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REVIEW ARTICLE

Management of Barrett's esophagus: Screening to newer treatments ☆

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Abstract   Barrett's esophagus is a premalignant condition of the esophagus in which the squamous epithelium of the lower end of the esophagus is replaced with columnar epithelium. Since the incidence of esophageal adenocarcinoma is on the rise, the major gastroenterology societies have come up with their recommendations for screening and surveillance. Specific factors like obesity, white race, age over 50 years, early age of onset of GERD, smoking and hiatal hernia have been identified as increasing the risk of Barrett's esophagus and adenocarcinoma. The diagnosis requires both endoscopic identification of columnar-lined mucosa and histological confirmation with biopsy. Most medical societies recommend screening people with GERD and other risk factors with endoscopy, but other alternatives employing less invasive methods are currently being studied. Surveillance strategies vary depending on the endoscopic findings and the Seattle biopsy protocol with random 4-quadrant sampling is recommended. Biomarkers have shown promising results, but more studies are needed in the future. White light endoscopy is the standard practice, but other advanced imaging modalities have shown variable results and hence more studies are awaited for further validation. Endoscopic eradication techniques, including both resection and ablation, have shown good but variable results for treating dysplastic lesions confined to the mucosa. Resection procedures to remove visible lesions followed by ablation of the dysplastic mucosa have shown the best results with higher eradication rates and lower recurrence rates. Surgical management is reserved for lesions with sub-mucosal invasion and lymph node spread with increased risk of metastasis.
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Manejo del esófago de Barrett: del tamizaje a los nuevos tratamientos

Resumen   El esófago de Barrett es un trastorno premaligno del esófago en el cual el epitelio escamoso de la porción distal del esófago es reemplazado por epitelio columnar. Debido a que la incidencia de adenocarcinoma esofágico se encuentra al alza, la mayoría de las sociedades de Gastroenterología han emitido sus propias recomendaciones para el tamizaje y la vigilancia. Factores específicos como la obesidad, la raza blanca, la edad por encima de los 50 años, el inicio del ERGE a edad temprana, el tabaquismo y la hernia hiatal han sido identificados como factores que incrementan el riesgo de esófago de Barrett y adenocarcinoma. El diagnóstico requiere tanto de la identificación endoscópica de mucosa con revestimiento columnar como de la confirmación histológica con biopsia. La mayoría de las sociedades médicas recomiendan tamizar a todas las personas con ERGE, así como aquellos con otros factores de riesgo con endoscopia; sin embargo, otras alternativas que utilizan métodos menos invasivos se encuentran bajo estudio en la actualidad. Las estrategias de vigilancia varían dependiendo de los hallazgos endoscópicos y se recomienda el protocolo de biopsias de Seattle con un muestreo de 4 cuadrantes aleatorizado. Algunos biomarcadores han mostrado resultados prometedores, aunque se requieren de más estudios en el futuro. La endoscopia de luz blanca es el estándar en la práctica, sin embargo, otras modalidades de imagen más avanzadas han mostrado resultados variables y, por lo tanto, se esperan más estudios para obtener validación adicional. Las técnicas de erradicación endoscópica, incluyendo tanto la resección como la ablación, han mostrado buenos resultados, aunque variables, en el tratamiento de lesiones displásicas confinadas a la mucosa. Los procedimientos de resección para remover las lesiones visibles seguida por la ablación de la mucosa displásica han mostrado los mejores resultados, con tasas de erradicación más altas y menores tasas de recurrencia. El manejo quirúrgico está reservado para lesiones con invasión de la submucosa y propagación a ganglios linfáticos con un riesgo incrementado de metástasis.

Introduction

Barrett's esophagus (BE) is a pre-malignant condition of the esophagus in which the squamous epithelium of the lower end of the esophagus is replaced with columnar epithelium. It is generally due to chronic mucosal damage caused by gastroesophageal reflux disease (GERD). The incidence of BE in the United States has been estimated at about 5.6% of the general population.[1] In recent years, BE has become a focus of studies as the incidence of esophageal adenocarcinoma (EAC) is on the rise in the western world and is currently the fifth leading cause of cancer-related deaths among men worldwide.[2] The sequence of GERD leading to BE, which is premalignant and eventually leads to EAC, has gained the attention of physicians around the world, resulting in the elaboration of guidelines for screening and surveillance.

