*REVIEW*

# Endoscopic resection techniques and ablative therapies for Barrett's neoplasia

Jacobo Ortiz-Fernández-Sordo, Adolfo Parra-Blanco, Alejandro García-Varona, María Rodríguez-Peláez, Erika Madrigal-Hoyos, Irving Waxman, Luis Rodrigo

Jacobo Ortiz-Fernández-Sordo, Adolfo Parra-Blanco, Endoscopy Unit, Department of Gastroenterology, Central University Hospital of Asturias, Celestino Villamil S/N, Oviedo 33006, Asturias, Spain

Jacobo Ortiz-Fernández-Sordo, Erika Madrigal-Hoyos, Irving Waxman, Center for Endoscopic Research and Therapeutics, Department of Medicine, Section of Gastroenterology, University of Chicago Medical Center, 5758 S, Maryland Avenue, Chicago, IL 60637, United States

Alejandro García-Varona, Department of Pathology, Central University Hospital of Asturias, Celestino Villamil S/N, Oviedo 33006, Asturias, Spain

María Rodríguez-Peláez, Luis Rodrigo, Department of Gastroenterology, Central University Hospital of Asturias, Celestino Villamil S/N, Oviedo 33006, Asturias, Spain

Author contributions: Ortiz-Fernández-Sordo J, Parra-Blanco A, Waxman I and Rodrigo L were involved in substantial contributions to manuscript concept and design; Ortiz-Fernández-Sordo J performed data collection, analysis and interpretation; all authors participated in drafting the article, revising and approval of content for final version.

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Correspondence to: Luis Rodrigo, Professor, Department of Gastroenterology, Central University Hospital of Asturias, Celestino Villamil S/N, Oviedo 33006, Asturias, Spain. lrodrigosaez@gmail.com

Telephone: +33-985-108058  Fax: +33-985-108115
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## Abstract

Esophageal adenocarcinoma is the most rapidly increasing cancer in western countries. High-grade dysplasia (HGD) arising from Barrett's esophagus (BE) is the most important risk factor for its development, and when it is present the reported incidence is up to 10% per patient-year. Adenocarcinoma in the setting of BE develops through a well known histological sequence, from non-dysplastic Barrett's to low grade dysplasia and then HGD and cancer. Endoscopic surveillance programs have been established to detect the presence of neoplasia at a potentially curative stage. Newly developed endoscopic treatments have dramatically changed the therapeutic approach of BE. When neoplasia is confined to the mucosal layer the risk for developing lymph node metastasis is negligible and can be successfully eradicated by an endoscopic approach, offering a curative intention treatment with minimal invasiveness. Endoscopic therapies include resection techniques, also known as tissue-acquiring modalities, and ablation therapies or non-tissue acquiring modalities. The aim of endoscopic treatment is to eradicate the whole Barrett's segment, since the risk of developing synchronous and metachronous lesions due to the persistence of molecular aberrations in the residual epithelium is well established.

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## INTRODUCTION

Esophageal adenocarcinoma (EAC) is the most rapidly increasing cancer in western countries. Its incidence has increased up to six-fold in the past decade in the United States[1] and it is estimated that about 10 000 new cases were diagnosed last year[2]. Barrett's esophagus (BE) increases the risk for developing EAC up to 30-40 times and the presence of high-grade dysplasia (HGD) is the most important risk factor[2,3].

The global incidence of EAC arising from BE is 0.5% per year[2,3] and increases to 10% per patient-year when HGD is present[4]. A recently published meta-analysis reports an estimated incidence of 6.3 cases/1000 patient-years of follow-up and a mortality by cancer of 3/1000 patient-years of follow-up[5]. Adenocarcinoma in the setting of BE develops through a well known histological sequence, from non-dysplastic Barrett's to low grade dysplasia (LGD) and then HGD and cancer[6]. Despite the lack of randomized controlled trials and cost-effective analysis, endoscopic surveillance programs, with targeted biopsies from any visible lesion and random four-quadrant biopsies according to the Seattle protocol[7], have been shown to detect the presence of neoplasia at a potentially curative stage. The widely accepted approach in high-risk selected patients; is further endoscopic surveillance at follow-up intervals which are determined according to the presence and grade of dysplasia[8,9].

A careful examination with high-resolution endoscopy (HRE) is the first step for an appropriate selection of patients who are potential candidates for endoscopic therapy. Newly developed imaging techniques such as narrow band imaging, autofluorescence imaging or confocal endomicroscopy can be helpful for detection of early neoplastic lesions. Surgery has been advocated as the appropriate treatment for HGD due to the high reported rates of occult adenocarcinoma in esophagectomy specimens, up to 40% in some series[10,11]. The current consensus definition of invasive cancer includes lesions involving the submucosal layer (T1sm/T1b). A recent review demonstrated that the true prevalence of cancer invading the submucosal layer in patients with prior diagnosis of HGD was 12.7%[12] although subsequent studies have shown rates of 7%, and even lower (3%) in the absence of visible lesions[13]. These large differences are explained by the use in several studies of an inaccurate definition of invasive cancer that included T1a lesions, and by the low proportion (30%) of patients included in these studies who had been enrolled in an endoscopic surveillance program with an appropriate biopsy protocol[12].

