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Screening and surveillance of Barrett esophagus with confocal endomicroscopy and volumetric laser endoscopy

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ABSTRACT

Barrett esophagus (BE) is a premalignant condition that progresses to esophageal adenocarcinoma through an intermediate stage known as dysplasia. Current guidelines recommend that individuals with BE undergo periodic endoscopic surveillance with white light endoscopy and random, 4-quadrant biopsies to identify and treat dysplasia. However, this surveillance strategy is limited by random sampling error and low sensitivity. Surveillance with random biopsies can miss up to 43%-57% of early neoplasia. This review will discuss the current role of 2 advanced imaging techniques, ie, confocal laser endomicroscopy (CLE) and volumetric laser endoscopy (VLE) in screening and surveillance for BE. CLE has the highest accuracy of any endoscopic technique and increases the diagnostic yield and sensitivity for dysplasia and intramucosal neoplasia and reduces the need for unnecessary biopsies. However, CLE is capable of imaging only a small field of mucosa and needs to be incorporated with other advanced imaging techniques to identify suspicious areas that need endomicroscopic evaluation. CLE can be used for the endoscopic evaluation of BE and for the accurate estimation of lesions' extent and lateral margins to guide endoscopic treatment. CLE is not helpful in assessing the depth of invasion of early neoplastic lesions or in endoscopic surveillance after ablative or resective therapy. VLE is a new imaging modality with limited studies. However, early experience suggests that VLE appears to be a valuable imaging modality in its ability to identify subsquamous BE and buried Barrett glands after mucosal ablation. Overall, CLE and VLE have not been adopted widely due to limited availability, high cost, and need for specific operator training. The major limitation of all studies assessing the role of CLE and VLE in screening and surveillance for BE is that they were all performed by expert endoscopists in tertiary referral centers with a population enriched regarding the proportion of patients with dysplasia. Despite developments in advanced imaging techniques, these techniques are not included in standard surveillance guidelines, and white light endoscopy with random biopsies remains the gold standard for BE surveillance.

1. Introduction

Barrett esophagus (BE) is the precursor lesion in which the normal stratified squamous epithelium above the gastroesophageal junction is replaced by metaplastic columnar epithelium. BE accumulates genetic changes over a period and evolves through nondysplastic metaplasia, low-grade dysplasia and high-grade dysplasia (HGD) to ultimately esophageal adenocarcinoma (EAC) [1]. The risk of progression of nondysplastic metaplasia to EAC is approximately 0.3% per year, BE-low-grade dysplasia to EAC is 0.5% per year, and BE-HGD to EAC is 6% or higher per year [2,3]. Patients with BE are at a 30-125-fold increased risk of developing EAC compared to patients without BE. The incidence of EAC has been rapidly increasing in the United States and is expected to increase by 140% over the next 10 years [4-6]. EAC carries a dismal 5-year survival rate (~17%) due to late diagnosis.

Screening for BE via endoscopy is not recommended for the general population but is recommended in high-risk populations. However, there is no clear evidence that screening leads to a reduction in mortality. The American College of Gastroenterology (ACG) supports the use of endoscopy as a screening tool but only if there are GERD symptoms in the presence of alarming symptoms (dysphagia, weight loss, and signs of gastrointestinal [GI] bleeding). An international consensus statement recommended to endoscopically screen men after the age of 60 years who have

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continous GERD symptoms for 10 years or longer [7]. However, risk-based screening may miss a considerable proportion of BE as a large number of patients with BE are asymptomatic and predicting which patients will have BE before endoscopy is very challenging. Further, at least 40% of patients diagnosed with EAC report no antecedent history of GERD.

Surveillance of BE is recommended to detect HGD or early cancer. Similar to screening, there is no clear evidence that surveillance is cost-effective or leads to a reduction in mortality [8]. Current guidelines recommend endoscopic surveillance of BE using white light endoscopy (WLE) with targeted biopsies of any endoscopically visible lesions and random 4-quadrant biopsies every 1-2 cm of the BE segment (Seattle Protocol). However, this method of multiple random biopsies has several limitations. Since both intestinal metaplasia and dysplasia have a patchy distribution, random sampling can lead to sampling error and poor sensitivity with studies revealing that as many as 43%-57% of early cancers can be missed by this sampling method [9,10]. Further, this approach is time-consuming and is associated with a potential risk of bleeding due to the need for multiple biopsies. In addition, in patients who have undergone endoscopic ablation of Barrett epithelium, recurrent metaplasia or dysplasia can be buried under the neo-squamous epithelium and can be missed on WLE during posttreatment surveillance [11].

Thus, there is a need for new endoscopic technologies which improve the ability of clinicians to identify precancerous lesions and early cancers. These technologies should have high sensitivity, and enhanced specificity, promoting a more accurate, targeted and cost-effective approach to endoscopic surveillance. Multiple advanced endoscopic imaging techniques have been developed to overcome the inherent limitations of standard endoscopic sampling techniques. For an advanced imaging modality with targeted biopsies to replace gold-standard, it should have a per-patient sensitivity of $>90\%$, a negative predictive value (NPV) of $>98\%$ for detecting HGD or early EAC compared with the current standard protocol, and a specificity of at least 80% to allow a reduction in the number of biopsies [12]. New imaging techniques can be subdivided into wide-field imaging systems or high-resolution imaging systems. Wide-field imaging systems enable examination of the entire luminal surface area and have a high sensitivity for disease detection and targeting therapy but a limited diagnostic specificity. High-resolution imaging systems have smaller fields of view, which provide an optical biopsy of the tissue and have high specificity for the detection of focal dysplasia and neoplasia but a limited sensitivity.