Epidemiology

The prevalence of BE has been difficult to estimate, as most of the patients are asymptomatic and remain undiagnosed. Various rates have been reported from different parts of the world. In a prospective study reported by Rex et al. based on upper endoscopy (EGD) offered to patients undergoing colonoscopy, the prevalence of BE was 6.8% with a short-segment BE rate of 5.5%.[3] A similar study with a smaller cohort conducted by Ward et al. revealed short-segment BE in 15% and long-segment Barrett's esophagus in 4%, but this cohort had a significantly older population.[4] Ronkainen et al. published a study from Sweden based on EGD done on 1,000 random individuals and reported a prevalence of BE of 1.6% with a short-segment BE of 1.1% and a long-segment BE of 0.5%.[5] Zagari et al. from Italy published a study with BE prevalence of 1.3% and long-segment BE of 0.2%,[6] whereas Zou et al. from China reported BE of 1.9% and long-segment BE of 0.5%.[7] Published studies have reported an increasing incidence and prevalence of BE in the male population with a ratio of almost 2:1, also associated with earlier presentation in males than in females.[8] This may partly be due to the protective effect of estrogens in females,[9] which may be lost as they age, and to the development of obesity, leading to reflux esophagitis[10] and consequent BE.

There are several other risk factors for BE and EAC which have been identified in clinical studies. Obesity, white race, older age, chronic heartburn, early age of onset of GERD, hiatal hernia, smoking, a family history of GERD or familial forms of Barrett's esophagus, and obstructive sleep apnea have been recognized as significant risk factors.[11] The use of nonsteroidal anti-inflammatory drugs, statins, *Helicobacter pylori* (*H. pylori*) infection and a diet rich in fruits and vegetables have been found to protect against BE. *H. pylori* infection causes gastritis, which leads to decreased gastric

acid production and hence decreased acid reflux, thus offering a protective influence against BE.[11]

There has been increasing incidence in both BE and EAC in the developed countries in the past few decades that has been attributed to several factors. The increasing incidence of obesity, especially truncal obesity, which promotes GERD and hence carcinogenesis, has been a major risk factor. It has been shown to increase GERD by 1.5-2% and risk of EAC by 2-2.5%.[11] Abdominal circumference (waist-hip ratio) has been identified as an independent risk factor.[12] Visceral obesity also leads to a pro-inflammatory state with the increase of several cytokines, such as interleukins, tumor necrosis factor alpha, C-reactive protein, and leptin, leading to elevated cell proliferation and reduced apoptosis, and eventually to EAC.[13,14] Decrease in the incidence of *H. pylori* infection in these countries leading to increased acid secretion and GERD has also been postulated.[15] Dietary modifications involving more nitrates in both the food and the fertilizers used in growing them, together with low levels of antioxidants in food, could also be a contributing factor.[16]

Diagnostic criteria

The diagnosis of BE requires both endoscopic identification of columnar-lined mucosa and the histologic presence of intestinal-type metaplasia.[17] The mucosa of the esophagus is normally lined with stratified squamous epithelium and it changes to columnar epithelium at the level of the gastroesophageal (GE) junction, which is identified by the end of the proximal gastric mucosal folds. The squamous epithelium is pale and glossy in architecture, whereas the columnar epithelium is salmon-colored. Normally the squamocolumnar junction coincides with the GE junction, but when it is proximal to the GE junction, there is a columnar epithelium-lined esophagus, which is considered BE. If the segment is < 3 cm, it is called short-segment BE and if ≥ 3 cm it is long-segment BE.[18] Short-segment BE was not widely recognized until 1994 and earlier studies generally reported long-segment BE.[19] More recent studies have found varying proportions of both, and thus they could influence symptoms and complications. The endoscopic extent of Barrett's segment should be reported using the Prague criteria, which includes both the circumferential extent (C) and the maximum extent (M) of the endoscopically visible columnar-lined esophagus and separate islands above the main segment noted in centimeters from the GE junction.[20] Several societies including the American societies require specialized columnar cells with secretory cells called goblet cells, otherwise known as intestinal metaplasia, to be present in the biopsy samples of the esophagus to diagnose BE.[21–23] There is a controversy as to whether to accept cardiac type columnar cells (without goblet cells) as a criterion, but the British Society of Gastroenterology accepts them according to their recently updated guidelines.[24]

