Title: American Gastroenterological Association Clinical Practice Guideline: Surveillance of Barrett's Esophagus

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Abstract

Introduction: Barrett's esophagus (BE) is the only identifiable precursor to esophageal adenocarcinoma (EAC). Endoscopic surveillance has been proposed for early detection of BE-related neoplasia and reducing EAC mortality. This clinical practice guideline aims to inform clinicians and patients by providing evidence-based practice recommendations for surveillance in patients with BE.

Methods: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess evidence and make recommendations. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients, conducted an evidence review, and used the Evidence-to-Decision Framework to develop recommendations regarding the role of endoscopic surveillance in patients with BE. The clinical domains addressed included: 1) overall role of endoscopic surveillance, 2) optimal imaging modalities, 3) adjunctive sampling techniques, 4) the utility of biomarkers in risk-stratification, 5) chemopreventive strategies, 6) anti-reflux procedures in the prevention of progression in BE patients and 7) surveillance in patients with columnar lined esophagus <1 cm. Clinical recommendations were based on the balance between the desirable and undesirable effects, patient values, costs, and health equity considerations.

Results: The panel agreed on 8 recommendations. Based on the available evidence, the panel provided a conditional recommendation in favor of surveillance for patients with non-dysplastic BE. The panel made a strong recommendation in favor of a combination of high-definition white light endoscopy and chromoendoscopy compared with white light endoscopy alone. The panel made no recommendation on the use of enhanced sampling techniques such as wide-are transepithelial sampling to enhance neoplasia detection and biomarkers such as p53 and TissueCypher to predict progression in BE. The panel provided a conditional recommendation for the use of daily proton pump inhibitor therapy compared to no therapy and compared to anti-reflux surgery to prevent progression in BE. In patients with columnar lined esophagus <1 cm, a conditional recommendation was made against endoscopic surveillance. Key implementation statements included in this document stress the importance of a high-quality endoscopy examination, sampling using a structured biopsy protocol, and confirming the diagnosis of BE-related neoplasia by an expert pathologist. This document also provides guidance on surveillance intervals and management of patients with BE-related low-grade dysplasia and indefinite for dysplasia.

Conclusions: This document provides a comprehensive outline on the role of surveillance in BE patients. Guidance is also provided regarding the considerations surrounding implementation of surveillance practices. Providers should engage in shared decision making based on patient preferences. Limitations and gaps in the evidence are highlighted to guide future research opportunities.

Keywords: Barrett's esophagus, esophageal adenocarcinoma, surveillance, chromoendoscopy, biomarkers, chemoprevention, proton pump inhibitors, anti-reflux surgery

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Abbreviations:

AGA: American Gastroenterological Association

BE: Barrett's esophagus

LGD: low-grade dysplasia

IND: indefinite for dysplasia

HGD: high-grade dysplasia

NDBE: non-dysplastic Barrett's esophagus

EAC: esophageal adenocarcinoma

EET: endoscopic eradication therapy

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

PICO: Population, Intervention, Comparison, Outcome

RCT: randomized controlled trial

WATS-3D: wide-area transepithelial sampling

SR: systematic review

MA: meta-analysis

PEEC: post-endoscopy esophageal adenocarcinoma

PEEN: post-endoscopy esophageal neoplasia

CE: chromoendoscopy

WLE: white light endoscopy

VCE: virtual chromoendoscopy

NBI: narrow band imaging

AI: artificial intelligence

CADe: computer-aided detection

CADx: computer-aided diagnosis

PPI: proton pump inhibitor

PCAB: potassium competitive acid blocker

SAE: serious adverse events

GERD: gastroesophageal reflux disease

TR: time ratio

NDR: neoplasia detection rate

ASGE: American Society for Gastrointestinal Endoscopy

IHC: immunohistochemistry

TP: true positive

TN: true negative

FP: false positive

FN: false negative

Executive Summary

Esophageal adenocarcinoma (EAC) is a lethal cancer with high incidence and mortality rates over the last several decades. Barrett's esophagus (BE) is the only identifiable precursor lesion for EAC and is characterized by the replacement of squamous epithelium in the distal esophagus by metaplastic specialized columnar epithelium in response to chronic gastroesophageal reflux-induced injury and inflammation. Given the stepwise and probabilistic progression of BE to EAC and that the prognosis of EAC is strongly related to stage at diagnosis, endoscopic surveillance of patients diagnosed with BE has been proposed. The primary goal of surveillance is early detection of BE-related neoplasia, endoscopic eradication therapy (EET) for treatment of dysplasia and early-stage cancer, reducing morbidity and mortality related to esophagectomy and ultimately preventing EAC mortality. This evidence-based guideline from the American Gastroenterological Association (AGA) aims to provide recommendations for surveillance in patients with BE. The panel agreed on 8 recommendations related to surveillance in BE and provided multiple additional implementation considerations.

How to Read These Guidelines

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

Introduction

Description of the Health Problem

Esophageal adenocarcinoma (EAC) is a lethal cancer with increasing incidence and sobering mortality rates over the last several decades.[1] The incidence of EAC rose 5-fold from the 1970s to the 2010s, and adenocarcinoma now represents the most common form of esophageal cancer in Western populations with a dismal overall 5-year survival rate of approximately 20%.[2] Survival from all but the earliest stage of EAC remains poor.[3] Barrett's esophagus (BE) is the only identifiable precursor lesion for EAC and characterized by replacement of squamous epithelium in the distal esophagus by metaplastic specialized columnar epithelium in response to chronic gastroesophageal reflux-induced injury and inflammation.[4, 5] Recent evidence suggests that most cases of EAC arise from BE or from intestinalized metaplastic precursor cells in the gastric cardia.[6, 7] BE is believed to progress to EAC in a stepwise and probabilistic fashion through steps of low-grade dysplasia (LGD), then high grade dysplasia (HGD) before developing into invasive EAC. Given that the prognosis of EAC is strongly related to stage at diagnosis, endoscopic surveillance in patients with BE has been proposed with the goal of early detection of BE-related neoplasia – patients who can be referred for endoscopic eradication therapy (EET), reducing the morbidity and mortality related to esophagectomy and ultimately preventing EAC mortality.[8-11]

Objective of the Review and Guideline

The American Gastroenterological Association (AGA) developed this systematic review and clinical guideline to provide evidence-based recommendations for endoscopic surveillance in patients with BE. This clinical guideline addresses the overall role and effectiveness of endoscopic surveillance, optimal imaging strategies, the role of adjunctive sampling techniques to improve detection of BE-related neoplasia, the role of biomarkers and other risk stratification strategies to guide surveillance and the role of chemoprevention and anti-reflux procedures in prevention of progression in patients with BE and the role of endoscopic surveillance in patients with columnar lined esophagus <1 cm. EET was addressed in a recent AGA guideline[11] and screening for BE and EAC will be addressed in a future guideline document.

Target Audience

The target audience for these guidelines includes primary care, internal medicine, family medicine, gastroenterology, oncology, and surgery healthcare providers; patients; and policymakers. The recommendations in this document are not intended to be used as the standard of care. Instead, they can be used to guide surveillance and management of patients with BE and related neoplasia.[11] Each recommendation in this guideline is accompanied by key implementation considerations and qualifying remarks that should be considered an integral part of the recommendation statement and should not be omitted. Although no single recommendation can encompass every individual circumstance and context, it can be used to address the benefits and harms of treatments and support the processes of shared decision making so that patients are treated based on their values and preferences.

Methods

Overview

This document represents the official recommendations of the AGA. These recommendations were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework for diagnostic tests and strategies and adheres to best practices in guideline development, as outlined by the National Academy of Medicine.[12]

Organization and Panel Composition

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

Management of Conflict of Interest and Guideline Funding

Panel members disclosed all potential conflicts of interest. Conflicts were managed according to AGA policies, the National Academy of Medicine, and Guidelines International Network standards.[13-15] Development of this guideline was wholly funded by the AGA Institute with no support from the industry. A full list of conflicts can be accessed at the AGA's National Office in Bethesda, MD.

Scope

The guideline panel and evidence review team formulated clinically relevant questions on endoscopic surveillance strategies and therapies for BE and related neoplasia. The most recent comprehensive position paper by the AGA on BE was published in 2011, and included guidance on screening, surveillance, biomarkers, and endoscopic therapy.[16] Since then, the AGA has published Clinical Practice Updates on the management of BE with LGD,[17] endoscopic

submucosal dissection (ESD. including outside of the setting of BE),[18] endoscopic treatment of neoplastic BE,[19] screening and surveillance[20] and most recently, clinical practice guideline on EET of BE and related neoplasia using the GRADE framework.[11] Similar to the document on EET, the current guideline panel undertook a comprehensive review following the GRADE approach, the results of which add to and update the prior documents addressing surveillance in BE. Given the breadth of the review, the guideline panel split the publication of the recommendations into this document on endoscopic surveillance and forthcoming guidance on screening for BE and EAC.

Formulation of Clinical Questions and Determining Outcomes of Interest

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

Search Strategy

A protocol guided the systematic review process. For all PICO questions we searched for recently published systematic reviews and meta-analyses that used a comprehensive search strategy (PubMed, Embase, and Cochrane Library). When identified, we then updated the search to January 2025, with the help from a medial librarian. Details were included under evidence summaries for each PICO question. When no pre-existing systematic review or meta-analysis meeting our inclusion criteria was identified, a new comprehensive search was conducted on the following databases: EMBASE, MEDLINE, Cochrane, and PubMed. The search terms used, and the final strategy can be found in the supplementary material (**Supplementary Tables 1-6**). References from included references and prior guidelines were searched to identify any missing relevant studies. Furthermore, content experts aided in the identification of potentially relevant ongoing studies.

Study Selection, Data Collection, and Analysis

Searches from all the databases were combined in Rayyan bibliographic software,[21] and duplicates were removed. One content expert and one methodologist screened each title and conducted a full-text review of the eligible studies, and a consensus was reached on inclusion (see **Supplementary Figure 1** for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram).[22] In summary, we prioritized randomized controlled trials (RCTs). Where RCT data for our outcomes of interest were not available or sparse, we also considered observational studies, giving preference to observational studies with control arms over un-controlled observations. Any conflicts were resolved with adjudication by the senior methodologist. Data were extracted from each study, including study characteristics, such as year of publication, study site, study population, intervention, comparison group, outcomes and methods for risk-of-bias assessment. Meta-analyses were conducted when more than 1 study contributed data for the same intervention and outcome. We combined the dichotomous outcomes to obtain a relative risk (RR) and 95% confidence interval (CI). For the meta-analyses, we used the generic inverse variance method of weighting and applied the random-effects model, unless 3 or fewer studies were present, we used a fixed-effects model due to the instability of between-study variance. We assessed the statistical heterogeneity by using the I^2 index. We used either STATA 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14.2 College Station, TX) or Review Manager RevMan software version 5.3 for the comparative studies (The Nordic Cochrane Centre. Copenhagen, Denmark: The Cochrane Collaboration, 2014), and OpenMeta analyst for statistical analyses of single arm studies (OpenMetaAnalyst: Byron C. Wallace, Issa J. Dahabreh, Thomas A. Trikalinos, Joseph Lau, Paul Trow, and Christopher H Schmid). We used the Cochrane Risk of Bias tool to assess the risk of bias in the included studies incorporated in RevMan. For quality assessment of diagnostic accuracy studies, we used the revised QUADAS-2 tool. [23] For quality assessment of observational comparative studies, we used the Newcastle Ottawa tool.[24]

Certainty of the Evidence

We used the GRADE approach to assess the certainty of evidence for the effect of the intervention on each outcome using the software GradePro Guideline Development Tool (https://gradepro.org). The GRADE approach considers factors such as study design, population studied, risk of bias, inconsistency, indirectness, imprecision, and risk of publication bias to rate

the certainty of evidence as high, moderate, low, or very low (**Table 2**).[25] The results of certainty assessment are reported in evidence profiles available in **Tables 5-12** for all the interventions included in this review.

Development of Recommendations

The process of translation of evidence into guideline recommendations followed the GRADE Evidence to Decision framework and was achieved by discussion during virtual meetings of the guideline committee.[26] The Evidence to Decision framework considers the certainty of evidence, balance of benefits and harm, patient values and preferences, feasibility, acceptability, equity, and resource use.[26] All Evidence to Decision tables are presented in **Supplementary Tables 7-11**. Consensus was reached for all the recommendations among the group. The interpretation of strength of recommendations is summarized in **Table 3**. In situations where the recommendation is only supported with very low certainty for the benefits and very low certainty for the harm outcomes, the guideline panel put a higher value on risk avoidance.

Document Review

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

PICO Question: What is the role of endoscopic surveillance versus no surveillance in patients with non-dysplastic Barrett's esophagus?

Recommendation: In patients with non-dysplastic Barrett's esophagus, the AGA suggests performing endoscopic surveillance compared to no surveillance (*conditional recommendation, low certainty*).

Implementation Considerations:

- Endoscopic surveillance is suggested every 3 years in patients diagnosed with non-dysplastic Barrett's esophagus if a high-quality endoscopic examination was performed. Surveillance intervals may be extended to every 5 years in patients at lower risk of progression, for instance those with short-segment BE (<3 cm).
- Discontinuation of surveillance endoscopy in patients with non-dysplastic Barrett's esophagus should be considered based on age and medical comorbidities.

Summary of the evidence

Evidence informing the recommendation regarding endoscopic surveillance versus no surveillance in patients with NDBE is derived from an RCT, comparative observational cohort studies, and case-control studies. A prior SR/MA evaluated the association of BE surveillance on EAC-related mortality as well as overall mortality and EAC stage at diagnosis, and included only observational studies published from January 1996 through September 2017.[27] We updated the search with a similar search strategy that spanned from September 2017 through January 2025 (**Supplementary Table 1**). Our updated search identified 832 studies for title and abstract screening, of which 36 underwent full text screening, and no additional relevant comparative cohort studies were identified for further analysis. The only available new evidence identified was a recently published RCT, the Barrett's Oesophagus Surveillance versus endoscopy at need Study (BOSS trial).[28]

For the critical outcome of EAC-specific mortality, evidence was derived from the prior SR/MA which evaluated four comparative cohort studies. There was no significant heterogeneity among the studies ($I^2 = 0\%$). The largest study included in this analysis was by El-Serag et al., which

included 209 patients with EAC diagnosed during BE surveillance endoscopy compared with 215 EAC patients and prior BE diagnosed by non-surveillance endoscopy.[29] Data addressing the critical outcome of overall survival was derived from the BOSS trial. This trial was performed at 109 centers in the United Kingdom, randomizing patients to surveillance endoscopy every 2 years versus "at need" endoscopy offered only for evaluation of symptoms. The primary outcome was overall survival in the intention-to-treat analysis, and secondary outcomes included cancer-specific survival (including cancers aside from EAC), time to diagnosis of EAC, and stage of EAC at diagnosis. In total, 3,453 patients were recruited, with 1,733 patients randomized to surveillance every 2 years and 1,719 patients randomized to "at need" endoscopy. For the primary outcome of overall survival, median follow-up time was 12.8 years. Mean age at time of randomization was 63 years, 71% of patients were male, and 56% of patients had long-segment BE.

Data regarding the harms of surveillance endoscopy were derived largely from two large national database studies as well as adverse events from the BOSS trial. The study by Kim et al. evaluated 387,647 patients in Korea who underwent upper endoscopy in a retrospective cohort study and assessed for serious complications within 30 days of procedure including bleeding, perforation, and cardiopulmonary events.[30] Additional evidence from Wang et al. evaluated over 7 million upper endoscopies in the United States and assessed for infections within 7 days of endoscopy.[31]

Benefits

The critical outcomes that informed the benefits for this PICO question were EAC-specific mortality and all-cause mortality (**Tables 4 and 5**). Other patient-centered critical outcomes were the diagnosis of early-stage EAC/HGD. Data for the critical outcome of EAC-specific mortality were derived from non-randomized studies. For the critical outcome of EAC-specific mortality, the SR/MA by Codipilly et al. found a pooled risk ratio (RR) of 0.60 (95% CI 0.50, 0.71) with an absolute risk reduction of 231 fewer per 1,000 (from 289 fewer to 168 fewer) (**Table 5**).[27] Data for the critical outcome of overall survival were derived from the BOSS trial. All-cause mortality in the surveillance group was 19.2% (333 deaths in 1,733 patients) versus 20.7% in the

"at need" endoscopy group (356 deaths in 1,719 patients) (HR 0.95; 95% 0.82, 1.10). The absolute risk reduction in the group undergoing scheduled endoscopic surveillance was 9 fewer per 1,000 (from 34 fewer to 18 more) (**Table 5**). As supportive evidence, for the outcome of all-cause mortality, the SR and MA by Codipilly et al. examined three studies with comparative groups and found a HR of 0.75 (95% CI 0.59, 0.94). The SR and MA also performed sensitivity analyses attempting to adjust for lead-time bias for the outcome of all-cause mortality, which also found an attenuated reduction in mortality in the group undergoing endoscopic surveillance versus no surveillance (HR 0.85; 95% CI 0.75, 0.95). Data for the important outcome of stage of EAC diagnosis were derived from the outcome of early-stage EAC and HGD detection rates from the BOSS trial. In the scheduled surveillance endoscopy group, 3.3% (58 of 1,733 patients) were found to have early-stage EAC or HGD versus 1.2% (20 of 1,719 patients) in the at-need surveillance group, with a relative risk of 2.82 (95% CI 1.73, 4.56). The absolute risk difference was detection of 21 more cases of early-stage EAC/HGD per 1,000 in the scheduled surveillance group (from 8 more to 41 more). As supportive evidence, for the outcome of early-stage disease detection, the SR and MA by Codipilly et al showed that prior BE diagnosis cohorts were significantly more likely to present with earlier stage EAC (Stage 0/I) compared to cohorts without a prior diagnosis of BE (RR 5.52; 95% CI 3.7-8.24, I^2=96%) (**Table 5**).

