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Changes in Screening, Prognostication and Therapy for Esophageal Adenocarcinoma in Barrett's Esophagus

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Abstract

Purpose of review—Significant changes in concepts of managing Barrett's esophagus have led to change in the recommendations concerning screening, surveillance, biomarkers, and therapies in this condition over the past several years. We summarize the important changes in this regard.

Recent findings—Narrow band imaging and esophageal capsule endoscopy are alternative methods to screen for Barrett's esophagus. Narrow band imaging provides clear visualization of the mucosal pit patterns and vascular patterns, which improve the diagnostic value for specialized intestinal metaplasia. Esophageal capsule endoscopy is a new potential tool which allows a direct noninvasive visualization of esophagus. Research efforts are currently directed towards risk stratification of patients and biomarkers have been developed to predict development of esophageal adenocarcinoma. Recent studies have reported that frequent loss of heterozygosity (LOH) as well as allelic imbalances in chromosomes in esophageal adenocarcinoma. Fluorescent in situ hybridization technique which uses fluorescently labeled DNA probes to detect chromosomal alterations in cells obtained from cytology specimens has been developed. It showed more sensitive and specific for abnormalities than PCR based techniques. Currently, many studies support the concept of endoscopic elimination of dysplastic lesions in the esophagus by a mucosal ablation therapy. Photodynamic therapy and radiofrequency ablation are recently developed, emerging techniques.

Summary—Recent advances in screening, prognostication and therapy for esophageal adenocarcinoma in Barrett's Esophagus have brought a significant new insight in clinical practices and will eventually ensure better patients outcomes.

Keywords

narrow band imaging; esophageal capsule endoscopy; fluorescent in situ hybridization; photodynamic therapy; radiofrequency ablation

Introduction

Barrett's esophagus (BE) is defined as a condition in which normal squamous epithelium of the distal esophagus is replaced by incomplete intestinalized columnar epithelium (1,2). The metaplasia has always been viewed as a complication of excessive esophageal mucosal

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damage caused by symptomatic gastroesophageal reflux disease (GERD). It was thought that generally a subset of patients with severe reflux-induced esophagitis develops metaplastic columnar epithelium and even a smaller group of these patients eventually develop dysplasia and finally, at the top of the large iceberg, a very small number would go on to develop esophageal adenocarcinoma (EAC) (3). A large cohort study recently reported the incidence of BE over 2 years was 0.5% to 1.4% for patients with GERD and 5.8% for patients with severe forms of esophagitis (4). Despite the advent of proton pump inhibitors and truly effective forms of acid suppression, the BE rates continue to increase. Along with this, EAC incidence rates rose from 1975 through 2004 among white men and women in all stage and age groups (5). This seems to occur irregardless of the presence of symptomatic GERD. The lack of symptomatic GERD even with progression disease has been a factor in decreasing the enthusiasm for surveillance. There is no longer an easily identifiable group to screen for BE.

One attenuating factor with EAC is the apparently relatively low risk of progression to adenocarcinoma in patients with BE at approximately 0.5% per year (6–9). Although this seems small, there are problems with this information. The first is that cancer risk is unevenly spread in any given subject's Barrett's lifetime (10). The evolution towards cancer seems to be weighted towards the first year after diagnosis with high-grade dysplasia and much lower after this. One explanation that has been proposed for this has been that the cancer may be present but just difficult to detect. This is supported by the stability of patients with lesser degrees of dysplasia. The development of EAC in patients with BE is not easily determined since our past methods depended on random biopsies that are difficult for the detection of cancer. The second consideration is that there are a very large number of patients that are at potential risk of BE and there does not seem to be an overwhelming number of cases. The majority of those patients with GERD symptoms do not progress to cancer (11).

In favor of surveillance and screening is the need to detect cancer at an early stage. Once the cancer has penetrated into the submucosa, our group has found that there is about a thirty percent chance of metastasis to regional lymph nodes (12). Although surgical resection for cure in cancer that is confined to the muscularis propria or above is still reasonable at about 97%, the problem is the esophagectomy can be quite invasive with mortality rates of up to 20% depending on the volume of esophagectomies performed at a given institution (13,14). Given these considerations, it seems reasonable for gastroenterologists to focus on early diagnosis of BE and surveillance for very early staged EAC in patients with BE.

