Screening and Prevention of Barrett's Esophagus

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Abstract

Barrett's esophagus (BO) is a risk factor for esophageal adenocarcinoma. However, screening for BO is difficult since it is not yet clear who should be screened and which screening method is cost-effective. Screening methods could be upper endoscopy at the time of the first screening colonoscopy, transnasal endoscopy, esophageal capsule endoscopy, or cytosponge. In order to prevent the development of BO or its neoplastic progression, there are modifiable risk factors like obesity or smoking that can be influenced. In addition, several drugs like proton pump inhibitors, aspirin, nonsteroidal anti-inflammatory drugs and statins have shown promising effects in mostly observational studies. However, data from prospective randomized trials are scarce in order to draw final conclusions.

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Screening for Barrett's Esophagus

Barrett's esophagus (BO) is the consequence of chronic gastroesophageal reflux and epithelial injury of regular squamous epithelium. BO is usually defined as segment of intestinal metaplasia in the distal esophagus of more than 10 mm in length (Fig. 1) [1]. The length of a BO should be assessed using the Prague C & M classification [2]. The circumferential (C) and the maximum extent (M) of the metaplastic segment should be measured. The lower level is defined as the upper end of the cardiac folds.

For example, a BO with a circumferential extent of 4 cm and a tongue-like extent of 3 cm results in a Prague classification of C4M7 (Fig. 2). An irregular Z-line with tongues of less than 10 mm are not considered BO, even when intestinal metaplasia is histologically confirmed [1, 2].

It is generally accepted that Barrett's metaplasia is considered a premalignant condition and predisposes patients to developing esophageal adenocarcinoma. The risk factors for BO and for malignant progression are similar and they are: gastroesophageal reflux disease (GORD), Caucasian race, male sex, increasing age, tobacco use, and obesity [1, 3]. In recent years there has been a dramatic increase of the incidence of Barrett's cancer. Since the 1970s, there has been a 6-fold rise in the incidence of Barrett's adenocarcinoma and this is higher than the rise in any other cancer in the Western world [4]. Therefore, most guidelines recommend endoscopic surveillance of patients with known BO in order to detect neoplastic progression early enough to be able to cure the patient.

It is very difficult to determine the prevalence of BO in the general population since population-based estimates are scarce. In Europe, the prevalence seems to be 1–2% and in patients with gastroesophageal reflux disease the prevalence is around 10% [3].

Who Should be Screened for BO?

Esophageal adenocarcinoma is mostly diagnosed outside a Barrett's surveillance program and when symptoms of an advanced cancer, like dysphagia and anemia, have developed. However, studies have demonstrated that a diagnosis of BO prior to a diagnosis of esophageal cancer

Fig. 1. a–d Work up of long-segment BO. **a** Long-segment BO with white-light endoscopy. **b** Inspection with narrow band imaging and near focus. **c** Long-segment BO after application of 1.5% acetic acid. **d** Long-segment BO with small high-grade dysplasia at 2 o'clock.

is associated with diagnosis at an earlier stage and therefore with a better survival [5, 6]. Thus, it would be desirable to identify most patients with BO in the general population and include them in a surveillance protocol.

Most available guidelines recommend screening of patients with long-standing reflux disease when additional risk factors are present. For example, ESGE guidelines recommend screening of patients with reflux disease with a duration of >5 years and the presence of multiple other risk factors like obesity, age >50 years, male sex, white ethnicity, and first-degree relatives with BO or esophageal adenocarcinoma [1]. Other guidelines include also smoking and presence of a hiatal hernia as risk factors [7, 8].

Using risk models can improve the screening for BO but developing a minimally invasive screening tool like a blood or breath test to detect BO would enable a more widespread screening.

How Should We Screen for BO?

Upper endoscopy is the gold standard to detect BO but it is not suitable as a screening method for widespread use since it is invasive and expensive. However, upper endoscopy could, for example, be offered in combination with the first screening colonoscopy, making screening for BO more cost-effective.

Another possibility to screen patients for BO is the use of less invasive screening methods like esophageal capsule endoscopy and transnasal endoscopy (TNE) without sedation.

Esophageal capsule endoscopy showed a promising diagnostic accuracy for BO compared to conventional endoscopy (sensitivity of 77% and specificity of 86%), but biopsies are not possible with this method [9]. Another limitation are the high costs associated with this method, limiting its potential use in many countries.

Fig. 2. Prague C & M classification.

TNE has a high acceptance rate and can be performed without sedation and even office based using disposable sheaths [10]. This enables the endoscopist to use the endoscope several times without reprocessing. Another advantage of TNE is the possibility of performing biopsies in many cases.

Another interesting minimally invasive nonimaging screening method is the cytosponge [11]. It is an encapsulated sponge device attached to a string that can be swallowed by the patient. The sponge is released in the stomach and by pulling the sponge out through the esophagus, epithelial cells are collected which can be analyzed for different biomarkers. The cytosponge has shown promising results and acceptability but the results of larger studies have to be awaited to draw final conclusions.

Staging of BO

As already explained, the length of BO should be measured according to the Prague classification [2]. The whole Barrett's segment should be inspected carefully using a high-definition video endoscope. The use of a transparent distal attachment cap can help to improve visualization of the whole Barrett's segment by stabilizing the tip of the endoscope and flattening out the gastric folds in the distal part. It has been shown that the detection rate of neoplastic lesions within the BO is significantly improved with longer inspection time [12]. Therefore, recent quality measures suggest spending about 1 min/cm of BO length [13].

