Advances in Barrett's Esophagus and Esophageal Adenocarcinoma

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Despite advances in diagnosis and therapy, esophageal adenocarcinoma remains an aggressive and usually lethal tumor. This review focuses on the epidemiology of esophageal adenocarcinoma and its presumed precursor lesion, Barrett's esophagus; the pathogenesis of the cancer; advances in treatment of adenocarcinoma and Barrett's esophagus; and strategies for cancer prevention. Emphasis is placed on recent literature. Although the absolute number of cases of adenocarcinoma in the United States is still small, the incidence of this cancer has increased dramatically in the last 40 years, and adenocarcinoma is now the predominant form of esophageal cancer in this country. Recent evidence suggests that Barrett's esophagus is more prevalent in asymptomatic individuals than previously appreciated. The pathogenesis of Barrett's esophagus is poorly understood. Given that some subjects will have repeated bouts of severe erosive esophagitis and never develop Barrett's esophagus, host factors must play an important role. The utility of neoadjuvant radiation and chemotherapy in those with adenocarcinoma, although they are widely practiced, is not of clear benefit, and some authorities recommend against it. Ablative therapies, as well as endoscopic mucosal resection, hold promise for those with superficial cancer or high-grade dysplasia. Most series using these modalities feature relatively short follow-up, and longer-term data will be necessary to better describe the effects of these therapies. The value of chemoprevention in subjects with dysplastic Barrett's esophagus by use of cyclooxygenase 2 inhibitors, nonsteroidal anti-inflammatory drugs, or proton pump inhibitors is unknown. Similarly, although endoscopic screening is widely practiced, its value in patients with chronic gastroesophageal reflux disease symptoms is of unproven value, and recommending bodies are divided as to its practice.

Because of its rapidly increasing incidence over the last 40 years, esophageal adenocarcinoma has gone from a somewhat esoteric disease entity to the predominant form of esophageal cancer in the United States. Although still a rare cause of cancer death internationally, esophageal adenocarcinoma has become a significant health concern in Western countries. Given the poor prognosis associated with the disease, a better understanding of the pathogenesis of the disease and the factors associated with increased risk is essential. Also, strategies for prevention of esophageal adenocarcinoma are hotly contested.

The following review will focus on new developments in the field of Barrett's esophagus (BE) and esophageal adenocarcinoma. Given the myriad aspects of these disease states, an exhaustive review of all that is known about them is beyond the scope of this article. Therefore, this work will concentrate on the epidemiology of the disease states, the pathogenesis of the cancer, advances in treatment, and strategies for cancer prevention. Special emphasis will be placed on recent data, with effort to place these data in the context of our knowledge of BE and esophageal adenocarcinoma.

Epidemiology of Barrett's Esophagus and Esophageal Adenocarcinoma

The incidence of esophageal adenocarcinoma in the United States has increased approximately 300%–500% in the last 40 years.[1–3] Although previous misclassification of some esophageal adenocarcinomas as gastric cardia tumors may be in part responsible for the noted increase, it does not likely explain the entire increase. If misclassification were to explain all of the increase, a concomitant decrease in the number of gastric cardia tumors might be expected over the same time period. The opposite is true; the incidence of gastric cardia tumors has not decreased and may have actually increased over this period.[4,5]

Less clear is the trend in the incidence of BE. Because BE is thought to be the precursor lesion to most or all cases of adenocarcinoma of the esophagus, increases in cancer might

Abbreviations used in this paper: BE, Barrett's esophagus; EMR, endoscopic mucosal resection; GERD, gastroesophageal reflux disease; HGD, high-grade dysplasia; PDT, photodynamic therapy.

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be expected to be preceded by increases in the incidence of BE. Longitudinal single-center studies do show an increase in diagnosis of BE over the past several decades.[6,7] However, this increasing trend mirrors the increasing use of upper endoscopy. It may, therefore, mean that the increased incidence of BE described in these studies is due to increased opportunity for detection, as well as the increasing appreciation of BE as a risk factor for cancer, as opposed to a true increase in prevalence.

The increasing trend in esophageal adenocarcinoma closely resembles the epidemic increase in obesity in the US population.[8,9] Additionally, obesity has been strongly associated as a risk factor for esophageal adenocarcinoma, even after controlling for the severity of reflux symptoms.[10,11] These 2 facts have led authorities to suggest a causal relationship between trends of increasing obesity and resultant esophageal adenocarcinoma in the US population.[12–14] Although such a relationship is certainly plausible, no causal chain has been definitely proven, and changes in other environmental exposures over the last 50 years may account for all or part of the observed increase.

