Management of nondysplastic Barrett’s esophagus: When to survey? When to ablate?

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Abstract: Barrett’s esophagus (BE), a precursor for esophageal adenocarcinoma (EAC), is defined as salmon-colored mucosa extending more than 1 cm proximal to the gastroesophageal junction with histological evidence of intestinal metaplasia. The actual risk of EAC in nondysplastic Barrett’s esophagus (NDBE) is low with an annual incidence of 0.3%. The mainstay in the management of NDBE is control of gastroesophageal reflux disease (GERD) along with enrollment in surveillance programs. The current recommendation for surveillance is four-quadrant biopsies every 2 cm (or 1 cm in known or suspected dysplasia) followed by biopsy of mucosal irregularity (nodules, ulcers, or other visible lesions) performed at 3- to 5-year intervals. Challenges to surveillance include missed cancers, suboptimal adherence to surveillance guidelines, and lack of strong evidence for efficacy. There is minimal role for endoscopic eradication therapy in NDBE. The role for enhanced imaging techniques, artificial intelligence, and risk prediction models using clinical data and molecular markers is evolving.

Keywords: Barrett’s esophagus, cancer, ablation, surveillance

Introduction
There has been a dramatic rise in the incidence of esophageal adenocarcinoma (EAC) over the past 40 years and this trend is expected to continue in the future.1,2 Barrett’s esophagus (BE), a precursor for EAC, is defined as salmon-colored mucosa extending more than 1 cm proximal to the gastroesophageal junction with histological evidence of intestinal metaplasia.3 A vast majority of patients newly diagnosed with BE do not have dysplasia and appropriate management of these patients can reduce the burden of invasive EAC.4 Even though BE patients are at an increased risk of EAC compared with general population, the actual risk of EAC in nondysplastic Barrett’s esophagus (NDBE) is low with an annual incidence of 0.3%.5 Therefore, control of gastroesophageal reflux disease (GERD) symptoms along with periodic surveillance with appropriate technique is recommended in most patients with NDBE. Certain patients with NDBE remain at high risk for neoplastic progression and consideration may be given to endoscopic eradication therapy (EET) in these high-risk groups. Risk prediction models based on various clinical, endoscopic, and molecular factors are being developed and validated for clinical implementation. In this review, we present the pros and cons of surveillance strategy in comparison with EET in patients with NDBE.

Initial management of NDBE
Acid suppression: Initial management of NDBE involves a multifactorial approach comprising the use of acid suppressive therapy to mitigate the caustic effects of acid and bile on esophageal mucosal lining, lifestyle modifications, and surveillance for early detection of dysplasia. Proton-pump inhibitors (PPI) are recommended for reflux symptom control and anti-reflux surgery is considered for patients with poor or partial...
response to PPI therapy. As chronic exposure to gastric refluxate promotes esophageal carcinogenesis, PPI use may reduce risk of neoplastic progression in BE (PIB). In a recent meta-analysis of seven observational studies with 2813 patients with BE, PPI use was associated with a 71% decrease in risk of neoplasia with an adjusted odds ratio (OR) 0.29 [95% confidence interval (CI): 0.12–0.79]. Furthermore, there was an illustrated trend toward a dose–response relationship where a longer duration of therapy was associated with an accentuated protective effect with PPI use. A landmark study evaluating the chemopreventive role of PPIs is the recent AspECT trial in which patients with BE were randomized to either low- or high-dose esomeprazole with or without aspirin to create a 2 × 2 factorial design. In this study, high-dose PPI was superior to low-dose PPI in preventing all-cause mortality, high-grade dysplasia (HGD), and EAC with a time ratio of 1.27 (95% CI: 1.01–1.58; p = 0.038). In an interesting note, the study also demonstrated that regular aspirin use may decrease all-cause mortality in BE patients. It is worthwhile to note that anti-reflux surgery is not superior to PPI therapy for the prevention of neoplastic progression of BE. An important consideration is the reflux control in post-EET patients. Persistent reflux can lead to recurrences after EET. However, it is currently not known if high-dose PPI therapy or tight control of reflux (as determined by objective testing) leads to lower recurrence rates following ablation. Therefore, routine use of twice-daily dosing is not recommended, unless necessitated because of poor control of reflux symptoms or esophagitis. Anti-reflux surgery can be considered in those with incomplete control of reflux on optimized medical therapy.

