Review Article

Optimizing the diagnosis and therapy of Barrett's esophagus

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Abstract: The incidence of Barrett's esophagus (BE) in the Western world has increased over the last decades. BE is considered a premalignant lesion that can progress to esophageal adenocarcinoma (EAC), a highly aggressive malignancy with poor survival rates. The close association between BE and EAC highlights the need for an early diagnosis in order to improve survival and outcomes in this group of patients. Although the evidence for BE screening with conventional endoscopy is controversial and limited by cost-effectiveness studies, screening can be suggested in patients with chronic gastroesophageal reflux disease (GERD) and two or more risk factors for EAC. Less invasive techniques with lower costs and higher acceptability by the patients may be useful for screening in the general population. Several novel techniques have been described to aid in the early diagnosis and management of BE and dysplasia. However, these techniques have shown variable results with higher costs, the need of specific training, and variable inter-observer imaging interpretation, making its widespread implementation problematic. High-definition/high-resolution white-light endoscopy (WLE) continues to be a well-accepted technique for the evaluation and surveillance of patients with BE. Further studies are required in order to establish the efficacy of less invasive methods that can be performed in an outpatient setting for BE screening in higher risk individuals.

Keywords: Barrett's esophagus (BE); gastroesophageal reflux disease (GERD)

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Introduction

An estimated 5–15% of adults in the Western world suffer from symptomatic reflux (1). Chronic gastroesophageal reflux disease (GERD) is one of the most important risk factors for the development of Barrett's esophagus (BE) (2). The continuous reflux of acidic, biliary and pancreatic secretions injuries the esophageal mucosa, triggering cellular and genetic changes that results in columnar metaplasia (3,4).

The replacement of the normal esophageal squamous epithelium with a more protective, mucus-producing, columnar epithelium is the first step in the progression to BE. The evidence of intestinal metaplasia (IM) with one or more definite goblet cells in a metaplastic columnar epithelium establishes the diagnosis of BE (3).

Commonly identified risk factors for the development of BE include chronic GERD, advanced age, white race, male sex, obesity and cigarette smoking (2). BE is considered a premalignant lesion, and is the most important risk factor for the development of esophageal adenocarcinoma (EAC).

The prevalence and incidence of BE have increased over time, with an estimated prevalence of 2–7% (5,6) and a reported incidence ranging from 23 to 62 cases per 100,000 individuals per year (7,8).

Similarly, the incidence of EAC has increased in the last decades (9,10) and its prevalence is now higher than that of squamous cell carcinoma (11). The rate of progression from non-dysplastic BE to EAC ranges between 0.33% and 0.82% per year (12-14), with higher rates of malignant transformation from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) (6.5%) (13,15) and from HGD to EAC (10–40%) (16-18).

The 5-year overall survival rate of patients with EAC is ~17% (19,20), thus early detection of BE should improve survival as patients can be enrolled in surveillance programs and be offered ablative therapies of their premalignant dysplastic BE.

Diagnosis of BE

The evidence supporting endoscopic screening for BE in the general population is controversial and has shown to be cost-ineffective. However, screening strategies could be beneficial in high risk patients, including men with chronic GERD (>5 years) and two or more risk factors for BE or EAC, including age >50 years, Caucasian race, central obesity, cigarette smoking and family history of BE (21).

Minimally invasive methods that can be performed in the primary care setting have shown good results in the detection of BE, and might be useful for massive screening with lower costs and higher patient acceptability. An example of this is the cytosponge. This technique has shown to be safe and effective in the diagnosis of BE. In a large cohort of patients, this method showed a success rate of 93.9% during capsule swallowing (22). The sensitivity for the diagnosis of BE was 79.9%, and 87.2% in patients with long segment BE (>3 cm), with a specificity of 92.4% (22).

Other less invasive techniques such as transnasal endoscopy (TNE) and esophageal capsule endoscopy (ECE) have been described as potential methods for screening. Unsedated TNE performed in an outpatient setting has shown to be safe, with comparable effectiveness for the evaluation of the esophageal mucosa, and shorter procedure and recovery times when compared with conventional endoscopy (23). ECE has shown to be safe, although the sensitivity and specificity for the diagnosis of BE are still low (24,25).