One recent important contribution to this field has been the demonstration of the prevalence of BE in asymptomatic populations. BE has long been recognized as a possible complication of chronic reflux disease. However, 40% or more of esophageal adenocarcinoma is found in subjects without previous symptoms of reflux[15–17]—an observation that is inconsistent with the theory that BE arises from gastroesophageal reflux disease (GERD) and is the predisposing lesion to adenocarcinoma. This apparent contradiction may be at least partially explained by recent prevalence data of BE in asymptomatic populations. Gerson et al[18] performed upper endoscopy on 110 subjects with no or negligible GERD symptoms who were presenting for colorectal cancer screening. The surprising and somewhat unsettling finding in this primarily Veterans Administration Medical Center cohort was that almost 25% of those with no GERD symptoms harbored BE, and 8% of the subjects had long-segment disease (>3 cm). Other groups[19,20] have found that lesser, but still substantial, proportions of asymptomatic individuals have BE (Table 1). Currently unknown is whether these asymptomatic individuals with BE have the same increased risk of cancer that has been shown in previous, symptomatic cohorts that have been followed up longitudinally.

Also unknown is the exact risk of cancer in subjects with BE. Initial reports pegged this risk at 1% or more per year. More recent reports and a meta-analysis have suggested this risk to be approximately half that amount.[21–24] Of course, these analyses provide rough estimates based on accumulated data from cohorts for multiple years. It is quite possible (perhaps even likely) that cancer risk is unevenly spread in any given subject's "Barrett's lifetime." For instance, it may be that the initial period immediately after the development of the BE is a critical time in which a subgroup of subjects experience rapid progression through degrees of dysplasia to cancer. Conversely, perhaps nondysplastic BE of 10 years' duration is at very little, if any, risk of progression. Because the exact time of development of BE in subjects diagnosed with the condition is unknown, we have no data as to cancer risk as a function of the duration of preceding BE.

Pathogenesis of Barrett's Esophagus and Cancer

BE is thought to be a sequela of chronic reflux disease. Subjects with chronic reflux disease seem to harbor BE 5%–15% of the time.[25–27] However, it is unclear why some subjects develop severe recurrent erosive esophagitis and never develop BE, whereas others with relatively few symptoms and little or no inflammatory disease on upper endoscopy develop long segments of severely dysplastic disease. It has been suggested that a genetic predisposition to the development of BE might be a necessary prerequisite to the disease. However, to date, a "Barrett's gene" (or genes) has remained elusive. Several groups have attempted to study the heritability of BE as presumptive evidence of a genetic contribution to the disease. Family cohort studies have shown that BE occurs in family groups more frequently than would be expected by chance.[28] However, if there is a Barrett's gene, the penetrance of the phenotype must be low, because most first-degree relatives of those with BE do not have BE themselves.[29]

Table 1. Prevalence of BE in Asymptomatic Cohorts

Study	Year	Patient population	n	Prevalence of BE	Prevalence of long-segment BE
Gerson et al[18]	2002	Veterans Administration medical center	110	25%	7%
Rex et al[19]	2003	University hospital	556	5.6%	0.36%
DeVault et al[20]	2004	Academic practice	138	12.3	NR

NR, not reported.

Exactly where the progenitor cells leading to BE arise is a matter of debate. Studies using cell markers suggested that BE arose from pluripotent cells found in the esophagus, which, in the presence of an acidic milieu, developed into columnar epithelium.[30,31] Recent work from Sarosi et al,[32] however, support an alternative explanation. Using a rodent model of BE, this group was able to show that the progenitor cells for BE arose in the animal's bone marrow. The mechanism by which these cells differentiate and the factors leading to the propagation of columnar instead of squamous mucosa are still largely unknown.

BE is thought to progress through stages of dysplasia to cancer, and, indeed, one of the strongest known predictors of cancer risk in the setting of BE is the degree of dysplasia. Subjects with nondysplastic BE and low-grade dysplasia have low rates of progression, whereas those with high-grade dysplasia (HGD) may experience disease progression at rates higher than 10% per year. [33,34] Additionally, surgical series show concurrent undetected cancer in the resection specimen in 50% or more of patients with HGD.[35–37] It has been more recently appreciated, however, that the progression through grades of dysplasia is neither orderly nor inexorable. Indeed, subjects may jump from nondysplastic BE straight to HGD or cancer without an intervening detectable low-grade dysplasia phase.[38] Alternatively, subjects with HGD may undergo apparent regression of the disease and spend months or even years with no detectable dysplasia whatsoever. Data on disease progression in BE are compromised by our random-sampling endoscopic biopsy techniques. Almost all the data available on progression rates in BE are from studies using a random biopsy method. Even groups that use jumbo forceps and 1-cm, 4-quadrant biopsies leave the vast majority of the mucosa unsampled. It is difficult to know what percentage of apparent disease regression is real and what is due to random sampling error missing small or mosaic areas of more advanced dysplasia. Although more sophisticated methods of sampling BE by using vital stains or magnification of mucosal crypt patterns have been described,[39–42] these methods have not been broadly adopted because of cost, increased time requirements, and lack of sufficient evidence of the effects of the methods on important outcomes.