It is also important to keep in mind that esophagectomy is associated with significant morbidity and mortality rates, even in high volume centers[14,15] and has been performed in patients with HGD or intramucosal carcinoma (IMC). These patients have a risk of lymph node (LN) metastasis lower than 1%[16-19] and could be successfully treated by endoscopic therapies. Newly developed endoscopic treatments have dramatically changed the thera-

peutic approach of BE. The rationale for endoscopic therapy is that lesions confined to the mucosal layer have negligible risk for developing LN metastasis and can be successfully eradicated by an endoscopic approach, offering a curative intention treatment with minimal invasiveness[20]. Risk of LN metastasis[16,21] and tumor differentiation grade[22,23] (G1 well differentiated, G2 moderately differentiated and G3 poorly differentiated) in early Barrett's adenocarcinoma are clearly related to the depth of tumor infiltration in the esophageal wall. The incidence of LN metastasis is between 0% and 3% for lesions limited to the mucosa (T1m), rising to 30% when the lesion involves the submucosal layer[17-19].

A recently published study, that includes a review of 805 endoscopic resections from 472 patients, showed that the depth of invasion correlates with differentiation grade (G3 0.9% in T1m1 *vs* 41.4% in T1sm3), lymphatic vessel involvement (0.6% in T1m1 *vs* 44.8% in T1sm3) and venous involvement (0% in T1m1 *vs* 13.8% in T1sm3), all well established risk factors for LN metastasis[22]. According to these findings, the endoscopic approach is clearly indicated for IMC and might be extended to lesions with limited invasion into the submucosa (< 200 μm, T1sm1) because of the low risk for LN metastasis reported in some studies[24-27]. Further investigations should be conducted to establish if patients with type I-II lesions, superficial submucosal invasion (T1sm1) and low risk of LN involvement, such as good differentiation grade (G1/G2) and no lymphovascular invasion, could be considered candidates for endoscopic therapy in high volume centers[27]. Figure 1 displays the esophageal layers and shows the subclassification of T1 lesions according to the depth of invasion. The aim of endoscopic therapy is to eradicate the whole Barrett's segment, since the risk of developing synchronous and metachronous lesions, due to the persistence of molecular aberrations in the residual epithelium, is well established[28]. Endoscopic eradication can be achieved through resection techniques (tissue-acquiring modalities), or through ablation therapies (non-tissue acquiring modalities)[29,30].

## ENDOSCOPIC RESECTION TECHNIQUES

Endoscopic resection is the basis of endoscopic therapy for BE and has been advocated not only as a therapeutic approach but also as a staging tool in Barrett's neoplasia. The major advantage of the tissue-acquiring modalities is their ability to provide resection samples of appropriate size and depth for an accurate histopathological diagnosis. *En-bloc* resection techniques allow lateral resection margins to be assessed for the need of further treatments[29]. In 1984 Tada *et al*[31] introduced the use of "strip-off biopsy" for treatment of early gastric cancer. Endoscopic mucosal resection (EMR) of early esophageal neoplasia was first described in 1991 in two different manuscripts by Makuuchi *et al*[32] and Inoue *et al*[33], who published their results in four patients, three with squamous cell cancer and one
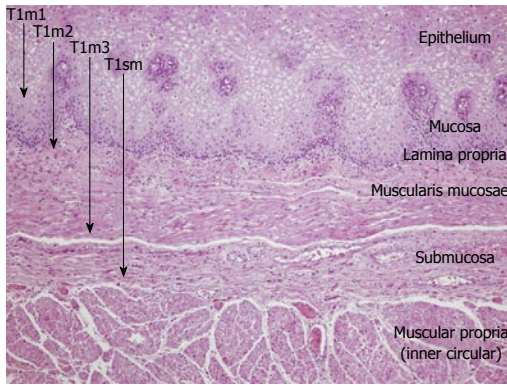
**Figure 1 Esophageal Layers and T1 staging (HE × 100).** T1m1: Lesion limited to the epithelial layer; T1m2: Invasion of *lamina propria*; T1m3: Invasion of *muscularis mucosae*; T1sm1-3: Invasion of submucosa (T1sm1 invasion into the superficial one third, < 200 μm).

