

REVIEW

Endoscopic diagnosis and therapies for Barrett esophagus. A review

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ABSTRACT

Barrett's esophagus is an area of great interest in Gastroenterology, with an increasing number of research studies being published in recent years and decades. Due to the fast growing evidence regarding this disease, it has become extremely difficult to keep updated on this subject. The present review article aims to summarize and update what is known regarding diagnosis and therapy in Barrett's esophagus. A critical and detailed review is made and the role of surveillance for this condition, techniques available for diagnosis (standard white light endoscopy, virtual chromoendoscopy, magnification...) and treatment (mucosectomy, ablation...) are presented. New and emerging technologies are described in detail and existing evidence is presented.

Key words: Barrett. Esophagus. Endoscopy. Dysplasia. Mucosectomy. Radiofrequency.

INTRODUCTION

Esophageal adenocarcinoma (EAC) has been increasing in the United States more than six-fold over the past three decades, faster than that of any other malignancy (1). Barrett esophagus (BE) is a well-established precursor of EAC and increases the risk of developing EAC by greater than 40-fold compared with the general population (2).

BE is currently 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" (3). Currently, only the presence of specialized columnar epithelium containing goblet cells is required for establishing a diagnosis of BE, prior to recommendations of surveillance, as it has been considered to be the only type of epithelium that clearly predisposes to malignancy (4).

But there is not a universal agreement for including intestinal metaplasia (IM) as a requisite for the diagnosis of BE. Non-goblet columnar metaplasia by itself also seems to predispose to cancer, but the true magnitude of this risk is unknown (5-9).

Dysplasia can be defined as the presence of neoplastic epithelium that is confined within the basement membrane of the gland within which it arises. The grading of dysplasia is critical in stratifying the risk of developing subsequent cancer in patients with Barrett's esophagus, and to date, it is the most important predictive marker for the development of invasive adenocarcinoma (10).

But grading of dysplasia is sometimes difficult, leading to disagreement among pathologists in the histological interpretation of the endoscopy specimens, especially in the low spectrum of dysplasia (Non Dysplastic Barrett Esophagus {NDBE}; and Low Grade Dysplasia {LGD}) (11-13).

RISK OF PROGRESSION AND ENDOSCOPIC SURVEILLANCE

The identification of early-stage cancer, when treatment is most effective, is the basis for all surveillance recommendations (14-16). Guidelines proposed by the principal societies provide different intervals for surveillance depending on the grade of dysplasia detected on pathology specimens (17-20) (Table I).

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Table I. Recommendations on surveillance for Barrett esophagus according to the following societies: ACG: American College of Gastroenterology; ASGE: American Society of Gastrointestinal Endoscopy; AGA: American Gastroenterological Association; and BSG: British Society of Gastroenterology

| | ACG 2008 (17)  | ASGE 2012 (19)  | AGA 2011 (18)  | BSG 2013 (20)  |
|--|--|---|---|--|
| <i>Non dysplastic BE (NDBE)</i> | Two EGDs with biopsy within 1 year Follow up every 3 years | Consider no surveillance. EGD every 3 to 5 years Consider endoscopic ablation in select cases | EGD every 3 to 5 years | SSBE with no IM - Consider discharge SSBE with IM - EGD every 3 to 5 years LSBE - EGD every 2 to 3 years |
| <i>Indefinite for dysplasia (IDBE)</i> | | Expert pathologist review Repeat EGD with maximal acid suppression | | Repeat EGD at 6 months with maximal acid suppression If IDBE survey as NDBE |
| <i>Low grade dysplasia (LGD)</i> | Expert pathologist confirmation Highest grade on repeat EGD with biopsies within 6 months Follow up every year | Expert pathologist confirmation Repeat EGD in 6 months to confirm LGD Follow up every year, Consider endoscopic resection or ablation | Expert pathologist confirmation Follow up every 6–12 months Consider endoscopic eradication therapy (RFA) | Expert pathologist confirmation Follow up every 6 months Ablation therapy cannot be recommended routinely until data from RCTs are available |
| <i>High grade dysplasia (HGD)</i> | Expert pathologist confirmation Repeat EGD with biopsies within 3 months Mucosal irregularity EMR Continued 3 month surveillance Endoscopic therapy Esophagectomy | Expert pathologist confirmation Consider EMR or RFA Consider surgical consultation Consider surveillance EGD every 3 months (only patients non candidates for endoscopic or surgical approach) | Expert pathologist confirmation Mucosal irregularity EMR Endoscopic eradication therapy (RFA, PDT or EMR) rather than surveillance or surgery Continued 3 month surveillance Esophagectomy only in specialized surgical centers | Expert pathologist confirmation Mucosal irregularity EMR Endoscopic therapy is preferred over esophagectomy or endoscopic surveillance |

EGD: Esophagogastroduodenoscopy; EMR: Endoscopic mucosal resection; RFA: Radiofrequency ablation; PDT: Photodynamic therapy; SSBE: Short segment Barrett's esophagus; LSBE: Long segment Barrett's esophagus; IM: Intestinal metaplasia. RCTs: Randomized control trials.

Non dysplastic Barrett esophagus (NDBE)

Data from two recent population studies and a recent meta-analysis found that the cancer risk in BE is around 0.1-0.3 % per year (8,9,21) much lower than the previously assumed risk of 0.5 %/year. A recent multicenter study showed that persistence of NDBE, based on multiple surveillance endoscopies, was associated with a gradually lower likelihood of progression to EAC (22).

Recent publications on mortality and cost effectiveness (23-28) bring into question about the rationale for ongoing surveillance in patients with NDBE, and support

the search for valid risk stratification tools to identify the minority of patients that are likely to benefit.

Low grade dysplasia (LGD)

There is controversy regarding management of LGD in Barrett esophagus, as the natural history of LGD is still poorly understood. Recent studies have calculated that the rate of progression of LGD to High Grade Dysplasia (HGD) or cancer to be 0.44 %-0.51 % per year, which is not substantially higher than NDBE (21,29).

In an interesting study the histopathology reports of all patients diagnosed with LGD between 2000 and 2006 in six non-university hospitals were reviewed by two expert pathologists. After pathology review, 85% of the patients were downstaged to NDBE. In patients with a consensus diagnosis of LGD the cumulative risk of progressing to HGD or cancer was 85.0 % in 109.1 months *vs.* 4.6 % in 107.4 months for the downstaged group ($p < 0.0001$) and the incidence rate of HGD or cancer was 13.4 % per patient per year, *vs.* 0.49 % in the downstaged group. According to this, LGD in BE might be overdiagnosed and yet underestimated in general practice and when this diagnosis is confirmed, patients are at much higher risk than previously reported of developing HGD/EAC (30).