Advances in Treatment

Neoadjuvant and Surgical Therapy for Cancer

The prognosis for esophageal adenocarcinoma remains dismal, with a 5-year survival for all comers of approximately 20%.[43–45] This poor result is due in part to the advanced stage of the cancer when it is usually diagnosed. More than 50% of those with this cancer present with stage III or IV disease.[45,46] However, some recent strides have been made in elucidating the best care for those with adenocarcinoma.

After initial enthusiasm for neoadjuvant chemotherapy as an adjunct to surgery, a well-performed randomized controlled trial showed that neoadjuvant chemotherapy before resection does not improve survival.[47] More promising have been the results of studies combining neoadjuvant chemotherapy with radiation therapy. Unblinded studies of neoadjuvant chemoradiation showed that approximately 25% of those undergoing therapy achieved a complete response and that those undergoing therapy had improved survival compared with historical controls.[48–50] Given these data, prospective randomized studies have been conducted comparing multimodality therapy with surgery alone. These trials have given somewhat conflicting data. Walsh et al[51] randomized 113 patients with adenocarcinoma to undergo either surgery alone or neoadjuvant chemotherapy and radiation with surgery afterward. The chemotherapy regimen was 5-fluorouracil and cisplatin based, and 40 Gy of radiation was delivered. These investigators found a significant downstaging of tumors in the multimodality group; fewer subjects in this group had stage III or IV disease at the time of surgery. Additionally, 3-year survival was improved in the multimodality group (32% vs 6%), and median survival was significantly longer in the multimodality group (16 vs 11 months). Weaknesses of this study included the poor rate of survival in the surgery monotherapy group, as well as the inclusion of some gastric cardia cancers in the study group.

A second study performed at University of Michigan showed less conclusive data.[52] This randomized controlled trial of 100 patients with both squamous cell carcinoma and adenocarcinoma of the esophagus compared surgery vs radiation combined with a chemotherapy regimen of 5-fluorouracil, cisplatin, and vinblastine. Unlike the study by Walsh et al,[51] this study showed only an insignificant trend toward improved survival at 3 years in the multimodality group (30% vs 16%; $P = .15$). The absolute difference between the groups, although not statistically significant, is certainly clinically significant, but the study was not powered to detect relatively small absolute differences in survival.

Given the conflicting nature of the data, as well as the shortcomings of the studies considering this question, many centers continue to practice multimodality neoadjuvant therapy for subjects with adenocarcinoma of the esophagus. Although some authorities have divergent points of view[53,54] and although other data suggest no

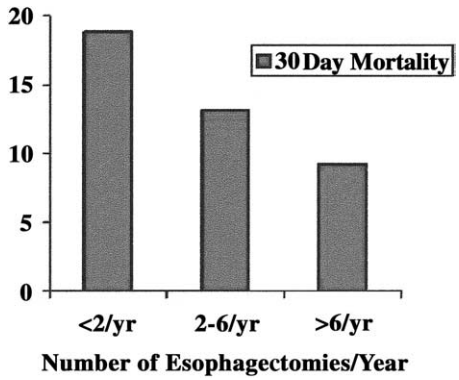


Figure 1. Thirty-day mortality of surgical esophagectomy as a function of the experience of the surgeon. Mortality approximately doubles from relatively inexperienced surgeons to high-volume practitioners. (Data adapted from Birkmeyer et al.[59])

benefit from neoadjuvant therapy in the setting of esophageal adenocarcinoma,[55] given the low likelihood of complete resection of disease in the absence of neoadjuvant therapy, this practice will likely continue in the absence of further definitive data.

Also becoming better understood is the optimal surgical approach to resection of cancer. Radical en bloc resection includes a laparotomy, a thoracotomy, and a cervical approach. This approach allows for extensive lymph node sampling and good assessment of extent of disease. Alternatively, transhiatal approaches involve dissection of the esophagus solely by use of abdominal and cervical approaches, thus obviating thoracotomy. A recent randomized controlled trial of the 2 approaches showed that neither was statistically superior to the other in 5-year survival, although the en bloc methods did provide an insignificant trend toward improved survival (39% for en bloc and 29% for transhiatal).[56] These results show that surgical approach is not a major predictor of survival and that individual factors, such as preoperative assessment of extent of disease and patient comorbidities, may best decide which approach is most appropriate. For instance, transhiatal resection might be most appropriate for the elderly patient with limited disease, whereas a more aggressive approach might be adopted in the younger, healthier patient with more extensive disease.

