

BARRETT'S ESOPHAGUS

Current Approaches to Diagnosis and Management

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ABSTRACT

Since its first description, the definition of Barrett's esophagus (BE) has evolved from the macroscopic visualization of gastric-appearing mucosa in the esophagus to the histologic identification of goblet cells confirming the presence of intestinal metaplasia within the esophagus. BE develops as a consequence of chronic mucosal injury in patients with long-lasting gastroesophageal reflux disease. The clinical significance of BE is that it is the only known risk factor for esophageal adenocarcinoma. Endoscopy and biopsy is necessary for the diagnosis of BE as well as for observing the development of dysplasia. The optimal treatment for Barrett's metaplasia and dysplasia is still being debated. Neither aggressive medical acid suppression nor antireflux surgery can induce a predictable regression of BE or exert a protective effect against its malignant degeneration. There is no consensus on a particular guideline for endoscopic surveillance with the means of repeating period and biopsy protocol. In the presence of low-grade dysplasia, endoscopic ablation modalities including multipolar electrocautery, argon plasma coagulation, endoscopic mucosal resection, heater probe, a variety of lasers, cryotherapy and photodynamic therapy should be subjected. Cancer can occur

under the re-epithelialized mucosa following ablation. None of these approaches can obviate the need for continued endoscopic surveillance. Since patients with high-grade dysplasia are at high risk for having a focus of adenocarcinoma, esophagectomy should be indicated to those who are medically fit.

Key Words: Barrett's esophagus, Gastroesophageal reflux, Endoscopy, Dysplasia, Esophageal cancer, Endoscopic ablation, Esophagectomy.

INTRODUCTION

Norman Barrett (1) first described the columnar-lined esophagus in 1950 and he believed it to be associated with a congenital short esophagus. Although its etiology, pathophysiology, and malignant potential are much clearer today, controversies remain. The transition from normal squamous mucosa to columnar epithelium, named as Barrett's esophagus (BE), is almost always in response to chronic gastroesophageal reflux (2). It occurs in about one in 400 of the general population and about 15% of the patients with reflux esophagitis (3-5). Moreover, the autopsy prevalence of 376 cases per 100.000 is much higher than the clinical prevalence of 22.6

cases per 100.000, and this shows that the majority of cases of BE in the general population are unrecognized. On the other hand, BE is the only identifiable premalignant condition for esophageal adenocarcinoma (6). The incidence of adenocarcinoma of the esophagus for these patients has been reported as 0.2-2.1% per year (2). In other words, cancer has been estimated to develop in patients with BE at the rate of one case per 100-200 patient-years of follow-up, a 30-125-fold increase in incidence over that in the general population (7,8). The original debate as to whether BE is congenital or acquired has shifted to a debate as to the exact cell of origin in the epithelium. Presence of goblet cells at the gastroesophageal junction identify BE and represents the earliest sign of BE (9). Although, there is some evidence for favoring surgical treatment rather than long-term acid suppression therapy, the facts need to be reviewed realistically with the current results of various clinical studies including medical therapy, antireflux surgery, and combined or sole endoscopic ablation modalities (10-20). The application of genetic markers is still deliberated and progressing (21). On the other hand, the need and details of surveillance programs to detect early cancer are also not resolved.

This article focuses on the controversies over diagnosis of high-grade dysplasia, recognizing early cancer, surveillance protocols and current therapeutic modalities as well as various endoscopic ablation methods, which promise satisfactory early results.

Histopathologic Definition of the Disease

Barrett's esophagus is usually diagnosed when an obvious segment of salmon pink columnar epithelium is seen to extend well above the gastroesophageal junction (9). The proximal junction of whitish squamous epithelium with pink columnar epithelium may be regular but is more commonly seen as presenting with flame-shaped extensions of the columnar epithelium (9). Histologic diagnosis is confirmed when three types of epithelium are found: a) gastric fundus-type epithelium lined by mucus-secreting cells, chief and parietal cells; b) gastric junctional-type epithelium with a foveolar surface and mucus-secreting cells; and c) specialized columnar

