REVIEW

Barrett's Esophagus in 2008: an Update

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Abstract: With the rising incidence and overall poor prognosis of esophageal adenocarcinoma (EA) there is great interest in furthering our understanding of Barrett's esophagus, the precursor lesion for most cases of EA. The best available evidence from true population-based analysis suggests that the prevalence of Barrett's is 1.6%. In addition, nearly half of the patients with Barrett's are asymptomatic. Several risk factors for development of Barrett's have been identified including gastro-esophageal reflux disease (GERD), central obesity, H. pylori eradication, and male gender. The precise incidence of progression from Barrett's to esophageal adenocarcinoma is not known, but it probably is less than 0.5% per year, and our ability to predict who is at highest risk for progression remains poor. The degree of dysplasia is currently used as a marker for risk of progression to cancer though there is increasing evidence that biomarkers and level of genetic instability may provide better predictive measures. Intensive acid-suppression and COX-2 inhibition are potential strategies to reduce the risk of progression, though definitive studies are needed. Endoscopic surveillance remains the mainstay of management for non-dysplastic and low grade dysplasia Barrett's. The advent of various endoscopic ablative therapies has provided a promising alternative to surgery for Barrett's patients with high grade dysplasia (HGD). (Keio J Med 57 (3) : 132–138, september 2008)

Key words: Barrett's, High Grade Dysplasia, Barrett's Surveillance

Introduction

Over the last 40 years, there has been a progressive rise in the incidence rate of esophageal adenocarcinoma in Western countries, and it now represents the most common form of cancer of the esophagus in the United States. This rise in incidence has affected whites and blacks of both sexes, though men are 6 to 8 times more likely to develop esophageal adenocarcinoma than women, whereas whites are at a 3 to 4 times higher risk compared to blacks.[1] On the positive side, our ability to detect disease at earlier stages has seen some improvement over the past few decades with decreases in percentages of distant or regional tumors and increases in cancer *in situ*.[2] However, survival after diagnosis of esophageal adenocarcinoma remains poor despite advances in our diagnostic and therapeutic endoscopic armamentarium. One and five year survival rates for esophageal adenocarcinoma have increased over the past 30 years, though they still remain dismal: 44% and 13% respectively. The rising incidence of esophageal adenocarcinoma and its quite poor prognosis at the time of diagnosis have led to increasing interest in preventative strategies. Barrett's esophagus is thought to be the precursor lesion in most cases of esophageal adenocarcinoma, and a better understanding of this predisposing lesion could lead the way to reducing the incidence and morbidity and mortality associated with adenocarcinoma of the esophagus.

Definition of Barrett's

Barrett's esophagus was first recognized in the early

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1950's with the advent of endoscopic visualization techniques and the condition was first termed "congenitally short esophagus pulling stomach into chest." The definition of Barrett's progressed through multiple variations over the ensuing years until the consensus definition of intestinal metaplasia of the distal esophagus of any length was formulated in the 1990's. Metaplasia is sometimes subdivided according to the Japanese nomenclature as incomplete or complete based on the presence (complete) or absence (incomplete) of digestive enzymes. It is felt that incomplete metaplasia occurs later in the transformative process in the esophagus and may be an indicator of increased risk for high grade dysplasia or cancer risk.[3] Endoscopic characterization of Barrett's lesions has undergone further evolution. Previous attempts to develop a standardized reporting system led to a classification scheme which described lesions as short (<3cm) or long (>3cm) segments. This method of reporting is common in the literature, with long segment Barrett's felt to be associated with a higher risk of progression to esophageal adenocarcinoma. However, there is wide variability in this reporting system and the length of an individual lesion does not sufficiently describe the burden of disease. A recent international working group was formed to address this issue and developed a new classification system which is comprised of the circumferential and the maximal extent of esophageal columnar tissue, the Prague C and M criteria.[4] Future investigations utilizing these new criteria will need to be done to assess its reporting variability and ability to discriminate patients at higher risk for progression to esophageal adenocarcinoma.

Prevalence of Barrett's

The true prevalence of Barrett's esophagus in the general population is not known with certainty due to few existing population-based studies. One study from the United States investigated a cohort of 961 patients over the age of 40 undergoing colonoscopy and reported a prevalence of Barrett's esophagus of 6.8% in all patients.[5] The only true population-based study of 1000 Swedish volunteers found a prevalence of Barrett's of 1.6%.[6] Studies from Asia suggest an overall lower prevalence compared to Western countries. Two recent prospective studies in Japan found a prevalence of 0.4 to 1.2% of Barrett's esophagus among patients undergoing upper endoscopies for various indications.[7] Among patients presenting with symptoms, prevalence rates of 2% to 3% have been reported in the Asian literature.

