

The Case for Endoscopic Treatment of Non-dysplastic and Low-Grade Dysplastic Barrett's Esophagus

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Abstract Non-dysplastic mucosa (ND-) in Barrett's esophagus (BE) shows clonal molecular aberrations, loss of cell cycle control, and other features of "neoplasia." These changes occur prior to morphologic expression of neoplasia (dysplasia). Morphologic evaluation of dysplasia is fraught with error, and, as a result, often leads to false-negative and false-positive diagnoses. Early "crypt dysplasia" is difficult to

detect, and is often missed in routine biopsy specimens. Some studies show substantial progression rates of low-grade dysplasia (LGD), and crypt dysplasia, to esophageal adenocarcinoma (EAC). Dysplasia, even when fully developed, may, in certain circumstances, be difficult to differentiate from non-dysplastic (regenerating) BE. Radiofrequency ablation (RFA) is a safe and effective method for removing mucosa at risk of

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cancer. Given the difficulties of dysplasia assessment in mucosal biopsies, and the molecular characteristics of ND-BE, this technique should be considered for treatment of all BE patients, including those with ND or LGD. Post-ablation neo-squamous epithelium reveals no molecular abnormalities, and is biologically stable. Given that prospective randomized controlled trials of ablative therapy for ND-BE aiming at reducing EAC incidence and mortality are unlikely to be completed in the near future, endoscopic ablation is a valid management option. The success of RFA in achieving safe, uniform, reliable, and predictable elimination of BE allows surgeons to combine fundoplication with RFA. Currently, there is no type of treatment for dysplastic or non-dysplastic BE that achieves a complete response in 100% of patients, eliminates all risk of developing cancer, results in zero adverse events, is less expensive in terms of absolute costs than surveillance, is durable for 20+ years, or eliminates the need for surveillance. Regardless, RFA shows established safety, efficacy, durability, and cost-effective profiles that should be considered in the management of patients with non-dysplastic or low-grade dysplastic BE.

Keywords Barrett's esophagus · Radiofrequency ablation · Esophageal cancer · Adenocarcinoma · Intestinal metaplasia · Low-grade dysplasia

Introduction

Barrett's esophagus (BE) develops as a result of chronic injury and inflammation of esophageal epithelium due to reflux of gastro-duodenal contents in the context of gastro-esophageal reflux disease (GERD) [1–3]. A diagnosis of BE is suspected and subsequently confirmed by showing goblet cells in mucosal biopsies, commonly referred to as intestinal metaplasia (IM), and is present in 1–2% of the US adult population, with an increasing prevalence rate recently [4–10]. BE is categorized endoscopically according to its length, and histologically according to the

absence or presence of dysplastic (neoplastic) changes: non-dysplastic (ND), low-grade dysplasia (LGD), or high-grade dysplasia (HGD). These morphological categories represent surrogate markers of increasing risk of esophageal adenocarcinoma (EAC). A meta-analysis by Wani et al. determined that ND-BE, LGD, and HGD confer a 200× (600 per 100,000), 560× (1,700 per 100,000), and 2,200× (6,600 per 100,000) increased risk, respectively, of developing EAC per year, compared to the general population (3 per 100,000) [11, 12].

The management of BE has two primary objectives; (1) treatment of GERD, and (2) avoidance of morbidity and mortality associated with incident EAC. Competing strategies for the latter objective include; (1) treatment to eradicate the surrogate markers for cancer, that is the metaplastic and dysplastic epithelium, with the intent to reduce the incidence of EAC, or (2) surveillance to detect incident cancer at an early stage with the intent to reduce the likelihood of cancer-related death. The most recent practice guideline from the American College of Gastroenterology recommends endoscopic therapy or esophagectomy for HGD and surveillance-only for LGD and ND-BE [13].

The authors of this review are gastroenterologists, surgeons, and pathologists whose basic or clinical research activities and clinical practices are focused on BE and they feel that there needs to be reassessment of the entrenched “surveillance-only” strategy for patients with ND-BE or BE with LGD for a number of reasons: (1) surveillance for ND-BE and BE with LGD is cost-ineffective and dangerously permissive of the development of EAC, (2) in clinical practice, both patient and physician compliance with surveillance recommendations are poor, (3) ND-BE and BE with LGD are surrogate markers for increased cancer risk, (4) oncogenetic changes precede morphological signs of dysplasia, and may be found in both ND-BE and BE with LGD, (5) even when diagnosed early, invasive EAC has a poor prognosis, and its therapy is associated with significant morbidity and mortality, (6) BE is easily accessed by endoscopy and is amenable to curative endoscopic treatment options, such as radiofrequency ablation (RFA) and focal endoscopic mucosal resection (EMR), both of which have been validated in prospective studies.

In this special article, we sought to review all the important issues and scientific evidence relevant to a treatment strategy for patients with BE who have ND-BE or LGD. We offer an evidence-based answer to each issue in the form of a management recommendation having graded the strength of each recommendation using the US Preventative Services Task Force grading system and having assigned a level of certainty regarding net benefit. We do not address the management of BE with HGD or EMR which may have a role in the treatment of HGD or

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intra-mucosal carcinoma, but no important role in the majority of patients with ND-BE or LGD.

Current Guidelines for Non-dysplastic and Low-Grade Dysplastic Barrett's Esophagus and Their Drawbacks

Surveillance endoscopy is intended to detect neoplastic progression, specifically EAC, at an early stage and therefore prevent cancer-related death. The American College of Gastroenterology practice guideline recommends that patients with endoscopy suggestive of a BE should have four-quadrant biopsies at least every 2 cm of the BE segment. If the worst histological grade is ND-BE, endoscopy is repeated within 1 year [1]. If ND-BE remains the worst histological grade, then the surveillance interval can be extended to repeat endoscopy with biopsy every 3 years. If LGD is found, it is recommended to confirm the histological diagnosis with a second independent reading by an expert pathologist and then repeat endoscopy in 6 months (biopsies obtained every 1 cm of the BE segment). If LGD remains the worst histological grade present, yearly surveillance thereafter is recommended [13].

