

PRACTICE GUIDELINES

Updated Guidelines 2008 for the Diagnosis, Surveillance and Therapy of Barrett's Esophagus

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PREAMBLE

The guidelines for the diagnosis, surveillance and therapy of Barrett's esophagus were originally published by the *American College of Gastroenterology* in 1998 and updated in 2002. These and other guidelines undergo periodic review. Significant advances have occurred in the area of Barrett's esophagus over the past four years leading to another revision of the prior guidelines. These advances include the potential use of esophageal capsule endoscopy for the diagnosis and screening of Barrett's esophagus, data regarding the outcome of low-grade dysplasia, the treatment of high-grade dysplasia using photodynamic therapy, and the development of new ablation techniques such as radiofrequency ablation. These guidelines are intended to be applied by physicians who see Barrett's esophagus patients and are intended to indicate a preferred, but certainly not the only, acceptable approach. Physicians need to choose the course best suited to the individual patient and to the variables that exist at the time of decision making. The guidelines are for adult patients with the diagnosis of Barrett's esophagus, as defined herein.

Both these and the original guidelines were developed under auspices of the *American College of Gastroenterology* and the *Practice Parameters Committee* and approved by the Board of Trustees. The world literature was reviewed extensively for the original guidelines and once again reviewed using the National Library of Medicine database. Search terms used included Barrett's esophagus, esophageal neoplasm, esophagus, intestinal metaplasia, esophageal diseases, and adenocarcinoma, all appropriate studies and any additional ones found in reference to these papers were obtained and reviewed. Evidence was available from a hierarchy of trials and randomized controlled trials were given the greatest weight. Abstracts presented at national and international meetings were only used when unique data from ongoing trials were presented. When scientific data were lacking, recommendations are based on expert opinion. The recommendations made are based on the level of evidence found. Grade A recommendations imply that there is consistent level 1 evidence (randomized controlled trials), Grade B indicates that the evidence would be level 2 or 3 which are cohort studies

or case control studies. Grade C recommendations are based on level 4 studies meaning case series or poor quality cohort studies, and Grade D recommendations are based on level 5 evidence meaning expert opinion.

SIGNIFICANCE OF BARRETT'S ESOPHAGUS

Barrett's esophagus continues to be increasingly recognized in the United States and is believed to be the major risk factor for the development of esophageal adenocarcinoma. The incidence of adenocarcinoma of the esophagus continues to rise rapidly. The rate of rise is alarming and is widespread in Western countries.

In a review by the epidemiologists of the National Cancer Institute of cancer incidences normalized to the year 1975, esophageal adenocarcinoma incidence rates were found to outpace even those of melanoma, breast cancer and prostate cancer in terms of the rapidity of rise (1). These epidemiologists also found there was no concomitant decrease in diagnoses of gastric cancers or more proximal cancers, making a classification change unlikely to be responsible for this increase in adenocarcinoma. In the Danish Cancer Registry, adenocarcinoma incidence rates actually decrease in patients older than 85 (14.14/100,00 (80–84 yr) decreasing to 7.2/100,000 (85+ yr)) unlike squamous cancer rates suggesting that this rise in adenocarcinoma incidence may be truly a recent phenomenon as evidenced by this age cohort effect (2).

DEFINITION OF BARRETT'S ESOPHAGUS

Barrett's esophagus is a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus. (Grade B recommendation).

This working definition of Barrett's esophagus has changed little over the last 10 years. A recent "critical review of the diagnosis" of Barrett's esophagus concluded that "the working definition of BE is displacement of the squamocolum-

nar junction proximal to the gastroesophageal junction” and “endoscopy with multiple systematic biopsies is needed to establish the diagnosis of Barrett’s esophagus” (3). This definition does not distinguish between short and long segment Barrett’s esophagus and implies that only columnar lined esophagus should be biopsied. Although intestinal metaplasia is not specifically mentioned in this definition, clearly the reason to do multiple biopsies in the columnar appearing esophagus is to identify the presence of intestinal metaplasia, the premalignant lesion for esophageal adenocarcinoma (EAC). The vast majority of adenocarcinomas of the esophagus are accompanied by intestinal metaplasia in multiple cohort studies (4–8) and many adenocarcinomas of the esophagogastric junction are also associated with esophageal intestinal metaplasia (9–11). The incidence of adenocarcinoma of the esophagus has continued to rise in the United States, at least until the year 2002 (12).

