Barrett's esophagus – Who, how, how often and what to do with dysplasia?

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One of the issues I struggle with in gastroenterology is when, if and whom to screen for Barrett's esophagus (BE). Although it is becoming common practice to screen patients with chronic reflux for BE, questions abound pertaining to whether screening is effective, as well as cost-effective, whom to screen and what to do when BE is found, not to mention the issues that arise when dysplasia is found. In light of the enormous clinical and economical implications of diagnosing patients with BE (1), some have questioned whether BE is a reasonable target for screening or whether resources would be better allocated to colon cancer prevention.

Most patients agree to endoscopic screening when explained that the initial endoscopy is performed to search for an abnormal lining of the esophagus which, if present, has the potential to lead to esophageal cancer. What most of us do not explain, in any great detail at least, is what happens when and if dysplasia is found. Until recently, the finding of dysplasia led to anxiety on the part of the patient and physician. The potential therapeutic avenues included more intense surveillance or referral for esophagectomy, with its inherent risks and complications. It is possible that if these risks and complications were explained to patients in the beginning, a higher proportion would opt out of a surveillance program. On the other hand, there is evidence that suggests that the majority of patients overestimate the risk of developing adenocarcinoma of the esophagus, and this is worsened in patients who research their condition on the Internet (2), thus making our role as physicians and patient educators even more important. With the advent of more advanced and efficacious endoscopic therapy for dysplasia in BE, one hopes that the transition from diagnosis of BE to therapy of dysplasia will be smoother.

DEFINITION AND EPIDEMIOLOGY

The definition of BE has gone through several renditions to arrive at its current form: the presence of columnar-lined esophagus with specialized intestinal epithelium confirmed on biopsy. In the literature, the length of BE has been classified into long segment BE (3 cm or greater) and short segment BE (less than 3 cm). Although, when first described, short segment BE was thought to be associated with a much lower risk of esophageal adenocarcinoma, current evidence suggests that this risk is still significant and one cannot treat these patients differently than those with long segment BE (3,4). The risk estimation of esophageal adenocarcinoma in patients with BE varies widely, ranging from one per 99 patient years to one per 300 patient years (3-8).

It is suggested that the incidence of adenocarcinoma has been steadily rising over the past 30 years (9,10). A significant majority of esophageal adenocarcioma arises from BE. The exact prevalence of BE is debatable, and has ranged from 0.4% (11) to 25% (12), depending on the study and the methodology used. Many studies (13-17) examined patients with reflux symptomatology and found higher rates of BE, while general population studies (15,18), which are much more difficult to perform, seem to suggest a much lower prevalence. A recently published report from Sweden (18) recruited a large random sample of the general population (n=1000), endoscoped them, and found BE in 16 individuals (1.6%). A North American study (15) of 961 individuals undergoing colonoscopy screening who also agreed to an endoscopy, reported a prevalence of 6.8%. While it may be reasonable to agree that the prevalence is somewhere between 2% to 6% in the general population, small changes in these estimates can dramatically affect calculations and modelling of cost-effectiveness of screening strategies. These epidemiology studies have allowed the identification of people at higher risk of developing BE, confirmed that it is linked to acid reflux, and that the extent of BE correlates with the degree of acid exposure (19). Other risk factors include patients older than 50 years of age, male, Caucasian, presence of a hiatus hernia, alcohol abuse and smoking (15,18). In spite of this knowledge, the prevalence of BE in patients without these risk factors is significant enough that screening only patients with known risk factors would miss too high a proportion of affected individuals.

ENDOSCOPIC SCREENING OF BE: IS THERE ANOTHER WAY?

The current standard for screening for dysplasia in BE involves taking four-quadrant biopsies every 2 cm of affected esophagus using jumbo biopsy forceps (the Seattle protocol [20]). Concerns with this type of surveillance include the time it takes to perform the screening and the relatively small proportion of tissue sampled. Hence, much effort has been expended in an attempt to enable endoscopists to perform targeted biopsies of areas suspected for dysplasia. Endoscopically

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evident lesions (such as nodules, strictures or BE ulcer) should be biopsied extensively because they are at higher risk for harbouring dysplastic tissue (21). However, in the absence of such lesions, nonenhanced endoscopy is incapable of distinguishing dysplastic from nondysplastic tissue. Chromoendoscopy using methylene blue, which reversibly stains absorbent cells such as intestinal epithelium, has been studied in a number of prospective trials (22-26), with conflicting results. The current evidence (22,23) suggests that although it may help target biopsies, it does not dramatically reduce the number of biopsies necessary, and actually lengthens the time of the procedure (25,26). Other techniques studied have similar results (fluorescence [27-31], enhanced magnification endoscopy [32] and optical coherence tomography [33-35]) or are currently too complicated and/or time consuming to use in daily practice (spectroscopy [36,37]). A new technique that seems promising is narrow band imaging (38), which seems user friendly and not very time consuming, however, more data are necessary to determine its efficacy.

