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A Practical Approach to Diagnosis and Treatment of Barrett's Esophagus

Abhilash Perisetti

Prateek Sharma

Barrett's esophagus (BE) is a condition characterized by transformation of the normal squamous epithelium of the distal esophagus with abnormal columnar epithelium. It can be detected in patients with gastroesophageal reflux disease (GERD, 2.3% to 8.3%) or without GERD (1.2% to 5.6%). Common risk factors include older age (approximately 1.1% in individuals older than 50 years and 0.3% in those 50 years or younger), Caucasian race, male gender, cigarette smoking, positive family history and long-standing GERD. BE can progress to neoplasia and if left untreated, could develop adenocarcinoma. BE increases the risk (annual rate of 0.2% to 0.5%) of developing esophageal adenocarcinoma (EAC) and it remains critical for early identification and treatment of this precancerous condition. High-quality upper endoscopy remains an essential tool for early identification, treatment and surveillance of BE. Despite advances in the endoscopic recognition, there is approximately a 20-25% rate of missed lesions and an urgent need to improve the rate of neoplasia detection. Management of BE is dependent on presence or absence of neoplasia. Non-dysplastic BE is treated with regular endoscopic surveillance (3-5 years) compared to neoplastic BE which requires endoscopic resection and ablation. In this review, we aim to describe recent updates on the screening, surveillance, diagnosis and management of patients with BE.

INTRODUCTION

Barrett's esophagus (BE) derives its term from a British surgeon Dr. Norman Rupert Barrett[1] who first described abnormal appearing esophageal lining in BE. The esophagus is normally lined by flat, stratified squamous epithelium which if exposed to chronic inflammation and tissue injury, could turn into mucus secreting tall and long columnar epithelium.[2] This metaplastic change (where a differentiated flat squamous epithelium transforms into another mature differentiated columnar cell type) is triggered by inflammation and chronic acid exposure. This change remains a precursor to dysplasia, a critical step for developing

Abhilash Perisetti MD[1] Prateek Sharma MD[1,2]
[1]Deparment of Gastroenterology, Kansas City VA Medical Center, Kansas City, MO [2]Professor of Medicine, University of Kansas School of Medicine, Department of Gastroenterology and Hepatology, Kansas City VA Medical Center, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Kansas School of Medicine, Kansas City, KS

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esophageal adenocarcinoma (EAC).[3] The natural history of BE involves a risk of transformation to full blown EAC in 3% to 5% of patients during their lifetime. This rate accelerates when an individual develops dysplasia.

Screening

Screening refers to evaluating individuals with GERD (without a prior history of BE) with upper endoscopy for BE. On the contrary, surveillance involves a prior established diagnosis of BE and to assess the progression to EAC. An algorithm approach for screening and surveillance for BE have published in prior studies (Figure 1).[4]

Patients with chronic gastroesophageal reflux disease with one or more risk factors (male sex, smoking history, age > 50 years, obesity and positive family history) are at risk of developing BE. A meta-analysis of 44 cross-sectional studies[5] included 26,521 GERD individuals, in whom the pooled prevalence of endoscopically suspected BE (suspected columnar epithelium in the esophagus without biopsy) was 12% (95% CI, 5.5%-20.3%) while histologically confirmed BE was 7.2% (95% CI, 5.4%-9.3%), short-segment (BE affecting 1 to 3 cm of the esophagus) was 6.7% (95% CI, 4.6%-9.1%) and long-segment (BE affecting more than 3 cm of esophagus) was 3.1% (95% CI, 2.0%-4.6%).[5] Male sex is associated with higher BE pooled prevalence of 10.8% (95% CI, 6.6%-15.9%) compared to females of 4.8% (95% CI, 2.7%-7.5%).[5] Although the precise reason for this difference is unclear, possible contributors include a male-predominant gender bias including GERD-related esophagitis, vulnerability of esophageal epithelium to acid exposure and estrogen induced acid protection in females.[6] Prevalence of BE is higher in White individuals compared to Hispanics (6.1% vs. 1.7%; $P = .002$).[7] Older individuals (>50 years) are at higher risk than younger individuals (50 years or younger). In a cohort of 29,374 patients, prevalence of BE was higher in older patients compared to younger individuals (1.1% vs. 0.3%; $P = .02$).[8] Further, tobacco smoking increases the risk of BE with higher prevalence noted in cigarette smokers compared to non-smokers (12% vs. 1.1%; $P < .001$).[9] Obesity poses a risk for higher prevalence of BE compared to lean individuals. A study of 13,434 patients (mean body mass index [BMI] of 39 to 51.2) showed for every 1-point increase in BMI, there is a 0.15% increase in prevalence of BE. This is likely attributed to adipocytokines increasing the risk of inflammation in obese individuals. Patients with positive family history (of BE or EAC) are at a higher risk of BE.[10]

While screening can assess for BE and need for further surveillance, an important consideration should be given to overall life expectancy. If the patient overall life expectancy is less than 10 years, the value of screening decreases significantly.

