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MINIREVIEWS

# Update on management of Barrett's esophagus

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## Abstract

Barrett's esophagus (BE) is a common condition that develops as a consequence of gastroesophageal reflux disease. The significance of Barrett's metaplasia is that predisposes to cancer development. This article provides a current evidence-based review for the management of BE and related early neoplasia. Controversial issues that impact the management of patients with BE, including definition, screening, clinical aspects, diagnosis, surveillance, and management of dysplasia and early cancer have been assessed.

**Key words:** Barrett's esophagus; Barrett metaplasia; Esophageal adenocarcinoma; Gastroesophageal reflux disease; Radiofrequency ablation



**Core tip:** Barrett's esophagus (BE) is a common condition that predisposes to cancer development. This article provides a current evidence-based review for controversial issues that impact the management of patients with BE, including clinical aspects, diagnosis, surveillance, and management of dysplasia and early cancer.

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## INTRODUCTION

Since Barrett's esophagus (BE) was first described in 1950[1], the definition of this condition has been modified on several occasions. Presently, it is defined as the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus[2]. Since

only intestinal metaplasia (with globet cells) clearly predisposes to malignancy, its presence is required for the diagnosis. Nevertheless, some scientific societies consider that the presence of cardiac mucosa (with mucus-secreting columnar cells without goblet cells) are also diagnostic of BE[3]. However, because the risk for malignancy of cardia-type epithelium remains unclear, it is not generally recommended to use the term "Barrett's esophagus" in that context[2,4].

## EPIDEMIOLOGY AND CLINICAL ISSUES

BE is a common condition, with an estimated prevalence in the general adult population between 2% and 7%[5,6], and an incidence rate varying between 23.1 and 32.7 per 100000 person-year[5,7,8]. It is observed in 4% of patients undergoing an upper gastrointestinal endoscopy, and in 9% of men over 50 years[9].

Risk factors for BE include the presence of severe and longstanding gastroesophageal reflux, for which the biliary-pancreatic content seems to have a significant role[10], as well as advanced age, male sex, white race, obesity, and tobacco use. Conversely, factors that might protect against BE include the use of NSAIDs, Helicobacter pylori, and high consumption of fruits and vegetables[11].

Although BE is an asymptomatic disease, it is the most important known risk factor for the development of esophageal adenocarcinoma (EA), a tumor that has increased its incidence six-fold over the last four decades in Western countries, becoming the fastest growing cause of cancer mortality[12]. For BE patients, with a probability of 0.5% per year[13], the risk of developing EA is between 40 and 50 higher than for the general population[14-16].

The malignant degeneration cascade is thought to occur from nondysplastic intestinal metaplasia, to low-grade (LGD) and then high-grade dysplasia (HGD), and eventually EA[2,17]. The rate of progression from LGD to either HGD or EA ranges from 0.5% to 13.4% per patient per year[18]. The annual risk of progression from HGD to EA is 10% (ranges between 6% and 19%)[19,20].

## SCREENIG FOR BE

Although this practice is not supported by high-quality evidence, screening for BE can be suggested in patients with chronic gastroesophageal reflux disease (GERD) symptoms who have at least one additional risk factor for EA. The risk factors include: 50 years or older, male sex, white race, hiatal hernia, elevated body-mass index, intrabdominal body-fat distribution, or tobacco use[21-24].

## ENDOSCOPIC DIAGNOSIS

The gastroesophageal junction (GEJ) is not anatomically well defined, but it is accepted as the proximal limit of the gastric folds under partial insufflation. The squamocolumnar junction is bounded by the pale pink squamous mucosa of the esophagus, which contrasts with the red columnar gastric mucosa. The diagnosis of BE requires that the columnar epithelium extends above the GEJ, and the presence of columnar metaplasia confirmed in the esophageal biopsy[21].