Supporting the primary role of BE as the premalignant lesion for EAC is the unmasking of underlying BE by chemotherapy of adenocarcinoma of the distal esophagus. A retrospective study reviewed 79 patients with locally advanced EAC who had preoperative chemotherapy and had restaging endoscopy and biopsy prior to resection. Pretherapy endoscopy showed BE in 75%, whereas 97% had documented BE on post-chemotherapy biopsy or in the resected specimen (13). This suggests that the cancer overgrows the fertile field of BE so that at presentation of the patient with EAC, BE may no longer be detectable. Esophagitis might also mask Barrett’s esophagus. In a recent study of 172 patients with erosive esophagitis, a full 12% were found to have Barrett’s metaplasia after healing of the esophagitis (14).

There is not universal agreement on the inclusion of intestinal metaplasia as a criterion for BE. The *British Society of Gastroenterology* has excluded the need for IM from the diagnosis of BE (15). It is well recognized that the yield of IM decreases as the segment of columnar lining shortens and fewer biopsies are taken. Repeat endoscopy and biopsy are often necessary to establish the presence of IM (16, 17). In patients with >1cm of columnar lined esophagus at endoscopy, multiple biopsies may be necessary to confidently detect intestinal metaplasia. Based on a recent retrospective study, eight biopsies may provide an adequate assessment of the presence of intestinal metaplasia (18). The issue becomes when to label a patient as having BE and having an increased risk for EAC compared to someone lacking BE. Because of the implication of the label of BE in the United States for obtaining health insurance and the increased cost of life insurance in the United States (19), it seems appropriate to establish the presence of IM before committing the patient to the diagnosis of BE and to surveillance endoscopy. There are no data on the risk of EAC in columnar lined esophagus lacking IM.

Another new development in the endoscopic standardization of Barrett’s esophagus is the Prague classification system of circumferential (CM) and maximal length (M). This system identifies the landmarks of the squamocolumnar junction,

the gastroesophageal junction, the extent of circumferential columnar lining and the most proximal extension of the columnar mucosa excluding islands to determine the length of Barrett’s esophagus. Twenty-nine endoscopists scored 29 videos with centimeter intervals marked on the image (20). The reliability coefficients (RC) for C 0.95, M 0.94, the gastroesophageal junction 0.88 and the location of the hiatus 0.85 were excellent. The overall RC for the endoscopic recognition of BE \geq 1cm was 0.72. However, for less than 1cm of columnar lining the coefficient was only 0.22. In an era of growing endoscopic therapy for neoplastic BE, this standardization is important. Unfortunately, proximal islands of columnar lining and ultra-short BE < 1cm are not included in this schema.

In summary, a strategy to decrease the recent rise in esophageal cancer would be earlier diagnosis of Barrett’s esophagus. The diagnosis should be made with endoscopy and biopsy of columnar lined esophagus only (Grade B Recommendation). Histological changes of intestinal metaplasia (goblet cells) are needed for the diagnosis prior to recommendations of surveillance. Ideally, erosive esophagitis should be healed prior to biopsy to increase the yield and avoid missing short segments of columnar lining (Grade B Recommendation). Endoscopic descriptions of a Barrett’s esophagus should be precise and ideally follow established classification systems (Grade D Recommendation).

SCREENING

Screening for Barrett’s esophagus remains controversial because of the lack of documented impact on mortality from EAC. The large number of patients that lack reflux symptoms but have Barrett’s esophagus provides a diagnosis challenge. The highest yield for Barrett’s is in older (age 50 or more) Caucasian males with longstanding heartburn.

Patients with the highest likelihood of BE are older Caucasian males with chronic reflux symptoms. The challenges to screening for BE include the inability to predict who has BE prior to endoscopy, the lack of evidence based criteria, the invasiveness and expense of endoscopy, and the increasing documentation of a subgroup of patients with BE who lack reflux symptoms. Investigators have attempted to predict BE with clinical and demographic features comparing documented BE patients to patients with GERD lacking BE. Predictors included age >40 (21), heartburn (21–23), long duration GERD symptoms (more than 13 years) (23), and male gender (22). Yet the only consistent correlation in most studies was heartburn and the sensitivity was poor. With the nation’s increasing obesity problems, it is not surprising that increased body mass index is correlated with Barrett’s esophagus, particularly visceral adiposity characterized by CT scan of the abdomen (24). The emerging data on the potential mechanistic role of cytokines from increasing visceral fat will bear watching.