A recently published study showed that the detection and delineation of BO-related neoplasia (BORN) can be significantly improved with a web-based training plat-

form (BORN project) [14]. One hundred eighty-nine international endoscopist assessors completed 4 batches of 25 videos containing BORN. They were asked to detect and delineate the lesions and after each batch they received mandatory feedback and could compare their delineations with that of 3 international experts. The detection and delineation score improved from batch 1 to batch 4 significantly, i.e., from 70 to 88% and from 44 to 78%, respectively. The complementary training tool can be accessed over the IWGCO or UEG website (<http://www.iwgco.net>; <https://www.ueg.eu/education/latest-news/article/article/born-module-detection-and-delineation-of-barretts-oesophagus-related-neoplasia/>).

During inspection of early Barrett's neoplasia, special attention should be paid to the area between the 12 and 3 o'clock positions since more than 50% are located in that quadrant and most lesions are located at the 12 o'clock position [15].

To date, 4-quadrant biopsies have been considered as the standard of care recommended by most national guidelines [1, 8]. Systematic biopsies should be taken of 4 quadrants every 1–2 cm and biopsies from a given segment should be submitted to pathology in a separate container. A recently published study showed that systematic 4-quadrant biopsies detect Barrett's neoplasia in more patients than nonsystematic biopsies [16]. However, 4-quadrant biopsies are time consuming, inaccurate, and not cost-effective. Therefore, there have been several efforts to improve or replace this insufficient standard of care. In addition to high-definition white-light endoscopy, chromoendoscopy, virtual chromoendoscopy, and acetic acid staining can increase the detection rate and should be used [1, 17, 18].

More detailed information of screening upper endoscopy can be found in the paper of Ebigo et al. [19] in the same issue.

Prevention of BO

Modifiable General Risk Factors

Obesity and smoking are accepted risk factors for the development of BO and its malignant progression [20–27].

Smoking has been shown to go along with an increased risk for the development of BO and Barrett's adenocarcinoma [25, 26]. A recent meta-analysis of 39 case-control studies including 7,069 patients with BO demonstrated an increased risk of developing BO in smokers. There was also a higher risk with an increased number of pack years [26]. Smoking has also been shown to be a risk factor for malignant progression of BO, with a 3-fold increased risk [25]. However, discontinuation of smoking goes along with a significant risk reduction [27].

Therefore, cessation of smoking seems to be a modifiable factor to reduce the risk of cancer development in BO.

Obesity has been considered a relevant risk factor for the development of BO [20–24]. BMI >30 and central obesity with a large amount of intra-abdominal fat are associated with an increased risk for the development of BO and esophageal adenocarcinoma. Beyond the promotion of GERD, obesity seems to have an additional influence due to trophic hormonal effects [23].

An infection with *Helicobacter pylori* is associated with a reduction of the risk for the development of BO and esophageal adenocarcinoma. This is most likely due to the reduced acid output in the stomach that is a consequence of a chronic *H. pylori* infection [3].

Pharmacological Prevention

In order to prevent malignant progression of BO, several drugs have been studied. The most important studied drugs are proton pump inhibitors (PPI), aspirin, NSAID, and statins.

Proton Pump Inhibitors

Most guidelines recommend PPI in patients with BO for symptom control only [1, 8, 28]. Data on whether PPI can prevent neoplastic progression in patients with BO are conflicting. In theory, acid suppressive therapy could reduce inflammatory pathways and carcinogenesis [29, 30]. A meta-analysis of 7 studies showed a significant reduction of the cancer risk (OR 0.29; 95% CI 0.12–0.79) [30]. However, those studies were observational and not randomized. Another Danish population study showed no effect of PPI [29]. The AspECT trial, a large multicenter prospective randomized trial comparing either low- or high-dose PPI with or without aspirin, was published recently [31]. They included 2,557 patients in 84 centers and the median follow-up was almost 9 years. That study showed only a delay of cancer development but aspirin did not reduce death. The trial dem-

onstrated that high-dose PPI (2 × 40 mg daily) was significantly superior to low-dose PPI (1 × 40 mg daily) regarding the composite endpoint time to all-cause mortality, esophageal adenocarcinoma, and high-grade dysplasia. However, PPI was not compared to no PPI in that study.

Aspirin and NSAID

COX2 inhibitors can reduce inflammation and neoplastic progression and therefore potentially have an impact on the neoplastic progression of BO [2, 32, 33]. Most observational and population-based studies have shown that the cancer risk can be reduced by about 30%. Liao et al. [32] demonstrated in a population-based study that the use of aspirin and other NSAID reduced cancer risk by 32%. In addition, a meta-analysis of 9 studies with more than 5,000 patients showed a similar effect of risk reduction [33].

High quality studies on this topic were missing for a long time. The AspECT trial finally delivered important results from a prospective randomized controlled trial [30]. It was able to show that aspirin in combination with high-dose PPI (2 × 40 mg daily) compared to low-dose PPI without aspirin had the highest positive effect on the composite endpoint (time to over-all mortality, esophageal adenocarcinoma, and high-grade dysplasia). The numbers needed to treat for PPI and aspirin were 34 and 43, respectively.

Statins

In addition to their lipid-lowering effect, statins can reduce cell proliferation and induce apoptosis in cancer cells [34–36]. The chemopreventive effect of statins has been demonstrated in several observational studies, with a risk reduction of esophageal adenocarcinoma progression between 43 and 74% in patients with BO. However, results from prospective randomized controlled studies have to be awaited until final conclusions can be drawn.

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