Revis(it)ing Barrett’s esophagus

“It is better to be looked over than overlooked.”
(Mae West (1893-1980); American actress, playwright, screenwriter, and sex symbol)

The incidence of esophageal adenocarcinoma is rising, and chronic reflux symptoms and Barrett’s esophagus are considered its key underlying risk factors. Reliable detection of Barrett’s esophagus during upper endoscopy is therefore mandatory but requires histology (or optical biopsy) for confirmation. Appropriate treatment of patients with endoscopic suspicion but negative histology, or vice versa, or of patients with no endoscopic suspicion but with a biopsy diagnosis of intestinal metaplasia at the gastroesophageal junction, remains clinically challenging.

The definition of Barrett’s esophagus remains controversial and varies worldwide. The American Gastroenterological Association medical position statement states the following: “Barrett’s esophagus is 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. Presently intestinal metaplasia is required for the diagnosis of Barrett’s metaplasia because intestinal metaplasia is the only one of the three types of esophageal columnar epithelium that clearly predisposes to malignancy.” This definition of Barrett’s esophagus is in conflict with the current United Kingdom and Japanese perspective and the definition of the British Society of Gastroenterology guideline, which defines Barrett’s esophagus as “an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1 cm) above the gastro-esophageal junction and confirmed histo-pathologically from oesophageal biopsies.” The Prague C & M classification, developed to standardize Barrett’s esophagus, has been globally well validated in various populations, and utility studies have shown excellent interrater reliability in the recognition of Barrett’s esophagus that are longer than 1 cm but not less.

In the current issue of Gastrointestinal Endoscopy, a retrospective study by Ganz et al. used the American Gastroenterological Association criteria, that is, any length of columnar-lined esophagus containing goblet cells, and revised the previously made diagnosis of Barrett’s esophagus after intensive consensus by anatomic, endoscopic, and strict histologic review. Eighty-eight (67.7%) patients had confirmed Barrett’s esophagus, and 42 (32.3%) had their diagnosis revised (95% confidence interval; 24.4% to 41.1%) because there was no visible columnar epithelium proximal to the gastric folds or no goblet cells were found on biopsy. Not surprisingly, there were several predictors of revision of the original diagnosis: younger age, female sex, shorter Barrett’s length, and shorter size of, or no, hiatal hernia. The authors concluded that Barrett’s esophagus is overdiagnosed in clinical practice, with important implications for patient care, including increased costs, reduced insurability, and patient psychological stress.

Unquestionably there is a need for better endoscopic and histological definition of the normal and abnormal gastroesophageal junction and what steps need to be taken regarding surveillance and pharmacologic or endoscopic management of properly defined Barrett’s esophagus.

Everyone acknowledges that Barrett’s esophagus is a mosaic of different epithelia with and without goblet cells, and this may lead to differences between endoscopy and histology. Metaplastic esophageal columnar mucosa is composed of both a glandular and a surface/crypt compartment. The surface/crypt epithelial compartment is typically composed of a mixture of mucinous columnar cells, goblet cells, and other cells of mixed squamous, gastric, and intestinal differentiation. The glandular component is composed of 1, or a combination of, mucous glands or oxyntic glands. Regardless of the presence of goblet cells, metaplastic columnar epithelium of the esophagus often resembles normal gastric cardia mucosa because the latter also shows mucinous columnar cells with underlying mucous glands, oxyntic glands, or both. Furthermore, intestinal metaplasia can develop in the proximal stomach in patients with chronic gastritis. Thus, differentiation of metaplastic esophageal columnar mucosa from proximal gastric columnar mucosa cannot be done reliably by histologic methods, unless one can identify features in the biopsy specimens that indicate that the mucosa was
obtained from the anatomic esophagus. These features include the presence of esophageal mucosal or submucosal glands and their ducts, multilayered epithelium, hybrid or buried glands, and diffuse severe incomplete intestinal metaplasia associated with gland atrophy. Unfortunately, 1 or more of these features are present in only a minority (up to 30%) of biopsy specimens of the gastroesophageal junction, and they therefore carry a low sensitivity.

Even in expert centers, the reproducibility of presumptive endoscopic or histological diagnoses of Barrett’s esophagus has been poor, with only 10% to 20% of cases with either endoscopic or histologic suspicion having been established as Barrett’s esophagus after 2.5 years of follow-up. The risk of dysplasia in this population is very low, and hence meticulous surveillance may not be required. Currently, there are no clear recommendations on how many biopsies are adequate for the detection of goblet cells other than the Seattle protocol, which uses large-capacity forceps and 4-quadrant biopsies every 1 to 2 cm for the detection of neoplasia, an unpopular practice among many gastroenterologists. It is also known that the density of goblet cells is highest (up to 94%) in the proximal part of columnar metaplasia. The number of biopsies needed to detect a goblet cell depends on the length of the columnar segment; according to 1 study, 100% could be reached with more than 16 biopsies.