The epidemiology of EAC in the United States identifies risk factors of male gender and Caucasian ethnicity: the annual incidence of EAC in Caucasian men is 3.6/100,000 com-

pared to 0.8 in African American men and 0.3 in Caucasian women (12). The precise magnitude of risk for gender, ethnicity and age are not defined.

Esophageal capsule endoscopy is a new technique that has the potential to provide a noninvasive diagnosis of suspected BE, i.e. a columnar lined esophagus. Early studies of small numbers of patients showing high sensitivity have been followed by data sets in abstract form documenting substantially lower sensitivity (25, 26). Although intriguing, this technique cannot be recommended in the screening setting at this time (Grade B Recommendation). It is anticipated that the cost of the capsule and its accuracy will be barriers to lowering the threshold for screening for BE.

A more definitive estimate of the population prevalence of BE – 1.6% - provides evidence of asymptomatic BE. Forty-four percent of the BE patients from a random sample of adults in 2 communities in Sweden lacked “troublesome heartburn and/or regurgitation over the past 3 months” (27). The inability to distinguish these patients’ poses a major problem in developing an effective screening strategy for BE based upon symptoms. There are no current risk factors recognized to identify asymptomatic patients with BE. Such identification will be necessary before screening can be expected to effectively detect the majority of patients with BE. The natural history of asymptomatic BE is undefined. In summary, screening for Barrett’s esophagus in the general population cannot be recommended at this time. (Grade B recommendation) The use of screening in selective populations at higher risk remains to be established (Grade D recommendation) and therefore should be individualized.

SURVEILLANCE OF BARRETT’S ESOPHAGUS

The grade of dysplasia determines the appropriate surveillance interval. Any grade of dysplasia by histology should be confirmed by an expert pathologist.

Surveillance endoscopy remains controversial because of the lack of randomized trials supporting its value. Critical analysis of the literature does suggest a survival advantage of endoscopic surveillance. Multiple retrospective studies have been published, all of which indicate that survival is statistically enhanced if the cancers are detected by endoscopic surveillance rather than presenting with symptoms (Table 1). In a California community-based population, surveillance detected cancer had lower staging with better survival (28). A larger SEER/Medicare database documented that an EGD 1 year prior to the diagnosis of EAC was associated with earlier stage and improved survival (29).

Surveillance is practiced by the vast majority of endoscopists in the US (30, 31). The strongest rationale for early case detection of EAC is the poor 5 year survival of EAC of 13% even with contemporary therapy (32). A patient with documented BE needs to be assessed as a candidate for surveillance. It is recommended that patients be advised of the benefits and risks of surveillance endoscopy. Consideration for beginning a surveillance program should include

Table 1. Retrospective Surgical Series of Survival for EAC Based on Surveillance Status

Author	Surveillance (N)	No surveillance (N)	P Value
Streitz, et al (81)	62% (19)	20% (58)	0.007
Peters, et al (82)	90% (17)	20% (35)	0.09
vanSandick, et al (83)	86% (16)	43% (54)	0.0029
Incarbone, et al (84)	100% (12)	25% (85)	0.01
Ferguson (85)	84% (12)	19% (68)	0.001
Corley (28)	73% (15)	13% (8)	0.001
Fountoulakis (86)	80% (17)	31% (74)	0.008

age, likelihood of survival over the next five years, patient’s understanding of the process and its limitations for detection of cancer, and the willingness of the patient to adhere to the recommendations (Grade B Recommendation).

Surveillance endoscopy should be performed in patients whose reflux symptoms are controlled with proton pump inhibitor therapy. The goal is healing the esophagitis to reduce the likelihood of the inflammatory process interfering with the visual recognition of BE (14) and contributing to cellular changes confusing the reading of dysplasia. Four quadrant biopsies every 2cm of the Barrett’s mucosa sample only a small fraction of the lining but offer the possibility of recognizing dysplasia. Ideally the biopsies from a given segment of Barrett’s esophagus should be submitted to pathology in a separate container to enable the focusing of subsequent biopsies on the area if dysplasia is identified. Cost effectiveness studies are needed to evaluate this approach. Even if the initial two endoscopies within one year lack dysplasia, there is no guarantee of the subsequent lack of neoplasia, but may allow an interval of three years for surveillance (Table 2). A combined cohort of BE patients documented that half of patients who developed HGD/EAC had no dysplasia on their first two endoscopies (33).