Perhaps the clearest message from the surgical literature is that the experience of the surgeon and the volume of the center providing the treatment are crucial predictors of the morbidity of the treatment.[57,58] Low-volume surgeons have average 30-day mortality rates of 18.7% for esophagectomy, whereas high-volume surgeons have corresponding rates[59] of 9.2% (Figure 1). These differences are likely due both to the greater experience of the surgical operators and to the specialized institutional support—such as skilled nursing, respiratory therapy, and intensive care units—that evolves in high volume centers. Morbidity for this procedure is also impressive, and serious postsurgical complications have been reported in more than 50% of subjects in some series.[60,61] In addition to the perioperative risks noted previously, the propensity of the esophageal remnant to develop recurrent BE above the anastomosis is becoming better recognized. Studies of subjects after esophagectomy show that 47% have some columnar epithelium in the tubular esophagus and that approximately 10% develop BE.[62,63]

What Is the Best Treatment for High-Grade Dysplasia?

Given the uniformly poor survival reported in series of patients with esophageal adenocarcinoma presenting symptomatically, many centers in the United States have developed endoscopic surveillance programs for patients with BE. Subjects are endoscopically assessed at fixed intervals, and intervention is contemplated on the basis of the degree of dysplasia noted on surveillance biopsies. Subjects with nondysplastic BE are generally followed up at intervals of 2–3 years, whereas those with HGD are considered for intervention.[64] Of current debate is the most appropriate care for those with HGD.

The presence of HGD is considered an appropriate criterion for surgical resection in many medical centers. Proponents of this position cite the high risk of progression, as well as the likelihood of metachronous cancer, as noted previously.[37,65–69] Recently, 2 other potential management strategies have been put forward. Intensive endoscopic surveillance relies on the principle that superficial adenocarcinoma of the esophagus rarely has lymph node involvement. Therefore, if early detection efforts are rigorous enough, survival should not be negatively affected even if a substantial proportion of the cohort does progress to cancer. These subjects would go on to get the surgery that they would have gotten anyway and to be cured of disease, whereas the remainder of the cohort is spared a morbid surgery and the subsequent attendant decrease in quality of life from living after esophagectomy. To date, only 1 large cohort has been reported with this approach. Seventy-five subjects with HGD were followed up by Schnell et al[38] with intensive endoscopic surveillance in a cohort study at the Hines Veterans Administration in Chicago. These subjects underwent intensive endoscopic surveillance (every 3 months for the first year, every 6 months for the second year, and yearly thereafter). At a mean follow-up of 7.3 years, only 16% of the cohort had developed cancer. The remainder of the group was cancer free with the esophagus intact. Twenty-one members of the cohort had died

over that time, but only a single person had died from metastatic esophageal cancer. This individual was a patient who had been lost to follow-up for 10 years after his diagnosis of HGD and who presented after that period with widely metastatic disease.

It is unclear why the prognosis of HGD in the Hines Veterans Administration cohort was superior to that in other previously reported groups with HGD.[34] Because this cohort underwent an extensive search for metachronous cancer before patients were enrolled in the surveillance program, some of the difference may be more apparent than actual—the group was better "purified" of metachronous cancer than other reported cohorts. Other alternative explanations include the possibility that variability between centers in the histological definition of HGD might explain these results. Certainly, if the Hines Veterans Administration patients with HGD had a less severe form of dysplasia than HGD patients in other cohorts, this finding might explain the discrepancy in the data. Regardless of these issues, on the basis of these data, some centers have been offering intensive endoscopic surveillance as an alternative to resection. This approach might be an especially attractive option in subjects who are poor surgical candidates or who are elderly. In such subjects, who might be most prone to a complication from interventions such as surgery or ablative therapy, intervention (and the risks associated with it) could be targeted to only that subgroup who went on to develop superficial cancer. Also, unifocal HGD (ie, HGD found on only 1 of a number of biopsy samples taken for endoscopic surveillance) might have a better prognosis than multifocal HGD.[70] If so, perhaps unifocality of disease might be a reasonable criterion for considering intensive endoscopic surveillance.

