Barrett's Esophagus

Medical Grand Rounds

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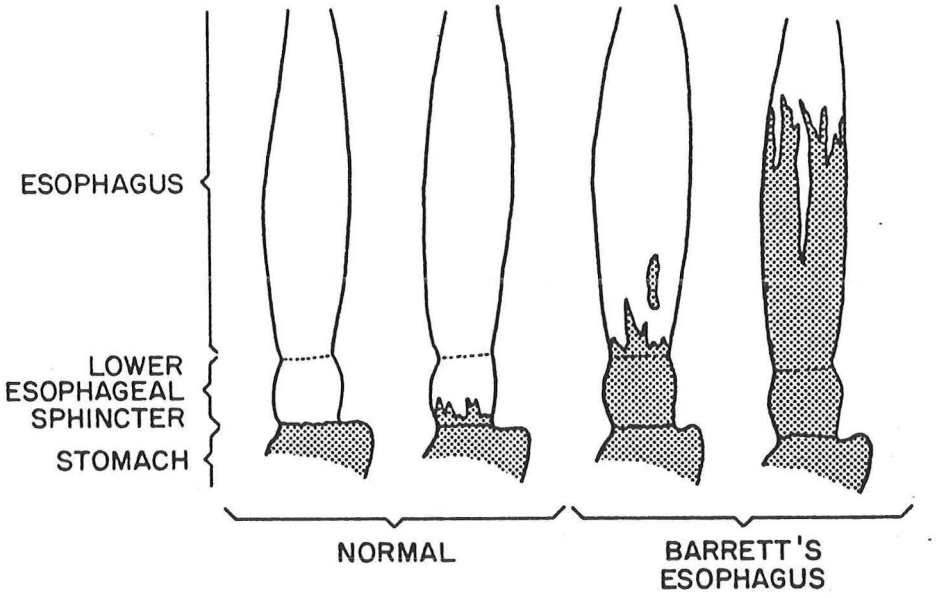
The normal esophagus is lined almost entirely by stratified squamous epithelium. In some normal individuals, gastric-type columnar epithelium can extend a short distance above the stomach to line the distal esophagus (see figure below) (1). When the distal esophagus is lined by a segment of columnar epithelium that is abnormal because it is extensive or because it has intestinal features, the condition has been called Barrett's esophagus (2). The abnormal columnar lining develops through the process of metaplasia wherein one adult cell type replaces another (3). In Barrett's esophagus, adult columnar cells replace mature squamous cells that have been injured by exposure to refluxed gastric contents. In addition to causing the esophageal injury, gastroesophageal reflux appears to be the factor that induces epithelial repair through columnar metaplasia. Intestinal-type metaplasia predisposes to malignancy, and Barrett's esophagus is the major recognized risk factor for adenocarcinoma of the esophagus and the esophagogastric junction (4,5). Consequently, Barrett's esophagus has been studied by investigators interested primarily in gastroesophageal reflux disease (GERD), and by those interested primarily in cancer. These divergent groups of researchers often have differed in their perspectives and in their approaches to patients with Barrett's esophagus. Such differences have contributed to ongoing confusion and controversy about the disorder.



Squamo-columnar junction in normal individuals and in patients with Barrett's esophagus

Diagnosis

In most cases, the diagnosis of Barrett's esophagus is established by the examination of biopsy specimens obtained during endoscopic evaluation of the esophagus (6). Endoscopically, columnar epithelium in the esophagus can be identified readily by its characteristic red color and velvet-like texture. These features contrast sharply with the pale, glossy appearance of the adjacent squamous epithelium. Endoscopists suspect that Barrett's esophagus is present when they see long segments of columnar epithelium extending up the esophagus, well above the esophagogastric junction. The diagnosis is confirmed when biopsy specimens from these long segments contain any of three types of columnar epithelia (7): 1) **Gastric junctional-type epithelium** (also called gastric cardiac epithelium) that has a foveolar surface and glands lined almost exclusively by mucus-secreting cells; 2) **Gastric fundic-type epithelium** that has a pitted

surface lined by mucus-secreting cells, and a deeper glandular layer that contains chief and parietal cells; and 3) **Specialized intestinal metaplasia** (also called specialized columnar epithelium) that has a villiform surface and intestinal-type crypts lined by mucus-secreting columnar cells and goblet cells. These three columnar epithelial types are identical in their endoscopic appearance, and distinction among them requires biopsy sampling for histologic examination. Histologically, the two gastric epithelial types often cannot be distinguished from those normally found in the stomach. Specialized intestinal metaplasia, in contrast, is readily distinguishable from normal gastric and esophageal epithelia on histologic examination. Specialized intestinal metaplasia usually can be found adjacent to squamous epithelium in the most proximal segment of the esophageal columnar lining. Gastric junctional-type epithelium may be encountered as one proceeds down the esophagus, followed by gastric fundic-type epithelium that eventually blends imperceptibly into the fundic mucosa of the stomach. Specialized intestinal metaplasia is the most common and important of the three epithelial types found in Barrett's esophagus. Dysplasia and carcinoma in this condition invariably are associated with intestinal metaplasia (8).

The diagnosis of Barrett's esophagus is clear when long segments of columnar epithelium extend to the mid-esophagus and beyond. Substantial diagnostic difficulties can arise, however, when patients are found to have short segments of columnar lining in the distal esophagus. Several factors contribute to the diagnostic problems in these cases. One major confounding factor lies in identifying the precise point at which the esophagus joins the stomach (the esophagogastric junction). Anatomists, radiologists, and physiologists all have used different landmarks to identify the junction, most of which are not applicable for endoscopists (9). Endoscopic criteria that have been used to recognize the esophagogastric junction include the point at which the tubular esophagus flares to become the sack-like stomach (6), and the proximal margin of the gastric folds (10). The distal esophagus *in vivo* is a dynamic structure whose appearance changes constantly, however. The location of the point of flare varies with respiratory and peristaltic activity, and with the degree of esophageal and gastric distention. With no "gold standard" for identifying the esophagogastric junction, it can be difficult to ascertain whether columnar epithelium found in this area lines the distal esophagus or the proximal stomach (the gastric cardia). Adding to the diagnostic confusion, some investigators have claimed that gastric mucosa normally can extend at least 2 cm into the distal esophagus (1,10). Therefore, the finding of gastric-type epithelia in this distal esophageal segment does not establish a diagnosis of Barrett's esophagus. Confronted with these diagnostic difficulties, investigators who designed studies on Barrett's esophagus often attempted to avoid making false-positive diagnoses by including only those patients whose esophageal columnar lining extended some specified distance (e.g >3 cm) above the esophagogastric junction (11). Although many gastroenterologists have adopted those investigative criteria into their clinical practices, diagnostic standards for Barrett's esophagus that are based on a specified extent of columnar lining clearly are arbitrary. For example, if one chooses 3 cm as the diagnostic criterion for Barrett's esophagus, then patients who have 2.5 cm of metaplastic esophageal columnar lining (with potential for neoplastic change) will be ignored. Furthermore, criteria based on the extent of esophageal columnar lining are subject to the considerable imprecision of endoscopic measurement (12).