Screening for Barrett's

An effective screening program for Barrett's would result in early detection of the condition or a cancerous lesion and lead to either intervention or surveillance, which would decrease the incidence of esophageal adenocarcinoma or cancer-related deaths. The low prevalence of Barrett's esophagus in the general population makes this condition unfavorable for screening with upper endoscopy in the general population and The American Gastroenterological Association Chicago Workshop in 2003, failed to endorse routine screening for Barrett's with upper endoscopy due to a lack of well-designed and controlled studies demonstrating an improvement in outcome with screening protocols.[8] Targeted screening of patients at higher risk for development of Barrett's has been considered and The American of College of Gastroenterology Practice Guidelines for Barrett's Esophagus states, "Patients with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo upper endoscopy.[9]" Several studies suggest that screening of older male patients with GERD symptoms may be cost-effective.[10–11] However, it remains unclear who is most likely to benefit from a targeted screening protocol since a large percentage of patients with incident cases of Barrett's do not report GERD symptoms and it remains difficult to predict those patients with Barrett's who will progress to high grade dysplasia or cancer. Thus, screening for Barrett's remains controversial. However, if the prevalence of Barrett's and esophageal adenocarcinoma continue to rise, we may see a shift in the pendulum favoring screening protocols in the future. Esophageal capsule endoscopy (ECE) has attracted interest in its use for screening and surveillance for Barrett's due to its less invasiveness, lack of sedation and decreased complication rate. One recent study by Lin *et al*. evaluated the operating characteristics of ECE for detection of Barrett's in 96 patients and found ECE was only 67% sensitive and 84% specific for identifying Barrett's esophagus.[12] Two recent studies compared traditional upper endoscopy vs ECE for Barrett's screening. In both studies, use of ECE for screening was found to be less effective and more expensive than traditional upper endoscopy screening.[13–14]. Based on the data gathered to date, ECE does not have a clear role in Barrett's screening.

Risk Factors for Barrett's

Gastroesophageal Reflux Disease

Several risk factors for the development of Barrett's esophagus and esophageal adenocarcinoma have been identified. Gastro-esophageal reflux disease (GERD) duration and severity are associated with risk for Barrett's and esophageal adenocarcinoma. Compared with patients with symptoms of GERD for less than 1 year, the odds ratio for Barrett's esophagus in patients with GERD symptoms for 1-5 years was 3.0 and increased to 6.4 in

patients with symptoms for more than 10 years.[15] In the study by Rex *et al*. reporting of heartburn symptoms was more common among those with long-segment Barrett's (55%) than those with short-segment Barrett's (13%) suggesting that greater burden of disease may be more likely to be symptomatic.[5] Consistent with these data, in a Swedish study of 451 cases of esophageal adenocarcinoma, the risk of cancer increased with increasing frequency and duration of GERD symptoms[16] Despite this strong association several recent studies have demonstrated that a substantial number of patients with Barrett' s and esophageal adenocarcinoma do not report heartburn symptoms. In the study by Ronkainen *et al*, 43% of identified cases of Barrett's did not report heartburn symptoms.[6] Findings from a recent trial in which Barrett's esophagus was detected in 25% of asymptomatic patients undergoing colonoscopy lend further support to the fact that development of Barrett's can be asymptomatic.[17] Data from a systematic review of incident esophageal adenocarcinoma cases found the prior prevalence of Barrett's at the time of surgical resection as low as 5% suggesting that a large number of patients with underlying Barrett's are going undetected prior to the development of adenocarcinoma.[18] The data taken together suggest two likely explanations: 1. Patients with preceding GERD symptoms are not being screened appropriately and 2. A significant proportion of patients are asymptomatic at the time of diagnosis of Barrett's and esophageal adenocarcinoma. It remains uncertain whether patients who do not report symptoms truly do not have GERD, or if they have GERD without symptoms. Furthermore, it is unclear if Barrett's in the absence of GERD symptoms carries the same risk as symptomatic Barrett's.