For patients with LGD, a confirmation diagnosis by a second pathologist is encouraged. When confirmed, surveillance endoscopy should be performed every 6-12 months. Both the American Gastroenterological Association (AGA) and American Society for Gastrointestinal Endoscopy (ASGE) recommend considering Radiofrequency Ablation (RFA) as a therapeutic option for patients with confirmed LGD in their more recent guidelines (18,19).

High grade dysplasia (HGD)

The risk of progression to adenocarcinoma among patients with HGD is approximately 6.6 cases per 100 patient-years (31). The purpose of surveillance in patients with HGD is to detect foci of intramucosal carcinoma (IMC) or EAC. Because safe and effective methods of endoscopic treatment of HGD and early EAC have emerged, continued surveillance should be offered only to patients unfit or unwilling to undergo operative or ablative therapy (19). Endoscopic management of HGD is discussed separately on this review.

ENDOSCOPIC DIAGNOSIS

The key of early diagnosis of esophageal adenocarcinoma is the detection of neoplasia arising in Barrett's esophagus. Visible lesions in the setting of HGD are at high risk of harboring cancer until proven otherwise. The recognition of subtle lesions will enable the detection of disease. Traditionally, the detection of dysplasia is based upon random four-quadrant biopsies protocol obtained every 1-2 cm in the Barrett segment (Seattle protocol) (32) which increases the detection of early neoplastic lesions when compared with randomly obtained biopsy specimens (33,34).

But this protocol is consuming, costly and subject to a considerable sampling error, as only a tiny fraction of the "at risk" Barrett's mucosa is sampled. In general practice, adherence to this protocol is poor (30 %-79 %) which

significantly decreases the rate of detecting dysplasia (35-37).

In order to improve the accuracy of endoscopic diagnosis, several endoscopic imaging techniques have been developed and tested recently. Potentially advantages of these imaging technologies include increased rates for the detection of high-risk lesions, the ability to target biopsies and resections, decreased total number of biopsies and costs for surveillance, and the ability to guide therapy in real-time.

High resolution white light endoscopy (HRE)

Detailed white light endoscopy (WLE) is the cornerstone in the detection of neoplasia in BE. Modern video endoscopes can be coupled with high-resolution technology, magnification devices and high definition screens. HRE appears to have higher sensitivity for detecting early neoplastic lesions in BE compared with standard endoscopy (38-40).

A careful WLE examination with HRE examination of the entire area of metaplasia is nowadays the standard of care for endoscopic surveillance of BE (Fig. 1).

Chromoendoscopy and narrow band imaging (NBI)

Chromoendoscopy with methylene blue, an absorptive dye, has been extensively studied, but largely has fallen out of favor due to lack of demonstration of superiority over protocolized biopsies and potential oxidative damage to cells (41,42).

Acetic acid and non absorbed contrast stains like Indigo Carmine have shown to increase diagnostic yield for neoplasia when used in combination with magnification or HRE (43-48).

NBI is a virtual chromoendoscopy that uses a special filter to illuminate tissue with light at specific wavelengths, enhancing underlying vasculature and emphasizing contrast between vessels and their surrounding mucosa. Vascular patterns identified by magnified NBI have shown a good correlation with HGD and cancer on BE (49,50) (Fig. 1).

Although some reports have shown superiority of NBI over WLE (51), it has not improved interobserver agreement or yield of detecting early neoplasia in BE when compared with HRE (39,52-54).

A recent international, randomized crossover trial showed NBI imaging with targeted biopsies to have the same detection rate of intestinal metaplasia as HRE-WLE and protocolized random biopsies, but with a higher proportion of dysplasia detected (30 % *vs.* 21 %) and a lower number of biopsies per patient (3.6 *vs.* 7.6) (55).

NBI can be a helpful tool in guiding endoscopists to get targeted biopsies with no additional risks to the patient but it has yet to be validated in large, randomized