In an attempt to avoid the diagnostic difficulties described above, some investigators have chosen to define Barrett's esophagus by the presence of specialized intestinal metaplasia anywhere in the esophagus, regardless of extent. Even this approach does not eliminate diagnostic problems, however. Intestinal metaplasia in the stomach can be histologically indistinguishable from esophageal intestinal metaplasia (13), and inadvertent biopsy of an intestinalized gastric

cardia could result in a false-positive diagnosis of Barrett's esophagus. Although intestinal metaplasia in the gastric cardia, like its counterpart in the esophagus, may well predispose to cancer of the esophagogastric junction (5), there is an obvious conceptual problem inherent in calling intestinal metaplasia of the stomach "Barrett's esophagus".

Perhaps the major problem with defining Barrett's esophagus solely by the presence of specialized intestinal metaplasia relates to the frequency with which short segments of this epithelium can be found in the region of the esophagogastric junction. In one recent study, all patients scheduled for elective endoscopic examinations in a general endoscopy unit, regardless of the indication for the procedure, had biopsy specimens obtained at the squamo-columnar junction (the Z-line) in the distal esophagus irrespective of its appearance and location (14). Among 142 patients who had columnar epithelium involving <3 cm of the distal esophagus, 26 (18%) were found to have specialized intestinal metaplasia in hematoxylin and eosin (H&E) stains of biopsy specimens from the squamo-columnar junction. Signs and symptoms of esophagitis were not reliable markers for the presence of intestinal metaplasia, and the metaplastic epithelium found in the study patients would have gone unrecognized if the protocol had not mandated the acquisition of biopsy specimens from a normal-appearing squamo-columnar junction. Four similar studies have been published since 1994 in peer-reviewed journals (15-18). The results of the five studies, all of which included consecutive, unselected patients seen in general endoscopy units, are summarized below:

Results of Studies on The Prevalence of Specialized Intestinal Metaplasia (SIM) Among Unselected Patients in General Endoscopy Units

Study first author	Spechler	Johnston	Nandurkar	Chalasani	Trudgill
Reference number	14	15	16	17	18
Year of publication	1994	1996	1997	1997	1997
Country	USA	USA	Australia	USA	UK
Number of patients	142	170	158	87	120
Prevalence of SIM at squamo-columnar junction	18%	9%	36%	18%	18%
Association of SIM with GERD symptoms	No	Yes	No	--	No
Association of SIM with endoscopic esophagitis	No	No	No	--	No

These studies show clearly that short, inconspicuous segments of specialized intestinal metaplasia can be found frequently at the squamo-columnar junction. The role of GERD in the pathogenesis of these short metaplastic segments is not clear. Some authorities refer to this condition as "short-segment Barrett's esophagus".

Barrett's esophagus of the endoscopically obvious variety ("long-segment Barrett's

esophagus") traditionally has been associated with severe GERD and with a high risk for developing adenocarcinoma (11). The risks for GERD complications and cancer development have not yet been established for patients with short segments of intestinal metaplasia at the esophagogastric junction. Preliminary data suggest that these risks are substantially smaller than those for patients with long segment disease. Therefore, it may not be appropriate to include patients with long segments of esophageal intestinal metaplasia and those with short segments both under the rubric "Barrett's esophagus".

There remains substantial controversy regarding the diagnostic criteria for Barrett's esophagus. An alternative diagnostic system that does not rely on arbitrary and imprecise endoscopic measurements has been proposed (2). Whenever columnar epithelium is seen in the esophagus, regardless of extent, the condition is called "columnar-lined esophagus". In these cases, biopsy specimens are obtained from the esophageal columnar lining to seek specialized intestinal metaplasia. The condition then can be classified as either "columnar-lined esophagus with specialized intestinal metaplasia" or "columnar-lined esophagus without specialized intestinal metaplasia". If desired, the term "Barrett's esophagus" can be applied to the subset of patients with columnar-lined esophagus who have long, endoscopically-obvious segments of columnar epithelium extending well above the esophagogastric junction. Most of the latter patients are found to have specialized intestinal metaplasia (2). Regardless of the diagnostic system used, the clinician should recognize that most studies on Barrett's esophagus have included only patients with endoscopically-obvious disease. *It is not clear that the conclusions of these studies are applicable to patients who have short segments of specialized intestinal metaplasia in the region of the esophagogastric junction.* Barrett's esophagus traditionally has been associated with severe GERD and with a high risk for adenocarcinoma. Many patients with short segments of specialized intestinal metaplasia have no apparent GERD, and their risk for developing adenocarcinoma may be far less than that for patients with long segments of intestinal metaplasia. Further studies are needed to define the epidemiology and natural history of this condition. The remainder of this protocol deals primarily with studies on patients who had endoscopically-obvious disease. Unless otherwise specified, the term "Barrett's esophagus" refers only to such patients.

Clinical Features

Barrett's esophagus usually is discovered during endoscopic examinations of middle-aged and older adults. The mean age at the time of diagnosis is approximately 55 years (11). Although Barrett's esophagus can affect children, specialized intestinal metaplasia has not been reported in a child younger than 5 years of age (19). The absence of this intestinal epithelium in the esophagus of neonates and infants supports the contention that Barrett's esophagus is not congenital, but an acquired, metaplastic condition. White males predominate in most series, and Barrett's esophagus appears to be decidedly uncommon in blacks and Asians. Whites are especially predominant among patients with adenocarcinoma of the esophagus and gastric cardia. In contrast, squamous cell carcinomas of the esophagus and adenocarcinomas of the gastric body exhibit a clear predilection for blacks and Asians (20). Most patients with Barrett's esophagus are seen initially for symptoms of the associated GERD such as heartburn, regurgitation, and dysphagia. In approximately 25% of cases, however, esophageal symptoms are absent, and the Barrett's esophagus is discovered during endoscopic examinations performed for unrelated conditions (21). The esophageal columnar epithelium itself causes no symptoms, and even may be less pain-sensitive than the native squamous mucosa (22).