While no prospective randomized trials support the utility of such a surveillance strategy for patients with BE, retrospective studies have demonstrated that patient survival is improved if a surveillance strategy detects cancer at earlier stages compared to a strategy of no surveillance [14, 15]. Surveillance as a primary strategy has not been shown to be cost-effective and there have been no randomized trials comparing it to the natural history of BE. There are, however, randomized trials comparing surveillance strategies to endoscopic treatment strategies (photodynamic therapy and RFA), and in each case these treatment strategies resulted in a lower rate of neoplastic progression than surveillance [16, 17]. It should be emphasized that surveillance as a strategy is designed to detect cancer, not to prevent cancer. To further confuse matters, there are some—not all—economic models claiming that, in fact, “routine” endoscopic surveillance for ND-BE and LGD will lead to more deaths, increased costs, and fewer quality-adjusted life years than a policy of no

surveillance (natural history) [18–21]. Overall, experts currently agree that surveillance is cost-ineffective and does not prevent cancer, yet in the absence of safe, effective, and cost-effective alternatives or adjunctive strategies, its role as the primary strategy has not been substantially challenged.

Radiofrequency Ablation for Non-dysplastic and Low-Grade Dysplastic Barrett's Esophagus

Device and Technique

RFA for BE consists of a radiofrequency energy waveform delivered upon contact with the targeted epithelium resulting in water vaporization, coagulation of proteins, and cell necrosis. The depth of injury is controlled by the electrode pattern and field geometry, as well as standardization of power density and energy density. Circumferential RFA is delivered using the HALO360 ablation system, which consists of a high-power energy generator, a sizing balloon catheter, and a number of balloon-based ablation catheters with varying outer diameters (Figs. 1, left panel, 2). Focal RFA is delivered using the HALO90 ablation system, consisting of an RF generator and endoscope-mounted electrode. The upper surface of the focal device consists of an articulated platform covered by a bipolar microarray of the identical pattern as HALO360, but overall smaller total surface area (Figs. 1, right panel, 3). The electrode is placed into contact with the target epithelium by deflecting the tip of the endoscope upwards, flatly apposing the electrode to the esophageal wall. Both RFA systems have 510(k) clearance by the US Food and Drug Administration and CE Mark in Europe for the treatment of BE.

Rationale for Endoscopic Intervention of ND-BE and BE with LGD

There are a number of reasons why a physician should consider endoscopic intervention (treatment) rather than “surveillance only” for patients with ND-BE or LGD: (1) the inability to predict what patients will progress to HGD

Fig. 1 *Left*, HALO-360 treatment balloon and generator. *Right*, HALO-90 device mounted on the tip of a standard endoscope

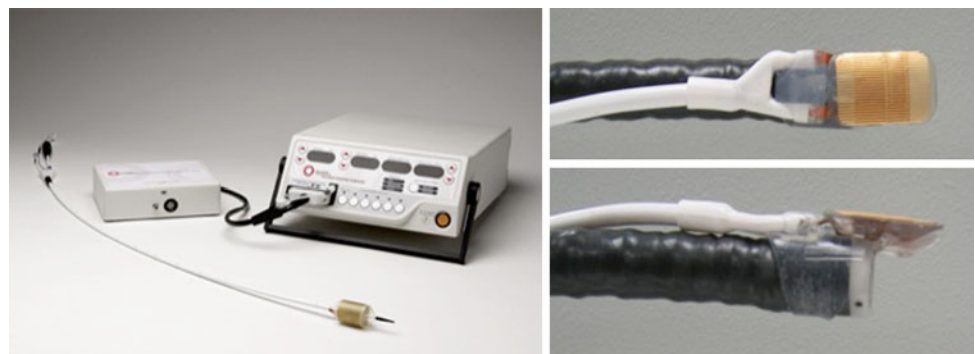
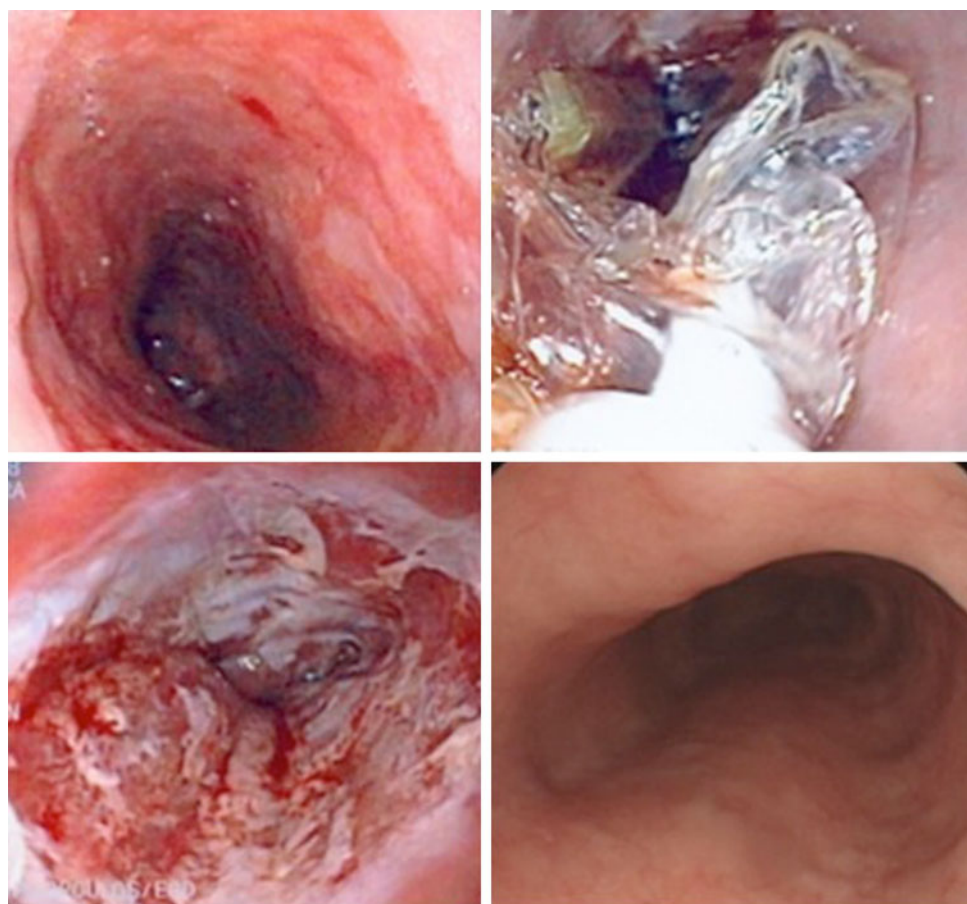


Fig. 2 *Top left*, circumferential, long segment (C5, M5, by the Prague classification) Barrett's esophagus. *Top right*, Barrett's epithelium immediately before circumferential ablation using radiofrequency energy (HALO-360) showing the treatment balloon in the deflated position. Subsequent balloon inflation and radiofrequency energy delivery ablated the epithelium circumferentially. *Bottom left*, endoscopic image of Barrett's esophagus immediately after circumferential radiofrequency ablation (HALO-360) revealing complete and circumferential desquamation of the mucosa. *Bottom right*, healed neo-squamous epithelium 1 year after ablation (Courtesy of Dr. Triadafilopoulos)



or EAC, (2) the inability to predict the time course of such progression, should it occur, (3) the risk for misdiagnosis (under-staging) due to inadequate mucosal sampling, lack of compliance with endoscopic surveillance guidelines, and inter-observer disagreement between pathologists, (4) the patients' anxiety for harboring a premalignant lesion and its impact on their quality of life, and (5) the availability of endoscopic modalities for completely removing the diseased tissue in a safe, effective, and cost-effective manner.

