and all other therapies were compared with this modality.[23] Esophagectomy, especially in patients in whom the cancer had not yet penetrated the muscularis mucosa, is associated with a high 5-year survival rate.[48] However, this treatment approach is associated with an operative mortality of 2% and a high morbidity rate seen even at high-volume centers.[48,49] The basic premise of EET is that BE patients with HGD and intramucosal EAC have a very low risk of lymph node metastasis (0% in patients with HGD and up to 2% in patients with intramucosal EAC).[50] The effectiveness and safety profile of EET in BE-related neoplasia has been well established.[14-22] However, comparative studies between esophagectomy and EET are limited. Unfortunately, no RCT(s) was available to provide

Study name	Subgroup within study	Comparison	Event rate	Lower limit	Upper limit	p-Value
Anders, 2014	EET	Paper	0.063	0.016	0.218	0.000
Kommineni, 2015	EET	Abstract	0.035	0.013	0.090	0.000
Nurkin, 2013	EET	Paper	0.028	0.004	0.173	0.000
Oliphant, 2015	EET	Abstract	0.181	0.108	0.287	0.000
Qumseya, 2013	EET	Paper	0.019	0.003	0.124	0.000
Ramay, 2016	EET	Abstract	0.032	0.005	0.196	0.001
Sharma, 2000	EET	Paper	0.020	0.001	0.251	0.006
Velanovich, 2009	EET	Paper	0.038	0.002	0.403	0.026
Wolf, 2015	EET	Paper	0.084	0.068	0.103	0.000
Zemlyak, 2012	EET	Paper	0.056	0.003	0.505	0.052
Lyday, 2010	EET	Paper	0.012	0.001	0.164	0.002
Overholt, 2005 (PDT)	EET	Paper	0.130	0.084	0.198	0.000
Shaheen, 2009 (RFA)	EET	Paper	0.024	0.003	0.151	0.000
Verbeek, 2012 (RFA)	EET	Paper	0.221	0.175	0.276	0.000
			0.074	0.045	0.117	0.000
Reid, 2000	Surveillance	Paper	0.592	0.479	0.696	0.110
Weston, 2000	Surveillance	Paper	0.267	0.104	0.533	0.083
Abela, 2008	Surveillance	Paper	0.222	0.056	0.579	0.118
Ajumobi, 2009	Surveillance	Paper	0.071	0.004	0.577	0.081
Alcedo, 2008	Surveillance	Paper	0.333	0.043	0.846	0.571
Kahn, 2015	Surveillance	Abstract	0.306	0.223	0.404	0.000
Overholt, 2005 (Surv)	Surveillance	Paper	0.286	0.192	0.402	0.001
Shaheen, 2009 (Surv)	Surveillance	Paper	0.190	0.073	0.412	0.009
Verbeek, 2012 (Surv)	Surveillance	Paper	0.399	0.347	0.453	0.000
			0.340	0.255	0.438	0.002
			0.199	0.153	0.256	0.000

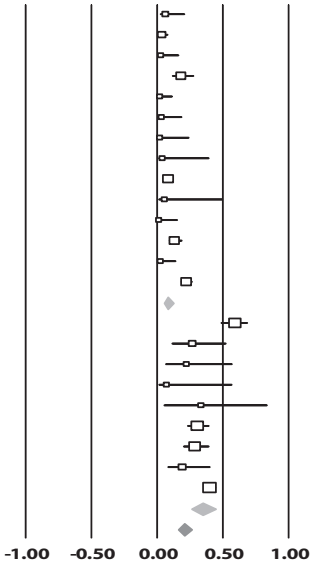

Figure 5. Forest plot of studies providing an indirect comparison of cumulative rates of disease progression between Barrett's esophagus patients with high-grade dysplasia treated with radiofrequency ablation compared with those undergoing surveillance. *CI*, Confidence interval.

Study name	Subgroup within study	Comparison	Time point	Event rate	Lower limit	Upper limit	p-Value
Gondrie, J.J._2	Prospective	Paper	2008	0.091	0.013	0.439	0.028
Ganz, R.A.	Retrospective	Paper	2008	0.007	0.001	0.048	0.000
Pouw, R.	Prospective	Paper	2010	0.125	0.041	0.324	0.002
McEwan, H.C.	Prospective	Abstract	2012	0.088	0.047	0.161	0.000
Perry, K.A.	Retrospective	Paper	2014	0.028	0.002	0.322	0.013
Strauss, A.C.	Retrospective	Paper	2014	0.222	0.115	0.385	0.002
Phoa, K.Y._2	Prospective	Paper	2015	0.189	0.131	0.265	0.000
				0.146	0.111	0.189	0.000

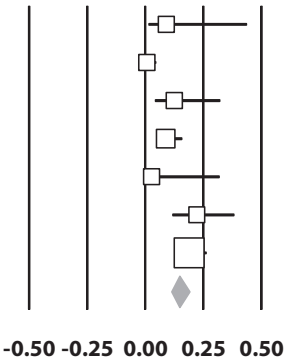

Figure 6. Forest plot with studies reporting adverse events in Barrett's esophagus patients with high-grade dysplasia/intramucosal esophageal adenocarcinoma treated with radiofrequency ablation with or without EMR. *CI*, Confidence interval.

conclusive evidence regarding superiority of 1 of these 2 treatment modalities, and no such trial is expected in the foreseeable future.

The effectiveness and safety of EET and adverse events associated with esophagectomy were important considerations for this recommendation. Another important determinant was the higher recurrence rate of neoplasia associated with EET compared with esophagectomy. Recurrence of intestinal metaplasia and neoplasia after EET was addressed in 2 recent systematic reviews and meta-analyses.[51,52] These studies demonstrated that >95% of all recurrences were successfully treated with EET, adding credence to use of EET for the management of BE-related neoplasia patients. The panel members also accounted for the multiple endoscopy sessions required to achieve the goal of EET: complete eradication of dysplasia and CE-IM.[14,22,41] Most patients achieve CE-IM within 3 ablative therapy sessions.[53,54]

Esophagectomy is considered as the treatment of choice for patients with submucosal cancer (T1b sm2-3 disease), poorly differentiated cancer, and cancer associated with lymphatic or vascular infiltration given the high risk of lymph node metastasis (at least 20%).[2,23,55] Long-term survival data in patients undergoing EET using contemporary treatment modalities and identification of stage T1b

EAC patients who may be able to undergo EET and achieve comparable outcomes with esophagectomy should be addressed in future studies. Studies identifying patient and provider-specific determinants of optimal outcomes,[14,41] and studies on patient preferences and quality of life should be a research priority.

Question 4: What is the role of EMR in BE patients with a visible lesion detected during screening or surveillance?

Recommendation: In BE patients referred for EET, we recommend endoscopic resection of all visible lesions compared with no endoscopic resection of visible lesions (strong recommendation, moderate quality evidence).

Summary of the Evidence: The patient-important outcomes for this clinical question were the difference in progression rates to cancer among BE patients who underwent EMR of visible lesions (typically described as areas with nodularity, ulceration, plaques, areas of depression, or mucosal discoloration) compared with those who did not undergo EMR of visible lesions (important outcome), proportion of patients with a change in diagnosis in grade of dysplasia and those with a change in management plan as a result of EMR (critical outcome), and adverse events related to EMR (critical outcome). There were no RCTs that addressed these outcomes; hence, indirect comparisons from observational studies were used to provide this recommendation. The evidence profile for this clinical question is summarized in Supplementary Table 1 (available online at www.giejournal.org).

A systematic review and meta-analysis was conducted to address the question of change in diagnosis based on EMR. Of the 1436 screened studies, 17 were reviewed in full-text format and 14 were included in the final analysis. These studies included a total of 1116 patients with a total number of 449 events. When a random-effects model was used, EMR resulted in a change in the pathologic diagnosis in 39% (95% CI, 34%-45%) of all patients. Most of this change was associated with upgrading of grade of dysplasia/neoplasia (Fig. 8). Review of published literature identified no studies comparing progression rates and adverse events between patients undergoing EMR of visible lesions with those not undergoing EMR for visible lesions.

The safety of EMR in BE patients has been established in multiple studies.[22,56,57] In a cohort study of 681 patients treated at a tertiary care center, a total of 1388 endoscopic procedures were performed, and 2513 EMRs were performed using the cap or multiband mucosectomy technique.[56] No perforations were noted, bleeding post-EMR was seen in 8 patients (1.2%: 7 treated endoscopically and 1 required surgery), and strictures were reported in 7 patients (1%). Another large cohort study that included 1096 consecutive patients with intramucosal EAC who underwent 2687 EMR procedures reported a major adverse event rate of 1.5% (15 patients: major bleeding 14, perforation 1, stricture 13), and all adverse events were managed endoscopically.[57] The outcome of adverse events for patients undergoing EET was also addressed using a recent systematic review and meta-analysis.[22] Although the pooled rate of all adverse events with EET (RFA with or without EMR) was 8.8% (95% CI, 6.5%-11.9%), in studies that compared RFA with versus without EMR, the adverse event rate was significantly higher for RFA with EMR (RR, 4.4; $P = .015$).

Certainty in the Evidence: For the outcome of change in diagnosis in grade of dysplasia, the quality of evidence was rated up for large effect; the consensus threshold was 20% among the panel members. There was no risk of bias, inconsistency, indirectness, imprecision, or publication bias.

Considerations: This recommendation placed a high value on the role of EMR in leading to change in diagnosis and the potential to impact patient management and outcomes. The benefits of EMR include assessment of histologic depth of invasion to improve confidence of clinical decisions made for patients with BE-related dysplasia and intramucosal EAC with EET.[58] By altering the diagnosis, EMR has the potential to impact the management plan (although the impact of EMR on the management plan was not consistently reported across published studies). Under-diagnosis or over-diagnosis may have substantial deleterious consequences for the patient. For example, a patient without cancer may undergo unnecessary esophagectomy or patients with submucosal invasive EAC may incorrectly be treated with EET instead of surgery. Given the importance and magnitude of the effect on patient management and low risk of adverse events, the panel members supported a strong recommendation for this clinical question.