Screening

The traditional strategy has been to screen patients with GERD with an endoscopy and to identify columnar metaplastic epithelium, obtain biopsy specimens to confirm BE, identify dysplasia, and then treat them. There are several pitfalls associated with this strategy. Despite the rising incidence of EAC, the annual cancer incidence of EAC from BE has been shown to be only 0.1 to 0.3%, which is still relatively low.[25–28] Nearly 40% of the patients with EAC have no prior history of GERD and only 10% of the patients with EAC have a prior diagnosis of BE.[29–31]

Most medical societies recommend endoscopic screening in patients with GERD, along with other risk factors for BE, such as age > 50 years, male sex, white race, intra-abdominal fat distribution with truncal obesity, tobacco use, elevated body mass index (BMI), and hiatal hernia.[17,22,23,32]

Newer less invasive screening modalities such as unsedated trans-nasal endoscopy and video capsule endoscopy have been studied. They had better participation rates than sedated endoscopy[33] and also proved to be cost-effective. Capsule endoscopy has shown a high diagnostic yield in a few pilot studies,[34,35] whereas other studies have reported a low sensitivity and specificity[36] with higher cost, making it a disadvantage. The cytosponge test, an ingestible sampling device that allows cytology samples to be retrieved from the esophagus to run immunohistochemical assays has shown promising results[37,38] with reduction in mortality compared with no screening.[39] Currently none of these have replaced the traditional endoscopy with sedation due to lack of evidence suggesting that they are superior to standard screening methods.

Surveillance

The goal of endoscopic surveillance is to identify precancerous lesions at an early stage and intervene with a curative intent. EAC had a very poor survival rate of only 13% at the end of 5 years.[40] Patients with BE were enrolled in endoscopic surveillance programs and were risk-stratified based on the presence of different grades of dysplasia after histopathologic study. There are no prospective randomized controlled trials that demonstrate the efficacy and superiority of these surveillance strategies in identifying the patients at risk, as the annual incidence of EAC is still low and a significant proportion of those patients do not have BE. In a Dutch cohort study, only 5.6% of the patients with BE died due to EAC.[41]

The biopsy protocol that is currently recommended during endoscopy is the Seattle protocol. It involves targeted sampling of the endoscopically visible lesions followed by random 4-quadrant biopsy sampling every 1-2 cm starting from the proximal gastric folds to the uppermost part of the squamocolumnar junction. The biopsy should proceed in a distal to proximal fashion. This has been proven to increase the yield with regards to diagnosis of dysplasia in BE.[42] Even with adherence to this protocol, it is possible to sample only up to 6% of the BE area.[43] Studies have shown that this rigorous protocol is not followed completely in many cases, especially in patients with the highest risk of dysplasia, leading to decreased rates of detection.[44,45] Furthermore, it is difficult to adhere to this protocol in patients with small-segment BE. Hence the need for better imaging and visual modalities, as described below, for better identification of dysplasia and those at the highest risk for EAC.

Recommendations for Screening and Surveillance for Barrett's Esophagus from various Gastro-intestinal Societies

	AGA	ASGE	ACG	BSG	SFED	ACP
Criteria for screening	Patients with multiple risk factors for EAC	Patients with multiple risk factors for EAC and must be informed that evidence is insufficient	Specific populations at high risk–has to be individualized	Patients with multiple risk factors for EAC	Patients with GERD and depending on age and general health status, if it would offer benefit	Age > 50 years, Chronic GERD > 5 years and additional risk factors for EAC
Surveillance of NDBE	Every 3-5 years	Every 3-5 years	Every 3 years	Every 2-3 years	SSBE 5 yrs, LSBE (3-6cm) 3 yrs, LSBE > 6 cm 2 yrs	Every 3-5 years
Surveillance of LGD	Every 6-12 months	Repeat endoscopy in 6 months and then annually	Repeat endoscopy in 6 months and then annually until 2 successive no dysplasias	Every 6 months	At 6 months, 1 year, and then annually	Not addressed
Surveillance of HGD	Every 3 months	Only for patients unfit for/ refusing therapy	Every 3 months	Endoscopic therapy preferred	Endoscopic or surgical therapy	Not addressed
Treatment of GERD	PPI recommended	Not addressed	PPI recommended	PPI recommended	Double dose PPI: 2 months for LGD and 1-2 months for HGD	Not addressed
Treatment of HGD/ IMC	Endoscopic eradication therapy	EMR and/or RFA	Should be individualized – surgery vs endoscopic eradication vs surveillance	Endoscopic therapy preferred	No specific recommendations	Not addressed

