Barrett's Esophagus Definition and Complications

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BARRETT'S ESOPHAGUS: METAPLASIA AND DYSPLASIA

1. Metaplasia

Barrett's esophagus (BE) is defined as columnar metaplasia of esophageal squamous epithelium, of any length, that can be recognized at endoscopy, and is confirmed to have intestinal metaplasia (goblet cells) by mucosal biopsy analysis of the tubular esophagus (1). By definition, this disease does not include intestinal metaplasia of the cardia. Thus, the current definition of BE includes individuals in whom metaplastic epithelium can be identified at endoscopy. Grossly, BE is subdivided into long-segment type (>3cm), short-segment type (1-3cm), and ultrashort segment type (0-1cm) (2-3). Ultrashort, and short, segment BE can be difficult to distinguish from H. pylori induced chronic carditis with intestinal metaplasia both by clinical and histologic methods (see below) (4). Pathologically, BE consists of fundic type, cardia type (junctional) and specialized intestinal type columnar epithelium (5-7). Depending on the location of the biopsy, the mucosa may show one, two or all three types of mucosa. However, in one study by Weinstein et al., intestinal type columnar epithelium was found in 99% of 250 cases of BE that were greater than 2cm in length (7).

Pathogenesis of BE: It is well known that BE develops as a result of chronic gastroesophageal reflux disease (GERD) and that major risk factors for the development of this condition include chronic GERD, and the presence of a hiatus hernia. Other risk factors include white ethnicity and alcohol consumption (8). Other contributing factors include duodenal gastric reflux, delayed esophageal acid clearance, and decreased resting pressure of the lower esophageal sphincter (1,9-11). Some studies suggest that the extent of intestinal metaplasia in BE is related to the severity

of GERD (12). More controversial, though, is the precise cell of origin for BE (13-23). Several animal based studies have shown that the cell of origin probably resides in the esophagus, rather than the proximal stomach (13,18,20). Possible sites of origin include a basally located "stem cell" in the squamous mucosa, or a stem cell located in the mucosal and/or submucosal glands and/or ducts. There is evidence in favor of both of these theories. We have recently described the presence of a characteristic type of stratified epithelium termed "multilayered epithelium" (ME), which is a hybrid epithelium that shows combined squamous and columnar cell features (13,24,25). ME is characterized by basal cells with a squamoid appearance and luminal cells with columnar differentiation. ME is a biologically active epithelium, which has been shown to be phenotypically similar to fully developed BE and has also been shown to be highly associated with BE in a recent prospective study by our group (25). We have also reported that ME is commonly associated with carditis secondary to GERD, but not with cases of carditis due to H.pylori infection (26). As such, ME has been proposed to be an early "transitional" precursor in the metaplastic conversion of squamous to columnar epithelium in BE. Alternatively, ME may represent an intermediary in the conversion of columnar to squamous epithelium. This reaction is common in BE patients that have been treated medically with a proton pump inhibitor, but the data for this type of reaction is much less convincing. Nevertheless, the significance of ME for pathologists is related to the fact that its identification in a mucosal biopsy specimen from the gastroesophageal junction (GEJ), or distal esophagus, helps confirm the presence of, or an evolving, columnar metaplasia, and, as such, can be used to confirm the presence of BE (25,26).

Ultrashort BE versus H. pylori chronic carditis with intestinal metaplasia: These two conditions are difficult to differentiate from each other based on clinical, endoscopic and histologic methods, but their distinction is important since they have different etiologies, natural history, and risk of malignancy (4,27-31,A). Table 1 summarizes some of the clinical, endoscopic, pathologic, immunohistochemical and mucin histochemical methods that can be used to differentiate these two disorders when confronted with mucosal biopsies from the distal esophagus/proximal GEJ in a patient with upper GI symptomatology. Clinical features in favor of BE include the presence of GERD symptoms, and, if available, appropriate manometric and luminal ph probe findings. In addition, BE occurs more often in white males of a younger age, and is more common in patients who consume alcohol and tobacco, compared to patients with chronic carditis secondary to H.pylori infection. The presence of a hiatus hernia is also strongly associated with BE. Endoscopically, the gross appearance of the distal esophagus, and the relationship of the squamocolumnar junction (z line) to the anatomic GEJ (defined as the most proximal limit of the gastric folds), is also helpful to separate these conditions. Features that favor BE include an irregular, proximally located, z-line relative to the GEJ, and/or the appearance of tongues of gastric type mucosa that extend into the distal esophagus. This endoscopic information is critical when evaluating biopsies of this region.