Discussion: EMR plays a critical role as a part of the armamentarium for Barrett's EET and has evolved into an important diagnostic/staging and therapeutic tool in the management of BE-related neoplasia patients.[3,59] The value of EMR as a diagnostic/staging tool is enhanced by the provision of larger and deeper tissue specimens (resection extends to muscularis mucosa and submucosal level in most EMR specimens) compared with biopsy specimens, with limited distortion allowing for an accurate assessment of depth of neoplastic involvement and adequacy of resection.[3] As highlighted above, a change in diagnosis in nearly 40% of patients was noted in BE patients undergoing EMR for visible lesions. In addition to the change in diagnosis, provision of a larger specimen (with EMR) to pathology results in an improvement in interobserver agreement among pathologists compared with biopsy specimens as demonstrated in at least 2 studies.[38,60] The recommendation of performing EMR of all visible lesions (no matter how subtle) is consistent with other recent guideline documents, quality indicator documents, and current clinical practice.[2,3,14,41,61]

TABLE 8. GRADE evidence profile for Question 3: comparing EET with esophagectomy, what is the optimal management strategy in BE patients with dysplasia (HGD and LGD) and intramucosal EAC?

Quality assessment						
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
Complete eradication of HGD/IMC (absence of HGD/EAC from biopsy specimen and/or EMR specimen on 2 successive EGDs)—important						
575 (5 observational studies)	Not serious	Not serious*	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕◯ MODERATE
Recurrence rate—important						
870 (7 observational studies)	Not serious	Not serious	Not serious	Serious†	None	⊕◯◯◯ VERY LOW
Overall survival at 1 year—important						
202 (2 observational studies)	Not serious	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕◯ MODERATE
Overall survival at 3 years—important						
215 (2 observational studies)	Not serious	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕◯ MODERATE
Overall survival at 5 years—important						
1506 (5 observational studies)	Not serious	Serious‡	Not serious	Not serious	None	⊕◯◯◯ VERY LOW
Neoplasia-related mortality—critical						
774 (6 observational studies)	Not serious	Not serious	Not serious	Serious§	None	⊕◯◯◯ VERY LOW
Major adverse events (including death, bleeding, stenosis, anastomotic leakage, and other)—critical						
870 (7 observational studies)	Not serious	Not serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕◯ MODERATE

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *EET*, endoscopic eradication therapy; *BE*, Barrett's esophagus; *HGD*, high-grade dysplasia; *EAC*, esophageal adenocarcinoma; *CI*, confidence interval; *RR*, relative risk; *LGD*, low-grade dysplasia; *RCT*, randomized control trial; *IMC*, intramucosal cancer; *RFA*, radiofrequency ablation.

*I^2 was 48%; however, we did not rate down for inconsistency.

†We rated down for imprecision because of very few events in the surgery arm (1 recurrence).

‡We rated down for inconsistency because I^2 was 82%, indicating considerable heterogeneity among studies, with some studies showing a benefit and others demonstrating no benefit.

§We rated down for imprecision because of sparse events (1 in each arm).

Question 5: What is the role of ablation of the remaining BE segment after EMR of all visible lesions in BE patients referred for EET?

Recommendation: In BE patients with visible lesions who undergo EMR, we suggest ablation of remaining Barrett's segment compared with no ablation (conditional recommendation, low quality evidence).

Summary of the Evidence: The critical outcomes for this question included differences in progression rate to cancer along with comparison of recurrence rates between the 2 groups. Important outcomes included differences in progression rate to a combined endpoint of HGD/EAC and adverse events. A systematic review was conducted for this clinical question (1799 studies identified from literature search, 17 reviewed in full text format and 2 studies met inclusion criteria).[19,62]

Supplementary Table 2 (available online at www.giejournal.org) is a summary of the evidence that informed this recommendation. Pech et al[19] compared rates of metachronous neoplasia in BE patients with HGD and intramucosal EAC treated with EMR alone with those treated with ablative therapies (PDT and argon plasma coagulation [APC]) after EMR. In patients receiving ablative therapies of the remaining BE segment, the metachronous neoplasia rate was significantly lower compared with patients receiving no ablation (16.5% vs 29.9%, $P = .0014$). Similar results were noted in the assessment of late occurrence of metachronous neoplasia (≥24 months after achieving complete remission from neoplasia), with lower

TABLE 8. Continued

Summary of findings				
Study event rates (%)			Anticipated absolute effects	
With esophagectomy	With EET	Relative effect (95% CI)	Risk with esophagectomy	Risk difference with EET
237/241 (98.3%)	314/334 (94.0%)	RR .96 (.91-1.01)	98 per 100	4 fewer per 100 (9 fewer to 1 more)
1/360 (.3%)	58/510 (11.4%)	RR 9.50 (3.26-27.75)	0 per 100	2 more per 100 (1 more to 7 more)
100/102 (98.0%)	97/100 (97.0%)	RR .99 (.94-1.03)	98 per 100	1 fewer per 100 (6 fewer to 3 more)
92/99 (92.9%)	111/116 (95.7%)	RR 1.03 (.96-1.10)	93 per 100	3 more per 100 (4 fewer to 9 more)
465/973 (47.8%)	324/533 (60.8%)	RR .88 (.74-1.04)	48 per 100	6 fewer per 100 (12 fewer to 2 more)
1/311 (.3%)	1/463 (.2%)	RR .00 (–.02 to .01)	0 per 100	0 fewer per 100 (0 fewer to 0 fewer)
90/360 (25.0%)	66/510 (12.9%)	RR .38 (.20-.73)	25 per 100	16 fewer per 100 (20 fewer to 7 fewer)

rates in the ablation group compared with the no ablation group (18% vs 32%, $P = .0053$). Lack of ablation of the remaining BE was a significant predictor of recurrence after EMR of BE-related neoplasia (RR, 2.5; 95% CI, 1.52-3.85; $P = .0003$). Manner et al[62] showed similar results in a RCT that compared EMR plus APC of the residual BE segment versus EMR alone. This trial was stopped early for benefit and showed that the risk of recurrence was significantly higher in the EMR alone group compared with the EMR plus APC group (36.7% vs 3%) at a follow-up period of 24 months.

Additionally, a recent multicenter study of BE patients treated with RFA with and without EMR used a logistic regression to evaluate factors associated with mortality.[18] On multivariate analysis, after adjustment for race, gender, and time in the study, predictors of mortality included increasing age (OR, 1.1/year) and increasing histologic grade (OR: LGD, 1.3; HGD, 2.7; intramucosal EAC, 2.1; and invasive EAC, 12). Achieving CE-IM was protective with an OR for mortality of .4 (95% CI, .3-.6). This evidence indirectly supports the need to ablate the remaining BE segment. The outcome of adverse events for patients undergoing RFA with or without EMR was addressed using a recent systematic review and meta-analysis.[22]

Certainty in the Evidence: Although the study by Pech et al[19] included noncontemporary ablative therapies such as PDT (contemporary therapies include RFA and cryotherapy), the panel members did not rate down for indirectness. The RCT by Manner et al[62] was rated down

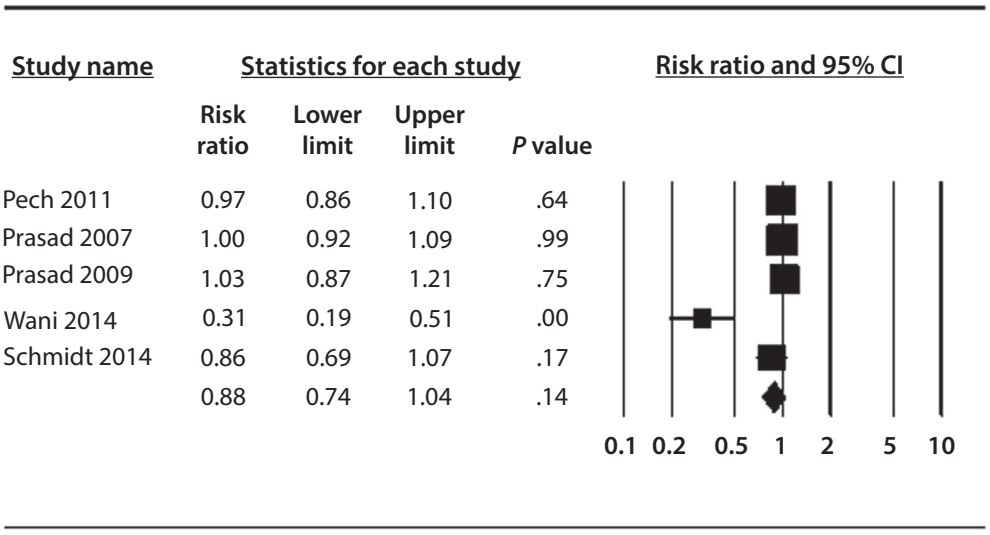

Figure 7. Forest plot of studies comparing overall 5-year survival between Barrett's esophagus patients with high-grade dysplasia/intramucosal cancer treated with endoscopic eradication therapy and esophagectomy. *CI*, Confidence interval.