The diagnosis of BE is based on the direct visualization of characteristic mucosal changes called columnar lined epithelium extending ≥1 cm proximal to the gastroesophageal junction (GEJ) with the confirmation of IM by endoscopic biopsies. The requirement of the evidence of IM for the diagnosis of BE could be explained by the demonstrated higher risk of developing EAC compared to columnar metaplasia without goblets cells (26,27). Furthermore, the identification of IM could be affected by the number of biopsies taken, with reported yields of 35% when four biopsies are taken, and almost 70% with eight biopsies taken during the endoscopic procedure (28).

It is recommended as part of the assessment for patients with BE to include in the endoscopy report the location of the GEJ, the squamocolumnar junction, and the diaphragmatic indentation, as well as describe the extent of metaplastic changes using the Prague classification (29).

Low-resolution, white-light endoscopy (WLE) is the standard of care for the visualization of the esophagus and the mucosal changes associated with BE. However, during the last decades, high resolution endoscopes with high definition (HD) systems have replaced these standard resolution devices enhancing the visualization of mucosal abnormalities (30). Amplification of endoscopic images with magnifying endoscopes has shown to be useful in the visualization of mucosal changes with good imaging resolution (31). Its use in combination with other techniques such as chromoendoscopy improves the detection of IM and HGD in patients with detected columnar metaplasia (32).

High-definition/high-resolution WLE is recommended for the evaluation and surveillance of patients with BE (21,33). Four-quadrant biopsies taken at 2 cm intervals in patients without dysplasia, and at 1 cm intervals for patients with suspected or known dysplasia are recommended (21).

High-definition white-light endoscopy (HD-WLE) has been used in combination with novel imagining techniques for the early detection of mucosal changes suggestive of dysplasia. Although, the combination of these techniques may not significantly increase the detection of BE or dysplasia compared to HD-WLE alone, targeted biopsies may be achieved and the number of biopsies may be reduced (34).

Several imaging techniques have emerged in order to identify BE and dysplastic changes in an early manner to improve patient outcomes.

Narrow band imaging (NBI) first described in 2004 (35), improves the resolution of the mucosal surface, superficial capillary networks, and sub-epithelial vessels by changing the wavelengths of light used during endoscopy (35). Recent studies have shown a sensitivity of 95% and a specificity of 65% for the detection of BE, and a sensitivity and specificity for the detection of HGD of 96% and 94% respectively (36). The combination of this technique with magnifying endoscopes has led to the identification of specific mucosal and microvascular patterns that are useful for the identification of IM, dysplasia and cancer (36,37). The ability of this technique to study mucosal and vascular patterns, its integration with standard endoscopic devices, and the ease of use, are some of the advantages offered for the evaluation of BE.

Chromoendoscopy in combination with WLE is another

technique that uses dyes such as methylene blue and acetic acid to better visualize the mucosal surface. Methylene blue is the most commonly used and is actively absorbed by the mucosa with IM. Some studies have shown that this method has a higher diagnostic accuracy for the diagnosis of IM with a lower number of biopsies needed compared to four-quadrant random biopsies (38,39). However, some other studies have found that the use of methylene blue is not superior to WLE with random biopsies for the diagnosis of IM or dysplasia (40).

Acetic acid has also been used to differentiate between dysplastic and non-dysplastic mucosa. This technique has shown to be useful for the detection of dysplastic lesions with higher accuracy compare to WLE alone (41). The sensitivity and specificity for the detection of dysplasia have been reported to be 95.5% and 80% respectively (42). The number of biopsies needed for the detection of dysplasia with this technique could be significantly reduced, with the subsequent reduction in costs (43).

Other novel imaging techniques using computer-based processors to reconstruct endoscopic images altering the wavelengths of reflected light to identify mucosal changes have been developed. I-scan, Fujinon intelligent chromoendoscopy, and autofluorescence imaging (AFI), are techniques that offer different filter options for the recognition and differentiation of mucosal abnormalities and vascular structures (14). I-scan, by manipulating the red, blue and green color of light, enhances vascular and mucosal structures. Its use in combination with acetic acid has shown a higher diagnostic yield for IM when compared to standard random biopsies (44).

