The case for ablating nondysplastic Barrett's esophagus

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The philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow.

—Osler

Controversy being in no short supply, the field of Barrett's esophagus (BE) continues to garner significant debate over the proper use of ablation, specifically the role of radiofrequency ablation (RFA), and even more specifically the role of ablation with regard to nondysplastic intestinal metaplasia.[1,2] In the next 3500 words or so, we will add to the Barrett's polemic by advocating for the routine ablation of Barrett's metaplasia using RFA. As the psychologist Daniel Kahnemann has famously noted, people generally see what they start out intending to see, a truism in psychology and frequently in medicine as well.[3] The field of BE being no exception, it appears to us that gastroenterologists have interpreted available data to conform to the conventional wisdom that the benefit of endoscopic surveillance of Barrett's metaplasia outweighs the benefit of RFA. Herein then, we offer our view of BE in a different endoscopic light.

We would remind the reader how quickly the general management of BE changes. Only 10 years ago, when balloon-based RFA was first invented and made available,[4] patients with Barrett's high-grade dysplasia were viewed as either having relatively innocuous disease that could be managed via surveillance[5] or disease so dangerous that it commonly required esophagectomy.[6,7] The advent of photodynamic therapy, RFA, and endoscopic resection (ER) and the results of randomized, controlled trials clearly demonstrated that high-grade dysplasia was both highly dangerous and could be safely and successfully treated endoscopically, with a reduction in risk for adenocarcinoma.[8,9] This was transformative, so that today, the typical patient with Barrett's high-grade dysplasia is treated endoscopically (RFA and ER), and only a rare patient either undergoes esophageal resection or surveillance.[10,11]

Likewise, for many years, patients with Barrett's low-grade dysplasia were generally viewed as having relatively benign disease, largely because study methodology lacked the requirement of dysplasia confirmation, resulting in misleadingly decreased neoplastic progression rates.[12-14] Indeed, when this issue was finally well-studied with a robust, randomized, controlled trial, the results demonstrated that confirmed low-grade dysplasia progresses in a manner not very different from that of confirmed high-grade dysplasia and is in need of curative endoscopic ablative therapy to prevent neoplastic progression.[15]

And now, to the subject at hand. Although most patients with BE die of other causes (cardiovascular, etc),[10] a diagnosis of nondysplastic Barrett's metaplasia renders an esophageal adenocarcinoma risk 30-fold to 400-fold that of a patient without BE.[12,16] Despite this high risk, BE experts frequently express surprise that seemingly rational patients would behave so irrationally as to consider ablation.[17,18] With our high-definition endoscopic spectacles firmly in place, we advance 4 arguments, any one of which is dispositive, regarding the rationale for ablative therapy of BE without dysplasia by using RFA: (1) Surveillance of BE is unproven and is ineffective in reducing the risk of neoplastic progression; (2) The reported risk of neoplastic progression in BE is artificially depressed by recent published definitions of prevalent and incident disease; (3) BE is significantly overdiagnosed in clinical practice, inflating the denominator with non-BE "Barrett's cases," resulting in underestimates of published cancer risk; and (4) RFA is now proven to be highly safe and efficacious in ablating all BE, regardless of dysplasia status.

BE SURVEILLANCE

What physicians believe they know and what they actually know are often two different things.

—Dr House

Abbreviations: BE, Barrett's esophagus; ER, endoscopic resection; NNT, number needed to treat; RFA, radiofrequency ablation.

DISCLOSURE: *R. Ganz is the inventor of balloon-based radiofrequency ablation and cofounder of BARRX Medical, Inc. In the past, the author received equity and honoraria from Covidien, Inc but has no current conflicts and does not anticipate any in the future. No other financial relationships relevant to this article were disclosed.*

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Despite the fact that surveillance endoscopy has been the accepted standard of practice for Barrett's metaplasia, there is a surprising paucity of data to support its use. There are few prospective trials and no randomized or controlled trials of surveillance strategies, and none that demonstrate an association of surveillance with cancer risk reduction or even neoplastic progression risk reduction.[10,19] Most surveillance recommendations are based on cost-utility modeling, not study outcomes.