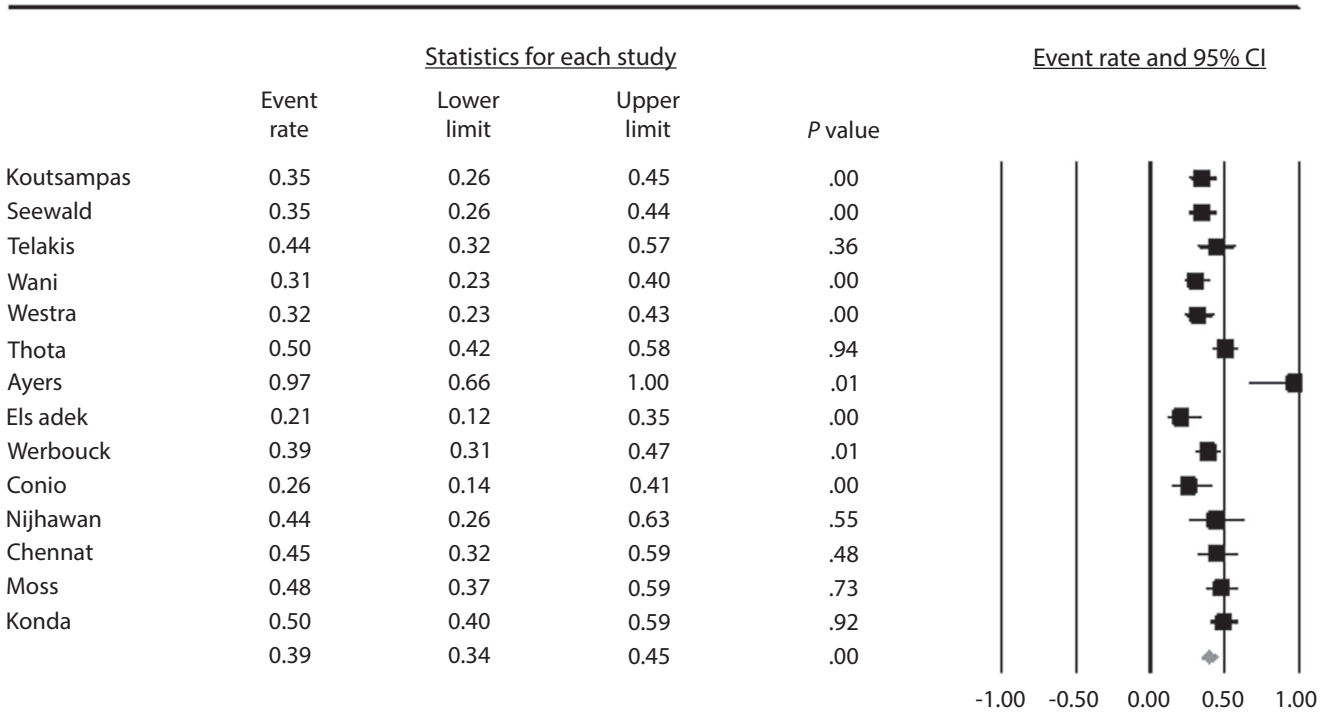

Figure 8. Forest plot of studies reporting the change in diagnosis based on EMR of visible lesions in Barrett's esophagus patients. *CI*, Confidence interval.

for risk of bias, because the study was stopped early, and imprecision, given the few events noted. The overall quality of evidence across studies was low.

Considerations: This recommendation placed a high value on the potential benefits and a low value on potential adverse events including burden and cost. The benefits include reduction in the risk of metachronous neoplasia and thus the potential to reduce the risk of progression to invasive EAC. Multiple endoscopies are required to achieve the CE-IM, creating a burden to patients related to the risks of adverse events, discomfort, and time required to complete treatment. On the other hand, the risk of metachronous neoplasia and progression to invasive EAC may contribute to patient anxiety. Limited data

address the issue of patient values, preferences, and burden associated with either of these treatment approaches.

Discussion: Available data support the current paradigm and goal of EET, which is CE-IM defined as the absence of endoscopically visible BE and all surveillance biopsy specimens demonstrating no intestinal metaplasia.[22] Based on the overall low quality of evidence, the panel members provided a conditional recommendation for ablation of the remaining Barrett's segment after performing EMR of all visible lesions. This recommendation is consistent with those provided by recent guidelines and quality indicator documents.[2,3,14,41,61]

Question 6: Comparing EMR of visible lesions followed by ablation of the remaining BE segment with EMR of the entire BE segment, what is the optimal EET approach in BE patients with dysplasia or intramucosal EAC referred for EET?

Recommendation: In BE patients with dysplasia and mucosal EAC referred for EET, we recommend against routine complete endoscopic resection of the entire Barrett's segment compared with endoscopic resection of the visible lesion followed by ablation of the remaining Barrett's segment (strong recommendation, very low-quality evidence).

Summary of the Evidence: The patient-important outcomes for this clinical question were difference in progression rates to HGD/EAC, difference in rates of recurrence, and adverse events, specifically rates of stricture and bleeding (see evidence profile presented in Table 9). This recommendation was informed by a recent systematic review and meta-analysis by Desai et al[63] published in 2017. This meta-analysis included 774 patients from 9 studies of EMR of visible lesions followed by RFA of the remaining Barrett's segment (EMR+RFA) and 751 patients from 11 studies of describing complete EMR of the entire Barrett's segment (cEMR). One additional study of EMR+RFA was included in the analysis of adverse events (for a total of 863 patients). Because of the limited head-to-head studies comparing these 2 strategies, the authors extracted data from prospective and retrospective cohort studies (including RCTs) and calculated pooled estimates of effect across studies for each of the efficacy and adverse events outcomes. The authors also conducted an indirect comparison of these 2 strategies using mixed logistic regression models. Across 9 studies of EMR+RFA (n = 774), the pooled estimate for complete eradication of neoplasia (HGD/EAC) was 93.4% (95% CI, 90.8%-96.1%; I^2 = 46%). Across 11 studies of cEMR, (n = 747) the pooled estimate for complete eradication of neoplasia (HGD/EAC) was 94.9% (95% CI, 92.2%-97.5%; I^2 = 72%) (Supplementary Fig. 3, available online at www.giejournal.org). Although the following was not included in our evidence profile as a critical or important outcome, the authors also analyzed pooled estimates of rates of CE-IM. In the EMR+RFA group the pooled rate was 73.1% (95% CI, 63%-83.1%; I^2 = 93.3%) and in the cEMR group, 79.6% (95% CI, 75.2%-84.1%; I^2 = 52.48%) (Supplementary Fig. 3).

Based on indirect comparisons of pooled estimates, no significant differences between these 2 strategies were detected for complete eradication of neoplasia or CE-IM. However, significant differences in rates of adverse events were noted. Based on indirect comparison, cEMR was more likely to cause strictures (OR, 4.73; 95% CI, 1.61-13.85; P = .005), bleeding (OR, 6.88; 95% CI, 2.19-21.62; P = .001), and perforations (OR, 7.00; 95% CI, 1.56-31.33; P = .01) compared with EMR+RFA. There were no differences between the 2 groups with regards to recurrence rates of EAC (pooled estimate: EMR+RFA, 1.4% [95% CI, .2%-2.7%; I^2 = 32%] vs cEMR, .7% [95% CI, .1%-1.4%, I^2 = 0%]) or dysplasia (pooled estimate: EMR+RFA, 2.6% [95% CI, .5%-4.7%; I^2 = 35.3%] vs cEMR, 3.3% [95% CI, 1.4%-5.2%, I^2 = 51%]).

Certainty in the Evidence: Across outcomes, the overall certainty was very low. There was concern about heterogeneity across the studies for both EMR+RFA and cEMR pooled effect estimates. Additionally, there were concerns about imprecision because of few events for the harm outcomes, and, finally, publication bias was suspected based on the Eggers regression test across the cEMR studies. An indirect comparison was performed comparing the pooled estimates for EMR+RFA and cEMR studies using mixed logistic regression, which added more uncertainty to the body of evidence comparing EMR+RFA with cEMR. Hence, the overall quality of evidence was very low.

Considerations: Despite the overall very low-quality evidence, the panel members made a strong recommendation against routine cEMR for BE patients with dysplasia. This recommendation placed a high value on avoiding adverse events. With relatively similar benefits regarding complete eradication of neoplasia and intestinal metaplasia, there were many more adverse events among patients undergoing cEMR compared with patients who underwent EMR+RFA, and thus the panel placed a high value on avoiding harms. There were limited data on cost/resource use and patient preferences to guide this clinical question.

Discussion: Given the lack of difference in outcomes (complete eradication and recurrence rates) between the 2 approaches and significantly higher adverse events associated with cEMR, the panel members agreed that performing EMR of all visible lesions followed by ablation of the remaining BE segment was the preferred strategy in patients undergoing EET. The main advantage of cEMR is the provision of true histology for the entire BE segment. The panel members acknowledge that the strategy of cEMR may be acceptable in a select group of patients. Whether there is a subgroup of BE-related neoplasia patients (multifocal disease, diffuse nodularity, select cases with short-segment BE) more likely to benefit from cEMR needs to be evaluated in future studies. Improvement in prevention of stricture formation post-cEMR is also

TABLE 9. GRADE evidence profile for Question 6: comparing EMR of visible lesions followed by ablation of remaining BE segment with EMR of entire BE segment, what is the optimal EET approach in BE patients with dysplasia?

Quality assessment						
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
Complete eradication of HGD/EAC when comparing EMR + RFA (9 observational studies) vs cEMR (11 observational studies): indirect comparison						
1521	Not serious	Serious*	Not serious	Not serious	Publication bias strongly suspected†	⊕◯◯◯ VERY LOW
Recurrence of HGD/EAC when comparing EMR + RFA vs cEMR: no studies						
Strictures rates when comparing EMR + RFA (12 observational studies) vs cEMR (11 observational studies): indirect comparison						
1607	Not serious	Serious‡	Not serious	Serious§	Publication bias strongly suspected†	⊕◯◯◯ VERY LOW
Bleeding rates when comparing EMR + RFA (12 observational studies) vs cEMR (11 observational studies): indirect comparison						
1614	Not serious	Serious¶	Not serious	Serious§	Publication bias strongly suspected†	⊕◯◯◯ VERY LOW

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *BE*, Barrett's esophagus; *EET*, endoscopic eradication therapy; *RFA*, radiofrequency ablation; *cEMR,* complete EMR; *OR*, odds ratio; *CI*, confidence interval; *HGD, high-grade dysplasia; EAC*, esophageal adenocarcinoma.
*Significant heterogeneity was noted for the pooled estimate across the EMR + RFA studies (I^2 = 46%) and across the cEMR studies (I^2 = 72%).
†Publication bias was noted by Desai et al[64] using Eggers regression test for the cEMR studies.
‡Significant heterogeneity noted for the pooled estimate across the EMR + RFA studies (I^2 = 59.4%) and across the cEMR studies (I^2 = 96.4%).
§Because of few events and failure to attain optimal information size, we rated down for imprecision across the EMR + RFA and cEMR studies.
¶Significant heterogeneity noted for the pooled estimate across the cEMR studies (I^2 = 69.4%).

required before this treatment strategy can be recommended as a primary treatment modality.[51]

Question 7: After achieving CE-IM, what is the role of surveillance endoscopy?