Addressing modifiable risk factors: Patients should also be counseled about modifiable risk factors such as obesity and tobacco use. Obesity increases risk of EAC not only by increasing risk of GERD but also by reflux-independent mechanisms such as low-grade inflammation and the altered secretion of adipokines such as increased leptin levels and decreased adiponectin levels which are associated with esophageal carcinogenesis. In a registry study of 3167 patients with BE, smoking doubled the risk of developing HGD/EAC with a hazard ratio (HR) of 2.03 (95% CI: 1.29–3.17). Smoking cessation and weight reduction should be a part of the conversation as a controllable facet of their health that has significant impact in the progression of their disease.

In addition, patients with BE may benefit from increasing their consumption of fruits and vegetables and reducing their intake of red meat and other processed food items. The current evidence points to an inverse relationship between intake of vitamin C, β-carotene, fruits and vegetables, particularly raw fruits and vegetables and dark-green, leafy and cruciferous vegetables, carbohydrates, fiber, and iron and the risk of EAC and BE.

Role of surveillance in management of NDBE

The goal of surveillance in NDBE is early detection of dysplasia or cancer with timely intervention and ultimately leading to improved survival. The annual risk of progression of NDBE to EAC is 0.33 per year in NDBE. Even though the absolute risk is low, the relative risk (RR) compared with general population is high, leading to recommendation of surveillance every 3–5 years from major gastroenterology societies.

While surveillance leads to early detection of neoplasia, its role in prolonging survival when lead-time and length-time bias are taken into account remains controversial. A case–control study of 8272 BE patients failed to show any benefit from endoscopic surveillance on EAC-related mortality (adjusted OR: 0.99; 95% CI: 0.36–2.75). On the contrary, in a recent meta-analysis of 12 cohort studies, patients with regular surveillance had reduced EAC-related and all-cause mortality compared with those without surveillance (HR: 0.59; 95% CI: 0.45–0.76) and RR 0.73 (95% CI: 0.57–0.94). Of note, these benefits were modestly attenuated when adjusting for lead-time and length-time bias. In another cohort study of 5532 patients based on the Surveillance, Epidemiology and End-Results Medicare database, serial surveillance endoscopy was associated with EAC being diagnosed in a localized stage (OR: 2.95; 95% CI: 2.07–4.19). Even when adjusting for lead-time and length-time bias, improved survival rate was noted in patients who received serial endoscopies (HR: 0.45; 95% CI: 0.37–0.55). The reasons for these disparate results are many: (1) most of these are retrospective cohort studies or are based on administrative claims data; (2)
they may not have adequately addressed lead-time and length-time bias; (3) they have excluded younger populations with aggressive tumors who are already dead; and (4) lack of standardized surveillance biopsy protocols and inferior optical resolution for identifying abnormal areas of mucosa in the older studies. A currently ongoing randomized controlled trial (RCT), Barrett’s Oesophagus Surveillance versus endoscopy at need study (BOSS) will examine the difference in patient outcomes between routine endoscopic surveillance for BE patients and ‘at-need’ endoscopies for patients that develop symptoms such as dysphagia or unexplained weight loss. These results will help provide objective evidence on the efficacy and cost-effectiveness of regular surveillance endoscopy for BE patients.

Limitations of surveillance

Despite the current recommendations for surveillance of all patients with NDBE, several challenges remain in clinical practice.

Missed cancers: BE surveillance involves the Seattle protocol wherein random four-quadrant biopsies every 2 cm (or 1 cm in known or suspected dysplasia) are performed. Sampling of BE mucosa with Seattle protocol is cumbersome, time-consuming, and samples less than 5% of BE mucosa. In addition, dysplasia in BE segment is patchy and may present with subtle abnormalities which may be difficult to recognize. Therefore, there is a high chance of missed cancers in surveillance programs. Visrodia et al. conducted a systematic review and meta-analysis of missed EACs during surveillance and found that missed EAC diagnosis rate can be as high as 23.9% (95% CI: 15.3–35.4) in NDBE patients in the first year of index endoscopy.

Inconsistent adherence: Variations in adherence to Seattle protocol and surveillance intervals exist. In a meta-analysis, pooled proportions of adherence ranged from 18 to 89% and for NDBE, adherence to surveillance intervals was 55% (95% CI: 44–66%), and for Seattle protocol was 49% (95% CI: 36–62%). Factors most frequently reported in this study to be associated with better adherence were shorter BE length, salaried employment, surveillance in university hospitals, and dedicated programs. Racial disparities also exist and studies have shown that black patients with NDBE were less likely to be recommended appropriate surveillance intervals (OR: 0.78; 95% CI: 0.68–0.89). Adherence rates to the Seattle protocol found in this study were modestly higher among black patients overall (OR: 1.12, 95% CI: 1.04–1.20), although significantly lower among blacks with BE segments > 6 cm.