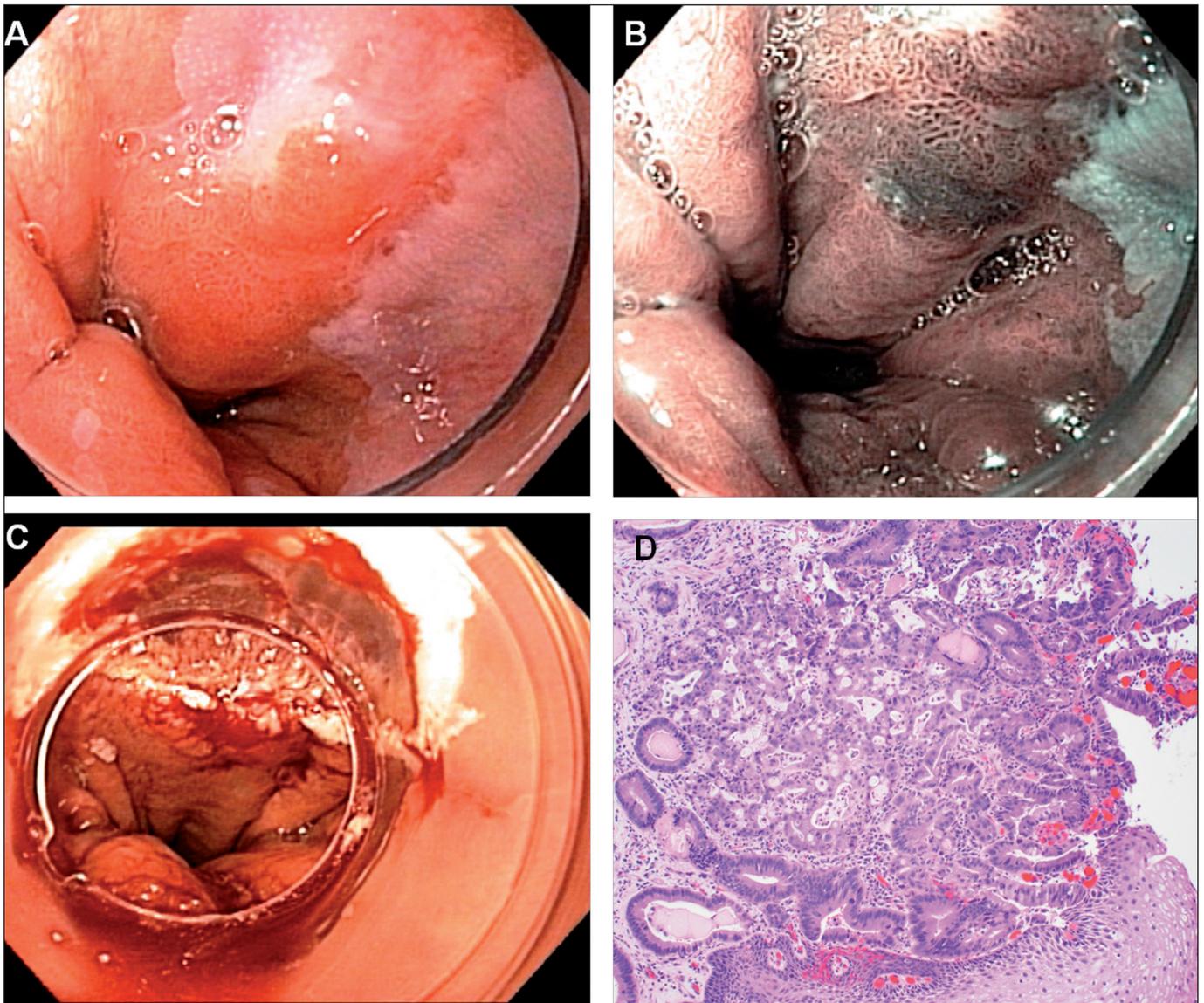


Fig. 1. A. Short segment Barrett esophagus (BE) with a slightly elevated lesion. B. Narrow band imaging (NBI) examination shows short segment BE with a 0-IIa lesion showing an irregular pattern. C. Cap assisted endoscopic mucosal resection (EMR). D. Histopathology shows intramucosal carcinoma (IMC) arising from an area of high grade dysplasia (top right). Normal squamous mucosa is identified in the lower right corner.

multicenter trials before detailed inspection with NBI can replace histological sampling

Confocal laser endomicroscopy (CLE)

CLE allows *in vivo* functional imaging of Barrett mucosa by using topically or systemically administered contrast agents. Several studies have shown high accuracy rates when compared with standard examinations, with a substantial interobserver agreement (56-62). An international multicenter trial demonstrated that CLE significantly improved sensitivity for the detection of

HGD or cancer compared with HD-WLE with random and targeted biopsies alone (34.2 % vs. 68.3 %) with no decrease in specificity (87.8 %) (63). Classification systems for Barrett's and dysplasia been described for endomicroscopy (56,64-66).

Disadvantages of CLE include additional procedural time and its elevated cost.

Autofluorescence

Autofluorescence imaging (AFI) is based on the excitation of endogenous molecules (fluorophores)

by short wavelengths, resulting on the emission of fluorescent light. Normal, metaplastic and dysplastic tissue have different autofluorescence spectra because of their different compositions of fluorophores (67).

While this technique has shown in studies a high sensitivity for the detection of HGD, specificity was poor with false positive rates up to 81 % (38,68,69).

A multicenter study demonstrated a significant reduction of false positives when integrating NBI and AFI to a HRE in a trimodal prototype (70).

Other techniques: Spectroscopy, optical coherence tomography (OCT)

Spectroscopy is based on the study of the absorption, emission, or scattering of an incident light when applied to certain tissues (71). *In vivo* and *ex vivo* studies have shown the potential of spectroscopic information compared with neoplastic with non neoplastic tissue in BE (72-74).

Optical coherence tomography can provide cross sectional images of tissue structure on the micron scale *in situ* and in real time by measuring back scattered or back reflected light (75). OCT has been studied for the diagnosis of NDBE and dysplasia in BE with promising results (76-78). OCT has also been described to reveal subepithelial glands in naive and in post-RFA Barrett's epithelium (79,80).

According to current guidelines, there is lack of evidence for recommending the use of advanced imaging techniques for routine endoscopic evaluation of BE. All the advances in these technologies are bound to the ability of the endoscopist to understand subtle abnormalities and recognize concerning lesions. In expert hands, they can become a valuable tool in the detection of neoplasia and represent an incremental gain, not yet a substitute, for standard procedures.

ENDOSCOPIC THERAPIES FOR BARRETT ESOPHAGUS

Endoscopic ablative therapies can be divided into tissue-acquiring and non-tissue-acquiring methods. Tissue-acquiring methods include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Non-tissue-acquiring methods include photodynamic therapy (PDT), radiofrequency ablation (RFA) and cryotherapy.

The rationale of these therapies resides in the risk of lymph node metastases when there is submucosal invasion.

High-grade dysplasia (HGD) is characterized by carcinoma *in situ* with malignant cells that do not invade the lamina propria. Intramucosal carcinoma (IMC), so called T1a by the AJCC (81), is defined as neoplastic changes confined to the lamina propria, with no invasion into the submucosal layer (82). In this stage, the risk of

lymph node involvement is lower than 5 % (83-86). On the other hand, submucosal involvement increases the risk of nodal metastases (20 %) and thus a surgical and/or systemic approach is required (83,84,87,88).

Traditionally, patients with Barrett Esophagus and HGD underwent immediate esophagectomy because of the estimated risk that 40 % of such patients harbored occult cancer (89,90). In a meta-analysis of 23 studies involving 441 patients undergoing surgery for HGD, the pooled rate of adenocarcinoma was 39.9 %. However, the majority of these patients had IMC, whereas the rate of submucosal invasive cancer was decreased to 12.7 % (91). Subsequent studies from the surgical and endoscopic resection literature have reported even lower rates, between 4 % and 6.7 % (92,93).

Based on a recent systematic review, the risk of lymph node metastasis is approximated to be 1-2 % among patients with IMC and 0 % among patients with HGD (86).

Endoscopic therapy has emerged in this context as a minimally invasive approach for treatment of HGD or IMC as an alternative to esophagectomy, which is associated with significant mortality and morbidity (94,95).

Tissue acquiring techniques

Visible lesions in patients with dysplastic Barrett esophagus are associated with higher risk of invasive carcinoma (85,96) and should be treated with a tissue-acquiring modality so these lesions can be appropriately resected and staged histologically (97).

The updated Paris classification categorizes superficial lesions in esophagus into: Protruding pedunculated (type 0-Ip), protruding sessile (0-Is), slightly elevated (0-IIa), completely flat (0-IIb), slightly depressed (0-IIc), excavated (0-III), or a mixed pattern (98). A Dutch retrospective study on 293 endoscopic resection specimens with correlation to endoscopic characteristics found that type 0-I and 0-IIc lesions significantly more often penetrated the submucosa ($p = 0.009$) (99).

Standard endoscopic procedures for obtaining biopsy samples have several limitations, including limited tissue sample size and depth, and artifacts that result from compression of the specimen (100). Appropriate diagnosis and staging of visible lesions is, therefore, achieved by use of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) techniques that yield large and intact tissue specimens and can provide a more reliable diagnosis than is possible with standard procedures (101).

Endoscopic mucosal resection (EMR)

Endoscopic mucosal resection (EMR) permits an accurate evaluation of the depth and lateral resection

margins and also provides information about the presence of submucosal involvement.

