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AGA Clinical Practice Update on Reducing Rates of Post-Endoscopy Esophageal Adenocarcinoma: Commentary

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Esophageal adenocarcinoma (EAC) has sobering incidence and mortality statistics over the last several decades. The incidence of EAC has risen 7-fold from 1975 to 2016, according to data from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute.[1] Despite screening and surveillance programs and improved treatment paradigms for Barrett's esophagus (BE), as much as 40% of EACs present with advanced disease, with a dismal 5-year survival rate.[2] Several factors contribute to this. Curable EAC has no reliable presenting symptom, and population-based screening of at-risk individuals is not effective because of low EAC incidence. Targeted screening for BE within gastroesophageal reflux disease (GERD) populations also has limitations, as only 7%–10% of individuals with chronic GERD have BE, nearly 40% of EAC patients describe no history of GERD, and up to 50% of patients with short-segment BE lack GERD symptoms.[3] In addition, use of endoscopy as a screening tool is compromised by expense, facility/physician expertise needed, and limited effectiveness, because >90% of EACs do not have a prior BE diagnosis.[4] Broadening the at-risk population to include risk factors independent of GERD (age >50 years, male sex, white race, cigarette smoking, and central obesity) would incur increased resource utilization, costs, and potential harm from endoscopy.

Similarly, BE surveillance endoscopy also has limitations. Compliance with guideline recommendations for appropriate endoscopic surveillance intervals with application of the Seattle protocol is suboptimal.[3,5] Data from the GI Quality Improvement Consortium registry demonstrated that 30% of patients with nondysplastic BE undergo endoscopy earlier than guideline recommendation without strict adherence to the Seattle protocol.[6,7] Current surveillance programs are time consuming, and there is potential for sampling errors with even the most thorough surveillance programs. Finally, significant inter- and intra-observer variability exists among both community and expert pathologists in dysplasia interpretation.[3]

Even in the face of suboptimal impact of current strategies on population-based EAC mortality, medical societies consistently recommend BE screening and surveillance.[3,5,8] In this context, similar to post-colonoscopy colorectal cancer (PCCRC), the concept of missed EAC is gaining importance in endoscopic BE screening and surveillance. The aims of this review of literature pertaining to post-endoscopy esophageal adenocarcinoma (PEEC) are to lay the groundwork for standardizing terminology and definitions for PEEC, to describe the scope of PEEC and contributing factors, and to provide best practice advice to improve dysplasia and neoplasia detection in patients undergoing BE screening and surveillance, thereby reducing rates of PEEC. This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*.

Definitions and Taxonomy

Although providing evidence-based consensus definitions for PEEC and interval EAC will be our next step, we propose the following definitions for current use. We propose that PEEC be defined as EAC and/or BE-related high-grade dysplasia (HGD) identified within a finite time period (typically 1 year) after a nondiagnostic endoscopy. Interval EAC may be defined as EAC or BE-related HGD diagnosed after a negative screening or surveillance endoscopy before the date of the next recommended test. Defining interval EAC, primarily a measure of screening, is important, given the robust development of noninvasive, nonendoscopic screening tools under investigation.

Post-Endoscopy Esophageal Adenocarcinoma: Scope of the Problem

Rates of Post-Endoscopy Esophageal Adenocarcinoma in Barrett's Esophagus Screening and Surveillance Programs

PEEC incidence extracted from population and cohort studies reporting EAC/dysplasia within 1 year after index

Abbreviations used in this paper: **ADR, adenoma detection rate; AGA, American Gastroenterological Association; BE, Barrett's esophagus; CRC, colorectal cancer; DDR, dysplasia detection rate; EAC, esophageal adenocarcinoma; GERD, gastroesophageal reflux disease; HGD, high-grade dysplasia; NDR, neoplasia detection rate; PCCRC, post-colonoscopy colorectal cancer; PEEC, post-endoscopy esophageal adenocarcinoma.**