Harms

The patient-important outcomes that informed the harms for this PICO question included serious adverse events associated with endoscopy. Assessing for adverse events within 30 days after endoscopy, Kim et al. found a bleeding rate of 7.9 per 10,000 persons and perforation rate of 0.4 per 10,000 individuals. Thirty-day cardiopulmonary events included cerebrovascular accidents in 2.8 per 10,000 individuals, acute myocardial infarction in 2.8 per 10,000 individuals, and congestive heart failure in 1.5 per 10,000 individuals.[30] In addition, the large database study by Wang et al. found a 7-day infection rate after endoscopy of 30 per 10,000 individuals, including respiratory infections in 0.3% of patients and bacteremia in 0.07% of patients.[31] The BOSS trial found serious adverse events in 8 (0.46%) patients in scheduled surveillance and 7 (0.41%) patients in the "at need" endoscopy group.[28]

Certainty of the Evidence

The overall certainty in the evidence considering the benefits of the intervention across the critical outcomes was low (**Table 5**). For the critical outcome of EAC-related mortality, we relied on data from non-randomized studies included in a SR/MA. This evidence was very low in certainty due to serious risk of bias, as these studies did not adjust for length time bias and only three studies adjusted for lead-time bias. For the critical outcome of overall mortality and early stage EAC/HGD, we utilized data from a single RCT with a low certainty of evidence with supporting data from non-randomized studies from an SR/MA. This evidence was rated as low in certainty due to serious or very serious imprecision. We defined the minimally important difference (MID) for overall survival of 1-1.4%, and for this outcome, there was crossing of 2 MID thresholds, from clinically significant mortality reduction to clinically significant increase in mortality. To assess adverse events associated with surveillance endoscopy, we utilized data with low certainty of evidence from non-comparative observational cohort studies.

Discussion

Endoscopic surveillance is suggested in patients with NDBE with the primary goal of early detection of BE-related neoplasia (early EAC or HGD); patients who may be managed by EET reducing the morbidity and mortality associated with esophagectomy and preventing mortality related to EAC.[8-11] The BOSS trial is the first and only RCT of surveillance of BE and contributed important evidence to address the PICO. The guideline panel acknowledged several factors that ultimately impacted the evidence to decision process for this recommendation. This trial did not directly report on EAC-specific mortality, one of the critical outcomes for this PICO. Cancer-specific mortality was reported as a secondary outcome, which included all cancers, and separately reported esophageal cancer (not necessarily EAC) with 22 in the surveillance arm and 19 in the "at need" endoscopy arm. BOSS was likely underpowered for the outcome of overall mortality and for the outcome of EAC-specific mortality if it had been ascertained, as the study planned for a mortality rate of 1.25% per year and HR of 1.3 without surveillance, translating roughly to an absolute expected difference of 0.29% per year. Even though 5-year mortality from EAC is 79%,[32] BE patients are 10-times as likely to die from non-EAC causes than EAC,[33] so EAC is a small proportion of all-cause mortality, making that a laudable, but difficult primary end-point to achieve. A recent SR and MA that assessed EAC and non-EAC mortality risk in

patients with BE showed all-cause mortality was elevated in BE patients compared to population controls [pooled standardized mortality ratio (SMR) 1.24 (95% CI 1.01-1.53)] driven in part by increased EAC mortality risk (SMR 8.98; 95% CI 5.12-15.77). BE patients were 10 times more likely to die from non-cancer etiologies than EAC (RR 10.71, 95% CI 5.98-19.16).[33]

Observational studies suggest a progression rate of NDBE to EAC of 0.6% per year and a RR with surveillance for EAC mortality of 0.6,[27, 34-36] which would roughly translate to a substantially smaller expected absolute difference in mortality of 0.19% per year with surveillance compared to no surveillance. The BOSS trial observed 356 deaths in 1,719 patients over a median of 12.8 years in the "at need" arm for a mortality rate of roughly 1.6% per year. A difference of 0.19% per year with surveillance as expected based on observational studies would roughly equate to a HR of 0.88 for overall mortality, which is within the confidence intervals of the effect observed in the BOSS trial. In addition, a prominent feature of BOSS was that subjects in the control arm were allowed to have upper endoscopies "at need," including for subjectively worsening symptoms of gastroesophageal reflux disease (GERD). Upper endoscopies were utilized in 59% of subjects in the "at need" group, with median intervals between endoscopies only slightly longer than those assigned to surveillance (25.7 months vs 24.8 months), thereby greatly diminishing the power and precision to detect differences between surveillance and no surveillance arms needed to address this PICO. The indications for the endoscopies in the "at need" group were not available. The guideline panel also recognized that nearly 25% of patients at study inception did not have intestinal metaplasia limiting the generalizability of these results as these patients would not be routinely enrolled in endoscopic surveillance programs in the United States. It is unclear how many surveillance endoscopies adhered to the basic tenets of a high-quality endoscopic exam. More than half the EACs were diagnosed in the surveillance arm with T stage greater than 1 which is far greater than observed in prospective high quality surveillance programs.[37] For these reasons, the panel relied heavily on observational studies to inform most of the outcomes of this PICO. The guideline panel acknowledges the limitations of the observational studies as well, including potential for selection effects for whom upper endoscopy was performed, lead-time and length-time effects, and potential unmeasured confounders.

The sum of available data indicates that there are likely benefits from surveillance, and those benefits are likely small to moderate, but with low certainty. Undesirable effects of surveillance were judged to be trivial, and surveillance was expected to be acceptable to patients and feasible to implement. Costs of surveillance were judged to be moderate. The cost-effectiveness analysis of the BOSS trial results concluded that surveillance was unlikely to be cost-effective, but it did not account for the contamination described above and in the Markov analysis modeling extension of the trial beyond the observed period, it assumed there was no mortality benefit from shifting stages with earlier diagnosis.[38] A prior SR of cost-effectiveness analyses regarding surveillance strategies that included EET for dysplasia, found that each of the identified studies concluded that surveillance was cost-effective.[39-41] The panel concluded that the available data probably favors endoscopic surveillance in patients with NDBE compared to no surveillance, but the quality of available data only permits endorsing a conditional recommendation and there may be important variability in patient values and preferences with regard to surveillance.

Implementation considerations

Endoscopic surveillance intervals

Though the evidence discussed above supports endoscopic surveillance in NDBE, the data supporting specific surveillance intervals are weaker. Surveillance intervals for NDBE suggested by the earliest published guideline (every 2 to 3 years) were based on expert opinion informed by the observed incidence of progression to cancer in a few small case series of patients undergoing surveillance.[42] There have been very few empiric studies to directly guide surveillance intervals, and no RCTs. For instance, a few small cohort studies from before the widespread use of endoscopic therapy for dysplasia (and before availability of high definition endoscopes with virtual chromoendoscopy, and with unknown quality of biopsy sampling) totaling 21 patients who progressed to cancer demonstrated that dysplasia was detected in 54% at endoscopies performed 2 years before cancer detection, but only in 18%, 20%, and 25% at 3, 4 and 5 years, respectively.[43-45] A case-control study comparing patients with GERD who died from EAC or gastric cardia adenocarcinoma compared to controls with GERD found that the only statistically

significant interval of a prior endoscopy associated with protection from cancer death were those performed at 2 or 3 years; however, none of the controls spared from cancer death had undergone esophagectomy raising concerns about the biological mechanism explaining the observed association.[46] A cohort study of patients undergoing close surveillance with Seattle protocol biopsies demonstrated that somatic chromosomal alterations increased dramatically between 24 and 48 months prior to progression to cancer, along with co-selection of large regions of gains or losses in chromosomes and chromosome instability, which occur with or before evidence of histological dysplasia.[47, 48]

The risk of neoplastic progression from NDBE has since been evaluated by numerous studies, with larger and varying designs.[34, 35] The observed incidence of progression to cancer depends on study design (population-based vs. active surveillance cohort), duration of follow-up, definition of BE and whether patients with neoplasia diagnosed within the first year are excluded. A modeling study indicated that the study designs would converge to an incidence of 6.4 per 1,000 patient-years with long enough follow-up.[36] Guidelines have primarily relied on cost-effectiveness analyses for suggesting surveillance intervals, which in turn, rely on, or are calibrated to these observed progression rates. Cost-effectiveness analyses that have included strategies of endoscopic therapy of dysplastic BE have identified optimal surveillance intervals of every 2 to 5 years in non-dysplastic BE, depending on the setting (U.S. with shorter intervals than U.K. where the willingness-to-pay threshold is lower) and sex (shorter intervals in men than women).[39-41] Based on the modeling of male individuals with BE in the U.S. and the cohort studies above, we suggest endoscopic surveillance intervals of every 3 years in patients with NDBE.[41]

The performance of these surveillance exams is dependent on a high-quality endoscopic exam. Studies have shown a high prevalence of missed dysplasia and cancer especially on index exam, as indicated by high rates of post-endoscopy esophageal adenocarcinoma (PEEC) and post-endoscopy esophageal neoplasia (PEEN) in BE patients undergoing surveillance.[1, 49] Pooled analysis reports PEEC of 17% in patients diagnosed as NDBE on index exam.[49] Prior guidelines and these recent observations have fueled the discussion on repeating an upper endoscopy in

patients with NDBE within the first year of index endoscopy to reduce the rates of PEEC and PEEN. However, this approach of repeat endoscopy within the first year has limitations due to potential overuse of resources and associated costs. The recommended approach is to maximize the quality of the endoscopic exam along with sampling using a structured biopsy protocol (detailed in subsequent sections) for detection of dysplasia and EAC at the index endoscopy when BE is suspected. However, if clinical circumstances preclude this optimal endoscopic assessment of BE, repeat endoscopy within the first year of diagnosis of NDBE may be considered.

The suggested surveillance intervals of every 3 years in NDBE might be modified based on clinical risk factors. The risk factor with the greatest evidence is length of BE,[50] and other guidelines have also recommended surveillance every 5 years in patients with short segment BE (<3 cm). [51-53] The data supporting this concept of using BE length as a risk stratification tool are derived from several observational studies. A SR and MA that examined risk factors for progression to HGD/EAC reported that increasing BE length per centimeter was associated with an increased risk of progression (OR 1.25; 95% CI 1.16-1.36).[54] Another MA of 10 studies that assessed risk of progression based on BE length among 1979 patients with BE length <3 cm and 2118 patients with BE length of ≥3 cm.[50] The annual risk of progression to EAC was significantly lower for shorter segments than for long-segment BE [0.06% vs. 0.31% (OR 0.25, 95% CI 0.11-0.56)]. For the combined endpoint of HGD/EAC, progression rates were lower for short-segment compared with long-segment BE [0.24% vs. 0.76% (OR 0.35, 95% CI 0.21-0.58)]. It should be noted that while some clinical factors, particularly shorter BE length, are associated with lower risk of progression from NDBE to cancer, direct evidence indicating short segment BE is associated with a longer dwell time in the dysplastic state or intramucosal cancer is not available. If patients with lower risk of progression to cancer do not also have longer dwell times in those states, then less frequent surveillance in low-risk BE may only add cost and risk without maintaining benefit relative to surveillance every 3 years.

Risk Stratification Based on Clinical Variables

There are a number of clinical variables that might be used to stratify risk of progression and guide surveillance intervals. The risk of progression to HGD or EAC doubles for every 4 cm increase in length.[55] Smoking has also been associated with approximately 1.5 greater odds of progressing.[55] In 2 meta-analyses, male sex was associated with approximately double the risk of progressing compared to female sex.[55, 56] However, in a MA of 11 of 66 eligible studies that provided individual-level data, the association was found to be weaker (HR 1.44).[57] The Progression in Barrett's Esophagus (PIB) score was developed by combining known risk factors: male sex (9 points), smoking (5 points), BE length (1 point/cm) plus including confirmed LGD (11 points).[58] A low risk category defined as <11 points had an annual risk of progression to HGD or EAC of 0.13% per year over mean follow-up of 6 years in the development cohort, and 0.2% per year over a median follow-up of 7.5 years in a validation study.[59] It should be noted that the point estimates used in PIB for the effects of male sex and smoking (HR 3.0 and 1.8, respectively) were stronger than identified in the MA above, and weaker for length (doubling every 6 cm). Age might be an additional useful clinical risk, but additional studies are needed. In a meta-analysis, the risk of progression appeared to double with each additional 26 years of age, but in the few studies that adjusted for other risk factors, the risk appeared to double even with every 3.5 years of advancing age but did not reaching statistical significance.[55] Increasing body mass index has also been associated with increased risk of progression (OR 1.06 per increments of 5 kg/m^2).[60] Although family history has been associated with BE and with EAC,[61] there is very limited data regarding the risk of family history on progression from non-dysplastic BE.[62]

Discontinuation of surveillance

As patients age and develop comorbidities, the risks of complications from surveillance increase, and the risks of competing causes of death increase while the potential benefits from surveillance endoscopy commensurately decrease. This may be particularly so among many individuals with BE, who are at increased risk of mortality from cardiovascular disease compared to the general population.[63, 64] A survey of gastroenterologists endorsed the paradigm that surveillance of NDBE should be discontinued at some point, dependent on age and comorbidities.[65] There are no RCTs or prospective studies to guide the precise decision about when to discontinue

surveillance. A comparative cost-effectiveness analysis with 3 independent models suggested that the optimal timing of last surveillance EGD for NDBE ranged from less than 65 to 83 years, depending on sex and comorbidities.[66] In all 3 models, optimal discontinuation was at younger ages in women compared to men despite the longer life expectancy in women due to the lower risk of progression to cancer. We suggest initiating the conversation about deciding when to discontinue surveillance at the earliest potential penultimate EGD (e.g., age 75 in a man without comorbidities), introducing the concept of diminishing benefit and rising risk with continued surveillance with advancing age. We suggest shared decision making with the patient to determine when to discontinue surveillance. Length of BE might also be used to help narrow the range of ages (shorter segments discontinuing earlier). Another important factor, tied to patient life expectancy and comorbidities, is the patient's fitness to undergo repeat endoscopy, and ability to tolerate endoscopic, surgical or oncological therapies for esophageal neoplasia. The European Society for Gastrointestinal Endoscopy recommends cessation of endoscopic surveillance in individuals at age 75 years in the absence of a prior history of dysplasia.[51]

PICO Question: What is the optimal imaging strategy for Barrett's esophagus patients undergoing endoscopic surveillance? Should adult patients with Barrett's esophagus undergo screening or surveillance endoscopy using high-definition white-light endoscopy plus chromoendoscopy versus white-light endoscopy alone?

Recommendation: In patients undergoing screening or surveillance endoscopy for Barrett's esophagus, the AGA recommends using a combination of high-definition white light endoscopy plus chromoendoscopy compared white light endoscopy alone (*strong recommendation, moderate quality of evidence*).

Implementation Consideration:

- Among the chromoendoscopy modalities that meet optimal performance characteristics, the choice of chromoendoscopy modality (virtual or dye-based chromoendoscopy) should be based on endoscopist and center expertise.
- Chromoendoscopy-directed biopsies should be used as an adjunct to sampling using a structured biopsy protocol rather than a substitutive technique to a structured biopsy protocol.

Summary of the Evidence

Evidence informing the recommendation for chromoendoscopy (CE) plus high-definition white light endoscopy versus white light endoscopy (WLE) alone was driven from RCTs. CE included both conventional dye-based CE and virtual chromoendoscopy (VCE). We identified a systematic review and meta-analysis published by the American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee in 2019[67] that included 12 RCTs which were assessed against our inclusion criteria. One study was removed because it was an unpublished conference abstract before the year 2020. We conducted a new search to update the results of this previous meta-analysis. We limited our search strategy to include only RCTs and identified a total of 1033 studies (**Supplementary Table 2**). We selected RCTs that included BE

patients undergoing surveillance comparing CE plus WLE to WLE alone. We identified 1 additional RCT[68] and thus, a total of 12 RCTs were included in the final meta-analysis. These RCTs were either crossover or tandem studies in design. Six studies used dye-based CE [68-73], 5 studies used VCE [74-78] and 1 study used both [79]. All studies were full papers from western countries. Baseline pathology varied between studies including HGD/EAC (3 studies) [70, 74, 79], all degree of dysplasia including NDBE (6 studies) [68, 71-73, 75, 78], all degree of dysplasia including NDBE except EAC (1 study)[69], BE with dysplasia (1 study) [77] and LGD only (1 study). [76]

Benefits

The critical outcome for this PICO question was incremental detection of HGD/EAC during surveillance (**Table 4**). MA of 11 RCTs using random-effects models (795 patients in the CE plus WLE group and 795 patients in the WLE alone group) demonstrated a significantly higher detection rate of HGD/EAC using CE plus WLE [RR: 1.2 (95% CI:1.03-1.4, I^2: 0%)] (**Figure 1**). The absolute increase in HGD/EAC detection was 33 more cases per 1000 patients (95% CI: 5 more to 67 more cases) (**Table 6**). Dysplasia detection (endpoint of LGD/HGD/EAC) was considered an important outcome. Ten RCTs were included with 817 participants in each arm. CE plus WLE detected 368/817 dysplasia cases compared to 311/817 with WLE alone [RR: 1.16 (95% CI: 1.07 – 1.27, I^2: 0%)] with an absolute increase of dysplasia detection of 61 more cases per 1000 patients (95% CI: 27 more to 103 more) (**Figure 1, Table 6**).