Although some surveillance trials that used advanced endoscopic imaging techniques such as narrow-band imaging or confocal laser endoscopy (and confined to expert centers) demonstrate an increased yield of dysplasia,[20,21] many do not.[22] Some case-control and cohort studies have demonstrated diagnosis of earlier-stage cancer and improved survival with surveillance[12]; however, most published studies are retrospective and single center, with inherent lead and length time bias,[19] and several computer models and meta-analyses that use existing data demonstrate this practice to be cost ineffective by generally accepted standards.[23-25] Biopsy protocols are poorly studied; for example, the recommendation to use jumbo biopsy forceps for surveillance is based on one small, single-center study published 20 years ago and has never been confirmed.[26,27] Even in the unlikely event that surveillance biopsy was demonstrated to be a cost-effective practice, and an optimized biopsy protocol and forceps size could be agreed upon, it is likely that most endoscopists would not adhere to stated biopsy guidelines anyway.[28,29]

What John Inadomi stated in 2007 continues to be true today: "The cancer prevention, mortality, or survival benefit of Barrett's esophagus surveillance has not been confirmed, and remains to be proven through prospective, clinical trials."[19] In this regard, it is interesting to look at the various GI society guidelines that have been published over the years regarding surveillance intervals and biopsy protocols for patients negative for dysplasia. In 2002, the American College of Gastroenterology proposed 3-year surveillance intervals after 2 consecutive negative examinations (no time interval noted), with 4-quadrant biopsy specimens taken every 2 cm. In 2008, this recommendation was changed to a repeat examination within 1 year, then 3-year intervals. In 2005, the American Gastroenterological Association published a recommendation for a repeat examination at 1 year, then at 5-year intervals, with 4-quadrant biopsy specimens taken every 1 or 2 cm. In 2011, they changed their recommendation to every 3, 4, or 5 years, with 4-quadrant biopsies every 2 cm. The 2012 American Society for Gastrointestinal Endoscopy guideline recommends either no surveillance, surveillance every 3, 4, or 5 years, or endoscopic ablation in patients with metaplasia thought to be at higher risk of cancer progression. All of these guidelines are vague on biopsy forceps size, and none recommend any advanced endoscopic technique beyond traditional white-light endoscopy (Table 1).[10,30-33] In other words, mixing and matching these various guidelines, an endoscopist can, to a large degree, do whatever he or she wants! It appears that the guideline variations are not based on any compelling data—rather, the variations amount to conflicting "expert" opinions.

TABLE 1. GI Society Surveillance Recommendations for Non-dysplastic Barrett's

Gastroenterology society, y	Frequency of interval examination	Biopsy protocol
ACG 2002	2 consecutive examinations (no time internal noted) then every 3 y	4-quadrant biopsies every 2 cm
ACG 2008	Repeat examination within 1 y then every 3 y	4-quadrant biopsies every 2 cm
AGA 2005	Repeat examination at 1 y then every 5 y	4-quadrant biopsies every 1 or 2 cm
AGA 2011	Examinations every 3, 4, or 5 y	4-quadrant biopsies every 2 cm
ASGE 2012	Consider no surveillance at all or examinations every 3, 4, or 5 y or endoscopic ablation	4-quadrant biopsies every 2 cm

ACG, American College of Gastroenterology; *AGA,* American Gastroenterological Association; *ASGE,* American Society for Gastrointestinal Endoscopy.