In this review, we will focus on the use of 2 advanced endoscopic imaging techniques; confocal laser endomicroscopy (CLE) and volumetric laser endomicroscopy (VLE) with particular emphasis on the screening and surveillance of BE and areas for future research.

2. Confocal laser endomicroscopy

2.1. Technology

CLE has been used for screening and surveillance of BE for the last 10 years. By using CLE, microscopic images of the mucosa are produced at up to 1250-fold magnification with imaging from the mucosal surface to 250 μm below the surface. With this level of magnification, goblet cells can be identified which are usually considered as a distinction between intestinal metaplasia and cardia. This level of magnification also helps in the diagnosis of short segments BE. During the CLE procedure, a standard WLE examination is performed first, and after locating areas of interest, an intravenous fluorescent dye which stains the extracellular matrix or topical fluorescent dye which stains the nuclei is administered, followed by fluorescent image acquisition [13]. There are 2 CLE systems, an endoscopic-based CLE (eCLE) in which a confocal microscope is incorporated into the tip of an endoscope and a probe-based CLE (pCLE) in which a probe is passed through the accessory channel of the endoscope. By providing microscopic diagnostic information in real time with high accuracy, CLE allows, in theory, immediate decision making, and subsequent resection or ablation if applicable.

The confocal BE classification criteria are known as the Mainz criteria. The classification was created by Kiesslich et al who published the first study on CLE in 63 patients undergoing screening or surveillance for BE. The Mainz criteria uses the cellular and vascular architecture to distinguish between BE and neoplasia with high accuracy. In this investigator-masked evaluation, Mainz's classification system predicted histologic findings of BE and neoplastic BE with a sensitivity of 98.1% and 92.9%, specificity of 94.1% and 98.4%, and accuracy of 96.8% and 97.4%, respectively. Interobserver and intraobserver agreement (IOA) were high among with a mean κ value of 0.843 and 0.892, respectively. Endoscopists received training before interpretation of CLE images with a minimum of 50-75 cases required to achieve accuracy rates of $>85\%$ [14]. Tofteland et al compared the accuracy and IOA of pathologists with GI endoscopists who reviewed the same set of video clips. For the prediction of histology, the overall accuracy of GI endoscopists (81.5% [95% CI: 77.6-85.0]) was similar to the accuracy of pathologists (77.8% [95% CI: 72.4-82.3]). The IOA among endoscopists ($\kappa = 0.61$) was similar to pathologists ($\kappa = 0.65$) [15]. The ease of performing pCLE, ease of interpreting pCLE images, and ease of performing biopsies was graded by Sharma et al on a 5-point Likert scale from 1 (easy) to 5 (difficult). The percentages of subjects who scored 1 or 2 with regard to the ease of performing pCLE was 79.3%, interpreting pCLE images was 77%, and performing biopsies was 81.6% [16].

2.2. Screening and surveillance for BE

The preservation and incorporation of valuable endoscopic innovation (PIVI) initiative implemented by the American Society of Gastrointestinal Endoscopy (ASGE) in 2012 states that to replace the current Seattle Protocol, a targeted imaging technique should have a per-patient sensitivity of at least 90%, NPV of at least 98%, and specificity of at least 80% for detecting HGD or EAC compared with the current standard protocol [17]. The ASGE conducted a meta-analysis of 5 studies examining 361 patients who underwent CLE-guided targeted biopsies compared with standard protocol biopsies during endoscopic surveillance of BE with a pooled sensitivity of 90.4% (95% CI: 76-97), NPV of 96.2% (95% CI: 93-98), and specificity of 89.9% (95% CI: 84-94) for detection of BE. The per-patient sensitivity and specificity values for CLE were high, but the NPV did not meet the established a priori PIVI thresholds hence CLE cannot replace the Seattle Protocol on the basis of the results of the PIVI initiative. However, significant heterogeneity was noted in the analysis. Subgroup analysis of studies focusing on eCLE indicated an overall sensitivity, NPV, and specificity of 90.4% (95% CI: 72-97), 98.3% (95% CI: 94-99), and 92.7% (95% CI: 87-96), respectively. Although these values meet the PIVI thresholds, the eCLE is no longer commercially available. The subgroup analysis of studies that used pCLE indicated an overall sensitivity, NPV, and specificity of 90.3% (95% CI: 54-99), 95.1% (95% CI: 91-98), and 77.3% (95% CI: 54-91), respectively which did not meet the PIVI thresholds [17]. Xiong et al conducted a recent meta-analysis of 14 studies with 789 patients, and 4047 BE lesions examined by CLE. Pooled sensitivity and specificity was 89% and 83%, respectively in the per-patient analysis arm. In the per lesion analysis arm, sensitivity decreased to 77%, and specificity increased to 89% [18].