Although it is generally assumed that BE progresses in a stepwise fashion from ND to LGD to HGD to intramucosal cancer and then eventually to invasive cancer, in practice, this is unusual. Sharma et al. [22] reported that EAC incidence in patients with BE was 0.5% per patient per year of follow-up, but also demonstrated that patients may develop invasive cancer despite having ND-BE as their worst histological grade immediately before being diagnosed with cancer. Therefore, since we cannot reliably identify who will go on to develop cancer and in what time frame, and since surveillance is imperfect and economically unsound, ablation for ND-BE and LGD seems even more reasonable to consider. Despite our ability to inform patients of the precise risks associated with neoplastic

progression, to them its presence poses a broad range of quality of life issues. A recent systematic review of 25 studies using both generic and disease-specific quality-of-life instruments has documented compromises in multiple facets of patients' quality of life [23]. The anxiety caused by the identification of a premalignant lesion, despite its relatively low rate of progression to malignancy, has been identified in other screened populations, most notably in patients undergoing mammography. Frequently, as an example, surgeons perform a breast biopsy so that the patient knows "for sure what is going on" and also because the patient "wants the thing out." Ignoring the anxiety that these lesions cause is ignoring an opportunity to improve the patient's life.

Pathologic and Molecular Features of Barrett's Esophagus

Traditionally, BE is believed to evolve through a series of architectural and cytological alterations, referred to as dysplasia. Molecular abnormalities in BE, however, occur in advance of the morphologic expression of dysplasia [24–28]. In fact, many authorities believe that ND-BE meets the definition of a "neoplasm," consisting of hyper-

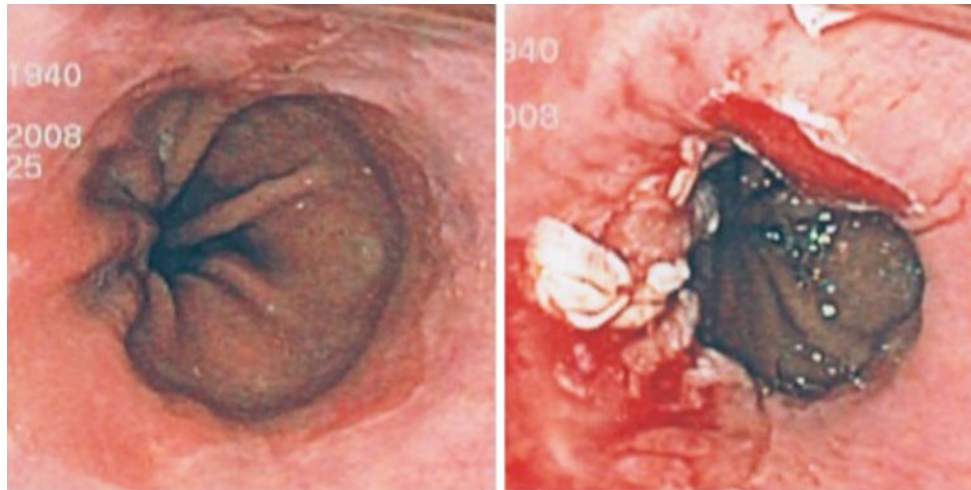


Fig. 3 *Left*, short segment (C0, M1, by the Prague classification) Barrett's esophagus containing non-endoscopically visible low-grade dysplasia. *Right*, endoscopic image of Barrett's esophagus immediately

after focal radiofrequency ablation (HALO-90) revealing desquamation of the mucosa (Courtesy of Dr. Triadafilopoulos)

proliferative epithelium, and by showing independence from growth signal regulation, disruption of architecture, widespread clonal abnormalities, progressive behavior, increased ability to avoid programmed cell death (apoptosis), and lack of spontaneous regression without intervention [24, 25, 29–35].

In ND-BE, for example, genes that control biological aspects of neoplastic progression are commonly mutated. These include increased cyclin D1, CDX2, TGF- α , and EGFR expression, clonal P16 and P53 abnormalities (loss of heterozygosity, mutation and methylation), increased VEGF and VEGF-R expression, increased MMP-7 and MMP-9 expression, altered DNA content, and telomerase reactivation, among others [24, 25]. Abnormalities of P53 are relatively early events in neoplastic progression in BE, since they develop in diploid cells prior to aneuploidy [36, 37]. Elevated cyclin D1 has been detected in the majority of ND-BE patients and shows increased expression in those who progress to EAC [38]. Inactivation of tumor suppressor genes, such as P16 and P27, also occur early in ND-BE [28, 31]. Hypermethylation of the APC gene has been detected in up to 50% of patients with ND-BE as the highest histologic grade [39, 40]. ND-BE cells express low levels of telomerase, which increases the tendency for neoplastic progression [41]. Further, increased cyclooxygenase-2 (COX-2) expression and activity (prostaglandin release, hyperproliferation) have been shown in ND-BE, and these peptides become upregulated in response to *ex vivo* or *in vivo* exposure to components of the refluxate, such as acid or bile salts [42–47].

Altered DNA content (aneuploidy) is a common (up to 50%) and early finding in ND-BE. In some studies, aneuploidy heralds an aggressive genotype [42, 48–50]. DNA content abnormalities, similar to those found in LGD,

occur in the basal portions of crypts in ND epithelium [51]. Chromosomal instability, in the form of gains of chromosome 7 and 18, has been detected in ND-BE and in metaplastic columnar epithelium without goblet cells [52]. Gene expression profiles of endoscopically obtained biopsy specimens using DNA microarrays have shown that both ND-BE and EAC express a unique set of stromal genes distinct from normal tissues, but similar to other types of cancers [53].

Given that molecular changes detected in ND-BE precede morphological changes associated with dysplasia, molecular markers may represent a more sensitive and specific method of assessing risk of progression compared to histological grading of dysplasia [54–57]. In one 5-year study, 64% of ND-BE patients with aneuploidy developed EAC, compared to 5.2% of those without aneuploidy [48, 58].

