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Endoscopic Treatment for Barrett's Esophagus and Early Esophageal Cancer

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Barrett's esophagus offers two unique opportunities to endoscopically study neoplasia in the esophagus. The first is the effect of chronic inflammatory change produced by reflux of acid and bile into the distal esophagus, producing a partially intestinalized metaplastic epithelium. Most endoscopic therapies for neoplasia do not address this issue since the significance of this process in neoplastic progression is unclear. The pre-neoplastic condition though allows investigators the opportunity to examine the pathogenesis of metaplasia and to assess potential biomarkers. The second opportunity is the ability to treat the metaplasia producing normal appearing squamous mucosa using endoscopic therapies. These techniques have been adapted from the strategies developed from squamous cancers of the esophagus. However, the apparent reversal of the metaplastic process is unique to Barrett's esophagus. The epidemiology of this disease suggests that it is rapidly increasing in Western populations and may be increasing in Asian countries as well.

Like most epithelial malignancies, the inflammatory process is believed to be critical in the generation of a cancer-like stem cell. Although the pathogenesis of the intestinal phenotype has still not been totally elucidated, it seems clear that inflammatory pathways can upregulate cytosolic phospholipase A2 which is known to increase prostaglandin E2 production leading to increased cell proliferation.¹ In addition, the EGFR pathway is also upregulated by these inflammatory mediators. Transcriptional regulators such as BMP4 and CDX2 have been found to be involved in the phenotypic transformation of the squamous mucosa to intestinal-type mucosa. It is believed that the esophageal cancer stem cell is a small nearly quiescent population that then differentiates into a intestinal phenotype under the influence of inflammatory mediators such as IL-6 and the STAT3 pathway.² IL-6 has been found to be important in other cancer stem cells as well as interactions between mesenchymal stem cells. These cells are typically translocated from the bone marrow to regions of inflammation or neoplastic growth. The interactions between cancer stem cells and mesenchymal stem cells produce increased growth. It is important that any therapies that treat Barrett's esophagus also address these issues.

Endoscopic treatment is focused on destruction of the existing metaplastic tissue using thermal or photochemical treatments that eliminate the mucosa. It is unclear why the removal of the metaplastic epithelium almost always results in squamous epithelium, although this effect may not be durable. In addition, it is unclear if the stem cells that gave

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rise to Barrett's esophagus are affected by this therapy. Genetic abnormalities are not found in the squamous mucosa, although they may be present in non-dysplastic appearing metaplastic mucosa after ablative therapy. Current treatment requires combinations of mucosal resection techniques to eliminate visible lesions followed by ablation of residual metaplastic tissue.³ Endoscopic resection can be accomplished by either single or multiple mucosal resection cap devices. It is important that all mucosal abnormalities are first eliminated with mucosal resection devices, since this provides critical information regarding the presence of a malignancy and important information regarding depth of invasion of an existing cancer. Mucosal resection is the only ablative technique that actually acquires histology. After the areas of mucosal abnormality are removed, ablation of the residual Barrett's mucosa is most commonly performed with radiofrequency ablation, though photodynamic and recently cryotherapy have also been used. Results are similar with ablation rates over 80% for all of these therapies. Side effects of these therapies include stricture formation and chest pain after treatment. Photodynamic therapy has the unique adverse event of cutaneous photosensitivity. Photodynamic therapy also is known to have an increased depth of penetration and stricture formation. Long-term results are only available for photodynamic therapy, revealing that durable remission of Barrett's esophagus and high grade dysplasia (HGD) is possible.⁴

Each of the ablative therapies have certain strengths. Radiofrequency ablation is associated with the fewest complications since it has a limited depth of injury, although stricture formation is approximately 6% in a prospective series.⁶ This prospective randomized controlled radiofrequency ablation study with 12-month follow-up found that the success rate in patients with high grade dysplasia was 81%. A patient with a straight esophageal segment without strictures is ideal for this modality. Patients with a tortuous esophagus may well do better with a treatment like photodynamic therapy that can be applied more readily in this situation. In addition, Barrett's segments that do not seem to respond to one form of ablation often respond well to another. Cryotherapy has been used in the situation of preexisting strictures, with some anecdotal success.

However, recurrence of cancer and dysplasia (HGD), is not well established after ablative therapy. After combination photodynamic therapy and endoscopic mucosal resection for high grade dysplasia, the risk of recurrence is 8% in patients treated for HGD.⁴ The risks increase with length of Barrett's esophagus, number of treatments required to eliminate the metaplasia, and the presence of p16 LOH.⁵ Lifetime continued surveillance is still required. Biomarkers that would predict recurrence and identify best patients for treatment are needed.

At the current time, it appears that the best candidates for ablative therapy have shorter segments of Barrett's esophagus with high grade dysplasia (<8 cm), are p16 negative, have straight esophagus, and are compliant with physician instructions. Surgical resection is favored for patients with longer segments, healthier patients (as most endoscopic therapy is performed in patients with significantly more comorbidities), and in patients who do not have a tolerance for treatment failure.

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