The finding of low grade dysplasia (LGD) warrants a follow-up endoscopy within six months to ensure that no higher grade of dysplasia is present in the esophagus. If none is found, then yearly endoscopy is warranted until no dysplasia is present on two consecutive annual endoscopies. LGD should be confirmed by an expert GI pathologist because of the problem of reading variability (34). When two pathologists agree on the diagnosis of LGD, the patient has a greater likelihood of neoplastic progression (35). Forty percent of biopsies following the recognition of LGD will be negative (20). Two thirds of 156 patients with LGD had no dysplasia after a mean follow-up of 4 years.

The finding of high grade dysplasia (HGD) in flat mucosa should lead to confirmation by an expert GI pathologist and a subsequent endoscopy within three months. HGD with mucosal irregularity should undergo endoscopic mucosal resection. Although the natural history of HGD is variable, there is a five year risk of EAC exceeding 30% (not excluding prevalent cases in the first year). It is because of the high risk of prevalent cancers that these patients are often evaluated as if cancer is present. Staging procedures with endoscopic

Table 2. Dysplasia Grade and Surveillance Interval

Dysplasia	Documentation	Follow-Up
None	Two EGDs with biopsy within 1 year	Endoscopy every 3 years
Low Grade	<ul style="list-style-type: none"> ● Highest grade on repeat EGD * with biopsies within 6 months ● Expert pathologist confirmation 	1 year interval until no dysplasia x 2
High Grade	<ul style="list-style-type: none"> ● Mucosal irregularity ● Repeat EGD with biopsies to rule out EAC * within 3 months ● Expert pathologist confirmation 	ER * Continued 3 month surveillance or intervention based on results and patient

*EGD – esophagogastroduodenoscopy; ER – endoscopic resection; EAC – esophageal adenocarcinoma.

ultrasonography, CT scans, and even PET scans have been performed although there is not sufficient evidence to warrant their routine application. Patients with confirmed high grade dysplasia, even if unifocal should be counseled regarding their therapeutic options including intensive surveillance, esophagectomy, or ablative therapies. Most experts would use HGD as a threshold for therapeutic intervention or intensive surveillance.

Patient's who appear to have lost their dysplasia on surveillance should be treated according to the highest degree of dysplasia previously found. This recommendation is based upon the problem of sampling error on subsequent biopsies. Complete absence of intestinal metaplasia mucosa can also occur especially with short segments of columnar lining, so the patient should still undergo periodic surveillance. If ablative therapy has been applied, patients should be followed and biopsied in the entire area of prior Barrett's mucosa at intervals appropriate for their prior grade of dysplasia until there is reasonable certainty of complete ablation is documented on at least three consecutive endoscopies. (Grade D recommendation) Periodic surveillance is still recommended since Barrett's mucosa has been known to occur again. Precise recommendations regarding these intervals are not made given the paucity of data about recurrence of intestinal metaplasia but case series have established that the phenomenon does occur.

In summary, the surveillance of Barrett's esophagus does have indirect evidence suggesting benefit. The more advanced the disease in terms of dysplasia, the more frequently surveillance is needed. However, using histological evidence of dysplasia as the primary biomarker to establish surveillance programs is problematic. There are issues with interpretation, sampling, and need for frequent endoscopies which make this an imperfect approach that will need future refinement. Surveillance is recommended but is a Grade C recommendation as long term prospective controlled studies are not available.

THE MANAGEMENT OF DYSPLASIA

Low grade dysplasia requires expert pathologist confirmation and more frequent endoscopy and biopsy. High grade dysplasia (HGD) also requires confirmation by an expert

pathologist and represents a threshold for intervention. A more intensive biopsy protocol is necessary to exclude the presence of concomitant adenocarcinoma. Any mucosal irregularity, such as nodularity or ulcer, is best assessed with endoscopic resection for a more extensive histologic evaluation and exclusion of cancer. Management of patients with high grade dysplasia is dependent on local expertise, both endoscopic and surgical and the patient's age, comorbidity and preferences. Esophagectomy is no longer the necessary treatment response to HGD.