epithelium that has a villiform surface, mucus-secreting columnar cells, and goblet cells (intestinal metaplasia) (22). Ordinary epithelium is distinguished from specialized epithelium with the presence of goblet cells (9). It used to be accepted that at least 3 cm of macroscopic pink columnar epithelium seen at endoscopy was necessary for the diagnosis of BE. This hypothesis was based on the Hayward's statement that up to 2 cm segment could be seen in normal people (23). It has been shown that the short-segment columnar-lined esophagus could contain goblet cells and give rise to cancer (24). Segments shorter than 3 cm should be divided into two types, columnar epithelium with or without intestinal metaplasia. The presence of intestinal metaplasia varies with the extent of columnar epithelium lining the esophagus, and most long segments therefore have goblet cells (25). BE is now defined as any length of columnar epithelium in the tubular esophagus with specialized intestinal metaplasia and has artificially been separated into long-segment (3 cm or longer) and short-segment (less than 3 cm) disease (2). Small patches of gastric epithelium in the proximal esophagus can be seen in 2% to 5% of endoscopic procedures (2). Esophageal adenocarcinoma is extremely rare in these inlet patches; they do not need to be biopsied or followed in surveillance programs.

Pathogenesis

It is generally accepted that columnar replacement at the gastroesophageal junction is a repairing response to reflux trauma at that site, but the reason for the inclusion of goblet cells remains to be clarified (9). Premalignant potential possibly arises after a further stimulus by the addition of duodenal contents to the acid refluxate. Clinical evidence also supports the role of duodenal contents in the pathogenesis of dysplastic epithelium. However, the columnar lined epithelium that contains chief, parietal, and Paneth cells is not so simple and may secrete 5-hydroxytryptamine, somatostatin, gastrin, glucagon, motilin, pancreatic polypeptide, secretin, peptide tyrosine, and neurotensin (26). More recently, Shields et al. (27) and Sawhney et al. (28) have demonstrated and confirmed a distinctive cell type at the squamocolumnar junction in about one third of BE patients. It has been shown by electron microscopy that the cell

is morphologic hybrid that shares features of both squamous and columnar cells (9). It may represent an intermediate step in the development of BE. If it is the basal cell in squamous esophageal epithelium, it could give rise to the distinctive cell and the development of BE. The finding of specialized intestinal metaplasia at a normal-appearing gastroesophageal junction is frequently associated with *Helicobacter pylori* infection (2). However, the fact that it is not associated with ethnic background or reflux symptoms, suggests that it is not clinically significant with respect to the development of esophageal adenocarcinoma. Similarly, columnar epithelium in the distal esophagus without specialized intestinal metaplasia is also not associated with ethnic background or reflux symptoms.

Molecular Basis of the Disease

Generally, carcinogenesis in metaplastic cells is thought to proceed through a series of genetic mutations that activate oncogenes and disable tumor suppressor genes. Adenocarcinoma arising on BE is characterized by a peculiar molecular profile that includes allelic loss of a number of tumor suppressor genes (p53, MTS1, APC, VHL, DPC4, Rb, DCC), p53 gene mutations, p16 gene promoter methylation, increased FHIT (fragile histidine triad) and

telomerase transcription (2). Recent data in biopsies from patients with early BE have shown both individual-and multiple-gene abnormalities in up to 50% of the cases (2,29,30). The genetic alterations appear to be equally distributed between cases with and without intestinal metaplasia. BE with intestinal metaplasia is mainly characterized by p53 gene mutation whereas there is a tumor suppressor gene allelic loss in patients with BE without intestinal metaplasia (2). These results suggest that a genetic instability due to the loss of heterozygosity of distinct oncosuppressor genes occurs first, while p53 gene mutations take place later and parallel to the morphological switch from nonintestinal to intestinal type of metaplasia. The clinical importance of intestinal metaplasia may be incorrect under these molecular biologic findings. Further studies concerning the molecular basis of the disease will bring light to the controversies.

Diagnosis

The definitive diagnostic study for BE is endoscopy. Whereas other modalities such as radiology, scintigraphy, potential difference, manometry or pH studies may be suggestive, the diagnosis cannot be made without histologic proof (31).