Assessment of dysplasia in mucosal biopsies has many limitations (Fig. 4). Differentiation of dysplasia from regenerating, or inflamed, metaplastic epithelium is difficult since the morphologic features of these processes overlap [59]. Inter-observer agreement, even among expert GI pathologists, is moderate at best and, in some studies, is simply poor [60–62]. Many cases cannot be diagnosed reliably as dysplastic, and as such, are termed “indefinite,” which further punctuates the limitations of pathologic assessment of dysplasia in mucosal biopsy specimens. Some forms of HGD, such as non-adenomatous and foveolar types, are difficult to detect and diagnose for general pathologists [59–63].

Dysplasia forms in the basal portions of crypts and, in its early phase, retains its capacity for cellular maturation and differentiation, features that mimic reactive epithelium [51, 64]. Dysplasia limited to the basal portions of the crypts demonstrates increased proliferation, P53 abnormalities,

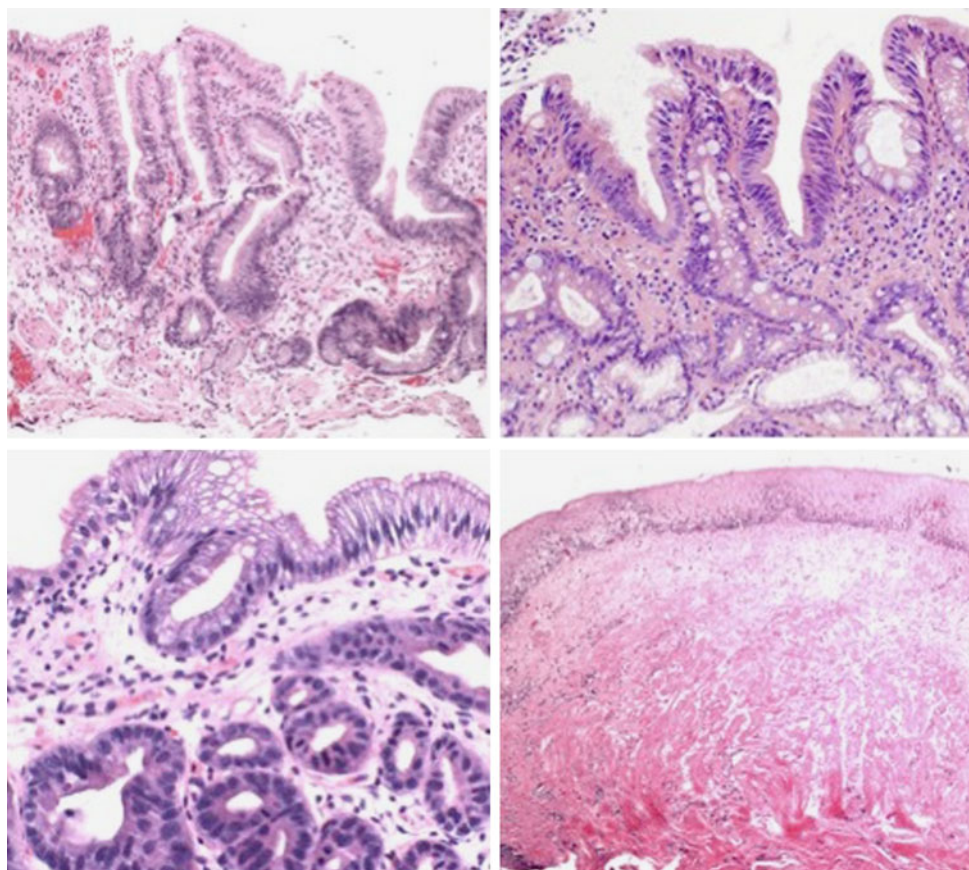


Fig. 4 *Top left*, low-power photomicrograph of non-dysplastic Barrett's esophagus exhibiting features of intestinal metaplasia (goblet cells). *Top right*, low-power photomicrograph of low-grade dysplastic Barrett's esophagus. *Bottom left*, medium-power view of Barrett's mucosa showing marked cytologic atypia in the bases of the crypts, but without involvement of the surface epithelium. Cytologically, the cells fulfill the criteria for high-grade dysplasia, but the lack of

surface involvement, architectural changes, and stratification of the nuclei may be interpreted as negative or indefinite for dysplasia. This area of mucosa revealed cells with aneuploid DNA content, a late-stage alteration of dysplastic epithelium. *Bottom right*, low-power view of fully re-epithelialized esophagus after radiofrequency ablation of dysplastic Barrett's esophagus. There is no evidence of residual metaplasia (courtesy of Drs. Odze and Goldblum)

and altered DNA content, similar to traditional dysplasia, but these changes are difficult to detect histologically. One study showed a high rate of synchronous or metachronous HGD in patients with dysplasia located only at the crypt bases but without traditional features of LGD or HGD [64].

Endoscopic biopsy sampling error is another limitation [59, 65, 66]. Dysplasia may not be associated with an identifiable endoscopic abnormality and, thus, can easily be missed at endoscopy. BE often consists of a mosaic of non-dysplastic and dysplastic tissue. These represent serious limitations with regard to strategies based solely on identification of dysplasia in biopsy specimens.

One advantage of using RFA for ND-BE is that abnormal columnar epithelium harboring morphologic and molecular abnormalities is replaced with genetically normal neosquamous epithelium (NSE) [67, 68]. Although the source of the progenitor stem cell of the NSE is unknown, several molecular studies have documented complete absence of

molecular abnormalities in this epithelium [69–71]. Paulson et al. micro-dissected and evaluated NSE and adjacent BE specimens for genetic alterations at exon 2 of the P16 gene, or exon 5–9 of the P53 gene [70]. They found that 95% of NSE showed wild-type P16 and/or P53 gene expression, whereas the surrounding BE exhibited mutations of these genes. Pouw et al. [71] using immuno-histochemistry and FISH probes, found that all patients with BE and HGD and/or early cancer had multiple oncogenetic abnormalities within the columnar epithelium. After complete eradication with RFA, the resulting NSE demonstrated absence of these oncogenetic abnormalities. These data suggest that post-ablation NSE probably does not possess carcinogenic potential. Furthermore, buried glandular epithelium is rare post-RFA. Some studies have suggested that buried BE shows decreased crypt proliferation and less DNA content abnormalities in comparison to non-buried BE and that this may be due to isolation from noxious luminal contents [72, 73].

