Review Article

Unmet needs in Barret's esophagus diagnosis and treatment: a narrative review

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Background and Objective: This narrative review discusses Barrett's esophagus management in the context of perceived deficiencies or controversies. Barrett's adenocarcinoma incidence has not clearly been impacted by Barrett's screening and surveillance.

Methods: The following report was derived from articles using PubMed and Google searches. The search was concentrated on Barrett's esophagus screening and management guidelines,

Key Content and Findings: Comprehensive literature searches that highlight potential deficiencies or controversies regarding the current approach to Barrett's esophagus were employed. Esophageal adenocarcinoma incidence is rapidly increasing and this malignancy usually presents in an advanced and unresectable state. This is despite the significant expenditure of resources and time in endoscopic screening for and surveillance of Barrett's esophagus. Thus, more widespread screening for Barrett's esophagus may be considered. In addition, there are apparent inefficiencies and precision lack in the performance of endoscopic surveillance. This relates mainly to the lack of endoscopic cues for dysplasia. On the other hand, relatively low-risk subjects have frequent screening or surveillance procedures increasing cost. Lastly, endoscopic ablation for Barrett's with dysplasia has moderately good efficacy, especially for eradication of dysplasia, but mandates intensive post-therapy endoscopic surveillance. There is some concern for subsurface development of advanced Barrett's lesions. Fortunately, there is intense research in improving Barrett's esophagus diagnosis and treatment. Our narrative review will delineate deficiencies and potential measures to remedy them.

Conclusions: In conclusion, screening for Barrett's esophagus and surveillance in Barrett's subjects have minimal established benefits, but proposed changes in screening practices and innovations in Barrett's esophagus endoscopic surveillance and dysplasia therapy have great promise.

Keywords: Barrett's esophagus (BE); screening; Barrett's diagnosis; Barrett's therapy; narrative review

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Introduction

Esophageal adenocarcinoma (EAC) derives from Barrett's esophagus (BE) and globally almost 86,000 patients were diagnosed with EAC in 2020 (1). Barrett's adenocarcinoma is possibly the fifth deadliest cancer globally with a 5-year survival less than 20% (2). Only 13% of EAC patients in one cohort were known to have BE (3). There is an enormous cost associated with both screening for BE and surveillance in subjects with confirmed BE. The cost utility of Barrett's screening depends on the population screened and the method used. One study noted a cost of $22,000 for quality-adjusted life year (QALY) using sedated endoscopy

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Table 1 Search strategy summary

Items	Specifications
Date of search	February 1, 2023
Databases and sources searched	PubMed, Google
Search terms	Barrett's esophagus (screening, surveillance therapy)
Time frame	2000 to February 1, 2023
Inclusion/exclusion criteria	Inclusion: publication types—review, cohort studies, editorial, case series. English language
	Exclusion: non-English publications
Selection process	Author directed
Guidelines	Major US and UK gastroenterology societies

for screening (4). Costs include endoscopy as well as the not-insignificant cost of long-term acid suppression. This article is presented in accordance with the Narrative Review reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-12/rc).

Methods

This review utilized information from PubMed and Google databases up to February 1, 2023. Key search terms included but were not limited to BE, screening, Barrett's surveillance, and Barrett's therapy. The review aims to describe the basis for current Barrett's screening and surveillance practices and perceived areas of deficiencies and potential innovations for improvement. *Table 1* denotes the search strategy with only inclusions of English language publications since 2000.

Discussion

Barrett's screening and surveillance is based on the paradigm of biological progression from normal esophageal squamous mucosa to non-dysplastic Barrett's esophagus (NDBE) to BE-low-grade dysplasia (LGD) and ultimately to high-grade dysplasia (HGD) and EAC. This paradigm is suspect or the transformation potentially rapid as EAC is not infrequently diagnosed in NDBE subjects (5). The annual incidence of EAC in NDBE is <0.5% with about 1.7% developing HGD or EAC in LGD (6). EAC development in HGD varies widely in published cohorts but may be as high as 19% annually (7). The progression rate of LGD is more challenging to delineate due to varying study design and cohorts; HGD/EAC incidence has ranged from slightly more than NDBE to much higher rates (6). One study noted with persistent LGD that 2.3% progressed annually and almost 1.5% developed EAC (8). Dysplasia presence on endoscopy biopsies determines surveillance frequency and eligibility for specific intervention. American College of Gastroenterology guidelines recommend NDBE endoscopy screening every 3–5 years and denotes more frequent screening for LGD (every 6–12 months) if no intervention and HGD (every 3 months) with esophagectomy a last resort option for HGD (9).

Proton-pump inhibitor (PPI) use may decrease progression including development of EAC in Barrett's subjects (10). This benefit may be enhanced by concomitant use of anti-inflammatory drugs such as aspirin (11). The utility of fundoplication to prevent Barrett's progression is more controversial, but may have a role in enhancing endoscopic ablation (12,13).