Obesity

The rise in incidence of Barrett's and esophageal adenocarcinoma mirrors the obesity epidemic in Western countries. This temporal relationship has generated interest in a possible link between the two conditions. In a Swedish study of 189 cases of newly diagnosed esophageal adenocarcinoma, a strong positive association was found between BMI and esophageal adenocarcinoma when controlling for GERD symptoms.[19] A study from the Veterans Association in the United States found those with a BMI > 30 had a 4 fold greater risk for Barrett's esophagus when compared to controls with a BMI < 25. Central obesity in this study was independently associated with Barrett's esophagus when controlling for BMI suggesting that central obesity, and not only BMI, was the link with Barrett's esophagus.[20] More recently, Corely *et al*. found that waist circumference, but not BMI, had modest independent associations with the risk of Barrett's esophagus and Edelstein *et al*. found higher waist to hip ratios to be associated with Barrett's esophagus when adjusted for GERD symptoms and BMI.[21–22] Thus, it appears central adiposity may play a role in the development of Barrett's esophagus and esophageal adenocarcinoma, independent of GERD symptoms and BMI. Further investigation is needed to determine the pathophysiologic mechanism underlying this association.

Male Sex

There is a clear gender difference in the prevalence of Barrett's, with men outnumbering women by 8 fold. This gender difference is attenuated in the progression to esophageal cancer with a male:female ratio of only 2:1 being observed. The gender difference observation raises the possibility of a protective effect of estrogen or perhaps, a deleterious effect of androgen in Barrett's development and/or progression. However, small studies investigating childbearing status, hormone replacement therapy or antiandrogen therapy[23] have found these to be non-protective factors. Further investigation is needed to determine the underlying mechanisms leading to these gender differences.

Helicobacter pylori eradication

Several studies have looked at the role Helicobacter pylori infection may play in Barrett's esophagus and esophageal adenocarcinoma. Two main mechanistic roles for formation of Barrett's and esophageal adenocarcinoma have been postulated for H. pylori infection: 1. Induction of atrophic gastritis which results in less gastric acid secretion and 2. Neutralization of the gastric acid by ammonia production independent of gastric atrophy. Ye *et al*. found Cag-A positive H. pylori infection to be associated with a significantly reduced risk of esophageal adenocarcinoma (OR 0.3), however this association was independent of gastric atrophy and suggested a mechanism other than a less acidic gastric refluxate.[24] As the prevalence of H. pylori infection falls throughout the world, particularly in countries like Japan, it remains to be seen if this will lead to an increase in incidence for Barrett's esophagus and esophageal adenocarcinoma.[7] Additional factors likely play a role in development of Barrett's esophagus and adenocarcinoma. Duodenal reflux, smoking, and alcohol have all been linked to these conditions and further investigation is needed to identify additional risk factors.

Progression of Barrett's to Esophageal Adenocarcinoma

Incidence of Progression

Early studies reported 5% to 10% of patients diagnosed with Barrett's esophagus develop esophageal adenocar-

cinoma over their lifetime.[25–26] Predicting who is likely to progress from Barrett's esophagus to dysplasia and adenocarcinoma is difficult and this uncertainty has lead to acceptance of surveillance protocols in patients with documented Barrett's esophagus. Adequate evaluation of the cost-effectiveness of these surveillance practices requires knowledge of the true incidence of progression from Barrett's to cancer. However, the true incidence of progression in this population is uncertain for several reasons. First, no longitudinal study has included asymptomatic Barrett's patients. Second, the risk of adenocarcinoma of the esophagus in asymptomatic patients is unknown. Lastly, it is unlikely that the risk of progression to adenocarcinoma is constant for each year in a patient with Barrett's. Prior studies evaluating the reported incidence of adenocarcinoma in the Barrett's population have noted a paucity of studies with small sample sizes reporting lower incidence rates.[27] One explanation for this observation is publication bias. Alternatively, heterogeneity in study factors such as patient risk, surveillance rigor, validity of Barrett's diagnosis, and follow up may also play a role in the observed inverse relationship in study size and reported cancer risk.

Predictors of Progression

The current management strategy for prevention and early detection of cancer in patients with Barrett's esophagus is targeted at detection of dysplasia as it is felt to provide information on the likelihood for progression to cancer. However, low grade dysplasia is non-specific for cancer and is associated high inter-observer and intra-observer variability. Due to these limitations, its significance regarding risk of progression to adenocarcinoma is uncertain. Alternatively, the finding of high grade dysplasia has lower inter-observer and intra-observer variability and estimates suggest that 30-50% of these cases harbor concurrent cancer. Thus, a histologic finding of high grade dysplasia is felt to carry a significant likelihood of progression to cancer though overall it is an imperfect measure of cancer risk.