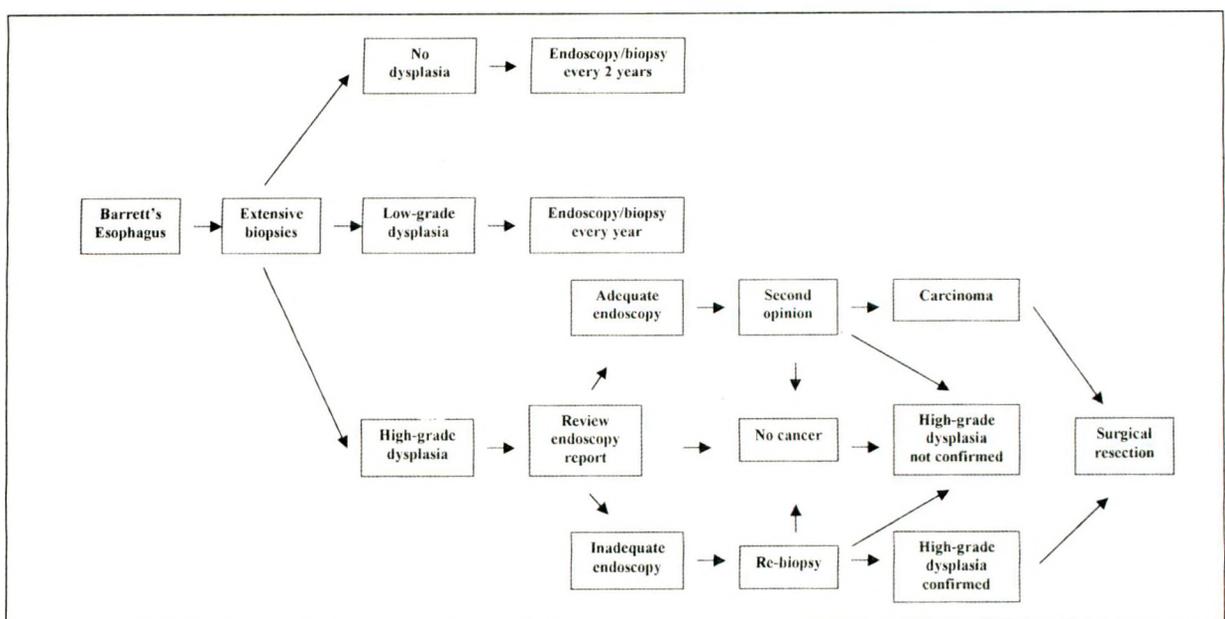


Fig. 1.: Current endoscopic surveillance in patients with Barrett's esophagus.

Radiologic findings vary greatly, and the spectrum found in this disease ranges from stricture, hiatal hernia, free reflux, and/or esophageal ulceration to normal (32). There has been some interest in the reticular mucosal pattern as described by Levine et al, (33) but detection of such requires precise double-contrast techniques and a trained eye. The sensitivity appears low, especially if seen in the absence of a stricture or hiatal hernia, because superficial carcinomas, varices, and drug-induced esophagitis may also give this appearance (34). However, as mentioned by Chernin et al (35) the presence and characteristics of a stricture have been the most important features leading to the diagnosis of BE. The diagnosis is strongly suggested by the findings of a complication occurring in the columnar epithelium. These complications are stricture, ulceration and carcinoma, especially in the patient with free reflux and hiatal hernia. It is important that the radiologist be aware of the implications of these findings and consider the diagnosis of BE. The ^{99m}Tc -pertechnetate test is of limited diagnostic value, because of its low sensitivity although it has a high specificity (36). The columnar lining of BE has been found to have a potential difference unlike that of the squamous lining of the esophagus, but it has little practical value due to its low sensitivity (37). It is not surprising that BE is associated with the characteristics of the extreme end of the spectrum of patients with an incompetent lower esophageal sphincter (LES) (38). The overall length, intra-abdominal length, and pressure profiles are all lower than in patients with other degrees of reflux (9). Similarly, results of pH studies show that the esophageal exposure to both acid and alkaline secretions falls at the extreme end of the spectrum in reflux disease (38). However, no data suggest that particular characteristics of the pH and motility studies have any diagnostic accuracy for BE. On the other hand, the endoscopic features of BE are well described. The level of mucosal change is measured with respect to the gastroesophageal junction, which is recognized by the proximal extent of the gastric folds (9, 39, 40). The columnar segment has been described using terms such as "salmon-pink-tongues" and "flame extensions" into the surrounding "pearly white" squamous epithelium (9). The suggestion of the endoscopic appearance of BE must prompt