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endoscopy suggests rates of 3%–13%. In a study from Olmstead County that included 210 patients with BE, repeat endoscopy within 1 year revealed a PEEC incidence of 2% (4 patients with HGD/EAC).[9] Among 79,460 BE patients identified through a claims-based database, 76% of 1595 EAC diagnoses were considered prevalent (EAC detected within 90 days of index endoscopy) and 10% were designated interval (EAC diagnosed between 90 and 365 days of BE diagnosis).[10] A population study of 13,159 BE patients from the Northern Ireland BE Registry had 267 patients with HGD/EAC $\geq$3 months after BE diagnosis, of which 34 (12.7%) were classified as potentially missed.[11] Meta-analyses of BE surveillance studies suggest a higher incidence of PEEC. In a meta-analysis of 24 BE surveillance studies, 25.3% of HGD/EAC diagnosed were designated as missed (using $<$1 year as a threshold interval for missed neoplasia), and 27% of all HGD/cancer was found within the first year of surveillance.[12] In another meta-analysis of 8 surveillance trials of BE-related low-grade dysplasia, the weighted incidence in the first year was 8.8 per 100 patients, with a median first-year incidence to overall progression ratio of 2.34, indicating that the first-year incidence was approximately twice the overall annual progression rate.[13] Therefore, meta-analyses as well as cohort studies indicate high PEEC incidence (3%–25%) within the first year after index endoscopy, commonly from missed HGD/EAC, which accounts for a large proportion if not the majority of PEECs found throughout the entire BE surveillance period.

Rates of Post-Endoscopy Esophageal Adenocarcinoma in Barrett's Esophagus Patients Undergoing Endoscopic Eradication Therapy

Reevaluation of surveillance data after endoscopic eradication therapy for BE-related neoplasia also demonstrates recurrence skewed to the first year after therapy, concordant with PEEC rates in the screening and surveillance populations. Others report incidence peaking at 1–2 years after complete eradication of intestinal metaplasia. A meta-analysis of 22 studies involving 1973 patients achieving complete eradication of intestinal metaplasia by radiofrequency ablation and/or endoscopic resection, dysplasia detection had a relative risk of 1.92 in the first year compared with subsequent years.[14] These data support that HGD/EAC identified within 1 year after complete eradication of intestinal metaplasia likely represents missed and/or incompletely treated prevalent disease rather than recurrent or incident neoplasia. Of key importance is the identification of risk factors for missed dysplasia and/or EAC in patients undergoing endoscopic eradication therapies. In a meta-analysis of 40 studies, including 4410 patients undergoing endoscopic ablation, failure to achieve complete eradication of intestinal metaplasia carried a relative risk of 2.2 for recurrent HGD/EAC (pooled cumulative incidence rate, 6%; 95% confidence interval, 0%–16%) compared with complete eradication of intestinal metaplasia (3%, 95% confidence interval, 2%–4%).[15] These data indicate that residual intestinal metaplasia may be a marker of prevalent dysplasia rather than a predictor of recurrence.

Lessons Learned From Colorectal Cancer and Measurement of Colonoscopy Quality

Although colonoscopy is highly effective in diagnosis and prevention of colorectal cancer (CRC), interval cancers have been found months and years after negative colonoscopy and before the next scheduled colonoscopy. The World Endoscopy Organization defines PCCRCs as cancers diagnosed after a colonoscopy where no cancer was found, a term that measures the quality of the examination and is not screening-specific.[16] PCCRCs consist mostly of missed cancers or incompletely resected adenomatous polyps on index colonoscopy, rather than rapidly progressive precancerous polyps. A recent analysis suggested that 89% of all PCCRCs may be avoidable, attributable to technical endoscopic factors, compromised decision-making, and administrative factors.[17] An adenoma detection rate (ADR) of $\geq$20% for individuals undergoing average-risk screening colonoscopy is a well-established quality indicator in CRC screening, first established in 2002 by the US Multi-Society Task Force on Colorectal Cancer. It is also known that ADR is inversely proportional to risk of developing PCCRC.[18] These lessons learned from CRC screening have been utilized to formulate the following steps to reduce PEEC and to maximize the benefits of BE screening and surveillance programs.

Implications of Post-Endoscopy Esophageal Adenocarcinoma

Similar to PCCRC, there are 3 predominant explanations for PEEC: missed dysplasia or EAC, incompletely resected or ablated lesions, and rapidly progressive cancer (Figure 1). Missed lesions are likely the most important PEEC mechanism, with rapidly progressive cancer a smaller contributor.