Screening deficiency

The most glaring deficiency in the approach to Barrett's adenocarcinoma is simply that not a sufficient proportion of eligible subjects are screened for BE. Most EAC subjects present in an advanced state and treatment is not curative. EAC is derived from BE which in turn relates to gastroesophageal reflux disease (GERD). BE can occur in up to 14% of patients with GERD and up to 1% of BE subjects develop EAC (14). A greater than fourfold increase in EAC in the U.S. has been noted recently (15). Most EAC subjects were not in a screening program at diagnosis yet screening improves prognosis as screened patients are diagnosed at an earlier stage usually than unscreened subjects (16). Risk factors for EAC are the same as for BE and include

Table 2 Barrett's and esophageal adenocarcinoma epidemiology

Promoting
Major
Age >50 years
Male gender
Obesity-especially central
Smoking
Family history BE/EAC
Minor
Hiatus hernia
GERD symptoms >5 years
Protecting
H. pylori infection
ASA and other NSAIDs
Statins

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; ASA, aspirin; NSAIDs, non-steroidal anti-inflammatory drugs.

age >50 years old, male gender, central obesity, Caucasian race, smoking and a family history of EAC. *Table 2* denotes epidemiologic characteristics associated with a greater or lesser propensity for BE and EAC; the presence of a hiatus hernia and chronic GERD symptoms are only modest predisposing factors. Age is a significant factor for development of EAC; one cohort noted only 10% EAC subjects <50 years old (17). Asian and African Americans are considered to be at lower risk for BE (18). *Helicobacter pylori* (*H. pylori*) infection, aspirin and other non-steroidal anti-inflammatory drugs, and statins diminish propensity for BE and EAC (19). Symptom-based vetting of patients eligible for Barrett's screening is problematic. Heartburn and regurgitation are considered classic GERD symptoms but GERD may have a variety of atypical and extra-esophageal manifestations. The U.S. prevalence of GERD exceeds 20% in adults denoting a potentially enormous pool for Barrett's screening (20). A quarter of a large cohort of US veterans without GERD complaints had BE detected when endoscopy was performed after screening sigmoidoscopy (21). A Swedish study noted almost half of subjects diagnosed with BE did not note symptoms on a pre-endoscopy survey (22). A global study suggested that eliminating heartburn as a necessary criterion significantly increased eligibility for screening (23).

Screening and surveillance

The major US and UK gastroenterology societies have similar Barrett's screening and surveillance guidelines (24-27). Biopsies of irregular Z lines including minuscule BE are commonly performed despite recommendations of only performing biopsies if there is one centimeter or more of salmon colored mucosa above the top of gastric folds (28). A minimum of eight biopsies are recommended to exclude BE which may be challenging with small areas of salmon-appearing mucosa (29). Surveillance of established BE is dictated by BE length and dysplasia grade with recent appropriate increase of interval to every 5 years for non-dysplastic short segment BE (24,25). Unfortunately, dysplasia in flat mucosa is indistinguishable from other Barrett's epithelium and the time-honored practice of random sampling of the Barrett's areas is employed to assess for dysplasia. Typically, white light examination is initially performed with intent to follow the Seattle protocol of four-quadrant biopsies every 2 cm longitudinally without dysplasia and 1-cm intervals with dysplasia. The vast majority of advanced BE including HGD and EAC are detected but this practice is suboptimal and missed pathology is consequential (30). There is a concern that we are not adequately examining BE at endoscopy with over half of EAC subjects in one cohort diagnosed within 1 year of index screening endoscopy (31). Moreover, there is inadequate adherence to protocol; especially in community centers (32). Adherence may diminish with increasing BE length despite a likely higher risk of advanced pathology (33). Electronic chromoendoscopy (narrow band imaging, I scan, blue laser imaging) is readily available and improves visualization and delineation of advanced Barrett's lesions (34). Acetic acid chromoendoscopy is a simple technique that can also enhance detection of advanced Barrett's lesions (35). These adjunctive methods can enhance dysplasia detection by 33% and direct biopsies but do not obviate the need for biopsies of the entire Barrett's area via Seattle protocol (34-36). Confocal laser endoscopy and volumetric laser endomicroscopy are more costly adjunctive methods of delineating advanced pathology and have promise but need further validation and dependable tagging to designate areas for subsequent biopsy or resection (37,38). The most promising developments are in the utilization of artificial intelligence (AI) to enhance dysplasia and carcinoma detection within Barrett's epithelium (39).