MA of 5 RCTs comparing dye-based CE plus WLE to WLE alone included 323 participants in each arm and demonstrated a similar point estimate for the RR of detection of HGD/EAC as in the overall analysis, but not reaching statistical significance [RR: 1.19 (95% CI: 0.96-1.46, I^2: 0%)] and absolute increase of HGD/EAC detection of 12 more cases per 1000 patient (95% CI: 3 fewer to 30 more) (**Table 6, Supplementary Figure 2**). MA of 6 RCTs comparing VCE plus WLE to WLE alone included 472 participants in each arm and likewise demonstrated no significant difference in detection of HGD/EAC [RR: 1.22 (95% CI: 0.97-1.52, I^2: 0%), but with a similar point estimate as overall, and absolute increase of HGD/EAC detection of 52 more cases per 1000 patient (95% CI: 7 fewer to 123 more)] (**Table 6, Supplementary Figure 2**). For

the endpoint of dysplasia detection (LGD/HGD/EAC), MA of 6 RCTs comparing dye-based CE plus WLE to WLE alone included 443 participants in each arm and demonstrated that dysplasia detection was significantly higher with dye-based CE [RR: 1.19 (95% CI: 1.02-1.39, I^2:28.4%) and absolute increase of dysplasia detection of 53 more cases per 1000 patients (95% CI: 6 more to 108 more)] (**Table 6, Supplementary Figure 2**). MA of 4 RCTs comparing VCE plus WLE to WLE alone included 374 participants in each arm and demonstrated no difference in dysplasia detection with RR: 1.16 (95% CI: 0.99-1.37, I^2: 0%) and absolute increase of dysplasia detection of 80 more cases per 1000 patient (95% CI: 5 fewer to 186 more) (**Table 6, Supplementary Figure 2**).

Given the potential for selection bias by including studies with enriched populations (patients with an established diagnosis of HGD/EAC), a subgroup analysis was performed by restricting the analysis to the 7 RCTs [68, 69, 71-73, 75, 78] that included patients undergoing endoscopy for NDBE and BE-related neoplasia which reflects the general BE surveillance population more accurately. The studies included 564 participants in each arm and demonstrated a significantly higher detection of HGD/EAC using CE with WLE versus WLE alone [RR: 1.55 (95% CI: 1.05 -2.29. I^2: 0%)]. There was no difference in dysplasia detection between CE with WLE versus WLE alone [RR: 1.17 (95% CI: 0.95 -1.46, I^2: 0%)].

For the outcome of number of biopsies required to diagnose dysplasia, a single crossover RCT was identified that compared HD-WLE using the Seattle biopsy protocol to narrow band imaging (NBI) with targeted biopsies of abnormal mucosal or vascular patterns.[78] In this study, a total of 123 patients with BE were randomized and both HD-WLE and NBI detected 92% patients with intestinal metaplasia but NBI required fewer biopsies per patient (3.6 vs. 7.6, p<0.0001). NBI detected a higher proportion of areas with dysplasia (30% vs. 21%, p=0.01), and all 14 cases of HGD/EAC but only 29% of LGD cases. All areas that harbored HGD and EAC had an irregular mucosal or vascular pattern. This study showed that NBI-targeted biopsies can have the same rates of intestinal metaplasia detection as HD-WLE with the Seattle biopsy protocol while requiring fewer biopsies. We found no studies specifically addressing the role of CE in reducing rates of PEEC and PEEN.

Harms

CE is generally well-tolerated with no significant adverse events reported in the included studies. The group considered potential harms associated with CE especially with dye-based CE. One such risk is an allergic reaction to contrast dyes, although this is rare. Additionally, there is a theoretical concern that methylene blue, when photosensitized by white light, may cause oxidative DNA damage. This effect has been observed to be more pronounced in Barrett's mucosa, raising concerns that it could potentially accelerate carcinogenesis.[80] Finally, the use of CE may lead to an increase in the number of biopsies taken, potentially raising the risk of procedural complications, though this risk remains minimal. The use of CE may increase procedure time. Despite these concerns, the overall risk of harm is considered very low, particularly with VCE. With regards to cost-effectiveness of CE, no additional cost is incurred for VC as this technology is now available in most endoscopes and does not add any significant risks to the patient. A single cost-effectiveness study showed that dye-based CE using acetic acid in high-risk BE patients was more cost effective than random biopsy sampling.[81]

Certainty in Evidence of Effects

The overall certainty in the evidence across the outcomes was moderate (**Table 6**). Our certainty in the critical desirable outcome of detection of HGD/EAC was moderate. No risk for bias and inconsistency among studies was detected. Furthermore, we considered the indirectness of the outcome due to lack of longitudinal follow up period to determine long term impact of CE. Additionally, studies lacked a true gold standard which could have led to incorrect categorization of the outcomes. However, this would be applicable to increased detection of dysplasia and EAC using both imaging strategies and hence we assumed that the effect would not change with time and decided not to rate down for indirectness. The panel also discussed the potential selection bias in studies using enriched populations that included patients with BE-related neoplasia referred for EET. This was mitigated by performing a sensitivity analysis that included studies with all degrees of dysplasia which was felt to represent the surveillance population more

accurately. The evidence was rated down for imprecision because all the CI were crossing the pre-defined MID threshold from no clinically significant increase in diagnosis to clinically significant increase in diagnosis of any dysplasia or HGD/EAC. The panel also acknowledged that all studies were conducted at expert centers largely by expert endoscopists and the assessment of diagnostic and incremental yields of dysplasia among non-expert centers may lead to different estimates.

Discussion

Several advanced imaging techniques have been developed and studied with the primary purpose of increasing dysplasia and early EAC detection, to identify lesions that may be missed by an examination using HD-WLE and sampling using a structured biopsy protocol alone. CE-directed examination may be conducted using dye-based approaches that requires the application of various topical dyes or solutions to the BE mucosa or VC that uses light filters within the endoscope to achieve enhancement of the mucosal surface abnormalities. Among the VC platforms, narrow band imaging (NBI) is the most widely studied and used VC technique in clinical practice. It uses blue light with narrow-band filters that enables detailed imaging of the mucosal and vascular surface patterns with a high level of resolution and contrast without the need for dye spraying.[82] Other VC platforms use proprietary post-image acquisition processing technology to modify the white-light image enhancing the superficial mucosal and vascular patterns. [67] Among the various dye-based CE approaches, acetic acid CE is the most widely studied and utilized in clinical practice. Acetic acid CE enhances mucosal surface patterns by contrast staining – initial application results in an initial whitening of the BE segment and areas of neoplasia lose this whitening more rapidly than NDBE epithelium.[51]

The performance characteristics of CE in BE surveillance patients have been reported on a per-lesion analysis and not per-patient analysis, the latter is more relevant, is patient centered and allows for an accurate assessment of the overall impact of CE on patient management. The ASGE Preservation and Incorporation of Valuable Endoscopic Innovations document has provided acceptable performance thresholds for advanced imaging techniques in BE

surveillance.[83] NBI (sensitivity 94.2%, NPV 97.5%, specificity 94.4%) and acetic acid CE (sensitivity 96.6%, NPV 98.3%, specificity 84.6%) met these acceptable performance thresholds.[84] The author panel acknowledged the multiple classification systems described using CE (VCE and dye-based CE). An international group of experts developed and validated an NBI classification system for detection of dysplasia and EAC in patients with BE using NBI images of NDBE, HGD and EAC to characterize regular and irregular mucosal and vascular patterns visible by NBI.[85] The overall sensitivity and specificity for these criteria to detect HGD/EAC in selected still images was 80% and 88% and improved to 91% and 93%, respectively when the assessment of images was made with high confidence. The panel suggests the use of this classification system in routine clinical practice acknowledging the limited data on the impact of CE on dysplasia and EAC detection in live endoscopies and the learning curves associated with these advanced imaging techniques. Training tools such as the "Barrett's Oesophagus-Related Neoplasia" (BORN) web-based training course is an available validated training course that primarily focuses on improving early neoplasia detection.[86] This tool can be accessed at www.iwgco.net, www.ueg.eu, or www.best-academia.eu. No comprehensive training course is currently available that covers all facets of best practices in BE and this deficit is the focus of ongoing research.

Implementation Considerations

Given the comparable incremental yield of dysplasia using VC and dye-based CE, [67] the guideline authors made no recommendation on the choice of CE technique (VC over dye-based CE, type of VC platform or type of dye). Among the CE modalities that meet optimal performance characteristics, the choice of CE modality should be based on endoscopist and center expertise. All contemporary endoscopy systems include VC platforms and circumvent several issues related to dye-based CE, such as the need for additional equipment (dye and catheters), time consuming and tedious nature of the procedure, difficulty achieving complete and uniform coating of the mucosal surface, and inability to detect superficial vascular patterns within the BE segment.

The guideline authors considered the role of CE-directed targeted biopsies as a substitute to HD-WLE with sampling using the Seattle biopsy protocol. The panel acknowledged the limited data addressing this question and the current PICO was designed to address the adjunctive role of CE to HD-WLE and not as a substitute for a structured sampling approach to BE patients undergoing surveillance.[78] Areas that do not appear suspicious on CE may still harbor dysplasia and a meta-regression analysis in a SR/MA showed that the overall number of biopsies strongly correlated with the diagnostic yield of dysplasia.[87] Thus, CE-directed biopsies should not be used as a substitute for sampling using a structured biopsy protocol. The substitutive role of sampling directed by CE or artificial intelligence platforms needs to be addressed in future studies.

Furthermore, the role of artificial intelligence (AI) in enhancing dysplasia and early EAC detection among patients undergoing endoscopic screening and surveillance examinations needs to be defined. AI platforms are currently being assessed as a method to target neoplastic areas for sampling using deep learning computer-aided detection (CADe) and computer-aided diagnosis (CADx) systems, characterize neoplastic lesions suitable for endoscopic resection, and potentially quantitate the comprehensiveness of endoscopic examinations.[88-94] Pilot studies have also demonstrated that these platforms can be utilized during live endoscopic procedures.[89, 90] A recent study aimed to develop, test and benchmark a CADe system for early neoplasia detection in BE using images and videos of NDBE and BE-associated neoplasia patients.[95] The sensitivity for neoplasia detection increased from 74% to 88% with CADe assistance (OR 2.04) for images and from 67% to 79% (OR 2.35) for videos without compromising specificity (primary outcome). Using the benchmarking test set, the CADe system was superior to endoscopists in detecting neoplasia (90% vs. 74%, OR 3.75) for images and 91% vs. 67% (OR 11.68) for videos and non-inferior to BE experts. A recent pilot study also showed that CADx assistance significantly increased characterization performance of BE-related neoplasia by general endoscopists to the level of expert endoscopists.[96] While it is anticipated that these AI platforms will impact the current approach to BE surveillance, the utility in enhanced detection of dysplasia and early EAC will need to be demonstrated in RCTs.[97]

General Implementation Considerations:

1. All patients with suspected or established Barrett's esophagus undergoing screening or surveillance endoscopy should be sampled using a structured biopsy protocol that includes targeted biopsies from any visible lesions and random 4-quadrant biopsies every 2 cm if no prior history of dysplasia and every 1 cm if there is a history of dysplasia.

Patients with suspected or established BE undergoing screening or surveillance endoscopy should undergo sampling using a structured biopsy protocol to minimize sampling bias. After careful examination of the Barrett's mucosa under optimal visualization, it is recommended that tissue sampling is performed according to a systematic approach using the Seattle biopsy protocol. The Seattle biopsy protocol includes targeted biopsies of all visible or visually suspected lesions detected using HDWLE or CE, as well as random four quadrant biopsies every 1-2 cm throughout the Barrett's segment extending from the squamocolumnar junction to the lower esophageal sphincter (**Figure 2**).[98] Additionally, it is recommended to place specimens from each level and biopsies from targeted lesions in separate jars identified by distance from the incisors. The goal of sampling with the Seattle protocol, while potentially time intensive, is to help increase the accuracy and yield of detection of dysplasia and EAC in BE patients undergoing screening or surveillance endoscopy.[99-101]

Multiple observational studies support the routine use of a structured biopsy protocol for screening and surveillance BE exams. Pooled data from two studies comprising of 506 patients with known BE undergoing surveillance showed a higher rate (19.1%) of dysplasia detection with Seattle protocol compared to those undergoing non-protocolized biopsies (2.6%), with a relative effect of 6.27 (95% CI: 2.75 to 14.33).[102] In a study from the UK of 222 patients there was a significantly higher proportion of dysplasia detection (LGD/HGD/EAC) with a systematic four quadrant biopsy protocol (73%) compared to solely targeted biopsy (27%) under WLE.[99] A retrospective study found that systematic 4-quadrant biopsies outperformed targeted biopsies

directed by narrow band imaging (NBI) alone, with 57.1% of HGD and 86.3% of LGD events diagnosed using biopsies from protocol 4-quadrant biopsies.[103]

There are some limitations with the Seattle biopsy protocol that need to be acknowledged including sub optimal adherence rates as low as 49% [104,101, 105] This sampling approach is time consuming and associated with considerable costs. An important factor associated with low adherence is longer BE segment length with the likelihood of non-adherence increasing by 31% for every 1 cm of BE in the GIQuIC national quality benchmarking registry.[106, 107] Arguably those with longer BE segment length, who have a higher probability of harboring dysplasia, would be the group who would benefit the most from the Seattle biopsy protocol. In sum, in the context of existing observational data, BE patients undergoing screening or surveillance endoscopy should be sampled using a structured biopsy protocol (i.e., the Seattle biopsy protocol).

General Implementation Considerations:

- Refer patients with Barrett's esophagus-related neoplasia, including patients diagnosed with low-grade dysplasia and indefinite for dysplasia to high volume endoscopists with expertise in endoscopic eradication therapy, pathologists with expertise in BE neoplasia and access to multi-disciplinary care.
- Histologic diagnosis of Barrett's esophagus-related dysplasia or early cancer should be confirmed by an expert pathologist.
- The diagnosis of Barrett's esophagus and indefinite for dysplasia and low-grade dysplasia should be confirmed by a repeat upper endoscopy by an expert endoscopist within 6 months on high dose acid suppressive therapy primarily to rule out prevalent high-grade dysplasia or esophageal adenocarcinoma.
- Patients with confirmed Barrett's esophagus and low-grade dysplasia choosing surveillance should continue high dose acid suppressive therapy and undergo an upper endoscopy at 6-month intervals for 1 year, then annually, by expert endoscopists, until there is a change in histologic grade of dysplasia.
- Endoscopic eradication therapy in patients with Barrett's esophagus and indefinite for dysplasia, confirmed by expert pathology review, is not recommended.
- Patients with Barrett's esophagus and indefinite for dysplasia should undergo annual endoscopy, by expert endoscopists, until there is a change in histologic grade of dysplasia.

<u>Surveillance intervals and management of low-grade dysplasia patients choosing surveillance over endoscopic eradication therapy</u>

As outlined in the AGA Guideline document on EET for BE, patients found to have dysplastic BE and EAC should be referred to high volume endoscopists with expertise in endoscopic examination and resection, and pathologists with expertise in its interpretation.[11] Up to 27% of patients with BE and LGD, referred from community settings without a documented visible lesion to expert EET endoscopists are in fact found to have a visible lesion by the expert endoscopists, which requires endoscopic resection.[108] In addition, LGD can be upgraded to HGD/EAC based on expert pathology review and 26% of patients thought to have BE and LGD were upgraded by the expert endoscopist's tissue sampling to EAC in 7 to 11% of cases including some cases with advanced EAC not amenable to EET.[108-111] Regenerative changes in

esophageal mucosa secondary to inflammatory injury related to uncontrolled reflux can share some of the same histologic features as dysplasia, and can lead to an interpretation of LGD or indefinite for dysplasia (IND).[112] Assessment with ambulatory reflux monitoring has demonstrated that regression of ostensible LGD is associated with more effective suppression of esophageal reflux.[113, 114] Therefore, patients should have a repeat EGD performed by an expert endoscopist while on maximum acid suppression (PPI BID 30 to 45 minutes before meals for at least 2 months) with resection of any visible lesion to rule out prevalent HGD or EAC.

As outlined in the AGA Guideline on EET, a shared decision needs to be made with BE patients and confirmed LGD between pursuing EET or continued endoscopic surveillance.[11] For a detailed discussion regarding the equipoise between EET and endoscopic surveillance for BE with LGD, refer to the AGA Guideline on EET.[11] An expert pathologist classification of BE with LGD is associated with an annual incidence of progression to combined HGD or EAC of 5.7%, so if surveillance is chosen, it should be performed more frequently than in NDBE.[115] In a comparative cost-effectiveness analysis of 3 independent models, the optimal management strategy for LGD excluding strategies of EET following the confirmatory EGD would be surveillance at 6 month intervals for 1 year, then annually (from re-calculation of incremental cost-effectiveness ratios excluding EET strategies).[41] Preferably, those surveillance EGDs should be performed by an expert endoscopist with targeted tissue sampling of any visible lesions or endoscopic resection and random 4 quadrant biopsies every 1cm. If the patient reverts to NDBE under such tissue sampling, surveillance should be reverted to intervals of every 3 years.

Management of Barrett's esophagus and indefinite for dysplasia

BE and IND is commonly encountered in clinical practice and noted in up to 8.4% of BE patients.[116] A systematic review and meta-analysis from 2020 reported outcomes from 8 studies in BE patients with IND.[116] The pooled incidence of HGD and/or EAC (89 cases in 1441 patients over 5306.2 person-years) was 1.5 per 100 person-years (95% CI 1.0-2.0) with modest between study heterogeneity (I^2=56.5%). The pooled incidence of EAC alone (40 cases in 1266 patients over 4520.2 person-years) was 0.6 per 100 person-years (95% CI 0.1-1.1) with considerable between study heterogeneity (I^2=89%). A recent cohort study from two centers in the United Kingdom identified 102 biopsies with BE and IND in 88 patients.[117] Endoscopic follow-up was performed in 88% (n=78) patients and 12/78 progressed to LGD (15%, 2.6 per 100 person-

years), 6/78 progressed to HGD (7.7%, 1.3 per 100 person-years) and 6/78 progressed to EAC (7.7%, 1.3 per 100 person-years). Predictors of progression included longer BE segment, multifocal and persistent IND. Another recent multicenter cohort study reported outcomes on 242 BE patients with IND.[118] During follow-up, 184 (76%) had no evidence of dysplasia, prevalent neoplasia was identified in 23 (9.5%) patients (20 LGD, 2 HGD, 1 EAC) and 35 (14.5%) patients developed incident neoplasia (27 LGD, 5 HGD, 3 EAC) after a median follow-up of 1.5 years. The incidence rate of any neoplasia was 3.2 per 100 patient-years and HGD/EAC was 0.6 per 100 patient-years.