**Table 1 Focal endoscopic mucosal resection in early Barrett's neoplasia**

| Author | n | Complete regression of dysplasia/esopha- geal cancer (%) | Histology | Follow- up (mo) |
|---|---|---|---|---|
| Ell *et al*[43], 2000 | 64 | 86 | HGD/EC | 12 ± 8 |
| May *et al*[44], 2002 | 28 | 79 (100[1]) | HGD/EC | 34 ± 10 |
| May *et al*[45], 2002 | 70 | 70 (98[1]) | HGD/EC | 34 ± 10 |
| Behrens *et al*[48], 2005 | 14 | 93 (100[1]) | HGD | 38 |
| Peters *et al*[49], 2005 | 33 | 79 (100[1]) | Barrett's esophagus | 19 |
| Conio *et al*[50], 2005 | 39 | 97.5 | HGD/EC | 35 |
| Ell *et al*[53], 2007 | 100 | 88 (99[1]) | Adenoca. | 36 |
| Pech *et al*[41], 2008 | 231 | 95.7 | EC | 61 |
| Moss *et al*[54], 2010 | 35 | 77 (85[1]) | HGD/EC | 31 |

[1]Results after second treatment. EC: Esophageal cancer; HGD: High grade dysplasia.

**Table 2 Changes in final histopathological diagnosis after endoscopic mucosal resection**

| Author | n | Discrepant diagnosis (%) | Upstaging (%) | Downstaging (%) |
|---|---|---|---|---|
| Hull *et al*[59], 2006[1] | 41 | 39 | 34 | 5 |
| Chennat *et al*[60], 2009 | 49 | 44.8 | 14 | 31 |
| Moss *et al*[54], 2010 | 75 | 48 | 20 | 28 |

[1]Includes esophageal and gastric neoplasms.

with adenocarcinoma. In all cases complete resection was achieved and no recurrence neither metachronous lesions were observed during follow-up[33].

### Endoscopic mucosal resection

Several EMR techniques have been developed for excision of mucosal based lesions; the most commonly used are the cap-assisted technique (ER-Cap) and the multi-band ligation assisted technique (MBM). No significant differences in the safety and efficacy profiles have been reported between these two approaches. The only observed difference was the maximum diameter of the resected specimens, where the ER-cap method was favoured[34-36]. In both modalities, after marking 2 mm away from the lesion margins and lifting with saline solution injection, the targeted area is suctioned into the cap and grasped by the snare or by releasing the rubber band to create a pseudopolyp. The lesion is then cut using a snare with blended-current electrocautery. If the MBM technique is performed, the procedure can be carried out safely with no prior submucosal injection and lifting[37-40].

There is extensive experience of performing focal EMR for treatment of macroscopically visible lesions arising in BE. The available data show complete regression of neoplasia in 97%-100% of cases and 5-year survival rates of 98%-100%[41-54] (Table 1). EMR is the only endoscopic technique that has proved increasing the 5-year survival rate in Barrett's patients in uncontrolled trials[41]. In addition, endoscopic resection has been demonstrated to be a highly safe technique. Alvarez-Herrero *et al*[38] reporting the outcome of more than 1000 EMR procedures performed in 243 patients, observed an acute bleeding rate was 2.9% and delayed bleeding rate of 2.1%, with no perforations and successfully management of all adverse events by an endoscopic approach.

The radical differences between treatments for T1m and T1sm tumors make a definitive histopathological staging essential, in order to identify the patients amenable for curative endoscopic therapy. There are several concerns about the ability of conventional biopsy specimens to provide an accurate histological diagnosis. The sampling error associated with the random biopsy protocol is well known and there are also important doubts about the adequacy of the depth of specimen obtained with conventional biopsy forceps. Published studies have reported a limited reproducibility, particularly for dysplasia, as well as low inter-observer agreement rates. Rates are between 61% and 75% when three categories are evaluated (no dysplasia, indefinite for dysplasia/LGD and HGD/carcinoma), but go down to $\kappa$ value of 0.49 when HGD is diagnosed separately from carcinoma[55].

A recent study performed in two tertiary referral centers, has demonstrated a higher inter-observer agreement for diagnosis of dysplasia from the analysis of EMR specimens than from conventional biopsies ($\kappa$ 0.33 *vs* 0.22, $P < 0.001$ for LGD; 0.43 *vs* 0.35, $P = 0.018$ for HGD). Submucosa was present in up to 88% of EMR specimens but only in 1% of biopsy samples and the presence of muscularis mucosae was observed only in 58% of biopsy specimens[56]. EMR samples permit an accurate evaluation of depth and lateral resection margins and also provide information about the presence of submucosal involvement. The histological examination of EMR pieces can also asses the degree of lymph and blood vessel invasion, important risk factors for the presence of LN metastasis[57-59]. Different studies have shown that final staging by EMR modifies the previous diagnosis in up to 48% of cases[54,59,60] and dramatically changes the clinical management of these patients (Table 2). Similar discrepancy rates have been reported for gastrointestinal neoplasia from other locations[61]. Finally, EMR staging has shown to be consistent

