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Barrett's Esophagus: Clinical Issues

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Barrett's esophagus has been defined conceptually as the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus (1). The condition develops as a consequence of gastroesophageal reflux disease (GERD). Barrett's metaplasia has clinical importance primarily because of its malignant predisposition, and virtually all of the contentious clinical issues in Barrett's esophagus are related in some way to its cancer risk. This report will consider some key clinical issues that impact the management of patients with Barrett's esophagus.

Diagnosis

Although more than 60 years have passed since Norman Barrett published his original treatise on the condition that now bears his name (2), authorities still dispute the diagnostic criteria for Barrett's esophagus. The conceptual definition proposed above does not translate readily into clear-cut diagnostic criteria, in part because it is not clear which of the multiple columnar cell types that can be found in Barrett's esophagus have a malignant predisposition.

In 1976, Paull reported that patients with Barrett's esophagus could have up to three types of columnar epithelia lining the distal esophagus (3): 1) a junctional (also called cardia-type) epithelium comprised of mucus-secreting cells, 2) a gastric fundic-type epithelium with parietal and chief cells, and 3) intestinal-type metaplasia (also called specialized columnar epithelium or specialized intestinal metaplasia) with prominent goblet cells. By the early 1980s, it had been established that Barrett's esophagus was a risk factor for esophageal adenocarcinoma, and intestinal metaplasia was reported to be the esophageal epithelial type most frequently associated with that cancer (4). By the late 1980's, intestinal metaplasia was widely regarded as both the most common type of Barrett's epithelium and the one that predisposed to malignancy (5). In addition, intestinal metaplasia was readily identified histologically by its distinctive goblet cells and, unlike the cardia-type and gastric fundic-type epithelia, intestinal metaplasia clearly was abnormal when found in the region of the

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gastroesophageal junction. Consequently, some authorities chose to define Barrett's esophagus by the presence of intestinal metaplasia, and this diagnostic criterion was adopted into clinical practice (6). Since the 1990s, an esophageal biopsy specimen showing intestinal-type metaplasia with goblet cells has become virtually a *sine qua non* for the diagnosis of Barrett's esophagus (7).

In 1994, Spechler *et al.* reported that 18% of consecutive patients in a general endoscopy unit who had columnar epithelium that involved <3 cm of the distal esophagus had intestinal metaplasia (8). Before then, endoscopists infrequently took biopsy specimens from such short segments of esophageal columnar epithelium. Since then, Barrett's esophagus has been categorized as long-segment (when the metaplastic epithelium extends at least 3 cm above the GEJ) or short-segment (when there is <3 cm of metaplastic epithelium lining the esophagus) (9). The Prague C and M classification, which calls for identifying both the circumferential extent (C) and the maximum extent (M) of Barrett's metaplasia, is an even more recent system for describing the extent of Barrett's esophagus endoscopically (10). Although studies have demonstrated excellent inter-observer agreement among endoscopists using the Prague C and M criteria (when columnar epithelium extends >1 cm above the GEJ), the clinical benefit of using this system has not been established and, presently, patients with any extent of intestinal metaplasia in the esophagus are managed similarly.

When evaluating studies on Barrett's esophagus, physicians should consider how changes in diagnostic criteria over the years have impacted the conclusions of those investigations. For example, short-segment Barrett's esophagus was not widely recognized until 1994, and the vast majority of studies reported before that year included only patients with long-segment disease. More recent studies, however, include a substantial proportion of short-segment Barrett's patients, whose GERD severity and esophageal cancer risk may differ considerably from those for patients with long-segment disease. It may not be appropriate to extrapolate the results of older studies on the epidemiology and natural history of long-segment Barrett's esophagus to patients with short-segment disease.

Another recent issue that has caused considerable controversy is whether the diagnosis of Barrett's esophagus should be limited to patients who have an esophageal biopsy specimen demonstrating intestinal metaplasia (with goblet cells), or whether the finding of gastric cardia-type epithelium in the esophagus also warrants that diagnosis (11). Cardia-type epithelium (also called cardiac or junctional-type epithelium) traditionally has been considered the normal lining of the proximal stomach (the gastric cardia). However, there are data to suggest that cardia-type epithelium might not be normal, but rather a metaplastic lining that develops as a consequence of GERD (12). Histochemical and molecular studies of cardia-type epithelium have revealed abnormalities that could predispose to carcinogenesis (13,14), and several limited clinical studies support the concept that cardia-type epithelium has malignant potential (15–17). Consequently, some authorities have proposed that cardia-type epithelium in the esophagus should be considered Barrett's esophagus (11).