BE has been divided in short (< 3 cm) or long-segment (≥ 3 cm), depending on the length of the metaplastic epithelium[25], but it is not clear that this classification can be clinical helpful, since there is no definitive evidence that the extent of the metaplastic segment increases the risk of cancer[26]. Prague's classification is a more recent system for describing BE endoscopically that evaluates both the circumferential extent (C) and the maximum extent (M) of Barrett's metaplasia[27]. However, since no endoscopic technique allows to either differentiate the intestinal metaplasia from gastric metaplasia or recognize the presence of dysplasia, a biopsy specimen is always required for diagnosis.

## SURVEILLANCE IN BE

Although there is no data from randomized controlled trials, surveillance is generally recommended because it has been correlated in published studies with earlier stage diagnosis and improved survival from cancer[3]. However, surveillance strategies are limited by the low incidence of cancer in patients with BE, and by the various difficulties in the interpretation of the presence of dysplasia (because of random sample collection, possibility of false negatives in the evaluation of the biopsies, or high variability for the interpretation of dysplasia). Nevertheless, most clinical guidelines[2,3,28] recommend endoscopic surveillance in patients with BE. The goal is the early detection of LGD and of its progression to HGD or early stage cancer (lymph node involvement varies between 0% and 2%, respectively). However, no long-term trials have been performed to definitively answer the question of whether endoscopic surveillance really reduces cancer incidence or mortality.

A high-resolution endoscopy is strongly recommended for the accurate evaluation of BE. A 4-quadrant biopsy sampling should be performed every 2 cm or every 1 cm (if known or suspected dysplasia). Additionally, specific biopsies of any suspicious lesions should be submitted separately.

Advanced imaging techniques (such as chromoendoscopy or electronic chromoendoscopy, narrow band imaging, confocal laser endomicroscopy or magnification) are not superior to standard white light endoscopy and, therefore, are not recommended for routine use. However, these technologies may be helpful to adequately address biopsies if dysplasia is suspected[2,29].

When no dysplasia is detected after 2 consecutive endoscopies within 6-12 mo, the usual recommendation is to repeat the test after 3-5 years. When indeterminate-grade dysplasia is detected, it is recommended

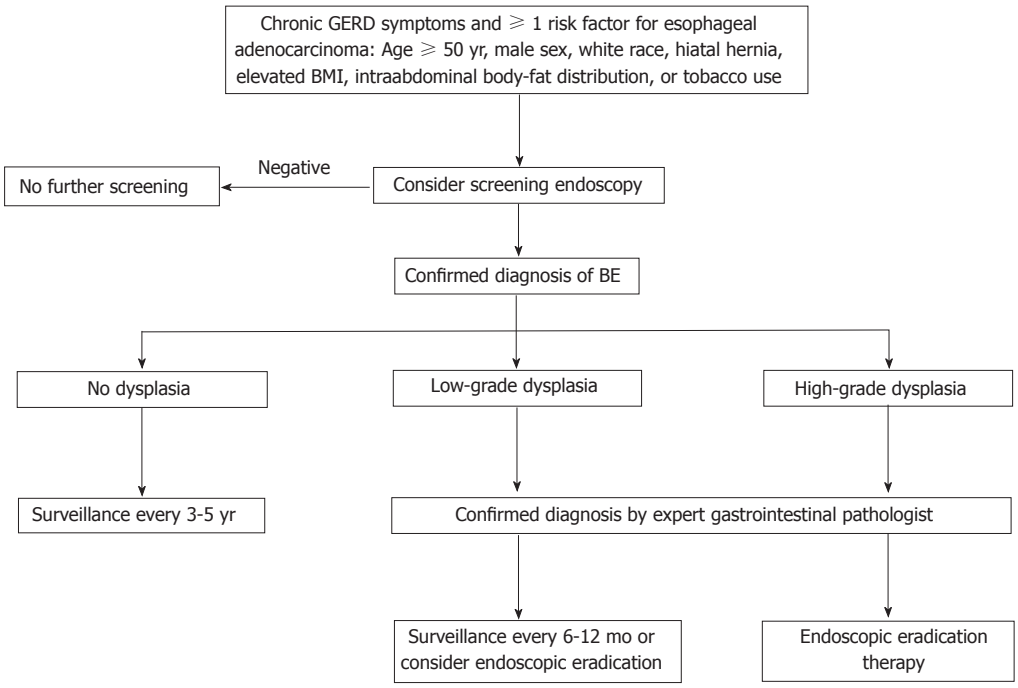


**Figure 1 Algorithm for the screening, surveillance and management of Barrett's esophagus.** GERD: Gastroesophageal reflux disease; BMI: Body mass index. BE: Barrett's esophagus.