Pathology

Acute esophagitis confounds the diagnosis of BE and dysplasia and its presence mandates repeat endoscopy after more aggressive acid suppression (24). However, inflammation may be microscopic contributing to an over-diagnosis of dysplasia including HGD (40). There is notable interobserver variability in the pathology interpretation of NDBE, INDBE (indefinite for Barrett's dysplasia) and LGD (41). The delineation of BE pathology is critical in determining prognosis and treatment, and therefore concordance from at least two expert pathologists is required (24). The qualification of an expert pathologist is somewhat subjective but designated as someone with an interest in BE and associated experience in interpretation (42). Staining for p53 is a well validated method to detect early dysplasia within the crypts (43). Aberrant p53 immunostaining in Barrett's epithelium is strongly associated with progression towards HGD and EAC (44). The rate of progression of BE subjects with NDBE, INDBE and LGD can vary from indolent to rapid progression, and the TissueCypher^{TM} system developed a risk score within these groups utilizing clinical and pathological data including biomarkers (45). If validated, this could better dictate management within these heterogeneous groups. For instance, this model noted 78% of a cohort of 155 BE-LGD subjects did not progress pathologically when followed for almost 8 years with the remainder developing HGD or EAC usually within 3 years (46). Wide-area transepithelial sampling (WATS) utilizing brushings is a useful adjunct to biopsies during endoscopy and allows sampling of a larger surface area-this device received societal endorsement (26). A meta-analysis demonstrated that the incremental yield of WATS for dysplasia was largely dependent on the dysplasia rate within the study populations and ranged from 2% to 13% (47).

Alternative screening

Subjects deemed low risk or reluctant for traditional endoscopy may be considered for alternative screening modalities. Capsule endoscopy utilizing a two-camera capsule and a high frame acquisition rate has been available for about two decades but is seemingly unpopular with practitioners and patients alike (48). Unsedated transnasal endoscopy can be performed with only topical anesthesia but its use is hindered by patient discomfort, lack of procedural training and occasional inability to biopsy (49). Intriguing novel devices for tissue acquisition utilize dissolvable capsules (Cytosponge, EsophaCap) attached to a string or suture which contain a compressible polyurethane sponge and this sponge expands spherically with capsule dissolution (24,50). These devices and a balloon device (EsoCheck) obtain material upon withdrawal (24,50). The cellular material obtained, depending on the device, is analyzed for various biomarkers such as trefoil factor 3 or methylated DNA markers (24,50). In one analysis, Cytosponge resulted in cost-effectiveness of $15,700 per QALY (4). Cytosponge is not operator dependent with relatively simple equipment and can conceivably be applied to the primary care setting (51). In a pilot study, almost 40% of subjects were willing to utilize the Cytosponge and the positive predictive value in GERD subjects without prior endoscopy was almost 60% (52). One society guideline accepted the Cytosponge as an alternative screening method for BE in patients with GERD and other risk factors (24). An "electronic nose" has been shown to detect volatile organic compounds in exhalations with correlation for BE (53). These screening tests have generally demonstrated good to excellent sensitivity and specificity, but endoscopy is still needed to assess the BE and biopsies obtained in the usual fashion to determine dysplasia. More validation is anticipated and most experience has been with the Cytosponge.

Utility of screening

The track record of preventing the development of EAC generally and even in those with known BE is so wanting that screening for BE has been called into question (5,54). Major impediments include implementation of screening and hence detection of BE before cancer development (54,55). Another provocative hypothesis is that most EAC emanates from the gastroesophageal junction (GEJ) or short segment BE-this runs counter to current guidelines (54). A sobering finding from resected EAC specimens is that intestinal metaplasia is not always identified and a recent hypothesis is that metaplasia is not necessary for EAC development (56). A large British study will compare biennial endoscopic screening versus only symptom-based endoscopy for Barrett's subjects without dysplasia up to a 10-year period; this study design infers dubious value for regular screening (57).

Resection and ablation

Recent innovations in BE resection and ablation have revolutionized the field where previously BE-HGD and

intramucosal EAC usually mandated esophagectomy. Photodynamic therapy was an alternative but had limited availability and was hindered by costs and associated complications such as prolonged photosensitivity after treatment and predilection towards esophageal strictures. Guidelines advocate endoscopic resection of any protuberant or suspicious Barrett's areas with subsequent ablation of the entire Barrett's epithelium. Subsequent endoscopic surveillance is dictated by the pathology and may be intensive.

Endoscopic mucosal resection (EMR) is performed either via band ligation or submucosal injection with "suction and cut" and both techniques have associated technical ease and usually minimal complications. Endoscopic submucosal dissection (ESD) is usually reserved for larger areas (>2 cm) requiring resection as well as depressed/ulcerated areas and manipulated areas (prior ablation, EMR) (58). These resection techniques have the dual benefit of removing potentially progressive lesions and yielding extensive tissue pathology to allow optimal decision management. Endoscopic ultrasound has not been demonstrated to be particularly useful in assessing Barrett's lesions (59). Submucosal invasion usually mandates esophagectomy but there has been support regarding ESD resection for lesions with limited submucosal invasion (<500 μm), well differentiation and no lymphovascular invasion (60). Patient preference and condition factor as well. T1b EAC may have less propensity for lymph node metastases than previously thought and therapy is shifting towards endoscopic resection for lower risk subjects and those who are not good surgical candidates; clinical trials are ongoing (61,62). Piecemeal EMR of larger lesions is problematic because of the significant recurrence rate and ESD is preferred (58,60).