Diagnosis of BE and Related Neoplasia

BE is primarily diagnosed by high-quality upper endoscopy followed by multiple biopsies of the columnar lined esophagus to confirm intestinal metaplasia. To minimize variability in measuring the extent of BE during endoscopy, the Prague criteria with methodological inspection of the diaphragmic area, upper end of gastric folds, circumferential and maximum extent of squamocolumnar area has been introduced.[11] Further, use of expert esophageal histopathologist could improve the interobserver variability for diagnosis of dysplasia in BE.[12]

A high-definition endoscope could improve the detection of the visible and potentially curable lesions (BE-related neoplasia [BERN]). Multiple strategies are available to improve the detection of these subtle BERN lesions on upper endoscopy.[13] High-quality endoscopy requires CLEAN-adequate cleaning [C], learning [L] slow withdrawal with inspection of BE segment, use of virtual chromoendoscopy [E], acquiring [A] education to identify BERN lesions (by web-based and interactive sessions), and use of quality metrics (neoplasia detection rate [NDR]), which could potentially enhance detection of these lesions (Figure 1).[13] The evaluation of the BE requires extensive cleaning of the concerned segment and slow withdrawal during the inspection. Endoscopists with a mean inspection time longer than 1 minute per centimeter of BE detected more lesions compared to those with less than 1 minute inspection time (54.2% vs. 13.3%; $P = .04$).[14]

For individuals who cannot tolerate sedation, office-based procedures such as swallowed cell-collection devices (unsedated transnasal endoscopy, esophageal capsule endoscopy) have been advocated.[12] In unsedated transnasal endoscopy,