Cost-effectiveness: There have been studies reporting on the cost-effectiveness of surveillance compared with no surveillance in NDBE patients. In a pre-EET era study that used theoretical modeling of 50-year-old white men with GERD, endoscopic surveillance of NDBE every 5 years had a high incremental cost-effectiveness ratio (ICER) of $596,000 per quality-adjusted life year (QALY) compared with no surveillance. In contrast, a recent Dutch study comparing no surveillance with surveillance at 1, 2, 3, 4, or 5 years in the setting of EET for HGD and a theoretical willingness-to-pay (WTP) of €35,000/QALY, the optimal strategy was surveillance every 5 years. Another study compared results from three US population–based models of different strategies of management of 60-year-old patients with BE with either NDBE or low-grade dysplasia (LGD) and stratified by sex with a WTP of $100,000/QALY. This model found the optimal strategy was surveillance every 3 years for men with NDBE and treatment of LGD after confirmation by repeat endoscopy with an ICER of $53,044/QALY. The optimal surveillance interval for women with NDBE was 5 years with an ICER of $36,045/QALY.

Technique of surveillance

Prior to enrolling in a surveillance program, patients need to be counseled on the risks, benefits, limitations, and importance of adherence to periodic endoscopies along with the possibility of EET or surgery. An ideal surveillance examination involves adequate visualization of the mucosa and adequate sampling of the tissue to maximize the detection of dysplasia. The esophageal landmarks such as the location of diaphragmatic impression, GE junction, and length of BE segment using Prague classification should be identified and noted. For identification of subtle abnormalities, studies have recommended the mucosa should be thoroughly irrigated to clear the mucus, partial deflation may be used to accentuate surface abnormalities, and adequate time spent under high-definition white light. A minute increase in inspection time above the mean time for every centimeter of the BE
mucosa increases the odds of finding an ‘endoscopically suspicious lesion’ by almost fourfold (54.2% versus 13.3%, \( p = 0.04 \)). A distal cap attachment may help to separate the folds at GE junction. Careful attention should be paid to the right hemisphere of the BE segment, extending from the 12 o’clock to 6 o’clock where early cancer appears to have a predilection to develop. A web-based teaching tool (available at www.iwgco.net; www.ueg.eu; www.best-academia.eu) has been developed and tested for improving detection and delineation of BE-associated neoplasia. It has been shown to lead to relative increases in scores of 46% for detection and 129% for delineation independent of assessors' level of endoscopic experience.

To improve the detection of dysplasia, various advanced imaging techniques have been proposed such as virtual chromoendoscopy [narrow-band imaging (NBI) (Olympus, Center Valley, PA 18034, USA)], I-Scan (Pentax, New Jersey, 07645-1782 USA), flexible-spectral imaging color enhancement (FICE) (Fujinon, Valhalla, NY 10595-1356, U.S.A), blue light imaging (Fujinon, Valhalla, NY 10595-1356, U.S.A), volumetric laser endomicroscopy, and confocal microscopy. Recently, wide-area transepithelial sampling with an abrasive brush and 3D analysis (WATS-3D) has been shown to increase detection of dysplasia; however, the clinical significance of this increased dysplasia detection remains uncertain.

Artificial intelligence (AI) is a promising new tool that may provide real-time detection and characterization of early neoplastic lesions in BE segment. A recent meta-analysis of 19 studies of dysplasia detection by AI found a sensitivity of 94% (95% CI: 89–96%) and specificity of 88% (95% CI: 76–94%) for detection of neoplasia in image-based studies and 93% (95% CI: 86–96%) and 85% (95% CI: 78–89%), respectively, for the patient-based studies.

**Cessation of surveillance**

With advancing age and comorbidities, life expectancy is reduced and therefore the benefit of surveillance is decreased. While indefinite surveillance would not be an appropriate use of healthcare resources, there is no decisive consensus suggesting an appropriate age to stop surveillance particularly in patients with known NDDBE. In a survey of gastroenterologists, 91% of respondents cited comorbidity burden as a factor as to when to stop surveillance, 89% cited patient age, 75% adapted their cut-off to patient preference, and 62% of respondents adjusted according to length of BE segment in their patients. Current guidelines do not recommend when to discontinue surveillance except for the European Society of Gastrointestinal Endoscopy (ESGE) which suggests that surveillance endoscopies be stopped if a patient has reached 75 years of age and has no previous evidence of dysplasia.