Pathologically, the finding of esophageal mucosal, or submucosal, glands and/or ducts in a biopsy confirms that the specimen was obtained from the tubular esophagus and, thus, if columnar epithelium is identified, then a diagnosis of BE can be established. Also helpful are the features in the squamous epithelium of the esophagus and in the distal stomach (corpus or antrum), since most H. pylori-associated carditis cases also show H. pylori antritis as well. In contrast, active reflux esophagitis combined with the finding of a normal antrum, is strong evidence in favor of BE. Microscopically, biopsies from the GEJ region in cases of true BE

show a higher amount of eosinophilic infiltration in the lamina propria and epithelium, in contrast to plasma cells, neutrophils, and reactive lymphoid aggregates which are more prominent in GEJ or cardia biopsies that have inflammation due to H.pylori infection. The finding of ME in a biopsy from the GEJ region is also highly suggestive of BE since this type of epithelium has never been identified in H. pylori carditis(13,25,64).

Special studies may be helpful as well. High iron diamine positivity, indicating the presence of sulphomucins, in non-goblet columnar cells in a biopsy from the GEJ region has been shown to be highly suggestive of columnar metaplasia (32). Recently, immunohistochemical expression of MUC 1 and 6 have been shown to be highly associated with goblet cell metaplasia related to BE, but not with that associated with chronic H. pylori carditis (33). Finally, although some authors have suggested that a Barrett's CK7/20 staining pattern in a biopsy from the distal esophagus (diffuse strong CK 7 staining combined with superficial CK20 staining), or GEJ, is highly suggestive of BE, other studies, including one from our group, have not been able to confirm these findings, and instead, have shown that the CK7/20 staining profile in biopsies from this region are non-specific (4,27,35,36).

2. Dysplasia

Introduction and Risk factors: Similar to dysplasia at other locations in the GI tract, dysplasia in BE is defined as unequivocal neoplastic epithelium confined to the basement membrane (37-39). It is classified as negative, indefinite or positive (low or high-grade). At present, dysplasia is the best marker of an increased risk of malignancy in BE. Risk factors for dysplasia include increasing length of BE and increasing patient age (40,B). Other studies have shown that Hiatal hernia size, length of BE and severity of GERD are also risk factors for adenocarcinoma (41). Many studies have documented progression from intestinal-type columnar epithelium to dysplasia (low and high-grade) and eventually invasive adenocarcinoma (42-44). Although patients with long-segment BE are at greater risk for dysplasia and carcinoma compared to those with short-segment BE (29,45-47), recent studies suggest that patients with either of these types may benefit from endoscopic surveillance (1). Recent studies suggest that the incidence of adenocarcinoma in BE is overestimated and is more in the range of 1/220 patient years (48).

Pathologic Features: There are two general histologic types of dysplasia in BE; adenoma and non adenoma-like. Adenoma-like dysplasia resembles IBD-related dysplasia (37-39. Low-grade dysplasia shows relatively preserved crypt architecture, with only minimal distortion, and cytologically atypical nuclei limited, for the most part, to the basal half of the cell cytoplasm. Nuclei are typically hyperchromatic, elongated, show a clumped chromatin pattern, either with or without multiple nucleoli, and an irregular contour. Dysplastic goblet cells and mucin depletion are usually present in addition to increased mitoses and occasional atypical mitoses. Slight loss of cell polarity is a characteristic feature as well. With progression to high-grade dysplasia, the degree of cytologic and architectural complexity increases to the point where there may be branching complex crypts, back to back gland formation, or a villiform configuration of the surface epithelium. Cytologically, the cells show a greater degree of hyperchromatism, nuclear pleomorphism, atypical mitoses, loss of polarity, and mucin depletion. Most importantly, by definition, dysplasia does not show surface maturation, in contrast to reactive epithelium. However, rarely dysplasia may affect the base of the crypt only and may be associated with maturation to the surface (C). With progression, cancer cells may penetrate the basement