multiple biopsies both to prove the diagnosis and to exclude the possibility of dysplasia or malignancy (9). Tytgat (41) suggested that four-quadrant biopsies must be taken every 2 cm of the columnar lining, whereas Nishimaki (42) stated that the area just above the endoscopically obvious columnar segment must always be biopsied carefully because it is a high-risk zone for dysplasia and malignancy. It has been known that severe dysplasia and adenocarcinoma may arise in segments of columnar lining of less than 3 cm (43). On the other hand, Clark et al (44) suggest performing routine retroflexed biopsies of the gastroesophageal junction from "below" in order not to miss a short-segment BE before a carcinoma develops.

Spectroscopic diagnosis of dysplasia in patient with BE has recently been advanced. Reflectance and fluorescence spectroscopy target chemical and structural features of biological tissue and the resulting spectra can provide quantitative diagnostic information (2). The short penetration depth of visible light makes these techniques well-suited for probing the epithelial linings of the body. Reflected light is the simplest spectroscopic technique. This strategy is based on the elastic scattering of white light, in which photons incident on the tissue are "scattered" back without change in wavelength. The targets for reflectance are tissue absorbers and scatterers. Hemoglobin is the most important tissue absorber. Mitochondria and cell nuclei are examples of important tissue scatterers. Reflected light thus contains morphological information about the tissue, such as data on the scattering and absorption properties of tissue, and the size distribution of the epithelial cell nuclei. Sites with high-grade dysplasia scatter light less than nondysplastic cells. The wavelength pattern of scattered light is dependent on the number and size of nuclei in the epithelial cell layer. This quantitative information is of direct interest because nuclear enlargement and crowding are key features used by pathologists to identify dysplasia. Wallace et al. (45) give the rate of sensitivity and specificity of this technique to distinguish dysplasia (low- and high - grade) from nondysplastic Barrett's tissue as 92% and 97%, respectively. Fluorescence is the most widely-used spectral diagnostic technique. Fluorescence spectra in

biological tissue contain distortions due to the interplay with scattering and absorption in the tissue. Spectroscopic signals can provide the same type of information as histochemistry and histopathology, but without the removal of tissue.

Treatment

Management of BE is controversial. There are two different modalities: 1) medical therapy with proton pump inhibitors (PPI) and prokinetics, and 2) minimally invasive laparoscopic techniques to repair the defective LES (9). PPI reduce the gastric output and also the volume of the refluxate, but some reflux of both acid and duodenal content may continue. It is not exactly known whether this reduction will prevent complications. It has been shown that elevation of the head of the bed, decreased fat intake, cessation of smoking, and avoiding recumbency for 3 hours postprandially diminish reflux episodes. PPI gives better results than H₂ receptor antagonists in the medical management of reflux esophagitis (46). However, it has been shown that after 12 months of therapy with lansoprazole, 30 mg daily, one third of patients were still symptomatic, and only 52% of grade III and IV esophagitis remained healed (47). Omeprazole and lansoprazole gave similar healing rates, which were excellent for grade I and II esophagitis and less effective for more severe esophagitis. On the other hand, Kuipers et al. (48) reported that patients with reflux esophagitis and *Helicobacter pylori* infection who were treated with omeprazole were at an increased risk for developing atrophic gastritis. The patients having similar status who were treated by fundoplication did not develop atrophic gastritis. Therefore, it can be suggested that it is important to eradicate *Helicobacter pylori* infection if omeprazole therapy is used to treat patients with reflux esophagitis.

