

# ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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## Barrett Esophagus and Surveillance in the United Kingdom

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**G&H** In the United Kingdom, what is the incidence of Barrett esophagus in the general population and the incidence of Barrett esophagus progressing to esophageal adenocarcinoma?

**JJ** The incidence rate of Barrett esophagus in the United Kingdom, which is higher than anywhere else in the world, is between 1.5–2.5% of the adult population. The incidence rate of Barrett esophagus progressing to cancer in the United Kingdom, which is also higher than anywhere else in the world, is approximately 1% per year compared to 0.4% in North America. We published these figures as part of a research communication in the journal *Gastroenterology* in 2002.

However, in clinical practice, I have noticed that most Barrett esophagus patients are often more anxious about their risk of cancer than necessary. Even considering the fact that the United Kingdom has the highest rates, the lifetime risk of an individual here developing esophageal cancer is likely no more than 1 in 20. These same individuals are 6 times more likely to die from a stroke or heart attack than from Barrett adenocarcinoma. Half of this group will have cancer in their esophagus but die because of a stroke or heart attack; only approximately 1 in 40 Barrett patients will actually die from their Barrett esophagus causing cancer.

**G&H** Could you discuss the current surveillance guidelines for Barrett esophagus in the United Kingdom and whether they differ from US guidelines?

**JJ** In the United Kingdom, surveillance for Barrett esophagus involves any individual who has endoscopic

Barrett esophagus, based upon C and M criteria (circumference and maximum extent of Barrett esophagus), which has been universally adopted since its development 3 years ago. Thus, all individuals who have endoscopic Barrett esophagus and biopsies that are consistent with Barrett, even if they do not necessarily have interstitial metaplasia, would be placed into a surveillance program. It is probable that we survey patients in the United Kingdom who would not be surveyed in the United States, as the United States relies on the presence or absence of interstitial metaplasia on histology, though this is beginning to change. Where the United Kingdom needs to improve is in regard to the number of biopsies; I do not think that an adequate number of biopsies and, therefore, tissue samples are obtained in the United Kingdom. (A minimum of 2 biopsies per circumferential cm length has been proposed in a recent paper.)

**G&H** How were the UK guidelines created?

**JJ** The UK guidelines for Barrett esophagus are based upon expert evidence, as there has not been, as of yet, any randomized controlled trials (which would be considered grade 1 evidence) to justify surveillance. However, we are very fortunate in that the BOSS (Barrett Oesophagus Surveillance Study) is currently underway. The chief investigator, Dr. Hugh Barr, from Gloucester, is undertaking one of the largest randomized controlled trials looking at endoscopic surveillance every 2 years in patients with Barrett esophagus, but not dysplasia, and randomizing them to either surveillance every 2 years or endoscopy at the time of need (ie, when they become symptomatic). It would not be possible to perform this trial outside of the

United Kingdom, as the main impetus of the trial was the recognition of the variable frequency of surveillance in the United Kingdom, though of a low standard. This trial primarily asks whether high-quality surveillance makes a difference in a randomized cohort of patients with Barrett esophagus. Although we do not have evidence to justify surveillance, this study, which already has started recruiting 2,500 individuals, will report its interim analysis in the next 4 years.

### **G&H** How effective have the current UK guidelines been for detecting Barrett esophagus or progression to adenocarcinoma?

**JJ** The guidelines for Barrett esophagus are not that effective. They are very poorly adhered to, not just in the United Kingdom, but also in North America and even in Europe. There have been multiple papers published over the last 5 years indicating that adherence to guidelines, whether in terms of biopsy sampling, frequency of intervals, or other issues, is quite weak. This is because most people know that the guidelines are only so-called expert opinion and not based on hard, randomized-quality evidence. There is clearly a need for improved guidance. In this regard, in fact, the American College of Gastroenterology, American Gastroenterological Association, International Society of Diseases of the Esophagus, and British Society of Gastroenterology are currently in the process of establishing guidelines called the BAD CAT (BARrett and Dysplasia and CARcinoma Taskforce) guidelines with the help of 80 experts throughout the world. We are looking at surveillance guidelines focused on the question of how to optimally manage patients with high-grade dysplasia in Barrett esophagus. For example, in the United Kingdom, if a patient in a surgical center is diagnosed with high-grade dysplasia Barrett esophagus, the only option that would be offered is esophagectomy, which has a 2% peri-operative risk of death. In contrast, if a similar patient is seen by general gastrointestinal physicians, they may undergo endotherapy by physicians who are not experts on radiofrequency ablation or endoscopic mucosal resection. Our goal is to establish better tertiary referral centers where patients can be offered a balanced opinion of whether they should undergo endotherapy or surgery for high-grade dysplasia. This is just one example as to our current state of affairs.

### **G&H** What new technologies are available in the United Kingdom to potentially improve the sensitivity of surveillance protocols?