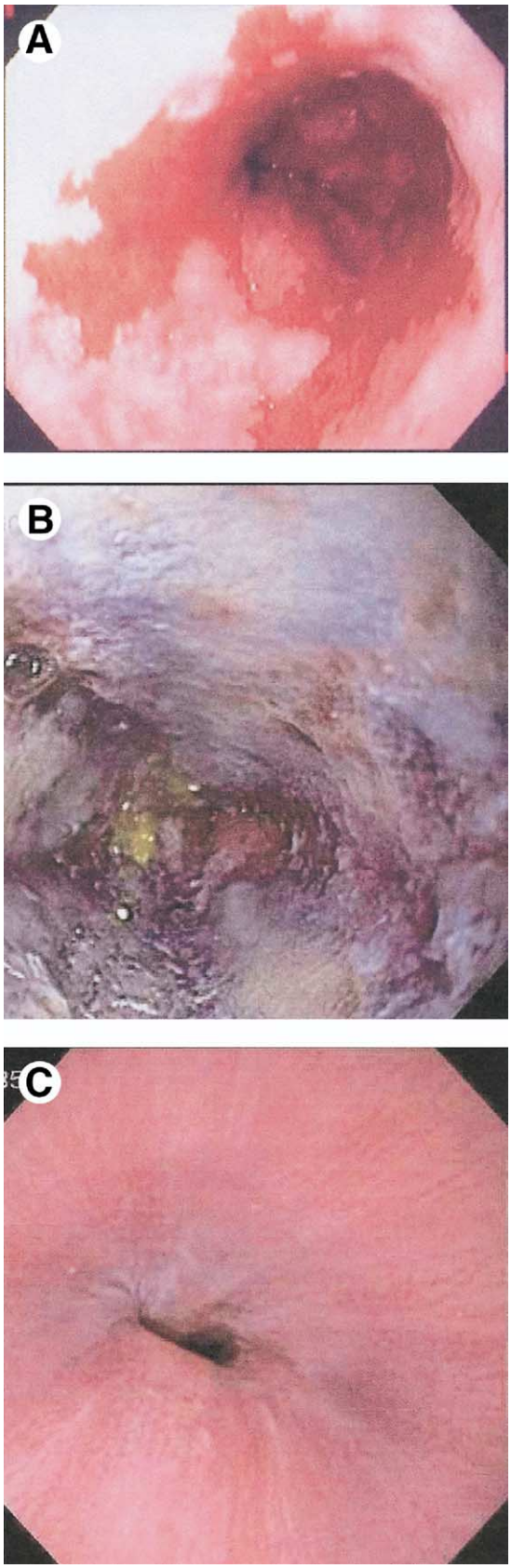
One rapidly evolving area of investigation in the treatment of HGD is the use of endoscopic ablative therapies. These modalities offer the promise of diminishing the cancer risk in the setting of HGD while avoiding the morbidity and mortality of esophagectomy.

Multiple different modalities have been described, including electrocoagulation therapy, lasers,[71–73] argon beam coagulation therapy,[74–76] yttrium–aluminum–garnet laser therapy,[77,78] radiofrequency ablation,[79] and photodynamic therapy (PDT).[80,81] Of all the modalities available, perhaps the most extensive available experience in the literature is with PDT. PDT relies on the interaction of a chemical compound, porfimer sodium, with light of a specific wavelength (630 nm) to cause an intracellular reaction that results in the death of the cell. Treatment of the affected segment of BE for a preset period of time results in a predictable degree of tissue damage, such that tissue destruction is deep enough to destroy most or all of the BE cells but not deep enough to cause full-thickness necrosis of the esophagus with subsequent perforation (Figure 2).

A controlled trial of subjects randomized to either PDT therapy with high-dose proton pump inhibition or proton pump inhibition alone has recently been performed.[82] All subjects in the study had BE with HGD. This study, the result of which is currently available only in abstract form, shows a greater than 50% reduction in the number of subjects who developed adenocarcinoma in the group treated with PDT (28% vs 13%; $P = .006$). Given these data, as well as uncontrolled data suggesting that ablation of HGD provides diminution of the cancer risk compared with historical controls,[81] PDT has been approved by the US Food and Drug Administration as a treatment of BE with HGD.

Two conflicting concerns regarding the performance of PDT are the subsequent stricture rate in subjects undergoing the procedure and the likelihood of submucosal Barrett's glands under the neosquamous epithelium. These concerns are in a way complementary—ablative modalities that provide the deepest mucosal burn, such as PDT, feature relatively low rates of buried glands but higher rates of stricture. The opposite seems true of more superficial treatments of BE, such as argon beam coagulation, which are associated with a lesser rate of stricturing but more buried glands.[83] The stricture rate associated with 1 treatment of PDT approximates 20% and increases to approximately 50% if multiple treatments are necessary.[81,84] These strictures are amenable to endoscopic therapy, but, because the strictures are thick and fibrous, multiple sessions of dilation may be necessary before good relief of dysphagia is obtained. Concomitant therapy with steroids does not decrease the subsequent stricture rate in subjects undergoing PDT.[80] The rate of retained buried Barrett's glands under normal-appearing squamous mucosa is less well described. Clearly, these glands have the potential to progress through stages of dysplasia to cancer, because several case reports of submucosal adenocarcinoma in subjects with apparently normal neosquamous epithelium have been described.[85–87] Whether the neosquamous epithelium itself has an increased risk of squamous cancer is similarly unclear.

Given the current state of the data, a reasonable approach to the patient with HGD might be consideration of either ablative therapy or intensive surveillance for those with unifocal disease. For those with multifocal disease, ablative therapy or surgical resection might be more appropriate.