Screening

Screening for BE is promoted on the basis that detecting lesions at a risk of development of a neoplasia can lead to reducing an incidence of cancer and lead to a possible better outcome. However, the most recent guideline from the American College of Gastroenterology states that screening for Barrett's esophagus remains controversial because of the lack of documented impact on mortality from adenocarcinoma (15). The concept of lead time bias influences this recommendation (Fig1). Controversies including who, when, how and how often to screen for the presence of BE are also frequently raised. Although GERD is thought to be essential to the pathogenesis of BE, a screening program which targets only patients with GERD symptoms can unfortunately have a limited impact on mortality of EAC (16). It appears the majority of EAC develop in the BE (17–19), but a significant proportion of patients with BE will not be found if screening is based only on symptoms of GERD. This does raise the issue of asymptomatic but nonetheless clinically important GERD. The fact that neoplasia can arise despite denial of any GERD symptoms is

troubling and further questions the strategies that have suggested in the past such as screening endoscopy.

Standard endoscopy with biopsy is the “gold” standard of establishing a diagnosis of BE at this point although it has several limitations as a screening tool including its low negative predictive value, risks, issues with patient compliance and in our current environment, especially cost. One study that investigated the endoscopist’s ability to predict the presence of BE at the index endoscopy, the positive predictive value was only 34 % using standard endoscopy (20). The negative predictive value of a white-light endoscopy does not appear to meet the satisfactory level for an appropriate screening method at this point either. The detection of the lesion is difficult since it is based on the subtle mucosal changes but new imaging modalities have been developed as adjuncts to a white light endoscopy for better visualization of the mucosal changes.

Narrow band imaging (NBI) allows clear visualization of the mucosal pit patterns and vascular patterns in combination with optical magnification. Several studies have been conducted to evaluate its utility for detection of specialized intestinal metaplasia (SIM) in BE. Kara et al. evaluated the mucosal morphology in non-dysplastic BE and high-grade dysplasia (HGD) in BE using NBI with magnifying endoscopy from 198 sites in 63 patients (21). They found that regular mucosal/vascular patterns were associated with non-dysplastic BE while irregular mucosal/vascular patterns and abnormal blood vessels were associated with HGD. They also demonstrated that the negative predictive value of NBI with magnification for HGD was 98%. Sharma et al. assessed the role of NBI for prediction of histology during screening endoscopy from 204 mucosal patterns and 133 vascular patterns in 51 patients with BE (22). In this study, they correlated NBI images with histology in a prospective, blinded manner and found that irregular mucosal/vascular patterns predicted the presence of SIM. These studies were conducted at a referral center and it must be remembered that positive and negative predictive value is dependent on the underlying prevalence of disease in the population. We have no data on intra- and interobserver agreement from the studies reported and a standardization of the definition of mucosal/vascular patterns for NBI that can be interpreted by non-experts is also needed before NBI can be routinely implemented as a reliable screening tool.

The problems with screening using standard endoscopy are primarily related to the costs. The costs of screening for almost an estimated 90 million Americans is substantial and it is unclear if the yield would be worth the expenditure (23). It is clear that widespread screening cannot be conducted unless the costs were decreased and the negative predictive value of the evaluation increased.

Esophageal capsule endoscopy (ECE) might help to overcome these challenges. ECE is a new technique that allows a direct noninvasive visualization of the esophagus and potential for diagnosis of suspected BE. The Pillcam ESO video capsule (Given Imaging Ltd, Yoqneam, Israel) is a dual-camera wireless capsule endoscope developed specifically for esophageal visualization. There are two similar prospective blinded studies evaluating the diagnostic accuracy of this new ECE for diagnosis of BE using histologically confirmed BE as the gold standard. One study which included 66 screening patients with GERD and 24 surveillance patients with BE reported that sensitivity and specificity of the ECE was 67% and 84%, respectively with negative predictive value of 98% for BE (24). Another study of a total of 94 patients with GERD symptoms and who underwent BE surveillance reported that the sensitivity and specificity was 78% and 75%, respectively with negative predictive value of 79% (25). For the purpose of accurate screening of BE by using ECE, it is critical to visualize the esophagogastric junction. String-capsule endoscopy (M2A, Given Imaging Ltd, Yoqneam, Israel) has recently introduced. The M2A capsule to which strings attached in