To complicate matters, there seems to be a risk of malignant transformation in columnar metaplasia that does not contain goblet cells. Defining intestinal metaplasia by the identification of goblet cells has now been shown to be problematic because there is evidence that the non-goblet columnar epithelium may be intestinalized, showing similar molecular abnormalities as goblet cell epithelium, and with a similar risk of neoplastic progression. Several studies suggest that nongoblet columnar metaplasia of the distal esophagus shows biological features of intestinal differentiation and harbors molecular abnormalities that may enhance cancer risk. For instance, gains of chromosome 7 and chromosome 18 were present in 9.8% and 7.9% of nongoblet epithelium, compared with 0.7% and 1.9%, respectively, in esophageal epithelium. Similarly, there was no difference in the frequency or type of mutations in goblet, compared with nongoblet, columnar epithelium of the esophagus regarding P53 mutations or allelic imbalances, loss of heterozygosity, or microsatellite instability of 5Q, 17P, and RB. Finally, DNA content abnormalities, evaluated by high-fidelity DNA histograms based on image cytometry, occurred with equal frequency and extent in metaplastic columnar epithelium of the esophagus without goblet cells, compared with such epithelium with goblet cells. Recently, nongoblet columnar epithelium of the esophagus has been shown to reveal phenotypic evidence of intestinal differentiation, such as expression of DAS1, CDX2, MUC2, and villin. These findings suggest that metaplastic nongoblet columnar epithelium of the esophagus may have neoplastic potential and questions the “revisional” study by Ganz et al as being too restrictive. The difference in definition clearly has the potential to influence the frequency of diagnosis of Barrett’s esophagus, its surveillance, the rates of malignant transformation, and, overall, our understanding of the natural history of this disease.

Only 2 studies have evaluated the risk of neoplasia in patients with esophageal columnar metaplasia either with or without goblet cells. The first evaluated 379 patients with esophageal intestinal metaplasia and 309 without intestinal metaplasia for the development of adenocarcinoma after a median follow-up interval of 12 years (range, 8-20 years). In that study, adenocarcinoma developed in 4.5% of patients with and 3.6% without intestinal metaplasia. In the second study, the frequency of development of low-grade dysplasia, high-grade dysplasia, and adenocarcinoma was compared in 2 patient groups with esophageal columnar metaplasia: those with and those without intestinal metaplasia. Overall, the incidence of cancer was similar in the 2 patient groups (3.1% vs 3.2%, respectively). The incidence of low-grade and high-grade dysplasia was slightly higher in the intestinal metaplasia group, but this difference was not statistically significant.

We are currently awaiting data from the Barrett’s Oesophagus Surveillance Study in the United Kingdom to prospectively show the utility of endoscopy in preventing progression to esophageal cancer. In the meantime, endoscopic surveillance of nondysplastic Barrett’s esophagus is recommended and is routinely performed in many countries, usually every 3 to 5 years. Whether or not such passive surveillance practice without intervention (such as ablation or mucosal resection) translates to a lower mortality rate from esophageal adenocarcinoma is unclear. A case-control Kaiser-Permanente study evaluating all patients with Barrett’s esophagus failed to demonstrate a survival benefit from surveillance within the 3 years before the diagnosis of esophageal cancer. In 1 of the largest retrospective studies involving 15,728 patients with Barrett’s esophagus and spanning over 726,873 person-years, the annual esophageal cancer mortality rate was only 0.14%, and most of the deaths (95.5%) were unrelated to esophageal cancer. The current strategy of surveillance of all patients with nondysplastic Barrett’s esophagus might need to be reevaluated, particularly in the light of new findings of lower than expected annual risk for cancer (0.12%) and a low mortality rate from esophageal adenocarcinoma in these patients, and the lack of cost-effectiveness of endoscopic surveillance, particularly for nondysplastic Barrett’s esophagus, which makes up to 90% of all Barrett’s esophagus cases. In the study by Ganz et al, 32% of patients with previously diagnosed Barrett’s esophagus did not receive histologic confirmation of intestinal metaplasia, and, on this basis, the diagnosis was revised. Almost all of the reversals occurred in patients with previously “termed” short-segment Barrett’s esophagus; indeed, in 55% of revisions,
The authors could not identify any columnar-lined epithelium proximal to the gastric folds. Other predictors of reversal included younger age, female sex, and small, or absence of, hiatal hernia, again suggesting an “overcall.” Of the revisions with no visible columnar lined esophagus in the distal tubular esophagus, 5 patients had cardia intestinal metaplasia, and 18 did not have goblet cells. It is impossible to tell why the original histology was not confirmed, but it could have been a sampling error, initial overdiagnosis, or squamous overgrowth induced by proton pump inhibition. In their discussion, the authors appropriately raise the questions on how to classify such patients, and, more importantly how to treat them in the long term while considering the burdens (emotional and fiscal) to patients, insurers, and society at large.5

Unquestionably there is a need for better endoscopic and histologic definition of the normal and abnormal gastroesophageal junction and what steps need to be taken regarding surveillance and pharmacologic or endoscopic management of properly defined Barrett’s esophagus. A worldwide consensus definition of Barrett’s esophagus would be of enormous value and needs to take place. Instead of “revising,” we should be “revisiting” Barrett’s esophagus as a modern global, albeit mostly Western, epidemic with ominous potential consequences and enormous personal and public health implications.

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