Endoscopic Mucosal Resection: An Evolving Place in the Treatment Armamentarium

Because of the morbidity and mortality associated with esophagectomy, as noted previously, investigators have become increasingly bold in their efforts at endoluminal therapy for superficial esophageal cancers and polypoid HGD. Endoscopic mucosal resection (EMR) offers the promise of definitive treatment of these lesions with a less invasive approach than thoracotomy. Several different endoscopic techniques have been developed. Piecemeal resection using a saline lift technique imitates the technique used for sessile colonic adenomas.[88] This lift technique can be used in association with snare removal of the lesion. Other lesions may be amenable to resection with a banding technique similar to that used for esophageal varices; a snare is used to remove the pseudopolyp produced after banding so that the specimen can be sent to pathology to ensure complete removal.[88–90] Finally, novel EMR resection caps, with a beveled edge and a snare that fits along a groove at the top of the cap, have been described.[91] These caps may be positioned over the lesion of interest, after which suction is applied, and the lesion is pulled into the cap. The snare is tightened over the base of the lesion, which is then truncated. This method is especially useful for larger lesions, which will not easily fit in a variceal ligation cap.

Reports regarding the success of EMR at removing superficial lesions have been largely positive; however, the evidence to date consists of mostly case series, and publication bias may inflate the value of these procedures. Multiple endoscopic procedures may be necessary to accomplish complete removal of the lesion. With respect to the recurrence of cancer, most series report little or no progression to more advanced cancer. However, it should be noted that most reported series noted previously feature a mean follow-up of less than 24 months.

Recently, attempts have been made to treat large portions of mucosa with HGD but no masses or nodules by using EMR to remove portions of columnar epithelium, as opposed to discrete lesions.[92] Although preliminary experience with these techniques has been encouraging, the relatively large portions of the mucosa that require resection, as well as the preliminary nature of

Figure 2. Typical findings in photodynamic therapy for Barrett's esophagus. (*A*) A typical segment of BE with HGD. (*B*) Extensive mucosal necrosis is evident 48 hours after application of the laser to the mucosa, which was pretreated with photofrin. (*C*) The area of previous BE 3 months later, now epithelialized with normal squamous mucosa.

these reports, make total removal of BE by endoscopic resection a procedure best performed as part of a clinical trial. Currently, large-scale EMR of nonnodular BE is not recommended as a standard practice.

Chemoprevention of Esophageal Adenocarcinoma

Extensive observational data substantiate that nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a 50% or greater decrease in esophageal cancer.[93–96] The exact mechanism of any chemopreventive effect is unclear, and no randomized controlled trial has confirmed that this observed association is causative. However, given the poor prognosis associated with esophageal cancer, authorities have suggested the potential use of chemoprevention in the setting of BE.[97] Especially in subjects with HGD, such chemoprevention, if effective, might markedly reduce the risk of cancer. Indeed, cost-effectiveness analyses have suggested that chemoprevention for HGD might be a very cost-effective maneuver. A recent cost-effectiveness model[98] examining the utility of aspirin as a chemopreventive agent in association with surveillance endoscopy showed that, compared with no therapy, an additional quality-adjusted life-year could be obtained for an acceptable cost of $49,600. A second analysis also suggested that chemoprevention with NSAIDs provided gains in life expectancy at potentially reasonable costs.[99] These calculations assume, of course, that NSAID use retards the progression of HGD to cancer. If the actual mechanism of chemoprevention of cancer by NSAIDs is to prevent the initial formation of BE, it may well be that attempts at treating HGD with NSAIDs to stop cancer are fruitless, because the critical point for intervention has already been missed. Recent work has concentrated on the potential use of cyclooxygenase 2 inhibitors as chemopreventive agents. It was hoped that a superior side-effect profile of these agents compared with nonselective NSAIDs might improve the risk–benefit ratio of chemoprevention. However, given recent revelations about potential cardiac side effects with rofecoxib,[100] the use of cyclooxygenase 2 inhibitors as chemoprevention in the setting of BE is not currently advisable.

Another recent topic of interest has been the effect of rigorous acid inhibition with proton pump inhibitors on the natural history of BE. Early after the advent of proton pump inhibitors, multiple studies showed that proton pump inhibitor therapy did not lead to the reliable regression of BE.[101–103] Recently, however, longitudinal cohort studies of subjects with BE have suggested that the use of proton pump inhibitors may be associated with a decreased risk of dysplasia in the BE[104,105] (Figure 3). In vitro work suggests that pulsed acid exposure promotes proliferation of cell cultures of BE.[106] It may be that the chronic inflammation associated with ongoing GERD promotes carcinogenesis. If so, then acid suppression of subjects with BE may retard the progression to cancer. It is unclear presently whether subjects with BE need to undergo acid suppression to the point of complete obliteration of esophageal acid exposure or whether less rigorous acid suppression will still confer any benefits against progression of disease. Although the effect of vigorous acid suppression on the likelihood of progression of BE is unclear, the common occurrence of reflux symptoms in these patients and the benign nature of the intervention make it reasonable to maintain these patients on acid suppression with a proton pump inhibitor.