Recommendation: In BE patients with dysplasia who have achieved CE-IM after EET, we suggest surveillance versus no surveillance (conditional recommendation, very low-quality evidence).

Summary of the Evidence: The primary outcomes for this clinical question were recurrence rates of intestinal metaplasia and neoplasia, progression rates to cancer, and EAC-specific and all-cause mortality between patients enrolled in surveillance programs after achieving CE-IM compared with those who are not. The outcome of recurrence of intestinal metaplasia and neoplasia was addressed using evidence from a recent systematic review and meta-analysis by Fujii-Lau et al.[51] This study aimed to determine the incidence of recurrent intestinal metaplasia and dysplasia after achieving CE-IM using treatment modalities that included RFA and EMR. From a total of 3311 identified studies, full texts from 144 studies were reviewed, and 39 studies (25 RFA, 13 stepwise complete EMR, 2 combined) were included in the final analysis. The pooled incidence rate of any recurrence was 7.5 (95% CI, 6.1-9.0) per 100 patient-years (Supplementary Fig. 4, available online at www.giejournal.org). The pooled incidence rate of intestinal metaplasia recurrence was 4.8 (95% CI, 3.8-5.9) per 100 patient-years and dysplasia recurrence rate was 2.0 (95% CI, 1.5-2.5) per 100 patient-years. Significant heterogeneity between studies was identified (I^2 = 86) with no evidence of publication bias. A jackknife sensitivity analysis removing 1 study at a time did not meaningfully change the results. No data evaluated the impact of surveillance on progression rates to EAC, all-cause mortality, and EAC-related mortality after assessing the evidence.

Certainty in the Evidence: The quality of evidence was rated as very low, given the significant heterogeneity in studies reporting this outcome.

Considerations: The overall benefits and harms were important drivers for this recommendation. The potential adverse events of an active management strategy of routine endoscopic surveillance after achieving CE-IM include those associated with standard upper endoscopy with biopsy sampling and EET for management of recurrence of intestinal metaplasia and dysplasia (discussed above). The benefits include early detection of neoplasia and the potential to reduce the risk of progression to invasive EAC (although not demonstrated in any prospective trials). In addition, endoscopy is associated with added costs and creates a moderate burden to patients related to discomfort and time off work. The lack of surveillance and monitoring may contribute to patient anxiety. Limited data address the issue of patient values, preferences, and burden associated with either of these treatment approaches.

Discussion: Although the effectiveness of EET has been demonstrated, variable rates of recurrence of intestinal metaplasia and dysplasia have been reported after EET. A reliable estimate of the risk of recurrence after achieving

TABLE 9. Continued

Summary of findings				
Study event rates (%)		Relative effect: OR comparing cEMR with EMR + RFA (95% CI)	Anticipated absolute effects	
With EMR of visible lesions followed by ablation of BE (EMR + RFA)	With complete EMR of entire BE (cEMR)		Risk with EMR of visible lesions followed by ablation of BE (EMR + RFA)	Risk difference with complete EMR of entire BE (cEMR)
717/774 (92.6%)	699/747 (93.6%)	OR 1.33 (0.56 to 3.15)	93 per 100	2 more per 100 (5 fewer to 5 more)
88/863 (10.2%)	268/744 (36.0%)	OR 4.73 (1.61-13.85)	10 per 100	25 more per 1000 (5 more to 51 more)
15/863 (1.7%)	59/751 (7.9%)	OR 6.88 (2.19-21.62)	2 per 100	9 more per 100 (2 more to 26 more)

CE-IM, as highlighted above, is critical in the education of physicians and patients before embarking on EET, determining cost-effectiveness of EET, and establishing surveillance guidelines (duration and frequency of surveillance endoscopy).[51,52] Despite the lack of comparative data assessing the impact of surveillance endoscopy in patients achieving CE-IM, a recommendation of surveillance was provided given the risk of recurrence after achieving CE-IM. The panel members also agreed that patients in whom the goal of EET is to achieve complete eradication of dysplasia (select few patients) should also be enrolled in surveillance programs after achieving this endpoint.

Several issues remain unresolved even after a critical assessment of the evidence. Substantial heterogeneity noted in the recurrence rates could not be accounted for in the published analyses, and potential factors contributing to this heterogeneity include patient characteristics, variation in the baseline histology (proportion of patients with HGD/intramucosal EAC), EET treatment techniques and protocols, endoscopic surveillance intervals, surveillance biopsy protocols, confirmation of diagnosis by expert pathology review, differences in acid suppressive regimens, and variability in definition of recurrence. Recurrence of intestinal metaplasia or neoplasia is defined by the presence of intestinal metaplasia on surveillance biopsy specimens in the presence or absence of endoscopically visible BE after achieving CE-IM.[22] Although the number of endoscopies with negative biopsy specimens required to achieve CE-IM is not standardized (CE-IM defined by 1 or 2 consecutive negative endoscopies), no difference in recurrence rates have been reported based on the definition of CE-IM.[51,53] Available data do not allow for a time-to-event analysis accounting for individual patient data and patients lost to follow-up. Although the temporality of recurrence after achieving CE-IM cannot be established with the available reports, recent reports suggest that most recurrences are reported within the first 3 years after achieving CE-IM.[53,54] A limited number of studies report on the risk factors associated with recurrence (ongoing reflux and presence of erosive esophagitis, older age, nonwhite race, smoking, obesity, pretreatment BE length, number of EET sessions), and these associations need to be explored and confirmed in future studies.[51,53,54,64-66]

Surveillance intervals suggested by current guidelines are largely driven by expert opinion and low quality evidence.[2,14] An initial endoscopic examination at 3 to 6 months after CE-IM is achieved is suggested followed by surveillance intervals based on pretreatment histology. For patients with baseline diagnosis of HGD, surveillance endoscopies every 3 months in the first year after CE-IM followed by endoscopies every 6 months in year 2 followed by yearly endoscopies has been suggested. For patients with LGD who have achieved CE-IM, the most recent American Gastroenterological Association guidelines suggest surveillance every year for 2 years and then every 3 years thereafter.[3] Consistent with recent guidelines and consensus documents, the panel agreed that histology is required for confirmation of recurrent intestinal metaplasia or neoplasia.[2,14] The technique for surveillance biopsy sampling after achieving CE-IM has not been

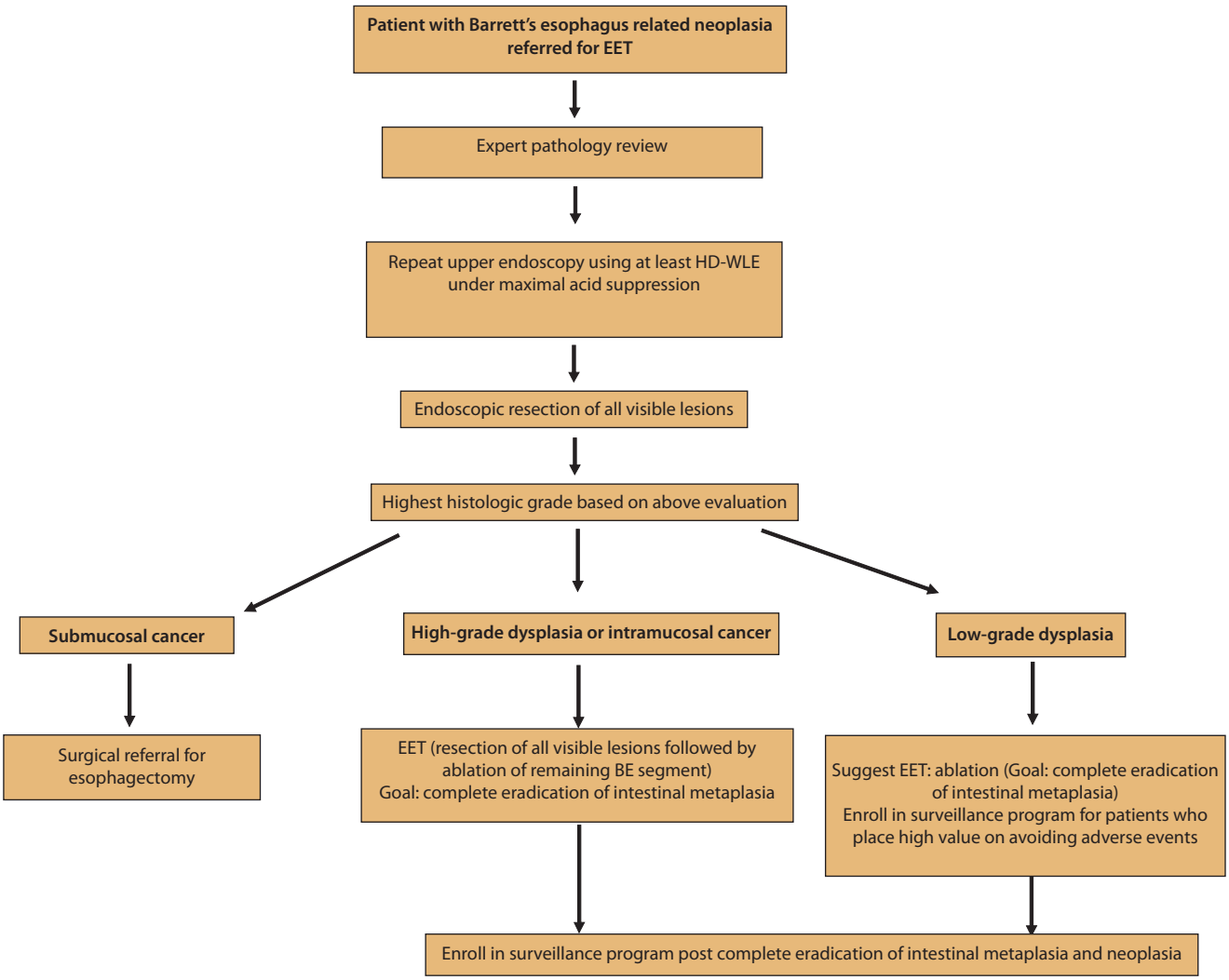

Figure 9. Decision tool with an algorithmic approach to management of Barrett's esophagus patients referred for endoscopic eradication therapy. *EET*, Endoscopic eradication therapy; *BE*, Barrett's esophagus.