AFI is based on the fluorescence of endogenous mucosal molecules that emit fluorescence when exposed to specific light wavelengths. Based on this principle, it has been shown that the normal mucosa appears green, while the dysplastic mucosa and neoplastic tissue seems magenta (45). Although several studies have been conducted to assess the value of AFI in the detection of IM and neoplasia (46,47), further studies are needed to determine the utility of this technique as an adjuvant for the detection of IM and dysplastic changes.

In vivo histologic evaluation of the esophageal mucosa has also been shown to be possible with the use of WLE in conjunction with advanced endoscopic imaging techniques such as confocal laser endomicroscopy (CLE) and endocytoscopy. Real-time histological assessment after mucosal imaging magnification is possible with the use of CLE (48). This system uses blue laser light and either topical or intravenous fluorescent contrast allowing for the visualization metaplastic intestinal mucosa and the presence of goblet cells. An endoscope-based confocal system (eCLE), which integrates a confocal microscope into the tip of the standard endoscope, showed a sensitivity for the diagnosis of BE of 98.1% and a specificity of 94.1%. This technique also showed good performance for the diagnosis of BE associated neoplasia, with a sensitivity and specificity of 92.9% and 98.4% respectively (49). Moreover, additional studies have shown that the use of eCLE with targeted biopsies has a higher diagnostic yield for BE associated neoplasia compared to standard biopsy protocol, with reduction in the number of biopsies needed (50,51). Real-time microscopic visualization of the mucosa is also achieved with the use of endocytoscopy, however its use has been limited in the management of BE patients due to poor image quality (48).

While significant advances in the field of endoscopic imaging have occurred in the last decades, limitations for the general adoption of these techniques are evident. Further technological improvements, endoscopist training, standardize imaging interpretation protocols, and lower costs, are needed for the widespread acceptance of these novel techniques for the evaluation and management of patients with BE.

Management and treatment of BE

The development of BE is closely associated with the presence of GERD, and the continuous stimulus of reflux contents perpetuates mucosal injury. For this reason, it is recommended that patients with BE should receive proton pump inhibitors (PPI) as part of the therapy. Moreover, several studies have shown that patients on PPI's have a lower risk of neoplastic progression compared to patients without acid suppressive therapy (52,53).

The main goal of surveillance in patients with BE is the recognition of dysplasia. The early detection of histological changes suggestive of progression is essential to improve survival rates in this group of patients.

The surveillance of patients with BE should be performed with high-definition/high-resolution WLE, which has shown better results for the detection of dysplasia compared to standard WLE (54). For patients with BE and no evidence of dysplasia, endoscopic surveillance should be performed at intervals of 3 to 5 years, and annual evaluation for the presence of dysplasia is not required (21).

Despite the inter-observer variability in the interpretation

of dysplasia, there is an acceptable agreement for the diagnosis of IM without dysplasia and HGD/EAC (55). However, determining the presence of LGD may be more difficult, with higher inter-observer variability (56). Therefore, current evidence recommends confirmation of histopathological diagnosis by a second pathologist with extensive experience in the interpretation of BE dysplasia (21).

The management of these patients will be determined by the grade of dysplasia. As mentioned above, patients with non-dysplastic BE should be managed with PPI therapy and HD-WLE at 3 to 5 year intervals due to the low risk of progression to EAC (21). Ablation therapies are not recommended due to the low risk of progression to EAC (21).

In patients with findings indefinite for dysplasia, twice-daily PPI therapy may be useful to decrease ongoing inflammation, and a repeat endoscopy after 3 to 6 months should be performed. Due to the similar risk of progression to EAC compared to LGD (57) it has been suggested that surveillance of these patients should follow the indications established for LGD.