There are several challenges in the management of BE and IND patients similar to those encountered in the management of BE and LGD patients. As noted above, highly variable rates of progression to the diagnosis of HGD and EAC have been reported in a small number of studies with a retrospective study design with variable follow-up and selection bias. A high proportion of BE and IND patients do not demonstrate any dysplasia on subsequent endoscopy especially when performed on high dose PPI therapy (phenomenon of regression).[117] In addition, the interobserver variability among pathologists for this diagnosis is well described and related to the difficulty differentiating between true dysplasia and inflammatory changes or reactive atypia.[119] Consistent with recommendations provided in the EET Guideline document, the diagnosis of BE and IND should be confirmed by expert pathologist(s).[11] BE and IND patients are at risk for prevalent and incident neoplasia. These patients should also be evaluated at expert centers and undergo repeat endoscopy on BID PPI therapy within at least 3 months with repeat sampling using the Seattle biopsy protocol and resection of any visible lesions to confirm the diagnosis of IND and rule out prevalent HGD or EAC. Given the uncertainties in the true risk of neoplastic progression and the reduction in risk of progression to HGD/EAC using EET, EET is not recommended in patients with confirmed BE and IND. However, patients with confirmed BE and IND should undergo surveillance in 1 year and annually thereafter until there is a change in histologic grade of dysplasia. The role of risk stratification tools including the use of biomarkers to more accurately prognosticate the finding of BE and IND is discussed in another section of this guideline.

PICO Question: What is the role of adjunctive sampling techniques in patients with Barrett's esophagus undergoing screening or surveillance endoscopy? Should adult patients with Barrett's esophagus undergoing screening or surveillance endoscopy be sampled using structured biopsy protocol plus wide-area transepithelial sampling (WATS-3D) versus sampling using a structured biopsy protocol alone?

Recommendation: In patients undergoing screening or surveillance endoscopy for Barrett's esophagus, the AGA makes no recommendation for or against the use of WATS-3D as an adjunctive sampling technique to a structured biopsy protocol (*knowledge gap*)

Implementation Consideration:

- WATS-3D sampling should not be used as a substitutive sampling technique to a structured biopsy protocol.
- Findings of neoplasia on WATS-3D but a structured biopsy protocol without neoplasia (discordant results) should undergo repeat surveillance endoscopy by an expert endoscopist within 3-6 months on high-dose acid suppressive regimen with repeat sampling using a structured biopsy protocol and endoscopic resection of any visible lesions.
- If embarking on endoscopic eradication therapy in patients with high-grade dysplasia or esophageal adenocarcinoma solely based on WATS-3D sampling, discuss risks and benefits of endoscopic eradication therapy, need for adherence with reflux management, expected outcomes, need for continued surveillance after completion of endoscopic eradication therapy, with adequate time to assess patient values and preferences.
- In patients with Barrett's esophagus and crypt dysplasia, indefinite for dysplasia or low-grade dysplasia solely based on WATS-3D sampling, endoscopic eradication therapy should not be performed.

Summary of the Evidence

Evidence informing the recommendation for the use of WATS-3D as an adjunctive test to a structured biopsy protocol (Seattle biopsy protocol) was derived from RCTs, cross-sectional studies, and observational cohort studies. No direct comparative evidence with longitudinal follow-up from any RCTs or comparative non-randomized studies was found. A prior SR/MA evaluated the incremental yield of dysplasia detected by WATS-3D in conjunction with forceps biopsy compared with forceps biopsy alone.[120] The composite outcome of dysplasia in this prior

SR/MA included IND, LGD, HGD, and EAC. Those authors conducted a systematic search of prospective studies up to December 31, 2020, which yielded 7 studies (5 cross-sectional studies, 1 retrospective cohort study, and 1 RCT) included for analysis (**Supplementary Table 3**). We updated this systematic search using a similar strategy, starting from January 2021 until January 2025, which yielded 76 studies for abstract review. We excluded studies examining use of WATS-3D for the purpose of surveillance after EET. We identified 4 additional studies to include in our analysis (2 cross-sectional studies, 1 RCT, and 1 retrospective cohort study).[121-124] Our search strategy also included abstracts published within 3 years or less that did not have corresponding full text, although this yielded no new additional studies. We cross-referenced studies from the aforementioned SR/MA as well as a separate SR/MA also published in 2022, which additionally included 4 abstracts that we did not include in the analysis because they were published over 3 years prior to the end of our search date.[125]

Our primary outcome was adjunctive yield of neoplasia (LGD, HGD, or EAC) using WATS-3D with Seattle biopsy protocol versus Seattle biopsy protocol alone, defined as the proportion of cases of neoplasia identified by WATS-3D plus Seattle biopsy protocol divided by the proportion of cases identified by Seattle biopsy protocol alone (**Table 4**). In contrast to some of the included studies in the previously published SR/MA, we decided not to include crypt dysplasia (CD) or IND in our outcome of dysplasia due to their low risk of progression as well as variability in conventional histologic diagnosis of IND.[51] We excluded 2 of the 9 studies included in the 2022 SR/MA: 1) the study by Johanson et al. because the dysplasia outcome included CD, and 2) the study by Agha et al. because this study reported dysplasia only for the WATS-3D/Seattle protocol biopsy-discordant cases and thus we could not obtain adjunctive yield rates.[126, 127] To assess risk of progression to HGD/EAC among cases of BE with NDBE or LGD, we used the cohort study published by Shaheen et al. in 2022 which described progression rates based on WATS-3D diagnosis and compared this to natural history data available in the literature.[128] Historical progression rates published in prior SR for natural progression of BE with LGD was used as a comparator for the outcome of progression.[129]

For our final analysis, we included 4 studies including screening and/or surveillance populations and 5 studies including populations enriched for patients with a known prior history of BE-related neoplasia who were undergoing surveillance or potentially referred for EET. We conducted subgroup analyses for each of the two groups. Demographics among the screening or surveillance populations was similar, with male patients making up 39%-78% and mean age of 56-61 years. Among the patient groups enriched for neoplasia, male patients made up 53%-82% of the population with average age 63-68 years. The largest included study of an enriched population was the cross-sectional study by Trindade et al. which included 8,471 patients with baseline histology of LGD in 89 patients (1.1%), HGD in 11 patients (0.13%), and EAC in 22 patients (0.26%). In this study, 74% of patients had short-segment BE.[124] Demeester et al. performed an RCT randomizing 1,002 patients (786 for BE screening, 118 for BE surveillance) to undergo WATS-3D as stand-alone sampling method (497 patients) vs. Seattle biopsy protocol (505 patients), with most endoscopies performed for screening. Demographics included 66% females, mean age of 57 years, 89% of patients being White and 21% having short-segment BE. They found no difference in detection of LGD between the two methods of sampling [4/ 497 (0.8%) vs. 4/ 505 (0.8%), respectively]. Both WATS-3D and Seattle protocol biopsy detected 0 cases of HGD, and Seattle protocol biopsy detected 1 case of EAC whereas WATS-3D detected 0 cases of EAC.[122] For our outcome of progression to HGD/EAC, data from a single-arm, retrospective cohort study of 4,545 patients with NDBE, CD, or LGD who underwent both WATS-3D and forceps biopsy and had at least 1 follow-up upper endoscopy with WATS-3D at least 12 months after the index upper endoscopy were assessed. Their primary outcome was progression to HGD/EAC on subsequent forceps biopsy. [128] The mean overall follow-up was 2 years, included 50% females, mean age of 62 years, and 51% with short-segment BE.

Benefits

The critical outcomes that informed the benefits for this PICO question were: 1) yield of HGD/EAC, and 2) yield of neoplasia (defined as LGD, HGD, or EAC) (**Table 4**). Other patient-important outcomes we evaluated included reduction in rates of PEEC and PEEN, prediction of disease progression defined as a composite outcome of progression to HGD and/or EAC, and adverse events related to WATS-3D sampling. For the critical outcome of incremental detection

of HGD/EAC, pooled analysis of all 9 studies included a total of 33,132 patients, and found an increase in detection of HGD/EAC in the WATS-3D plus Seattle protocol biopsy vs. Seattle protocol biopsy alone with a relative risk of 1.61 (95% CI 1.25-2.08), with little between study heterogeneity (I^2=18%) (**Figure 3**). In the subgroup analysis for the 5 studies including only screening/surveillance populations, the relative risk was 1.35 (95% CI 0.92-1.99), and in the subgroup analysis including the population enriched for prior neoplasia, the relative risk was 1.75 (95% CI 1.18-2.58). Overall, the absolute difference for detection of HGD/EAC was 2 more per 1,000 patients, from 1 to 4 more per 1,000 patients. Including only the 4 screening/surveillance studies (excluding the 5 enriched studies), incremental detection of HGD/EAC with WATS-3D plus Seattle protocol biopsy versus Seattle protocol biopsy was 1 more per 1,000 patients, from 0 to 2 more per 1,000 patients.

For the critical outcome of detection of any neoplasia (including LGD/HGD/EAC), MA of 6 studies that reported this outcome included a total of 19,901 patients, and found an increase in detection of neoplasia in the WATS-3D combed with Seattle protocol biopsy vs. Seattle protocol biopsy alone with a relative risk of 1.36 (95% CI 1.14-1.64) with no between study heterogeneity (I^2=0%) (**Figure 3, Table 7**). In the subgroup analysis for the 3 studies including screening or surveillance populations alone, the relative risk was 1.42 (95% CI 1.00-2.00), and in the 3 studies in the subgroup analysis including the population enriched for prior dysplasia, the relative risk was 1.33 (95% CI 1.06-1.68). Among all included studies, the absolute incremental difference for neoplasia detection was 2 more per 1,000 patients, from 0 to 4 more per 1,000 patients. In the 3 screening or surveillance studies the incremental yield of all dysplasia detection using WATS-3D in addition to Seattle protocol biopsies was 3 more per 1,000 patients, from 0 to 7 more per 1,000 patients.

Assessing for the outcome of progression to HGD/EAC, we used data from the retrospective cohort study by Shaheen et al. [128] and compared this indirectly to previously described natural history data on progression of LGD to HGD/EAC. In this study, LGD was diagnosed by WATS-3D in 43 of 4,545 patients. Five of these 43 patients (11.6%) with LGD diagnosed by WATS-3D later developed HGD/EAC identified on forceps biopsy in the 2-year follow up period (5.79 per

100 person-years). In comparison, a previous meta-analysis reported the progression of LGD diagnosed on forceps biopsy to HGD/EAC was 1.7 per 100 person-years,[129] and studies of LGD with expert pathology confirmation have found progression rates of 0.8 to 13.4 per 100 person-years.[17] Additionally, in the Shaheen et al. study, 28 of 43 patients with LGD diagnosed by WATS-3D (65.1%) had regression to NDBE on subsequent endoscopy. We found no studies specifically addressing the role of WATS-3D sampling in reducing rates of PEEC and PEEN.

Harms

The patient-important outcomes that informed the harms for this PICO question included serious adverse events (SAE). There were no adverse events reported in any of the 9 included studies. One perforation was reported in the WATS-3D group in the RCT by Demeester et al, which occurred in a patient on chronic steroids who underwent upper endoscopy with WATS-3D in the operating room after a hiatal hernia repair/fundoplication for GERD. There were no details whether the perforation was related to the surgery or upper endoscopy.[122] Additional considerations included added time and cost. WATS-3D added a mean of 4.5-4.8 minutes to procedure time in addition to Seattle biopsy protocol.[121, 130] The cost-effectiveness of WATS-3D sampling as an adjunct to the Seattle biopsy protocol in BE patients undergoing screening or surveillance has not been assessed. Lastly, potential harms that should be considered with the use of WATS-3D include downstream effects of potential false positive results for dysplasia detection (where the diagnosis of dysplasia is not confirmed on subsequent follow-up endoscopy). Prior studies on cancer screening have suggested psychosocial harms or negative impacts of subsequent screening adherence that can be associated with false positive test results.[131, 132] Other potential harms could include unnecessary use of endoscopy for closer surveillance or adverse events following EET for treatment of false positive dysplasia that may be detected on adjunctive WATS-3D sampling (including bleeding, stricture or perforation) as described in the previously published AGA guideline on EET for BE neoplasia.[133]

Certainty of the Evidence

The overall certainty in the evidence across the critical outcomes and considering both benefits and harms was very low (**Table 7**). Our certainty in the critical outcomes of detection of HGD/EAC or neoplasia (LGD/HGD/EAC) was very low. The included cross-sectional studies reported adjunctive diagnostic yield of WATS-3D in addition to Seattle protocol biopsies without reference standard tests (e.g. confirmatory endoscopic biopsy). Thus, no downstream harms from false-positive testing were assessed. Given the adjunctive role of the test, there was lower concern for potential false negatives. The major concern in the quality of evidence was in the risk of bias. First, there was limited follow-up to assess outcomes related to increased dysplasia detection on WATS and lack of dysplasia confirmation on subsequent biopsy. Second, 5 of the 9 studies included study populations enriched for patients with dysplasia. We attempted to address this concern by performing subgroup analyses separating the 4 studies with solely screening or surveillance populations and the 5 studies with enriched populations.. The outcome for dysplasia detection was considered important but the data on benefits was very low in certainty. For the outcome of adverse events, the certainty of evidence was very low, and the effect estimate was very imprecise, and no data regarding downstream harm from false positive (FP) results are available. The panel was less concerned regarding false negative (FN) results given the adjunctive role of the test.

Discussion

Given the limitations of current endoscopic surveillance strategies, as highlighted above, the use of techniques to improve detection of BE-related neoplasia in patients undergoing surveillance endoscopy has received much attention in recent years. While advanced imaging techniques focus on increasing detection of dysplasia and early EAC by improving visualization of neoplastic areas, WATS-3D attempts to improve detection of intestinal metaplasia and dysplasia by increasing the surface area sampled.[67] This sampling platform uses an abrasive brush that is passed through the channel of the endoscope to sample deeper layers of the glandular Barrett's epithelium across areas with columnar lined mucosa. The sample acquired by this brush contains disaggregated clumps of structurally intact tissue, sample is then smeared on a slide, yielding a tissue specimen that is up to 150 µm in thickness, unlike a typical forceps biopsy slide in which tissue sectioning produces samples that are only 3-5 µm thick. This is followed by analysis using

a neural network algorithm designed to detect intestinal metaplasia and dysplasia and computer analysis that results in generation of 3-dimensional images of the sampled BE. These images are scanned and high-risk features are flagged for pathologists trained in interpretation of WATS-3D samples to review and provide a final diagnosis.[51, 134]

The guideline authors considered several factors while providing a recommendation for this PICO question. Several included studies were conducted using an enriched population of BE patients (patients with an established diagnosis of BE-related neoplasia referred for EET). The rationale for including these patients is for efficiency in design by increasing the event rates in these trials. However, the real clinical relevance of these adjunctive sampling techniques is best addressed in BE patients undergoing surveillance endoscopy without known dysplasia. For the critical outcome of HGD/EAC, WATS-3D was associated with increased dysplasia detection with a very low certainty of evidence. Both the absolute and adjunctive effects were attenuated when the impact of WATS-3D was restricted to a screening or surveillance population. Another major issue in most studies is that the incremental benefit in dysplasia detection was not confirmed in subsequent sampling and the longitudinal follow-up is limited. This makes it difficult to ascertain whether the incremental benefit is due to better sampling of the BE mucosa by WATS-3D with improved detection of dysplasia by the analysis platform and how much may be related to overdiagnosis of dysplasia (false-positive). The increase in dysplasia detection reported on WATS-3D is also largely driven by higher detection rates of LGD. The controversies related to this diagnosis are discussed extensively in the recent AGA guidelines on EET.[11] There is no RCT that has evaluated the adjunctive yield of dysplasia detection using WATS-3D in BE patients undergoing surveillance using high-definition white light endoscopy and chromoendoscopy. There are no studies assessing the cost-effectiveness of WATS-3D as an adjunctive sampling technique to the Seattle biopsy protocol for routine surveillance of BE patients and patient preferences and values have not been addressed. All reported studies were conducted using pathologists employed by CDx Diagnostics. Future studies need to demonstrate that these results can be reproduced by other non-industry pathologists improving the generalizability and utilization of this sampling technique in routine clinical practice. A recent pilot study showed that GI pathologists, without any prior experience in interpretation of WATS-3D, can interpret these specimens with a high level of accuracy and reproducibility after a short training session.[135] Future studies also need to assess the role of adjunctive sampling techniques

primarily in a community setting or among non-expert endoscopists; variables associated with lower adherence to surveillance guidelines and dysplasia detection rates.

Implementation Considerations

WATS-3D sampling should not be used as a substitutive sampling technique to a structured biopsy protocol (Seattle biopsy protocol). The use of WATS-3D sampling technique alone versus the Seattle biopsy protocol in BE patients undergoing screening or surveillance has not been assessed. This knowledge gap, the use of WATS-3D as a substitutive sampling technique, is currently being assessed in an ongoing multicenter RCT that will compare the diagnostic yield of LGD/HGD/EAC in BE patients undergoing surveillance between the Seattle biopsy protocol (4-quadrant biopsies every 2 cm with target biopsies from any visible lesions) with sampling using WATS-3D plus target biopsies from any visible lesions (NCT05530343).