EMR specimens enhance the ability of pathologists to establish accurate diagnoses and stage tumors, compared with mucosal biopsies (Figs. 1 and 2). Furthermore, different studies have shown that staging by EMR can modify the previous biopsy diagnosis in up to 48 % of cases (93,102,103), which can dramatically change the clinical management of these patients, some of whom would be no longer suitable for endoscopic treatment due to histological evidence of submucosal invasion. Tumor staging using EMR pathology assessment is accurate when compared with surgical pathology, as shown in a study in 25 patients with HGD, IMC in Barrett's esophagus, where

there was perfect agreement in T staging after EMR and esophagectomy (104).

Several techniques have been described for endoscopic resection of superficial lesions: Free-hand, lift-and-cut, cap-assisted, or band-assisted (105). These techniques have been shown to be equivalent in terms of safety, efficacy and the depth of the tissue specimen obtained (100,106,107). The most commonly used are cap-assisted technique after submucosal lifting and the multiband ligation assisted technique (MBM), which is based on modification of the variceal ligation devices (108) (Figs. 1 and 2).

Focal EMR has shown to have a low profile of complications. Bleeding has been reported in 0.6-11 % of cases (most of them minor episodes managed intraprocedure)

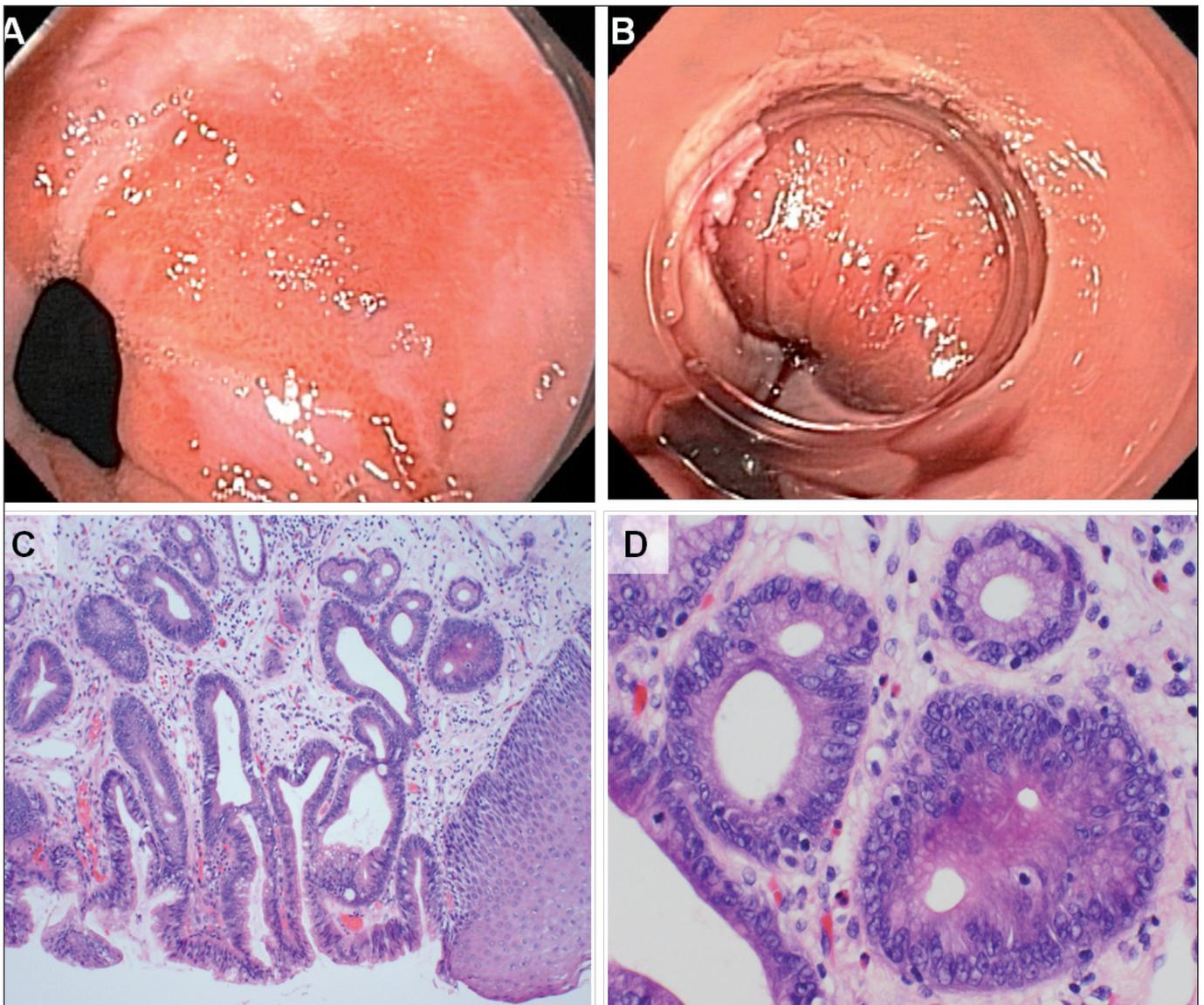


Fig. 2. A-B. Barrett esophagus cap assisted mucosectomy of an area of mucosal irregularity. C. Low power field demonstrates normal squamous mucosa (lower right corner) adjacent to an area of both low and high grade dysplasia (left). D. Examination at high power (40 X) reveals a few neoplastic glands displaying high grade morphology: High nuclei: Cytoplasm (N:C) ratio, loss of polarity and cribriform architecture (right).

and perforations in less of 2 % of cases. Stricture formation for focal EMR is < 5 % and increases significantly when longer segments of BE are resected and when used in combination with ablative techniques (109-113).

EMR can be performed focally for staging endoscopically visible lesions that are suspicious for malignancy, but focal resection has been associated with a high rate of synchronous, metachronous and recurrent lesions in the residual Barrett's mucosa, which can reach to more than 30 % after a follow-up period of 3 years (92,111,114-116). Therefore, once that all areas of localized neoplasia have been removed and appropriately staged, the remainder of the Barrett epithelium, in which there is a well established presence of molecular

abnormalities, should be eradicated (5,117). Eradication of the "at risk" BE may be done by tissue acquiring or non-tissue acquiring means.

Complete Barrett's eradication endoscopic mucosal resection (CBE-EMR)

CBE-EMR, also known as circumferential endoscopic mucosal resection or stepwise radical endoscopic resection, involves resecting the entire Barrett's segment after a targeted ablation of visible lesions in patients with HGD or IMC. This minimizes the risk of potential development of synchronous or metachronous lesions (93) (Fig. 3).

