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Buried (but not dead) Barrett's Metaplasia: Tales from the Crypts

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Barrett's esophagus is a risk factor for esophageal adenocarcinoma, a tumor whose frequency has increased more than seven-fold over the past few decades in the United States.

¹ The metaplastic mucosa of Barrett's esophagus, which predisposes to malignancy, can be destroyed by the modern endoscopic technique of radiofrequency ablation (RFA). In RFA, an endoscope is used to position a device that delivers radiofrequency energy to the Barrett's metaplasia in order to inflict a lethal thermal injury to the metaplastic cells. Patients are treated with proton pump inhibitors to control acid reflux, and the ablated Barrett's epithelium heals with the growth of new (neo)squamous epithelium.

In a recent, randomized, sham-controlled trial, RFA resulted in few serious complications and significantly decreased the rate of progression from high-grade dysplasia to cancer in Barrett's esophagus at one year.² Consequently, RFA is now considered the treatment of choice for most patients with high-grade dysplasia in Barrett's esophagus.³ In one uncontrolled study, RFA caused no serious adverse events and resulted in complete eradication of non-dysplastic Barrett's metaplasia in 60 of 61 patients (98%).⁴ Noting these and other data on the safety and apparent efficacy of RFA, some authorities have proposed that even non-dysplastic Barrett's metaplasia should be ablated routinely to prevent the development of esophageal cancer.⁵ Indeed, some have argued that RFA for non-dysplastic Barrett's esophagus is, in principle, equivalent to the widely accepted practice of routinely removing all colonic polyps found during colonoscopy.⁶ To restrict RFA only to Barrett's esophagus with neoplasia, these authorities contend, is like limiting colonoscopic polypectomy only to polyps that are very large or already malignant.

Despite these interesting arguments, enthusiasm for using RFA to treat patients with non-dysplastic Barrett's esophagus should be tempered by the fact that no study has established the efficacy of RFA for cancer prevention in those patients. Rather, that efficacy is inferred from studies showing that RFA can eliminate visible and histological evidence of Barrett's metaplasia for a number of years in most patients. Such studies do not establish that the cancer risk has been eliminated, however, largely because of the problem of "buried metaplasia" (also called buried glands, buried Barrett's metaplasia, buried intestinal metaplasia or subsquamous intestinal metaplasia). After endoscopic ablation of Barrett's esophagus by a number of different techniques (e.g. argon plasma coagulation, photodynamic therapy, RFA), biopsy specimens of what appears to be normal neosquamous

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epithelium can reveal metaplastic glands “buried” under the epithelium in the lamina propria. This buried metaplasia can have malignant potential, as evidenced by a recent systematic review that found reports describing 34 patients who had neoplasms discovered in buried metaplasia after endoscopic ablation of Barrett’s esophagus.⁷

The aforementioned systematic review found 18 studies in which endoscopic biopsy of neosquamous epithelium was performed after RFA of Barrett’s esophagus in a total of 1,004 patients, and buried metaplasia was found in only 9 cases (0.9%).⁷ In 22 reports on photodynamic therapy (PDT) for 953 Barrett’s patients, in contrast, buried metaplasia was found in 135 (14.2%).⁷ Thus, the frequency of buried metaplasia after RFA appeared to be low, and far lower than that described after PDT and other endoscopic ablative therapies. However, the authors of the systematic review noted that, although these studies relied on esophageal biopsy specimens to detect buried metaplasia, none of the reports provided crucial information on the adequacy of those biopsy specimens for identifying buried glands. Buried metaplastic glands typically are located in the subepithelial lamina propria, and most biopsy specimens from esophageal squamous mucosa do not go that deep. In a recent study in which the investigators evaluated the adequacy of 1,692 biopsy tissue pieces of esophageal squamous epithelium, for example, fewer than 11% had subepithelial lamina propria.⁸ Since esophageal biopsies sample only a tiny fraction of the esophageal mucosal surface, and since the large majority of those biopsy samples are not of sufficient depth to be informative for the presence of buried metaplasia, the frequency of buried metaplasia after RFA has not been clear.

In this issue of *Gastrointestinal Endoscopy*, Zhou *et al.* report the results of a study using optical coherence tomography (OCT) to determine the frequency of buried glands in patients with short-segment Barrett’s esophagus before and after treatment with RFA.⁹ In a fashion similar to endoscopic ultrasonography, which uses reflected sound waves to image the bowel wall, endoscopic OCT uses light reflected from tissues to construct cross-sectional and three-dimensional (3D) images of the bowel wall with a resolution close to that provided by a low-power microscope. Endoscopic OCT can image the wall of the esophagus to a depth of 2 mm, which is more than deep enough to detect buried metaplastic glands. In this study, furthermore, each 3D-OCT dataset covered 160 mm² of the esophagus, an area some 60-fold larger than that sampled by a standard biopsy forceps. Thus, endoscopic 3D-OCT is especially well suited to provide information on the presence of buried glands in the esophagus.