GERD and Barrett's Esophagus

The GERD associated with Barrett's esophagus often is severe and frequently is complicated by esophageal ulceration, stricture, and hemorrhage (13). Physiologic abnormalities that have been proposed to contribute to the severity of GERD in these patients are listed in the table below:

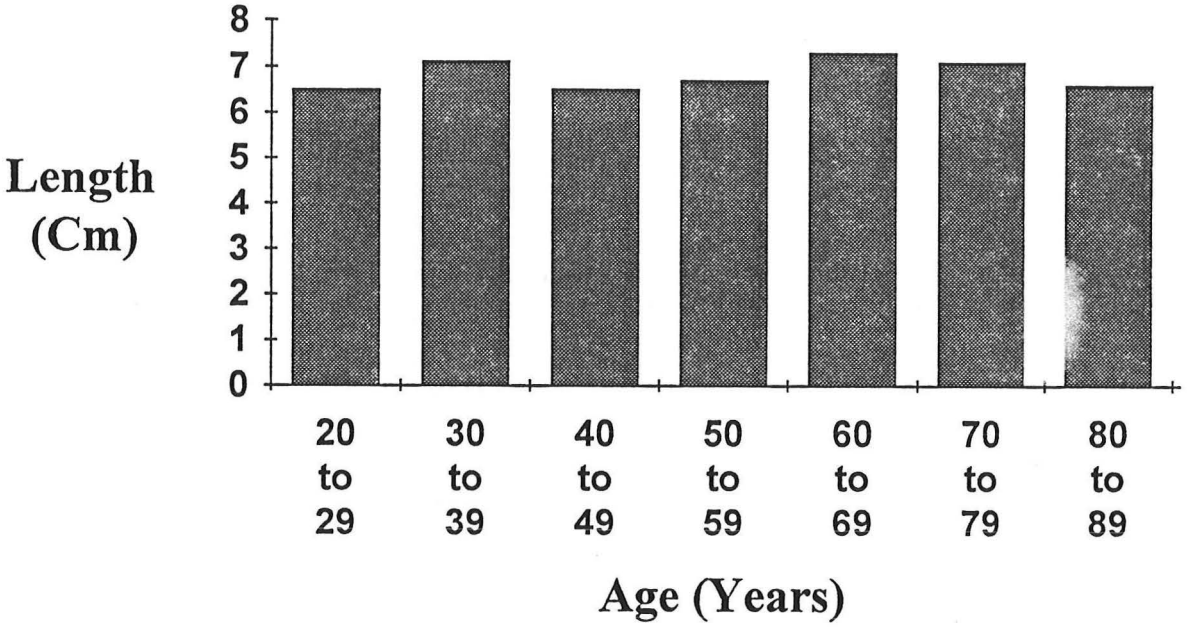
Proposed Physiologic Abnormalities that Contribute to GERD in Patients with Barrett's Esophagus

Abnormality	Contribution to GERD
Gastric acid hypersecretion (23) Duodenogastric reflux (24)	Gastric contents available for reflux are highly caustic to the esophagus [high concentrations of acid and bile]
Extreme LES hypotension (25)	Dysfunction of major antireflux barrier results in strong predisposition to reflux
Poor esophageal contractility (26)	Decreased ability to clear esophagus of refluxed material
Diminished esophageal pain sensitivity (22)	No warning of esophageal damage; little incentive to comply with antireflux therapy
Decreased salivary secretion of epidermal growth factor (27)	May delay healing of esophagitis

As a result of these abnormalities, patients who have endoscopically-obvious Barrett's esophagus are exceptionally predisposed to reflux highly caustic gastric contents, often without warning, into an esophagus whose ability to protect and heal itself may be compromised severely. Clearly, this is a formula for severe GERD. As mentioned above, it is not clear that patients with short segments of intestinal metaplasia at the esophagogastric junction exhibit similar abnormalities.

Given the propensity for severe GERD in patients with Barrett's esophagus, one might assume that metaplasia should progress in extent over the years as columnar epithelium replaces more and more squamous epithelium that is damaged by ongoing reflux. Such progression is observed infrequently, however, and Barrett's esophagus appears to develop to its full extent relatively quickly in most cases. For example, Cameron and Lomboy reviewed the records of 377 patients found to have Barrett's esophagus at the Mayo Clinic between the years 1976 and 1989 (28). When these patients were grouped according to age, the length of esophagus lined by Barrett's epithelium was not found to differ significantly among the various age groups (i.e. 20 year-old patients had a segment of columnar-lined esophagus similar in length to that of the 80 year-olds) [see figure on next page]. Furthermore, no significant change in the extent of Barrett's epithelium was found among 101 patients who had follow-up endoscopic examinations performed after a mean interval of 3.2 years. It is not known why Barrett's esophagus usually does not progress in extent despite ongoing GERD.

Age-Related Length of Metaplastic Mucosa in the Esophagus



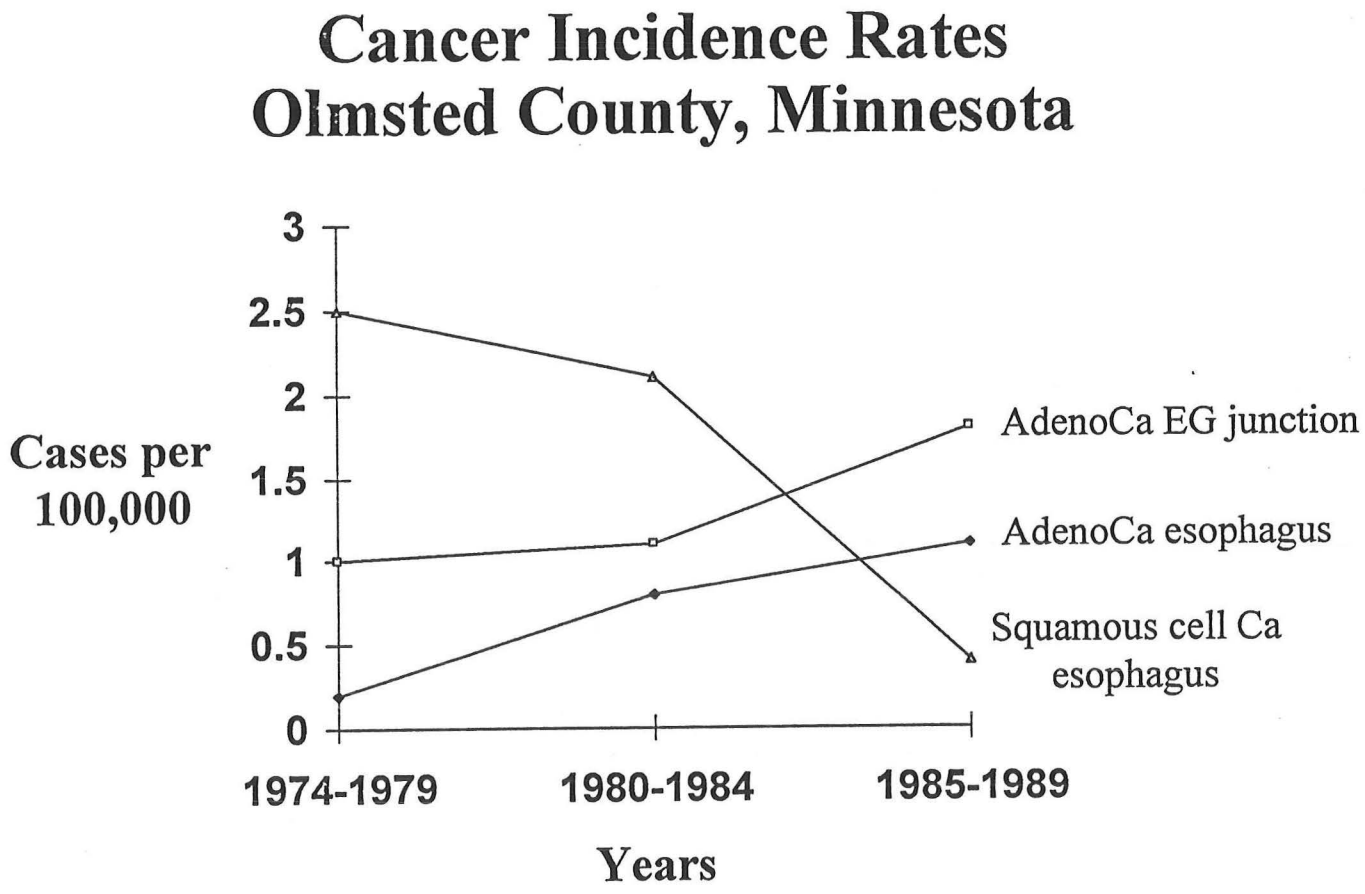
This graph shows how the length of esophagus lined by columnar epithelium varied with age in 377 patients with Barrett's esophagus. [Data adapted from Cameron AJ, Lomboy CT. Gastroenterology 1992; 103:1241-1245.]