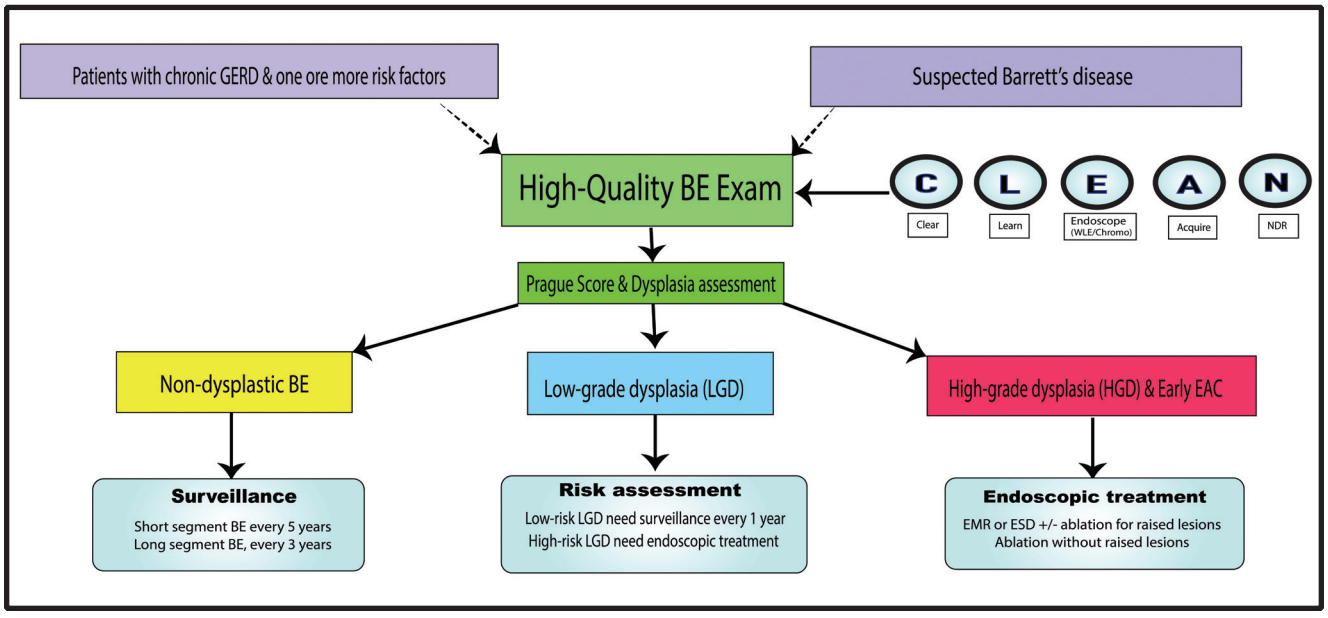

Figure 1. Algorithm for Barrett's Esophagus Diagnosis and Treatment.
GERD- Gastroesophageal reflux disease; BE- Barrett's Esophagus; C (cleaning esophagus), L (learning slow withdrawal), E (white light endoscopy [WLE], chromoendoscopy), A (acquire education on raised lesions), N (neoplasia detection rate [NDR]); LGD- Low-grade dysplasia; HDL- High-grade dysplasia; EMR- Endoscopic mucosal resection; ESD- Endoscopic submucosal dissection. Please refer to text for references.

an ultrathin endoscope is passed through the nose and advanced to the esophagus to evaluate for mucosal abnormalities. Non-endoscopic capsule sponge device (once swallowed, the capsule dissolves, compressed sponge emerges which is pulled out by a string for laboratory biomarker assessment) combined with biomarkers (trefoil factor 3, methylated DNA markers) can be used in individuals with chronic GERD.[12]

Missed Lesions

The visible lesions noted in the BE segment, also called BE-related neoplasia (BERN), are abnormalities noted on the BE surface mucosa (raised or abnormal pattern) indicative of dysplasia or invasive cancer. The prevalence of LGD remained relatively stable at approximately 12-13%, HDG increased by 148% (2.7% [1990-1994] to 10% [2010 and beyond]).[15] Further, prevalence of EAC increased by 112% (3.3% [1990-1994] to 7.6% [2010 and 2016]).[15] This correlated with increase in BERN lesions from 5.1% [1990-1994] to 16.3% [2010-2019]. While this increase in prevalence of HGD or EAC could be theoretically related to increase in recognition of BERN lesions, further studies are needed to corroborate these findings. On the contrary, the rate of missed BERN lesions on endoscopy is an important finding to assess for potential targets for improving lesion detection. Recent studies reported a missed rate up to 23% from Netherlands (flat BERN from community centers had higher grade when referred to expert centers), 27% from Australia (BE referral centers identified advanced BERN lesions with a prior diagnosis of LGD). A meta-analysis of 24 studies reported a missed rate of 25.3% (95% CI, 16.4%-36.8%) for EAC.[16] These studies indicate an approximate missed rate of EAC/HGD as high as up to one-quarter of all cases suggestive of an area of huge improvement.

Progression of BE to EAC

The annual rate of progression of BE to EAC is dependent on length of BE segment, and the presence or absence of dysplasia. In a study involving 4097 patients with BE,[17] the annual rate of progression to EAC in short-segment BE (non-dysplastic) was 0.06% (95% CI, 0.01%-0.10%), in long-segment BE 0.31% (95% CI, 0.21%-0.40%).[17]

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Similarly, a meta-analysis of 2694 patients with BE and LGD (low-grade dysplasia) found that annual incidence of HGD/EAC was 1.73% (95% CI, 0.99%-2.47%).[18] The progression of BE to HGD/EAC is critical and risk stratification tools have been developed. In a study involving 4584 patients with BE in the US and Europe, Progression in Barrett Esophagus (PIB) score was developed.[19] This scoring system (composed of 30-point score, validated externally) combines data from age, sex, tobacco smoking history, BE segment length and presence of any LGD. An annual progression risk is determined based on score, 0.13% (score: 0-10), 0.73% (score: 11-20), 2.1% (score: 21-40).

Prevention

Given that GERD is a risk factor for development and progression of BE to EAC, acid exposure elimination remains an important strategy for prevention. Aspirin (given its anti-inflammatory properties) have been used as a chemo preventative agent against multiple cancer including progression of BE to EAC. This combined with a proton pump inhibitor (PPI) could potentially reduce the progression of BE. To evaluate this, a large, randomized trial published (ASPECT trial) in Lancet[20] was conducted in the UK and Canada (84 centers, 2557 participants). Four groups: high-dose PPI with aspirin group, low dose PPI with aspirin group, twice-daily PPI group and daily PPI group. At 9 year follow up, the first group (high-dose PPI with aspirin) had overall reduced rates of a combination of: EAC, all-cause mortality and HGD without significant adverse events. High-dose PPI added the highest beneficial effect and combination with aspirin added another 38% benefit to the time to an event.[20] Health et al.[21] studied Celecoxib (n= 49, 200 mg twice daily) vs. placebo (n = 51) to evaluate for change in dysplasia progression and found no difference at 4-year follow-up (-0.08% vs. -0.06%). Despite this benefit, given the risk of non-fatal, fatal bleeding events[22] and cerebrovascular events, the American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) recommend against routine use of aspirin and/or nonsteroidal anti-inflammatory drugs for chemoprevention of BE.