With 3D-OCT, the investigators identified buried glands in 13 (72%) of 18 patients before complete eradication, and in 10 (63%) of 16 patients after complete eradication of visible Barrett’s metaplasia by RFA.⁹ RFA caused a significant decrease in the number of buried glands per patient, from a mean of 34 before complete eradication to a mean of 7 glands per patient after complete eradication. The buried glands were found within 5 mm of the squamo-columnar mucosal junction (SCJ) in approximately two-thirds of cases. The investigators did not take esophageal biopsy specimens to seek histological confirmation of their OCT findings in most cases, but they present compelling arguments to suggest that most of the subepithelial glands identified by OCT were indeed metaplastic. Furthermore, these *in vivo* findings are consistent with the results of an *ex vivo* study in which 14

esophagectomy specimens removed because of high-grade dysplasia or adenocarcinoma in Barrett's esophagus were examined by OCT, and subsquamous metaplastic glands were detected by OCT (and confirmed histologically) in 10 (71%) of 14 cases.¹⁰

Earlier, histological studies of pinch biopsy and endoscopic mucosal resection specimens have suggested that buried metaplasia often is found in areas where metaplastic columnar epithelium abuts squamous epithelium, even in patients who have not been treated with ablation therapy. At the endoscopic Z-line (the SCJ) in patients with unablated Barrett's esophagus, for example, biopsy specimens have revealed buried metaplasia in up to 28% of cases.⁷ In squamous islands in Barrett's esophagus, buried metaplasia has been found in biopsy specimens in up to 38.5% of cases.⁷ This important study by Zhou *et al.* suggests that buried metaplasia is even more frequent at the SCJ than previously suspected.⁹ Indeed, this study suggests that most patients with Barrett's esophagus have metaplastic glands hidden under squamous epithelium near the SCJ *before* endoscopic ablation. Although it has been assumed widely that buried glands are a consequence of endoscopic ablation procedures, with neosquamous epithelium growing over incompletely ablated metaplastic glands, Zhou's study suggests that this may not be the case. In this study, RFA caused a *decrease* in both the number of buried glands per patient and in the percentage of patients with any buried glands. It is possible that metaplastic glands grow underneath squamous epithelium spontaneously at SCJ areas. It is also possible that, as a consequence of extensive biopsy sampling of metaplastic epithelium during endoscopic surveillance, the esophageal biopsy sites heal via growth of neosquamous epithelium that buries metaplastic glands.¹¹

The risk of cancer development in buried glands is not known. Authorities have proposed plausible, competing hypotheses for why that risk might be greater or less than that of the surface metaplastic epithelium. For example, it has been proposed that genetic abnormalities acquired during carcinogenesis might convey survival advantages that render neoplastic Barrett's cells more resistant than non-neoplastic cells to ablative therapies.¹² If so, then ablative therapies might preferentially destroy normal cells rather than neoplastic ones, and ablation might be predisposed to bury neoplastic cells that have a high risk of malignancy. Others have suggested that the overlying layer of squamous epithelium protects the buried metaplastic cells from the carcinogenic effects of refluxed acid and bile. In support of this hypothesis, one group found fewer DNA content abnormalities and lower crypt proliferation rates in buried metaplasia than in the surface metaplastic epithelium.¹³ Further studies are needed to resolve this issue.

Zhou's study has shown that, after apparent complete eradication of Barrett's metaplasia by endoscopic therapy, most patients still have buried glands located near the SCJ.⁹ If those glands retain their neoplastic potential, this might explain the high frequency of metachronous neoplasia reported in long-term studies of patients with mucosal neoplasms in Barrett's esophagus treated by endoscopic eradication therapy. In one of the largest, long-term studies of patients who had endoscopic treatment of mucosal neoplasms, for example, metachronous neoplasms developed in 33 (16.5%) of 200 patients who had their Barrett's esophagus eradicated by a combination of endoscopic mucosal resection, PDT and argon plasma coagulation treatments.¹⁴ Buried neoplastic glands seem a likely contributor to this

phenomenon, especially for those patients whose surface metaplasia appeared to have been eradicated completely by endoscopic ablation.

Over the years, developers of endoscopic ablative therapies for Barrett's esophagus have strived to achieve the ideal treatment - one that inflicts an injury deep enough to eradicate all of the metaplastic cells, but not so deep as to cause complications. RFA appears to have come closer to this ideal than any other available ablative therapy, and I am not aware of any report describing neoplasia appearing specifically in buried metaplasia after RFA. Nevertheless, Zhou's study shows that RFA is far from perfect, and that most patients have buried glands at the SCJ after apparently successful RFA treatment. Only time will tell whether this is an important phenomenon. For now, it is clear that the problem of buried metaplasia has not been eliminated by RFA. Consequently, patients cannot yet be assured that RFA eliminates their long-term risk of cancer or their need for surveillance endoscopy.

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