ACG: American College of Gastroenterology; ACP: American College of Physicians; AGA: American Gastroenterology Association; ASGE: American Society of Gastrointestinal Endoscopy; BSG: British Society of Gastroenterology; EAC: Esophageal adenocarcinoma; EMR: Endoscopic mucosal resection; GERD: Gastroesophageal reflux disease; HGD: High-grade dysplasia; IMC: Intra-mucosal carcinoma; LGD: Low-grade dysplasia; LSBE: Long-segment Barrett's esophagus; NDBE: Non-dysplastic Barrett's esophagus; PPI: Proton pump inhibitor; RFA: Radiofrequency ablation; SFED: French Society of Gastrointestinal Endoscopy; SSBE: Short-segment Barrett's esophagus

Biomarkers

Risk stratification for cancer in patients with BE is currently based on the presence of dysplasia in histology, although the diagnosis and grading of dysplasia are limited by moderate to poor interobserver agreement. Several biomarkers have been proposed to predict the neoplastic progression from BE, but only cross-sectional studies have been performed and there are no validated prospective trials. Immunohistochemistry staining of p53 has been studied and proposed as an adjunct to dysplasia for diagnosis.

Aberrant p53 expression was associated with an increased risk of progression to cancer with overexpression having a relative risk of 5.6 and loss of expression with a relative risk of 14. The positive predictive value increased from 15% with LGD alone to 33% with concurrent LGD and aberrant p53 expression.[46] Other biomarkers like aneuploidy/tetraploidy,[47,48] 17p loss of heterozygosity (LOH),[49] 9p LOH, and gene methylation-based biomarkers have shown promising results.[50] Current data suggests that these biomarkers are no better than a histological finding of high-grade dysplasia (HGD) in predicting cancer progression, but may be

superior in prediction compared with non-dysplastic Barrett's esophagus (NDBE), indeterminate dysplasia, or LGD. The combination of biomarkers and histology can provide even better results. More studies may be available in the future and hence these biomarkers can be used to predict which patients would benefit from surveillance vs ablation.

Advanced imaging modalities

Apart from high resolution white light endoscopy, other advanced techniques, such as narrow band imaging (NBI), chromo-endoscopy, autofluorescence imaging (AFI), confocal laser micro-endoscopy, diffuse reflectance spectroscopy, light scattering spectroscopy, and optical coherence tomography (OCT) have recently emerged. Currently white light inspection of the esophagus using high resolution endoscopy is the standard of practice and guidelines do not recommend routine use of advanced endoscopic imaging either for screening or surveillance of patients with BE. With the advances in technology, combining normal white light endoscopy with magnification devices and high resolution television systems has enabled the production of higher quality images that have been shown to have a higher sensitivity for the detection of dysplasia and early neoplastic lesions in BE.[51,52]