to increase the antisecretory treatment to heal the esophageal inflammation and then repeat the biopsy after 6 mo. When LGD is detected, the recommendation is to perform an endoscopic control after 6-12 mo, and then an annual endoscopy until the absence of dysplasia is confirmed in two consecutive annual controls; alternatively, endoscopic eradication therapy can also be considered. When HGD is detected, endoscopic eradication therapy is strongly advised (consider surveillance every 3 mo only in selected cases). An algorithm for the screening, surveillance and management of BE is shown in Figure 1.

## MANAGEMENT OF DYSPLASIA AND EARLY CANCER

### *HGD and intramucosal EA*

Traditionally, esophagectomy has been recommended for patients with BE and either HGD or early EA, but the high morbidity and mortality of this technique, alongside with the development of new endoscopic techniques, are modifying this approach. Even in high-volume centers, the mortality rate of esophagectomy for HGD or early EA ranges from 0% to 4%[30]. Actually, surgery should be reserved for those patients with infiltration of the submucosal layer, and/or low grade or lack of response to endoscopic treatment.

The goal of endoscopic eradication therapy for patients with BE is to permanently eradicate all intestinal metaplasia and achieve a complete reversion to squamous epithelium[2,31]. Several studies have shown that HGD/T1m neoplasms can be eradicated in up 80%-100% cases, as well as the BE with intestinal metaplasia can be removed of in > 75% of cases[20,32-36]. Moreover, a significantly higher rate of progression to cancer has been shown in the endoscopic surveillance group comparing with the ablative treatment group (after initial endoscopic mucosal resection (EMR) where appropriate)[20,37]. Therefore, instead of surveillance, endoscopic eradication therapy with radiofrequency ablation (RFA), photodynamic therapy (PDT), or EMR is recommended for treatment of patients with confirmed HGD or intramucosal adenocarcinoma (T1a) within BE[2]. Major complications of these techniques include strictures, hemorrhage and perforation. Minor complications include temporary chest pain, fever and odynophagia.

Survival after endoscopic resection is similar to that expected after surgical treatment, but with less morbidity[32-34]. Therefore, since HGD is not associated with metastatic nodal spread when the existence of a deeper invasion has been excluded by EMR, endoscopic treatment is preferred over surgery in most patients with BE and HGD[32,33,38-40]. But, on the other hand, endoscopic therapies are associated with a higher rate of recurrence of the HGD[32-34,38,41], although it can usually be treated endoscopically[32-34,42]. Because of that, surgical resection should be reserved until the endoscopic treatment fails[32-34].

RFA is effective transforming an esophagus with pathological cells into an esophagus with a normal mucosa, without genetic abnormalities that may become premalignant[43]. A recent systematic review[44] suggests that success rates are higher with RFA, with a sustained disappearance of the HGD in up to 90% of patients[20,23,35,43,45]. RFA ablation is a safe, long-