Dysplasia is the phenotypic expression of underlying DNA damage and is an intermediate between undamaged cells and cancer. A more useful predictor for the likelihood of progression to cancer would be a marker for the DNA damage which could be detected prior to the expression of dysplasia. Inactivation of the tumor suppressor gene, p53, through a mutation that leads to loss of heterozygosity of 17p is found in 50% to 90% of esophageal adenocarcinoma.[28] Biopsies of Barrett's esophagus have found inactivation of the tumor suppressor gene p16 via methylation, loss of heterozygosity, or mutation in 73%-87% of patients, and there is some evidence that this inactivation is the first genetic lesion in neoplastic progression of Barrett's cells.[29–30] COX-2 over-expression has been detected in Barrett's esophagus as well as esophageal adenocarcinoma and *in vitro* studies have demonstrated reduced rates of apoptosis with overexpression.[31] Aneuploidy is a marker of genetic instability and is defined as a genetic abnormality in which the total DNA content of cells is different from the normal diploid (2n) or tetraploid (4n) amount. Tetraploidy is considered abnormal if it is found in > 6% of cells in a tissue and this condition is referred to as an elevated 4n fraction. Both aneuploidy and elevated 4n fraction conditions were recently evaluated in a large study of Barrett's patients followed over 5 years in which flow cytometry was performed at baseline. In patients with aneuploidy as defined by populations with over 2.7n, the 5 year incident rate for cancer was 64%, whereas patients with an elevated 4n fraction had a 5 year incident rate of 57%. In those with *both* aneuploidy and tetraploidy, the 5 year incident rate of cancer was 75% compared to only 5.2% in patients without either baseline condition, and all patients in the latter group had high grade dysplasia on histology.[32] Further understanding of the mechanisms underlying cancer formation will likely lead the way to identification of additional biomarkers and measures of genetic instability as well as refinement of existing measures with the goal of better predicting those who are likely to progress from Barrett's to cancer.

Management of Barrett's

Surveillance

Once the Barrett's diagnosis is made, the current guidelines from the American College of Gastroenterology (ACG) recommend a surveillance protocol based upon the histologic diagnosis. For Barrett's patients who have no dysplasia on biopsies from 2 endoscopies, surveillance endoscopy should be repeated every 3 years. A patient with low-grade dysplasia (LGD) on biopsy should have repeat endoscopy and if low-grade is confirmed, that patient should undergo repeat endoscopy every year until no dysplasia is observed. For those with high-grade dysplasia (HGD) on biopsy, a repeat endoscopy should be performed to evaluate for cancer and the pathology should be reviewed by an expert gastrointestinal pathologist. Further intervention is determined by the specific findings. In focal high grade dysplasia, follow-up endoscopy is recommended in 3 months. For multi-focal high grade dysplasia, surgery or photodynamic therapy is recommended. And if mucosal irregularity is seen, endoscopic mucosal resection followed by surgery or photodynamic therapy is advised. These recommendations represent the most recent consensus algorithm from the ACG based on the data available at the time it was formulated. It is important to note several shortcomings associated with traditional optical endo-

scopic surveillance. There is a limitation to the biopsy sample size with endoscopy and significant intra and inter-observer variability exists. Technological advances may eliminate some of these limitations. Several new promising techniques include narrow band imaging, chromoendoscopy, high resolution endoscopy, and autofluorescence imaging. However, each of these techniques will need to demonstrate reproducibility, prove to be easily applied, and cost-effective. Improved endoscopic mucosal resection and endoluminal eradication techniques are being increasingly utilized for high grade dysplastic and intramucosal carcinoma lesions and may provide an alternative means to surgery for management of these conditions.

Secondary Prevention

Secondary prevention in Barrett's can be thought of in two parts: anti-reflux surgery and chemoprevention. Anti-reflux surgery has been shown to effectively alleviate reflux symptoms in Barrett's patients. However, the long-term durability of surgery is an ongoing question. Furthermore, reports of post-operative development of dysplasia and cancer in addition to the increasing recognition of a significant percentage of patients who develop Barrett's and esophageal adenocarcinoma without precedent GERD, raise significant questions about the utility of this procedure for secondary prevention.