SHOULD THEY ALL HAVE FUNDOPLICATION?
Long-term acid suppression is recommended for all patients diagnosed with BE. Treatment with proton pump inhibitors is associated with partial regression of the length of affected esophagus (39), but the clinical significance of this is unclear. There are numerous reports of partial regression of BE after fundoplication operations, with some centres reporting a high proportion of patients (33%) having complete regression (40), but most do not have quite such good results (41-43). Some authors have combined endoscopic ablation techniques, such as argon plasma coagulation, with fundoplication, and reported promising preliminary results (44). Nonetheless, in the setting of a patient with BE whose reflux is well controlled on proton pump inhibitors, there does not seem to be a compelling reason to undertake the risk and recovery time of a surgical fundoplication in the absence of other indications.

SURGERY AND BE
Traditional therapy for high-grade dysplasia (HGD) and/or intramucosal adenocarcinoma arising from BE is a surgical esophagectomy. This is a major surgery with significant potential for mortality and morbidity. Surgical series (45-48) published in the past 20 years still report mortality ranging from 3.3% to 11.2%. Complications are also common after surgical esophagectomy, with rates ranging from 20% to 73% (45-48), and include anastomotic leaks and strictures, and pulmonary complications. A study (47) examining limited esophageal resection for patients with HGD or intramucosal carcinoma demonstrated good clinical outcomes with less perioperative risk, including no deaths and a lower complication rate (20.8%), when compared with the traditional radical esophagectomy. The reasoning behind undertaking such a major operation when only HGD has been found is largely based on data suggesting that when HGD is present there is already a 38% to 50% rate of occult adenocarcinoma, although these numbers are based on a relatively small series of patients (46,49).

ENDOSCOPIC THERAPY FOR HGD AND INTRAMUCOSAL CARCINOMA IN BE
Considering the fact that numerous patients are not good surgical candidates when diagnosed with dysplasia in BE, alternative therapies, mainly endoscopic, have been explored

for several years now. More and more patients who may be surgical candidates are also becoming interested in these alternative therapies as they evolve. Numerous techniques have been tried, all with a view of ablating the dysplastic area, and some with the additional goal of ablating the BE completely. The principle of many of these techniques is to use thermal energy to necrose the columnar BE. In an anacid environment, one then hopes that the esophageal lining is replaced with normal squamous epithelium. Argon plasma coagulation (50), potassium-titanyl-phosphate lasers (51), multipolar electrocoagulation (52,53) and liquid nitrogen cryoablation (54) have all been reported in this context. Results are mixed, but a resounding theme tends to be promising preliminary results followed by less impressive results when applied to a larger group of patients. Of additional concern is the risk of development of 'buried glands', or columnar epithelium underneath the new squamous epithelium. Surveillance of these changes is difficult, and there has been one report of adenocarcinoma arising from this tissue (55). Photodynamic therapy (PDT) has been studied in various forms in the treatment of BE. It consists of the administration of a photosensitizer, followed by laser light application to the target tissue, in this case, the esophagus. The light releases intracellular free radicals, resulting in a type of burn that heals, in the absence of acid, with squamous epithelium. There are currently two types of photosensitizers – porfimer sodium (Photofrin, Axcan Pharma Inc, Canada) and 5-aminolevulinic acid. While the latter has a much better side effect profile due to its rapid clearance from the body, it does not appear to give a deep enough injury, thereby resulting in lower rates of ablation of BE (56-59) when compared with porfimer sodium cases (39). However, the deeper burn of porfimer sodium is not without a price, because rates of stricture formation are higher and the drug lasts in the system for weeks, thereby placing the patient at risk of serious skin injury from sun exposure.

Endoscopic mucosal resection was initially described as a technique for removing nodules or suspect lesions in BE, and has been shown to be efficacious (60-65). However, it has further evolved, and now seems most promising when it is used in an attempt to remove all of the BE, and the patient then undergoes PDT for ablation of any remaining BE. Results from a small series of patients are promising (66-68), and the logic behind such combination therapy seems compelling. However, as with all of these techniques, we await larger multicentre trials with appropriate follow-up to detect potential complications and recurrences.

ROLE OF ENDOSCOPIC ULTRASOUND IN BE
Endoscopic ultrasound has the potential to enhance the care of patients with BE, albeit after the diagnosis of dysplasia has been made. Although it has not been shown to be overly efficacious at discerning the level of invasion of a suspect lesion itself, it can assess for lymph node involvement and/or distant metastasis.

SUMMARY
When I see a patient with chronic reflux symptoms, I do discuss the possibility of screening for BE, and outline what would happen if we did find the condition, or if we found dysplasia or adenocarcinoma. In patients with known BE, I screen them every two years with endoscopy and four-quadrant biopsies every 2 cm, plus biopsies of any suspect lesions. I also

ensure they are on long-term proton pump inhibitor therapy. After a number of negative endoscopies, I may increase the interval of screening to every three to four years. If I find low-grade dysplasia, I arrange for a repeat endoscopy in six months. If HGD is seen in a nodule, after an endoscopic ultrasound has ruled out metastatic disease, I will then discuss treatment options, including surgery and endoscopy, making sure they are aware that endoscopic therapies are still relatively new and long-term data are not yet available. If HGD is found in random biopsies, I will again discuss options, but often repeat the endoscopy in three months with repeat biopsies. If the dysplasia is still present, I will outline options such as endoscopic mucosal resection of the entire BE, and/or PDT, versus surgical esophagectomy.

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