Given the limited data addressing confirmation of dysplasia diagnosis noted WATS-3D sampling by repeat endoscopic sampling, patients with discordant results (neoplasia identified only on WATS-3D) should undergo repeat surveillance endoscopy within 3-6 months with repeat sampling using a structured biopsy protocol and endoscopic resection of any visible lesions. The management of patients diagnosed with HGD solely based on WATS-3D sampling (without confirmation on repeat endoscopic sampling) should be individualized and the risks and benefits of EET should be adequately discussed with patients. In addition to the traditional diagnosis of intestinal metaplasia and BE-related neoplasia reported on endoscopic samples and WATS-3D, [134, 136] pathologists report crypt dysplasia (CD) on WATS-3D samples when dysplasia is detected only in crypts and not in the surface epithelium.[128] Although previous studies suggest that the biologic and molecular properties of CD may be similar to LGD, clinical outcomes data associated with this diagnosis of CD are limited but appear to have intermediate risk between NDBE and LGD. [128] Based on these diagnostic uncertainties, patients diagnosed with CD, IND and LGD solely based on WATS-3D should undergo surveillance endoscopy on a high-dose acid suppressive regimen within 6 months.

Implementation Considerations:

Endoscopic evaluation in patients with suspected or confirmed Barrett's esophagus should meet the requirements of a high-quality endoscopic examination

In patients with known or suspected BE, it is important to perform a meticulous high-quality endoscopic exam with appropriate sampling for accurate disease staging and minimize the risk of missed dysplasia or neoplasia. The AGA Clinical Practice Update for a high-quality upper endoscopy exam[137] suggests pre-procedure, intra-procedure, and post-procedural best clinical practices. These best clinical practices as it relates to patients with BE are highlighted below and in **Table 13**.

Pre-procedure: Indications, benefits, and potential harms of the procedure should be discussed in detail as part of obtaining informed consent. Optimization of acid suppressive therapy prior to embarking on endoscopic surveillance for BE can help minimize potential challenges in interpreting results in the setting of active esophagitis and need for repeat procedures. Recommendations regarding periprocedural management of antithrombotic agents should be provided in accordance with published guidelines.[138]

Intra-procedure: Prior guidelines[51] have endorsed a ten-step approach to a high-quality endoscopic exam in BE.[139] The first steps rely on achieving and documenting adequate mucosal visualization. To ensure optimal visualization, consider using a distal attachment cap especially in patients who are referred for a diagnosis of BE-related neoplasia. Appropriate use of insufflation and desufflation enhances mucosal visibility and ensures accurate identification of landmarks such as a gastroesophageal junction and hiatal narrowing. Using mucosal cleansing agents as needed and cleaning the mucosa well using water, followed by aspiration of luminal contents, helps remove any mucosal debris. Once adequate mucosal visualization is achieved, the next step is to identify the esophageal landmarks including the top of the squamocolumnar junction (both the maximal and circumferential extent), the gastroesophageal junction, and the diaphragmatic hiatus. Accurate measurement and documentation of landmarks on each exam, serves as a reference point to help inform future exams and therapeutics.

Following landmark identification, adequate time should be taken to carefully examine the Barrett's segment using multiple pull-throughs and careful inspection of the distal esophagus, gastroesophageal junction and gastric cardia under retroflexion using high-definition WLE and CE (virtual or dye-based) to enhance identification of subtle mucosal lesions and vascular pattern abnormalities. It is suggested that endoscopists spend adequate time inspecting the Barrett's segment. Although data are limited, adequate inspection time would potentially increase detection of BE-related neoplasia. A single study showed that average inspection time of more than 1 minute for every 1 cm of Barrett's mucosa was associated with a higher detection rate of suspicious lesions (54% vs. 13.3%, p=0.04) and a trend towards higher detection of advanced neoplasia including adenocarcinoma (40.2% vs. 6.7%, p=0.06) compared to less inspection time.[140] Future studies are needed to define the optimal inspection time per cm of the BE segment. Although the guideline panel could not provide a time period comprising an adequate exam due to limited data, a European society guidelines recommend a procedure time of ≥7 minutes for upper endoscopy and inspection time of ≥1 min/cm of the circumferential extent of the BE mucosa.[141]

For documentation, use of a standardized reporting system is recommended. Prague classification is optimal to describe the circumferential and maximal extent of the columnar mucosa and location of the proximal gastric folds and diaphragmatic hiatus. Size and location of any islands proximal to the maximal extent of the BE segment should be documented. The Prague classification system (**Figure 4**) has been studied in endoscopists with varying degrees of experience[142] and in different settings[143] and has been shown to have excellent reliability in describing the circumferential and maximal extent of Barrett's mucosa with a reliability coefficient of 0.94-0.95 in videos BE segments of 1 cm or greater. [144] Size, location, and macroscopic appearance of any visible lesion using the Paris classification (**Figure 5**) is best to describe superficial neoplasia.[145] Representative images of visible lesions in patients with BE are highlighted in **Figure 6**. In addition to photo documentation of routine landmarks, any suspicious lesions or findings would benefit from more rigorous photo-documentation with annotation and inclusion of descriptive details to help inform future management. Finally, any presence or absence of erosive esophagitis should be graded and reported using the Los Angeles (LA) classification system (**Figure 7**). In the presence of active LA Grade C or D esophagitis, BE

surveillance endoscopy should be repeated at least six weeks after optimizing anti-reflux therapy with random biopsies obtained on the follow-up exam after healing of active esophagitis. However, a detailed inspection and targeted biopsies of any suspicious lesions is recommended even in the presence of severe reflux esophagitis. The guideline panel discussed the importance of preventing delays in diagnosing dysplasia and malignancy when concerning endoscopic findings are encountered in the setting of esophagitis. While the potential for overcalling dysplasia (especially LGD) in the setting of active inflammation exists, this should not preclude obtaining biopsies as expert pathologists have been shown to be able to distinguish inflammation from true LGD.[146] When such samples are obtained, documentation should include the presence and severity of the esophagitis visualized. Treatment for eight weeks was recommended as this has been the typical duration of most trials of PPI for the healing of esophagitis and has been recommended by prior guidelines.[147-149] The panel noted that a relook endoscopy is likely only needed for those with LA Grade C and D esophagitis (which means a significant portion of mucosal surface is destroyed)[150]. The indication for repeat endoscopy is to document healing of significant esophagitis and to assess for any persistent features of malignancy. Furthermore, follow-up EGD may reveal underlying BE in up to 10-12% of patients.[151-153] Only after completion of all the above described steps, Seattle protocol biopsy should be utilized for sampling of the BE segment, as previously detailed in this document.

Post-procedure: Immediately post-procedure, detailed instructions should be provided regarding any new recommendations based on endoscopic findings, as well as the timeframe to resume antithrombotic agents, if applicable. In the setting of tissue sampling, endoscopists are encouraged to document that further guidance would be provided once pathology is reviewed. Most patients suspected of harboring BE on index endoscopy are not confirmed as such on histology.[154] Therefore, endoscopists should refrain from recommending surveillance endoscopy in the report of the index endoscopy until pathology results are available. It is advisable to have a recall system in place for patients with BE undergoing surveillance at intervals in accordance with guidelines and presence of dysplasia.

Biomarkers in Barrett's Esophagus

A biomarker, as defined by the World Health Organization, is any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease.[155] Grade of dysplasia on histologic assessment of samples obtained during endoscopy is the biomarker that is currently utilized in clinical practice for risk stratification and management of BE. The rationale for the use of dysplasia is that progression in BE occurs in a stepwise and probabilistic fashion with progression through the stages of LGD to HGD to mucosal EAC and finally, invasive EAC. This progression is due to a series of genetic and epigenetic alterations,[156] leading to chromosomal instability and eventually carcinogenesis. However, there are several limitations to this strategy making dysplasia a far from perfect biomarker for risk stratification in BE. These include the existence of patchy and focal distribution of neoplasia within the BE segment escaping detection in a field of NDBE. This is not uncommon as a structured biopsy protocol samples only a fraction of the entire BE segment. This coupled with the lack of adherence to these biopsy protocols adds to the risk of sampling errors.[107] Even when present, the high degree of interobserver variability among pathologists for detecting dysplasia, including expert pathologists, decreases the impact and the efficiency of relying on a histologic diagnosis of dysplasia.[51, 157-159] Finally, recent data suggests that a substantial proportion of EACs develop more rapidly through an alternate pathway of genetic and epigenetic alterations, followed by genome doubling and then catastrophically acquiring genomic instability, oncogene amplification, and EAC. This pathway may explain in part EACs not detected through endoscopic surveillance programs.[156, 160, 161] These factors have provided the impetus to identify biomarkers for improved risk stratification in patients with BE.

The objective of this guideline was to evaluate the role of commercially available biomarkers for the neoplastic progression of BE in the United States. The outcomes of interest were the overall performance characteristics [sensitivity, specificity, true positive (TP), false positive (FP), true negative (TN) and false negative (FN), positive predictive value (PPV) and negative predictive value (NPV)] and biomarkers as predictors for progression among patients with BE. Similar to previous AGA guidelines on the role of biomarkers in inflammatory bowel disease,[162, 163] the guidelines panel considered the downstream consequences on important patient outcomes

corresponding to each possible outcome of the diagnostic test. Patients with TP results are identified as patients at increased risk of progression and would be considered for endoscopic surveillance at shorter intervals or undergo EET. Patients with TN results are at lower risk of progression and might undergo endoscopic surveillance at longer intervals. On the other hand, patients with FN results may be falsely reassured and may undergo endoscopic surveillance at longer intervals or no surveillance increasing the risk of undetected progression to EAC that is not amenable to EET. Patients with FP results may undergo unnecessary endoscopies and EET, increase patient anxiety and resource utilization.

PICO Question: What is the role of p53 assessment in patients with Barrett's esophagus undergoing endoscopic surveillance? Is p53 assessment superior to the grade of dysplasia in predicting progression in patients with Barrett's esophagus?

Recommendation: In patients diagnosed with non-dysplastic Barrett's esophagus, Barrett's esophagus with indefinite for dysplasia or Barrett's esophagus with low-grade dysplasia, the AGA makes no recommendation for or against the routine use of p53 assessment as an adjunct test to histopathology (*knowledge gap*).

Summary of the Evidence

Evidence informing the recommendation for the use of p53 as an adjunct test to standard assessment of dysplasia during endoscopic surveillance for BE surveillance was driven from both observational cohort and case-control studies. We identified a SR/MA by Snyder et al.[164] that evaluated the risk of progression to HGD/EAC associated with aberrant p53 expression. This SR/MA analyzed data from 14 studies including 7 cohort and 7 case-control studies ending in August 2017. We conducted a new literature search to update the results of this previous MA and studies included in this MA were assessed for inclusion in our updated SR and MA. The updated search spanned from August 2017 to January 2025, and we identified a total of 581 studies (**Supplementary Table 4**). We selected studies that evaluated the use of p53 immunohistochemistry (IHC) as an adjunct test to histopathology assessment of dysplasia/EAC on esophageal biopsies during BE surveillance and reported subsequent progression to HGD/EAC. We restricted our analysis to patients with baseline NDBE, IND or LGD and

excluded those studies with follow-up of <1-year, cross sectional studies and studies assessing p53 on cell collection devices alone. We included a total of 29 studies including 15 case-control studies, 13 cohort studies and 1 study with a case-control cohort and a prospective validation cohort. All studies were full papers from Western countries. Baseline pathology in case-control studies varied between NDBE only (5 studies), IND only (1study), NDBE/LGD (5 studies), and a combination of NDBE/IND/LGD (6 studies). Baseline pathology in cohort studies were IND only (1 study), IND/LGD (1 study) and a combination of NDBE/IND/LGD (11 studies). The average duration of follow-up in the studies was 4.4 years (range: 2.3-6.2 years). Studies defined aberrant p53 as either strictly overexpression of the p53 protein on IHC (13 studies) or as absent or overexpression of the p53 protein (13 studies) and the definition of aberrant p53 expression was not available for the remaining 3 studies. There was considerable variability between studies in how aberrant p53 expression was assessed and scored. The threshold for overexpression varied with some studies using a percentage of positive cells in the epithelium or the glands, while others relied on qualitative assessments by pathologists. Additionally, there was inconsistency in antibody selection and staining protocols. All these differences may have contributed to the significant variation in diagnostic performance of aberrant p53 expression between studies.

Benefits

The critical outcomes that informed the benefits for this PICO question were predicting progression to HGD/EAC, and diagnostic test characteristics (**Tables 4 and 8**). We relied on cohort studies to assess the risk of progression to HGD/EAC. The pooled proportion of patients with aberrant p53 expression based on the combined baseline pathology of NDBE, IND and LGD was 20% (95% CI: 14%, 27%; I^2: 90%). The pooled rate of progression among patients with BE undergoing endoscopic surveillance with aberrant p53 expression to HGD/EAC was 8 per 100 person-years (95% CI: 6, 11; I^2: 26.5%). In contrast, the pooled rate of progression to HGD/EAC among patients without aberrant p53 expression was 0.3 per 100 person-years (95% CI: 0.1, 0.6; I^2: 26.6%). Compared to patients without aberrant p53 expression, patients with aberrant p53 had significantly higher risk for progression to HGD/EAC [RR: 10.17 (95% CI: 6.89, 15; I^2: 12%)] (**Figure 8**).

The pooled proportion of aberrant p53 expression in patients with NDBE was 5% (95% CI: 1%,11%; I^2: 83%). The pooled rate of progression to HGD/EAC among NDBE patients with aberrant p53 was 7 per 100 person-years (95% CI: 4,11 per 100 person-years; I^2: 0%) compared to 0.5 per 100 person-years (95% CI: 0, 2.2 per 100 person-years; I^2: 90%) without aberrant p53 expression. Compared to NDBE without aberrant p53, NDBE patients with aberrant p53 had significantly higher risk for progression to HGD/EAC RR: 4.8 (95% CI: 3.12,7.38; I^2:92%). Using standard annual risk of progression of 0.6% among patients with NDBE [165], p53 testing resulted in an absolute increase of 23 additional cases of HGD/EAC per 1,000 individuals tested-years (95% CI: 13, 38 more cases) (**Table 8**).

The pooled proportion of aberrant p53 expression in patients BE with LGD was 52% (95% CI: 34%,70%; I^2: 79.4%). The pooled rate of progression into HGD/EAC among BE and LGD patients with aberrant p53 expression undergoing endoscopic surveillance was 11 per 100 person-years (95% CI: 4, 20 per 100 person-years; I^2: 61.9%) compared to 1 per 100 person-years (95% CI: 0,5 per 100 person-years; I^2: 55.9%) without aberrant p53 expression. Compared to BE and LGD patients without aberrant p53, LGD patients with aberrant p53 had significantly higher risk for progression to HGD/EAC [RR: 2.53 (95% CI: 1.56,4.1; I^2:0%)]. Using standard annual risk of progression of 1.7% among patients with LGD[166], p53 testing resulted in an absolute increase of 6 additional cases of HGD/EAC per 1,000 individuals tested (95% CI: 1, 13 more cases) (**Figure 8 and Table 8**).

The pooled proportion of aberrant p53 expression in patients with BE and IND was 28% (95% CI: 16%,42%; I^2: 81.6%). The pooled rate of progression to HGD/EAC among BE and IND patients with aberrant p53 expression undergoing endoscopic surveillance was 6 per 100 person-years (95% CI: 0,15 per 100 person-years; I^2: 73%) compared to 1 per 100 person-years (95% CI: 0,2 per 100 person-years; I^2: 0%) without aberrant p53 expression. Compared to BE and IND patients without aberrant p53 expression, BE and IND patients with aberrant p53 expression had a significantly higher risk for progression to HGD/EAC [RR: 4.99 (95% CI: 2.98, 8.35; I^2:0%)]. Using standard annual risk of progression of 1.5% among patients with IND [116], p53 testing resulted in an absolute increase of 20 additional cases of HGD/EAC detected per 1,000 individuals tested (95% CI: 10, 36 more cases) (**Figure 8 and Table 8**).

Harms

No studies specifically addressing harms associated with p53 testing were identified. The main concern was the possibility of unnecessary surveillance endoscopies at shorter intervals or EET for FP results and extending surveillance intervals for FN results. This was determined by assessing the diagnostic characteristics of p53 in nine studies providing information to conduct a MA for this outcome. The pooled sensitivity was 0.48 (95% CI 0.39,0.57) and the pooled specificity was 0.85 (95% CI 0.77,0.90) (**Table 8 and Figure 9**). Test characteristics such as TP, TN, FP, FN along with PPV and NPV were calculated using a 0.6% progression rate in NDBE patients. For 1 year of follow-up, for every 3 per 1000 TP test results there were 149 FP results and for every 845 TN results there were 3 FN test results. The calculated PPV was 2%, and NPV was 99.6% for 1 year of follow-up (**Table 8**). Furthermore, a subgroup analysis on diagnostic characteristics among patients with BE and IND and LGD was performed [IND only (6 studies), LGD and IND together (1 study) and LGD only (5 studies)]. The pooled sensitivity for BE and IND/LGD was 0.75 (95% CI 0.62,0.85) and specificity was 0.80 (95% CL 0.67,0.88). For BE and IND patients, the pooled sensitivity was 0.71 (95% CL 0.47,0.87), and the pooled specificity was 0.79 (95% CL 0.59,0.90). Using an annual progression rate of 1.3%, the test accuracy per 1000 individuals was: TP 9, FP 207, TN 780 and FN 4 for calculated PPV of 4.2% and NPV of 99.5%. Similarly, for LGD only, the pooled sensitivity was 0.85 (95% CI 0.68, 0.94), and the pooled specificity was 0.68 (95% CI 0.62, 0.72). Using a 1.73% progression rate, the test accuracy per 1000 individuals was: TP 15, FP 315, TN 668 and FN 2 for calculated PPV of 4.5% and NPV of 99.7% (**Table 8 and Figure 9**). The author panel had extensive discussions regarding the risk of unnecessary endoscopies and possible EET among patients with FP results. This could result in exposure to potential adverse events related to surveillance endoscopy or EET without any added benefit. Similarly, these FP results could result in financial and psychological burden on patients along with unnecessary healthcare costs and resource overutilization. The FNs could result in the potential for false reassurance leading to extending surveillance intervals placing patients at risk for disease progression and poor overall outcomes. The author panel also recognized the significant variability among pathologists in the interpretation of these results and the lack of standardized criteria that may contribute to inconsistent reporting adding to the diagnostic uncertainty complicating clinical decision-making.