standardized. The biopsy protocol of obtaining biopsy specimens in 4 quadrants every 2 cm throughout the length of original BE segment and any visible columnar mucosa/lesion has been suggested.[3] The panel members reviewed recent data suggesting the lack of additional yield from biopsy specimens obtained >2 cm from the gastroesophageal junction in the absence of any visible lesion in the neosquamous epithelium.[67]

The importance of medical antireflux therapy, with a goal of minimizing the frequency of reflux symptoms, achieving the absence of esophagitis on endoscopy, and potentially reducing the risk of recurrence, is critical in the management of patients after achieving CE-IM.[2,14,54] A recent observational study demonstrated that EET with a structured reflux management protocol achieved a high rate of CE-IM with a significantly lower rate of recurrence after EET (recurrence of IM, 4.8%; dysplasia, 1.5%) compared with published literature.[54]

FUTURE DIRECTIONS

Systematic review of the literature related to EET in BE patients identified several knowledge gaps. Given the significant interobserver variability among pathologists, there is a need for international standardization and validation of histologic criteria (especially for LGD), creation of a uniform reporting system, and training among pathologists.[3] Limited data exist on the extent of training required to perform EET, and a formal determination of what constitutes "competency" in EET by using a validated competency assessment tool is required.[14,68-70] Experts suggest that EET practitioners need to (1) demonstrate expertise in the use of high-definition white-light endoscopy and optical chromoendoscopy in the inspection of BE, (2) use uniform grading systems and recognize visible lesions within the BE segment, (3) demonstrate the expertise in performance of both EMR and ablative techniques,

and (4) be able to manage adverse events related to EET (including recurrences).[14] Another area of interest for future research is the identification and application of risk factors for disease progression in BE patients. Risk stratification and development of reliable and objective predictive models to identify those NDBE and LGD patients most likely to progress and benefit from EET is critical. Such models should include a combination of demographic variables, endoscopic findings, histopathologic assessment, and biomarkers.[3]

Furthermore, future prospective studies that use standardized definitions for study endpoints and focus on durability of EET and recurrence risk as the primary outcomes are required to more precisely define the annual recurrence risk and the predictors associated with recurrence. This will allow for evidence-based recommendations with regard to surveillance endoscopic and biopsy protocols after successful EET of BE-related neoplasia patients with the goal of stopping or reducing the frequency of surveillance in low-risk individuals and enrolling high-risk patients in an intensive surveillance protocol.[51] The role of gastroesophageal reflux monitoring and pH control in patients undergoing surveillance and EET with a focus on reducing progression rates or achieving CE-IM and reducing rates of recurrence, respectively, needs to be addressed in future studies. Finally, although GI societal endorsed quality indicators in EET have been published,[14,41,61] these will need to be refined and updated based on developments in this field. Future studies will need to assess the challenges in the process of implementation of these quality indicators and most importantly evaluate the impact of implementation of these quality indicators on key patient outcomes (progression to cancer, adverse events, and mortality).

SUMMARY AND CONCLUSIONS

These evidence-based ASGE practice guidelines for EET in BE patients were developed using the GRADE methodology.[24] In addition, these guidelines comply with the standards for guideline development set forth by the Institute of Medicine for the creation of trustworthy guidelines. This guideline evaluated the available data for EET in BE patients within the context of several key clinical scenarios encountered in clinical practice, such as the role of an expert pathology review; optimal management strategy of BE patients with LGD, HGD, and intramucosal EAC; the role of EMR; the optimal strategy for EET; and management of patients after achieving CE-IM. This guideline, along with a clinical decision tool (Fig. 9), aims to help clinicians understand the published literature and the quality of available data with the ultimate goal of optimizing care of these patients.

DISCLOSURE

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Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; BE, Barrett's esophagus; APC, argon plasma coagulation; ASGE, American Society for Gastrointestinal Endoscopy; CE-D, complete eradication of dysplasia; CE, complete eradication; CE-IM, complete eradication of intestinal metaplasia; CI, confidence interval; EAC, esophageal adenocarcinoma; EET, endoscopic eradication therapies; GRADE, Grading of Recommendations Assessment, Development and Evaluation; EMR, endoscopic mucosal resection; GERD, gastroesbageal reflux disease; GI, gastrointestinal; IR, incidence rate; HGD, high-grade dysplasia; IM, intestinal metaplasia; LGD, low-grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; OR, odds ratio; PDT, photodynamic therapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; QOL, quality of life; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; SEER, Surveillance Epidemiology and End Results; SOP, standards of practice.

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SUPPLEMENTARY TEXT 1

Search Strategy

A medical librarian (B.H.) performed a comprehensive literature search of Ovid Medline (Ovid MEDLINE in-process and other nonindexed citations, Ovid MEDLINE) Daily and Ovid MEDLINE 1946 to present), Embase (via Embase.com), and the Cochrane Database of Systematic Reviews/Cochrane Register of controlled trials (via Wiley Online Library). No language or date limits were applied. Medline records were excluded from Embase search results before export to an EndNote library. All search strategies were run on March 11, 2016. All search strategies consisted of text words and their corresponding controlled vocabulary counterparts (MeSH/Emtree terms). For PICO question 2, postsearch coordinating occurred in EndNote. The search strategy located articles mentioning the general term "dysplasia," and then the EndNote internal search tool was used to separate citations into low- or high-grade dysplasia groupings. This allowed for a more efficient duplicating process between the databases.

All searches were ended on March 11th, 2016
All search strategies are for Ovid Medline

PICO 1:
1 barrett*.tw,kf. or exp barrett esophagus/ 9362
2 pathologist*.tw,kf. 26757
3 1 and 2 250
4 remove duplicates from 3 247

PICO 2:
Note: high/low grade dysplasia will be sorted in the EndNote library.

Dysplasia + EET
1 barrett*.tw,kf. or exp barrett esophagus/ 9365
2 (dysplasia* or ((intramucosal or intra-mucosal or mucosal) adj3 (cancer* or carcinoma* or neoplasm* or tumo?r or malignanc*))).tw,kf. or Esophageal Neoplasms/ 99023
3 (EET or (eradicat* adj3 (therap* or treatment*)) or cryotherap* or ((cold or cryogenic or hypothermal or cryoballon) adj3 (therap* or surg* or ablation*)) or cryotherm* or cryotreatment* or cryosurg* or cryo-surg* or cryoablation* or ((endoscop* or oesophagoscop* or Esophagoscop* or oesophagogastroduodenoscop* or esophagogastroduodenoscop* or gastroscop* or mucosal or submucosal) adj3 (resect* or dissect* or mucosect*)) or ((catheter or electric* or radiofrequenc* or radio frequenc* or RF or surgical or technique* or thermal or RFA or laser*) adj3 ablation*) or electrocautery).tw,kf. or exp cryotherapy/or exp cryosurgery/or exp catheter ablation/ 92248
4 1 and 2 and 3 743
5 remove duplicates from 4 739

Dysplasia + Surveillance
1 barrett*.tw,kf. or exp barrett esophagus/ 9365
2 (dysplasia* or ((intramucosal or intra-mucosal or mucosal) adj3 (cancer* or carcinoma* or neoplasm* or tumo?r or malignanc*))).tw,kf. or Esophageal Neoplasms/ 99023
3 (surve* or watchful waiting* or observ* or monitor* or endoscop* or oesophagoscop* or esophagoscop* or oesophagogastroduodenoscop* or esophagogastroduodenoscop* or gastroscop*).tw,kf. or Watchful Waiting/or endoscopy/or esophagoscopy/or exp endoscopes/ 3825581
4 1 and 2 and 3 3163
5 remove duplicates from 4 3136

PICO 3:
1 barrett*.tw,kf. or exp barrett esophagus/ 9365
2 (dysplasia* or ((intramucosal or intra-mucosal or mucosal or esophagi* or oesophag*) adj3 (cancer* or carcinoma* or neoplasm* or tumo?r or malignanc*))).tw,kf. or Esophageal Neoplasms/ 100528
3 (EET or (eradicat* adj3 (therap* or treatment*)) or cryotherap* or ((cold or cryogenic or hypothermal or cryoballon) adj3 (therap* or surg* or ablation*)) or cryotherm* or cryotreatment* or cryotherap* or cryosurg* or cryo-surg* or cryoablation* or ((endoscop* or oesophagoscop* or Esophagoscop* or oesophagogastroduodenoscop* or esophagogastroduodenoscop* or gastroscop* or mucosal or submucosal) adj3 (resect* or dissect* or mucosect*)) or ((catheter or electric* or radiofrequenc* or radio frequenc* or RF or surgical or technique* or thermal or RFA or laser*) adj3 ablation*) or electrocautery).tw,kf. or exp cryotherapy/or exp cryosurgery/or exp catheter ablation/ 92248
4 (Surger* or esophectom* or oesophectom*).tw,kf. or exp Esophagus/su or esophagectomy/ 956197
5 1 and 2 and 3 and 4 271
6 remove duplicates from 5 269