There are no clinical studies that investigated the optimal age to discontinue surveillance of patients with NDDBE due to the feasibility of time and cost. Recently, a modeling study was reported using simulated patients diagnosed with NDDBE varying in age, sex, and comorbidity level. For men with no, mild, moderate, and severe comorbidity, the optimal ages of last surveillance were 81, 80, 77, and 73 years, respectively. For women, these ages were younger: 75, 73, 73, and 69 years, respectively.

**Role of ablation in the management of NDDBE**

In view of low risk of progression to cancer in NDDBE patients, lack of survival benefit from ablative therapy and risk of postablation recurrence leading to ongoing surveillance, gastroenterology societies around the world do not recommend ablation in NDDBE except under rare circumstances such as long-segment NDDBE in younger patients or BE patients with family history of BE or EAC (Table 2). While current guidelines recommend routine surveillance only for managing NDDBE, several experts have made a case for incorporating radiofrequency ablation (RFA) to treat NDDBE. Proponents of ablation argue that RFA is a safe and effective method to prevent progression of NDDBE to dysplasia. The number needed to treat to prevent a case of cancer progression is 45 patients, which is a low enough number to make a compelling case to advocate RFA in NDDBE. Another argument is that RFA ablation is analogous to routine polypectomy during colorectal
cancer screening with colonoscopy. Just as a polyp would not be left unresected barring extenuating circumstance during a colonoscopy, BE, a potentially precancerous lesion, should not be left untreated.\textsuperscript{38} The limitations of current surveillance strategies including difficulties with identifying dysplasia endoscopically, sampling error during surveillance biopsies, and low interobserver reproducibility in the diagnosis of dysplasia among pathologists also favor ablation therapy in NDBE patients.\textsuperscript{39}

\textbf{Drawbacks of ablation in NDBE}

RFA therapy in management of NDBE has documented benefits in preventing dysplastic prevention, but also comes with its own set of drawbacks as well. A major factor to consider in the conversation of ablation for NDBE is the cost-effectiveness of this approach. Earlier studies have investigated and reported positive cost–benefit using RFA in managing NDBE. Das \textit{et al.} theoretically modeled in a hypothetical cohort of 50-year-old men comparing the costs between the ablation therapy and surveillance endoscopy using parameters such as progressing to dysplasia and estimated QALY.\textsuperscript{41} This study found an ICER of $48,626/QALY using endoscopic ablation in comparison with the alternative strategy. Inadomi \textit{et al.} reinforced this conclusion, finding in their study that RFA of NDBE without surveillance is cost-effective with ICER of $16,286/QALY in comparison with not monitoring NDBE at all.\textsuperscript{42} However, juxtaposed with the encouraging results for RFA as initial intervention as a cost-effective strategy, studies have illustrated the contrary as well. Hur \textit{et al.} found that each QALY gained with RFA as an initial approach to managing NDBE incurred an incremental cost of $124,796 to $205,500/QALY, depending on the rate of progression of NDBE to adenocarcinoma per year ranging from 0.12 to 0% per year.\textsuperscript{43} Also of note is the possibility of recurrence of BE after endoscopic ablation. Most recent data report CE-IM rate of 94% with annual recurrence risk of dysplasia of 1% and NDBE of 3.4%.\textsuperscript{44} Even though these studies include only patients with neoplastic BE not NDBE, we can infer that ablation is not 100% effective and recurrences do occur necessitating postablation surveillance.