Certainty in Evidence of Effects

The overall certainty in the evidence was very low. Evidence was assessed across all critical outcomes where the benefits and the harms for the diagnostic characteristics and test accuracy overall were considered based on baseline histology (**Table 8**). Several factors contributed to this assessment: the risk of bias was assessed using the QUADAS-2 tool and there were issues in multiple domains leading to very serious risk of bias: (1) patient selection: case-control study design was used in more than a half of the studies and not all the studies stratified results based on baseline histology; (2) index diagnostic test (p53): there were concerns regarding applicability of the index test since there was significant variability in interpretation of the test results; (3) reference test was standard biopsy and progression to HGD/EAC with variable follow-up periods leading to variable interpretation of results between studies. Furthermore, there was significant heterogeneity leading to inconsistent results, which could have been largely driven by significant variability in the methodology to perform p53 testing and the criteria applied for its interpretation. There was imprecision in the results with FPs crossing the clinical threshold of 20% (200/1000) and low event rate for number of patients progressing to HGD/EAC. Finally, the indirectness of the available data was another concern. The author panel acknowledged the lack of studies reporting on how p53 results impacts decision-making in clinical practice. Studies addressing the cost-effectiveness of p53 assessment are limited and with methodological issues.[167,168]

Discussion

The guideline panel decided to make a recommendation neither in favor of nor against the use of p53 testing and the role of p53 for risk stratification among patients with BE as a knowledge gap. p53 is an important tumor suppressor gene and alteration in function is a key event during progression of BE to EAC. The detection of p53 abnormalities in BE by immunostaining is the most widely investigated biomarker that can be used as an adjunct to aid in the diagnosis of dysplasia and as a biomarker for risk-stratification in BE. Aberrant expression of p53 protein is evidence of alteration in p53 function (either overexpression or absent expression).[51] Abnormalities in p53 expression can be detected by p53 immunostaining of formalin-fixed, paraffin-embedded BE tissue or sequencing. While sequencing provides an objective evaluation of p53 status and can be combined with other genomic biomarkers, this approach is time

consuming, expensive, requires special instruments and DNA isolation. On the other hand, p53 IHC has the largest body of evidence, is faster, relatively inexpensive and can be performed at any pathology laboratory that has the technical capability of performing it.

There are several issues with the routine use of p53 IHC in clinical practice. One major limitation is the subjective nature in the interpretation of p53 and the need for interpretive skill. There is no consistent scoring system and different criteria have been reported. The criteria proposed by Redston et al have undergone internal validation with a large longitudinal cohort and have been validated by sequencing.[169] These criteria and others have suggested that abnormal p53 IHC stain in a single-positive crypt is a sensitive and specific marker of dysplasia.[169, 170] To what degree that scoring system can be reproducibly used by pathologists in other settings is uncertain. In arriving at this recommendation, the guideline panel heavily weighed the following factors - the lack of data from RCTs, limited prospective validation data, the overall suboptimal diagnostic characteristics and the subjective nature of this test. In particular, the panel was uncertain how the results of routine p53 IHC in NDBE should be used to guide management. Patients with aberrant p53 may not have a great enough risk of progression to warrant EET, and patients with normal p53 may not have low enough risk to warrant infrequent surveillance or cessation of surveillance.

PICO Question: What is the role of TissueCypher testing in patients with Barrett's esophagus undergoing endoscopic surveillance? Is the TissueCypher test superior to the grade of dysplasia in predicting progression in patients with Barrett's esophagus?

Recommendation: In patients diagnosed with non-dysplastic Barrett's esophagus, Barrett's esophagus with indefinite for dysplasia or Barrett's esophagus with low-grade dysplasia, the AGA makes no recommendation for or against the routine use of TissueCypher testing as an adjunct test to histopathology (*knowledge gap*).

Summary of the Evidence

Evidence informing the recommendation for the use of TissueCypher (also known as Tissue Systems Pathology-9 test, Castle Biosciences, Friendswood, TX) as an adjunct test to standard assessment of dysplasia during endoscopic surveillance for BE was driven from both cohort and case-control studies. We identified two individual level data SRs and MAs by Iyer et al conducted in 2022[171] and Davison et al in 2023[172] that evaluated the risk of progression to HGD/EAC based on TissueCypher risk class (high, intermediate and low). Both MAs included the same 5 studies, 4 case-control and 1 cohort by Frei et al. 2021 (the latter included patients from the screening cohort for the SURveillance vs. RadioFrequency ablation - SURF trial).[173] We conducted a new literature search to update the results of the previous MA implementing the same search strategy used for p53 staining spanning from August 2017 to January 2025 (**Supplementary Table 4**). We did not identify any additional study since these MAs were published. Baseline pathology in these studies were: NDBE (1 study)[174], LGD (1 study)[173] and a combination of NDBE/IND/LGD (3 studies). [175-177] . The training set cases and controls used to train the algorithm were excluded from both MAs. Four studies assessed the utility of TissueCypher in predicting incident HGD/EAC (≥1 year after a BE diagnosis) and 1 study assessed the utility of TissueCypher in predicting prevalent HGD/EAC (within 1 year of BE diagnosis). TissueCypher risk class was divided into high, intermediate and low.

Benefits

The critical outcomes that informed the benefits for this PICO question were: 1) predicting progression to HGD/EAC, and 2) test performance (**Tables 4 and 9**). The MA by Iyer et al. analyzed individual level data from 552 patients with BE who were tested with TissueCypher (152 progressed to incident HGD/EAC and 400 non-progressors). Baseline pathology included NDBE (472), IND (32) and LGD (48). When high-risk TissueCypher was compared to the intermediate/low-risk category combined in the overall cohort, TissueCypher had a sensitivity of 38% and specificity of 94% with an OR of 6 (95% CI: 2.99, 12) for progression to HGD/EAC. When combined high/intermediate risk TissueCypher was compared to the low-risk category, TissueCypher had a sensitivity of 55%, specificity 82% and OR of 1.58 (95% CI: 0.8, 3.12) for progression to HGD/EAC. Among 472 patients with NDBE only (112 progressors, 360 non-progressors), high risk TissueCypher had a sensitivity of 37%, specificity 96% and OR of 13.55 (95% CI: 4.90, 37.43) for progression to HGD/EAC. When combined high/intermediate risk TissueCypher was compared to low-risk category in patients with NDBE, TissueCypher had a sensitivity of 52%, specificity 85% and OR of 6 (95% CI: 3.73, 9.52) for progression to HGD/EAC. Among 48 patients with LGD only (31 progressors, 17 non-progressors), combined high/intermediate risk TissueCypher had a sensitivity of 71% and specificity of 35% with OR of 1.33 (95% CI: 0.38, 4.71, P: 0.65) for progression to HGD/EAC. Among 32 patients with IND only (9 progressors, 23 non-progressors), combined high/intermediate risk TissueCypher had a sensitivity of 33%, specificity of 74% and OR of 1.42 (95% CI: 0.27, 7.52, P: 0.68) for progression to HGD/EAC (**Table 9**). Data were not available for high risk only among the subgroup of patients with LGD and IND. Davison et al[172] assessed the use of TissueCypher in predicting prevalent HGD/EAC. The study included 40 prevalent progressors, and 509 non-progressors. TissueCypher had a sensitivity of 77.5% in detecting missed prevalent cases of HGD/EAC. Patients who scored high or intermediate risk were more likely to harbor prevalent HGD/EAC with HR 30.9 (95% CI 13.4,87.6) and HR 7.6 (95% CI: 2.9, 20.8), respectively.

Harms

We did not identify any study addressing harms associated with the use TissueCypher testing. As described above for high/intermediate risk TissueCypher, results compared to the low-risk

category in patients with NDBE yielded a sensitivity of 52%, and specificity of 85%. Using the 0.6% HGD/EAC progression rate per year, among 1000 NDBE there were 3 TP, 3 FN, 845 TN and 149 FP (**Table 9**). Calculated PPV and NNP was 2% and 99.6%, respectively. Lastly, for IND (n=48) and LGD (n=32), the numbers of participants in the studies were very low making the pooled sensitivity and specificity estimates very imprecise. Similar to the discussion regarding the use of p53 testing, the author panel assessed harms by addressing the possibility of unnecessary surveillance endoscopies at shorter intervals or EET for FP results and extending surveillance intervals for patients at risk who had FN results. The panel again acknowledged the potential adverse events related to surveillance endoscopy or EET without any added benefit among patients with FP results. Similarly, these FP results could lead to financial and psychological burden on patients along with unnecessary healthcare costs and resource overutilization. The FNs could result in the potential for false reassurance leading to extending surveillance intervals placing patients at risk for disease progression and poor overall outcomes.

Certainty in Evidence of Effects

The overall certainty in the evidence for TissueCypher was very low. Certainty was assessed across all critical outcomes with consideration of the benefits and the harms for the diagnostic characteristics and test accuracy overall and based on baseline histology (**Table 9**). The risk of bias was assessed using the QUADAS-2 tool and there were issues in multiple domains leading to very serious risk of bias. Many of the same limitations to the use of p53 staining were identified with the use of TissueCypher testing (**Table 9**). In addition, the number of patients with IND and LGD was very small, leading to very serious imprecision. The author panel also acknowledged the lack of robust studies demonstrating how TissueCypher results should impact decision-making in clinical practice. The panel also recognized limited data addressing patient preferences and values and cost-effectiveness analysis.[168, 178]

Discussion

The guideline panel decided to make a recommendation neither in favor of nor against the use of TissueCypher testing and the role of TissueCypher testing for risk stratification among patients

with BE as a knowledge gap. TissueCypher, a tissue systems pathology assay, is an innovative approach to biomarker studies that uses systems biology, viewing tissue as a system comprising multiple compartments that can be analyzed quantitatively for genetic, immunologic, vascular and morphologic features relevant to progression from BE to EAC.[156] This test is performed on formalin-fixed, paraffin-embedded biopsy specimens that demonstrate BE. This test uses a spatialomics-based, multiplexed fluorescent imaging platform to automatically and objectively quantify 9 protein-based biomarkers, nuclear morphology and tissue architecture. The quantitative image analysis is linked to a risk prediction algorithm that integrates 15 quantitative image analysis features to produce a risk score ranging from 0-10, which then classifies patients into high, intermediate and low risk for progression to HGD/EAC within 5 years.[175, 176, 179, 180] TissueCypher has the advantage of being an objective test using a locked, automated assay algorithm. The factors underpinning the inability to provide a recommendation for the routine use of TissueCypher for risk stratification in patients with BE undergoing surveillance include the overall suboptimal diagnostic characteristics, the lack of data from RCTs and prospective validation data. The cost of TissueCypher is much greater than for p53, but with relatively similar test characteristics as p53 when combining high and intermediate risk score as suggested by the company (albeit without direct comparison with p53 within the same cohorts). Ongoing studies, including a multicenter RCT, will help determine whether TissueCypher can accurately predict progression in BE and LGD patients and in turn benefit from EET.[181]

Future research needs to focus on validation of biomarkers in prospective trials (ideally RCTs), cost-effectiveness analysis of routine use, automated assessment of p53 expression to reduce subjectivity, patient values and preferences, assess critical endpoints of EAC incidence and mortality and ultimately define the cohort likely to benefit the most from these tests. In addition, there are several other novel biomarkers (single or panel) that are being investigated currently using biopsy specimens or brushings to improve risk stratification.[182, 183] Studies performing a careful comparison between the available risk stratification strategies will be needed. Finally, a judgement must be made for acceptance of a FN biomarker test (if at all) that could increase the risk of missed cancer.

What Do Other Guidelines Say?

These recommendations are consistent with the 2022 American College of Gastroenterology guidelines on diagnosis and management of BE.[51] The British Society of Gastroenterology guidelines state that biomarker panels cannot yet be recommended as routine of care until evidence from RCTs is available. However, these guidelines suggest that p53 immunostain may improve the diagnostic reproducibility of a diagnosis of dysplasia in BE and should be considered as an adjunct to routine clinical diagnosis.[184] Similarly, the European Society of Gastrointestinal Endoscopy guidelines do not recommend the routine use of molecular biomarkers in patients with no evidence of dysplasia. Those guidelines recommend the use of p53 IHC to support reproducibility of dysplasia diagnosis and aid the assessment of atypia of uncertain significance.[53]

PICO Question: What is the role of chemopreventive strategies in the prevention of neoplastic progression in patients with Barrett's esophagus?

Recommendation: In adult patients with Barrett's esophagus, the AGA suggests the use of daily proton pump inhibitor therapy compared to no proton pump inhibitor therapy for the prevention of neoplastic progression of BE (*Conditional recommendation, low quality of evidence*)

Implementation Consideration:

In patients with Barrett's esophagus, counsel tobacco cessation and weight loss if overweight.

Summary of the evidence

Evidence informing the recommendation for the use of proton pump inhibitor (PPI) therapy versus no PPI to prevent progression to HGD/EAC in BE patients is derived from RCTs, observational cohort and case-control studies. A prior SR and MA evaluated the risk of progression to HGD/EAC in patients on versus off PPI.[185] This prior SR/MA analyzed data from 12 studies with a systematic search ending in September 2020. This included 6 cohort studies and 6 case-control studies. We updated the search with a similar search strategy that spanned from October 1, 2020, to January 2025 (**Supplementary Table 5**). Our updated search identified 355 studies for title and abstract screening, of which 11 underwent for full text screening, and no relevant studies were identified for further analysis. The prior SR/MA extracted odds ratios from individual studies, which used multivariate analyses to control for various confounders including age, sex, race, smoking, and BE length. There was significant heterogeneity among the studies (I^2 = 78%).

The two largest cohort studies included in the prior SR/MA were by Krishnamoorthi et al. and Gaddam et al.[186, 187] Krishnamoorthi et al. analyzed 12,373 patients in a United Kingdom research database and assessed the outcome of incident EAC among patients on versus off PPI, adjusting for age, gender, smoking, body mass index, hiatal hernia, type 2 diabetes, and use of various medications.[186] The mean age was 63 years, and 63% of the study participants were male. Absence of dysplasia at study inception was not identified definitively in this study;

however, inclusion of patients who had not had an upper endoscopy within 3 years prior to study date was used as an indicator of absence of dysplasia. Gaddam et al. conducted a prospective cohort study of 3,635 BE patients undergoing screening/surveillance and assessed the outcome of HGD/EAC adjusting for sex, age, race, BE length, histamine-2 receptor antagonist (H2RA) use, smoking history, and aspirin or non-steroidal anti-inflammatory drug (NSAID) use.[187] Mean age of participants was 61 years, with 88% being male and mean BE length of 3.5cm.

Indirect evidence, as supportive data, informing the recommendations for the use of PPI was derived from the AspECT trial, an RCT examining the impact of twice daily PPI versus once daily PPI to prevent progression to HGD/EAC, as well as of the use of PPI with aspirin versus PPI alone.[188] The AspECT trial is the only RCT thus far assessing the role of PPI therapy in the prevention of neoplastic progression in BE. This multi-center RCT was conducted in the United Kingdom and Canada, utilizing a 2x2 factorial design to randomize patients with BE into high-dose or low-dose PPI with or without aspirin. High-dose PPI consisted of esomeprazole 40mg twice daily, low-dose PPI was defined as esomeprazole 20mg once daily, and aspirin dose was defined as 300mg daily in the UK and 325mg daily in Canada. All medications were taken for at least 8 years. Mean age of study participants was 59 years, 80% were male, and mean BE length was 4cm. Median follow-up was 8.9 years (interquartile range [IQR] 8.2-9.8 years), making up 20,095 patient-years of follow-up. The primary composite endpoint was time to HGD, EAC, or all-cause mortality. Secondary aims for which the study was not fully powered included time to the individual outcomes of HGD, EAC, or all-cause mortality, as well as cause-specific mortality. In total, 2,557 patients were recruited between 2005-2009, including 1,281 in the high-dose PPI group (704 without aspirin, 577 with aspirin) and 1,276 in the low-dose PPI group (705 without aspirin, 571 with aspirin). Ultimately, 1,270 patients on high-dose PPI and 1,265 patients on low-dose PPI were included in the intention-to-treat analysis.

Evidence regarding harms associated with PPI use are derived from the AspECT trial and two additional RCTs, the COMPASS and MANAGE trials.[189, 190] The COMPASS trial was an international, double-blind, placebo-controlled trial with a 3x2 factorial design including patients with stable atherosclerotic disease, where patients were randomized to receive low-dose rivaroxaban with aspirin, high-dose rivaroxaban alone, or aspirin alone to compare primary cardiovascular outcomes. Participants not already taking a PPI at baseline (64% of study cohort)

were randomized to receive either pantoprazole 40mg or placebo once daily. The study's primary outcome was rate of cardiovascular disease. Safety outcomes included PPI adverse effects including pneumonia, *C difficile* infection, non-*C difficile* enteric infections, fracture, gastric atrophy, chronic kidney disease, and dementia. In total, 17,598 participants were included, with 8,791 randomized to PPI and 8,807 randomized to placebo. The mean age was 67.6 years, 78% were male, and 60% were White European. The median follow-up was 3 years (IQR 2.5-3.6 years).