After pathological confirmation by a second expert pathologist, patients with LGD should also receive aggressive PPI therapy to decrease inflammation. Annual endoscopic surveillance can be performed with four-quadrant biopsies at 1 cm intervals until two consecutive examinations show no dysplasia. However, endoscopic treatment is the preferred therapy in the absence of life-limiting comorbidities (21). Radiofrequency ablation (RFA) has been shown to be a good option for the treatment of patients with LGD and HGD with low rate of complications and good cost-effective results (58). Moreover, the use of RFA for the treatment of patients with confirmed LGD has shown a significant reduction in progression to HGD and EAC in one randomized trial (59).

Patients with a diagnosis of HGD confirmed by a second expert GI pathologist should be managed with endoscopic therapy. If any mucosal irregularities are detected during endoscopy, the abnormal mucosa should be resected. Endoscopic mucosal resection has shown to be a good method for the resection of nodularity and other mucosal abnormalities and is often used in patients with HGD (60). Endoscopic ablation therapy of the remaining BE using RFA is recommended in these patients to reduce the risk of recurrence (21).

Cryoablation (CSA), an alternative ablation modality that uses low-pressure liquid nitrogen has also shown to be safe with good results in downgrading and eradicating HGD and intramucosal carcinoma (61,62). However, further studies are required to determine its value as a routine technique for the management of patients with dysplastic BE.

In cases where a diagnosis of EAC is made after EMR, the depth of invasion and the degree of lymphovascular involvement will determine the appropriate therapeutic approach. It has been shown that esophageal lesions limited to the mucosa have a low rate of lymphovascular involvement (63) making EMR followed by ablation therapy with eradication of the remaining BE, a well-accepted therapeutic approach. The effectiveness of endoscopic therapies for the treatment of neoplastic lesions with submucosal involvement will depend on the depth of invasion and patient surgical risk. In cases with superficial submucosal invasion and high risk of complications with esophagectomy, endoscopic resection and ablation therapies can be considered a good therapeutic option, with encouraging results in highly selected patients (64). Ablation therapies after mucosal resection are highly recommended to eliminate the remainder BE, decreasing the risk of recurrence (65). In contrast, patients with deeper submucosal invasion have higher rates of lymphovascular involvement (63) and a multidisciplinary surgical oncology evaluation should be performed to assess the utility of endoscopic therapies, which are usually aimed to palliation (21).

Esophagectomy is the treatment of choice for patients with EAC with submucosal involvement, either alone or in combination with neoadjuvant radiation and/or chemotherapy.

The follow-up of patients with BE and dysplasia after endoscopic treatment is essential to detect early mucosal changes indicative of recurrent disease. Recurrence rates after complete eradication of IM have been reported to be higher than 20% after 2–3 years of follow-up (66,67). This is why a close follow-up for these patients should be performed with four-quadrant biopsies at 1 cm intervals throughout the previous BE segment and targeted biopsies of suspicious mucosal findings (21). Follow-up HD-endoscopy for patients with history of LGD should be performed every 6 months in the first year after initial therapy and annually thereafter if no recurrence is found. Surveillance for patients with history of HGD or intramucosal EAC should be performed every 3 months during the first year after initial therapy, every 6 months in the second year and annually thereafter if no recurrent disease is evidenced (21).

In the case of recurrent IM or any grade of dysplasia found during surveillance, endoscopic treatment is recommended with the use of EMR and ablation therapies

such as RFA and CSA (68).

Conclusions

Although the risk of progression from BE to EAC is very low, an early diagnosis of patients with IM is essential to improve survival and outcomes. Strong evidence supporting the screening of BE in the general population is lacking, mostly due to dismal cost-effectiveness results. However, screening for male patients with symptomatic chronic GERD (>5 years), and two or more risk factors for BE or EAC has been suggested.

The development of less costly techniques, with less invasiveness and with the possibility of being performed in an outpatient setting could help overcome these difficulties, improving survival and outcomes in patients diagnosed with BE and/or dysplasia or EAC.

High-definition WLE continues to be a well-accepted method for the evaluation and surveillance of patients with BE. Adjunctive imaging technologies have shown to be useful in improving diagnostic rates. However, the implementation of these techniques may be difficult due to high costs, need for specific training and inter-observer variability of imaging interpretations.

Further studies and technological advances are still required in order to establish the best strategies for the evaluation and management of patients with BE.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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