Prevalence

As discussed above, short and endoscopically-inconspicuous segments of intestinal metaplasia can be found at the esophagogastric junction in approximately 18% of patients in a general endoscopy unit. Endoscopically-obvious Barrett's esophagus occurs far less frequently, although the condition can be found in 10% to 15% of patients who have endoscopic examinations for symptoms of GERD (29,30). Even endoscopically obvious disease goes unrecognized in the large majority of cases, however, probably because most patients with Barrett's esophagus in the general population either do not seek medical attention or do not have endoscopic evaluations for the condition (31). Cameron et al. reviewed the records of all patients known to have Barrett's's esophagus in Olmsted County, Minnesota, and estimated the prevalence of the condition to be only 22.6 cases per 100,000 (31). When these same investigators prospectively looked for Barrett's esophagus (with >3 cm of columnar lining) in all post-mortem examinations performed at the Mayo Clinic during a period of 18 months, however, a dramatically higher prevalence rate of 376 cases per 100,000 was found. This study suggests that for every case of Barrett's esophagus treated by a physician, there are approximately 20 cases in the general population that go unrecognized. These observations have important public health implications. If physicians identify only the small minority of patients with Barrett's esophagus in the general population, then cancer surveillance programs targeted at patients known to have intestinal metaplasia will have little impact on the overall incidence of esophageal adenocarcinoma. Such programs will include only a tiny fraction of the patients at risk for developing esophageal cancer.

Dysplasia and Adenocarcinoma

In the United States and Western Europe, there has been a dramatic change in the relative frequencies of squamous cell carcinoma and adenocarcinoma of the esophagus over the past few decades (see figure below) (32,33). In the 1960's, squamous cell cancers comprised well over 90% of all esophageal tumors in this country, whereas adenocarcinoma of the esophagus was considered so uncommon that some authorities questioned the very existence of the disease. Since the 1960's, the frequency of adenocarcinoma of the esophagus and adenocarcinoma of the esophagogastric junction (a similar if not identical tumor) has increased dramatically in the United States and Western Europe (34,35). Presently, there are approximately 12,000 new cases of esophageal cancer diagnosed in the United States each year, of which one-half are squamous cell carcinomas and one-half are adenocarcinomas (34-36). Both tumors affect men far more often than women. Perhaps the most striking epidemiologic difference between the two histologic types of esophageal cancer is the dramatic racial variation in incidence rates. Squamous cell carcinoma affects blacks six times more often than whites, whereas adenocarcinoma is at least four times as common in whites. Although either histologic type of cancer can be found anywhere in the esophagus, squamous cell tumors are located most often in the mid-esophagus, whereas adenocarcinomas are distal tumors that often cross the esophagogastric junction.

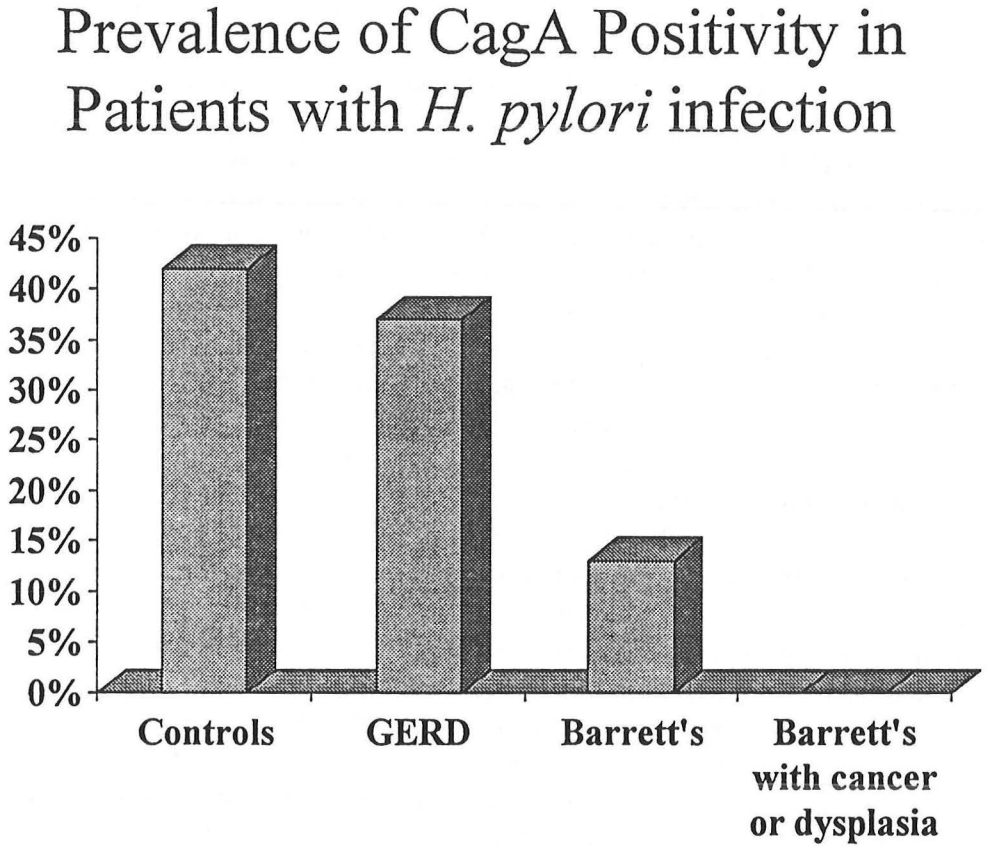


These data from the Mayo Clinic reflect national trends in predominantly white populations. [Data adapted from Pera M et al. Gastroenterology 1993; 104:510-513.]