membrane and permeate the lamina propria and muscularis mucosa features that are indicative of intramucosal adenocarcinoma. However, in biopsies, it may be difficult to differentiate intramucosal adenocarcinoma from high-grade dysplasia. One should rely on the presence of single cells, or small clusters of infiltrating cells within deeper parts of the mucosa in order to firmly establish a diagnosis of adenocarcinoma. Cases that show mild to moderate cytologic atypia in areas that contain active inflammation or ulceration may be considered indefinite for dysplasia for the purposes of patient management. The category of negative for dysplasia is reserved for cases of regeneration, which in BE, can be extreme, particularly in biopsies with active inflammation and ulceration.

Non-adenomatous dysplasia is rare and has been poorly characterized with regard to its biologic characteristics and natural history. However, most cases should be considered high-grade for the purpose of treatment. Non-adenomatous dysplasia is characterized by a more prominent back to back gland proliferation containing cells that are more epithelioid in shape with round, oval or irregular shaped nuclei, clumped chromatin and greatly increased N/C ratio.

Features that may be helpful in differentiating reactive from dysplastic epithelium include the presence of active inflammation and/or ulceration, the presence of surface maturation, lack of nuclear pleomorphism, and loss of polarity, and atypical mitoses, all of which support epithelial regeneration. Unfortunately, given the subtle gradation of changes that occur in the progression of dysplasia in BE, and various morphologic patterns of atypia related to regeneration, there is a significant degree of intra and interobserver variability in the diagnosis of dysplasia, even among experienced GI pathologists (38,39). The greatest degree of variability occurs in the differential of indefinite from low-grade dysplasia; higher levels of agreement occur at the two ends of the dysplasia spectrum (regeneration and high-grade dysplasia). Sampling error is also a potential problem (49,50). Unfortunately, there are, at present, no reliable adjunctive diagnostic techniques that may be helpful in this differential diagnosis. In addition, new endoscopic techniques, such as autofluorescence endoscopy and light-scattering spectroscopy, although still considered investigative, may be helpful in detecting dysplasia in BE (51-53). Furthermore, as discussed below, the presence of p53 staining in atypical epithelium should not be considered evidence in favor of dysplasia, since this finding may occur in non-dysplastic reactive metaplastic epithelium as well (54-56).

Occasionally, dysplasia may grow in a polypoid fashion and resemble a colonic "adenoma" in its endoscopic and microscopic appearance (57). Polypoid dysplasia is generally high-grade and often shows intramucosal, or even invasive, adenocarcinoma. The biological and molecular properties, and natural history, of polypoid dysplasia are similar to flat dysplasia, and, thus, should be treated similarly (57). Thus, the term "adenoma" should be avoided in the setting of BE.

Natural history of low-grade dysplasia: Little is known about the natural history of low-grade dysplasia, particularly since there is a high degree of interobserver variability in establishing this diagnosis, even among experienced GI pathologists (58,D). However, for the cases that show good agreement as to the presence of low-grade dysplasia, the risk of progression to high-grade dysplasia, or cancer, ranges from 7-80% (59-60). The natural history of dysplasia including low-grade, is summarized in the database of studies from five centers that have performed prospective studies, and one registry (60-65). Among these studies, a total of 783 patients were followed for up to 7 years in duration. In this cohort, overall, 2% of patients without dysplasia and 7% and 22% of low and high-grade dysplasia cases, respectively, progressed to cancer. In

some studies, low-grade dysplasia has been reported to be a transient finding (59). In one series, 73% of patients with low-grade dysplasia had no evidence of dysplasia in any of their follow-up endoscopies (59). However, this result may be due to sampling error and, also, may in part be related to inclusion of markedly reactive cases in the dysplasia group. In fact, several studies have shown that when at least 2 experienced GI pathologists have agreed on a diagnosis of low-grade dysplasia, there is a significant association with progression to high-grade dysplasia or cancer (59,67).