PICO 4:
1 barrett*.tw,kf. or exp barrett esophagus/ 9365
2 (lesion* or ulcer* or nodul*).tw,kf. or Ulcer/ 910630
3 ((endoscop* or oesophagoscop* or Esophagoscop* or oesophagogastroduodenoscop* or esophagogastroduodenoscop* or gastroscop* or mucosal) adj3 (resect* or dissect* or mucosect*)).tw,kf. 8880
4 1 and 2 and 3 262
5 remove duplicates from 4 261

PICO 5 and 6:
1 barrett*.tw,kf. or exp barrett esophagus/ 9362
2 (dysplasia* or ((intramucosal or intra-mucosal or mucosal) adj3 (cancer* or carcinoma* or neoplasm* or tumo?r or malignanc*))).tw,kf. or Esophageal Neoplasms/ 98996

3 (EET or (eradicat* adj3 (therap* or treatment*)) or cryotherap* or ((cold or cryogenic or hypothermal or cryoballon) adj3 (therap* or surg* or ablation*)) or cryotherm* or cryotreatment* or cryosurg* or cryo-surg* or cryoablation* or ((endoscop* or oesophagoscop* or Esophagoscop* or oesophagogastroduodenoscop* or esophagogastroduodenoscop* or gastroscop* or mucosal or submucosal) adj3 (resect* or dissect* or mucosect*)) or ((catheter or electric* or radiofrequenc* or radio frequenc* or RF or surgical or technique* or thermal or RFA or laser*) adj3 ablation*) or electrocautery).tw,kf. or exp cryotherapy/or exp cryosurgery/or exp catheter ablation/ 92200
4 1 and 2 and 3 742
5 remove duplicates from 4 738

PICO 7:
1 barrett*.tw,kf. or exp barrett esophagus/ 9365
2 ((Post or diseas* or barrett* or complete or total or dysplasia* or metaplasia*) adj4 (eliminat* or eradic* or remiss* or regres* or abate* or diminut*)).tw,kf. or Disease Eradication/ 67348
3 (surve* or watchful waiting* or observ* or monitor*).tw,kf. or Watchful Waiting/ 3662149
4 (endoscop* or oesophagoscop* or esophagoscop* or oesophagogastroduodenoscop* or esophagogastroduodenoscop* or gastroscop*).tw,kf. or endoscopy/or esophagoscopy/or exp endoscopes/ 195753
5 3 or 4 3825581
6 1 and 2 and 5 403
7 remove duplicates from 6 402

SUPPLEMENTARY TEXT 2

Inclusion/exclusion criteria for each PICO question:

PICO 1: Expert GI pathology review
Inclusion
- Clinical trials, prospective, or retrospective studies
- Published in peer-reviewed journal
- Meeting abstracts published within the last 2 years (2014-2016)
- BE dysplasia/neoplasia grade classified based on expert GI pathologist review vs community/nonexpert pathologists
- Studies report on at least 1 of the following outcomes:
  - Interobserver agreement (among expert GI pathologists, expert and nonexpert GI pathologists, and community/nonexpert GI pathologists)
  - Report on difference in rates of progression in patients with low-grade dysplasia (endpoint high-grade dysplasia/intramucosal cancer/invasive cancer) or high-grade dysplasia (endpoint intramucosal cancer/invasive cancer)
  - Report on proportion of cases with a change in diagnosis based on expert GI pathology review

Exclusion
- Studies including nondysplastic BE where subjects with dysplasia/neoplasia could not be separated

PICO 2: Comparison of EET with surveillance
Report on outcomes
- Combining LGD and HGD
- LGD alone
- HGD alone

For LGD
Inclusion
- Clinical trials or prospective studies
- Retrospective studies reporting disease progression after the first year of follow-up or after 2 consecutive endoscopies confirm LGD
- Published in peer-reviewed journal, or meeting abstracts published within the last 2 years
- Assessed patients with BE LGD and reported rates of progression to HGD or EAC
- Treatment modality: EMR, radiofrequency ablation, cryotherapy, APC (multimodality therapy)

Exclusion
- Reported patient with HGD or EAC only (no LGD) or summed patients with LGD and HGD in 1 cohort
- Time to progression could not be assessed
- Patients diagnosed with HGD/EAC within the first year of diagnosis of LGD (prevalent HGD/EAC)
- Less than 20 patients with LGD included in the study

For HGD
Inclusion
- Clinical trials, prospective studies, or retrospective studies
- Published in peer-reviewed journal, or meeting abstracts published within the last 2 years
- Assessed patients with BE HGD and reported rates of progression to EAC
- Treatment modality: EMR, radiofrequency ablation, cryotherapy, APC (multimodality therapy)

Exclusion
- Reported patient with NDBE or LGD only, or summed patients with LGD and HGD in 1 cohort
- Less than 20 patients with HGD included in the study
- Patients diagnosed with HGD/EAC within the first year of diagnosis of LGD (prevalent HGD/EAC)

Outcomes
- Progression to cancer
- Progression to HGD/cancer (for LGD patients)
- Cancer-specific mortality
- All-cause mortality
- Morbidity and adverse event rates

PICO 3: Comparison of EET with surgery

Inclusion

- Clinical trials, prospective studies, or retrospective studies
- Published in peer-reviewed journal, or meeting abstracts published within the last 2 years
- Assessed patients with BE LGD or HGD comparing surgery (esophagectomy) with endoscopic therapy (RFA + EMR + cryotherapy AND EMR + RFA)

Exclusion

- Reported patient with NDBE only
- Less than 20 patients included in the study

Outcomes

- Progression to cancer
- Progression to HGD/cancer (for LGD patients)
- Cancer-specific mortality
- All-cause mortality
- Morbidity and adverse event rates

Discussion point

Only include studies that compare the 2 treatment options in 1 study

PICO 4: EMR of visible lesions

Inclusion

- Clinical trials, prospective studies, or retrospective studies
- Published in peer-reviewed journal, or meeting abstracts published within the last 2 years
- Assessed patients with BE and nodules/lesions on endoscopy treated with EMR/ESD with those treated with ablation without EMR/ESD
- Studies must report on at least 1 of the following outcomes:
  - Difference in progression rates to HGD/cancer or cancer alone in BE patients with visible lesions between patients undergoing EMR vs no EMR
  - Proportion of cases with change in dysplasia/neoplasia grade
  - Proportion of cases with change in management plan

Exclusion

- Could not differentiate patients with lesions vs flat BE
- Less than 20 patients included in the study

Outcomes

- Difference in progression rates to HGD/cancer or cancer alone in BE patients with visible lesions between patients undergoing EMR vs no EMR
- Proportion of cases with change in dysplasia/neoplasia grade
- Proportion of cases with change in management plan
- Adverse event rate

PICO 5: EMR followed by ablation

Inclusion

- Clinical trials, prospective studies, or retrospective studies
- Published in peer-reviewed journal, or meeting abstracts published within the last 2 years
- Studies that compare progression rates or recurrence between groups of patients undergoing EMR followed by ablation of remaining BE with EMR alone

Exclusion

- Less than 20 patients included in the study

Outcomes

- Progression to cancer
- Progression to HGD/IMC
- Recurrence rates
- Adverse events

PICO 6: EMR plus ablation vs EMR entire BE

Inclusion

- Clinical trials, prospective studies, or retrospective studies
- Published in peer-reviewed journal, or meeting abstracts published within the last 2 years
- Studies that compare outcomes (see below) between groups of patients undergoing EMR followed by ablation of remaining BE with EMR of entire BE segment

Exclusion

- Less than 20 patients included in the study

Outcomes

- Complete eradication of intestinal metaplasia and neoplasia
- Progression to cancer
- Progression to HGD/IMC
- Recurrence rates
- Adverse events

PICO 7: Surveillance after EET

Inclusion

- Clinical trials, prospective studies, or retrospective studies
- Published in peer-reviewed journal, or meeting abstracts published within the last 2 years
- Studies that compare recurrence rates between groups of patients undergoing surveillance after CE-IM with patients not enrolled in surveillance programs

Exclusion

- Less than 20 patients included in the study

Outcomes

- Progression to cancer
- Progression to HGD/IMC
- Recurrence rates
- Adverse events
- Cancer-specific and all-cause mortality

PICO 8: Discussion of risks/benefits

Motherhood statement: no search required

SUPPLEMENTARY TABLE 1. GRADE evidence profile for Question 4: What is the role of EMR in BE patients with a visible lesion detected during screening or surveillance?

Quality assessment						
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
Progression rate to HGD/EAC: no studies were found to inform this outcome—important						
0						
Change in dysplasia/neoplasia diagnosis—critical*						
1116 (14 observational studies)	Not serious	Not serious	Not serious	Not serious	Rated up for large effect	⊕⊕⊕◯ MODERATE
Adverse events with EMR†—important						
0						

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *BE*, Barrett's esophagus; *CI, confidence interval; HGD, high-grade dysplasia; EAC*, esophageal adenocarcinoma; *RFA*, radiofrequency ablation; *RR,* relative risk.

*Upstaging occurred in 23% (range, 19%-28%) and downstaging occurred in 17% (range, 12%-24%);however, change in management or treatment not consistently reported across studies.

†Based on Qumseya et al,[22] EMR + RFA = 22.2% (95% CI, 16.4%-29.4%); RFA alone = 5% (95% CI, 2.9%-8.3%); RR = 4.4; P = .015. Additional data on safety of EMR from Tomizawa et al[57] and Pech et al.[58]

SUPPLEMENTARY TABLE 2. GRADE evidence profile for Question 5: Should BE patients undergoing EET undergo ablation of the remaining BE after undergoing EMR of all visible lesions compared with no ablation?