order to be able to control its movement up and down in the esophagus provides multiple endoscopic images in an operator-dependent procedure. In a feasibility study with a total of 50 patients with BE (mean Barrett's length of 4.47 centimeter), all patients were correctly diagnosed with this technique (26). The same group of investigators subsequently conducted a prospective blinded study of consecutive patients with GERD symptoms who were referred for screening of BE. In the study, 27 patients had histological confirmation of BE (21 with short segment, 6 with long segment). The sensitivity, specificity and negative predictive value of the M2A for BE when using histological diagnosis as the criterion standard was 93.5%, 78.7% and 96% respectively, compared with 87.1%, 68.9% and 91.3% respectively, of EGD. Moreover, the sensitivity, specificity and negative predictive value of the M2A for short segment BE was 92%, 78.7% and 96%, respectively compared with 84%, 68.9% and 95.5%, respectively with EGD (27). The string attached ECE appears to solve a major drawback for the use of ECE which is its unreliable transit time past the esophago-gastric junction. There have only been preliminary studies that analyzed the cost-benefit and cost utility of screening for BE with capsule endoscopy and these analysis have concluded that thus far, EGD is still the preferred cost-effective strategy (28,29). The reason this occurs is also dependent on the underlying rate of detection of BE which would necessitate an EGD for histological analysis.

Prognostication

There has been an attempt to diagnose patients who are progressing to adenocarcinoma in BE based on the realization of the association between BE and EAC. Endoscopic surveillance for patients with BE is recommended due to this evidence. It is thought that BE sequentially progresses from SIM through to low-grade dysplasia (LGD), to HGD and to EAC (30). This stepwise progression appears to make it suitable for endoscopic surveillance program. However, this smooth transition is hampered by sampling error created by the dependency of dysplasia detection on random sampling and interpretation error created by the lack of agreement among even expert pathologists of the diagnosis of dysplasia. In addition, it is very difficult to conduct reasonable validation of recommendations for surveillance since the progression rates of 0.5% of patients with BE per year are so small that very large numbers will be required to achieve sufficient statistical power to validate prognostic markers (31).

Research efforts are currently directed towards risk stratification of patients. Given the apparent spottiness of involvement of BE by dysplasia, it is clear that new biomarkers will need to be developed. Biomarkers need to be developed that can predict development of EAC with reasonable negative and positive predictive values to allow better usage of resources for surveillance. It has been established that histological changes in general are accompanied by alterations at the molecular level. Molecular studies have found that frequent loss of heterozygosity (LOH) as well as allelic imbalances in chromosomes in EAC. Those reports demonstrated that a sequential accumulation of alterations and microsatellite changes as metaplasia progresses to EAC (32–35). p53 and p16 are the two best accepted gene abnormalities as a biomarkers to predict progression of the BE. Early follow-up study of cohort of 23 patients whose biopsy-specimens were stained for p53 protein on both baseline and follow-up visit reported that p53 abnormalities were associated with a neoplastic progression in BE (36). A recent prospective study has evaluated 269 patients with BE using a baseline characterization of p53 LOH as a predictor of progression. This prospective study reported that the prevalence of p53 LOH at baseline increased from 6 % in negative for dysplasia to 57% in HGD ($p<0.001$). Patients with p53 LOH had increased rates of progression to cancer (relative risk [RR] =16, $p<0.001$), HGD (RR = 3.6, $p<0.001$) (37). p16 tumor suppressor gene has also been evaluated and it is thought that its alteration is involves early in molecular progression to EAC (38,39). The effect of a loss of p16