As the American Gastroenterological Association notes, "Endoscopic surveillance has become the standard of practice for patients with Barrett's esophagus based on the unproven assumption that the practice will reduce deaths from esophageal adenocarcinoma and thereby prolong survival."[10] A recent, representative study by Corley et al[34] clarifies the lack of benefit of BE surveillance. Corley looked at 8300 patients with BE undergoing surveillance at Kaiser-Permanente, age-matched and sex-matched with patients with BE not undergoing surveillance, and demonstrated that surveillance within 3 years was not associated with a decreased risk of death from esophageal adenocarcinoma (odds ratio [OR] 0.99; 95% confidence interval [CI], 0.36-2.75). In this study, fatal cases were just as likely to have received surveillance as were controls. Corley concluded that, "Endoscopic surveillance of patients with Barrett's esophagus was not associated with a decreased risk of death from esophageal adenocarcinoma."[34]

If a patient with BE asks, "Doc, what is the benefit of having me undergo surveillance?" the appropriate answer has to be, "None, as far as I know. The surveillance intervals and biopsy protocols are largely unproven, each society has a different recommendation, and there is no known cancer risk reduction associated with what we're currently doing." Furthermore, with current surveillance strategies, there is no stratification of risk; a dot of BE is followed in the same manner as a patient with 20 cm of BE, which is highly illogical considering the disparate progression rates in patients based on disease segment lengths.[35] Given the state of affairs regarding surveillance for BE, it is increasingly difficult to regard surveillance as a valid standard practice, and until such time as better data become available, surveillance should realistically be considered investigational and largely confined to ongoing clinical trials.[36]

BE CANCER RISK

The combination of some data and an aching desire for an answer does not ensure that a reasonable answer can be extracted from a given body of data.

—Tukey

Roughly 30 years ago, as surveillance endoscopy was becoming instituted, authors began excluding from analysis advanced esophageal adenocarcinomas diagnosed simultaneously with BE.[37] The rationale for doing this was clear; the authors wanted to assess the value of surveillance endoscopy, and because advanced esophageal cancers were almost uniformly fatal in that era, any patient simultaneously diagnosed with a prevalent cancer would not have been benefitted by surveillance. Thus, this practice informed the potential benefit and yield of surveillance (vide infra) but was not designed to be an assessment of BE incident cancer risk.

After that, however, the practice gradually expanded so that current authors exclude from cancer risk analysis any patient with BE with "prevalent" cancer, of any stage, occurring within 12 months of diagnosis, and they typically exclude from analysis any patient with prevalent high-grade dysplasia found either at the time of BE diagnosis or within 6 to 12 months of initial diagnosis.[5,35,38-40] Because patients with early stage esophageal adenocarcinoma and high-grade dysplasia are now routinely cured endoscopically,[11,41] this practice no longer informs the outcomes of surveillance, but, even worse, this practice has led to inaccurate estimates of the incidence of adenocarcinoma arising from BE. As this custom has become the norm, the published incident rate of BE cancer progression has dropped substantially from the traditionally accepted approximate risk of 0.5% per year[12] to published annual cancer progression rates as low as 0.12% per year.[39] Is this a valid decrease in incident cancer risk, or has a conceptual misperception of this risk taken place?

Consider a recent, highly cited, *New England Journal of Medicine* article by Hvid-Jensen et al[39]—a retrospective, registry cohort study of 11,028 patients with BE, with a mean 5.2-year follow-up. No minimum BE length was required for diagnosis, and the annual incident rate of BE progressing to adenocarcinoma was stated to be 0.12% per year, much lower than the commonly accepted risk. However, and as noted earlier, Hvid-Jensen et al[39] excluded from analysis all "patients with a previous or concurrent diagnosis of high-grade dysplasia at the time they received the diagnosis of Barrett's esophagus," and the study also excluded all "adenocarcinoma cases diagnosed during the first year of study." Not just stage 4 cancer—all stages, even intramucosal cancers, were excluded. There were 197 cancers identified in the study—131 cases were found in the first year of follow-up, and these were all excluded. With all cancers counted, the incident rate of cancer was actually 0.36% per year, and if one adds in the presumed high-grade dysplasia progression rate to cancer of approximately 20% per year[8] (the actual number of excluded high-grade dysplasia cases was not supplied), then the annual cancer rate would have been higher yet.