Radiofrequency ablation (RFA) is the most frequently employed method of Barrett's ablation and has the best track record and is thus considered the gold standard (60,63). RFA is designated for only planar BE and any nodular or depressed areas are resected or referred to surgery depending on pathology. RFA has a superlative efficacy and complication record. Systematic review and pooled analysis of 20 studies of RFA in BE ablation often after EMR noted 73% had a complete eradication of intestinal metaplasia and 93% eradication of dysplasia/intramucosal EAC (64). The approximate complication rate was strictures 10%, bleeding 1% and perforation 0.2% (64). The rate of recurrent intestinal metaplasia/dysplasia/EAC was 16%/3%/1.4%, respectively (64). This study also suggested complete EMR of the entire BE is associated with more complications than segmental EMR followed by RFA (64). EMR before RFA and increasing BE length are associated with more complications and perhaps decreased efficacy (65,66). Technical failures include non-healing acute esophagitis and persistent BE and intervention should include smoking cessation, PPI compliance assessment and possibly increased dosage, and the occasional need for fundoplication (67).

Cryotherapy of BE applied either via spray (liquid nitrogen) or balloon (nitrous oxide) has also been shown to be efficacious and relatively safe (68,69). Some centers offer cryotherapy as well as RFA, and crossover therapy may be beneficial (70). Argon plasma coagulation (APC) is available in most centers and has been used for BE for many years, but efficacy seems to be somewhat less and safety may be a concern for large areas of ablation (71). Hybrid APC where a submucosal lift is created prior to ablation may be safer and has had promising results to date including as a rescue modality (72).

There is a concern for recurrent or residual BE after apparent complete ablation by RFA or any modality. Detection at surveillance endoscopy may be challenging due to overlying neo-squamous mucosa. Buried or sub-squamous BE glands may occur in in up to 91% post-RFA subjects but the significance of this is unclear and authorities suggest a likely indolent progression (73,74). Current evidence-based guidelines promote surveillance intensity depending on the pre-intervention pathology and less frequent than typically practiced; LGD subjects can be assessed at 1 and 3 years and those with HGD or EAC assessed at 3, 6, and 12 months and then annually (75). Most recurrences are noted within 1 year after therapy and are at the GEJ or within the distal esophagus (76). In view of this, it may be more rational to take extensive biopsies in these areas as the yield of random biopsies in the neo-squamous area is quite low though any area that is protuberant should be at least biopsied and preferably removed via EMR (77).

Prospects

The yawning gap between the resources invested in both the screening for BE and surveillance of established BE subjects as compared to the minimal proportion of EAC detected at a curable stage is self-evident. However, there are optimistic prospects in this arena. More broad but practical endoscopic screening are suggested for those with epidemiologic features that would increase BE propensity but with less emphasis on symptoms such as heartburn. Implementation of flagging patients in electronic records

by characteristics that would make them candidates for BE screening has been suggested (78). Practically, endoscopy can be considered at the time of screening of surveillance colonoscopy. The increased cost of such screening for BE could be offset by avoidance of unproductive endoscopic practices such as biopsies of the GEJ and "mini-Barrett's". Better adherence to recommended intervals for BE screening could also possibly decrease cost as would avoiding endoscopic screening in those with little likelihood of BE or in those with clearly diminished remaining lifespan. Better adherence to recommended endoscopic practices during screening and surveillance is also paramount. Electronic chromoendoscopy or acetic acid chromoendoscopy should be employed.

Non-endoscopic methods of BE detection after more validation could be offered as an initial exam for those in lesser risk groups (non-Caucasians, women) over 50 years old. Thus, the goal of widespread screening could be approached. Clinical/pathologic gradations (e.g., TissueCypher™) could potentially optimally dictate surveillance intervals for heterogeneous groups (NDBE, INDBE, LGD). AI will likely further impact the endoscopic and pathologic gradation of BE. Endoscopic ablative therapies for BE with dysplasia and intramucosal EAC are remarkably effective and subsequent innovations may justify less stringent post-ablative monitoring.

Conclusions

There are numerous challenges in the management and treatment of BE and EAC with recent innovations that will likely improve screening practices and positively impact the prognosis for BE patients. The paradigm for BE diagnosis and treatment is rapidly changing with recent technological innovations and more impactful developments are likely on the horizon.

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Footnote

Reporting Checklist: The author has completed the Narrative Review reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-12/rc

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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