From a practical point of view, missed dysplasia and EAC in BE patients are not surprising for several reasons. First, neither the human eye nor endoscopic equipment used in BE surveillance is perfect. Only subtle differences exist between normal and dysplastic esophageal mucosa, intuitively suggesting that dysplasia and EAC can be easily overlooked. Recognition of these subtle differences and utilization of adjunct endoscopic visualization techniques require a learning curve, repetitive procedures, and consistency of performance that favors the expert over novice endoscopists. Second, the Seattle biopsy protocol is not assiduously pursued by many endoscopists. In addition, it is estimated that $<$5% of BE is sampled with this method, even when performed correctly, still woefully inadequate for subtleties of BE neoplasia often characterized by a mosaic of neoplastic foci. This has been supported by the use of the wide-area transepithelial sampling with computer-assisted 3-dimensional analysis, which may demonstrate dysplastic cells even without endoscopically visible lesions or abnormal routine histology.[3,19]

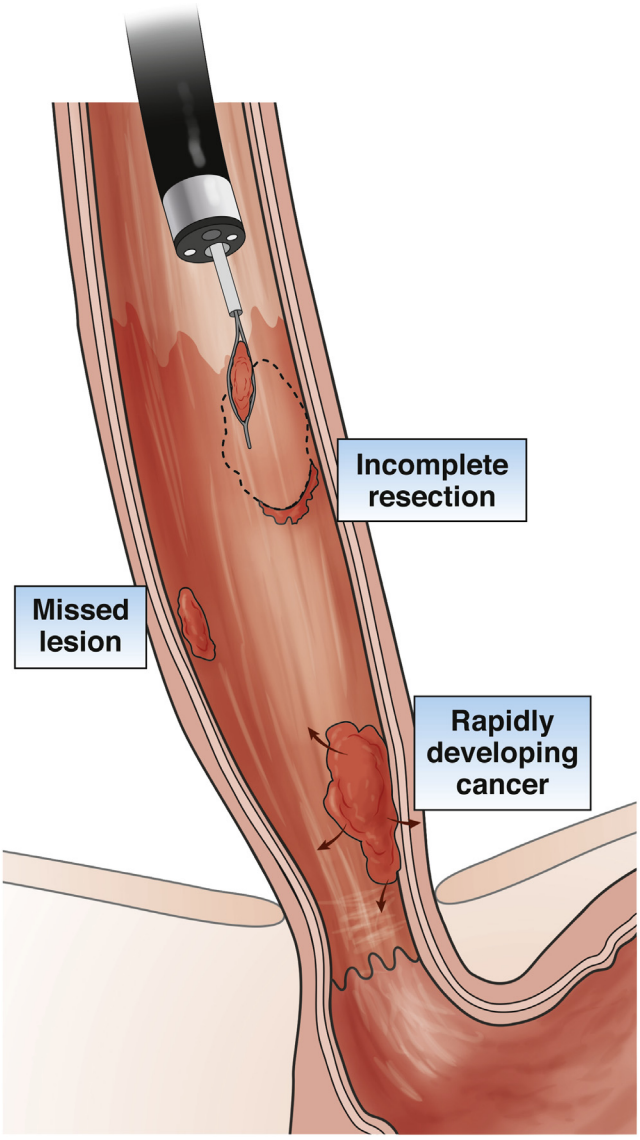

Figure 1. Potential explanations for post-endoscopy esophageal adenocarcinoma.

Furthermore, despite the fact that the Seattle protocol advocates 4-quadrant biopsies every 1 cm for optimal dysplasia or cancer detection, with 50% higher cancer detection compared with biopsies every 2 cm, the latter represents typical endoscopic practice. Third, the amount of time utilized to examine colon segments for polyps during colonoscopy is not proportionately applied to esophagoscopy in BE surveillance. Proposals that exist to overcome these caveats, as discussed below, are intended to enhance endoscopic detection of dysplasia and cancer. However, reliance on histology alone as a marker for HGD or EAC may not be as sensitive as previously assumed. For instance, a 4-gene methylation marker panel demonstrated high marker content suggestive of prevalent neoplasia even with just intestinal metaplasia without dysplasia on routine histopathology.[20] In other words, dysplasia as a histologic measure may not be the only predictor of cancer presence.

Quality Indicators in Barrett's Esophagus Screening and Surveillance

Medical practice has been trending away from high-volume toward high-value care, as key stakeholders have begun to tie reimbursement to performance based on established quality indicators. This is best highlighted by the inclusion of ADR in the Centers for Medicare and Medicaid Services Merit-Based Incentive Payment System. Similar to colonoscopy quality metrics, there is a critical need for endoscopists to lead the development and implementation of quality indicators in BE screening and surveillance. Although a number of quality indicators specific to BE screening, surveillance, and endoscopic eradication therapy have been proposed, none have been incorporated into value-based care plans.[21,22] Most of these quality indicators are based on weak evidence, metrics not tied to clinical outcomes, and consensus expert opinions. To reduce unnecessary endoscopy in nondysplastic Barrett's esophagus patients, surveillance endoscopies at appropriate intervals (no sooner than 3–5 years), along with adherence to the Seattle biopsy protocol, have been proposed as quality indicators.