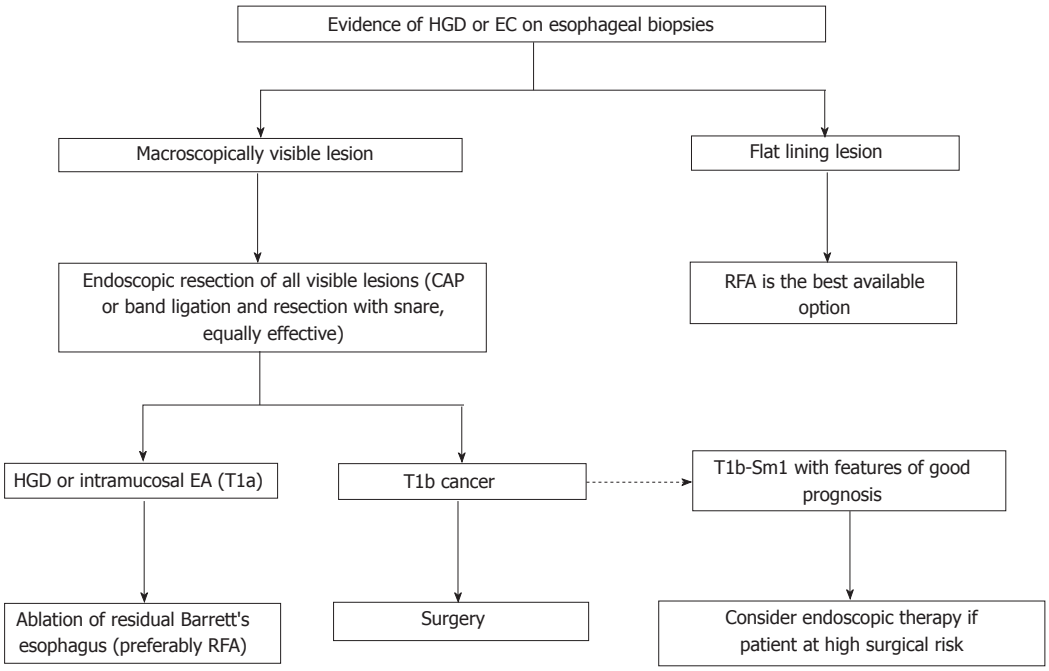


**Figure 2 Management of high-grade dysplasia and early cancer in Barrett's esophagus.** RFA: Radiofrequency ablation; BE: Barrett's esophagus; HGD: High-grade dysplasia; EC: Early cancer; EA: Esophageal adenocarcinoma.

lasting therapy (up to 5 years) that is associated with a significant reduction in the relative risk for neoplastic progression[20,35,46-48]. This technique is usually performed in various sessions to completely eradicate the metaplasia. The most common adverse event is the stenosis (up to 5% of patients)[49], but the rate of severe side effects of RFA is lower than with other ablative techniques[2]. Compared to other options, such as surgical treatment, photodynamic therapy, or follow up, RFA ablation is the most cost-effective strategy in patients with HGD[50].

In cases of HGD on a visible mucosal lesion, EMR is needed for an adequate diagnosis and depth staging[51] that can lead to a significant change in the management[52-55], since if an EA is found in the EMR sample, the risk of malignant adenopathy is related to the depth of invasion[56,57]. In this sense, the cap and snare technique with submucosal injection, and the band ligation technique without submucosal injection are considered to be equally effective[3]. Ideally, EMR should be applied in less than two thirds of the circumference of the esophagus to avoid strictures[29]. If a stenosis appears, it can be usually treated with endoscopic dilatation[58-60].

Endoscopic ablation of residual BE is currently recommended after completion of EMR of all visible HGD/T1a lesions. Several case series have reported recurrence of neoplasia if any residual BE is left untreated (11% to 30%, with a mean follow-up of 3 years)[32,58], and ablation of the residual BE is associated with a lower recurrence[20,36,40,41,61,62]. Consequently, RFA is currently the best available technique for the treatment of flat HGD and for eradicating residual BE after EMR[3,29,63].

Among alternative ablative techniques, PDT has been effectively used to ablate HGD, reducing the risk of progression to cancer compared with surveillance alone[64]. However, adverse events associated with this technology are common (development of esophageal stricture, 36% after PDT *vs* 6% after RFA) and may be severe[22,42]. Moreover, HGD can even persist in up to 33%-50% of the patients[65,66]. Long follow-up controlled studies comparing PDT with surgical resection and the other endoscopic therapies are needed to adequately assess this technique. Cryotherapy has not been assessed in randomized controlled trials, and it is not currently indicated as an alternative endoscopic eradication therapy. Small randomized controlled trials using argon plasma coagulation have reported anecdotal high-success rates[67].