**Table 3 Complete Barrett's eradication-endoscopic mucosal resection results**

| Author | n | Complete regression of intestinal metaplasia (%) | Complete regression of dysplasia/esophageal cancer (%) | Sessions (%) | Recurrence (%) | Progression (%) | Follow-up (mo) |
|---|---|---|---|---|---|---|---|
| Seewald et al[65], 2003 | 12 | 100 | 100 | 2.5 | 0 | 0 | 9 |
| Giovannini et al[66], 2004 | 21 | 75 | 86 | 2 | 14 | 0 | 18 |
| Peters et al[67], 2006 | 39 | 89 | 95 | 3 | 0 | 0 | 11 |
| Larghi et al[68], 2007 | 24 | 87 | 100 | 1.8 | 4 | 0 | 28 |
| Lopes et al[69], 2007 | 41 | 76 | 90 | 1.5 | 12 | 0 | 31.6 |
| Chennat et al[60], 2009 | 49 | 97 | 100 | 2.1 | 0 | 0 | 17 |
| Moss et al[54], 2010 | 35 | 97 | 97 | 2 | 0 | 0 | 31 |
| Pouw et al[63], 2010 | 169 | 97.6 | 85.2 | 2 | 1.8 | 0.6 | 27 |

**Table 4 Complete Barrett's eradication-endoscopic mucosal resection complications**

| Author | n | Perforation (%) | Bleeding[1] (%) | Stricture (%) |
|---|---|---|---|---|
| Seewald et al[65], 2003 | 12 | 0 | 0 | 16.6 |
| Giovannini et al[66], 2004 | 21 | 0 | 0 | 0 |
| Peters et al[67], 2006 | 39 | 2.56 | 2.56 | 26 |
| Larghi et al[68], 2007 | 24 | 0 | 0 | 12.5 |
| Lopes et al[69], 2007 | 41 | 9.5 | 0 | 4.76 |
| Chennat et al[60], 2009 | 49 | 0 | 0 | 36.7 |
| Moss et al[54], 2010 | 35 | 0 | 0 | 14.3 |
| Pouw et al[63], 2010 | 169 | 2.4 | 2.4 | 50 |

[1]Only bleeding cases in which endoscopic treatment was needed.

with surgical pathology staging. The presence of free of disease margins in EMR samples, directly correlates with the absence of residual tumor at esophagectomy[62].

The major drawback of using focal EMR as the only treatment for Barrett's neoplasia is the possible development of synchronous, metachronous and recurrent lesions, arising in the residual Barrett's epithelium. After a mean follow-up period of 3 years, the reported incidence rates range between 11% and 47% and are even higher with longer follow-up. Because of this, complete Barrett's resection has been proposed as an alternative treatment[41-54].

### Complete Barrett eradication endoscopic mucosal resection

The rationale for radical endoscopic resection of BE is the proven coexistence of multifocal HGD in Barrett's mucosa, the aforementioned high rate of synchronous and metachronous lesions when focal EMR is performed as single treatment and the lack of histological correlation of the non-tissue acquiring ablative techniques[29,30,63]. With this approach, the whole Barrett's segment is eradicated by endoscopic resection in a single or multiple sessions, achieving the treatment of any occult neoplasia and preventing the development of any new lesion during follow-up[60]. It was firstly described by Satodate et al[64], and since then, several studies have been conducted involving a total of 390 patients with HGD or IMC[54,60,63,65-69] and achieving complete eradication of IM in 86% to 100% of cases and eradication of any neoplasia from 75% to 100% of patients (Table 3). The global recurrence rate of

neoplasia after a follow-up period of up to 32 mo was 3% (12/390), much lower than the previously reported with focal EMR[54,60,63,65-69].

Only one case of disease progression was observed (0.25%) with this approach. In the largest published series, Pouw et al[63] reported one case of progression to T1sm1 tumor after complete removal of a T1m2 cancer, the subsequent surgery showed neither residual tumor nor LN involvement. In the same study, all cases with recurrence of neoplasia [3 patients (1.8%), two HGD and one of T1sm1 tumor] were found distally to the neo-esophagogastric junction. This finding highlights the recommendation of a careful inspection of this area[63]. The complete Barrett's eradication EMR (CBE-EMR) is a safe procedure when performed by expert endoscopists and complications are successfully treated by an endoscopic approach with no need of additional surgery in most of cases (Table 4).

The major limitation for CBE-EMR is the high incidence of symptomatic stenosis, with rates reaching 50% in some reports. The rate of esophageal stricture was related to the length of Barrett's resected segment[63] and significant statistical differences were found with regard to the number of EMR procedures between patients who did and did not develop strictures[60]. New strategies to prevent the development of strictures should be evaluated[63]. A recent study reports a decrease in the incidence and severity of stricture after EMR/endoscopic submucosal dissection (ESD) involving more than 75% of circumference when preventive dilation is performed. Endoscopic balloon dilation was carried out 1 wk after treatment and once a week thereafter, until the mucosal defect was healed. No complications related to endoscopic dilation were observed[70]. Despite the relative low number of patients enrolled in these studies and the short follow-up period, CBE-EMR has shown excellent endoscopic and histological short-term results and could be considered as an alternative to esophagectomy in high volume centers for selected patients with short Barrett's segment ($\leqslant$ 5 cm)[60,63].