Does Endoscopic Screening of Subjects With Chronic Gastroesophageal Reflux Disease Symptoms Prevent Death From Esophageal Adenocarcinoma?

Endoscopic screening of subjects with chronic GERD symptoms has been proposed as a method for detecting subclinical cancers, as well as BE. Subjects found to harbor BE could then be entered into surveillance programs designed to monitor the lesion for progression.[64] Although data in support of the efficacy of this approach are lacking, the practice is widespread among gastroenterologists.[107]

Recommending organizations are somewhat conflicted as to the appropriate approach for screening subjects with

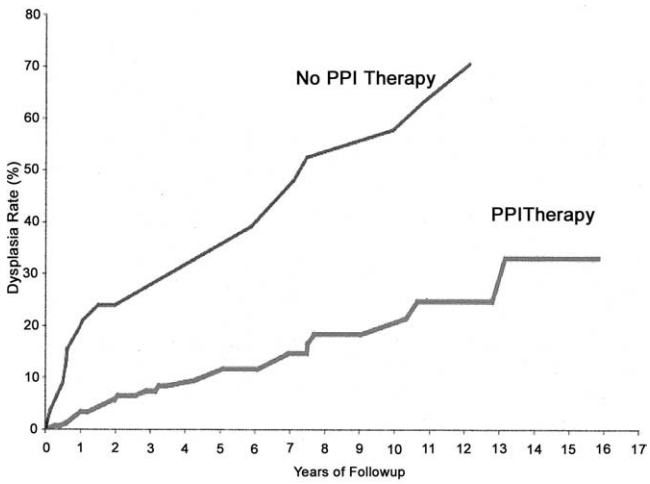


Figure 3. Dysplasia risk as a function of acid-suppressive therapy. In 236 US veterans with nondysplastic BE, El-Serag et al.[105] showed that protection from dysplasia development was strongly associated with proton pump inhibitor (PPI) therapy (Reprinted from the *American Journal of Gastroenterology*, Saunders, published with permission).

chronic GERD. The Practice Parameters Committee of the American College of Gastroenterology notes in their most recent guidelines that "patients with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo upper endoscopy."[64] This once-in-a-lifetime endoscopy would screen for BE and allow enrollment of eligible subjects into surveillance protocols. Conversely, at a recent American College of Gastroenterology Consensus Conference, a multidisciplinary panel of 18 experts in BE believed that there was insufficient evidence to accept the proposition that screening for BE improved mortality from adenocarcinoma or was cost-effective.[108] Contrary to the American College of Gastroenterology clinical guidelines, the American College of Gastroenterology participants did not believe that adequate data were available to support screening for adults over older than 50 years, regardless of age or duration of heartburn.

The source of this discrepancy of opinion lies in the lack of convincing data to show any beneficial effect of screening endoscopy, as well as the substantial theoretical concerns about the effectiveness and cost-effectiveness about such an approach. The data supporting screening upper endoscopy are weak. Patients who have their cancers detected as part of an endoscopic screening and surveillance program have their lesions discovered at an earlier stage and are more often eligible for surgical resection. Also, the life expectancy of individuals with esophageal adenocarcinoma diagnosed by endoscopic screening programs is longer than the life expectancy of those who present symptomatically.[109–114] Although data such as these seem suggestive, several biases, including lead-time and length bias,[115,116] often accentuate the apparent benefits of endoscopic screening and surveillance programs in observational studies. Therefore, the only available data supporting screening endoscopy are observational and subject to bias.

However, substantial theoretical concerns argue against the effectiveness of screening upper endoscopy for those with GERD. First, the ubiquity of GERD in the United States means that the pool of subjects to be screened is enormous. Even if we limit potential screenees to those older than the age of 55 years with at least weekly GERD symptoms, according to US census statistics and our knowledge of the epidemiology of GERD, more than 10 million subjects in the United States would be eligible for screening (Figure 4). Second, the cancer that we are trying to prevent is relatively rare; a little more than half of the 14,250 cases of esophageal cancer in the United States in 2004 are expected to be adenocarcinomas.[117] Third, a large portion of those with adenocarcinoma never experience significant reflux symptoms. Case-control studies suggest that approximately 40% of those with adenocarcinoma never experienced reflux symptoms before their cancer diagnosis.[15,16] Clearly this group would not benefit from screening programs aimed at those subjects with reflux symptoms. Next, the age of onset for this cancer in most series is in excess of 70 years. Many patients of that age have significant comorbidities that make effective intervention difficult and limit the number of life-years that can be saved even if effective intervention is attained.[15,118] In fact, longitudinal studies show that those with BE have the same survival as age- and sex-matched controls without BE from the general public.[119,120] Finally, even if upper endoscopy is obtained before the diagnosis of cancer, BE might not be correctly identified, and the subject might not be entered in a surveillance program. In a recent retrospective cohort study in the Kaiser Permanente group in California, out of 64 patients who developed adenocarcinoma and had an upper endoscopy before the development of cancer, only 23 had identification of BE.[121] Whether short segments of BE were missed on endoscopy in the remaining 64% of patients or whether their cancer did not originate in segments of BE is unknown.