Variable and Unknown Natural History of Non-dysplastic and Low-Grade Dysplastic Barrett's Esophagus

The natural history of ND-BE or BE with LGD is unknown. Various confounding factors, inherent to studies that have evaluated risk, adversely impact routine care of BE patients. For instance, endoscopic biopsies sample only a tiny proportion of BE mucosa and may not detect existing dysplasia and EAC. In routine clinical practice, compliance with biopsy protocols (four-quadrant biopsies at 2-cm intervals every 3 years in ND-BE and 1-cm intervals every 6–12 months for LGD) is poor [74]. Four-quadrant biopsies at 1-cm intervals in BE patients with HGD has been shown to miss prevalent EAC [75]. There is well-recognized variability in pathologic interpretation of ND-BE and BE with LGD or HGD. Furthermore, there are significant differences in the populations studied, and the types of institutions used to estimate risk of progression in these trials [76].

How often do patients with ND-BE progress to EAC? A meta-analysis of 25 studies found the incidence of EAC ranges from 0.0 to 2.7% per patient-year of follow-up (mean 1%). After adjustment of values in order to account for publication and study-size biases using a funnel plot analysis, an estimate of annual EAC risk was 0.5% per patient-year of follow-up [76]. In another meta-analysis that evaluated the natural history of ND-BE, pooled data showed that the incidence of EAC was 5.98 per 1,000 patient-years, or approximately 0.6% per patient-year [12]. A higher incidence was found in a prospective, population-based study (ProGERD) where the progression rate from ND-BE to invasive EAC was 2.5% over 2 years, or 1.3% per patient-year of follow-up [77]. In a multicenter cohort of 1,376 patients with a first-time diagnosis of BE, 17% of patients were found to have prevalent dysplasia or EAC (LGD 7.3%, HGD 3.1%, and EAC 6.6%) at initial endoscopy [22]. Surveillance was conducted on 618 remaining ND-BE patients for a mean 4.12 years. Patients who developed dysplasia or EAC during the first year of surveillance were eliminated because it was assumed that they were missed at endoscopy due to sampling error. After 2,546 total patient-years of follow-up, 21.7% progressed to LGD (16.2%), HGD (3.6%), or EAC (2.0%). This equated to an EAC risk of 0.5% per patient-year, similar to data by Shaheen et al. [76]. The risk of disease progression from ND-BE to dysplasia, or EAC, was 5.2% per patient year. The risk of disease progression from ND-BE to HGD or EAC, was 5.6% overall, and 1.4% per patient-year. Of the patients who developed HGD or EAC, 53% had at least two initial consecutive endoscopies that showed only ND-BE, suggesting that neoplastic progression from ND-BE to EAC does not always progress in a predictable manner.

How often do patients with LGD progress to EAC? While conventional wisdom has suggested that ND-BE and LGD have similar neoplastic progression rates, recent studies suggest that LGD progresses to EAC at a much higher rate than ND-BE. Although meta-analysis showed that the incidence of EAC in LGD patients was 16.98 per 1,000 patient-years, or approximately 1.7% per patient-year [12], higher rates of progression have been reported. For instance, Skacel et al. [78] found that LGD progressed to HGD at a rate of 12.9% per patient-year and to EAC at 3.7% per patient-year. Gatenby et al. [79] reported that LGD progressed to HGD at 4.6% per patient-year, and to EAC at 2.7% per patient-year. Lim et al. [80] reported that LGD progressed to HGD or EAC at a rate of 3.4% per patient-year. Veith et al. [81] reported that LGD progressed to HGD at a rate of 17.2% per patient-year, and to EAC at a rate of 14.6% per patient-year. Hence, the incidence of EAC associated in ND-BE falls in the range between 0.5 and 0.6% per patient-year. LGD is higher, in the range of 1.7–14.6% per patient-year. The latter figure correlates with the accuracy of the baseline reading of LGD. Perhaps a more important metric from the patients' standpoint, however, is the lifetime cancer risk. Lifetime risk has been estimated to be in the range of 5–8% for ND-BE patients, and is unknown for patients with LGD, but it is likely higher [82]. Although this data suggests that the majority of patients with ND-BE (or LGD) never develop cancer, cancer does develop in a significant proportion. At present, there is no practical way to distinguish the majority of patients who will not develop cancer, from the unfortunate few who will.

Radiofrequency Ablation for Non-dysplastic or Low-Grade Dysplastic BE: Results of Outcome Studies to Date

A US multi-center prospective clinical trial assessed the long-term safety and efficacy of stepwise circumferential and focal ablation for patients with long segment ND-BE [83]. In the first phase of the study, 70 patients underwent circumferential ablation at baseline and 4 months (if residual IM), followed by biopsy at 6 and 12 months. At the 1-year endpoint, 70% of patients had a complete response for IM (CR-IM) defined as no residual IM in any esophageal biopsy. After 1-year follow-up, focal ablation was applied to those patients with residual IM (and in those cases with an irregular z-line negative for IM). At 2.5-year follow-up, CR-IM was achieved in 98% of patients. There were no reported strictures, buried glands, or cases of neoplastic progression. Longer-term durability data for this cohort reveals that 92% of patients remain CR-IM at 5-year follow-up.

In a multi-center community practice study of 429 patients with ND-BE ($n = 326$), indefinite for dysplasia or

IND ($n = 12$), LGD ($n = 52$), HGD ($n = 39$) with a mean follow-up of 20 months ($n = 137$), CR-IM was achieved in 76% of ND-BE patients, while CR-IM and CR-D was achieved in 78 and 100% of dysplasia patients, respectively [84]. There were no serious adverse event and strictures occurred in 1.1% of procedures. Similar safety and efficacy results for step-wise RFA for BE containing ND-BE have been reported from a number of other prospective single-center studies [85, 86]. Further, all studies which have studied RFA for BE containing with dysplasia have CR-IM as a primary endpoint, with similar CR-IM outcomes as seen in the ND-BE patient trials. Specifically, in a RCT, Shaheen et al. [17] reported in their intention-to-treat analysis that RFA resulted in CR-IM in 77% of treated patients while sham resulted in CR-IM in only 2% of cases (83 vs. 3% in per protocol analysis).