### Endoscopic submucosal dissection

ESD is regarded in Japan as the treatment of choice for intramucosal gastric neoplasias, and when performed by experts the results for esophageal and colonic lesions are

**Table 5  Endoscopic submucosal dissection in esophageal cancer**

| Author | *n* | *En bloc* resection rate (%) | Curative resection rate (resection margins free of neoplasia) (%) | Recurrence (%) | Histology | Follow-up (mo) |
| --- | --- | --- | --- | --- | --- | --- |
| Oyama *et al*[75], 2005 | 102 | 95 | 95 | - | Squamous | - |
| Fujishiro *et al*[76], 2006 | 43 | 100 | - | 2.3 | Squamous | 17 |
| Kakushima *et al*[77], 2006 | 30 | 97 | 70 | 0[1] | Adenoca.[2] | 15 |
| Motohashi *et al*[78], 2009 | 9 | 100 | 100 | 0 | N/D | 12 |
| Ono *et al*[79], 2009 | 84 | 100 | 88 | 3.6 | N/D | 21 |
| Ishii *et al*[80], 2010 | 35 | 100 | 95 | 0[1] | Adenoca./Squamous | 19 |
| Neuhaus *et al*[81], 2010 | 18 | 83 | 22 | 5.5 | BE (HGIN/IMC) | 1.5 |
| Yoshinaga *et al*[82], 2008 | 24 | 100 | 72 | 0[1] | Adenoca.[2] | 30 |

[1]R0 margin lesions (free of disease margins); [2]Esophagogastric junction lesions; N/D: No data; BE: Barrett's esophagus; HGIN: High-grade intraepithelial neoplasia; IMC: Intramucosal carcinoma.

**Table 6  Endoscopic mucosal resection *vs* endoscopic submucosal dissection in esophageal cancer**

| Author | *n* | | *En bloc* resection rate (%) | | Curative resection rate (resection margins free of disease) (%) | | Complications[1] (%) | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | EMR | ESD | EMR | ESD | EMR | ESD | EMR | ESD |
| Ishihara *et al*[84], 2008 | 148 | 29 | 78.5 | 100 | 57.8 | 97 | 0.03 | 0.03 |
| Jung *et al*[85], 2008 | 69 | 37 | 25 | 97.3 | 53.1 | 86.5 | 12.5 | 16 |
| Teoh *et al*[86], 2008 | 26 | 11 | 71.4 | 94.4 | - | - | 0.06 | 0.36 |
| Deprez *et al*[87], 2010 | 25 | 25 | 0 | 96 | 24 | 64 | 52 | 24 |

[1]Perforations + bleeding + stricture demanding dilatation. All of them were successfully treated by endoscopic approach. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

encouraging and superior to conventional EMR in terms of curative resection rate and recurrence[71-73]. With this approach, *en bloc* resection can be achieved regardless of the size of the lesions but it is a challenging technique, time consuming and is associated with a higher rate of adverse events[72,74,75].

The first step is marking the targeted lesion 5 mm away from its limits and perform submucosal injection using any of the available solutions (saline solution, hyaluronic acid, glycerine). The addition of epinephrine (1:100 000-1:300 000) is used for vasoconstriction of small submucosal vessels and indigo-carmine for a better visualization of the stained submucosal layer. Incision at the proximal and distal margins and then circumferential cutting of the surrounding mucosa is performed. Finally, dissection of the tissue beneath the isolated mucosa is carried out to achieve the removal of the lesion in one piece. Many different knives have been designed and developed.

Because of the low incidence of BE and adenocarcinoma in Japan and other eastern countries, the reported experience with early esophageal neoplasia is mainly limited to squamous cancer[75-81] (Table 5). Yoshinaga *et al*[82] reported a 100% of *en bloc* resection and a curative resection rate of up to 72% in adenocarcinoma located at the esophagogastric junction. When compared to EMR, ESD shows a better *en bloc* resection rate and a better curative resection rate (free of disease resection margins) for treatment of superficial tumors in the gastrointestinal tract, leading to a dramatically reduced local recurrence rate[75,83,84]. Perforation and bleeding were significant

higher in the ESD group, although most of them were successfully managed by endoscopic intervention. There were no studies from western countries and no randomized controlled trials included in this analysis[83-87] (Table 6).