Quality assessment						
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
Progression to HGD/EAC: no studies were found to inform this outcome—important						
0						
Rate of recurrence of HGD/EAC (after 2 negative EGDs in individuals with complete remission)—critical						
279 (1 observational study)	Not serious	Not serious	Not serious*	Not serious	None	⊕⊕◯◯ LOW
Rate of recurrence of HGD/EAC (after 2 negative EGDs in individuals with complete remission)—critical						
63 (1 RCT)	Serious†	Not serious	Not serious‡	Serious§	None	⊕⊕◯◯ LOW
Adverse events including perforation, strictures, bleeding, pain, hospitalization—important						
9200 (37 observational studies)	Not serious	Not serious¶	Not serious	Not serious	None	⊕⊕◯◯ LOW

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *BE*, Barrett's esophagus; *EET*, endoscopic eradication therapy; *HGD*, high-grade dysplasia; *EAC*, esophageal adenocarcinoma; *PDT*, photodynamic therapy; *APC*, argon plasma coagulation; *RCT,* randomized control trial; *RFA*, radiofrequency ablation.

*We noted that ablative therapy in the study of Pech et al consisted of PDT and/or APC but not RFA (which is the current standard); however, we did nor rate down for indirectness.

†The trial was stopped early for benefit, introducing potential bias in the findings.

‡We again noted that APC was used as ablative therapy, which is not the current standard, and that the duration of follow-up was limited to 2 years.

§Very few events.

¶We rated down for significant heterogeneity.

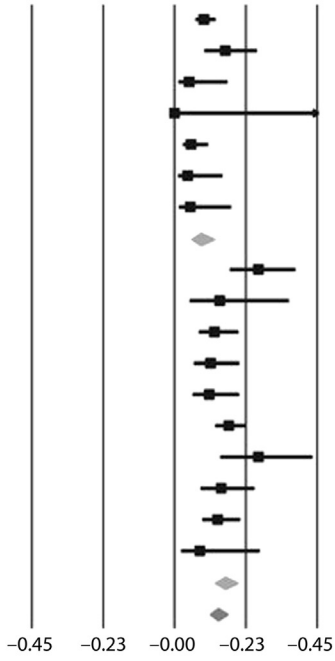
SUPPLEMENTARY TABLE 1. Continued

Summary of findings				
Study event rates (%)			Anticipated absolute effects	
With no EMR	With EMR of visible lesions	Relative effect (95% CI)	Risk with no EMR	Risk difference with EMR of visible lesions
Change in dysplasia/neoplasia diagnosis with EMR (pooled event rate across 14 studies) was 39% (95% CI, 34%-45%) with most cases being upstaged				

SUPPLEMENTARY TABLE 2. Continued

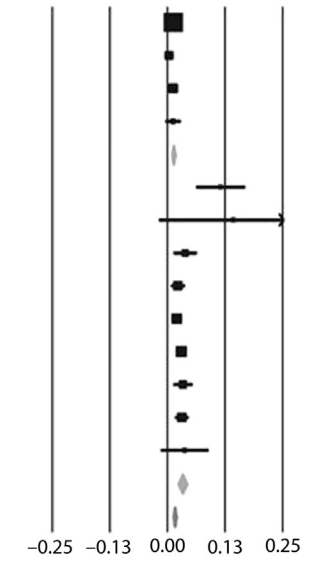
Summary of findings	
Study event rates (%)	
With no ablation	With ablation of remaining BE (with or without dysplasia)
Progression to HGD/EAC: no studies were found to inform this outcome—important	
Rate of recurrence of HGD/EAC (after 2 negative EGDs in individuals with complete remission)—critical	
Pech et al[19] reported rates of recurrence in 2 cohorts: 1 group that underwent ablation therapy (PDT and/or APC) after EMR and 1 group only underwent EMR. The rate of recurrence was 33/200 or 16.5% (EMR + ablation) as compared with 41/137 or 29.9% (EMR only) at a median follow-up of 61 months.	
Rate of recurrence of HGD/EAC (after 2 negative EGDs in individuals with complete remission)—critical	
Manner et al[63] conducted an RCT of EMR plus APC vs EMR alone that was stopped early for benefit. Rates of recurrence were 1/33 or 3% in the EMR + ablation arm vs 11/30 or 36.7% in the EMR alone arm over a median follow-up period of 24-28 months	
Adverse events including perforation, strictures, bleeding, pain, hospitalization—important	
Overall adverse event rate across 37 studies was 8.8% (95% CI, 6.5%-11.9%). Treatment modality EET included RFA ± EMR. Stricture post-treatment most common adverse event 5.6% (95% CI, 4.2%-7.4%). EMR contributed to RFA.	

Study name	Subgroup within study	Comparison	Event rate	Lower limit	Upper limit	*P* value
Bhat 2011	National Registry	Surveillance	0.093	0.066	0.130	0.000
Gatenby 2009	Retrospective	Surveillance	0.160	0.093	0.261	0.000
Reid 2000	Retrospective	Surveillance	0.047	0.012	0.168	0.000
Alcedo 2009	Retrospective	Surveillance	0.000	0.000	1.000	0.743
Dulai 2005	Retrospective	Surveillance	0.052	0.025	0.106	0.000
Weston 2001	Prospective	Surveillance	0.042	0.010	0.152	0.000
Conio 2003	Retrospective	Surveillance	0.050	0.013	0.179	0.000
			0.081	0.053	0.120	0.000
Phoa 2014 (Surv)	RCT	Surveillance	0.265	0.174	0.382	0.000
Shaheen 2009 (Surv)	RCT	Surveillance	0.143	0.047	0.361	0.004
Sikkema 2011	Prospective	Surveillance	0.126	0.076	0.202	0.000
Duits 2015	National Registry	Surveillance	0.114	0.060	0.205	0.000
Picardo 2015	National Registry	Surveillance	0.110	0.056	0.204	0.000
Thota 2015	Retrospective	Surveillance	0.171	0.127	0.227	0.000
Lim 2007	Retrospective	Surveillance	0.265	0.144	0.435	0.009
Wani 2011	Retrospective	Surveillance	0.147	0.081	0.252	0.000
Small 2015 (Surv)	Retrospective	Surveillance	0.136	0.086	0.208	0.000
Skacel 2000	Retrospective	Surveillance	0.080	0.020	0.269	0.001
			0.157	0.127	0.193	0.000
			0.135	0.111	0.162	0.000



A

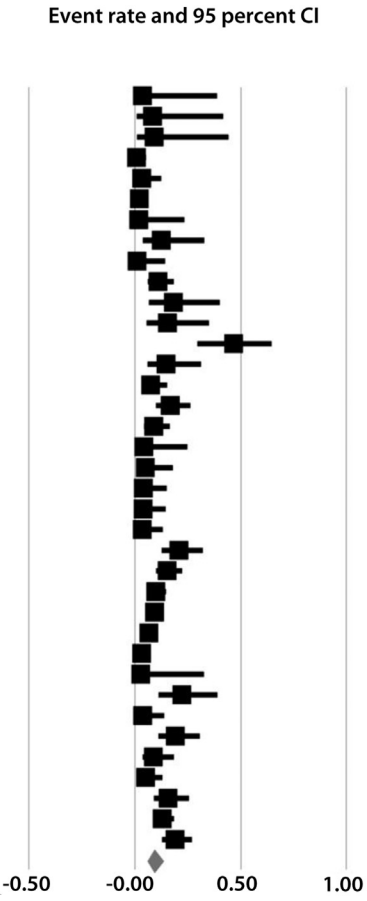
Group by confirmed path	Study name	Comparison	Rate	Lower limit	Upper limit	*P* value
No	Bhat 2011	Surveillance	0.013	0.008	0.018	0.000
No	Alcedo 2009	Surveillance	0.004	−0.006	0.014	0.480
No	Dulai 2005	Surveillance	0.013	0.003	0.022	0.008
No	Weston 2001	Surveillance	0.012	−0.005	0.029	0.157
No			0.012	0.008	0.016	0.000
Yes	Phoa 2014 (Surv)	Surveillance	0.116	0.062	0.169	0.000
Yes	Shaheen 2009 (Surv)	Surveillance	0.143	−0.019	0.305	0.083
Yes	Dutis 2015	Surveillance	0.039	0.013	0.064	0.003
Yes	Picardo 2015	Surveillance	0.023	0.007	0.038	0.005
Yes	Gatenb y2009	Surveillance	0.020	0.009	0.032	0.001
Yes	Thota 2015	Surveillance	0.030	0.021	0.040	0.000
Yes	Wani 2011	Surveillance	0.034	0.013	0.055	0.002
Yes	Small 2015 (surv)	Surveillance	0.031	0.016	0.046	0.000
Yes	Skacel 2000	Surveillance	0.037	−0.014	0.089	0.157
Yes			0.031	0.022	0.041	0.000
Overall			0.014	0.011	0.018	0.000



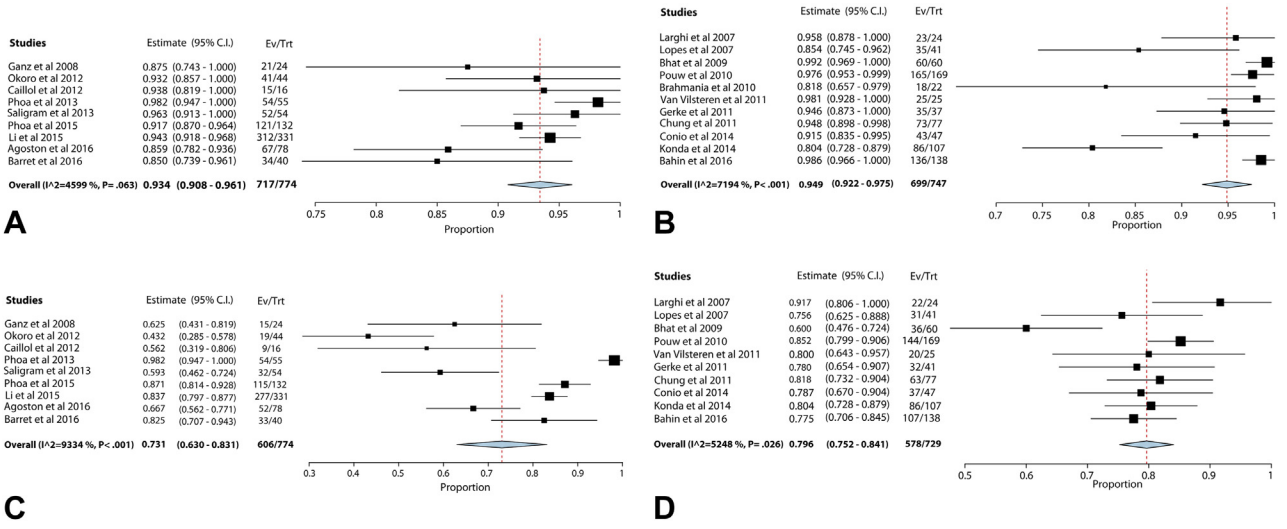
B

Supplementary Figure 1. Progression rates in Barrett's esophagus patients with low-grade dysplasia based on expert pathology review. **A,** Forest plot of pooled cumulative progression rates stratified by expert pathology review. **B,** Forest plot of pooled incidence rate of disease progression based on expert pathology review. *CI*, Confidence interval (Reprinted with permission from: Qumseya BJ, Wani S, Gendy S, et al. Disease progression in Barrett's low-grade dysplasia with radiofrequency ablation compared with surveillance: systematic review and meta-analysis. Am J Gastroenterol 2017;112:849-65).