The neoplasia detection rate (NDR), defined as the prevalence of HGD and EAC within BE during the index screening endoscopy, has been recently proposed as a process quality indicator. A meta-analysis reported a pooled HGD/EAC prevalence of 7% (95% confidence interval, 4%–10%) and proposed 4% as the NDR threshold on index BE screening endoscopy.[23] In a time-trend analysis using the GI Quality Improvement Consortium registry, a metric similar to NDR (dysplasia detection rate [DDR]) performed similarly, with prevalence rates ranging from 4%–6% and no change during a 5-year period.[24] The Barrett's Inspection Time, a metric similar to colonoscopy withdrawal time, measures the proportion of routine BE surveillance examinations incorporating 1 minute of visual inspection per centimeter of circumferential BE and requires validation before adoption in clinical practice.[25]

Regulatory entities have adopted ADR as a high-value quality indicator because this inversely correlates with interval CRC and mortality. Similarly, BE quality indicators, such as NDR/DDR must correlate with important clinical outcomes, such as PEEC and mortality, and drive performance improvement to be considered a high-value quality indicator. Although easier to measure compared with PEEC rates, NDR remains a surrogate endoscopy quality marker in BE surveillance, and PEEC rates serve as a true outcomes measure that matters clinically.

What Are Some Solutions to Reducing Post-Endoscopy Esophageal Adenocarcinoma

Because most PEECs result from missed lesions, improving endoscopic screening, both refining upper endoscopy as a screening test and improving how it is delivered, could substantially reduce PEEC rates. This can be accomplished through several strategies. The first is by assiduous identification and photo-documentation of esophageal landmarks by localizing the diaphragmatic

hiatus, gastroesophageal junction, and squamocolumnar junction, and using the Prague classification to describe the circumferential and maximal length of the BE segment. Additionally, visible lesions (eg, nodularity, ulceration, or areas of depression) should be described using the Paris classification and resected when identified or on referral to a center of expertise. A second solution is to consistently use high-definition white light endoscopy and virtual chromoendoscopy (such as narrow band imaging, with findings described using a validated classification system—Barrett's International Narrow Band Imaging Group), a practice now endorsed by societal guidelines for increasing dysplasia detection.[3] A third solution is to spend adequate time for inspection, with consistent and correct use of the Seattle biopsy protocol. Endoscopists should embrace a strategy of "look more and biopsy appropriately." Finally, an infrastructure for continuous monitoring of upper endoscopy quality should be established by endoscopy practices performing BE screening and surveillance.

Future Directions

There is an urgent need for an evidence-based consensus to standardize PEEC terminology and calculation (including the inclusion of HGD vs EAC alone in the calculation of PEEC), to describe the relationship between PEEC and interval EAC, to standardize potential explanations for PEEC, to establish infrastructure for future PEEC research, and to develop PEEC as a performance measure. Research must continue examining EAC carcinogenic pathways to determine whether subpopulations of BE progress more rapidly and whether prevalent missed EAC is biologically equivalent to incident cancer.

Future research needs to focus on improving NDR/DDR as quality measures to improve critical clinical outcomes associated with PEEC and EAC in general. Prospective trials are needed to evaluate the impact of better dissemination of guidelines and quality indicators, improved endoscopic dysplasia detection using interactive web-based educational tools, advanced imaging techniques with artificial intelligence, and improved sampling modalities that reduce sampling errors. Finally, increased emphasis is needed on improving training in both the cognitive and procedural aspects of BE endoscopy through structured educational programs among trainees and practicing endoscopists.

Conclusions

Emerging technologies may significantly alter how we perform endoscopy and serve as adjunctive approaches to impact key quality measures in BE patients including NDR/DDR and PEEC rates. However, in the short term, improving upper endoscopy quality will rely on well-trained and vigilant endoscopists rather than technology enhancements. The practice of high-quality upper endoscopy is critically important to the success of any BE screening or surveillance program designed to reduce the incidence and mortality associated with PEEC and EAC.

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Conflicts of interest
The authors disclose the following: S. Wani: Consultant for Boston Scientific, Medtronic, Cernostics, Interpace; C. P. Gyawali: Consultant for Medtronic, Diversatek, Ironwood, Isothrive, Quintiles; and D. A. Katzka: Advisory board member of Celgene and Shire.

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