The large majority of studies on cancer risk in Barrett's esophagus have included patients with intestinal metaplasia, either primarily or exclusively. Therefore, the magnitude of the

cancer risk associated with cardia-type epithelium in the esophagus is not clear. Pending such clarification, it seems reasonable to limit the diagnosis of Barrett's esophagus to patients who have intestinal metaplasia. This diagnostic criterion could change in the near future. However, it should be noted that the conceptual definition of Barrett's esophagus (the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus) does not change, even if specific diagnostic criteria are altered.

Prevalence

Barrett's esophagus (predominantly the short-segment variety) is found in 10% to 20% of patients who have endoscopic examinations for the evaluation of GERD symptoms (18). Two relatively recent studies have provided information on the prevalence of Barrett's esophagus in the general population (19,20). In one study from Sweden, 1,000 randomly-selected adults in the general population had an endoscopic examination performed to look for Barrett's esophagus (19). The condition was identified endoscopically and confirmed by an esophageal biopsy specimen showing intestinal metaplasia in 16 individuals (5 long-segment and 11 short-segment Barrett's esophagus), representing an overall prevalence of 1.6%. This prevalence rate is likely an underestimate, however, because 60 patients (6%) were found to have intestinal metaplasia in biopsy specimens taken at the gastroesophageal junction, and some of those patients probably had short-segment Barrett's esophagus that was not recognized by the endoscopists. Interestingly, only 9 (56%) of the 16 individuals identified with Barrett's esophagus had a history of GERD symptoms [4 of the 5 (80%) with long-segment, 5 of the 11 (46%) with short-segment Barrett's esophagus]. In an American study in which 961 patients scheduled for elective colonoscopy agreed to have an upper gastrointestinal endoscopy performed to detect Barrett's esophagus, the overall prevalence of the condition was 6.8% (20). Among the 556 patients who had no history of heartburn, short-segment Barrett's esophagus was found in 5.2%, whereas 5.7% of 384 patients who complained of heartburn had short-segment Barrett's esophagus.

The aforementioned studies suggest that the prevalence of Barrett's esophagus in the general adult population is between 2% and 7%. Clearly, Barrett's esophagus is a very common condition. The studies also suggest that GERD is not a reliable marker for Barrett's esophagus, especially the short-segment variety. These observations have at least two important implications for clinicians who treat patients with Barrett's esophagus. First, since the condition is so common, virtually any interventional management strategy applied to the general population of patients with Barrett's esophagus will entail a considerable healthcare expenditure for society. Second, screening programs for the condition that include only patients with GERD symptoms will miss approximately 50% of individuals who have Barrett's esophagus.

Cancer Risk

Published estimates on the incidence of cancer in Barrett's esophagus have ranged from 0.2% to 2.9% per year (21). By pooling data from those reports, investigators in the 1990s estimated that patients with Barrett's esophagus developed cancer at the rate of 1% per year

(22). In 2000, Shaheen reported that this estimate was too high, because many of the studies on which the estimate was based were small series, and those reports suffered from publication bias (the selective reporting of studies with positive or extreme results) (21). Presently, the risk of cancer in Barrett's esophagus is judged to be approximately 0.5% per year.

Although the difference between an annual cancer incidence of 0.5% and 1% may seem trivial, in fact this difference has important implications for the management of patients with Barrett's esophagus. Computer models on the value of different endoscopic surveillance and interventional strategies for patients with Barrett's esophagus can be extremely sensitive to the value chosen for the incidence of esophageal cancer. In one such model, for example, endoscopic surveillance every 2 years is the preferred strategy if the annual cancer incidence is 1%, whereas surveillance every four years is preferred for an annual cancer incidence of 0.5% (23).

One important consideration when evaluating reports on the risk of cancer in Barrett's esophagus is the year of publication. As already discussed, short-segment Barrett's esophagus was not widely recognized before 1994, and reports published before then included patients with long-segment disease exclusively. It is logical to assume that the risk of cancer in Barrett's esophagus should increase with the extent of metaplastic epithelium. Patients with longer segments of metaplasia have more cells at risk for mutation and, therefore, should be more likely to acquire the critical combination of DNA alterations that results in malignancy. Data from a number of observational studies support this hypothesis (24–26), but there is yet no proof that the risk of cancer in Barrett's esophagus varies with the extent of the metaplastic lining (27).