When an adenocarcinoma straddles the esophagogastric junction, it can be difficult to determine whether the tumor arose from columnar epithelium located in the distal esophagus or in the proximal stomach (the gastric cardia). Glandular tumors that straddle the esophagogastric junction are approximately twice as common as adenocarcinomas that clearly arise from the esophagus (5). Adenocarcinomas of the esophagus and adenocarcinomas of the gastric cardia cannot be distinguished from one another morphologically, and they share a number of epidemiological features including an association with GERD, a strong predilection for white males, and a rapidly rising incidence rate in Western countries (5). Recent studies suggest that esophagogastric junction tumors, like adenocarcinomas of the esophagus, arise from foci of intestinal metaplasia in the junctional region (5,37). Patients with traditional, long-segment Barrett's esophagus develop adenocarcinomas at the rate of approximately 1% per year (38). For patients with short segments of intestinal metaplasia the cancer risk is not known. Considering the large number of such individuals and the infrequency of esophageal adenocarcinoma in the general population (despite the rising incidence), the cancer risk for patients with short segment disease must be substantially less than 1% per year.

The factors underlying both the rising frequency of adenocarcinoma of the esophagogastric junction in Western countries and the striking racial differences in attack rates are not known. One intriguing hypothesis is that differences in the frequency of infection with *Helicobacter pylori*, a bacteria that infects more than one-half of the world's population, may account for differences in the frequency of reflux esophagitis, Barrett's esophagus, and adenocarcinoma among different races and countries. *H. pylori* infection is especially prevalent in black and Asian populations (39). The International Agency for Research on Cancer has classified *H. pylori* as a group 1 carcinogen, i.e. a definite cause of adenocarcinoma of the stomach (40). Although there is a clear association between *H. pylori* infection and cancers in the gastric body and antrum, cancers of the gastric cardia and cancers of the esophagogastric junction do not appear to be associated directly with this infection (41,42). Indeed, several recent reports have suggested that gastric infection with *H. pylori* may protect the esophagus by preventing the development of reflux esophagitis, Barrett's esophagus, and adenocarcinoma of the esophagus and esophagogastric junction. For example, one prospective study of consecutive patients in a general endoscopy unit found that *H. pylori* infection was significantly less prevalent in patients with reflux esophagitis than in control patients without reflux disease (43). Labenz et al. found that patients with duodenal ulcers whose *H. pylori* infections were eradicated with antibiotics developed reflux esophagitis twice as often as those whose infections persisted (44). Also, at least one preliminary study has found a significant negative association between *H. pylori* infection and esophageal adenocarcinoma, suggesting that this infection may help to prevent the development of glandular tumors in the esophagus (45). Strains of *H. pylori* that contain a CagA gene associated with cytotoxin expression may be especially protective against esophageal disease. In a study of 129 patients with adenocarcinomas of the esophagus and gastric cardia and 224 population controls, Chow et al. found that infection with CagA-positive *H. pylori* was associated with a reduced risk for these cancers (OR 0.4, CI 0.2-0.8) (46). In a very recent study, Vicari et al. found CagA-positivity in 42% (11 of 26) of control subjects (without GERD) who were infected with *H. pylori*, but in only 13% (2 of 15) of patients with Barrett's esophagus and *H. pylori* infection (13%) ($P<0.05$) (47). Furthermore, none of 7 infected patients who had Barrett's esophagus complicated by dysplasia or carcinoma were cagA-positive (see figure on following page). The hypothesis that *H. pylori* infection protects against Barrett's adenocarcinomas fits well with the observation that the frequency of these tumors has increased in

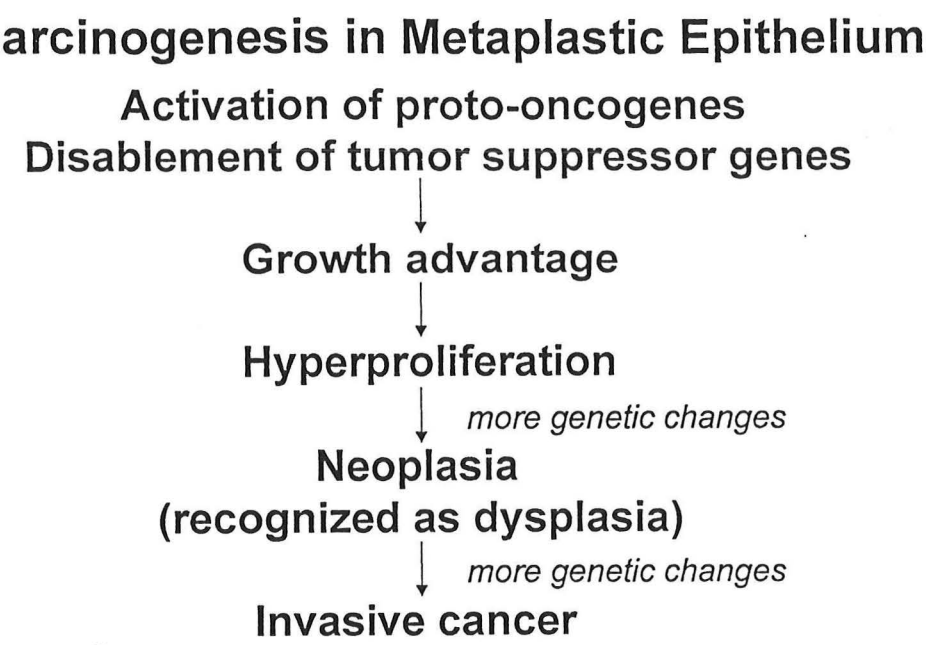
Western countries during a period when the frequency of *H. pylori* infection in the general population has declined (39).



Data from Vicari JJ et al. Gastroenterology 1998; 115:50.

Dysplasia. The figure on the following page shows that carcinogenesis in Barrett's esophagus begins with genetic alterations that either activate proto-oncogenes, disable tumor suppressor genes, or both (48). These DNA abnormalities endow the cells with certain growth advantages, and the advantaged cells hyperproliferate. During hyperproliferation, the cells acquire more genetic changes that eventuate in autonomous cell growth (neoplasia). When enough DNA abnormalities accumulate, a clone of malignant cells emerge that have the ability to invade adjacent tissues and to proliferate in unnatural locations. Before the cells acquire enough DNA damage to become frankly malignant, the genetic alterations often cause morphologic changes that can be recognized by the pathologist as dysplasia. Dysplastic cells are neoplastic, but not necessarily malignant. In dysplasia, the neoplastic cells remain confined within the basement membranes of the glands from which they arose (49). The dysplastic changes are graded as low-grade or high-grade depending upon the degree of alterations in nuclear morphology and glandular architecture. Endoscopic surveillance for cancer in Barrett's esophagus is performed primarily to seek high-grade dysplasia, with the rationale that resection of the dysplastic epithelium may prevent the progression to invasive malignancy (50).