Natural History of high-grade dysplasia: The natural history of high-grade dysplasia is better understood. High-grade dysplasia is associated with adenocarcinoma in up to 30-50% of cases at the time of esophageal resection (43,50,68). However, the incidence of adenocarcinoma in a resection specimen from a patient who had high-grade dysplasia diagnosed on a biopsy sample is highly related to the presence or absence of a mucosal nodule, an ulcer, or a mass lesion (69-71). Patients with flat, endoscopically undetectable, high-grade dysplasia have a much lower incidence of synchronous adenocarcinoma, compared to those who have an endoscopically detectable lesion. In one study, the presence of mucosal nodularity in patients with high-grade dysplasia increases the risk of cancer by a factor of 2.5 (66). However, not all studies confirm this finding (67). In this study, the extent of high-grade dysplasia was also important in estimating the risk of progression to cancer (66). However, not all studies confirm this finding (67). In a recent prospective study of patients with unifocal high-grade dysplasia with long-term follow-up, 53% progressed to multifocal high-grade dysplasia, or invasive carcinoma (72). In general, the cancer risk in patients with high-grade dysplasia that is endoscopically undetectable ranges from 20-40% (60-66). In one study from the Hines VA Hospital, of 1099 patients with BE, 79 (7.2%) initially had high-grade dysplasia, and of these, 4 had an unsuspected adenocarcinoma detected within the first year of endoscopic surveillance (64). Of the 75 remaining patients, 16% subsequently developed carcinoma during a follow-up period of 7 years. Thus, data from this study suggests that a proportion of patients with high-grade dysplasia may follow a relatively benign course. Reid et al reported an excellent success rate of detecting early adenocarcinoma in BE-related dysplasia in patients who were followed with an aggressive biopsy protocol (four quadrant biopsies every 1cm of affected mucosa) performed at closely timed intervals (73). Some studies suggest that the extent of either low (D) or high-grade dysplasia is a significant risk factor for progression to adenocarcinoma (E,F).

Management of Dysplasia: Management of patients with BE, particularly those with dysplasia is controversial and varies significantly between various institutions primarily because of the lack of prospective data regarding the natural history, and the time course of conversion from dysplasia to carcinoma (74-76). A summary of the current guidelines recommended by the American College of Gastroenterology is summarized in Table 2 and is reproduced from an article by Sampliner et al, in 2002 (1). In brief, annual endoscopy is recommended for patients with confirmed low-grade dysplasia until dysplasia is not detected. The finding of high-grade dysplasia should prompt an immediate repeat endoscopy with special attention to the presence of mucosal irregularity, the latter of which would exclude the potential for an endoscopic mucosal resection (78,79). Biopsy protocols should, ideally, be performed using large sized "jumbo" biopsy forceps, on all four quadrants of mucosa, at every 2 cm in areas without dysplasia, and every 1 cm in areas with dysplasia (69,73,80). Some data suggest that an intensive biopsy protocol is helpful in differentiating high-grade dysplasia from invasive carcinoma (80).