The most data for chemoprevention in Barrett's focus on acid suppression and COX-2 inhibition. A study using ex vivo Barrett's tissue appears to suggest that complete elimination of acid in the distal esophagus is required in order for acid suppression to have an impact on reducing progression of intestinal metaplasia to dysplasia.[33] Bearing this point in mind, it is important to note that anti-acid therapy sufficient to eliminate symptoms of reflux may not adequately suppress acid exposure in the distal esophagus.[34] In a study comparing proton pump inhibitor (PPI) to Histamine-2 blockers in patients with Barrett's, both were successful in eliminating symptoms of reflux though only the PPI therapy demonstrated nearly complete elimination of acid exposure at the distal esophagus and significant regression in the area and length of Barrett's. Whether acid suppression therapy will reduce the cancer risk in Barrett's will require a prospective randomized control study with a sufficient sample size and follow up time and documentation of abolished acid exposure.

COX-2 expression may affect Barrett's progression through several mechanisms including increasing proliferation, promoting angiogenesis, and increasing the invasiveness and metastatic potential of Barrett's cells. COX-2 overexpression in Barrett's cells leads to reduced apoptosis *in vitro*.[31] Selective inhibition of COX-2 can decrease the rate of proliferation of Barrett's cells as well as esophageal adenocarcinoma cells in an animal model.[35] Though COX-2 inhibition remains an intriguing area of research in the area of Barrett's progression, the cardiovascular risk associated with COX-2 inhibitors recently described[36] may limit the practical applications of these findings.

High Grade Dysplasia or Intra-mucosal Cancer: Endoscopic Therapy or Surgical Esophagectomy

Estimates for risk of progression from high-grade dysplasia (HGD) to cancer vary from 5% to 59% up to 7 years from initial diagnosis.[37–38] Unsuspected carcinoma may be detected at esophagectomy performed for high-grade dysplasia in 40% of cases.[39] Currently, there is no agreement among the United States gastrointestinal society guidelines for management of HGD in Barrett's esophagus. However, it is recommended that whenever HGD is found, it should be confirmed by an experienced gastrointestinal pathologist.

Due to the malignant potential associated with Barrett's lesions with HGD, esophagectomy has traditionally been the recommended treatment for patients with high grade dysplasia or intramucosal cancer who were deemed appropriate surgical candidates. This remains an option for selected patients though multiple studies have confirmed improved outcomes at centers with high surgical volume. Over the past 2 decades endoscopic esophageal mucosal ablative techniques such as photodynamic therapy, argon plasma coagulation, and laser therapy have been utilized for advanced Barrett's lesions. Additionally, endoscopic mucosal resection techniques have been utilized to achieve potentially curative removal of the Barrett's mucosa, allow for histological examination of resections and reduce the morbidity associated with surgical esophagectomy. Endoscopic mucosal therapy is generally reserved for those at highest risk for cancer (HGD or intramucosal cancer) and currently does not have a role in patients with low-grade dysplasia or non-dysplastic Barrett's.

Existing data suggest that coupled with a rigorous surveillance program, mucosal ablative therapy may be a reasonable alternative to surgery in carefully selected patients with HGD. In a Veterans Administration study of Barrett's esophagus, 79 of 1099 (7.2%) of patients were found to have HGD. At one year follow up, 75 of the 79 patients remained cancer free whereas at 7 year follow up, 12 of 79 (16%) developed cancer. 11 of 12 patients were subsequently considered cured with surgical or ablative therapy.[38] In a recent study comparing ablative therapy with photodynamic therapy (PDT)/endoscopic mucosal resection (EMR) to surgical esophagectomy, mortality rates were similar at 9% and 8.5% respectively. 30% of patients in the ablative group had recurrence of HGD with 5.4% progressing onto cancer. Of note,

12.7% of patients in the surgical group had cancer in resected specimen.[40] Ongoing investigations with newer techniques such as radiofrequency ablation and circumferential EMR in addition to combination EMR and thermal methods, should add to our understanding of the utility of endoscopic mucosal ablation for the management HGD. Though at this time, the optimal approach to management of HGD remains controversial.

Conclusion

Barrett's esophagus remains an area of great interest as it is the precursor lesion in most cases of esophageal adenocarcinoma, a malignancy with increasing incidence in Western countries. Several risk factors for Barrett's esophagus have been identified in recent years though further work is needed to improve our ability to detect Barrett's in patients, particularly those who do not report reflux symptoms. Furthermore, additional work is required to determine who with Barrett's will progress to HGD and cancer, and additional studies investigating biomarkers and measures of genetic instability may allow us to more accurately identify those at high risk for progression. The management of HGD remains controversial with many endoscopic ablative techniques available and ongoing studies to evaluate combination therapies and emerging technologies will hopefully add to our knowledge in this area.

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