The surgical treatment of BE can be summarized as antireflux surgery and esophagectomy. Antireflux surgery is used to restore LES function and to abolish reflux of gastric and duodenal contents into the esophagus. Although the Nissen fundoplication is the most widely-used procedure, the choice of the surgical approach varies with the surgeon's preference as well as according to the status of the esophageal

peristaltis and the pressure in the body of the esophagus (9). If the mean pressure in the body of the esophagus is less than 25 mmHg and the patient has lost peristaltis, a full 360-degree fundoplication should be avoided (49). In such cases a partial fundoplication is preferred. However, partial fundoplication such as Toupet, Belsey-Mark IV, Watson or Dor procedures, may not control all reflux and the long-term results of follow-up may not be as good as in the case of the Nissen fundoplication (9). In the case of mean pressure in the esophageal body greater than 25 mmHg with normal peristaltis, the esophagus is effectively cleared of a swallowed bolus (50). Antireflux surgery can be performed either with open or laparoscopic procedure, but the latter is most commonly preferred. The results of laparoscopic Nissen fundoplication have been excellent with a mortality rate of less than 0.1% and a morbidity rate ranging from 6% to 25% (51). This is the most important point that laparoscopic fundoplication should be performed identically to the open technique. In other words, the crura should be approximated and a floppy Nissen performed over an adequate size of bougie (52). The taking down of short gastric vessels depends on the surgeon's preference even though it is most widely performed. On the other hand, if the patient has a shortened esophagus, which seldom occurs, besides a hiatal hernia greater than 5 cm and stricture and narrowing, the alternative transthoracic Collis lengthening and antireflux procedure such as Belsey-Mark IV should be considered (9).

Esophagectomy is performed in patients which have BE and high-grade dysplasia or adenocarcinoma of the esophagus developed on BE. The decision to operate for high-grade dysplasia should be based on balancing the risk of overlooking and adenocarcinoma against the hazards of surgery. The overall mortality rate of esophagectomy for high-grade dysplasia has been reported as 0-14% (53-55). Esophagectomy carries some early and late complications. Esophagectomy can be performed either with laparotomy and transhiatal resection with cervical anastomosis or complete laparoscopic or combined laparoscopic and thoracoscopic resection with cervical anastomosis, which is called minimally invasive esophagectomy. Nguyen et al. (56) advise the latter technique for its feasibility and safety.

Zaninotto et al. (57) performed esophageal resection in patients with high-grade dysplasia and BE and found that these patients had a 33% probability of harboring invasive esophageal carcinoma but even a second endoscopy failed to identify patients with invasive tumor. They gave good results of esophagectomy without any mortality in their series.

Despite recent advances in surgical and multidisciplinary treatment, the prognosis for patients with adenocarcinoma of BE remains poor. Bottger et al. (58) studied tumor DNA ploidy, an additional parameter to pathologic TNM staging, to determine the prognosis of the patients who underwent transhiatal or transthoracic esophageal resection due to adenocarcinoma of BE. They found that patients with a diploid or tetraploid tumor without distant metastasis and a tumor stage pT1-pT3 had curative (R0) resection, whereas in the case of an aneuploid DNA content or a pT4 tumor resection alone showed no advantage as compared to palliative nonoperative procedures. These data are contradictory to the conclusion of Zaninotto et al. (57) that molecular biology markers cannot improve diagnostic accuracy.

Endoscopic Surveillance for BE

During the last 10 years, numerous endoscopic surveillance algorithms have been suggested and used. The recommendations made by the Barrett's Esophagus Working Party in 1991 are not followed, possibly because they are not practical (59). The most popularized algorithm in current practice, formed by Stein (60) in 1996, is shown in Fig. 1. Using a strict biopsy protocol is helpful for differentiating high-grade dysplasia from carcinoma, but contradictory results about this type of rigorous biopsy protocol have been published (61). Most groups propose four biopsy specimens, in a circular fashion, from every 2 cm of the Barrett's epithelium, with additional biopsies from any mucosal abnormality. De Looze (61) suggests a four quadrant biopsies at 1 cm interval in patients who have low-grade dysplasia if numerous biopsies reveal dysplasia to detect foci of high-grade dysplasia or cancer. Morales and Sampliner (62) recommend endoscopic surveillance every 3 years for patients who do not develop dysplasia, every 6 months for patients with low-grade dysplasia

over the next year, then at 1-year intervals if there has not been progression to high-grade dysplasia. They also suggest that, when a high-grade dysplasia is shown, the patients should undergo surgical resection, if they are medically fit for this procedure.