Studies have suggested that for high-grade dysplasia the spacing of four quadrant biopsies should be every 1 cm because larger intervals (2 centimeter) lead to a 50% greater miss rates of cancer (36). In addition, any nodular areas within the Barrett's segment, especially if high-grade dysplasia has previously been found, should undergo endoscopic resection to obtain adequate tissue for more accurate diagnosis. Nodularity has been demonstrated to be associated with a much higher frequency of malignancy (37) and with spread to regional lymph nodes. Despite careful endoscopic surveillance, occult malignancy may still be present. Lacking mucosal abnormalities, these occult lesions are likely intramucosal carcinoma without lymph node involvement (38).

The use of large capacity forceps has been advocated, especially in the setting of high-grade dysplasia, although direct comparisons to standard biopsy forceps have not been conducted in terms of measuring changes in patient outcome. The endoscopic technique to be used to maximize tissue yield is a turn-and-suck technique, which should bring the mucosa in direct apposition to the biopsy forceps (39).

Endoscopic brush cytology has also been used during surveillance of Barrett's esophagus in the hope that increased ability to sample the cells might lead to better diagnoses (40). Studies are conflicting as to how much additional information can be obtained from cytological examination. However, the use of new genetic markers, such as fluorescent in situ hybridization may be promising in increasing the clinical utility of brush cytology (41).

Mucosal ablation therapy has also been advocated to decrease the risk of development of cancer within Barrett's esophagus. This is always done in conjunction with acid suppression, which appears to be a key element. The degree of acid suppression has not been established (42). However, all

studies on mucosal ablation therapy have been in conjunction with at least daily and most often twice daily proton pump inhibitor therapy.

Photodynamic therapy has been the only therapy shown in a randomized prospective control trial to significantly decrease cancer risk in Barrett's esophagus (43). In this study, 208 patients were randomized 2:1 to photodynamic therapy plus PPI or PPI alone with the primary endpoint of eliminating HGD. Photodynamic therapy using sodium porfimer, 630 nanometer red light, and photoradiating balloons, was demonstrated to decrease the risk of carcinoma by 50% but not eliminating the development of cancer after at least 48 months of follow up. The therapy was also able to eliminate high-grade dysplasia in 78% of patients treated, although 39% of patients in the control arm also lost high-grade dysplasia during follow-up. These endpoints were reached if high-grade dysplasia regressed at any subsequent endoscopy.

Thermal ablation techniques were originally utilized for the treatment of Barrett's esophagus lacking dysplasia. The initial thermal coagulation devices were lasers that produced deep tissue injury. The feasibility of mucosal ablation was first demonstrated with these laser devices (42, 44). Thermal ablation has subsequently been primarily done with either argon plasma coagulation or multipolar coagulation, which appear to have relatively similar effects based upon recent small randomized prospective trials (45, 46).

Argon plasma coagulation at high power outputs (80 watts) has been shown in case series to be able to treat high-grade dysplasia and even small cancers, although long-term follow-up is not available (47). Multipolar coagulation has been used to treat primarily low-grade dysplasia and nondysplastic Barrett's. Success rates of ablating the entire Barrett's mucosa usually are in the 80–90% range with multiple applications of the devices. Most of the thermal devices have been utilized in relatively small cohorts of patients followed over short periods of time.

Photodynamic therapy with 5-aminolevulinic acid, an oral agent with superficial effects, has been utilized in Europe. It is very successful in eliminating high-grade dysplasia and early EAC in case series (48). It does have drawbacks of hypotension and even reported patient death (49). Radiofrequency ablation using a balloon based catheter system has been reported to be of value in elimination of Barrett's esophagus in 70% 12 months after initiation of treatment (50). Recently, a targeted radiofrequency application device mounted on the endoscope has enabled treatment of focal areas with this technique. This device was created to target the superficial mucosal of the esophagus with high power radiofrequency energy. Though infrequent, stricture formation and esophageal perforation have been reported (FDA Maude database). Endoscopic application of cryotherapy has also been reported to eliminate Barrett's esophagus, although there is very limited data about its efficacy (51).

