

# Barrett's Oesophagus, Limitations of Current Surveillance Strategies

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### Editorial

Volume 4 Issue 1

**Received Date:** May 09, 2019

**Published Date:** May 16, 2019

**DOI:** 10.23880/ghij-16000152

## Editorial

Barrett's oesophagus (BO) is the only identifiable premalignant condition for oesophageal adenocarcinoma (OAC) which represents the eighth most common cancer and the sixth cause of cancer-related deaths worldwide [1]. BO is defined as an oesophagus in which any portion of the normal distal squamous epithelial lining is replaced by metaplastic columnar epithelium, which is clearly visible endoscopically ( $\geq 1$  cm) above the gastroesophageal junction and confirmed histopathologically from oesophageal biopsies [2]. BO-associated cancers arise via a sequence of metaplasia-dysplasia-carcinoma [3], subsequently patient outcomes can be improved by early detection and treatment of dysplasia and prevention of neoplasia in BO. The present guidelines from all major gastroenterology societies recommend surveillance endoscopy in BO to be performed every 2-5 years using Seattle protocol of systematic biopsies [4]. This protocol involves obtaining random and thereby untargeted 4 quadrant biopsies in every 1-2 cm intervals of a BO segment, in addition to targeted biopsies on macroscopically visible lesions. This approach is based on 2 small retrospective studies and is fraught with problems. Sampling error can frequently occur as it covers only 3.5% of a given sampled segment of BO, missing out the other 96.5%. In addition, studies have shown that only about half of all endoscopists (41-56%) adhere to this systematic biopsy protocol Abrams JA, et al. [5]. Thus, missing out dysplastic lesions or even cancer is potentially possible with surveillance under Seattle protocol.

Effective endoscopic surveillance of BO is a key in the management of OAC and the only tool that we have got to reduce its rising incidence and high mortality which owing from delayed diagnosis. The gold standard by which the dysplasia can be precisely assessed in each Barrett's segment is through histology of a surgically resected segment. Since this can't be applied even in clinical practice multiple random biopsies represent a reasonable substitute as reference standard test to study the effectiveness of any surveillance tool in BO.

Chromoendoscopy has been used in conjunction with white light endoscopy to improve detection of premalignant lesions. Various dyes or contrasts are applied topically permitting visualization of mucosal morphology that cannot be seen with standard endoscopy. However, a meta-analysis performed comparing rates for detection of neoplasia in BO with Methylene Blue compared to random 4 quadrant biopsies found no significant yield for the detection of high-grade dysplasia or early cancer [6]. There have also been reports of toxicity associated with Methylene Blue. Furthermore, conflicting results have been reported, the use of various dyes can sometimes be cumbersome, messy and time-consuming. This technique has therefore not gained widespread acceptance and has largely been abandoned.

Image enhancing technologies such as narrow band imaging (NBI) (Olympus, Tokyo, Japan), Fujinon intelligent chromoendoscopy (FICE) (Fujinon, Tokyo,

Japan), blue laser imaging (BLI) (Fujifilm, Tokyo, Japan) and I-Scan (Pentax, Tokyo, Japan) have emerged as a substitute for dye-based chromoendoscopy, hence commonly referred to as electronic chromoendoscopy. They are user-friendly and could provide an alternative to both random biopsies and dye-based chromoendoscopy. NBI enhances vascular features of oesophageal mucosa and submucosa, potentially allowing the endoscopist to take only targeted biopsy from areas that show an abnormal pattern that is suggestive of dysplasia. The targeted biopsy taken via NBI endoscopy is by far the most studied tool in BO surveillance with results in several studies have shown high accuracy and precision. There have been two published meta-analyses that found a high performance of NBI endoscopy in BO, the latest been published by Song, et al. [7]. In these two meta-analyses, data was pooled from all NBI studies in BO, up till 2014. Almost all the studies included in both meta-analyses were conducted in tertiary centres with high expertise in BO treatment and NBI. Moreover, most of included studies haven't used random biopsy as a comparator hence their results might have not been reflective of the true discriminate function of NBI. Furthermore, in another systematic review by ASGE [8], the yields of targeted biopsy method taken by NBI in addition to other methods of targeted biopsy using chromoendoscopy and confocal laser endomicroscopy were pooled to calculate sensitivity and specificity of the method of targeted biopsy. Similarly, most of the included studies in this review weren't comparative ones as they didn't involve taking random biopsy. Absence of a comparator in these trials may have impacted significantly their internal validity in two main aspects. First, the cross classification of true negative and false negative that was used to calculate the outcome of the sensitivity and specificity wasn't accurate as biopsies were taken only from Barrett's areas that deemed by an endoscopist to be suspicious for dysplasia during the examinations using these tools of targeted biopsy. Secondly, the absence of direct head to head comparison between random versus target biopsy method renders the outcome coming out of either method is completely different in terms of interpretation and application of the results.

There are other novel diagnostic tests have been used to enhance the endoscopic appearance of the oesophageal mucosa looking for dysplasia. Auto fluorescence imaging which emits fluorescent light of a shorter wavelength to excite fluorophores (endogenous substances in mucosa) thereby highlights the mucosa for the endoscopist. Confocal laser endoscopy (CLE) magnifies the mucosa up

to 1000 times producing images of up to 250 µm below the mucosal surface, assessing mucosal and sub-cellular structures. CLE uses blue laser light and a locally or intravenously applied fluorescent to enhance the vascular-supplied mucosal structures. Transnasal endoscopy has been shown to have a sensitivity and specificity of 98% and 100% respectively, for the endoscopic diagnosis of BO when compared with standard endoscopy [2]. Non-endoscopic sampling techniques like an oesophageal capsule and cytological sampling with cytosponge device have been considered for BO surveillance too [6]. However, all these novel techniques are limited in terms of their availability, expert users and the evidence that endorses their application in routine clinical practice.

In conclusion, new approaches and techniques are increasingly being advocated for and utilized for the detection of dysplasia and early cancer in BO in real time via targeted biopsy. So far, the NBI endoscopy is the most commonly used approach. However, no study has systematically assessed the literature to provide findings that support this shift in practice from random to target biopsy. It has not yet been established whether these anecdotal endoscopic findings are consistent and generalizable across populations, settings, and treatments, or whether findings vary significantly by particular subgroups.

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