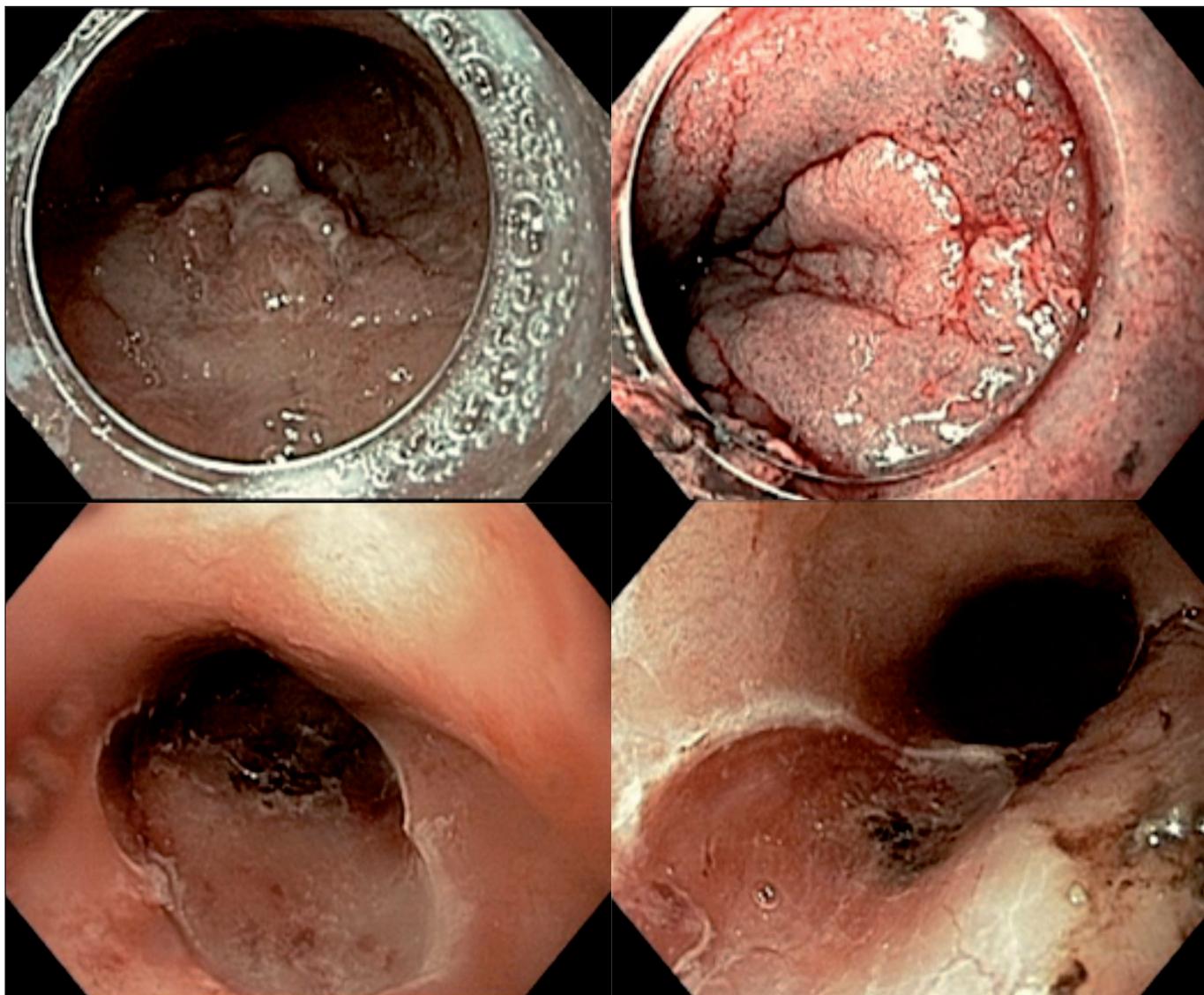


Fig. 3. Up. A 17 cm long Barrett's esophagus with a mixed 0-IIa+IIc lesion (high resolution endoscopy [HRE] on the left, and narrow band imaging [NBI] on the right). Down. Endoscopic view after first session of complete Barrett's esophagus endoscopic mucosal resection (CBE-EMR) with a total of 17 resections.

Complete response from CBE-EMR in studies has ranged from 76 to 100 % and complete eradication of dysplasia in 86 % to 100 % of cases (93, 118-123) (Table II).

The major limitation for CBE-EMR is the high incidence of symptomatic stenosis, with rates reaching 50 % in some reports. The length of BE resected segment and the number of EMR procedures performed were associated with higher rates of strictures (92,93,124). Noteworthy, strictures caused by CBE-EMR respond favorably to endoscopic dilation.

When compared to other approaches that combine endoscopic resection with non-tissue acquiring modalities such as RFA, van Vilsteren et al. found similar rates of complete response of neoplasia -100 % for CBE-EMR vs. 96 % for endoscopic resection plus RFA (ER/RFA)- and complete remission of intestinal metaplasia (92 % vs. 96 %). The stenosis rate was significantly higher in CBE-EMR (88 % vs. 14 %; $p < 0.001$), resulting in more therapeutic sessions (6 vs. 3; $p < 0.001$) due to dilations (123).

CBE-EMR has some potential advantages when compared with non tissue acquiring ablative therapies. It allows complete removal of the whole mucosa at risk for malignant progression, though providing tissue samples for optimal histopathology diagnosis. It may also reduce the risk of buried glands of Barrett's mucosa underneath the neosquamous epithelium mucosa compared with ablative therapies, and finally It may reduce the likelihood of persistent and/or induced genetic abnormalities that are associated with the progression of BE to adenocarcinoma, as there is recent concern that ablation may select for certain clonal populations (125). CBE-EMR may be optimal for patients with multifocal disease, diffuse nodularity, deep Barrett's glands or other high-risk markers that have yet to be elucidated.

Endoscopic submucosal dissection (ESD)

ESD has been widely used for treating gastrointestinal neoplasms in Japan. With this approach, *en-bloc*

resection can be done regardless of the size of the lesion. It is considered the treatment of choice for intramucosal gastric cancer and it has shown excellent results in esophageal and colon cancer, superior to conventional EMR in terms of curative resection and recurrence rates (126-128).

ESD has shown excellent curative rates in squamous cell cancer and, as BE incidence is much lower than in western countries, most of the reports on BE are limited to adenocarcinomas of the esophagogastric junction (129-132). The advantages of ESD over EMR might be not as clear for lesions smaller than 15mm (133,134).

Given the excellent long term outcomes of EMR, advantages of ESD compared to conventional EMR could be less relevant in treatment of early Barrett's neoplasia. ESD is a technically demanding procedure, time consuming and is associated with a higher rate of adverse events (128,132). A high level of endoscopic expertise and a minimum training requirement are recommended for its safe application (135-137).