Surgical resection (esophagectomy) has been a standard of therapy for Barrett's esophagus with high grade dysplasia based upon concerns that endoscopic surveillance protocols

may not detect early cancers in up to 43% of patients and the opportunity for intervention prior to development of incurable metastatic cancer may be missed (38). More recently, the frequency of EAC at resection in patients with HGD at biopsy has been as low as 17% (52). Also, recent studies have indicated that the risk of metastatic cancer in the setting of intramucosal carcinoma is low at 4% (3/78) especially if there is no evidence of mucosal lesions (53). Most cancers detected in the presence of prior high grade dysplasia are early stage (54). This has led to changes in the way esophagectomy is performed in these patients. Esophagectomy can be performed with minimally invasive techniques that involve the use of laparoscopy and thoracoscopy (55). However, despite the decreased invasiveness of the procedures, one large series of 206 patients reported the over-all major complication rates (32%), mean time in hospital (7 days), and time of procedures (4 hours) to be similar to that reported from trans-hiatal esophagectomy (56). Vagal-sparing esophagectomy which involves leaving the adventitia of the esophagus intact while replacing the mucosa and muscle layers with colonic tissue has also been advocated in order to decrease the dumping syndrome after esophagectomy. This procedure has been shown to maintain vagal integrity but has not generally been accepted by the surgical community because of the need for the colonic interposition (57). Patients requiring esophagectomy need to be referred to a higher volume institution for the best results. A recent analysis of the literature has suggested there needs to be at least 20 esophagectomies done a year at an institution to decrease operative mortality to 5% or less (58).

A recent retrospective comparison study comparing the long-term mortality of 199 patients with high-grade dysplasia treated with photodynamic therapy and endoscopic mucosal resection compared with surgical resection found similar mortality (9% versus 8.5%) between the two groups at about 60 months of follow-up. No patients in either group had an esophageal cancer related death (59).

In summary, high-grade dysplasia is associated with a 30% risk of cancer development. Treatment needs to be individualized with options of careful intensive surveillance, endoscopic ablation therapy, and surgical resection being presented to the patient based on their appropriateness for these options and the expertise available to provide them. At the current time, it appears as if surveillance with intensive biopsies, endoscopic ablative techniques (most likely a combination of techniques), or esophagectomy may produce similar outcomes in retrospective cohort studies from expert centers. The selection of which of these therapies must be individualized and will depend on the expertise available in the patient's community, the patient's preferences, and the gastroenterologists own experience (Grade B recommendation).

IMAGING IN BARRETT'S ESOPHAGUS

Barrett's esophagus has been the focus of several new imaging modalities. It is not surprising since the esophagus is

easily accessible using existing fiberoptic technology and the degree of mucosa to be examined is limited. There have been several different technologies proposed to help image Barrett's esophagus. The most commercially available technique is narrow band imaging, a method of filtering the illuminating light to two major colors, blue and green which are actually absorbed more by blood vessels in the mucosa and subepithelium. These differences help the endoscopist to visually the mucosa better in combination with a high resolution endoscope. This technology has been termed narrow band imaging since the white light illumination source has been filtered or narrowed. A similar enhancement can be performed after image acquisition and has been termed FICE by another endoscope manufacturer. The imaging is based on spectral emission technology with specific wavelengths of enhancement determined by the user. Both of these technologies can be applied to Barrett's esophagus (60–62). In one study of 51 patients with Barrett's esophagus studied with NBI, 7 of whom had high grade dysplasia, the sensitivity of NBI detection for a irregular mucosal pattern was 100% with a specificity of 98.7% (63). However, studies regarding the interobserver variation in interpretation of these patterns has not been studied. Autofluorescence imaging has also been used in investigations to help discern areas of dysplasia in Barrett's esophagus. This technology uses blue light illumination to detect fluorescence from cellular components in the esophagus. Areas of dysplasia do not have as intense autofluorescence as normal tissues and appear dark red. This technology may be more suitable for screening larger areas of mucosa. In Barrett's esophagus, one study has found that autofluorescence was 100% sensitive for areas of high grade dysplasia in 20 patients but had a 40% false positive rate (64).