\textbf{Risk prediction models}

A reasonable middle of the road approach is identifying progressors, the true target population that will benefit from endoscopic management as majority of patients with NDBE never progress to

\begin{table}
\caption{Guidelines for surveillance in NDBE.}
\begin{tabular}{|c|p{10cm}|}
\hline
\textbf{AGA}\textsuperscript{14} & Surveillance every 3–5 years. \\
\textbf{ACG}\textsuperscript{3} & \\
\textbf{ASGE}\textsuperscript{32} & \\
\hline
\textbf{BSG}\textsuperscript{6} & If length < 3 cm without intestinal metaplasia on biopsies→repeat EGD. \\
& If repeat EGD is negative→discharge from surveillance. \\
& If repeat EGD shows intestinal metaplasia→surveillance every 3–5 years. \\
& If length ≥3 cm→surveillance every 2–3 years. \\
& Refer patients with a very long segment (>10 cm) to tertiary referral centers for endoscopic surveillance. \\
\hline
\textbf{ESGE}\textsuperscript{23} & <1 cm→no surveillance, \\
& ≥1 cm and <3 cm→surveillance every 5 years, \\
& ≥3 cm and <10 cm→surveillance every 3 years \\
& ≥10 cm→refer to BE expert center. \\
& Consider cessation of surveillance at 75 years of age. \\
\hline
\textbf{Australian Guidelines}\textsuperscript{34} & Short segment (<3 cm): repeat EGD in 3–5 years. \\
& Long segment (≥3 cm): repeat EGD in 2–3 years. \\
\hline
\multicolumn{2}{|c|}{ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy; BE, Barrett’s esophagus; BSG, British Society of Gastroenterology; EGD, esophagogastroduodenoscopy; ESGE, European Society of Gastrointestinal Endoscopy; NDBE, nondysplastic Barrett’s esophagus.} \\
\end{tabular}
\end{table}
cancer and EET in this population is met with diminishing returns. Indeed, the quest to identify progressors and risk stratify patients with BE has been pursued by many. These risk stratification tools can be broadly separated into those based on clinical features and molecular biomarkers.

Clinical markers: Older age, male sex, obesity, BE length, nodularity in BE segment, smoking, LGD have all been identified as factors associated with increased risk of PIB patients. Several studies incorporating these features into risk prediction models have been reported. The BE Assessment of Risk Score (BEAR Score) was developed from a single-institution, retrospective data set based on male sex, lack of PPI use, long segment BE, and esophageal candidiasis. As most BE progression studies at the time were limited by the inclusion of patients with LGD, it is worth noting that patients with any level of dysplasia at baseline were excluded in this study. However, the limitation of this study is the inclusion of patients based on International Classification of Diseases – Ninth Revision (ICD-9) diagnosis code for BE, without endoscopic or histological confirmation. In fact, close to 40% of the patients included in the study had ‘regression’ of BE, which calls into question the initial diagnosis of BE.

In a prospective, multi-institutional study that calculated a score for PIB based on male sex, history of smoking, length of BE segment, and LGD, patients were stratified into low-, intermediate-, and high-risk groups. Even while excluding the LGD group, the risk score was still able to risk stratify NDBE patients, although to a lesser effect. This risk score was externally validated as well.

Table 2. Recommendations for ablation in nondysplastic Barrett’s esophagus.

| Society          | Guidelines for ablation                                                                                                                                                                                                 |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ACG              | Given the low rate of progression in NDBE patients, the low but real rate of complications of ablation, and the costs associated with its delivery, ablative therapy cannot be recommended. Whether these therapies are warranted in subjects judged to have a higher lifetime risk of cancer, such as those with familial BE/EAC and young patients with long segments of BE, is unclear. |
| ASGE             | Ablation may be a preferred management option in select patients with NDBE, such as those with a family history of EAC. Additional research evaluating this management strategy is eagerly awaited. |
| AGA              | Although endoscopic eradication therapy is not suggested for the general population of patients with BE in the absence of dysplasia, we suggest that RFA, with or without EMR, should be a therapeutic option for select individuals with NDBE who are judged to be at increased risk for progression to high-grade dysplasia or cancer. Specific criteria that identify this population have not been fully defined at this time. When such criteria are identified from controlled trials, then management recommendations should be updated. Because of the paucity of evidence supporting EET in nondysplastic BE, current guidelines do not recommend EET in such patients. |
| BSG              | - No recommendations for ablation in NDBE.                                                                                                                                                                               |
| ESGE             | Prophylactic endoscopic therapy (such as ablation therapy) for NDBE should not be performed.                                                                                                                                 |
| Australian Guidelines | No recommendations for ablation in NDBE.                                                                                                                          |

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy; BE, Barrett’s esophagus; BSG, British Society of Gastroenterology; EAC, esophageal adenocarcinoma; EET, endoscopic eradication therapy; EMR, endoscopic mucosal resection; ESGE, European Society of Gastrointestinal Endoscopy; NDBE, nondysplastic Barrett’s esophagus; RFA, radio frequency ablation.
1.02/year; 95% CI: 1.01–1.03), male sex (OR: 2.8; 95% CI: 1.9–4.1), and increasing maximum BE length for segments 3–8 cm (OR: 2.3; 95% CI: 1.4–3.9) and segments ≥8 cm (OR: 4.3; 95% CI: 2.5–7.2) increased the risk of EAC/HGD. A model based on age, sex, and maximum BE length predicted 71% of all EAC/HGD cases.