Virtual chromo-endoscopy involves the application of chemical agents and dyes that highlight specific areas of the esophageal mucosa and therefore aid in targeted biopsies. Several agents, such as methylene blue, Lugol's iodine solution, indigo carmine dye, and acetic acid have been used for this purpose. Lugol's iodine stains the squamous cells of the epithelium which contains glycogen and thus enables the identification of Barrett's islands with columnar mucosa after eradication therapy for BE.[53] The studies using methylene blue to stain the non-dysplastic areas in the BE have reported mixed results. Horwhat et al. conducted a randomized, prospective, cross-over trial in 48 patients and demonstrated that the yield of detecting BE or dysplasia was similar among patients who received targeted biopsies using methylene blue and in those patients who had random 4-quadrant biopsies, but required significantly fewer biopsies compared with random 4-quadrant biopsies (9.23 ± 2.89 and 18.92 ± 6.36, respectively) (p < 0.001).[54] Lim et al. concluded a randomized cross-over study with 30 patients with a mean length of Barrett's segment of 5 cm. Overall, 17 out of the 18 patients with dysplasia were identified by random 4-quadrant biopsies, whereas only 9 were identified using methylene blue (p = 0.02).[55] Ngamruengphong et al. conducted a meta-analysis reporting the diagnostic yield of using methylene blue chromoendoscopy. There was no significant incremental yield (IY) over random 4-quadrant biopsies for metaplasia (IY 4%), dysplasia (IY 9%), and early cancer (IY 5%).[56] Olliver et al. claimed that it could lead to DNA damage in Barrett's epithelium, and thus could potentially accelerate carcinogenesis.[57] Four specific pit patterns have been identified in studies using application of both acetic acid and indigo carmine–round, reticular, ridged, and villous. Guelred et al. described that the ridged and villous patterns were associated with intestinal metaplasia using acetic acid, whereas another study used indigo carmine in 80 patients and reported that the ridged/villous pattern

had a sensitivity of 97% and specificity of 76% for intestinal metaplasia.[53]

NBI is a form of electronic chromo-endoscopy that uses spectral narrow band optical filters, optical band imaging, and I-scan to highlight the vascular patterns or to differentiate the contrast between squamous and columnar epithelium.[58] Prospective trials comparing NBI with high resolution white light endoscopy have been published. In the study conducted by Wolfsen et al. with 65 patients known to have dysplasia in BE, NBI identified more patients with dysplasia and also higher grades of dysplasia compared with white light endoscopy.[59] In another randomized, multicenter cross-over trial which compared both, NBI detected the same number of patients with metaplasia, but a higher proportion of areas with dysplasia (30% vs 21%, p = 0.01).[60] Regular-appearing mucosa and vessels with NBI did not harbor any high-grade dysplasias. Moreover, they required significantly fewer biopsies than with white light endoscopy (3.6 vs. 7.6, p < 0.0001)

AFI endoscopy is based on the principle that when a laser light is emitted by endoscopy, cells would re-emit a fluorescent light with distinct spectroscopic characteristics. Kara et al. found that it is a study with very good sensitivity for identifying HGD, but with poor specificity and a high false positive rate.[61] Mannath et al. published a recent report studying the interobserver agreement between experts and non-experts for AFI.[62] They concluded that there was fair-to-moderate agreement for AFI alone, which improved when it was combined with high resolution white light endoscopy. Curvers et al. published a report that utilized a ''trimodal imaging'' technique in which the esophagus was first examined using the normal high resolution white light followed by AFI to highlight abnormal areas not seen with white light, followed by NBI to confirm the abnormal areas in AFI.[63] AFI diagnosed a significantly higher proportion of abnormal areas than white light, but with a higher false positive rate of 81%, which was reduced to 26% with NBI. It could still not replace the traditional 4-quadrant biopsy, as 10% of the cases were missed by all 3 modalities.

Confocal micro-endoscopy uses the technique of translation of reflected endoscopy-derived laser light onto the computer into a cross-sectional image of the mucosal architecture. Real time analysis of the blood vessels and the crypts can be performed. Reports published so far have shown good accuracy rates (85%-94%) of dysplasia detection.[64,65] Pohl et al. conducted a prospective 2-center trial and reported that the confocal laser microscopy criteria for BE were more frequently detected in HGD and early cancer than in low-grade dysplasia, with good interobserver agreement with a kappa value of 0.6.[66] The spectroscopic techniques are based on the analysis of the light scattered from the tissue. Diffuse reflectance spectroscopy analyses the light scattered multiple times within the tissue, whereas light scattering spectroscopy uses light reflected only once. These techniques have been reported to distinguish higher grades from lower grades of dysplasia and also from no dysplasia up to 88% with a sensitivity and specificity approaching 90%. OCT uses near-infrared light to provide high resolution images and initial studies have reported higher sensitivity and specificity rates of > 90% in the detection of metaplasia.[67–69]

Despite having promising results, more studies are needed to validate these techniques, optimizing the associated costs and developing ideal teaching methods to get this technology to gastroenterologists beyond the tertiary centers. Currently high resolution endoscopy with white light with random 4-quadrant biopsies has been the most widely accepted modality for diagnosis of metaplasia and dysplasia in BE.