Older technologies have been used to image the esophagus with chromoendoscopy. Methylene blue stain binds to the mucosa of areas of intestinal metaplasia but will not bind if there is high grade dysplasia or cancer present. The method by which methylene blue is applied and the degree of mucus clearing performed prior to application of the methylene blue affects this technique (65). Studies have had mixed results and prospective crossover studies have not found a clear advantage to methylene blue chromoscopy in comparison to random four quadrant biopsies in detection of dysplasia (66–68). Other contrast agents such as crystal violet, indigo carmine, and acetic acid have also been proposed to enhance the detection of mucosal patterns in Barrett's esophagus in combination with high resolution endoscopy (69). There is promise in these technologies although it is unclear how easily reproducible the identification of patterns will be in clinical practice.

The above imaging methods can examine the entire mucosa; however, other techniques have been developed that examine very small areas mucosa that might be suspicious on these broader imaging techniques. These technologies include optical coherence tomography and laser confocal microscopy which can magnify the mucosa and actually image cellular structures. Initial studies are promising in detect-

ing neoplasia in Barrett's esophagus. Laser confocal microscopy in 63 patients had an accuracy of 94% for detection of neoplasia (70). Optical coherence tomography which functions in a manner more similar to ultrasonography but using light to create interference patterns also has promising results for the detection of intestinal metaplasia at the gastric junction although prior studies have not been very rewarding in detecting dysplasia (71). Spectroscopic devices can analyze the light coming from the mucosa and assess its components to determine the degree of dysplasia that is present. Newer instruments that can assess optical properties such as reflectance, fluorescence, and light scattering have been combined to allow improved characterization of the mucosa (72). At the present time, commercial availability of these instruments is limited to laser confocal microscopy in an endoscope and probe systems.

Although very promising, there is not sufficient evidence at this time to recommend the use of these imaging systems on a routine clinical basis.

BIOMARKERS IN BARRETT'S ESOPHAGUS

Multiple biomarkers have been proposed but very few have actually been adequately studied prospectively. There is promise in the use of nuclear DNA content abnormalities such as aneuploidy and tetraploidy in biopsy specimens in predicting cancer risk, as well as loss of heterozygosity of specific genes such as P16 and P53. In addition, recent studies demonstrate that methylation of P16, RUNX3 and HPP1, as well as demographic characteristics of the patients and BE length are indicators of cancer risk. No biomarkers or panel is currently ready for routine clinical use.

There is a large cohort of patients that has been followed systematically with biomarkers measuring the DNA content in the mucosa. This has been done using flow cytometry of fresh frozen specimens that have been flow cytometry sorted by ki67 to acquire a very pure concentration of epithelial cells. Based on these studies, there is virtually no risk of cancer development for five years if there is no evidence of increased tetraploidy (greater than 6%) or aneuploidy present. However, if tetraploidy was present, there was an increased risk of cancer (relative risk= 11.7, 95% CI = 6.2–22) whereas evidence of aneuploidy increased relative risk 9.5 fold (CI = 4.9–18) (73). However, these methods have been difficult to translate into clinical practice because of the number of biopsies required in the processing needed to maintain laboratory consistency.

In addition, the same group in Seattle, Washington, has looked at loss of heterozygosity as a marker using single nucleotide polymorphisms to detect loss of heterozygosity of p16 and p53. Once again, these markers are quite indicative of cancer with a 16 fold increased relative risk of cancer if loss of heterozygosity is detected (74). However, these techniques have really only been applied to tissues that have been specially processed. Clinical validation of these markers in a

multi-center study is needed before it can be recommended for standard practice.

In a recent publication, an evaluation of tissue from patients who had developed cancer compared to case controls who had not found that methylation of three genes, RUNX3 HPP1 and P16 in their promoter regions once again helped to predict cancer risk. These tests could be done on paraffin-fixed tissues, which is an advantage over the previously mentioned techniques. However, these studies have only been done retrospectively on patient samples and have not been applied in a large prospective fashion (75).

Additional biomarkers that have been proposed over time include markers of cell immortalization, loss of apoptotic control, angiogenesis, cell proliferation, and cell cycle abnormalities. Although multiple markers have been shown to be important in small sub-sets of patients, none of these has been validated in prospective multicenter studies.