The role of ESD in the therapeutic algorithm for Barrett's esophagus in Western countries is still not established, and so far experience in Europe and USA is limited (136,138).

Cost effectiveness

A recent decision analysis suggest that endoscopic therapy (diagnostic EMR combined with RFA to achieve complete ablation of BE) is more cost-effective than esophagectomy for IMC but also with superficial infiltration of the submucosa. According to this, endoscopic therapy may be best suited for patients with an a priori high surgical risk, such as the elderly or patients with comorbid illnesses, in whom perioperative mortality and postoperative morbidity outweigh the lower risk of recurrence after surgery compared with endoscopic therapy (139).

Table II. Overview of studies reporting endoscopic mucosal resection (EMR) for complete removal of BE

| Author | n | Follow up (months) | EMR sessions (median) | Complete regression of IM (%) | Complete regression of dysplasia (%) | Recurrence (%) | Progression (%) | Strictures (%) | Other major complications |
|--------------------------|-----|--------------------|-----------------------|-------------------------------|--------------------------------------|----------------|-----------------|----------------|---------------------------|
| Peters 2006 (118) | 32 | 11 | 3 | 89 | 100 | 0 | 0 | 26 | 5 |
| Lopes 2007 (119) | 41 | 32 | 1.5 | 75.6 | 100 | 36 | 0 | 5 | 9.5 |
| Larghi 2007 (120) | 24 | 28 | 3 | 87 | 100 | 4 | 0 | 12.5 | 0 |
| Chennat 2009 (93) | 49 | 17 | 2.1 | 97 | 100 | 0 | 0 | 37 | 0 |
| Pouw 2010 (121) | 169 | 32 | 2 | 97.6 | 85.2 | 1.8 | 0.6 | 49.7 | 1.2 |
| Gerke 2011 (122) | 46 | 25 | 2.4 | 78 | 85.4 | 4 | 0 | 43.9 | 4.9 |
| van Vilsteren 2011 (123) | 25 | 24 | 2 | 92 | 100 | 4 | 0 | 88 | 24 |

The role of EUS in Barrett esophagus

Endoscopic ultrasonography (EUS) is considered the most accurate imaging modality for the T staging of gastrointestinal cancers, but the role of EUS has limited value in the pre-therapeutic algorithm of patients with early Barrett's neoplasia (140).

EUS is not optimal for differentiation between HGD, a T1a tumor (IMC) and a T1b (SMC) tumor, and EMR is better suited for depth staging at this range (141,142). High frequency probes have also shown to have a limited accuracy for identifying invasive cancer in HGD/IMC patients (143). These limitations of EUS for an accurate diagnosis of early Barrett's cancer seem to be higher in flat and depressed lesions (141).

However, given the risk of lymph node metastasis in patients with visible lesions or confirmed superficial submucosal invasion, EUS with fine needle aspiration (FNA) might identify patients not eligible for endoscopic therapy (142).

Non tissue acquiring techniques

As aforementioned the rationale for ablative methods for BE is the well established presence of molecular abnormalities in the remaining Barrett's epithelium after focal resection of neoplastic lesions and the risk for developing metachronous or synchronous lesions, making the eradication of the entire Barrett's segment essential. When no visible lesion is macroscopically detected after a carefully examination with HRE, ablative methods may be the first of choice therapy for HGD.

Radiofrequency ablation (RFA)

This technique uses an electrode to deliver high frequency energy to the superficial lining of the esophagus over a very short period of time. RFA of BE tissue can be achieved in either a circumferential (BARRX-Halo 360°) or localized fashion for focal areas of residual Barrett's epithelium (BARXX Halo 90°) (144) (Fig. 4).

The available data from prospective trials are summarized in Table III (123,145-156).

Efficacy

In a multicenter randomized, sham-controlled trial on 127 patients with dysplastic BE complete eradication of dysplasia was achieved in 91 % and 81 % of patients with LGD and HGD in the RFA group, respectively, compared with 3 % (LGD) and 19 % (HGD) in the control group ($p < 0.001$) after one year (150). After 3 years, dysplasia remained eradicated in > 85 % of patients and IM in > 75 %, without maintenance RFA (151).

In the *AIM II trial*, which included patients with NDBE, complete eradication of IM was achieved in 98.4 % and 92 % at 2.5 and 5 year follow up, respectively (152).

In a recent meta-analysis of 20 studies comprising more than 4,000 patients, complete eradication of dysplasia was achieved in 91 % and eradication of all IM in 78 % of patients with a rate of esophageal strictures of 5 % of patients (157).

EMR appears to be safe to perform prior or posterior to RFA. Stricture rates among patients who receive only RFA are comparable to those of patients who had prior subsequent EMR for residual lesions (149,158,159).

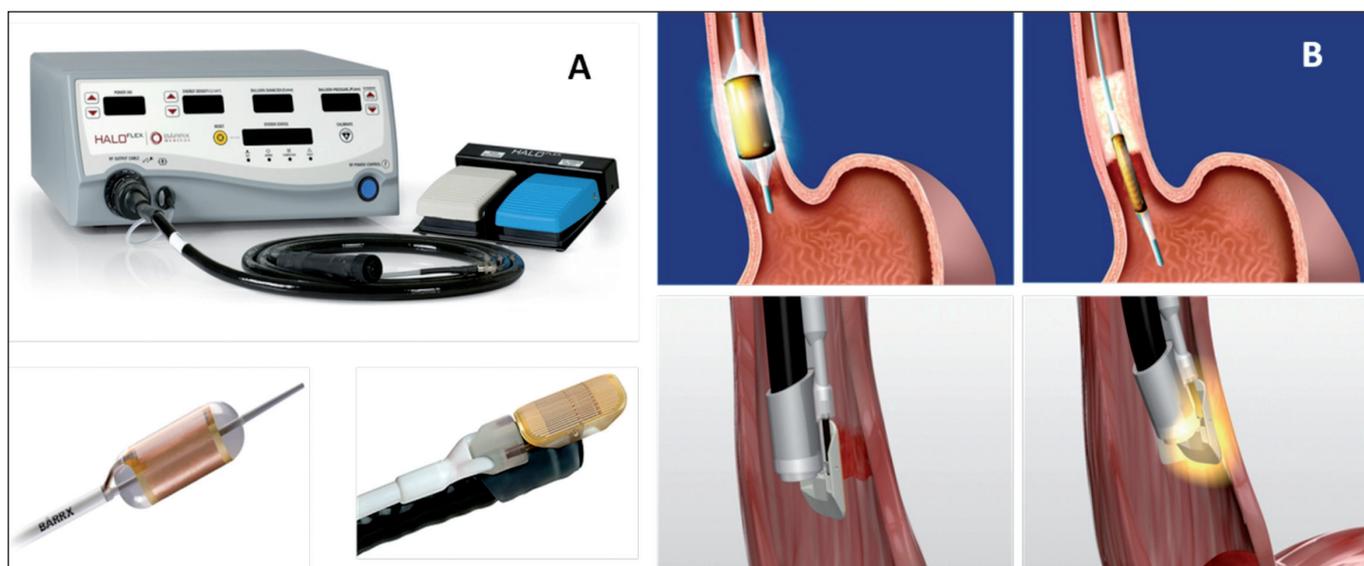


Fig. 4. HALO FLEX™ generator for radiofrequency ablation. HALO 360 and HALO 90 ablation catheters. B. Diagram showing circumferential RFA (up) and focal RFA (down) (Under permission of Izasa, sales representative of BARXX for Spain).