function is to allow cyclin D1 to bind the replication complex and promote the transition from G1 phase to S phase of the cell cycle. When p16 is intact, cyclin D1 alteration is a key cell cycle checkpoint for tumor progression. A polymorphism of the gene which codes cyclin D1 was reported to be associated with increased risk for EAC in a prospective case-control study (40). More recently there have been prospective studies using combinations of biomarkers to predict cancer progression. Maley et al. examined p53 lesions, p16 lesions and DNA ploidy abnormalities in a cohort of 267 patients with BE who were followed prospectively. The study showed that the size of clones with p53 LOH (RR = 1.27; 95% C.I. 1.07–1.50) or ploidy abnormalities (RR = 1.31; 95% C.I. 1.07–1.60) predicted progression to EAC while the size of a clone with a p16 lesion was not significant predictor of EAC when p53 LOH status was controlled (41). Chao et al. tested p53 as a predictor of progression of a cohort of 276 patients without detectable aneuploidy because aneuploidy has already been associated with a high risk of progression to EAC. The study reported that bi-allelic inactivation of p53 was associated with elevated 4N fractions, which had been associated with the future development of EAC (42).

Another molecular diagnostic technique, is fluorescent in situ hybridization (FISH). FISH is a technique that uses fluorescently labeled DNA probes to detect chromosomal alterations in cells. FISH is usually used in cytology specimens and abnormal cells contain chromosomal alterations is rationale for FISH (43). Generally, FISH is more sensitive and specific for abnormalities than PCR based techniques since it only requires a sample size as small as 50–100 cells. Recently different sets of probes were assessed for the detection of dysplasia and EAC in patients with BE and the study showed a probe set consisting of probes to 8q24 (c-myc), 9p21 (p16), 17q11.2 (HER-2/neu), and 20q13.2 had a sensitivity and specificity, respectively, of 70% and 89% for LGD, 84% and 93% for HGD, and 94% and 93% for EAC (44). Subsequently, another study compared the utility of this FISH probe set to DNA ploidy analysis with digital image analysis (DIA) for the detection of dysplasia and EAC in 92 patients undergoing endoscopic surveillance. In the study, the sensitivity of DIA and FISH for LGD was 5% and 50%, respectively; for HGD, 45% and 82%, respectively; for EAC, 45% and 100%, respectively. FISH was more sensitive than DIA for LGD, HGD and EAC ($p < 0.05$) and all patients with a polysomic FISH result ($n = 33$) had HGD and/or EAC within 6 months (45). This technique is promising in the detection of dysplasia and EAC and has potential to predict which patients are likely to progress advanced lesions even without visible mucosal abnormalities. This test also has the advantage of using a technology that is already CLIA certified meaning it can be reimbursed for by Medicare. Moreover, the esophagus is suitable for a cytology technique because of its characteristic of lumen organ. A prospective study is ongoing to validate the utility of FISH for a tool for prognostification of patients with BE in the clinical management.

Treatment

In the light of management of patients with BE, most therapy is focused on HGD. HGD is associated with a 30 % risk of cancer development. HGD represents a threshold for intervention whereas LGD often just requires frequent endoscopic surveillance by a recent guideline (15). This is based primarily on the risk of progression to cancer. Esophagectomy is a curative therapy for HGD and is based on the assumption that endoscopic surveillance may miss early cancers prior to development of incurable advanced cancers. However, despite the technical advance of surgical procedures, esophagectomy is still associated with a considerable perioperative risks especially for the elderly. A recent retrospective study compared the long-term survival of 199 patients with HGD treated with endoscopic treatment and surgical treatment. The study found that the overall mortality were similar between the two groups (9% versus 8.5%) at about 59 months of follow-up but there were no esophageal cancer related deaths in either groups (46). This study supports the concept of

endoscopic elimination of dysplastic lesions in the esophagus by a mucosal ablation therapy. Recently developed techniques include photodynamic therapy(PDT) and radiofrequency ablation (RFA). There is no good evidence that low-risk patients will benefit from endoscopic ablation therapies to diminish the risk of EAC and such interventions may not be indicated in the routine clinical setting at the present time (15).

