Management of Nondysplastic Barrett's Esophagus: Where Are We Now?

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INTRODUCTION

The increasing incidence of esophageal adenocarcinoma has stimulated great interest in Barrett's esophagus (BE), the condition associated with the majority of adenocarcinomas involving the distal esophagus and gastroesophageal junction (1). BE is a complication of chronic gastroesophageal reflux disease (GERD), a condition that is highly prevalent in the United States. Although approximately 10% of GERD patients have been shown to have BE, recent reports suggest that short-segment BE may be equally prevalent in subjects without reflux symptoms, with population estimates suggesting that BE affects more than 1 million US adults (2–4). However, there are only approximately 10,000 cases of esophageal/gastroesophageal junction cancers in the United States each year, and the majority of BE patients do not harbor dysplasia, which is currently the best marker for cancer progression (5). Thus, endoscopists are routinely confronted with the management of BE patients who do not have dysplasia, the large majority of whom will never develop cancer. Will surveillance help BE patients? Will acid-suppressive medications prevent cancer development? Should ablation be performed in this patient group?

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RISK OF CANCER IN BE

Published series of patients with BE have described annual esophageal cancer incidence rates ranging from 0% (6) to almost 3% (7). In 2000, a systematic review of 25 such reports found that there was a strong inverse correlation between the magnitude of the cancer incidence rate described and the size of the study population (8). There was evidence that many of the smaller series suffered from publication bias, the selective reporting of studies that have positive or extreme results. Funnel diagrams constructed with the use of data from the 25 series analyzed suggested that the true incidence of cancer in BE was approximately 0.5% per year, an estimate supported by the results of several larger, more recent series (9–11). The National Cancer Institute estimates that the incidence of esophageal cancer in the general population of the United States (all races, both sexes, all ages) is approximately 5 per 100,000 (0.005%) (12). Thus, the incidence of esophageal cancer for patients with BE appears to be increased 100-fold above that for the general population.

Although our updated estimate of cancer incidence in BE appears to be more accurate than older ones based on biased reports, it is important to appreciate the limitations of that estimate. In the reports described above, esophageal cancer incidence rates are determined by dividing the number of new esophageal cancers observed during the follow-up period by the total patient-years of follow-up. For example, if 100 patients are followed for 10 years (i.e., 1,000 patient-years of follow-up), during which time two patients develop esophageal cancer, then the annual cancer incidence rate is 0.5%. Note that this estimate provides no information on when the cancers developed during the follow-up period (e.g., during the first or the tenth year), and no information on the ages of the patients who developed the cancers. Consequently, it is not clear that the esophageal cancer incidence rate in BE remains constant over time, or that the rate is the same for patients in all age groups. Indeed, it seems highly unlikely that the risk of cancer remains constant over time, and that the risk for older patients is the same as that for younger ones. Thus, the lifetime cancer risk for a patient with nondysplastic BE is not clear, but is probably in the range of 5%–8% (13). In addition, these estimates are all based on small series that followed patients with the use of surveillance biopsies, which may affect the incidence rates of cancer by removing potentially neoplastic lesions.

With these limitations in mind, one can use the above estimate of cancer incidence to determine whether a cancer-preventive treatment for patients with BE might be a reasonable therapeutic option. For example, one can calculate the number needed to treat (NNT) using the formula NNT = 1/ARR, where ARR is the absolute risk reduction achieved by the treatment. Assume, for the sake of argument, that an endoscopic ablative treatment can reduce the risk of cancer development by one-half, e.g., from 0.50% to 0.25% per year. This represents an ARR of 0.25%. Therefore, the NNT = 1/0.25% = 400. If this optimistic assessment of risk reduction attributable to endoscopic ablation is correct, then 400 patients would need to be treated in order to prevent one cancer in one year. Such a large NNT might be acceptable

for a treatment that is very inexpensive, safe, and convenient, but endoscopic ablation techniques developed to date meet none of these criteria. One could argue that if one were to use the cancer incidence estimate to determine the risk of developing esophageal cancer over decades rather than over one year, then the NNT would be far smaller. However, the numerous, dubious assumptions inherent in such a calculation render it virtually meaningless. For example, this calculation would assume that the cancer risk remains stable over decades, which it almost certainly does not, and that the ablation procedure remains uniformly effective during that same time period, another highly questionable premise.