Furthermore, all dysplasia diagnoses should be confirmed by an experienced GI pathologist prior to definitive treatment. Focal high-grade dysplasia may be followed successfully with an aggressive 3 month interval biopsy surveillance protocol (1) in centers that have a lot of experience with high risk BE patients. However, surgical intervention or endoscopic mucosal resection should be considered in patients with multifocal high-grade dysplasia, or a mass lesion (75,76). One study suggests that endoscopic mucosal resection combined with photodynamic therapy is a viable and less morbid alternative to esophagectomy in patients with high-grade dysplasia and early adenocarcinoma in BE (77). Esophagectomy performed at a high volume institution with particular expertise in this area, remains a reasonable strategy in surgically fit patients with recurrent diffuse high-grade dysplasia (75,76). Nevertheless, the precise threshold for surgical intervention needs to be individualized particularly if the patient is being treated at a low volume institution where the morbidity and mortality rates from esophagectomy are higher (81). The goal of any surveillance program is to decrease the rate of mortality from adenocarcinoma. New methods of endoscopic ablation therapy, such as argon plasma coagulation, photodynamic therapy and cryotherapy may show promise in the future as non-surgical alternatives for treatment of BE patients with dysplasia (82-85). However, stepwise four quadrant biopsies still represent the gold standard for surveillance in BE (86,87). Finally, some studies suggest that proton pump inhibitor therapy and chronic intake of NSAIDs and Cox-2 inhibitors may decrease the risk of adenocarcinoma in BE (G,H,I). However, chronic proton pump inhibitor use may lead to the formation of squamous islands that cover the underlying BE glands, which can make surveillance for dysplasia difficult (J).

Adjunctive diagnostic techniques in assessing risk of neoplasia in BE: Many biological and genetic markers have been studied in BE, such as markers of proliferation (PCNA, Ki-67), DNA content abnormalities (aneuploidy), genetic mutations, various growth factors and apoptosis inhibitors, and, more recently, cyclooxygenase 2 expression (42,54,56,60,88-97). DNA content, measured by flow cytometry, has been studied in detail but the results have been controversial (60,89). Investigators in Seattle, led by Reid et al, have shown that there is an increased prevalence of DNA aneuploidy, and elevated S phase fractions, with increasing degrees of dysplasia in BE. In one study, 9 of 13 patients who had either aneuploidy or an increased G2/tetraploid cellular population in their initial mucosal biopsy subsequent developed high-grade dysplasia or carcinoma within 34 months (42). However, none of 49 patients without these features progressed. However, other authors, such as Fennerty et al, found discordance between flow cytometry abnormalities and dysplasia in BE (89). A recent study showed that image cytometric DNA analysis is a useful method to evaluate DNA abnormalities in formalin fixed tissues and may be more sensitive in predicting progression to adenocarcinoma than dysplasia (K).

Other studies have evaluated p53 immunoexpression or 17p (p53) LOH in the progression of BE (98-100). In one study of 269 BE patients, 17p LOH identified patients at increased risk of progression to adenocarcinoma (98). Three-year cumulative incidence rates for cancer was 38% compared to 3.3% for patients with two normal 17p alleles. However, the utility of these, and other markers, needs to be documented in long-term multicenter prospective studies prior to their use in clinical practice. Increased p53 immunoexpression and LOH of 9p and 17p are frequent early events in the metaplasia to dysplasia sequence and some preliminary studies suggest that these tests may be helpful as markers of increased risk of progression to high

grade dysplasia and carcinoma in BE (99-101). Increased COX-2 expression has also recently been shown to correlate with reduced survival in BE patients with carcinoma (102).

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Table 1. Esophageal versus Cardia Intestinal Metaplasia

	Feature	Esophagus IM (BE)	Cardia IM
1.	GERD clinical profile	+	-
2.	Irregular Z line	+	-
3.	Esophagitis (histologic)	+	-
4.	Gastritis (histologic)	-	+
5.	H. pylori	-	+
6.	Eosinophils	++	+
7.	Neut, Plasma, Lymphocytes	+	++
8.	Multilayered epithelium	+	-
9.	HID stain positive	+	-
10.	MUC 1, 6 positive	+	-
11.	BE CK 7/20 pattern	+	+/-
12.	Complete > incomplete IM	-	+

IM= Intestinal Metaplasia
BE= Barrett's Esophagus
Neut= Neutrophils
Plasma= Plasma cells

Table 2

ACG guidelines for Surveillance in Barrett's esophagus:

(Sampliner et al, Am J Gastroenterol 97:1888,2002)