The authors provided no rationale for excluding all cancers within the first 12 months, let alone early stage cancers that may actually appear within the stated period and that are curable endoscopically.[41] No rationale was given for excluding high-grade dysplasia from the analysis, even though high-grade dysplasia is now largely cured endoscopically.[8,9,11] No reference was supplied to support the decision to exclude all cancers and all high-grade dysplasias, no plausible biologic rationale was given, and there was no reason supplied for choosing 12 months as the appropriate interval of exclusion. Essentially, these appear to be arbitrary decisions on the part of the authors, with no supporting evidence and the net result of artificially decreasing incident cancer risk.

A widely cited meta-analysis applies similar logic.[40] In 2013 Desai et al[40] looked at numerous BE progression studies, including 10 "core" studies, and concluded that the incident cancer risk for BE was 0.33% per year. However, the 10 core studies also excluded as prevalent all cases of adenocarcinoma diagnosed within 1 year of commencing surveillance, and most of the studies also excluded all high-grade dysplasia, some diagnosed within the first 6 months of BE diagnosis and others within the first 12 months. In most of the core studies making up the bulk of the Desai et al meta-analysis, the excluded cases represented at least 15%, and in some articles almost 35%, of the studied population.[42]

We believe that the aforementioned practice represents a conceptual error for calculating the BE-associated incident cancer risk. Removing all or most high-grade dysplasia and all cancer patients within a 6 to 12 month interval and then following the remaining metaplasia patients provides an analysis that informs the natural history of an artificially created subset of patients with BE but is not a statistically valid sample of baseline incident cancer risk. This type of

analysis limits the studies to a specific subset of patients with Barrett's metaplasia, with no identifiable cancer or high-grade dysplasia at 6 or 12 months, who were then followed prospectively, which cannot be construed as a true incident cancer risk of a de novo group of unselected patients with BE embarking on a surveillance program. The a priori cancer risk in these studies must be greater than the published 0.12% to 0.33% risk because the excluded patients with high-grade dysplasia and cancer all started as having Barrett's metaplasia at some point. In essence, this type of analysis creates what we have termed *zombie* patients with BE, doomed to forever walk the earth with high-grade dysplasia or any stage of cancer (including intramucosal), never counted in any study, and with no certainty as to whether their dysplasia or cancer was missed at index endoscopy or whether it developed de novo within the stated exclusion period.

Without supplying a reference or plausible biologic reason for exclusion or for the intervals used, the authors artificially decreased the rate of incident cancer, but the magnitude of the manipulation cannot be determined. Using a 12-month interval artificially decreases the risk compared with using a 6-month interval. If, for example, one chooses the 6-month interval, then a cancer or high-grade dysplasia occurring at 180 days would be excluded, but one occurring at 181 days would not. Using the 12-month interval, a cancer occurring 365 days after initial endoscopy would be excluded, but one occurring at 366 days would not. There is no justification whatsoever for manipulating risk on this basis. Authors simply cannot take say 1000 patients with BE, eliminate (and never count) 150 or so with prevalent high-grade dysplasia and all stages of cancer arbitrarily defined as occurring within the first year after diagnosis, then follow the remaining 850 patients for the next 5 years, come up with an incident cancer risk value of 0.12% to 0.33% per year in that artificially generated subset, and then reassign that value to de novo patients with BE or to a de novo BE cohort. Although not a valid practice to assess true cancer incidence, this has become the new, and now widely accepted, mantra of decreased BE cancer risk.[43]