PREVENTION OF NEOPLASIA BY MEDICAL THERAPY

The medical management of BE is two-pronged: endoscopic surveillance for neoplasia and proton pump inhibitor (PPI) therapy to treat the underlying GERD and, perhaps, prevent neoplasia. Although case–control studies suggest that endoscopic surveillance leads to the detection of earlier-stage neoplasms with longer survival, there are no prospective, randomized trials to support the practice of surveillance, nor are such trials ever likely to occur in the United States (14,15). Such a prospective study is currently under way in the United Kingdom; however, meaningful results may not be available for some time. Nevertheless, the vast majority of endoscopists in the United States perform surveillance endoscopy. The guidelines for surveillance are variable and, arguably, not evidence based. The fundamental rationale for surveillance to look for dysplasia is that cancer evolves through a stereotypical sequence in which there is progression from no dysplasia to low-grade dysplasia, high-grade dysplasia, and, ultimately, esophageal adenocarcinoma. This sequence occurs over a variable time frame. The longest mean follow-up of a large patient cohort is 7 years (16). The interpretation of the grade of dysplasia is plagued with inter-observer variability (17).

Although a recent population-based study showed that approximately 40% of subjects diagnosed with BE did not have symptoms of acid reflux (18), the majority of clinically diagnosed patients with BE have reflux symptoms and are usually treated with PPIs. Two retrospective cohort studies have documented a reduction in dysplasia with PPI use. Among 236 veteran BE patients with a follow-up of 1,170 patient-years, the use of PPIs was associated with a hazard ratio of 0.25 (95% confidence interval (CI) 0.13–0.47) by Cox multiple regression analysis—a 75% reduction of dysplasia (19). In the second study, among 350 patients in an Australian Barrett's cohort with a median follow-up of 14.7 years, delay of PPI use for 2 years or more after diagnosis was associated with a 5.6-fold (95% CI 2.0–15.7) increased risk of developing low-grade dysplasia and a 20.9-fold (95% CI 2.8–15.8) increased risk of developing high-grade dysplasia or adenocarcinoma (20). However, both these studies were limited by a small sample size and a single-center and retrospective study design.

A prospective trial of PPI vs. placebo for patients with BE is unlikely to be performed because of the issue of withholding therapy from patients who have GERD symptoms. The AspECT trial in the United Kingdom is designed to randomize 5,000 BE patients to low- or high-dose PPI therapy in a phase IIIb two-by-two factorial design (21). The results of this trial are eagerly awaited. The impact of medical therapy on cancer prevention is yet to be proven. The large sample size necessary to document an impact on cancer development is testament to the difficulty and expense of this endeavor.

ROLE OF ENDOSCOPIC ABLATION IN NONDYSPLASTIC BE

For patients with nondysplastic BE, do the benefits of endoscopic ablation outweigh the inconvenience, risk, and expense? Ablation is performed primarily with the goal of decreasing cancer risk. Given the small risk of cancer development, however, it will be difficult to demonstrate this benefit in a clinical trial. Indeed, multiple cost-effectiveness models have found that even endoscopic surveillance may not meet the current criteria for incorporation into clinical practice (22). A secondary benefit of ablation would be to reduce or eliminate the practice of surveillance endoscopy. Since regular surveillance endoscopy is usually prescribed for patients with BE, a substantial reduction in surveillance could result in considerable savings of health-care dollars and time lost from work. There has been disturbing news regarding the potential recurrence of Barrett's mucosa after ablation using all the evaluated techniques. Argon plasma coagulation has been shown in randomized trials to perform similarly to multipolar coagulation in ablation of Barrett's mucosa (23). Compared with published information regarding radiofrequency ablation, another thermal therapy, argon plasma coagulation therapy, performs as well in eliminating intestinal metaplasia (24). In a recently published series of patients in whom complete ablation was performed with argon plasma coagulation, 14 of 21 (66%) were found to have recurrence of intestinal mucosa after a mean follow-up of 51 months (25). If these data hold for other thermal ablative therapies, then it is not clear that ablation reduces the need for regular surveillance.