Four studies have evaluated the safety and efficacy of RFA in patients with BE containing LGD confirmed by expert review. Each study has concluded that RFA results in high rates of complete eradication of both LGD and IM. In the first of these trials, Shaheen et al. [17] reported on a multi-center US randomized, sham-controlled trial of RFA versus sham for dysplastic BE including separate patient cohorts having LGD or HGD. Specific to the LGD cohort, after confirmation of the LGD diagnosis by a centralized, expert pathology center, 64 LGD patients were randomized 2:1 to receive RFA or sham, respectively. In the intention-to-treat analyses, complete eradication of dysplasia was reported in 91% in the ablation group compared to 23% in the control group ($p < 0.001$). The NNT to avoid one persistent dysplasia case was 1.5. The incidence of neoplastic progression from LGD to HGD was higher in sham (13.6%) as compared to ablation (4.8%), although this difference did not reach statistical significance due to sample size. The NNT to prevent one case of neoplastic progression in the LGD group was 11.

In a second trial, Sharma et al. [87] treated patients having confirmed LGD ($n = 10$) with step-wise circumferential and focal RFA, followed by endoscopy with four quadrant biopsies every 1 cm at 1, 3, 6, 12, and 24 months. Primary outcomes at 2-year follow-up showed that CR-IM and CR-D were achieved in 90 and 100% of patients, respectively. No patient demonstrated neoplastic progression, stricture, or buried glands. In a third trial, Sharma et al. [88] applied stepwise RFA to 39 patients having LGD confirmed by two expert pathologists. At a median follow-up of 24 months, CR-IM and CR-D were achieved in 87 and 95%, respectively. No patient demonstrated neoplastic progression, stricture, or buried glands.

In a fourth trial, Finkelstein et al. confirmed BE containing LGD in 16 patients and assessed microdissection specimens from the BE segment for a panel of 16 allelic imbalance mutational markers (loss of heterozygosity)

affecting 1p, 3p, 5q, 9p, 10q, 17p, 17q, 21q, and 22q using quantitative fluorescent PCR with capillary electrophoresis [89]. At baseline, all patients demonstrated multiple mutational abnormalities. After step-wise RFA, biopsies were obtained (1.0–2.5 years after initial RFA) demonstrating CR-IM and CR-D in 94 and 94% of patients, respectively. In each patient with CR-IM, all previously detected mutations were absent indicating that RFA could completely eradicate both ND-BE and LGD, and that the restored neo-squamous epithelium did not harbor any of the pre-existing oncogenetic abnormalities. The one case of persistent ND-BE and LGD continued to harbor mutations. A subsequent RFA session achieved CR-IM and CR-D in that patient, resulting in eradication of the persistent mutations.

Cost-Effectiveness of an Endoscopic Ablation Strategy for Non-dysplastic and Low-Grade Dysplastic BE

Cost-effectiveness is an important consideration before any medical intervention is incorporated in standard clinical practice. While endoscopic ablative therapies for management of patients with HGD have been considered cost-effective for some time and are considered by many to be a first-line therapy, the economic aspects of endoscopic ablative therapy in patients with non-dysplastic and low-grade dysplastic BE have only more recently been assessed upon the availability of RFA as a safe and effective modality [90–92].

Das et al. [93] designed a decision-analysis model specifically to study the threshold parameters for RFA to be cost-effective in a cohort of 50-year-old patients with ND-BE. In the baseline analysis, the strategy of RFA was more expensive compared to a strategy of endoscopic surveillance alone, but yielded higher quality-adjusted life years (QALYs). The incremental cost to gain an extra QALY with the ablative strategy was \$48,626 compared to the strategy of endoscopic surveillance alone. It should be pointed out by current standard of cost-effective medical interventions, any strategy with an incremental cost of \$50,000 or less per QALY gained is considered acceptable with respect to the willingness of society to pay. In the threshold analysis, the critical determinants of cost-effectiveness of the ablative strategy were (1) the rate of complete response to ablation, (2) the total cost of ablation, and (3) the risk of progression to LGD or HGD. Although prospective studies of RFA for ND-BE have not conclusively shown a reduction in the incidence of EAC, others have shown that ablation for non-dysplastic and low-grade dysplastic BE does significantly reduce the incidence of EAC. In a Monte Carlo analysis reported in this study, the relative risk of developing EAC in the strategy based on endoscopic ablation was decreased compared to the other

strategy of watchful surveillance with an estimated number needed to treat (NNT) to prevent one case of EAC of 198.

In a second study by Inadomi et al. [94], ablation of ND-BE was the most cost-effective strategy versus surveillance alone if the ablation resulted in CR-IM in 40% or more patients and surveillance was discontinued in such patients. They also reported that endoscopic ablation was also more cost-effective than surveillance alone for ND-BE if 40% was achieved and surveillance was continued in all patients. Inadomi et al. also included LGD in their cost-utility model, finding that the preferred strategy for this population was ablation, if CR-D could be achieved in 28% of patients, CR-IM in 0% of patients, and surveillance continued in all patients.

Although the decision models in these two studies were structurally different, both were modeled using sophisticated techniques of decision analysis to reflect the inherent uncertainties to simulate real-life clinical practice and also to derive valid statistical measures of effectiveness. Also, both the models were developed with a built-in bias “against” ablative interventions. Both were broadly applicable to different techniques of ablative therapy, although RFA was their primary focus. However, in both of these economic analyses, potential strategies based on risk-stratification (using potential biomarkers) of these patients were not studied. Given that a strategy based on ablation of ND-BE in all patients was reasonably cost-effective in both models, it is obvious that any strategy of risk stratification (enriching a targeted patient pool) will markedly increase the efficiency and decrease the overall cost of such ablative strategy, and will therefore make the ablative therapy even more cost-effective.

Number Needed to Treat to Avoid EAC in a Population with Non-dysplastic or Low-Grade Dysplastic BE

Some experts indicate that for ablation to be considered for non-dysplastic BE or LGD, there must be evidence that the intervention reduces the incidence of cancer. A recent meta-analysis demonstrated that ablation significantly reduces the risk for cancer in patients with ND-BE and LGD [12]. In this study, the pooled natural history data for ND-BE patients showed a cancer incidence of 5.98 per 1,000 patient-years, whereas the incidence of cancer was 1.63 per 1,000 patient-years in the ablation group. This represents an RRR of 73%, ARR of 0.435% (reduction in annual risk of developing cancer), and NNT (1/AAR) of 223 (number of patients needed to treat in order to avoid one cancer in 1 year). Because the studies included in this meta-analysis had multi-year follow-up intervals, not a 1-year follow-up interval, a 1-year NNT is not an accurate estimate of NNT over the study period, since the incident numbers are reported on a “per-patient per-year” basis.

Assuming a 5-year follow-up, the NNT is 45, not 223 (number of ND-BE patients needed to treat to avoid one cancer in subsequent 5 years).