Endoscopic eradication techniques

Eradication using endoscopic techniques involves either a resection procedure like endoscopic mucosal resection (EMR) and endoscopic sub-mucosal dissection (ESD) or ablative procedures of the BE mucosa with several techniques. The advantage with the resection procedures is that they are both diagnostic and therapeutic as we get a tissue sample, whereas the ablative procedures are only therapeutic. All endoscopic procedures should be followed by acid suppression therapy to allow for healing and re-epithelialization of the esophageal mucosa with squamous epithelium.

Surgical procedures used to be the treatment of choice even for early pre-malignant lesions, but endoscopic methods, thanks to the advances made, are now being used more widely. One important criterion to be considered before selecting endoscopic therapy is to assess the extent of the involvement of dysplasia in BE. It must be confined only to the mucosa (T1a stage) and there should be no involvement of the submucosa, in which case surgical management is the standard of care. It has been proven that early neoplasms involving only the mucosa have a 1-2% risk of lymph node metastasis,[70] whereas those with sub-mucosal invasion have a 10% risk of lymphadenopathy,[71] and a few reports have suggested up to 20%.[72,73] Therefore, an accurate T-staging is essential before deciding on therapy. Endoscopic ultrasound (EUS) is the most accurate imaging modality for T-staging of neoplasms, but they can predict the depth of invasion in only 50-60% of the cases. On the other hand, studies on EMR with biopsy of the specimen have been shown to have a better prediction rate of T-staging and to be superior to EUS studies.[74,75]

Retrospective studies comparing surgery to endoscopic therapy for early neoplasms have shown that surgery has higher short-term mortality,[76–80] whereas endoscopy has lower morbidity, better cost-effectiveness,[81] and a lower risk of complications.[82,83]

Endoscopic resection

EMR and ESD are the 2 resection procedures. They involve a systematic resection of a specific area of the esophagus with an endoscopic knife or a diathermy snare. They are used especially with visible nodular dysplasia and short-segment dysplastic BE, for which they are preferred over the ablative techniques. The BSG recommends 2 basic techniques that are the principle behind this technique. The band ligation technique involves suction of the desired area and deployment of a band that creates a pseudo-polyp, which can be removed by a diathermy snare.[24] The cap and snare technique involves lifting of the desired area with a sub-mucosal injection and placing a cap over the mucosa,

which can then be snared.[24] EMR for HGD and EAC T1a stages has been successful in 91-98% of the cases.[84–86] Moreover, cohort studies have shown that EMR eradicates BE in 75-100% of patients and eradicates dysplasia in 86-100% of the cases.[87–92] Water jet-assisted ESD has been attempted with an en-bloc resection rate of around 90%.[93] Not many direct studies comparing EMR and ESD are available, but the study by Ishihara et al. comparing EMR with ESD for esophageal squamous cell carcinoma revealed that EMR had a higher local recurrence rate (23.91% vs 3.13%), suggesting that ESD is the preferred technique when available, even though it is technically more demanding.[94] Their study results also suggest that despite the resection of the dysplastic mucosa, the remaining non-dysplastic BE is still at risk and hence has to be eradicated by further resection or ablation. Wani et al. reported in their multicenter cohort study that EMR could change the histological diagnosis in up to 30% of the patients, which could potentially change the course of management.[95] Complications of EMR are immediate bleeding up to 10%,[76,85,96] perforation in 3-7% of patients,[83,86,97] and delayed stricture formation in 17-37% of patients.[98]

Endoscopic ablative techniques

Ablative techniques can be thermal, radiofrequency ablation (RFA), photodynamic therapy (PDT), multipolar electro-coagulation (MPEC), cryotherapy, and argon plasma coagulation (APC). These techniques are generally performed when there are no visible lesions in the dysplastic epithelium, in which case resection techniques have a higher success rate.