The risks of therapies that have been used for the ablation of BE without dysplasia appear to be small. Stricture formation has been noted, but only rare serious complications such as perforation or bleeding have been found. Overall success rates of therapy in eliminating metaplasia have been about 70% for most thermal therapies (23,26). Radiofrequency ablation has been reported to be used successfully in BE without dysplasia, with approximately 70% complete-ablation rates with minimal complications (24). One major downside to these therapies is the number of endoscopies and treatments that are needed. None can be considered single-visit therapies, and most involve three to five treatments to eliminate the Barrett's

mucosa. So the problem with these therapies is the lack of ability to completely eliminate the BE in 30%, and a potential recurrence of intestinal metaplasia in those that are cleared. A theoretical risk for ablation therapy might be the potential that treatment could increase the risk of esophageal adenocarcinoma. In treating intestinal metaplasia without dysplasia, there is the possibility that the therapy could select for clones of metaplastic tissue that are more prone to neoplasia. In some patients who undergo ablation for nondysplastic Barrett's mucosa, the neo-squamous epithelium exhibits markers of hyperproliferation such as Ki-67 staining, COX-II expression, and even p53 staining (27). These markers are only rarely found prior to ablative therapy. These findings are worrisome, as very long-term studies in this patient population are lacking. In patients with high-grade dysplasia, long-term follow-up does not suggest that incomplete ablation is associated with increased cancer risk; most cancers appear soon after initiation of ablative therapy (28,29). One other important consideration is the difference between demonstrated efficacy in clinical trials and the effectiveness of these therapies in clinical practice. The clinical trials involve very specialized centers with expert endoscopists who carefully monitor patients, and the quoted efficacy rates must be assumed to be the best obtainable. In clinical practice, challenges with uniform follow-up, training, and availability of advanced techniques to assess for early cancers can often lead to much lower effectiveness in achieving the desired outcome.

Given this overview of the benefits and risks of ablative therapy for nondysplastic Barrett's mucosa, the weight of the evidence to date seems to favor a cautious approach in which patients should be treated in clinical protocols where the results can be carefully judged. Although it will be hard to await studies that truly show an elimination of cancer risk because of the length of time involved and the large numbers of patients required, one approach may be to determine whether the biomarkers for cancer development are stable and not provoked by these treatments. Furthermore, the durability of treatment must also be assessed, as there is evidence that suggests that intestinal metaplasia can reoccur, which would definitely decrease the desire to treat these patients.

CONCLUSIONS

The incidence of esophageal adenocarcinoma continues to increase at a rate greater than that of any cancer in the Western world in the face of stable or declining cancer incidence for other major malignancies (1). This increase has been persistent now for some time and shows no sign of slowing. However, in spite of the striking increase in the incidence of esophageal adenocarcinoma, the vast majority of patients with BE never go on to develop this cancer. Therefore, it should come as no surprise that esophageal adenocarcinoma is a rare cause of death in BE patients, and most of these patients die from other causes (13,30). Despite this, patients continue to overestimate their risk of developing cancer and continue to seek strategies to decrease their cancer risk (31). To date, there is no proof that any strategy, be it endoscopic, surgical, or medical, will decrease the cancer risk of a given patient with BE without dysplasia. Acid-suppressive medications should be used, because they are effective in controlling reflux in these patients, but their chemopreventive role has not yet been established. Endoscopic surveillance can be performed as suggested by the recently updated guidelines from the American College of Gastroenterology (32). Endoscopic ablation is increasingly being used in the nondysplastic BE cohort—an opportunity to be proactive in our approach to BE. However, although this concept is theoretically attractive, the lack of scientific data supporting it should be kept in mind; the number of patients without dysplasia who would need to be treated in order to prevent one cancer is substantial, devices are not inexpensive, multiple treatment sessions are required, and, most important, the need for continued surveillance is not eliminated. Finally, we should not forget the recent experience with endoscopic therapy of GERD, which was viewed as a minimally invasive alternative to surgery and medications. Not only was this therapy disappointing, but some patients died as a result of premature deployment of these techniques (33). These are clearly exciting times in endoscopic approaches to BE. Nevertheless, we should never forget one of the guiding principles of medicine: first, do no harm. Thus, in the clinical setting, endoscopic ablation of nondysplastic BE cannot be recommended at this time.

CONFLICT OF INTEREST

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