It is important to keep in mind that ESD is a time-consuming and technically demanding procedure. Learning methods should be standardized, with animal models playing a significant role[88-90] and the technique should be performed in an appropriate stepwise fashion. The minimum training requirements recommended by a panel of experts were recently published: enough previous experience with conventional EMR; knowledge of indications, instruments and complications management; visits to expert centers and observation of at least 15 live procedures performed by the experts; hands-on experience in isolated animal models and live pigs; starting with treatments on less challenging locations such as rectum and then moving to distal stomach, colon, proximal stomach and esophagus[73]. There is no consensus regarding of the minimum case load, but Japanese experts recommend at least 50 ESD procedures in distal stomach before performing the technique in the more challenging locations[91,92]. The role of ESD in the therapeutic algorithm of BE in the western countries is still not established[87,93]. Long-term results with EMR techniques are excellent, as previously shown, and ESD is a challenging technique with an increased risk of perforation compared to EMR and it does not provide a high R0 rate (lateral resection margins free of tumor) in Barrett's lesions. In these patients, the entire Barrett's segment must be eradicated af-

**Table 7 Radiofrequency ablation non-randomized prospective trials**

| Author | n | Complete regression of intestinal metaplasia (%) | Complete regression of dysplasia/early cancer (%) | Patients | Study | Follow-up (mo) |
|---|---|---|---|---|---|---|
| Roorda et al[97], 2007 | 13 | 46 | 71 | BE | Single-center | 12 |
| Sharma et al[98], 2007 | 70 | 70 | - | Non D-BE | Multic. | 12 |
| Fleischer et al[99], 2008[1] | 70 | 70-98 | - | Non D-BE | Multic. | 12-30 |
| Ganz et al[100], 2008 | 142 | 54.3 | 80.4-90.2 | HGD | Multic. | 12 |
| Pouw et al[101], 2008 | 44 | 98 | - | BE | Single-center | 21 |
| Gondrie et al[102], 2008 | 11 | 100 | 100 | BE | Single-center | 14 |
| Gondrie et al[103], 2008 | 12 | 100 | 100 | BE | Single-center | 14 |
| Sharma et al[104], 2008 | 10 | 90 | 100 | LGD | Single-center | 24 |
| Hernandez et al[105], 2008 | 10 | 70 | - | BE | Single-center | 12 |
| Sharma et al[106], 2009 | 63 | 79 | 89 | LGD/HGD | Single-center | 24 |
| Velanovich et al[107], 2009 | 66 | 93 | - | BE | Single-center | 12 |
| Vassiliou et al[108], 2010 | 25 | 78.5 | - | LGD/HGD/IMC | Single-center | 20 |
| Lyday et al[109], 2010 | 429 | 72 | 89 | LGD/HGD | Multic. | 9 |
| Eldaif et al[110], 2010 | 27 | 100 | - | Non D-BE/LGD | Single-center | 2 |
| Fleischer et al[111], 2010[2] | 50 | 92 | - | Non D-BE | Multic. | 60 |

[1]Outcomes at 2.5 years f/u; [2]Outcomes at 5 years f/u. Non D-BE: Non dysplastic Barrett's esophagus; BE: Dysplastic and non dysplastic Barrett's esophagus; LGD: Low grade dysplasia; HGD: High grade dysplasia; IMC: Intramucosal carcinoma.

ter resection of any visible lesion regardless of the negative resection margins. Thus, the potential advantages of ESD compared to conventional EMR could be less relevant in treatment of early Barrett's neoplasia[93].

## ABLATIVE THERAPIES

The rationale for developing new ablative methods for BE is the well established presence of molecular abnormalities in the remaining Barrett's epithelium after focal resection of neoplastic lesions[28], making the eradication of the entire Barrett's segment essential. The current consensus for use of non-tissue-acquiring modalities is in the eradication of all BE after endoscopic resection of all visible lesions for an accurate staging. When no visible lesion is macroscopically detected after a carefully examination with HRE, ablative methods may be the first of choice therapy for HGD[29].

### Radiofrequency ablation
Radiofrequency ablation (RFA) using the HALO® system (BÂRRX Medical Inc., Sunnyvale, California, United States) uniformly delivers thermal energy with a prefixed density (12-15 J/cm$^2$) and power (40 W/cm$^2$). With these settings, the tissue penetration depth of the RF energy is limited to 500-1000 μm, which has been demonstrated as sufficient for the successful ablation of esophageal epithelium with no submucosal injury in animal models and humans[94]. The HALO360® device is a balloon catheter with spindle-shaped electrodes on its surface that allows the ablation of 3 cm long segments in a circumferential fashion. In order to choose the appropriate balloon size (available diameters 18 mm, 22 mm, 25 mm, 28 mm, 31 mm and 34 mm) an inflatable sizing balloon is used to measure the esophageal inner diameter. The catheter is introduced into the esophagus over a guide-wire and the RFA is performed under endoscopic direct view. The HALO90® is a square-shaped catheter with the same electrodes on its external surface, which is attached to the tip of the endoscope. It allows the focal ablation of small areas of residual Barrett's epithelium[29,95,96].