The basis for PDT is the propensity of certain photosensitizers (chemicals) to bind in the area of neoplastic tissue and can produce cell death when exposed to intense white or specific wavelength laser light. It employs administration of an intravenous photosensitizing drug followed by application of a specific wavelength of light emitted from a light fiber two days following, leading to intracellular non-thermal cellular damage and vascular thrombosis and necrosis (47). Initially a follow-up (mean 19 months) study of 100 patients with HGD and superficial cancer reported an elimination of mucosal dysplasia and superficial cancer (48). This led to the first randomized controlled treatment trial in BE with HGD. In the study, 208 patients were randomized on a 2:1 basis to compare PDT using porfimer sodium (POR) plus proton pump inhibitor (PPI) with PPI only. The study showed that there was a significant difference ($p < 0.0001$) in favor of ablation group (77%) compared with non-ablation group (39%) in complete elimination of HGD noted at any time during the follow-up surveillance. The study also reported that the occurrence of EAC in PDT group (13%, $n = 18$) was significantly lower ($p < 0.006$) compared with the non-PDT group (28%, $n = 20$) (49). This 2-year trial was followed up for 3 more years. At 5 years PDT was also significantly more effective than PPI in eliminating HGD (77% versus 39%, $p < 0.0001$). There was a difference ($p = 0.27$) of the likelihood of cancer occurrence in PDT group (21/138, 15%) compared with non-PDT group (20/70, 29%), with a significantly ($p = 0.04$) longer time to progression to cancer favoring PDT group (50). Unfortunately, there are several complications associated with sodium porfimer based PDT. The first is PDT with this drug produces esophageal stricture. It occurs in less than 20% of patients who had a single treatment in our series and is more common with serial treatments and focused treatment of localized lesions. It is fortunate that most respond to serial esophageal dilation therapies and aggressive PPI therapy for several months. The second is the cutaneous phototoxicity. Patients should avoid bright light and wear light protective for at least 30 days after drug injection. Although there is no data of the maximal numbers of the application of PDT for a patient safety, the number is limited by consensus.

RFA (HALO³⁶⁰, Barrx Medical, Inc, Sunnyvale, California) was developed for circumferential ablation in the esophagus. The HALO³⁶⁰ system contains a radiofrequency generator with a foot pedal, an esophageal sizing balloon and ablation balloons in different sizes. After an initial endoscopy to locate the lesion for ablation, a 4-cm sizing balloon is passed into esophagus which can be activated by a foot pedal and inflated to an appropriate pressure. The balloon inflation machine then recommends the correct sized balloon. Then the ablation balloon is placed in the esophagus using the endoscope for visualization during therapy (51). In an initial dose-response and efficacy study of total 102 patients (no one had prior EMR), 70% ($n = 48/69$) of patients achieved complete response ([CR], defined as all biopsy fragments negative for BE for endoscopy follow-up) at a 12 months with mean sessions required of 1.5 (52). This study extended up to 30 months and reported that CR was achieved in 60 of 61 available patients at 2.5 years after ablation therapy (53). Recently a multicenter study of RFA for patients with HGD has been concluded. In the study, 92 patients (17% of patients had prior EMR) had at least 1 follow-up biopsy session at a mean follow-up of 12 months. The study reported that complete elimination of HGD, any dysplasia, and intestinal metaplasia were 90.2% of patients, 80.4%, and 54.3%, respectively (54). In these studies, only one patient reported an asymptomatic stricture and no other serious adverse events occurred. These ablation techniques appear promising, however there has been a concern regarding the widespread use of ablation. After the tissue is destroyed, it