PDT involves the use of a photosensitive chemical like 5-aminolevulinic acid or porfimer sodium to sensitize the tissues and destroy them with endoscopically delivered laser light. The laser light causes free radical generation upon exposure to the sensitized cells, thus leading to damage. Success rates of eradication of HGD up to 77% in 5 years have been achieved.[99,100] In a retrospective cohort study by Overholt et al. involving 103 patients presenting with BE with dysplasia and IMC that had a mean follow-up of 50 months, intent-to-treat success and eradication rates were 92.2% for low-grade dysplasia, 77.5% for HGD, and 44.4% for IMC.[99] Complications included stricture formation rates up to 30%, photosensitivity of the skin in up to 33% (p < 0.05), and buried BE epithelium beneath the squamous epithelium that was significantly higher in up to 48% of patients and may eventually become malignant.[99–102] Pain during the immediate post-operative period has been reported as a significant side effect in most of the patients, with studies reporting up to as high as 86% of patients.[103,104] Due to comparatively higher complication rates, PDT is not a highly favored option for BE therapy.

Cryoablation therapy is a non-contact technique that involves the spraying of liquid nitrogen or carbon dioxide to freeze and destroy the Barrett's mucosa.[105,106] Liquid nitrogen or carbon dioxide is sprayed to freeze the tissue for 10 to 20 s, then thawed for one minute, with 3-4 cycles per session. Another session may be repeated in a couple of months if needed. It has been shown to cause eradication of intestinal metaplasia and dysplasia in 46-78% and 79-87% of the cases, respectively.[106,107] Dumot et al. demonstrated in

their non-randomized cohort trial of 30 patients that 68% of the patients with HGD and 80% with IMC had downstaging of HGD or elimination of cancer.[108]

MPEC and APC are other endoscopic eradication techniques which have not been extensively studied for the treatment of BE, although there are several prospective case series that describe their use and success. Montes et al. reported an eradication rate of 100% of cases of NDBE in his series with 14 patients with a mean follow-up of 21.6 months,[109] whereas Sampliner et al. reported only a 78% eradication rate in a 6-month follow-up.[110] For APC, Madisch et al. reported an eradication rate of 98% and a recurrence rate of 12% in his series with a mean follow-up of 51 months,[111] whereas another study reported an eradication rate of only 84% and a recurrence rate of up to 66% in a follow-up of 30 months.[112] Randomized controlled studies comparing MPEC with APC found no significant difference between eradication rates, but both needed multiple treatment sessions.

RFA involves an assembly of closely placed electrodes to deliver radiofrequency energy to the esophageal mucosa, thus causing ablation. This generates uniform thermal energy in a circumferential fashion, while the power, duration, and density of thermal energy can be varied. Several studies have compared RFA with other ablative therapies and have shown that RFA has a better success rate, a lower recurrence rate of dysplasia, and is comparatively safer than other techniques. A prospective multicenter study demonstrated a 70% remission in BE in circumferential treatment,[113] but Ganz et al. published a subsequent report that described a 98% eradication rate when a focal ablation technique was used after circumferential ablation.[114] In a multi-center sham-controlled trial with 127 patients with dysplastic BE, there was complete eradication of LGD in 90.5% (p < 0.001) of the patients and in 81% of the patients with HGD (p < 0.001) during a 12-month follow-up.[115] In a

multicenter, randomized, controlled trial conducted by Phoa et al., comparing RFA with endoscopic surveillance for BE with LGD, it was shown that RFA reduced the risk of progression to HGD by 25% (p < 0.001) and adenocarcinoma by 7.6% (p = 0.03) during a 3-year follow-up.[116] There was complete resolution of the dysplasia in 92.6% of the patients. In a United Kingdom-based registry involving 335 patients with BE, with 72% of them having HGD, RFA ablation led to 86% resolution and clearance of HGD during a 12-month follow-up.[117] Shorter segment Barrett's responded better and reversal of dysplasia was 15% less likely with every incremented centimeter in the length of the BE segment.[117] A systematic review comparing sub-squamous metaplasia in RFA and PDT-treated patients showed that 0.9% of RFA-treated patients and 14.2% of PDT-treated patients had metaplasia, thus demonstrating the superior efficacy of RFA.[118] In a systematic review and meta-analysis by Orman et al., the most frequent complication was stricture formation (5%), followed by pain (3%) and bleeding (1%), which reflects the results in most of the other published articles and retrospective studies.[119] RFA has also been shown to have a lower stenosis rate than stepwise radical endoscopic resection (14% vs 88%, p < 0.001).[120] Despite the positive results of ablation procedures in eliminating dysplasia and reducing neoplastic progression, their role in NDBE has been questioned by studies in relation to the recurrence of metaplasia during follow-up due to sub-squamous metaplasia, durability of response, and in some analyses, a recurrence rate up to 33%.[121] Hence, ablation procedures might be a useful approach in LGD treatment, given the reduced rate of progression to cancer. However, the unnecessary subjection of NDBE patients to these endoscopic procedures with the consequent increase in complication rates demand the publication of long-term data. Under the present circumstances, ablation procedures are not recommended by the medical societies.