The available data from prospective trials are summarized in Table 7; they show a complete eradication of dysplasia in 70%-100% of cases and the eradication of IM in 50% to 100%[97-111]. Several trials assessing the efficacy and safety of RFA in BE have been conducted. After the publication of several studies in non dysplastic BE[97-99] Ganz et colleagues in 2008 conducted the first study in patients with HGD. A complete regression of IM, any dysplasia and HGD was achieved respectively in 54%, 80% and 90% of the 142 enrolled patients[100]. In the only multicenter, randomized and sham-controlled trial conducted to date, 127 patients with prior diagnosis of dysplastic BE (63 HGD and 64 LGD) were randomized in a 2:1 ratio to receive either RFA or sham endoscopic procedure (control group). After 1-year follow-up, all measured primary and secondary outcomes showed significant differences favoring the treatment group: progression rate, progression rate to cancer, complete regression of IM, complete regression of LGD and complete regression of HGD[112] (Table 8). Only three relevant adverse events occurred in the treatment group and five patients (6%) developed esophageal stricture (with or without dysphagia), a rate markedly lower than reported with resection therapies[112].

A systematic review of nine observational studies, involving 429 patients, and at least 12 mo of follow-up was recently published[113]. After analysis, complete eradication of IM was achieved in 46%-100% of patients and complete regression of neoplasia in 46%-100%. There were only 6 cases of stenosis after treatment (1.4%) and no major complications were observed. RFA has proved to be a safe procedure. Of all 657 patients involved in the aforementioned trials, only one case of perforation

**Table 8  Radiofrequency ablation randomized, prospective and sham-control trial[113]**

| Study characteristics | Radiofrequency ablation group | Sham group | *P* value |
|---|---|---|---|
| *n* = 127 Dysplastic Barrett's esophagus patients | 84 | 43 | - |
| Complete regression of intestinal metaplasia | 77.4% | 2.3% | < 0.001 |
| Complete regression of low grade dysplasia | 90.5% | 22.7% | < 0.001 |
| Complete regression of high grade dysplasia | 81.0% | 19.0% | < 0.001 |
| Global progression rate | 3.6% | 16.3% | < 0.05 |
| Progression to cancer rate | 1.2% | 9.3% | < 0.05 |

**Table 9  Stepwise treatment (endoscopic mucosal resection + radiofrequency ablation)**

| Results | End of treatment | Follow-up (22 mo) |
|---|---|---|
| Pouw *et al*[115], 2010 | | |
| Complete regression of neoplasia | 20/21 (95%)[1] | 24/24 (100%) |
| Complete regression of intestinal metaplasia | 21/24 (88%)[2] | 20/24 (83%) |
| Progression | 0% | 0% |
| Buried glands (1201 biopsies) | 0% | 0% |
| Pouw *et al*[116], 2010 | | |
| Complete regression of neoplasia | 55/55 (100%) | N/A |
| Complete regression of intestinal metaplasia | 53/55 (96%) | N/A |
| Progression | 0% | N/A |
| Buried glands | N/D | N/A |

[1]100% after escape endoscopic mucosal resection (EMR); [2]96% after escape EMR; N/D: No data.

has been reported (0.15%) and only 3 patients required hospitalization for any complication related to ablation. The global rate of stenosis is 2.3%, with all instances successfully treated by endoscopic dilation, and the most frequent adverse event is chest pain, usually controlled with conventional analgesics[97-111].

The Amsterdam group has reported excellent outcomes from the stepwise treatment in patients with HGD and any visible lesion in the index endoscopy exam. This approach consists of the resection of all macroscopic lesions and the subsequent ablation by RFA of the remaining Barrett's epithelium. Initially, circumferential ablation with HALO360® is performed with a maximum of three sessions; thereafter focal ablation with a HALO90® device is performed in order to eradicate any residual IM, with the same three session limit[102,103,114-116]. Complete eradication of neoplasia is achieved in up to 100% of cases and complete regression of IM in 96%. Escape EMR is performed if any abnormality is seen during follow-up. No recurrence of neoplasia has been observed 22 mo after treatment[114-116] (Table 9).

One of the most relevant concerns about RFA and other ablative therapies is the incidence of buried IM after treatment. The aforementioned review revealed only one case of buried Barrett's epithelium, after the assessment of more than 8500 biopsy samples obtained during follow up from the 429 patients enrolled in the 9 analyzed trials[113]. No randomized controlled trials comparing RFA *vs* CBE-EMR have been conducted to date. According to the published data, stepwise treatment should be the treatment of choice for patients with visible lesions arising on HGD[117] and CBE-EMR could be recommended, in high volume centers, for patients with short segment BE (SSBE).

## Photodynamic therapy

In this technique, ablation is achieved by light activation of a photosensitizer drug, which leads to oxygen radicals formation and thereafter cell death. The photosensitizing agent, usually porfimer sodium, is administered before the procedure and it is selectively accumulated in the malignant esophageal mucosa. Cylindrical or balloon-based diffuser fibers are then placed over the targeted lesion under endoscopic view[20,29]. The published trials have proved the efficacy of photodynamic therapy (PDT) in eradicating Barrett's dysplasia[118-123] (Table 10). The only randomized and controlled trial reported complete regression of IM in 52% of cases and complete regression of any dysplasia in 59% out of 138 patients with dysplastic BE[122].