The pooled natural history data for LGD patients showed a cancer incidence of 16.98 per 1,000 patient-years, whereas the incidence of cancer was 1.58 per 1,000 patient-years in the ablation group. This represents an RRR of 91%, ARR of 1.54% (reduction in annual risk of developing cancer), and NNT (1/AAR) of 65. Assuming a 5-year follow-up, the NNT is 13, not 65 (number of LGD patients needed to treat to avoid one cancer in subsequent 5 years).

When considering the impact of ablation on the neoplastic progression of ND-BE and LGD, the above NNT calculations consider only EAC incidence as the “event to avoid,” rather than considering the combined, higher-frequency endpoint of HGD/EAC incidence. If one were to calculate NNT based on this combined endpoint, the respective NNTs would be even lower than 45 and 13 to avoid one case of EAC.

Lessons from Colon Carcinogenesis

Formation of a columnar epithelium in the esophagus is the first clinically evident change in the metaplasia–dysplasia–carcinoma sequence of EAC, analogous to the precursor status of colon adenomas in the development of colorectal cancer (CRC). Hence, both BE and colon adenomas represent endoscopically detectable mucosal changes that signify malignant potential. Yet to date, the clinical management strategies of these conditions have been widely divergent. Non-dysplastic and low-grade dysplastic BE are approached with watchful endoscopic biopsy surveillance with the goal of detecting disease progression to EAC at a treatable stage. Adenomas, on the other hand, are endoscopically (or surgically) removed upon detection, regardless of histological grade. In both scenarios, patients undergo long-term surveillance at regular intervals [13, 95].

According to the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database, the annual US general population age-adjusted incidence rate for CRC was 49.1 per 100,000 as compared to 4.5 per 100,000 for esophageal cancer (EC) from 2002 to 2006. SEER reports that about two-thirds of esophageal cancers are EAC (3 per 100,000). SEER projected that 146,970 men and women would be diagnosed with CRC and 49,920 would die from CRC in 2009, compared to 16,470 and 14,530 individuals, respectively, for esophageal cancer (approximately 9,753 EAC deaths). Therefore, while there is a 15-fold difference in the annual incidence rates of CRC and EAC, this gap decreases to only a five-fold difference when considering associated mortality due to the markedly disparate overall 5-year survival rates between the two cancers: 65% for CRC versus 15% for EAC [11].

Whereas incidence and survival of CRC and EAC differ significantly, progression rates of their precursor disease states do not. The annual CRC progression rate for an adenoma is 0.52–0.58%, while the annual EAC progression rate for ND-BE is 0.50–0.60% [12, 22, 76, 96]. Rates for progression from LGD to EAC are much higher, as noted previously. Evaluation of these progression rates relative to the CRC and EAC annual incidence rates in the general population (49 per 100,000 and 3 per 100,000, respectively) reveals that a diagnosis of ND-BE imparts a 200× increased risk in the development of EAC, compared to a diagnosis of an adenoma, which imparts a 12× risk for CRC (versus the general population).

In the seminal work by the National Polyp Study Workgroup, Winawer et al. [96] reported a 76–90% reduction in the incidence of CRC in patients undergoing polypectomy. While recent studies suggest these reduction rates may overestimate what can be expected in day-to-day practice, polypectomy continues to be regarded as an effective, mainstream strategy in reducing the incidence and mortality of CRC [97, 98]. Similarly, the incidence of EAC after endoscopic ablative therapy was assessed in a meta-analysis [12]. The authors reported a cancer incidence of 6.0 per 1,000 patient-years in ND-BE patients undergoing endoscopic surveillance only (natural history group), compared to 1.6 per 1,000 patient-years in ND-BE patients who had undergone endoscopic ablation (5-year NNT = 45). They also reported that ablation reduced the incidence of cancer in LGD patients from 17.0 to 1.6 per 100,000, respectively (5-year NNT = 13). This relative risk reduction (RRR) in annual cancer incidence afforded by ablative therapy for ND-IM and LGD patients (73 and 91%, respectively), compares favorably to that afforded by polypectomy for the reduction of CRC incidence.

Hence, relative to adenomas, ND-BE has the same progression rate to a less common although more lethal cancer. Further, when considering EAC and CRC rates in the general population, the diagnosis of ND-BE implies a greater risk for the development of EAC (200×) than an adenoma does for the development of CRC (12×). Therapeutic intervention through removal of the diseased tissue significantly decreases the incidence of cancer for both ND-BE and colon polyps. Yet, current clinical practice guidelines paradoxically recommend adenoma removal during index colonoscopy followed by periodic surveillance and for non-dysplastic and low-grade dysplastic BE, periodic endoscopic surveillance alone.

One could argue perhaps that such divergent management strategies reflect unacceptable differences in safety, efficacy, durability, or cost-effectiveness outcomes between the two approaches. Thus far, the data for RFA would indicate that this is not the case. We acknowledge that ablative modalities of the past were scrutinized and fell out of favor

due to suboptimal outcomes in one or more of these clinical parameters [16, 99–101]. In contrast, RFA efficacy rates are high and consistent, its safety profile is excellent, the cost-effectiveness data favorable, and early durability data encouraging. Colonoscopy with polypectomy, while generally regarded as safe, efficacious, and cost-effective, is not without flaws, including a 6–12% miss rate for large adenomas, an approximate 5% miss rate for CRC, and 0.1–0.2% perforation rates [95].