For Barrett's esophagus, biopsy sampling error is a major problem that limits the utility of dysplasia as a biomarker for malignancy. For example, among patients who have esophageal



resections performed because endoscopic examination reveals high-grade dysplasia in Barrett's esophagus, approximately one-third are found to have an inapparent malignancy in the resected specimen (51,52). These cancers are missed by the endoscopist preoperatively because of biopsy sampling error. Sampling error can be reduced by increasing the number of biopsy specimens obtained during the endoscopic examination. Investigators from Seattle have reported that they could differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus by adherence to a very rigorous endoscopic biopsy protocol wherein the esophagus was sampled extensively (53). They obtained four-quadrant "jumbo" biopsy specimens at 2 cm intervals throughout the columnar-lined esophagus, and took many additional samples from sites of known dysplasia. After preoperative evaluation by this protocol, none of seven patients who had an esophageal resection for high-grade dysplasia in Barrett's epithelium was found to have invasive cancer in the resected esophagus. For each of those seven patients, however, 29 to 185 pre-operative biopsy specimens were available for review. In one patient, 185 biopsy specimens were obtained during 5 preoperative endoscopies from a segment of columnar epithelium that spanned only 3 cm! This extensive sampling undoubtedly minimized the problem of biopsy sampling error, explaining why this report contradicted the results of other investigations on the same issue. Interestingly, this report even contradicted the conclusions of an earlier study from the same group of investigators in which they described 4 patients who had high-grade dysplasia associated with intramucosal carcinoma (early cancer) in Barrett's esophagus (54). In one patient, the intramucosal cancer was found in only 1 of 154 biopsy specimens. This, and other observations, led the investigators to conclude that, "...there is no doubt that some intramucosal carcinomas accompanying high-grade dysplasia will be missed by endoscopic biopsies." Apparently, extensive biopsy sampling can reduce, but not eliminate, the problem of biopsy sampling error.

Another problem with the use of dysplasia as a biomarker for malignancy is the fact that the natural history of the condition is not well defined. A number of studies suggest, however, that high-grade dysplasia in Barrett's esophagus progresses to malignancy often and rapidly. For example, Hameeteman described 5 patients who had adenocarcinoma detected within one year of the discovery of high-grade dysplasia in Barrett's esophagus (55). In the aforementioned study by Levine et al., 7 of 29 patients (24%) with high-grade dysplasia were found to progress to invasive cancer during a follow-up period of 2 to 46 months (53). Although these studies suggest that

high-grade dysplasia frequently progresses quickly to cancer, there are verified reports of patients in whom high-grade dysplasia has persisted for years with no apparent progression to carcinoma (56).

Biomarkers. Noting the shortcomings of dysplasia as a biomarker for malignancy in Barrett's esophagus, investigators have sought alternative biomarkers as summarized below (57):

Proposed Biomarkers for Malignancy in Barrett's Esophagus

Ornithine Decarboxylase
Carcinoembryonic Antigen [CEA]
Mucus Abnormalities
Flow Cytometry - Aneuploidy and Abnormal Cellular Proliferation
Chromosomal Abnormalities [trisomy 7, loss of Y chromosome]
Oncogenes [ras, src, erb-B, bcl-2]
Tumor Suppressor Genes [p53, APC, retinoblastoma gene]
Growth Regulatory Factors [EGF, TGF-α, EGF-R, cyclins]
Proliferating Cell Nuclear Antigen and Ki67
Microsatellite Instability
Cell Adhesion Molecules

A number of recent reports have focused on the role of the p53 tumor-suppressor gene that is located on the short arm of chromosome 17 (allele 17p). Restriction fragment length polymorphism analysis revealed 17p allelic deletions in 12 of 13 cancers in Barrett's esophagus in one study (58). In one-half to two-thirds of patients with such cancers, overexpression of p53 protein also can be found in the metaplastic epithelium surrounding the tumor (58-60). Unlike the colon in which 17p deletion usually is a late event in cancer development, 17p allelic losses appear to occur early during carcinogenesis in Barrett's esophagus (48). One group recently reported that patients with Barrett's esophagus or esophageal cancer may have circulating antibodies to p53 (61). In some of their patients, the detection of anti-p53 antibodies predated the clinical diagnosis of esophageal cancer.

Flow cytometry, which can detect abnormalities in cellular DNA content and proliferation, also has received much attention as a potential biomarker for malignancy in Barrett's esophagus. In one study, flow cytometric analysis of biopsy specimens from 62 patients with Barrett's esophagus revealed abnormalities in 13 cases (62). During a mean follow-up period of 34 months, 9 of the 13 patients with flow-cytometric abnormalities on initial evaluation developed histological changes recognizable as high-grade dysplasia, adenocarcinoma, or both. In contrast, none of the 49 patients without flow-cytometric abnormalities developed high-grade dysplasia or cancer. It is important to note that no patient in this series progressed to invasive cancer without first exhibiting high-grade dysplasia. In an accompanying editorial, Cameron acknowledged that flow-cytometric abnormalities may be earlier and more specific markers for cancer development than dysplasia, but cautioned that the test did not provide sufficient additional information to justify its routine application in clinical practice (63). Similarly, none of the biomarkers listed above provides such information. Although the search for better tests continues, dysplasia

remains the most appropriate biomarker for the clinical evaluation of patients with Barrett's esophagus.

Treatment of Dysplasia. Esophageal resection is the only therapy that clearly interrupts the progression from dysplasia to invasive cancer in Barrett's esophagus. Unfortunately, esophageal resection is associated with substantial morbidity and mortality, and the role of this procedure in patient management is disputed.

Some authorities advocate intensive endoscopic surveillance rather than esophageal resection for patients found to have high-grade dysplasia in Barrett's esophagus (53). These authorities recommend resectional surgery only when surveillance unequivocally demonstrates invasive cancer. The arguments in favor of this approach can be summarized as follows: 1) There are verified cases of patients whose high-grade dysplasia in Barrett's esophagus persisted for years without progression to esophageal cancer. One recent report even has alleged that high-grade dysplasia rarely may regress completely with medical antireflux therapy (64). These reports suggest that some patients with high-grade dysplasia may not progress to adenocarcinoma, and therefore can avoid the hazards of esophageal resection. 2) There are documented cases of patients with high-grade dysplasia in whom rigorous endoscopic surveillance detected adenocarcinoma in an early, curable stage. 3) The mortality rate for esophageal resection is in the range of 4% to 10%, and there is substantial, long-term morbidity associated with the procedure.

Other authorities favor a more aggressive approach, and advocate esophageal resection (unless precluded by advanced age or comorbidity) for all patients found to have high-grade dysplasia in Barrett's esophagus (65). The arguments that support this approach are as follows: 1) As many as one-third of patients found to have high-grade dysplasia in Barrett's esophagus already may have an inapparent focus of invasive cancer. 2) Frequent and extensive biopsy sampling is required to exclude the presence of adenocarcinoma with any reasonable degree of certainty. 3) The progression to invasive cancer can be rapid, and appears to occur frequently. 4) The efficacy of endoscopic surveillance in detecting early, curable cancers is not clear. 5) Established esophageal cancers metastasize frequently, and often are not curable. These features suggest that expectant management of high-grade dysplasia in Barrett's esophagus can be hazardous.