ENDOSCOPIC DIAGNOSIS OF BE

What we see depends mainly on what we look for.
—John Lubbock

The consensus definition of BE is intestinalized columnar epithelium extending any distance proximal to the gastric folds.[10] Utilizing this definition, however, the published prevalence of BE varies widely in endoscopic studies from 1.6% to 25%[44-46] This wide discrepancy in endoscopic diagnosis may occur because of inconsistent interpretation of endoscopically determined landmarks such as the top of the gastric folds. There are no universally accepted landmarks for discerning precisely where the esophagus ends and the stomach begins.[10,47] Because approximately 20% of patients coming to endoscopy can have intestinal metaplasia limited to the cardia region of the stomach without intestinal metaplasia proximal to the gastric folds,[48] these patients can be misdiagnosed as having BE if the exact location of the top of the gastric folds is obscured. Discordant endoscopic prevalence rates are problematic because they raise concerns about the reliability and interobserver consistency of BE diagnosis. Without accurate prevalence rates of BE, a true cancer risk cannot be determined. To the extent that BE is overdiagnosed endoscopically, the denominator will be artificially inflated with falsely diagnosed BE patients, and the cancer risk will be artificially decreased.

Clearly this occurs in practice but is rarely accounted for when the BE cancer risk is considered. We recently published our findings regarding the inaccurate diagnosis of BE (BEER study) and determined that upon expert endoscopic and histologic review, 32.3% of those originally labeled as having BE did not have that diagnosis confirmed (OR 32.3%; 95% CI, 24.4-41.1).[49] To the extent that our cohort is representative of the general U.S. population, based on the CI, at least 24% of patients currently labeled as having BE in America would not have their diagnosis verified with a careful repeat endoscopic and biopsy examination.

In a multicenter Veterans Affairs study published in 1994, using a similar study design, Kim et al[50] had similar findings, that is, in 18% of previously diagnosed patients with long-segment BE and 33% of patients with short-segment BE, the original diagnosis could not be confirmed. Ten years later in 2004, in a European multicenter study, Meining et al[51] had comparable results—they could not find BE in 30% of those originally diagnosed. Thus, 3 studies, 20 years apart, in different settings, have confirmed that roughly one third of patients labeled as having BE, in all likelihood, are falsely diagnosed. This has important implications because published estimates of BE prevalence and cancer risk, based on retrospective chart reviews of unconfirmed endoscopic diagnosis of BE, particularly those studies in which the accepted diagnostic BE length is not predefined, need to be reconsidered because they very likely understate the BE cancer risk. For example, in the Hvid-Jensen et al[39] *New England Journal of Medicine* article, it is entirely plausible that up to one third of the 11,000 patients with BE included in that study may not have had conventionally diagnosed BE at all.

BALLOON-BASED RFA

I fell into a burning ring of fire
—Johnny Cash

It is now abundantly clear from numerous peer-reviewed studies, including 3 randomized, controlled trials,

that RFA of BE is effective and safe for long-term eradication of intestinal metaplasia with or without dysplasia, with minimal to no buried BE glands, and reduces the risk of neoplastic progression.[8,9,15,52] A recently published, comprehensive meta-analysis of 18 studies including 3802 patients assessed the efficacy, safety, and durability of RFA for BE.[53] This meta-analysis concluded that after ablation there was complete elimination (endoscopic and histologic) of all intestinal metaplasia in 78% of patients and complete elimination of all dysplasia in 91% of patients, with a recurrence rate of only 13% (recurrence included even focal intestinal metaplasia with only a few remaining glands or intestinal metaplasia found at the cardia), reported over a median follow-up of 16.5 months (range 13-51 months). Some of the included studies (eg, Betternet data) did not require routine ablation of the region of the gastroesophageal junction and consequently had higher recurrence rates (33% at 2 years).[53]

Because of the potential recurrence of Barrett's esophagus, some consider RFA a long-term treatment and not a cure because some interval follow-up is needed, however, the authors did conclude that "treatment of Barrett's esophagus with radiofrequency ablation results in complete elimination of dysplasia and intestinal metaplasia in a high proportion of patients, with few recurrences of intestinal metaplasia after treatment, and a low rate of adverse events." (The post-ablation stricture rate was only 5%, and the bleeding rate was about 1%. Significant post-ablation chest pain was seen in 3% of cases and rarely can be severe, requiring hospitalization. The procedure also engenders extra cost.)[53]