Recurrence rates and eradication rates of high-grade dysplasia and intra-mucosal cancer in Barrett's esophagus with various endoscopic eradication techniques

Study	Year	Endoscopic eradication technique	Number of patients	Mean length of follow-up (months)	Rate of recurrence (%)	Rate of eradication (%)
Overholt et al.[100]	2003	PDT	65	58.5	4.9	NA
Dunn et al.[101]	2013	ALA, Photofrin-PDT	64	24	14	ALA 47 Photofrin 40
Dumot et al.[108]	2009	Cryotherapy	30	12	NR	HGD 68, IMC 80
Shaheen et al.[106]	2010	Cryotherapy	60	10.5	3	HGD 97, dysplasia 87, metaplasia 57
Halsey et al.[122]	2011	Cryotherapy	36	24	Dysplasia 17 Metaplasia 30	92
Shaheen et al.[115]	2009	RFA	127	12		81

Study	Year	Technique	N	Follow-up (months)	Complications/Recurrence	Remission
Shaheen et al.[123]	2011	RFA	54	36		**24 months:** dysplasia 93, metaplasia 89 **36 months:** dysplasia 98, metaplasia 91
Van Vilsteren et al.[120]	2011	EMR + RFA vs SRER	47	24	0.02	**EMR + RFA:** HGD 96, IMC 96 **SRER:** HGD 100, IMC 92
Gupta et al.[121]	2013	RFA, EMR	448	24	33	56
May A et al.,[85]	2002	EMR, PDT	115	34	30% metachronous lesions	98% local remission
Seewald et al.[91]	2003	EMR	12	9	0	100
Pech O et al.[124]	2003	EMR	550	12	NA	82.5
Conio et al.,[87]	2005	EMR	39	34.9	NA	100
Larghi et al.[89]	2007	EMR	26	28	12.5	87.5
Lopes et al.[90]	2007	EMR	41	31.6	24.4	75.6
Pech O et al.[86]	2008	EMR/ PDT	349	63.6	21.5% metachronous lesions	96.6
Moss A et al.[75]	2010	EMR	75	7	11% metachronous lesions	94

ALA: 5-Aminolevulinic acid; EMR: Endoscopic mucosal resection; HGD: High-grade dysplasia; IMC: Intra-mucosal carcinoma; NA: Not addressed; PDT: Photodynamic therapy; RFA: Radiofrequency ablation; SRER: Stepwise radical endoscopic resection.

Surgical management

For several decades, esophagectomy was the traditional treatment option for HGD. It eliminates both dysplastic and non-dysplastic BE, providing a tissue sample for biopsy and also allowing removal of lymph nodes with metastasis. Surgical therapy is considered the treatment of choice when there is sub-mucosal invasion with an increased risk of metastasis. There are several esophagectomy techniques and they have shown similar outcomes. Transhiatal, thoracoabdominal, vagal-sparing, Merendino segmental, and minimally invasive laparoscopic or thoracoscopic esophagectomy options are practiced.[24] When compared with the endoscopic therapies, they have a significantly higher rate of mortality and morbidity, especially short-term, but with almost similar survival rates.[80] Most of the studies have been done on symptomatic, old, and debilitated patients who had a higher rate of mortality than the smaller series in younger populations that had a mortality of less than 3.3%.[79] It has also been shown to affect the quality of life in the short term while long-term studies have demonstrated results comparable to those in the general population. Rare occurrences of neo-metaplasia in the esophageal remnant due to acid reflux have been reported,[125] but nevertheless, the risk is very small. Therefore, esophagectomy is definitely an option to be considered in cases of mucosal breach or with lymphadenopathy, especially in the younger and fitter population.

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The authors declare that there is no conflict of interest.

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