Additional evidence on PPI adverse events was obtained from the MANAGE trial.[190] This was an international, randomized placebo-controlled trial with a 2x2 factorial design where patients were randomized to receive dabigatran versus placebo, and all patients not already taking PPI were also randomized to omeprazole 20mg once daily versus placebo. The study results regarding PPI outcomes have not yet been published in a peer-reviewed journal. However, we were able to obtain the results in preliminary form by contacting the study authors. In total 556 of the 1,754 patients from the MANAGE trial were randomized to omeprazole versus placebo. Patients were followed for a mean of 17 months to assess for a primary outcome of major upper gastrointestinal events. The study also assessed PPI adverse events including *C difficile*-associated diarrhea, diarrhea, community-acquired pneumonia, and fracture.

Benefits

The critical outcomes that informed the benefits for this PICO question were: 1) progression to HGD/EAC, and 2) progression to EAC (Tables 4 and 10). Other patient-important outcomes we evaluated included EAC mortality. For the critical outcome of assessing differences in progression to HGD/EAC between daily PPI versus no PPI use, pooled analysis using the SR/MA by Chen et al found a pooled odds ratio (OR) of 0.47 (95% CI 0.32, 0.71) with an absolute risk reduction of 84 fewer per 1,000 (from 44 fewer to 112 fewer).[185]

We also utilized indirect data from the AspECT trial, where the intervention was high-dose (twice daily) PPI versus low-dose (daily) PPI as the comparator. In the intention-to-treat analysis, 1,270 patients in the twice daily PPI group and 1,265 patients in the once daily PPI group were analyzed. HGD/EAC occurred in 84 (6.6%) of the twice daily PPI group versus 100

(7.9%) of the once daily PPI group (RR 0.84; 95% CI 0.63, 1.11). The absolute risk reduction was 13 fewer per 1,000 (ranging from 9 more to 29 fewer). For the critical outcome of difference in progression to EAC alone, only indirect evidence was available since the comparison was twice daily PPI to once daily rather than PPI to no PPI. Comparing twice daily PPI versus daily PPI in the AspECT trial, EAC occurred in 40 patients (3.1%) in the high-dose PPI group versus 41 patients (3.2%) in the low-dose PPI group (HR 0.97; 95% CI 0.63, 1.50). The absolute risk reduction was 1 fewer per 1,000 (from 16 more to 12 fewer) (**Table 10**).

For the patient-important outcome of difference in EAC-related mortality, only indirect evidence was available, also ascertained from the AspECT trial. Comparing patients receiving high-dose PPI versus low-dose PPI, there were 8 events (0.6%) versus 12 events (0.9%), respectively (HR 0.65; 95% CI 0.27, 1.57). Lastly, the AspECT trial evaluated the question of adding aspirin to PPI versus PPI alone. In the intention-to-treat analysis, 1,138 patients received aspirin while 1,142 patients did not receive aspirin. HGD/EAC occurred in 65 patients (5.7%) who received aspirin versus 93 patients (8.1%) who did not receive aspirin. EAC occurred in 31 patients (2.7%) who received aspirin versus 30 patients (2.6%) who did not receive aspirin (HR 1.0; 95% CI 0.62, 1.58). EAC-related mortality was not analyzed for this comparison due to too few events.

Harms

The patient-important outcomes that informed the harms for this PICO question included serious adverse events (SAE) related to PPI use. SAEs were reported in the AspECT trial according to the Common Terminology Criteria for Adverse Events, with serious events defined as grade 3-5. In total, 13 SAEs were attributed to esomeprazole in either the low- or high-dose PPI groups, corresponding to an SAE rate of 0.06% per year. Four of these SAEs occurred in the low-dose PPI group (0.3%) versus 9 events in the high-dose PPI group (0.7%).

We also evaluated several adverse events associated with PPIs, including *C. difficile* infection, non-*C. difficile* infections, chronic kidney disease, dementia, and fracture, which have been reported to be potentially associated with PPI use in several observational studies.[189, 191-197] While multiple observational studies have suggested other potential adverse events associated with PPI, we restricted our evaluation to these select events due to the availability of prospective

evidence in subsequently described RCTs as well as the perceived frequency with which patients may raise related concerns, such as in the case of dementia (**Supplementary Figure 3**) . In the COMPASS trial, only non-*C. difficile* enteric infections were statistically significantly more likely to occur in the PPI versus placebo group (1.4% versus 1.0%; OR 1.33; 95% CI 1.01, 1.75). The combined outcome of both *C. difficile* and non-*C difficile* enteric infections occurred in 1.5% of the PPI group versus 1.1% of the placebo group (OR 1.37, 95% CI 1.05, 1.79). The absolute risk was 4 more per 1,000 (ranging from 1 more to 8 more). Rates of *C. difficile*, chronic kidney disease, dementia, pneumonia, and fracture were similar between the PPI versus placebo groups (C. difficile: 0.1% versus <0.1%; OR 2.26; 95% CI 0.70, 7.34; CKD 2.1% versus 1.8%; OR 1.17, 95% CI 0.94, 1.45; dementia: 0.6% versus 0.5%; OR 1.20, 95% CI 0.81, 1.78; pneumonia: 3.6% versus 3.6%; OR 1.02, 95% CI 0.87, 1.19; fracture: 2.3% versus 2.4%; OR 0.96, 95% CI 0.79, 1.17). Results from the MANAGE trial were similar with regards to rates of adverse events between the omeprazole versus placebo groups. Between the PPI versus placebo groups, rates of *C. difficile*-associated diarrhea (0.7% versus 0), diarrhea (7.7% versus 6.7%), community-acquired pneumonia (3.8% versus 2.6%), and fracture (3.8% versus 2.6%) were similar.[198]

We were able to pool adverse event data on the outcomes of *C. difficile* infection, fracture, and pneumonia from the COMPASS and MANAGE trials. Comparing the PPI versus placebo groups, the relative risk of *C. difficile* infection, fracture, and pneumonia were 2.48 (95% CI 0.8, -7.44), 0.98 (95% CI 0.81, 1.18), and 1.03 (95% CI 0.88, 1.20), respectively (**Supplementary Figure 3**). The absolute risk of *C. difficile* infection with PPI use compared to placebo was 1 more per 1,000 (from 0 fewer to 3 more), the absolute risk of fracture with PPI use compared to placebo ranged from 5 fewer to 4 more per 1,000 (from 5 fewer to 4 more), and the absolute risk of pneumonia with PPI use compared to placebo was 1 more per 1,000 (from 4 fewer to 7 more). The author panel acknowledges that long-term AEs associated with PPIs are less well-established, since mean follow-up in both the COMPASS and MANAGE trials with regards to PPI use was relatively short (3 years and 1.4 years, respectively). PPI use required in BE patients can be in the order of years to decades, so further data on long-term adverse events are needed. A recent meta-analysis of RCTs found no association of cardiovascular events with PPI therapy.[199]

Certainty of the Evidence

The overall certainty in the evidence across the critical outcomes and considering the benefits of the intervention was low (**Table 10**). Despite having higher certainty in harms, given the low certainty in the benefits of PPI, the overall certainty in the evidence was rated as low. For the critical outcomes of progression to HGD/EAC between patients taking PPI versus no PPI, we largely relied on data from non-randomized studies included in a SR/MA. This evidence was very low in certainty due inconsistency, as there were studies demonstrating significant benefit with PPIs whereas some studies that did not show any benefit (I^2=78%). Although most of the studies were case-control in design with concern for residual cofounding, the pooled OR in the prior SR/MA used multivariable adjusted estimates, and thus, we did not further rate down for risk of bias. Due to the absence of high-quality direct evidence for this question, we also relied on indirect evidence from a single RCT evaluating the question of twice daily PPI versus once daily PPI to inform our recommendation. We rated down for indirectness on the level of comparison. To assess adverse events associated with PPI use, we utilized data from high-quality RCTs that had limited follow-up time, with overall moderate certainty of evidence. Studies addressing the cost-effectiveness of chemopreventive strategies and patient values or preferences using PPI therapy were not identified.

Discussion

PPIs are prescribed in patients with BE to control GERD symptoms, heal erosive esophagitis, and as a chemopreventive agent to reduce progression to dysplasia and EAC.[51] High dose BID PPI therapy is prescribed in BE-related neoplasia patients undergoing EET, details are highlighted in the AGA EET Guideline document.[11] Current available evidence from observational studies suggests that PPIs may reduce the risk of neoplastic progression to HGD/EAC. Studies have also highlighted the lack of any significant effect with the use of histamine receptor antagonists.[200]

The guideline panel recognized the potential for adverse events related to PPIs and conducted a detailed risk benefit analysis for the use of PPIs in patients with BE. The authors recognized several issues with studies reporting adverse events related to PPI therapy. Several of these studies describing these associations are low-quality, retrospective, observational studies that are limited by residual confounding and other analytic biases and most importantly, do not establish

causality.[201, 202] In most studies, the association is no more than modest and biases can account for the small but statistically significant associations frequently encountered in this literature. Many of the described associations also do not have any plausible biologic mechanism of action and the absolute risk to patients is small given the rarity of the adverse events.[202] It is recommended that patients with BE are prescribed at least once-a-day PPI therapy to reduce the risk of neoplastic progression. Control of reflux symptoms along with healing/prevention of erosive esophagitis should also be accounted for in the dose of prescribed PPI therapy. The AGA published a recent Clinical Practice Update on special considerations for long-term PPI therapy use that focuses on: (i) ensuring that the patient has a strong indication for long-term PPI use, (ii) when indicated, counseling the patient regarding the rationale, and efficacy, the issues related to published literature on adverse events and that benefits outweigh the potential risks, (iii) using PPI at the lowest dose necessary and (iv) for patients concerned about a specific adverse event, consider describing the absolute excess risk of the adverse event per-patient-year and management in patients with specific risk factors for the adverse event.[202]

Epidemiologic evidence using observational studies and biomarker-based preclinical studies have shown that aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of EAC by inhibiting the cyclooxygenase pathway.[203-208] The results of the AspECT chemoprevention study were discussed extensively among the guideline panelists and guided the recommendations regarding use of aspirin and high-dose PPI therapy as chemopreventive strategies in BE patients. This study demonstrated that high-dose PPI was superior to low-dose PPI for lengthening the time to reach the combined end point of death from any cause, HGD or EAC [time ratio (TR) 1.27; 95% CI 1.01, 1.58, p=0.038]. Censoring those with the use of concurrent NSAIDs, aspirin was superior to no aspirin (TR 1.29, 95% CI 1.01, 1.66, p=0.04). Finally, combining high-dose PPI with aspirin had the strongest effect compared with low-dose PPI without aspirin (TR 1.59; 95% CI 1.14, 2.23, p=0.006). Accounting for the several study limitations and caveats, the guideline panel did not make any recommendation regarding the use of aspirin or high-dose PPI therapy to prevent neoplastic progression in BE patients. This study showed that there was no difference between high-dose versus low-dose PPI and aspirin versus no aspirin groups for the composite endpoint of progression to HGD or EAC; cancer-related outcomes that are most relevant in patients with BE. The overall event rate was low, a small effect size was noted with benefit largely driven from reduction in all-cause mortality without a

concomitant significant reduction in EAC incidence, for which a biological rationale is lacking. Long-term data on adverse events related to high-dose PPI are limited. Thus, a decision to prescribe high-dose PPI therapy to prevent neoplastic progression needs to account for the above factors (net benefit versus harms) along with patient values and preferences. The guideline authors acknowledge that the clinical profile of several BE patients may require daily aspirin for cardio-protection. Evidence from the AspECT trial showed that participants taking aspirin were more likely to have adverse events than those who were not (RR 1.17, 95% CI 1.02, 1.35) and may have been attenuated by the use of high dose PPI therapy. [188, 209]

The guideline panel also acknowledged the growing body of literature describing the efficacy of potassium-competitive acid blockers (P-CABs) in the management of patients with GERD and discussed in depth in a recent AGA Clinical Practice Update. [210] The benefits of P-CABs over PPIs include more rapid onset with initial dosing, no premeal dosing requirement, less variability in pharmacodynamic effects related to CYP2C19 metabolism, higher potency, and longer duration of effects. These medications have higher costs and there are limited long term safety data among patients using P-CABs. The role of P-CABs in patients with BE needs to be evaluated in future studies for the endpoints of reflux symptom control, healing of erosive esophagitis, reduction in neoplastic progression and outcomes in BE-related neoplasia patients undergoing EET. Extrapolating the available data from GERD patients, P-CABs may be considered in patients with BE who continue to have symptoms or erosive esophagitis on twice-daily PPI therapy.

<u>Implementation Consideration:</u>

In addition to a chemoprevention strategy that includes use of acid suppression with PPIs, neoplastic progression prevention also includes behavioral modification. Tobacco use is both refluxogenic as well as mutagenic,[211] increasing the odds of developing BE by 67%. Many risk prediction models therefore include smoking history as a factor when evaluating eligibility for screening.[51] Further, tobacco use also has been identified as a significant risk factor in BE progression to HGD as well as EAC,[212] with a hazard ratio of progression that is nearly double among tobacco users compared to non-users. Likewise, tobacco cessation may reduce BE-associated risks. Previous data demonstrated that among smokers who had quit for >20 years, there was no increased risk of BE.[213] As a result, smoking cessation should be encouraged

among patients undergoing BE surveillance. Although quantifiable evidence for risk reduction with tobacco cessation among BE patients is lacking, encouraging such behavior has pleiotropic health benefits and plausible direct advantages for BE specifically. Recent GERD guidelines suggest avoidance of tobacco among those with GERD.[214] Likewise, screening for tobacco use and providing tobacco cessation counseling among all adult patients is an accepted quality measure and was recently adopted within a gastroenterology core measure set.[215]

Central adiposity is another important modifiable risk factor for BE. Obesity increases the risk of GERD[216] and weight loss has been recommended among overweight and obese individuals with GERD to control symptoms.[214] Although BMI alone is imperfect for measuring risks for BE,[217] markers of insulin resistance are associated with increased hazard for developing EAC among those with BE.[218] A recent SR and MA showed among a pooled population with NDBE and LGD that increasing BMI was associated with an increased risk of progression to HGD and EAC in a dose-dependent manner.[219] Behavioral modification has been effective for weight loss among patients with GERD,[220] therefore among those with BE who are overweight or obese, it is appropriate to encourage weight loss to reduce symptomatic GERD and reduce the risk of BE progression.

PICO Question: What is the role of anti-reflux surgery compared to medical management using acid suppressive therapy in the prevention of progression in patients with Barrett's esophagus?

Recommendation: In adult patients with Barrett's esophagus, the AGA suggests use of proton pump inhibitors over surgery for the prevention of neoplastic progression to high-grade dysplasia or esophageal adenocarcinoma (*Conditional recommendation, low quality of evidence*)

Summary of the evidence

Evidence informing the recommendation for the use of anti-reflux surgery versus medical management to prevent progression to HGD/EAC in patients with BE is derived from 5 observational cohort studies and 1 RCT. A prior SR/MA by Wilson et al. evaluated the risk of progression to HGD/EAC in patients who underwent anti-reflux surgery versus medical management with PPI/H2RA, conducting a systematic search ending in February 2021.[221] This MA analyzed data from 5 studies, including four cohort studies and one RCT. We updated the analysis with one additional cohort study by Akerstrom et al.[222] In the prior SR/MA, disease progression was defined as progression of intestinal metaplasia to LGD, HGD, or EAC or by progression of LGD to HGD and EAC. There was no heterogeneity between the studies (I^2 = 0%). For this PICO, we utilized data from the 5 studies from this SR/MA as well as the large cohort study by Akerstrom et al[222] that reported on neoplastic progression to HGD/EAC in BE patients.

There has been a single RCT comparing the impact of surgical versus medical management on progression in BE, which was included in the prior SR/MA.[223] This RCT randomized 101 patients with BE to receive either medical treatment, with 43 randomized to receive medical treatment and 58 randomized to undergo anti-reflux surgery. Medical treatment entailed H2RAs initially and omeprazole from 1992 onward, and anti-reflux surgery consisted of Nissen fundoplication in the majority of patients and Collis Nissen procedure in 2 patients. Median age in the medical therapy group was 50 years versus 43 years in the surgical treatment group, 71%

of patients were male, and median follow-up was 5 years. The largest included cohort study was conducted by Akerstrom et al. In this Nordic population-based cohort study, 33,939 patients with BE from multiple national registries were included. Of the cohort, 542 (1.6%) patients underwent anti-reflux surgery (fundoplication) and 33,397 patients underwent medical management. In the anti-reflux surgery cohort, 67% were men, mean age was 64 years, and mean follow-up was 4.9 years. In the medical management group, 69% were men, mean age was 53 years, and mean follow-up time was 11 years. While no formal SR/MA was conducted, indirect evidence regarding harms was obtained from a prior SR/MA examining outcomes after anti-reflux surgery versus medical management of GERD and reviews addressing complications of anti-reflux surgery.[224, 225]

Benefits

The critical outcomes that informed the benefits for this PICO question were: 1) progression to EAC, 2) progression to HGD/EAC (**Tables 4 and 11**). Other patient-important outcomes we evaluated included EAC mortality. For the critical outcome of assessing the impact of anti-reflux surgery versus medical management on progression to EAC, data from the 5 studies included in the prior SR/MA and the cohort study by Akerstrom et al. were analyzed.[221, 222] Of 33,528 patients who underwent medical management, 438 (1.3%) progressed to EAC versus 14 of 765 patients (1.8%) who underwent anti-reflux surgery (RR 1.33; 95% CI 0.29, 6.16) (**Supplementary Figure 4**). The absolute risk reduction was 4 more per 1,000 (from 9 fewer to 67 more). The largest cohort study was by Akerstrom et al., which showed that anti-reflux surgery did not reduce the risk of EAC among BE patients followed up for up to 32 years (adjusted HR: 1.9, 95% CI 1.1, 3.5).[222] To assess for progression to HGD/EAC, data from the same 6 studies were used.[221, 222] Of 33,528 patients who underwent medical management, 443 (1.3%) progressed to HGD/EAC versus 19 of 765 patients (2.5%) who underwent anti-reflux surgery (RR 0.86; 95% CI 0.30, 2.41) (**Supplementary Figure 4**). The absolute risk reduction was 2 fewer per 1,000 (from 9 fewer to 19 more). There was no available evidence for the impact of anti-reflux surgery versus medical management in patients with BE on EAC mortality.