Surveillance of BE

Management of BE includes surveillance endoscopy and treatment interventions (endoscopic resection and ablation). Surveillance refers to assessment for progression of EAC with an established diagnosis of BE in the past. The intervals for surveillance is dependent on the length of the BE segment. Major gastrointestinal societies recommend a 5-year surveillance for short segment (<3 cm) compared to 3-year surveillance for long segment (≥ 3 cm). Endoscopy image technology and pixel improvement resulted in high-definition white light endoscopy (HD-WLE) and chromoendoscopy (electronic or dye-based [acetic acid]). Acetic acid chromoendoscopy meets the Preservation and Incorporation of Valuable Innovations (PIVI) thresholds. A meta-analysis of 24 studies (2304 patients) with BE patients showed a sensitivity of 97% (95% CI, 95%-98%), negative predictive value (NPV, 98%, CI, 95%-99%) and specificity of 85% (95% CI, 69%-93%) for acetic acid chromoendoscopy.[23] Additionally, American Society of Gastrointestinal Endoscopy (ASGE) recommended chromoendoscopy in addition to WLE for biopsy specimens. In a meta-analysis including 12 randomized trials and 2433 BE patients, a 9% (95% CI, 4.1%-14%) increase in dysplasia detection was noted with chromoendoscopy compared to WLE.[23]

Endoscopic Resection

The initial step in endoscopic therapy includes either mucosal or submucosal resection. Prior to these advances, many of these esophageal lesions were treated surgically. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are most commonly performed procedures when lesions are restricted to mucosa and superficial third of the submucosa respectively. EMR and ESD are both highly effective with ESD achieving a higher R0 resection at the expense of time and higher adverse events. Further, prior endoscopic therapy (mucosal resection or ablation) can lead to submucosal fibrosis which can make further endoscopic therapy challenging. In these cases, ESD could offer definitive treatment. Band mucosectomy is the most commonly performed EMR technique which could assist with resection for margin free removal. This technique involves

evaluation of abnormal mucosal tissue and followed by targeted resection of visibly abnormal area. The resected area is assessed histologically for the depth and lateral margins for R0 resection. For well-differentiated lesion restricted to mucosa, without submucosal or lymphovascular involvement, EMR could be considered curative. ESD is a technique characterized by dissecting lesions in the submucosa with ability to remove entire lesions with varying length and depth. Given the ability to target a wider area, it could theoretically lead to higher R0 resections. In a small randomized controlled trial of BE patients[24] with focal area of HGD or early EAC ≤ 3 cm undergoing either ESD (20 patients) or EMR (20 patients), R0 (margin free of HGD/EAC) resection rates were higher in ESD compared to EMR (10/17 vs. 2/17, P = 0.01), but no difference was noted in neoplasia remission, recurrence or need for surgery.[24] Further, ESD was associated with longer procedure times with a mean ESD time of 83.3 minutes compared to EMR of 36.7 minutes limiting its generalizability.[24]

Ablation Therapies

Endoscopic ablative therapy with heat (radiofrequency ablation [RFA], argon plasma photocoagulation [APC]) or cold (cryotherapy) have been used for BE patients with HGD or visible neoplastic lesions after resection.[12] RFA remains the most studied and established method of ablation for neoplastic BE and HGD.[25] RFA could be used after resection (EMR/ ESD) or without resection for absolutely flat HGD. A systematic review of 20 cohort studies (9 studies with RFA post resection and 11 studies with only RFA) noted complete eradication of neoplasia (CE-N) in 93.4% (for RFA post resection) and 94.9% for RFA only groups.[26] Complete eradication of intestinal metaplasia (CE-IM) was 73.1% for RFA post resection compared to 79.6% in RFA only group.[26] Rates of recurrence were 1.4% (EAC), 2.6% (dysplasia) and 16.1% (IM) for RFA post resection. For RFA only group, recurrence rates were 0.7% (EAC), 3.3% (dysplasia) and 12.1% (IM). Adverse events associated with RFA were post treatment stricture formation, bleeding and perforation. The risk of adverse events with RFA have been studied in a systemic review and meta-analysis of 9200 patients in 7 studies with rates significantly higher in RFA with resection (EMR) compared to RFA without resection (22.2% vs. 5%; relative risk, 4.4; P = .015).[27] For every 1-cm increase in the median BE length, there was a 25% (95% CI, 16-35%) increase in adverse events.[27] Nevertheless, mucosal resection (to remove the neoplastic BE) followed by RFA remains the standard of care for patients to achieve eradication of IM.