The ideal biomarker panel for the detection of GERD patients who will progress to BE would be noninvasive – i.e. non-endoscopic – and sensitive – 85% or better. The ideal biomarker panel to risk stratify patients with BE would be noninvasive and relatively specific, thus enabling the focusing of surveillance endoscopy on this high risk group for EAC. This panel would identify patients with BE who will progress to EAC early enough for curative interventions, perhaps even identifying the appropriate therapy. A low risk group could also be identified, which might not require follow-up. More cost effective surveillance would thus be possible. At this time, validated biomarkers that can be performed on a clinical basis for widespread laboratory use are not available.

CHEMOPREVENTION IN BARRETT'S ESOPHAGUS

Chemoprevention represents a promising future strategy.

Chemoprevention in the pre-malignant stage of esophageal adenocarcinoma represented by Barrett's esophagus seems reasonable. Unfortunately, sufficient prospective evidence that any treatment prevents cancer and more importantly, cancer related deaths in this setting is lacking. The best evidence for any chemoprevention agent lies with non-steroidal anti-inflammatory agents that have been shown in multiple epidemiological studies to be associated with a significantly reduced risk of cancer with an odds ratio of 0.57 (95% confidence interval 0.47–0.71) (76). This decreased risk has also been substantiated with the observation that known biomarkers such as aneuploidy and tetraploidy were also reduced with NSAIDs (77). Unfortunately, in a randomized trial not meeting its patient recruitment goals, celecoxib 200mg bid was not more effective than placebo in patients with BE and dysplasia in the intermediate endpoint of the change of the proportion of biopsies with dysplasia (78). Animal model studies have shown risk reduction of cancer in rats given cyclo-oxygenase inhibitors (79). Large scale trials are being conducted investigating the use of aspirin and low and high dose proton pump inhibitor therapy in Barrett's esophagus but these will take

several years to complete (80). Data from two retrospective cohort studies suggest that PPI therapy significantly reduces the likelihood of developing dysplasia (81–82). This provides a rationale to treat even asymptomatic BE patients with PPI. The benefit of acid suppressive therapy as a means of preventing cancer has not been documented prospectively. No recommendation can be made to use these drugs as chemoprevention agents.

REFLUX CONTROL IN PATIENTS WITH BARRETT'S ESOPHAGUS

For patients with Barrett's esophagus, the goal of pharmacologic acid suppression with agents such as the proton pump inhibitors is to control reflux symptoms.

Reflux symptoms can be controlled in most patients with proton pump inhibitor (PPI) therapy. Twice a day dosing may be necessary in a subgroup of patients. Retrospective studies have shown a decrease in development of dysplasia in patients treated with or prescribed proton pump inhibitors (81). Studies have suggested that normalization of esophageal acid exposure may decrease markers of proliferation (83). However there are currently no data that directly support the use of high dose antisecretory therapy to delay or prevent the development of EAC.

Patients who are optimal candidates for surgery may elect fundoplication. These include patients lacking major comorbidity and whose reflux symptoms are controlled with PPI therapy. Long term results are disappointing with a 20% failure rate at 5 years (84). The vast majority of data do not provide support that fundoplication prevents EAC (85).

ANTICIPATED DEVELOPMENTS

- Non-endoscopic detection of B: It is anticipated that in the short term non-endoscopic methods may become available that identify Barrett's mucosa based on high resolution, spectroscopic or colorimetric means.
- A randomized trial assessing impact of surveillance endoscopy. A multicenter randomized controlled trial of surveillance is needed to determine the validity of this practice.
- Optical recognition of dysplasia: Various techniques are available that can distinguish degrees of dysplasia. These range from fluorescence, light scattering, reflectance, and Raman spectroscopy to imaging devices such as laser confocal microscopy, endomicroscopy, and optical coherence tomography. One or more of these technologies will become clinically available.
- Prospective definition of risk of diffuse versus focal dysplasia.
- Advances in the technology of endoscopic ablation therapy: Further evaluation of the most recent technology; radiofrequency ablation is awaited. Cryotherapy is beginning clinical trials and older technologies are becoming more

refined e.g.: photodynamic therapy with the development of new agents.

- Documentation of the frequency and duration of the surveillance protocol after endoscopic ablation therapy requires careful study.
- Validation of a biomarker panel to risk stratifies BE patients: There are many potential biomarkers but few clinical trials that validate their use. This undoubtedly will change given the many markers currently being investigated.

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