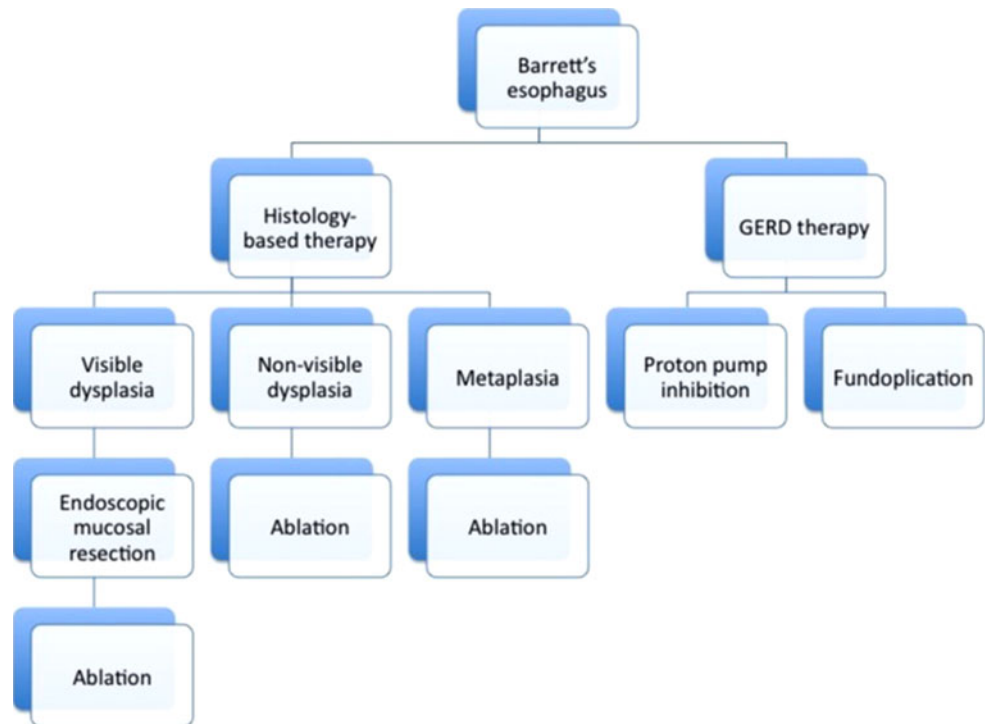
We also acknowledge that the clinical data addressing screening colonoscopy and polypectomy, by virtue of an approximate 20-year lead, is more extensive and established than that for ablative management of ND-BE and LGD. We must recall, however, that there are no prospective, randomized controlled trials (RCTs) of screening colonoscopy that show reduction in incidence or mortality of CRC; even the highly regarded National Polyp Study employed the SEER database and retrospective cohorts as reference groups [95, 96]. Critics of endoscopic removal of ND-BE assert that prospective RCTs with endpoints of mortality or—at least—cancer progression are necessary before endorsing a therapeutic approach, and call for biomarker-based risk stratification of ND-BE and LGD patients to determine who is most likely to progress so as to guide management strategies. In the absence of such an ideal natural history database, which will require decades of research and validation, it is both logical and ethical to recommend that non-dysplastic and low-grade dysplastic BE are treated with endoscopic ablation. At a most basic level, we struggle with the adenoma/BE “double standard” as it relates to our daily delivery of patient care, removing one patient’s pre-malignant lesion and watching another. The latter approach is often not palatable to either patient-centered physicians or to the patients themselves.

Role of Surgery and Radiofrequency Ablation

Surgeons typically get involved in the care of patients with BE under one of two circumstances: (a) anti-reflux surgery (fundoplication) is being considered in the management of medically refractory or complicated GERD and associated BE, or (b) an esophagectomy is being considered in a patient with HGD or cancer. In both of these situations, the availability and success of RFA for BE is being incorporated into a modern surgical management paradigm (Fig. 5).

Anti-reflux surgery is the only effective modality in the management of GERD that prevents not only acid but also bile reflux, thereby removing the exposure of the BE tissue to noxious agents. Not surprisingly, as many as 25% of patients that come to anti-reflux surgery have BE [102–104]. While anti-reflux surgery and elimination of reflux

Fig. 5 Diagram of management of non-dysplastic and dysplastic Barrett's esophagus outlining medical, endoscopic and surgical aspects, based on histopathology



may have a beneficial effect on neoplastic progression of disease, treatment of the BE segment with RFA safely and effectively eliminating BE now provides an additional tool for the surgeon. RFA can be performed before, during, or after anti-reflux surgery. Early in the use of RFA there were concerns that the wrap would restrict the expansion of the BE area and thereby limit the uniform effacement of the balloon and electrode to the involved mucosa. Experience with RFA after anti-reflux surgery reveals that this is not a problem, and in fact, the restriction of the wrap allows better tissue effacement and energy transfer [85, 105].

Conclusions

BE with a cellular morphological appearance of ND-BE or LGD commonly harbors numerous genetic alterations enabling neoplastic behavior and progression. The metaplasia–dysplasia–invasive neoplasia sequence is underway upon the first diagnosis of BE, and many cancers develop from ND-BE without signs of interval step-wise progression. Using morphology (histological grade) as a marker for progression risk is an imperfect practice due to issues of lack of compliance with surveillance, biopsy sampling error, and inter-observer variability for morphological grading. A surveillance strategy for non-dysplastic and low-grade dysplastic BE is cost-ineffective and does not prevent cancer or neoplastic progression. ND-BE and LGD have significant risks of neoplastic progression, with

ND-BE developing EAC at a rate of 0.5% per patient-year and 5–8% per patient life-time, while LGD develops EAC at a rate of 1.7% per patient-year. Some have shown higher rates of progression in LGD populations when the lesion is multi-focal and confirmed by expert pathologists. Ablation of ND-BE and LGD reduces the incidence of EAC with a 5-year NNT for ablation to avoid one cancer was 45 and 13, respectively. Endoscopic RFA has been shown to safely and effectively eradicate ND-BE, LGD, HGD, and early cancer in multiple well-designed trials. Endoscopic ablation using RFA is a preferred strategy in an LGD population if CR-D is achieved in 28% of patients, CR-IM in no patients, and surveillance continued in all patients. Endoscopic ablation using RFA is a preferred strategy in a ND-BE population if CR-IM is achieved in 40–50% of patients, and surveillance continued or discontinued depending on the cost-utility model assumptions. In clinical practice, efficacy outcomes of RFA for ND-BE and LGD significantly exceed these cost-utility thresholds.

Using the most recent version of the US Preventive Services Task Force (USPSTF) grades and levels of certainty we recommend that endoscopic ablation therapy using RFA for patients with non-dysplastic and low-grade dysplastic BE is indicated and is medically necessary (Grade B: Recommend this service. Certainty: There is moderate certainty that the net benefit is substantial). This recommendation is based on the uncertainties associated with the rate and timing of neoplastic progression, the documented reduction in neoplastic progression afforded by ablative versus surveillance strategies in these

populations, and the safety, effectiveness, durability, and cost-utility reported specifically for RFA.

In summary, we do not believe that any management strategy patients with non-dysplastic and low-grade dysplastic BE will ever achieve a complete response in 100% of patients, eliminate 100% of the risk for developing cancer, result in zero adverse events, be less expensive in terms of absolute costs than surveillance or doing nothing, be durable forever, or eliminate the need for surveillance forever. Unfortunately, such an ideal strategy does not exist for any disease state. However, today we have an endoscopic therapy in RFA (and focal EMR for staging as indicated) with an established safety, efficacy, durability, and cost-utility profile that should compel us to offer a therapeutic option for our patients with non-dysplastic and low-grade dysplastic BE in addition to a surveillance-only strategy [106].

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