**JJ** There are several new technologies, all of which are available in the United States as well. First, we are using improved imaging techniques, for example, magnification endoscopy, which, up until recently, had not been widely

used in the United Kingdom. Second, we are examining improved imaging techniques, including trimodal and confocal endoscopy, to detect subtle changes in the mucosal surface of the esophagus. Third, we are examining improved histologic biopsy markers of cancer risk during the procedure itself.

In the future, we are hoping to obtain access to a large-scale genetics study, which has been undertaken in the United Kingdom. (I think that this study is currently also being conducted in the United States, though it may be delayed until next year.) We have performed a genome-wide assessment study in 2,000 patients with Barrett esophagus by examining every gene to determine whether any inherited factors from the mother or father makes an individual more likely to develop Barrett esophagus or, in turn, more likely to progress to esophageal adenocarcinoma. These genes of Barrett patients are then compared to those of age- and gender-matched controls in the normal population. These data will be available in the near future.

### **G&H** According to the UK guidelines, what surveillance findings indicate a need for treatment to avoid cancer?

**JJ** This is a very controversial question because, at the moment, the current biomarkers are not very effective. For example, with conventional histology, discrimination of low-grade dysplasia is very poor even with gastrointestinal pathologists. In contrast, with high-grade dysplasia, a minimum of two expert pathologists is required to confirm the diagnosis. Having said this, the ASPECT (ASPirin Esomeprazole [Barrett Esophagus] Chemoprevention Trial) and BOSS trial groups involve an expert group of gastrointestinal histopathologists, probably 20 throughout the entire United Kingdom, who examine the biopsies of these patients. We are very confident that using an expert panel such as this results in high diagnostic accuracy. Currently, in all centers, we try to use an expert panel for the diagnosis of high-grade dysplasia to make an accurate diagnosis and then to decide whether these patients require intervention.

Researchers are also trying to develop state-of-the-art biomarkers so they can examine tissue samples or cytology to determine the likelihood of an individual progressing to cancer. Unfortunately, none of these biomarkers are currently ready for use in clinical practice and likely will not be ready for clinical use for at least 5–10 years.

### **G&H** Do the UK guidelines support the use of ablation and endoscopic mucosal resection for treating Barrett patients?

**JJ** The old guidelines from the British Society of Gastroenterology do not currently support these therapies, but

they are in the process of being updated by the National Institute for Clinical Excellence. Indeed, it is very likely that the new guidelines will indicate that ablation and endoscopic mucosal resection are appropriate.

Furthermore, on this issue, a significant trial to look out for is BEAT (Barrett Esophagus Ablation Trial), with Dr. John de Caestecker, from Leicester, as the chief investigator and Dr. Pradeep Bhandari, from Portsmouth, as the deputy chief investigator. This is a randomized controlled trial in the United Kingdom comparing various forms of endotherapy (ie, endoscopic mucosal resection alone versus endoscopic mucosal resection and radiofrequency ablation for high-grade dysplasia). This will be a unique trial, as it will be the only randomized trial randomizing patients to these endotherapy groups.

### G&H What are the next steps for future research?

**JJ** One of the most important research needs is the development of biomarkers. One of the substudies of the ASPECT and BOSS trial groups involves obtaining samples from all patients at two yearly time points to assess for changes in the tissue and examine biomarkers within the tissue to determine which biomarkers will predict who will progress to cancer. We are also looking at several biomarker studies in collaboration with American colleagues to determine their validity for clinical practice.

However, it should be emphasized that these improved biomarkers are only likely to be adequately validated well into the future. Many physicians assume that a biomarker will be easily and quickly developed to predict what individuals with Barrett esophagus will develop cancer, but, unfortunately, Barrett esophagus is very different from other premalignant conditions in the gastrointestinal tract. For example, a colonic polyp starts with a clonal lesion (ie, 1 cell becoming abnormal and populating the hole of a gland) and then gradually this lesion may become polyclonal (ie, several abnormal

clones develop). We know that in the very early stages of Barrett esophagus, there are oligoclonal lesions that quickly become polyclonal (ie, multiple abnormal clones within the Barrett esophagus). When examining a patient suspected of a premalignant condition other than Barrett esophagus, if a polyp is seen, it is discrete and clear evidence sticking into the lumen. The physician can easily biopsy the polyp and quickly understand its genetics. The same is not true for Barrett esophagus. It is very rare to have extraluminal lesions that grow into the lumen; the lesions are usually flat areas of dysplasia. By the time mucosal biomarkers are helpful, the dysplasia has often already developed and may even be early cancer. In addition, the genetics of Barrett esophagus may be far more complex compared to that of the colon. For example, we know that at least 25% of colonic cancers have a strong familial (genetic) element compared with only 2–5% of Barrett adenocarcinomas. Expectations for what biomarkers can offer should be tempered. State-of-the-art clinical practice with early diagnosis using conventional techniques, as well as early intervention therapy, should continue to comprise the mainstay of therapy. In the near future, perhaps early chemoprevention may be possible, depending upon the results of the ASPECT trial.

### Suggested Reading

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