Some very recent studies have described rates of cancer development in Barrett's esophagus considerably lower than the widely accepted estimate of 0.5% per year. In a cohort of 1,203 patients with Barrett's esophagus from 5 different medical centers who were followed for a mean duration of 5.5 years (6,644 patient-years), for example, Wani found that only 18 patients developed esophageal adenocarcinoma, which represents a cancer incidence rate of only 0.27% per year (0.17–0.43%, 95% CI) (28). Indeed, 99% of the 504 patients who were followed for 5 years remained cancer-free. It is not clear whether this surprisingly low rate of cancer development was due to the inclusion of a large number of patients with short-segment Barrett's esophagus, the result of aggressive acid-suppressive therapy or due to other, unknown factors.

Does the Cancer Risk Justify Invasive Therapy for Patients with Non-Dysplastic Barrett's Esophagus?

For reasons that are not well understood, the frequency of esophageal adenocarcinoma has increased profoundly in the United States over the past several decades (29). Barrett's esophagus is a major risk factor for this lethal tumor, and a number of invasive therapies (discussed elsewhere in this volume) are available to eradicate Barrett's metaplasia. As discussed above, however, the risk of developing esophageal adenocarcinoma for individual patients who have Barrett's esophagus (without dysplasia) is low. This low rate of cancer

progression raises concerns regarding the invasive treatment options. Does the benefit of an invasive procedure in preventing esophageal cancer justify the expense, inconvenience and risks of the procedure for patients who have Barrett's esophagus without dysplasia?

A recent randomized, sham-controlled trial of radiofrequency ablation (RFA) for patients with high-grade dysplasia in Barrett's esophagus has demonstrated that RFA, which has few serious side effects, decreases the progression from high-grade dysplasia to cancer at one year (30). Limited, uncontrolled studies also have shown that RFA can eradicate non-dysplastic Barrett's epithelium safely in the large majority of patients (31). Noting these results, some authorities recently have proposed that RFA should be considered a therapeutic option to prevent cancer for patients who have Barrett's esophagus without dysplasia (32). Their arguments can be summarized as follows: 1) Non-dysplastic Barrett's metaplasia frequently shows clonal molecular abnormalities that might predispose to cancer development. 2) The common clinical practice of performing endoscopic surveillance to detect curable neoplasia for patients with Barrett's esophagus is of limited benefit because dysplasia and cancer can be missed due to endoscopic biopsy sampling error, the interpretation of dysplasia by pathologists is subjective and inconsistent, patient and physician compliance with surveillance guidelines can be poor and, even with perfect compliance, cancers in Barrett's esophagus have developed without apparent antecedent dysplasia. 3) RFA safely eliminates Barrett's metaplasia in most cases and the results appear to be durable for up to 5 years in limited series. So, why not be pro-active and ablate Barrett's metaplasia with RFA rather than relying on endoscopic surveillance, which has dubious efficacy?

The counter arguments to the proposal for RFA treatment of non-dysplastic Barrett's esophagus are as follows: 1) Despite the molecular abnormalities that can be found in non-dysplastic Barrett's metaplasia, the rate of cancer development is low and adenocarcinoma of the esophagus remains an uncommon malignancy in the general population. 2) RFA may be safe compared to esophagectomy or to photodynamic therapy, but RFA has complications including esophageal stricture formation and bleeding. 3) RFA is a relatively new procedure and long-term results simply are not available. Although the results of RFA appear to be durable in very limited data extending to 5 years, the frequency of "buried metaplasia" (Barrett's metaplasia concealed by an overlying layer of squamous epithelium following ablation) and the long-term frequency of recurrent metaplasia are not known. 4) There are no data showing that RFA prevents cancer for patients with non-dysplastic Barrett's metaplasia. 5) In the absence of long-term data on the rate of recurrent metaplasia and efficacy in cancer prevention, patients who have had RFA will likely require continued endoscopic surveillance, with its attendant expense and inconvenience. 6) RFA is expensive. Using a combination of circumferential and focal RFA procedures, one uncontrolled study found complete eradication of Barrett's epithelium in 60 of 61 patients (98%) (31). However, this required a mean of 1.5 circumferential ablations and 1.9 focal ablations for each patient, representing considerable expense.

As discussed above, the prevalence of Barrett's esophagus in the general adult population is between 2% and 7%. For such a common condition, interventional management strategies will entail a considerable healthcare expenditure for society. When used in so many patients,

furthermore, even a relatively safe procedure like RFA will result in a substantial number of complications. Does the potential, but unproved, benefit of RFA in preventing cancer justify the enormous expense (3–4 RFA procedures per patient to eliminate Barrett's metaplasia), inconvenience and risk of a procedure that presently does not even eliminate the need for regular endoscopic surveillance?

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