Table III. Overview of main studies reporting radiofrequency ablation (RFA) for Barrett's esophagus

| | <i>n</i> | <i>Design</i> | <i>Setting</i> | <i>Histology</i> | <i>RFA sessions, mean/median</i> | <i>Follow up (months)</i> | <i>CE-IM (%)</i> | <i>CE-dysplasia (%)</i> | <i>IM recurrence (%)</i> |
|--------------------------|----------|---------------|----------------|---------------------------------|----------------------------------|---------------------------|------------------|-------------------------|--------------------------|
| Fleischer 2008 (145) | 70 | Prospective | Multicenter | NDBE | 3.4 | 30 | 98 | - | |
| Ganz 2008 (146) | 142 | Prospective | Multicenter | HGD | 1 | 12 | 54 | 80 | |
| Sharma 2009 (147) | 63 | Prospective | Single center | 62 % LGD 38 % HGD | 2 | 24 | 79 | 89 | |
| Lyday 2010 (148) | 429 | Retrospective | Multicenter | BE | 2.1 | 20 | 77 | 100 | |
| Pouw 2010 (149) | 24 | Prospective | Multicenter | HGD IMC | 2 | 22 | 96 | 100 | 17 |
| Shaheen 2011 (151) | 106 | Prospective | Multicenter | LGD HGD | - | 24 | 93 | 95 | 13 |
| van Vilsteren 2011 (123) | 22 | RCT | Multicenter | HGD IMC | 3 | 22 | 96 | 96 | |
| Fleischer 2010 (152) | 50 | Prospective | Multicenter | NDBE | - | 60 | 92 | | 9 |
| Haidry 2013 (153) | 335 | Prospective | Multicenter | LGD 4 % HGD 72 % IMC 24 % | 2.5 | 12 | 62 | 81 | |
| Gupta 2013 (154) | 592 | Prospective | Multicenter | BE | - | 24 | 56 | | 33 |
| Bulsiewicz 2013 (155) | 210 | Retrospective | Single center | LGD, HGD, IMC | | > 12 | 80 | 87 | |
| Phoa 2013 (156) | 54 | Prospective | Multicenter | HGD, IMC | - | 60 | 94 | | 10 |

CE-IM: Complete eradication of intestinal metaplasia; NDBE: Non dysplastic Barrett esophagus; LGD: Low grade dysplasia; HGD: High grade dysplasia; BE: Non dysplastic and dysplastic Barrett esophagus; RCT: Randomized controlled trial; IMC: Intramucosal carcinoma.

A poor initial response to RFA occurs more frequently in patients who regenerate their endoscopic resection scar with Barrett's epithelium, those with ongoing reflux esophagitis, neoplasia in BE for a longer time, or a narrow esophagus (156). Persistent total reflux, hiatal hernia and its size and the length of BE have been associated with the need for more RFA sessions (160,161).

Durability

Although RFA safely and effectively eradicates dysplasia and IM, the durability of the neosquamous epithelium that regenerates is not well defined.

Recently, three multicenter studies, from 3 different populations were published providing data of long term outcomes of patients treated with RFA (153,154,156). In the Dutch population study, among 54 patients with HGD or IMC who underwent RFA, 90 % remain in remission at 5-year follow-up, with all recurrences managed endoscopically (156). In the UK study, among 335 patients with BE and neoplasia who underwent RFA, dysplasia was cleared from 81 % and BE from 62 % of patients 12 months after treatment (153). In the multicenter US study, from 592 patients with BE (71% HGD or EAC)

treated by RFA, 56% were in complete remission after 24 months. However, 33 % of these patients had disease recurrence within the next 2 years. Most recurrences were nondysplastic and endoscopically manageable (154). Noteworthy, IM of the cardia was considered recurrence in the US study. Technique of ablation and acid suppression were also different between the three studies.

These data suggest that a large proportion of patients will have durable eradication of their dysplasia but there is a persistent risk of recurrent metaplasia and dysplasia. This emphasizes the importance of careful endoscopic surveillance after successful ablation with RFA.

Cost effectiveness

Recent analysis have shown that RFA is unlikely to be cost effective for patients with BE without dysplasia (162).

RFA might be cost effective for confirmed and stable LGD, but it depends on the long-term effectiveness of ablation and whether surveillance endoscopy can be discontinued after successful ablation (163).

There is high agreement that endoscopic therapy is the preferred strategy for managing patients with BE with HGD.

In the aforementioned decision analysis study initial RFA in HGD is more effective and less costly than endoscopic surveillance or surgery (162). Although endoscopic surveillance might be less expensive than endoscopic ablation, it is associated with shorter survival (164).

RFA for non dysplastic Barrett esophagus and low grade dysplasia BE

Although the low rates of recurrence of intestinal metaplasia (IM) after RFA have been published on patients with NDBE (152) these patients already have a low baseline risk for developing neoplasia, even lower than previously thought, societies like the AGA recommend against endoscopic eradication therapy for the general population of NDBE patients.

Whether RFA should be performed in the setting of low-grade dysplasia might be one of the most controversial debates in this field. As aforementioned, the risk of progression is poorly understood, and this risk could be much higher when diagnosis is confirmed by a second pathologist (30). Recurrence rates of RFA and significance of buried glands are yet to be defined, and currently endoscopic surveillance cannot be discontinued after eradication therapies.

A better understanding of ablative therapies, improvement on endoscopic detection of dysplasia and the urgency of identifying patients with a higher risk of progression to cancer probably by using biological markers are awaited to clarify current recommendations.

Photodynamic therapy (PDT)

Photodynamic therapy is based on the formation of oxygen radicals and subsequent cell death when light of an appropriate wavelength is delivered to a tissue previously exposed to a photosensitizing agent. The most widely used agent for esophageal PDT is porfimer sodium (Ps), 5-aminolevulinic acid (5-ALA) which can be administered orally, has been used in Europe. Light is delivered to the tissue via an endoscopic approach.