Ablative Therapy

Metaplasia is a potentially reversible process. If the noxious factors that lead to the development of metaplasia can be eliminated, the metaplastic epithelium may regress. Partial regression of intestinal metaplasia in Barrett's esophagus has been observed after medical and surgical treatment of gastroesophageal reflux (66,67). However, antireflux therapy alone rarely, if ever, causes complete regression of the metaplastic epithelium. A number of recent studies have shown that it is possible to ablate the metaplastic columnar lining in Barrett's esophagus using thermal or photochemical energy delivered perendoscopically (68). The modalities available for such ablation therapy are listed on the following page.

Endoscopic Modalities for Mucosal Ablation in Barrett's Esophagus

Modalities that induce tissue injury with heat:
Argon laser
Nd:YAG laser
KTP laser
Multipolar electrocoagulation
Argon beam plasma coagulator

Modalities that induce tissue injury with freezing:
Cryotherapy with liquid nitrogen

Modalities that induce tissue injury with photochemical energy:
Photodynamic therapy

When acid reflux is controlled with proton pump inhibitors or fundoplication, the ablated columnar epithelium in the esophagus heals with the regeneration of squamous epithelium. The relative merits of the modalities listed above are disputed, and it is not yet clear which is the "best" form of ablative therapy for Barrett's esophagus. When choosing among the available modalities, however, there appears to be a trade-off between the completeness of mucosal ablation and the frequency of complications. Modalities that induce relatively superficial mucosal injury (e.g. argon laser) cause few complications, but often leave residual foci of metaplastic epithelium behind. Conversely, modalities that can cause deep injury (e.g. Nd:YAG laser) appear to be more effective at eliminating metaplastic mucosa, but the rate of complications such as esophageal perforation and stricture formation is high.

In photodynamic therapy (PDT), patients are given a systemic dose of a light-activated drug (e.g. a porphyrin) that is taken up by the metaplastic columnar cells in Barrett's esophagus. Using an endoscopic approach and a low-power laser, the esophagus is irradiated with laser light (usually red laser light at a wave length of 630 nm) that activates the porphyrin. The activated porphyrin can transfer its energy to oxygen, thereby producing singlet oxygen that is toxic to cells. Thus, any cell that concentrates the photosensitizer is destroyed when the drug is activated by exposure to laser light. In Barrett's esophagus, the porphyrin photosensitizer is concentrated by both neoplastic and non-neoplastic cells. Therefore, PDT can ablate dysplastic cells, malignant cells, and non-neoplastic cells that line the esophagus.

Among the modalities available for mucosal ablation, PDT appears to be particularly well suited for the treatment of dysplasia for several reasons. The photosensitizing drugs tend to be concentrated preferentially in dysplastic (neoplastic) mucosa whose vasculature is abnormally permeable to large molecules such as porphyrins, and whose lymphatic drainage may be compromised. Thus, dysplastic mucosa may be especially susceptible to PDT-induced destruction. PDT uses a light diffuser to irradiate a wide area of the esophagus. This obviates the precise aiming required by time consuming focal treatments such as Nd:YAG laser or multipolar electrocoagulation, and enables the endoscopist to treat long segments of columnar-lined esophagus quickly and with relative ease. The endoscopic application of PDT also is more

comfortable for the patient than some of the heat-generating therapies such as Nd:YAG laser (69). In theory, PDT should induce an optimal depth of tissue injury, i.e. deep enough to eradicate the dysplastic mucosa, yet shallow enough to prevent complications such as esophageal perforation. This is because tissue attenuation of red light helps to limit the depth of injury induced by PDT to approximately 2 mm (70). Despite all these theoretical advantages, however, PDT for dysplasia in Barrett's esophagus is not always successful or free of complications.

Two photosensitizing agents have been used for primary PDT in Barrett's esophagus, viz. porfimer sodium and 5-aminolevulinic acid (5-ALA) (71). Porfimer sodium, a mixture of hematoporphyrins, must be administered intravenously and produces skin photosensitivity that can last for several months. The endoscopic application of laser light must be delayed approximately 2 to 3 days after the porfimer sodium is given, and PDT with this agent frequently is complicated by esophageal stricture formation. 5-ALA normally is produced endogenously as part of the heme biosynthetic pathway. The exogenous administration of large quantities of 5-ALA results in the intracellular accumulation of protoporphyrin IX, a potent photosensitizer that is the immediate precursor of heme. Unlike porfimer sodium, 5-ALA can be administered orally, laser light can be applied only 4 to 6 hours later, skin photosensitivity lasts several days rather than months, and esophageal stricture formation occurs infrequently. Unfortunately, 5-ALA does not appear to be as effective as porfimer sodium for eradicating dysplasia in Barrett's esophagus (71).

The published experience with PDT in Barrett's esophagus is limited, and comparisons among studies are confounded by differences in the photosensitizing agent used (porfimer sodium or 5-ALA), the dose of the agent given (porfimer sodium dose range 1.5-2 mg/kg), the wavelength of laser light irradiated (630 nm or 635 nm), the dose of light energy administered (range 100-300 J/cm), and the type of endoscopic delivery system employed (naked diffuser or centering balloon) (72-76). The largest series published in a peer-reviewed journal to date is that of Overholt and Panjehpour who have described the results of PDT with porfimer sodium for 36 patients with Barrett's esophagus (74). Fourteen of the 36 patients had superficial cancers, and 22 had dysplasia without apparent malignancy. Six months after PDT, no evidence of malignancy was found in any of the 14 patients with superficial cancers. During a follow-up period that ranged from 7 to 62 months, however, one of these patients developed a second primary esophageal cancer in an untreated area, and another was found to have an adenocarcinoma in the center of an area that had been treated with apparent success, i.e. there had been regrowth of squamous epithelium. The cancer occurred in residual glandular tissue that was "buried" under the new squamous lining. Among the 22 patients who had dysplasia without cancer, 16 had no dysplasia found on follow-up endoscopic examinations whereas 6 had residual foci of dysplastic epithelium. Substantial regression of columnar metaplasia was observed in all cases, although only 10 the 36 patients had apparent "complete" regression of esophageal columnar epithelium. In two patients, furthermore, biopsy specimens taken from treated areas that grossly appeared to be lined with squamous epithelium revealed residual areas of glandular epithelium. Also, the rate of side effects and complications was high. Most patients experienced minor problems with photosensitivity, although 4 of the 36 patients experienced substantial problems when they exposed themselves to direct sunlight. Most patients experienced chest pain and dysphagia of mild to moderate severity for five to seven days after the laser treatment, and many required treatment with intravenous fluids to maintain hydration during that period. Small, clinically

inapparent pleural effusions also developed in most patients (Overholt BF, personal communication). Two patients developed atrial fibrillation after PDT. Both were treated successfully with medical therapy, and both recovered without sequelae. Perhaps most worrisome was the high rate of esophageal stricture formation. Twenty-one of the 36 patients (58%) developed esophageal strictures that required one or more episodes of dilation therapy.