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. Number of PDT treatments per session, prior EMR and a previous history of esophageal stenosis are associated with development of strictures[124]. Buried glands under the neo-squamous epithelium after PDT have been described in up to 51% of patients[125] and cases of adenocarcinoma arising from buried Barrett's glands have also been reported[120]. For all these reasons, PDT has been abandoned in recent years in favour of other ablation techniques. Further investigations aimed to identify biomarkers, which may stratify the patients more likely to respond to this treatment, and the development new photosensitizing agents could improve its safety profile[29].

## Cryotherapy ablation

This is the latest added option to the therapeutical armamentarium of BE and has shown promising results in the available reports. For ablation, a liquid cryogen is focally sprayed onto the targeted lesion and results in freezing of the epithelium, causing intracellular disruption and ischemia. Liquid nitrogen and carbon dioxide have been used as cryogenic agents. The depth of ablation is limited to 2 mm and treatment sessions are performed every 4-6 wk until complete remission of the IM is achieved[126]. Several trials have shown cryotherapy as a safe and effective

**Table 10  Photodinamic therapy in Barrett's esophagus**

| Autor | n | Study | Sessions | Complete regression of intestinal metaplasia (%) | Complete regression of dysplasia/early cancer (%) | Recurrence (%) | Follow-up (mo) |
|---|---|---|---|---|---|---|---|
| Wolfsen et al[118], 2002 | 48 | Case series | 1 | 56 | 98 | S/D | 18.5 |
| Ackroyd et al[119], 2003 | 40 | Case series | 1 | 0 | 100 | 2.5 | 53 |
| Overholt et al[120], 2003 | 94 | Case series | 1-2 | 56 | 80 | S/D | 50 |
| Wolfsen et al[121], 2004 | 102 | Case series | 1 | 56 | S/D | S/D | 19 |
| Overhalt et al[122], 2005 | 138 | Randomized controlled trial | 2 | 52 | 59 | 1.4 | 24 |
| Pech et al[123], 2005 | 66 | Case series | 1.2 | S/D | 98 | 17 | 37 |

**Table 11  Cryotherapy in Barrett's esophagus**

| Author | n | Complete regression of intestinal metaplasia (%) | Complete regression of dysplasia (%) | Complete regression of high grade dysplasia (%) | Patients | Follow-up (mo) |
|---|---|---|---|---|---|---|
| Johnston et al[127], 2005 | 9 | 78 | - | - | Non D-BE/LGD/HGD | 6 |
| Canto et al[128], 2009 | 44 | 50 | 84 | 86 | HGD/IMC | 12 |
| Greenwald et al[129], 2010 | 21 | 46 | 79 | 83 | HGD/IMC | 12 |
| Shaheen et al[130], 2010 | 60 | 57 | 87 | 97 | HGD | 10.5 |

Non D-BE: Non dysplastic Barrett's esophagus; LGD: Low grade dysplasia; HGD: High grade dysplasia; IMC: Intramucosal carcinoma.

tool[127-130]. Short-term results are promising with eradication rates of IM in 46%-78% and of dysplasia between 79% and 87% of cases (Table 11). No major complications have been reported except for a gastric perforation in one patient with Marfan syndrome. This therapy is now contraindicated in patients with limited distensibility of the stomach. Multi-center randomized trials are required to confirm these results and determine the long-term response. It is still necessary to establish the optimal treatment protocol, duration and number of cycles per session, and frequency of treatment sessions. Finally, it remains to be determined if there is any clinical relevant difference in safety or efficacy profiles between $CO_2$ and $N_2$[126].

### Other ablation modalities

Argon plasma coagulation has reported eradication rates of IM in non dysplastic Barrett's patients of up to 100%[131-134] and about 75% in cases of HGD, although with significant long term recurrence rates[29,135]. Techniques such as multipolar electrocoagulation and laser therapies have been replaced by the ablation modalities discussed in this manuscript[20,29].

## CONCLUSION

According to the results achieved by endoscopic therapies, the reported rates of LN metastasis in lesions limited to the mucosal layer, and true prevalence of occult invasive adenocarcinoma in HGD, esophagectomy should not be routinely considered as a part of therapeutical algorithm for HGD in BE.

Barrett's patients with any visible superficial lesion should be treated by endoscopic resection for an accurate histopathological staging. In cases with favorable histology, all residual Barrett's epithelium should be ablated in order to avoid the risk of developing synchronous or metachronous lesions. Of all available ablation modalities, RFA has shown the best efficacy and safety profile. Patients with Barrett segment $\leqslant$ 5 cm could be considered for complete eradication by EMR in selected high volume centers[60,63]. The role of endoscopic ablation therapies is well established for HGD. Further investigations should be conducted to establish its role in LGD and non-dysplastic BE.

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