On the other hand, postoperative morbidity after correction of esophageal atresia is partly determined by gastroesophageal reflux disease, which has been proven to affect from one-half to two-thirds of the patients during childhood. Krug et al. (63) showed that the incidence of reflux symptoms, reflux esophagitis, and BE were significantly higher than in the normal population. They concluded that this group seems to be at risk for developing BE and advised endoscopy in all patients at adulthood.

In a recent study, aimed at determining the current practices that clinicians employ in the management of BE in the UK, it was shown that the majority (70%) performed surveillance despite the absence of a controlled trial showing a benefit for screening (7). In the group that did not carry out screening in this study, the most commonly cited reason was lack of evidence showing benefit. Similarly, the results of another trial about surveillance of BE in the Netherlands showed that most of the questionnaire respondents (84%) performed regular endoscopic follow-up of BE (64). But there is limited uniformity in the frequency and intensity of endoscopic histological follow-up resulting from conflicting data and recommendation in the literature. These facts indicate that an updated consensus is needed in this area.

Ablation therapy

The efforts to ablate the Barrett's mucosa with either chemical, thermal, or ultrasonic energy have given best results hoping that normal squamous epithelium will replace the Barrett's lining and its malignant potential (65). However, the clinical value of endoscopic ablation is controversial. Major concerns of these methods are the persistence of residual metaplastic glands beneath the new squamous epithelium and the absence of any knowledge of its impact on long-term outcome. Van Laetham et al. (66) recently reported a case of an intramucosal adenocarcinoma diagnosed 18 months after

apparently complete squamous reepithelization achieved using argon plasma coagulation and high dose omeprazole. Moreover, the patient initially had Barrett's esophagus without dysplasia. Similarly Bonavina et al. (15) reported a case with an adenocarcinoma undermining regenerated squamous epithelium, 6 months after eradication by endoscopic laser ablation. These reports show the fact that the residual glands might still be premalignant and that the early diagnosis of neoplastic changes might be compromised by the squamous re-epithelization. This finding also stresses that the histological proof of malignancy need not be established before esophagectomy is proposed controversially to some authors' beliefs (61). Although patients with high-grade dysplasia and intramucosal adenocarcinoma on biopsy who do not have an endoscopically visible lesion are unlikely to have lymphatic metastases, 7% do have submucosal invasion. Thus, even in these very early tumors, treatment directed only at the mucosa may be inadequate (67).

Photodynamic therapy (PDT) is a treatment modality that utilizes a photosensitizing drug activated by laser-generated light (13). PDT might establish itself as a minimally invasive treatment alternative compared with surgery for high-grade dysplasia or early mucosal cancer of the esophagus.

Argon plasma coagulation (APC) has been used with a curative aim for the destruction of high-grade dysplasia in BE and early esophageal cancer. May et al. (14) suggest that APC might offer an effective, minimally invasive alternative to mucosectomy or photodynamic therapy, as the treatment procedure is less cumbersome and the equipment less expensive. The early results of argon plasma coagulation for the eradication of BE in the short-term are very attractive, but long-term follow-up of treated patients seems mandatory before drawing definitive conclusions about this therapy (10,12,14,18).

Endoscopic Mucosal Resection

In view of the mortality and morbidity rates of esophagectomy and the relatively large group of inoperable patients, local therapeutic techniques are required for high-grade dysplasia and early

Barrett's cancer. Endoscopic mucosal resection of early carcinoma in BE is associated with promisingly low morbidity and mortality rates (11). This procedure may offer a new minimally invasive therapeutic alternative to esophagectomy, especially in low-risk situations.

In conclusions, since the development of Barrett's adenocarcinoma follows a multistep process from metaplasia through increasingly severe grades of dysplasia, close endoscopic surveillance with extensive biopsies currently remains the only means to identify patients at risk for malignant degeneration and detect esophageal adenocarcinoma at an early and curable stage. Moreover, columnar epithelium has been found underlying the regenerated squamous epithelium, suggesting that life-long surveillance is warranted. Several therapeutic modalities either medically or surgically give promising short-term results, but not satisfactory in all the patients. Although during the last decade of the second millennium, many changes including definition, pathogenesis, diagnostic approaches, and therapeutic modalities of Barrett's esophagus have been observed, it seems that the searches will be continued in this area at least in the early 2000's.

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