is replaced by a squamous lining, especially in a nonacid environment. There is a concern that buried glands, a phenomenon in which BE tissue is hidden underneath the squamous lining could happen. Patients who have dysplastic or neoplastic cells beneath the squamous tissue could be missed by visual inspection and are at potential risk for an advanced EAC. More recently, a study to assess the prevalence of squamous overgrowth and degree of subsquamous dysplasia or cancer in patients with HGD treated with PDT has been published (55). Patients in the 5-year randomized controlled trial of PORPDT plus PPI with PPI (50) were assessed histologically. The study reported that the highest grade of neoplasia per endoscopy was not found exclusively beneath squamous mucosa in any patients and there was no significant difference ($p>0.05$) in squamous overgrowth between groups when compared per patients or per biopsy. There has not been a similar data assessed in the RFA trial yet. As a general rule, endoscopic ablation therapy requires careful surveillance even if successful elimination is obtained. Anecdotal reports of adenocarcinoma occurring after successful ablation therapy have found that this can happen up to seven years after initial therapy. The important aspect of ablation therapy is therefore to select the patients who should most appropriately be treated by this modality and are compliant with treatment recommendations. EMR still remains the mainstream of endoscopic treatment for suspicious lesions in HGD, and combining EMR of visible lesions followed by an ablation of residual HGD lesions therefore seems to be the ideal treatment in the future direction.

Conclusion

The increasing incidence of EAC and its high mortality rate is very alarming. Earlier detection of the suspicious lesions through an appropriate screening technique is an important clinical goal. Standard endoscopy with biopsy is the current standard of screening but recent studies have found NBI has potential to add more conscious visualization of BE for screening. ECE is a new technology that has potential to provide a non-invasive diagnosis, however the sensitivity and specificity of ECE is still not sufficient to recommend its use for screening. The goal of surveillance is to diagnose an early stage of EAC and to intervene in order to prevent progression to a fatal cancer. We always face the dilemma of the conflicting facts that the low rates of incidence of EAC arising from BE but also the high mortality rates of the advanced EAC in patients in which the cancer is not found early enough. At the current time, an appropriate method of risk stratification of patients with BE for esophageal cancer risk remains to be established. Recently developing diagnostic modalities for a prognostication may provide better outcomes of screening and surveillance for EAC. Biomarkers have the potential to identify individuals that are at risk for developing EAC from those patients with BE that will not develop cancer. FISH has shown its promising data regarding risk stratifications of BE and EAC. Future studies are needed to determine if biomarkers will replace histology in the determination of cancer risk. HGD appears to be the most reasonable point at which intervention is currently required. Endoscopic therapy seems to be a reasonable option in most patients with HGD. We have been moving to the concept of entire elimination of suspicious lesions with EMR first for diagnostic as well as therapeutic goals. The EMR can identify the cancer as well as determine the depth of invasion. The remainder of the Barrett's segment can be eliminated with a mucosal ablation technique such as PDT or RFA with RFA having the least complications. RFA is an emerging technique and has potential to provide a good option for mucosal ablation, although the randomized trial data have not been published at this point.

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squamous overgrowth and degree of subsquamous dysplasia or cancer in patients with HGD treated with PDT trial. It reported the highest grade of neoplasia was not found beneath squamous mucosa in any patients and there was no significant difference in squamous overgrowth between PDT-group and non PDT-group.

Figure 1.

Lead time bias refers to two patients, A and B, who develop cancer at the same time and are destined to die at the same time. If one is detected earlier through screening, even though the disease runs the same course, it leads to an apparent increase in survival. Screening programs are susceptible to this bias.

Figure 2.

Treatment algorithm for Barrett's esophagus. Non-dysplastic Barrett's esophagus rarely has genetic abnormalities and is unlikely to progress. It would be beneficial to conduct surveillance in these patients only if there were reasonable expectations for good quality of life. Low-grade dysplasia should be confirmed by another expert pathologist. There are no good studies to demonstrate efficacy of therapy and treatment should probably be done at this time in the context of clinical trials. Surveillance is more reasonable in this group given the higher risk of cancer. High-grade dysplasia should be evaluated carefully for evidence of cancer with endoscopic mucosal resection of any mucosal abnormalities. Treatment options are open to the needs of the patient, the experience of the physicians, and the length of the Barrett's esophagus. Further surveillance, endoscopic ablation, and esophagectomy would be reasonable options.

Fig 3.
simplified schema of molecular alterations in metaplasia-dysplasia-carcinoma sequences of Barrett's esophagus