Overholt's experience with PDT using porfimer sodium now includes more than 100 patients with Barrett's esophagus (Overholt BF, personal communication). With refinements in technique including the use of a centering balloon, he now estimates that PDT results in esophageal stricture formation in approximately 35% of patients. Apparent complete elimination of columnar metaplasia occurs in approximately 40% of cases whereas, in most patients, squamous epithelium replaces 75% to 80% of the metaplastic columnar lining. The success rate for eradication of superficial cancers in Barrett's esophagus appears to be approximately 75%, whereas the apparent success rate for eradication of dysplasia is approximately 80%. These figures must be interpreted with caution, however, because of problems due to biopsy sampling error and because the duration of follow-up is relatively short. Although available reports document the feasibility of ablating metaplastic columnar epithelium in the esophagus with PDT, they do not establish the benefit of the technique. PDT with porfimer sodium is an expensive treatment that entails substantial risk and inconvenience as outlined below:

Complications of PDT with Porfimer Sodium in Barrett's Esophagus

Common complications:

Photosensitivity for months	All patients should be advised to avoid direct sunlight and wear protective clothing including hats, ski masks, and gloves when going outdoors
Chest pain and dysphagia for days	May require intravenous fluids to prevent dehydration
Small pleural effusions	Usually asymptomatic, require no treatment
Esophageal strictures	Develop in one-third of patients; usually respond to one or more sessions of esophageal dilation

Uncommon complications:

Large pleural effusions	Thoracentesis recommended for symptomatic patients
Atrial fibrillation	Responds to medical therapy; no permanent sequelae reported

When interpreting the results of studies on PDT, furthermore, it is important to consider the substantial problem of biopsy sampling error. As discussed earlier, patients found to have high-grade dysplasia in Barrett's esophagus often harbor inapparent foci of invasive cancer that are missed due to biopsy sampling error. Without histologic examination of the resected esophagus or very long durations of follow-up, it is not possible to verify the claims of available reports that dysplasia and cancer in Barrett's esophagus were "eliminated" by PDT. These claims were based on random biopsy sampling of the treated esophagus. Some of the patients who appeared to be cured in fact may still be harboring inapparent foci of cancer or dysplasia that might eventually cause illness. Reports from China have documented that untreated, early esophageal cancers can remain asymptomatic for five years or more (78). Thus, it is inappropriate to conclude on the basis of random biopsy specimens obtained within months of PDT that cancer and dysplasia have been eradicated. Also, PDT usually does not eliminate all of the metaplastic epithelium in the esophagus. Residual foci of metaplasia remain in most patients, and some of these foci may be buried under a superficial layer of squamous epithelium where they are invisible to the endoscopist. Failure to obliterate all of the metaplastic epithelium might leave patients at high risk for malignancy, and the inability to detect metaplasia hidden by the overgrowth of squamous epithelium might compromise surveillance programs. No study yet has established that PDT has any effect on the risk for cancer development in Barrett's esophagus.

Presumably, patients treated with PDT will require life-long antireflux therapy with potent antisecretory agents like proton pump inhibitors or with fundoplication to prevent the return of reflux esophagitis and columnar metaplasia. One report has described the results of Nd:YAG laser photoablation of Barrett's esophagus in a 43 year-old man with longstanding reflux esophagitis (78). An endoscopic examination performed 6 weeks after treatment revealed no endoscopic or histologic signs of metaplastic epithelium. However, a follow-up endoscopic examination at 14 weeks showed that metaplastic mucosa had returned despite ongoing treatment with omeprazole in a dose of 20 mg daily. This report suggests that columnar metaplasia in the esophagus is both reversible and revertible. Clearly, even patients treated successfully with PDT will require regular endoscopic surveillance to ensure that metaplastic epithelium has not returned and to monitor for neoplasia.

Presently, to recommend PDT in Barrett's esophagus for clinical purposes is to endorse an expensive and potentially hazardous therapy that usually does not obliterate all of the metaplastic mucosa, that has no proved efficacy in reducing cancer risk, that will likely require antireflux surgery or antisecretory drugs administered life-long in high doses to prevent recurrence, that might produce only temporary results, and that does not obviate regular endoscopic surveillance. These considerations must temper enthusiasm for the wholesale application of this technique in clinical practice. Nevertheless, this is an exciting area for research. For patients with high-grade dysplasia or superficial cancers in Barrett's esophagus who are too old, infirm, or unwilling to assume the considerable risks of esophageal resection and reconstruction, PDT is a very reasonable alternative provided the procedure is performed as part of an established study protocol.

Management

There are four major components in the management of patients with traditional ("long-segment") Barrett's esophagus: 1) Treatment of the associated gastroesophageal reflux disease

(GERD), 2) Endoscopic surveillance to detect dysplasia, 3) Treatment of dysplasia, and 4) Consideration of experimental techniques for ablating the metaplastic mucosa. The treatment of GERD for patients with Barrett's esophagus does not differ from that for patients without Barrett's esophagus. The latter three components of patient management all are controversial primarily because there are no studies that clearly establish the benefits of endoscopic surveillance, treatments for dysplasia, and mucosal ablation. My approach to patient management is a modern modification of the basic approach recommended by the 1990 Barrett's Esophagus Working Party of the World Congresses of Gastroenterology (79,80):

1. Presently, ablative therapies for Barrett's esophagus must be considered experimental, and their use should be limited primarily to patients enrolled in research protocols.
2. A program of regular endoscopic surveillance for dysplasia and early carcinoma is recommended for patients who have columnar lined esophagus with intestinal metaplasia unless contraindicated by comorbidity. For patients who have no dysplasia or cancer, endoscopy (with biopsy and brush cytology specimens taken from the columnar lined esophagus) is performed every two to three years.
3. If dysplasia is detected, the finding should be confirmed by at least one other expert pathologist. If any doubt remains, the endoscopic examination is repeated to obtain more biopsy and cytology specimens for analysis.
4. For patients confirmed to have persistent, multiple foci of high-grade dysplasia, surgery is advised to resect all of the esophagus lined by columnar epithelium unless the operative risk is prohibitive or there is an established research protocol available so that the patient can be enrolled in a study on ablative therapy for dysplasia in Barrett's esophagus. For patients whose operative risk is prohibitive due to advanced age or comorbidity, consideration should be given to experimental ablative techniques such as photodynamic therapy.
5. For patients confirmed to have low-grade dysplasia, intensive medical antireflux therapy (including a proton pump inhibitor) should be given for 8 to 12 weeks at which time the endoscopic examination is repeated to obtain multiple esophageal biopsy and cytology specimens.
    a. For patients whose specimens show histologic improvement, intensive surveillance (e.g. endoscopic examinations every 6 months) is recommended until at least two consecutive examinations reveal no dysplastic epithelium.
    b. For patients with persistent low-grade dysplasia, continued intensive surveillance (e.g. endoscopic examinations every year) is recommended.

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