A multicenter randomized trial by Overholt *et al.* (165) showed at 5 years follow up that PDT plus omeprazole was significantly more effective than omeprazole alone in eliminating HGD (77 % vs. 39 %). Progression to cancer was also significantly lower in the PDT group (15 % vs. 29 %). There is less evidence with other photosensitizers such as ALA; a study by Pech *et al.* showed a complete response in 97 % of HGD patients and in 100 % of IMC patients treated with ALA-PDT after a median follow-up period of 37 months (166).

PDT was comparable to surgery in terms of surgical mortality and long-term survival in a retrospective study after a mean follow-up period of approximately 5

years (104) PDT also showed to be cost effective when compared with esophagectomy in patients with HGD (167).

The major drawback of PDT is the relatively high rate of reported adverse events, mainly photosensitivity and symptomatic strictures, which have been reported in up to 36 % of patients (97). Another concern about PDT is development of sub-squamous BE glands that could harbor neoplastic potential, which was found to be 14 % in a systematic review (168). In one study that examined histological and pathological specimens after PDT, buried glands were found in 51 % of patients; 27 % of these harbored dysplasia or carcinoma (169).

Given these limitations, PDT has fallen out of favour in recent years, and referral centers have adopted EMR and RFA as the preferred endoscopic treatment modalities for BE.

Cryotherapy

Cryotherapy is based on spraying the targeted tissues with cycles of either liquid nitrogen or rapidly expanding carbon dioxide gas, causing rapid freezing and slow thawing that destroy tissues through immediate and delayed effects (170).

Short term studies have shown a safety and efficacy profile similar to other ablative techniques (171-173). In a single center study with 32 patients, complete eradication (CE) of HGD was 100 %, and CE of IM was 84 % at 2-year follow-up. At last follow-up (range 24-57 months), CE-HGD was 97 % and CE-IM was 81 %. No serious adverse events occurred. Stricture was seen in 3 patients (9 %) (174). Multi-center randomized trials are required to confirm these results and determine long-term response. The optimal treatment protocol and direct comparative data with RFA will be needed before the role of cryotherapy is defined among ablative techniques for BE.

Other ablative therapies

Argon plasma coagulation (APC) has been studied for ablation principally on NDBE (175-177). Given the high relapse rates observed, the concern regarding buried glands and a low benefit risk in this patients, APC is no longer used as ablation treatment, and is reserved as a "touch up" therapy to treat areas of IM left behind by other ablative modalities. Other techniques like multipolar electrocoagulation and laser therapies have also been replaced by other ablation modalities.

The concern of buried glands

A concern with regard to endoscopic ablation is the development of buried glands under the neosquamous

epithelium. When the ablation procedure does not destroy all of the metaplastic epithelium, then the partially ablated mucosa may heal with an overlying layer of neosquamous epithelium that buries metaplastic glands in the lamina propria, becoming undetectable to endoscopic surveillance.

The significance of buried glands is unknown, and whether they might be present or not before ablation, but the development of adenocarcinoma under squamous epithelium has been reported (140,178). A recent systematic review evaluated the evidence of buried metaplasia before and after ablation therapies. The baseline prevalences ranged from 0 % to 28 %, in patients after PDT 14.2 %; and after RFA in only 0.9 % (168).

But the true incidence and risk of progression to neoplasia might be underestimated. Besides the inherent sampling error from biopsy protocols, it is unclear whether the size and depth of biopsy specimens may be insufficient to identify buried glands (179,180).

A recent study using tridimensional optical coherence tomography (3D-OCT) found buried glands in 72 % of patients (13/18) before and in 63 % of patients (10/16) after complete eradication of intestinal metaplasia with RFA therapy (79).

Further studies are needed to resolve this issue.

Combined endoscopic techniques

The balance of tissue acquisition and adverse effect profile for patients with dysplasia may be best achieved with a hybrid approach where EMR is used for all visible lesions and the remainder of the epithelium is treated with serial RFA which carries a more favorable complication profile (123,149,181,182).

ESOPHAGECTOMY

As discussed above, endoscopic treatment is an appropriate and cost-effective approach for the treatment of many patients with HGD and IMC, but a surgical approach is still indicated in a subgroup of these patients.

Strong indications for esophagectomy include lymph node metastasis and failure of endoscopic therapy. Submucosal invasion carries a higher nodal metastasis risk and can still be considered a strong indication for esophagectomy. Although some investigators have reported that the upper third of the submucosa (sm1) has a very low risk of lymph node metastasis (110,166,183,184), further clinical trials are required before a general recommendation for endoscopic treatment in "low-risk" submucosal cancer can be given (185).

Selected patients with HGD or IMC and high risk features should be also considered for surgical therapy. These high risk features include multifocal HGD,

protruding or depressed lesions, poorly differentiated tumors, and invasion into lymphatic channels, blood vessels, or neural structures (186).

The main concern for esophagectomy is that it is associated with significant mortality and morbidity, with estimates of mortality ranging from 0 %-2 % at high-volume centers to 8 %-10 % at low volume centers (187). Increasing surgeon experience may similarly favorably impact operative mortality (188-191).

CONCLUSIONS

The advent of endoscopic ablative therapies has rapidly changed the management of Barrett esophagus. High grade dysplasia and intramucosal carcinoma are amenable for endoscopic treatment given the low risk of lymphatic spread in these stages, which increases substantially when submucosal invasion is present. Development in endoscopic diagnosis are meant to improve significantly the detection of dysplasia in the setting of BE, as a complement or potentially instead of random biopsies. Endoscopically visible lesions in the setting of dysplasia should be targeted with focal endoscopic mucosal resection for accurate histopathologic diagnosis and treatment. The remainder of the Barrett's epithelium should also be eradicated to address all synchronous and metachronous lesions, for which serial RFA currently carries a more favorable complication profile.

Further investigations with endoscopic ablative therapies are needed to characterize rates of clinical remission of neoplasia and Barrett esophagus, long-term survival, risk of progression to cancer, and procedure-related complications of the different modalities.

The significance of buried glands and their potential to harbor dysplasia or even cancer under squamous epithelium has yet to be elucidated. The role of ablative therapies for the treatment of low grade dysplasia and nondysplastic are yet to be defined. As long as the real risk of progression of low grade dysplasia remains unknown and the aforementioned questions regarding ablative therapies remain unanswered, endoscopic surveillance is recommended in these settings.

Although surgery is still an indication in selected cases, esophagus-sparing approaches will evidently become the mainstay of therapy for patients with high-grade dysplasia, intramucosal carcinoma and perhaps in case of superficial submucosal invasion.

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