Harms

The patient-important outcomes that informed the harms for this PICO question included serious adverse events (SAEs) related to anti-reflux surgery and PPIs. Adverse events related to PPI therapy are reviewed in the section on chemoprevention in BE. We did not conduct a systematic review on adverse events related to anti-reflux surgery. Instead, we evaluated data from an existing review focusing on the most common major adverse events after fundoplication as well as rates of SAEs in existing RCTs comparing anti-reflux surgery versus medical management for the treatment of acid reflux or BE.

A comprehensive qualitative review by Yadlapati et al. summarized both acute and long-term outcomes of laparoscopic fundoplication.[226] Their review highlighted a population-based cohort study of a Swedish cohort evaluating 2,655 patients who underwent primary laparoscopic fundoplication for GERD. Of this cohort, the 30-day all-cause mortality rate was 0.1%, and 4.1% had a complication within 30 days of surgery, which included infection (1.1%), bleeding (0.9%), and esophageal perforation (0.9%).[227] Reflux recurred in 17.7%, and 16.4% of the cohort required secondary anti-reflux surgery. An older review study evaluating outcomes after 10,489 primary fundoplication procedures found similar complication rates including mortality rate of 0.08%, perforation in 0.8%, and wound infection in 0.1%.[228] The mortality estimate of 0.1-0.2% in the qualitative review is further supported by a more recent population-based cohort study of 5 Nordic countries, which evaluated 26,193 patients who underwent primary laparoscopic anti-reflux surgery and found 90-day post-operative mortality of 0.13%.[229]

We also evaluated adverse events from multiple RCTs comparing anti-reflux surgery versus medical management for the treatment of acid reflux or BE. No deaths within 30 days of surgery were reported in the available RCTs.[223, 230-233] The SOPRAN study randomized 310 patients with chronic GERD to PPI versus open anti-reflux surgery.[232] Follow-up from the original study of 5 years was extended to 14 years, with similar rate of SAEs between both groups (anti-reflux surgery: 0.1% per patient-year; PPI: 0.1% per patient-year).[234] The LOTUS RCT randomized 554 patients with chronic GERD to acid suppression versus laparoscopic anti-reflux surgery,

with 372 patients who completed the initial 5-year follow-up.[231] At 5-year follow-up, SAEs were reported by 28.6% of patients who underwent anti-reflux surgery versus 24.1% of the PPI group. When follow-up was extended to 7 years, SAEs remained similar between the anti-reflux surgery (0.2% per patient-year) and PPI (0.2% per patient-year) groups.[234]

Certainty of the Evidence

The overall certainty in the evidence across the critical outcomes and considering the benefits of the intervention was low (**Table 11**). For the critical outcomes of progression to HGD/EAC and EAC between patients who underwent anti-reflux surgery versus medical management, we largely relied on data from non-randomized studies included in a SR/MA. This evidence was low in certainty due to imprecision. There was a concern for selection bias because majority of studies lacked inclusion of consecutive patients and baseline equivalence of treatment groups. However, the larger studies were without concerns, so we did not rate down for risk of bias. Studies addressing cost-effectiveness and patient values or preferences for these two strategies to reduce neoplastic progression in BE patients were not identified.

Discussion

Surgical anti-reflux procedures as an anti-neoplastic progression strategy is appealing given its ability to restore the gastroesophageal anatomic and physiological reflux barrier and reduce gastric contents (acid and bile) from reaching the esophagus.[235, 236] In addition, anti-reflux surgery is highly effective in reducing esophageal acid exposure, reducing gastroesophageal reflux episodes, healing esophagitis and reducing symptoms associated with reflux.[51] However, there are several issues that argue against the routine use of anti-reflux surgery in BE patients. The existing evidence does not document consistent superiority of anti-reflux surgery over medical management (typically using PPIs) in reducing the risk of neoplastic progression in patients with BE. Most of the studies included in the SR/MA that helped inform this recommendation were from single centers with small sample size, had limited long-term follow-up, and at least moderate heterogeneity among included studies. There is a risk of selection bias and it may be argued that patients with more severe disease were more likely to undergo anti-reflux surgery. Details regarding confounding factors such as BE length and other risk factors

such as tobacco smoking and body mass index, factors that could influence the decision to proceed with anti-reflux surgery, were not available in all studies.[222] Data on medication use was not available for most studies and compliance was not routinely monitored. The failure rate of anti-reflux surgery is 20-30% at 5 years and recurrence of GERD symptoms is reported in approximately 15% of patients who have undergone anti-reflux surgery.[227, 231, 237] A SR/MA that assessed outcomes of anti-reflux surgery in GERD patients reported that 28% randomized to surgical intervention still reported PPI use.[224] It should be noted that the need for concurrent medical therapy after surgery is not well reported. These factors potentially contribute to the lack of superiority of anti-reflux surgery. The event rate of HGD/EAC in the reported studies is low and the number of patients undergoing anti-reflux surgery was relatively small compared to the medical management group. The decision to recommend PPIs over anti-reflux surgery was also driven by the overall low risk of progression in patients with NDBE making it difficult to justify the risks associated with anti-reflux surgery highlighted above. The role of anti-reflux surgery in patients with BE-related neoplasia undergoing EET is highlighted in the AGA EET Guidelines document.[11] Finally, future studies need to better define if there are patients with BE who are most likely to benefit to anti-reflux procedures to reduce the risk of neoplastic progression.

PICO Question: What is the role of endoscopic surveillance in patients with columnar lined esophagus <1 cm with intestinal metaplasia without neoplasia?

Recommendation: In patients with columnar lined esophagus <1 cm with intestinal metaplasia without neoplasia, the AGA suggests against endoscopic surveillance (*Conditional recommendation, very low certainty of evidence*).

Summary of the evidence

Evidence informing the recommendation regarding endoscopic surveillance versus no surveillance in patients with columnar lined esophagus <1 cm with intestinal metaplasia was derived from single-arm observational cohort studies. The author panel did not identify any existing SR/MA evaluating this question and a de novo literature search that spanned until March 1, 2025 was conducted (**Supplementary Table 6**). This search identified 1,014 studies for title and abstract screening, of which 74 underwent full text screening and 6 relevant studies were included in the final analysis. All 6 included studies were single-arm, observational cohort studies informing progression to HGD/EAC in patients with columnar lined esophagus <1cm (critical outcome). We could not address the critical outcome of progression to EAC alone, as not all studies reported disaggregate outcomes for HGD and EAC. No study addressed the patient-important outcome of EAC-related mortality. There was no significant heterogeneity among the studies ($I^2 = 0\%$). The largest study included in this analysis with the majority of events was by Anaparthy et al., which included patients from 5 US tertiary care centers participating in the BE Study.[238] Included patients had a diagnosis of BE without dysplasia and at least 1 year of follow-up, excluding patients who developed HGD or EAC within 1 year of BE diagnosis to exclude prevalent neoplasia. Overall demographics for the entire BE cohort included mean age of 59.2 years, 88% men, and 93% of the cohort were of Caucasian ethnicity. Within this cohort, 408 patients were diagnosed with columnar lined esophagus <1 cm who were followed for 5.2 years. Incident HGD/EAC developed in 5 patients with an annual risk of HGD/EAC of 0.23% per year. Data regarding the harms of surveillance endoscopy were derived largely from two large national database studies, as previously summarized in PICO 1 on use of surveillance endoscopy in NDBE.[30 31]

Benefits and Harms

The critical outcomes that informed the benefits for this PICO question were progression to HGD/EAC (**Tables 4 and 12**). Data were not available for our other predefined critical outcome of progression to EAC or EAC-specific mortality. For the critical outcome of HGD/EAC, we performed a MA and found a pooled incidence for development of HGD/EAC of 0.1 per 100 patient-years using a random effects model (**Figure 10**). The patient-important outcomes that informed of the harms for this PICO question included serious adverse events associated with endoscopy, as previously summarized in PICO 1 on the use of surveillance endoscopy in NDBE.

Certainty of the Evidence

The overall certainty in the evidence considering the benefits of the intervention across the critical outcomes was low (**Table 12**). For the only outcome we were able to assess, the critical outcome of progression to HGD/EAC, we relied on data from single-arm, non-randomized studies. This evidence was very low in certainty due to serious risk of bias and indirectness, as these studies consisted only of studies without a comparator arm. Furthermore, it is unclear if patients with columnar lined esophagus <1 cm and intestinal metaplasia underwent endoscopic surveillance under a structured protocol or outcomes were based on endoscopy performed as needed. To assess adverse events associated with surveillance endoscopy, we utilized data from observational cohort studies with low certainty of evidence due to serious risk of bias. A recent study that evaluated the cost-effectiveness of endoscopic surveillance in patients with columnar lined esophagus <1 cm was utilized in the evidence to decision making.[239] No study addressing patient values and preferences were identified.

Discussion

The guideline panel made a recommendation against routine endoscopic surveillance in patients with columnar lined esophagus <1 cm with intestinal metaplasia without neoplasia. The panel considered several factors. [240-242]This recommendation was largely driven by the low risk of neoplastic progression to an endpoint of HGD/EAC as demonstrated in the SR and MA described above. The description of this finding at endoscopy is not uniform and several terminologies have been described [esophagogastric junction intestinal metaplasia (EGJIM) or irregular Z-line] adding to the uncertainty of this diagnosis. Columnar lined esophagus <1 cm is

a finding that has been reported in approximately 15% of the population undergoing upper endoscopy.[243] Observational studies have reported an up to 44% prevalence rate of intestinal metaplasia in patients with columnar lined esophagus <1 cm.[244, 245] The endoscopic diagnosis of columnar lined esophagus <1 cm is fraught by substantial interobserver variability.[246] The panelists considered the impact of life-long surveillance endoscopies in this patient population without much benefit; a practice that could potentially result in increased costs, risks of endoscopy, insurance premiums, unnecessary endoscopies that could directly compete with the current demand for other indicated procedures and further reduction in the availability of needed endoscopy resources and patient anxiety. A recent decision modeling analysis evaluated the cost-effectiveness of endoscopic surveillance in patients with a diagnosis of EGJIM.[239] Surveillance strategies of no surveillance, 1-time endoscopy at 3 years, endoscopy every 3 years and endoscopy every 5 years were assessed based on annual cancer progression incidence rates (0.01%, 0.05%, 0.12% and 0.22%). This model suggests that at the lowest progression rates, either no surveillance (annual incidence rate of 0.01%) or 1-time endoscopy (annual incidence rate of 0.05% or 0.12%) can be considered; however, more data are required on progression rates to identify the optimal strategy. The guideline panel acknowledged the very low quality of evidence and also reports describing prevalent neoplasia among patients with columnar lined esophagus <1 cm.[244] A critical component in the decision making regarding endoscopic surveillance in patients with columnar lined esophagus <1 cm with intestinal metaplasia is whether a high-quality endoscopic examination was performed. If the quality of the index exam is in question, a repeat one-time high-quality exam can be performed to rule out prevalent neoplasia. Based on the above uncertainties, patients who place a higher value on the potential benefit of endoscopic surveillance in preventing EAC progression, especially in patients who did not undergo a high-quality index endoscopic examination, and place a lower value on the risks of endoscopy, can reasonably choose to undergo a one-time repeat surveillance endoscopy.

Implementation Considerations:

To monitor care performance, endoscopists and practices are encouraged to utilize published quality metrics in screening and surveillance of patients with Barrett's esophagus.

The most widely utilized quality measures in surveillance include adhering to appropriate endoscopic surveillance intervals among patients with non-dysplastic Barrett's esophagus and appropriate sampling technique using the Seattle biopsy protocol in patients with suspected or confirmed Barrett's esophagus.

Endoscopists and practice should consider monitoring post-endoscopy esophageal adenocarcinoma (PEEC) and post-endoscopy esophageal neoplasia (PEEN) cases to understand contributing factors and areas of improvement.

Quality Indicators in Barrett's Esophagus Surveillance

In this era of value-based and quality focused health care, several quality metrics have been proposed to monitor and motivate improved outcomes in patients with BE undergoing surveillance endoscopy (**Table 14**). These quality metrics can be measured at an individual endoscopist level or across a facility, institution or system level by comparing performance to a benchmark. In this framework, non-adherence usually reflects suboptimal care. In this section, the term quality measures refer to metrics that are fully specified, tested and validated and in quality payment programs, the term quality indicators refer to metrics based on guideline documents, consensus recommendations and not necessarily specified with clear numerator and denominator and not submitted to quality payment programs. Two quality metrics that have received the most attention include: frequency of surveillance endoscopies at appropriate intervals (no sooner than 3-5 years in patients with NDBE) and sampling the BE segment using the Seattle biopsy protocol.[225, 247] These two metrics have been developed as fully specified quality measures according to the established AGA conception to implementation pathway (https://gastro.org/practice-resources/quality-and-performance-measures/), which requires a strong recommendation based on moderate or high quality evidence.[248] Several observational studies, including data from a national benchmarking registry (GI Quality Improvement

Consortium Registry – GIQuIC) have demonstrated suboptimal adherence and wide variability among endoscopists and participating.[105-107, 249-252]

This following section provides an overview on other proposed quality metrics in BE surveillance. Similar to adenoma detection rate, a quality metric used to measure colorectal cancer screening care and associated with the highest penetrance in clinical GI practice, neoplasia detection rate (NDR) has been proposed to monitor quality in BE screening and surveillance. NDR is defined as the prevalence of HGD or EAC (numerator) within BE during the index screening endoscopy (denominator). A meta-analysis reported a pooled HGD/EAC prevalence of 7% (95% CI 4-10%) and proposed 4% as the NDR threshold on screening endoscopy.[253] Rates of dysplasia detection rate (DDR), defined as LGD or HGD, were reported using the GIQuIC registry among patients undergoing surveillance of NDBE and recent studies have also highlighted the wide variability among endoscopists and participating sites for DDR in NDBE patients.[106, 250]

Similar to the phenomenon of post-colonoscopy colorectal cancer, there is a growing body of literature describing BE-associated HGD and EAC before the next recommended endoscopic evaluation after an endoscopy that was ostensibly negative for HGD/EAC. [254] To address this issue in BE endoscopy quality, an AGA Clinical Practice Update and an international expert panel introduced the concepts of PEEC and PEEN. PEEC is the preferred term for EAC and PEEN is the preferred term for HGD or EAC detected before the next recommended surveillance endoscopy in a patient with prior NDBE, provided it occurs between 6 months and 3 years after a screening or surveillance endoscopy.[254, 255] It is believed that most cases of PEEC/PEEN may be attributed to missed HGD/EAC while the remaining cases may be attributed to rapidly progressive neoplasia due to accelerated pathways of neoplasia.[255, 256] Several factors may contribute to missed neoplasia at endoscopy including suboptimal adherence to the Seattle biopsy protocol, limited mucosal sampling, inadequate time spent inspecting the BE segment, limited knowledge in the recognition of subtle findings of early neoplasia and interobserver variability among pathologists for the histologic classification of dysplasia. [1, 254, 255] Observational studies including a recent population-based cohort study have provided

contemporary estimates of PEEC and PEEN. A SR/MA reported that the proportion of EACs that were PEEC was 21% (95% CI 13-31) and the proportion of HGD/EAC that were PEEN was 26% (95% CI 19-34); outcomes of PEEC/PEEN defined as HGD/EAC detected within the first year after an index endoscopy that demonstrated NDBE, IND or LGD. [49] Similarly, a recent population-based study conducted in Denmark, Finland and Sweden (the Nordic Barrett's Esophagus Study) that included 20,588 patients with newly diagnosed BE and showed that 23.5% of EACs were categorized as PEEC and 17.2% of HGD/EACs were categorized as PEEN. Several sensitivity analyses that varied time intervals for occurrence of PEEC/PEEN demonstrated similar results. In addition, a time-trend analysis demonstrated rising incidence rates for PEEC/PEEN. [1] These findings suggest suboptimal performance among current screening and surveillance practices and provide improvement opportunities for early neoplasia detection in BE. The International Expert Panel on PEEC and PEEN and the AGA Clinical Practice Update suggested that services and individual endoscopists review PEEC/PEEN cases periodically and identify areas for improvement, provided a construct for categorizing PEEC/PEEN cases according to their most plausible explanations and best practice advice to reduce PEEC/PEEN.[255] Recent data from the Nordic Barrett's Esophagus Study demonstrated an overall inverse association between facility NDR and the risk of PEEC/PEEN adding to the validity of NDR and PEEC/PEEN as potential quality measures in BE.[257]

Although a number of additional quality metrics specific to BE have been proposed, incorporation into value-based care plans has been limited for several reasons, including lack of formal and validated testing. Several of these proposed quality metrics do not have established thresholds that are adjusted for risk factors. Most of these proposed quality metrics are based on weak evidence or consensus expert opinions and most importantly, not tied to clinical outcomes. Adherence to quality metrics such as adherence to the Seattle biopsy protocol, Barrett's inspection time, appropriate endoscopic surveillance intervals, monitoring of NDR/DDR must correlate with important clinical outcomes such as PEEC and EAC mortality, and drive performance improvement to be considered a high-value quality measure.[258] Other challenges include operationalizing these, especially NDR/DDR and PEEC/PEEN, given the low number of endoscopies performed for BE and low incidence of EAC. Future efforts will need to focus on

how these proposed QIs should be calculated in an automated fashion and establish minimum standards using risk-adjusted strategies.

Knowledge Gaps

These evidence reviews identified several important knowledge gaps that need to be addressed in future studies and highlighted in **Table 15**.

Plans for Updating

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

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