Study name	Subgroup within study	Comparison	Time point	Statistics for each study			
				Event rate	Lower limit	Upper limit	*P*-value
Roorda, A.K.	Prospective	Paper	2007	0.036	0.002	0.384	.002
Gondrie, J.J.	Prospective	Paper	2008	0.083	0.012	0.413	.022
Gondrie, J.J._2	Prospective	Paper	2008	0.091	0.013	0.439	.028
Ganz, R.A.	Retrospective	Paper	2008	0.007	0.001	0.048	.000
Sharma, V.	Prospective	Paper	2009	0.032	0.008	0.120	.000
Lyday, W.D.	Retrospective	Paper	2009	0.021	0.011	0.040	.000
Eldaif, S.	Retrospective	Paper	2009	0.018	0.001	0.230	.005
Pouw, R.	Prospective	Paper	2010	0.125	0.041	0.324	.002
Fleischer, D.E.	Prospective	Paper	2010	0.010	0.001	0.138	.001
Shaheen, N.	Prospective	Paper	2011	0.109	0.064	0.179	.000
van Vilsteren, F.G.	Prospective	Paper	2011	0.182	0.070	0.396	.007
Herroro, L.	Prospective	Paper	2011	0.154	0.059	0.345	.002
Martinek, J.	Prospective	Abstract	2012	0.467	0.299	0.642	.715
Caillol, F.	Retrospective	Paper	2012	0.147	0.063	0.308	.000
Hersebach, D.	Retrospective	Paper	2012	0.074	0.036	0.148	.000
Okoro, I.	Retrospective	Paper	2012	0.167	0.103	0.258	.000
McEwan, H.C.	Prospective	Abstract	2012	0.088	0.047	0.161	.000
Kline, M.M.	Prospective	Abstract	2012	0.042	0.006	0.244	.002
van Vilsteren, F.G.	Prospective	Paper	2013	0.049	0.012	0.175	.000
Ertan, A.	Retrospective	Paper	2013	0.040	0.010	0.146	.000
Alnahdi, N.	Retrospective	Abstract	2013	0.038	0.010	0.141	.000
Choi, K.D.	Retrospective	Abstract	2013	0.034	0.009	0.128	.000
Dulai, P.	Retrospective	Paper	2013	0.208	0.130	0.317	.000
Bisshcops	Retrospective	Abstract	2013	0.152	0.103	0.219	.000
Bulsiewicz, W.	Retrospective	Paper	2013	0.098	0.067	0.143	.000
Haidry, R.J.	Retrospective	Paper	2013	0.093	0.066	0.129	.000
Gupta, M.	Retrospective	Paper	2013	0.066	0.048	0.089	.000
Shaheen, N.J.	Retrospective	Paper	2013	0.032	0.027	0.037	.000
Perry, K.A.	Retrospective	Paper	2014	0.028	0.002	0.322	.013
Strauss, A.C.	Retrospective	Paper	2014	0.222	0.115	0.385	.002
Bidari, K.	Prospective	Abstract	2014	0.036	0.009	0.134	.000
Phoa, K.Y.	Prospective	Paper	2014	0.191	0.114	0.302	.000
Oh, S.	Retrospective	Abstract	2014	0.087	0.040	0.180	.000
Battaglia, G.	Retrospective	Abstract	2014	0.050	0.019	0.126	.000
KuNzli, H.	Retrospective	Abstract	2015	0.157	0.093	0.251	.000
David, W.	Retrospective	Paper	2015	0.129	0.091	0.181	.000
Phoa, K.Y._2	Prospective	Paper	2015	0.189	0.131	0.265	.000
				0.088	0.065	0.119	.000



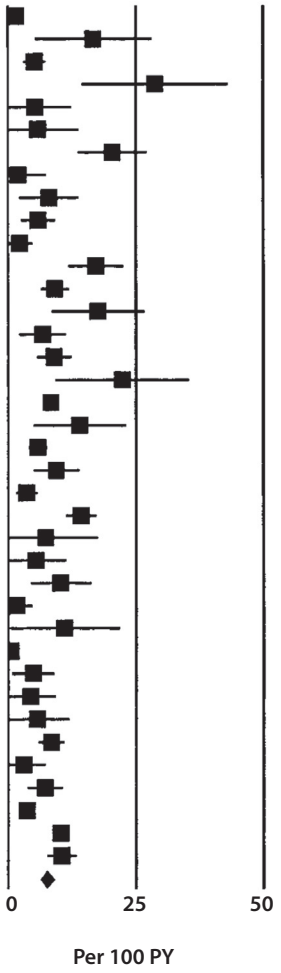
Supplementary Figure 2. Forest plot of 37 studies with overall adverse events for patients with Barrett's esophagus undergoing radiofrequency ablation with or without EMR. *CI*, Confidence interval (Reprinted with permission from: Qumseya BJ, Wani S, Desai M, et al. Adverse events after radiofrequency ablation in patients with Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016;14:1086-95.e6).



Supplementary Figure 3. Forest plots of proportion of patients achieving complete eradication of neoplasia after focal EMR followed by radiofrequency ablation (**A**) compared with stepwise EMR of entire Barrett's esophagus segment (**B**) and complete eradication of intestinal metaplasia after focal EMR followed by radiofrequency ablation (**C**) compared with stepwise EMR (**D**). *C.I.*, Confidence interval (Reprinted with permssion from: Desai M, Saligram S, Gupta N, et al. Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled analysis. Gastrointest Endosc 2016;85:482-95).

Incidence of Total Recurrence Across all Studies

Study name	Rate	Lower limit	Upper limit	*P* value
Fleischer DE 2010	1.6	0	3.2	.046
Alvarez Herrero L 2011	16.7	5.1	28.2	.005
Shaheen NJ 2011	5.2	2.9	7.6	.000
Vaccaro BJ 2011	28.8	14.2	43.3	.000
van Vilsteren FGI 2011	5.3	0	12.6	.157
Caillol F 2012	5.9	0	14.0	.157
Gupta N 2012	20.4	13.6	27.3	.000
van Vilsteren FGI 2012	2.0	0	7.7	.480
Akiyama J 2013	8.0	2.1	14.0	.008
Dulai PS 2013	5.9	2.4	9.4	.001
Ertan A 2013	2.3	0	4.9	.083
Gupta M 2013	17.2	11.7	22.8	.000
Haidry RF 2013	9.1	6.2	12.1	.000
Korst RJ 2013	17.6	8.4	26.8	.000
Orman ES 2013	6.8	2.1	11.5	.005
Phoa KN 2013	9.1	5.5	12.6	.000
Shue P 2013	22.4	9.2	35.6	.001
Pasricha S 2014	8.4	7.5	9.3	.000
Strauss AC 2014	14.1	4.9	23.2	.003
Cotton CC 2015	5.9	3.9	7.8	.000
Lada MJ 2015	9.5	4.9	14.2	.000
Phoa KN 2015	3.7	1.4	5.9	.002
Small AJ 2015	14.3	11.2	17.4	.000
Giovannini M 2004	7.4	0	17.7	.157
Larghi A 2007	5.4	0	11.6	.083
Lopes CV 2007	10.3	4.2	16.4	.001
Chennat J 2009	1.6	0	4.9	.317
Brahmania M 2010	11.1	0.2	22.0	.046
Moss A 2010	0.6	0	2.2	.480
Chung A 2011	4.9	0.6	9.2	.025
Gerke H 2011	4.5	0	9.5	.083
van Vilsteren FGI 2011 - EMR	5.7	0	12.2	.083
Anders M 2014	8.5	5.7	11.2	.000
Conio M 2014	3.1	0	7.4	.157
Konda VJA 2014	7.2	3.6	10.9	.000
Belghazi K 2016	3.7	1.9	5.4	.000
Wani S 2016	10.4	8.6	12.2	.000
Waxman I 2016	10.5	7.6	13.5	.000
	7.5	6.1	9.0	.000



Supplementary Figure 4. Forest plot with overall pooled incidence of any recurrence (intestinal metaplasia or dysplasia) after achieving complete eradication of intestinal metaplasia after endoscopic eradication therapy using stepwise complete endoscopic resection or radiofrequency ablation with or without focal EMR. *CI*, Confidence interval (Reprinted with permission from: Fujii-Lau et al. Recurrence of intestinal metaplasia and early neoplasia after endoscopic eradication therapy for Barrett's esophagus: a systematic review and meta-analysis. CC BY-NC-ND 4.0. Endosc Int Open 2017;05(06):E430-E449. https://doi.org/10.1055/s-0043-106578. © Georg Thieme Verlag KG 2017).