In the case of an early EA extending into the submucosal layer, surgery should be considered as the best option[29], since in T1a context the rate of lymph node involvement is extremely low (< 3%) but the risk increases up to 20%-25% when the submucosal layer is affected. However, in selected T1b-Sm1 cases (invasion limited to the superficial layer of the submucosa), and with low-risk histopathologic features (invasion < 500 μm; G1-G2 grade, no lympho-vascular invasion), endoscopic therapy could be an option instead of esophagectomy (especially in high surgical risk patients)[68,69]. Endoscopic ultrasound evaluation of visible lymph nodes is advised in this setting.

The algorithm for the management of BE with HGD or early cancer is shown in Figure 2.

### *LGD*

Up to 25%-40% of BE patients will be diagnosed with

LGD during follow-up[70]. Most guidelines recommend endoscopic surveillance (every 6-12 mo) to rule out dysplastic progression. However, there are several doubts related to the evolution of the LGD. In some cases LGD may progress to HGD or EA, but it can also remain stable or even disappear in subsequent controls. Still, a significant progression rate from LGD to HGD or EA (13.4% per person-year) has been recently reported[18], suggesting that the endoscopic treatment in this population may also be justified.

The impact of RFA on the risk of neoplastic progression in BE patients with LGD is not clear, but RFA leads to reversion to normal-appearing squamous epithelium in > 90% of LGD cases[2]. A recent randomized controlled study[71] including 136 BE patients with confirmed LGD (68 patients undergoing RFA ± EMR *vs* 68 patients followed endoscopically) showed that RFA was associated with a significant reduction on the risk of neoplastic progression at 3 years follow-up: 26.5% in the follow-up group *vs* 1.5% in the ablative treatment group (95%CI: 14.1% to 35.9%; $P < 0.001$). This result corresponds to an NNT of 4. Full eradication of dysplasia and intestinal metaplasia were persistently achieved in most patients of the ablative group. Therefore, the authors conclude that ablative therapy should also be considered for patients with a confirmed LGD.

### *BE without dysplasia*

Endoscopic eradication therapy could not yet be recommended in patients with BE without dysplasia, because the low risk of progression to EA (0.1% to 0.3% per year)[14,72-74] and the side effects potentially associated with the endoscopy therapy (10%-15%).

## FOLLOW-UP AFTER ERADICATION

After endoscopic or surgery eradication of HGD, endoscopic follow-up is mandatory[75,76]. An evidence-based strategy for surveillance after subtotal esophagectomy is to perform endoscopy at 2, 5, and 10 years after surgery, and every 2-year once BE has been detected[29]. The follow-up interval for the endoscopic ablative therapy is still unclear.

## CHEMOPREVENTION AND SYMPTOMATIC CONTROL IN BE

GERD therapy is clearly indicated in the presence of GERD symptoms and/or reflux esophagitis. Although chemoprevention with acid-suppressing drugs can not yet be recommended, some observational studies have found an association between anti-reflux therapy and a lower rate of progression to EA, even in patients without GERD symptoms[77]. These results indirectly suggest a cancer-protective role for proton pump inhibitors (PPIs) in BE, and are strong enough to warrant conventional-dose PPI treatment for patients who have no symptoms or endoscopic signs of GERD[11]. However, acid- suppressing therapies, specifically PPIs, have not proven to reduce risk of progression to dysplasia or cancer[2,3]. PPIs are also used to prevent acid reflux and allow for reepithelialization by squamous epithelium after EMR or ablation.

The risk of EA among patients treated with antireflux surgery, and among those who received medical treatment with PPIs is similar[78]. Thus, antireflux surgery does not protect against cancer, and its indications in BE patients are the same as in GERD patients.

There is currently no definitive evidence to advise the use of aspirin or other chemopreventive agents in BE patients. The use of aspirin is only recommended in BE patients with cardiovascular risk factors (for which aspirin therapy is indicated) because the benefit-risk balance is clearly favorable only in this situation.

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