In the accompanying editorial, it was noted that many recurrences were actually limited to focal intestinal metaplasia at the gastroesophageal junction, which could be considered an irrelevant finding.[54] Furthermore, the editorialist noted that, "For example, a patient with focal intestinal metaplasia at the cardia after successful radio-frequency ablation of a 10-cm long Barrett's esophagus segment logically does not have the same risk of neoplastic progression as before treatment." Not counting focal intestinal metaplasia at the gastroesophageal junction, he concluded that the treatment was actually 90% effective at eliminating all intestinal metaplasia at 5 years.[54]

Additionally, the number needed to treat (NNT) to avoid BE cancer progression in patients with nondysplastic BE is highly acceptable. This works out to be an NNT of 45, assuming 5-year durability of the procedure as demonstrated by longer-term post-ablation follow-up studies.[1,52,55,56] (We would point out that the NNT to prevent a colon polyp from progressing to cancer is in the same range, ie, 38.)[1] Higher published[12] NNT numbers are calculated by assuming cancer prevention limited to 1 year only; if calculated over a 5-year durability, these NNT numbers also would fall to the 45 range.[1,57] The NNT numbers are lower still if prevention of high-grade dysplasia is incorporated into the analysis. Furthermore, the U.S. Radiofrequency Ablation Registry, a long-term BE follow-up trial including 5521 treated patients with BE at 140 academic and nonacademic centers, noted only 3 cancers in 5691 non-dysplasia person-years of observation after ablation. This represents a >90% cancer risk reduction in patients with nondysplastic BE treated with RFA, compared with historical controls. These data will inform additional highly acceptable NNT numbers.[58]

CONCLUSION

> *Two epidemiologists meet on the street after not seeing each other for over 20 years. After exchanging pleasantries, the first epidemiologist says, "How's your wife?" The second epidemiologist thinks for a second and then responds, "Compared to whom?"*
>
> —Anonymous

In this brief narrative, we have made our case for the routine ablation of Barrett's metaplasia: (1) Surveillance strategies are not cost effective, not preventative of neoplastic progression, and not curative; (2) The BE-associated incident cancer risk is artificially underestimated because of the current propensity to not count patients with prevalent cancer and high-grade dysplasia occurring within a year of diagnosis; (3) In practice, BE is overdiagnosed, falsely inflating the denominator and causing an artificial underestimate of cancer risk; (4) Numerous high-quality studies and a recent meta-analysis clearly demonstrate that RFA is highly effective and highly safe, with a very acceptable NNT to prevent cancer (even lower NNT to prevent cancer or high-grade dysplasia), with demonstrable cancer risk reduction.

It is entirely rational that any person with BE, in the absence of effective surveillance for a disease with a 1 in 200 annual risk for a highly lethal cancer, would compare, and in most instances choose, a quick outpatient ablative procedure, usually curative of the disease, with excellent durability, that offers significant cancer risk reduction with a limited side effect profile (relatively small risk of stricture). Some have argued against routine ablation, noting the need for follow-up examinations to assess for recurrence of intestinal metaplasia[54]; however, repeat ablation of recurrent precancerous lesions by using RFA is exactly what we do in other conditions such as colon polyps, and BE is conceptually the same.[2] Also, computer models claiming cost ineffectiveness of routine ablation need to be taken with a grain of salt because, as noted earlier, the true prevalence of BE is difficult to determine endoscopically, resulting in inaccurate cancer risks.[49] Without prospective studies using strict endoscopic definitions, models can only guess at true rates.[59]

We conclude that not all patients with BE offered RFA will undergo the procedure, but the procedure should be offered to all patients with BE, regardless of dysplasia

status. We recognize that this may represent a substantial departure from current practice for some, but as we have demonstrated, current practice is not well-supported by existing data, and until such time as we have more compelling knowledge, rational patients will avail themselves of a safe and effective cure of their disease.

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