These barriers to effective screening are compounded by the fact that our screening test, upper endoscopy, is relatively expensive. Also, although it is a very safe test, because the yield with respect to cancer is so low, the number of cancers averted may be rivaled by the number of complications of endoscopy.[122–125] Although some cost analyses have suggested that screening and surveillance may be cost-effective,[126,127] the authors note that the results of these analyses are sensitive to several poorly defined variables. It is interesting to note that 1 recent analysis suggested that although an initial endoscopic screening looking for BE with dysplasia was cost-effective, subsequent endoscopic surveillance of subjects with nondysplastic BE was highly cost-prohibitive.[128]

At this juncture, it is highly unlikely in the United States that a randomized trial of endoscopic screening and surveillance vs usual symptomatic care of GERD will ever be performed. However, data may become available from other countries where endoscopic screening and surveillance are not widely practiced. In the meantime, clinicians will need to weigh the risks and possible benefits of screening on a case-by-case basis, and all decisions on the subject should be prefaced with a frank discussion with the patient about the lack of hard evidence for the practice. More targeted

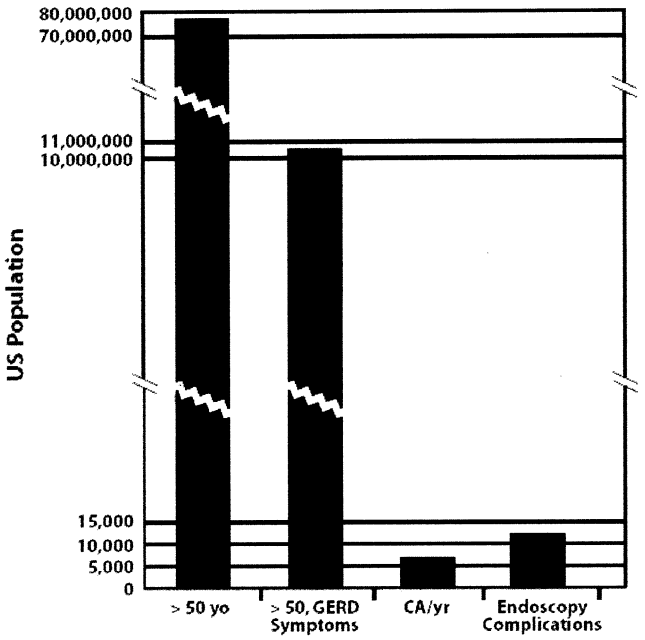


Figure 4. Performance of a hypothetical national screening program for esophageal adenocarcinoma. Given the vast number of subjects with chronic GERD symptoms who would need to be screened, even if we limited our screening to those older than the age of 50 years, more than 10 million Americans might be eligible for screening. We know that the absolute number of cancers approximates 8000 per year and that almost half of these occur in subjects without significant chronic GERD. Although upper endoscopy is a safe procedure, such a program might have more major endoscopy complications than cancers discovered (data adapted from Shaheen and Ransohoff[130]). CA, cancer; yo, years old.

screening, perhaps aimed at high-prevalence subgroups,[129] may improve the effectiveness of these practices.

Conclusion

Despite some strides in our understanding of the pathophysiology and treatment of the disease, esophageal adenocarcinoma remains a deadly tumor. Although it is rare in the United States, the incidence of this disease has increased rapidly in the last 40 years, commanding the attention of clinicians and makers of public health policy. Many centers specializing in the care of this cancer perform neoadjuvant chemoradiation, although the benefits of this approach are unclear. In an effort to avoid the morbidity associated with esophagectomy, rapid evolution has occurred in the endoscopic treatments of superficial adenocarcinoma and BE with HGD. Although the results of these techniques are promising, most follow-up to date is short-term, and the effectiveness of these therapies is not fully elucidated.

Although chemoprevention in the setting of BE with NSAIDs, proton pump inhibitors, or both may be of benefit, randomized data are lacking to prove this. Because most subjects with BE undergo initial investigation because of GERD symptoms, proton pump inhibitor therapy, both for symptomatic relief and any benefit conferred from slowing progression to dysplasia, seems warranted in subjects with BE. Although widely practiced, endoscopic screening of those with chronic GERD symptoms, with enrollment of subjects with BE into endoscopic surveillance programs, is of unclear benefit.

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