Molecular biomarkers: Before NDBE epithelium transforms into dysplasia or carcinoma, genomic or epigenetic changes may be detectable several years in advance. Aberrant p53 expression including both overexpression and loss of expression is reported to increase the risk of neoplasia anywhere from 4 to 17 times in various studies. However, the subjectivity in p53 stain interpretation remains a limiting factor. A prediction model based on a cohort of 334 patients with BE with a median follow-up time of 86.5 months was constructed incorporating age, BE circumferential length, and a clonogenic score over the genomic set including chromosomes 7, 17, 20q, and c-MYC. The sensitivity and specificity of this model were 0.91 and 0.38, respectively, and the positive predictive value (PPV) and negative predictive value were 0.13 (95% CI: 0.09–0.19) and 0.97 (95% CI: 0.93–0.99), respectively, allowing identification of NDBE patients, who are required to remain in surveillance programs with 3-yearly surveillance intervals from those that can benefit from less frequent or no surveillance. This was a well-designed study that highlights the key challenge in the search for progressor markers in BE – the low rate of progression despite the magnitude of the study and the length of follow-up. In Amsterdam-based ReBus nested case–control study of 130 progressors and 130 controls, LGD (OR: 8.3; 95% CI: 1.7–41.0), Aspergillus oryzae lectin (AOL) (3 versus 0 epithelial compartments abnormal, OR: 3.6; 95% CI: 1.2–10.6), and p53 (OR: 2.3; 95% CI: 1.2–4.6) were independently associated with neoplastic progression. This biomarker panel was able to discriminate well between BE patients that progressed to EAC and nonprogressors with a C statistic of 0.73.

Recently, a TissueCypher BE assay was developed, which consists of nine protein-based biomarkers (p16, p53, AMACR, HER2, cytokeratin 20, CD68, COX-2, HIF-1alpha, and CD45Ro), as well as tissue architecture and nuclear morphology. This commercially available assay can be utilized to predict a risk score – the sensitivity and specificity of a ‘high-risk’ score for progression were 29% and 86%, respectively, and a PPV of 23%. Although this was a rigorous validation study, the predictive performance of the test appears to be modest with a PPV of 23% making any intervention unnecessary in almost 80% of the high-risk group.

In a multicenter study of 145 nonprogressors and 50 progressors, a panel of eight methylated DNA markers plus age was evaluated and found to predict progression with a sensitivity of 44% and a specificity of 90%. However, this study was limited due to questionable definition of progressors. For instance, progressors who progressed 2 or 4 years after index endoscopy were redefined as nonprogressors. In another, small study based on 13 nonprogressors and 12 progressors, a 12-miRNA panel comprising miR-1278, miR-1301, miR-1304-5p, miR-517b-3p, miR-584-5p, miR-599, miR-103a-3p, miR-1197, miR-1256, miR-509-3-5p, miR-544b, miR-802 accurately predicted 91.6% of cases. Further studies are needed to determine when to incorporate these into clinical practice and at what probability of EAC that the pathway to ablation is triggered.

Conclusion
Management of NDBE requires a multipronged approach involving risk factor reduction, on one hand, and diligent surveillance, on the other. GERD control with PPI therapy has been shown to reduce neoplastic progression in NDBE. During surveillance, meticulous visual examination with high-definition white light endoscopy with four-quadrant biopsies every 2 cm and separate sampling of visible abnormalities are performed and repeated every 3 to 5 years. Dysplasia detection can be improved by formal training in recognition of visible abnormalities in BE segment, enhanced imaging techniques, and spending adequate time for visual inspection. While eradication of BE using RFA therapy is enticing, the indications of use, the cost-effectiveness of this method, and optimal postablation surveillance are unclear at this time. Stratifying patients with biomarkers associated with neoplastic progression may help identify candidates for ablation therapy and those better observed with less frequent surveillance. Further investigations into
this optimization of intervention and observation will help refine the current guidelines for management of NDBE and prevent progression to advanced EAC.

**Author contributions**

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