Cryoablation involves the application of a cryogen such as liquid nitrogen spray or nitrous oxide via flexible catheter to achieve a temperature as low as –196 ^{0}C. These extremely low temperatures cause ice crystallization and destruction of plasma cell membranes and denature the proteins. The tissue architecture and extracellular matrix (which are cryoresistant) are preserved reducing the underlying risk of tissue scaring, post-procedure pain and stricture formation. A multicentric nonrandomized and noncontrolled clinical trial of 120 patients using nitrous oxide cryoballoon focal ablation system achieved eradication of IM in 91% and dysplasia in 97%.[28] Post-procedure pain was well tolerated with a score of 2 which was considered mild (visual analog score of 0 [no pain] to 10 [most severe pain]) which resolved within 2 days. Some reported adverse events included post-procedure chest pain, stricture formation, bleeding and perforation.[29] Hybrid- Argon plasma coagulation (APC) uses injection therapy followed by heat for achieving eradication of metaplasia in BE. A randomized pilot study of 65 patients with BE showed that APC compared to RFA achieved ablation in BE patients in 55.8% vs. 48.3% (OR, 1.4 [95% CI, 0.5-3.6]) with comparable adverse events and quality of life scores.

Approach to Neoplastic BE

Endoscopic therapy remains first-line of treatment for high-grade dysplasia and early EAC (T1a and superficial T1b) lesions. In LGD, the risk of progression to EAC should determine the intensity of treatment versus surveillance. Given the variable risk of LGD patients progressing to EAC (0.02%-11.4%), shared decision making based on the patient preferences, risk factors and annual progression risk could be considered. Surgical options (esophagectomy) could be considered for HGD or early EAC, however are associated with higher adverse events compared to endoscopic therapy. A

systematic review of 870 patients (510 undergoing endoscopic therapy and 360 undergoing surgical esophagectomy) in 7 studies[30] showed no difference in rates of CE of dysplasia (314/334 in endoscopy arm vs. 237/241 in surgical esophagectomy arm, relative risk, 0.86 [95% CI; 0.91-1.01]). Survival rates and mortality did not differ between groups at 1 year and 5 years. However, adverse events (stricture formation, bleeding, perforation) were significantly lower in endoscopic therapy (66/510) compared to esophagectomy (90/360, relative risk, 0.38; 95% CI, 0.20-0.73; $P = .004$).[30] For lesions extending to superficial submucosa (early T1b), a multidisciplinary team approach is needed to assess the candidacy for ESD. Patients with low-risk lesion (good to moderate differentiation), no lymphovascular invasion, and superficial submucosal lesion (up to 500-mm invasion) could be offered ESD in high-volume center with experienced advanced endoscopist. In an observational study of 61 patients with low risk T1b lesions with ESD, eradication of dysplasia was noted in 87% of patients with maintenance of eradication in 84% over a 47 month period.[31]

Limitations

This review aims to provide updated information on the diagnosis, treatment and management of BE. First, due to use of practice guidelines, they could be subjected to expert opinion bias. Second, since this review did not systematically search the literature, some relevant publications may have been missed. Observational data without randomized controlled trials could decrease the strength of recommendations.

The Future

Given the high miss rate of BERN lesions, artificial intelligence (AI) could be a promising tool in identifying subtle neoplastic lesions with improved sensitivity (>90%) and specificity (>80%).[13] Use of machine learning with convolutional neural networks, deep learning can assess the lesion accurately for depth and precise mucosal patterns. This combined with areas in long segment BE could improve quality, blind spot assessment, could provide feedback and report quality metrics needed to reduce the missed BERN lesions. Use of high-quality BE examination with CLEAN (cleaning, learning, endoscopic [virtual], acquiring and neoplasia detection metric [NDR quality metric assessment]) could further improve our ability to identify and manage these lesions effectively. Newer treatment modalities such as radiofrequency vapor therapy can generate heat therapy (vapor at 100 °C using a RF electrode) and could be used for ablation of the dysplastic segment, the efficacy and feasibility needs to be studied in the future.[32] ■

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