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Review article

New advances in the diagnosis and treatment of early onset dysplasia and adenocarcinoma in Barrett's oesophagus

Manuel Pera,[a,] Luis Grande,[a] Mar Iglesias,[b] José M. Ramón,[a] and Mássimo Conio[c]*

[a]*Sección de Cirugía Gastrointestinal, Hospital Universitario del Mar, IMIM-Hospital del Mar, Barcelona, Spain*
[b]*Servicio de Anatomía Patológica, Hospital Universitario del Mar, IMIM-Hospital del Mar, Barcelona, Spain*
[c]*Departamento de Gastroenterología, Hospital de San Remo, San Remo, Italy*

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Periodic endoscopic follow-up is recommended after the diagnosis of Barrett's oesophagus, particularly in patients with dysplasia. The new endoscopic techniques show promising results in identifying areas suspected of housing high grade dysplasia and adenocarcinoma. Endoscopic resection of the mucosa has become a fundamental technique for the complete histological assessment of these lesions and is able to establish appropriate therapeutic decisions. Likewise, this technique may be the therapeutic option in patients with high grade dysplasia and adenocarcinoma, although its application must be complemented with ablation techniques such as radiofrequency to eliminate the residual Barrett's metaplasia. Oesophagectomy associated with lymphadenectomy is the option of choice in patients with submucosal adenocarcinoma. The diagnosis and treatment of patients with early onset high grade dysplasia and adenocarcinoma must be carried out with multidisciplinary teams who can evaluate each case individually. This strategy will enable the oesophagus to be preserved in many patients with high grade dysplasia and indicate oesophagectomy in selected cases..

Nuevos avances en el diagnóstico y el tratamiento de la displasia y el adenocarcinoma precoz en el esófago de Barrett

Palabras clave:
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R E S U M E N

Tras el diagnóstico del esófago de Barrett se recomienda el seguimiento endoscópico periódico, especialmente en pacientes con displasia. Las nuevas técnicas endoscópicas muestran resultados prometedores en la identificación de áreas sospechosas de albergar displasia de alto grado y adenocarcinoma. La resección endoscópica de la mucosa se ha convertido en una técnica fundamental para la valoración histológica completa de estas lesiones y poder establecer decisiones terapéuticas adecuadas. Asimismo, esta técnica puede ser la opción terapéutica en pacientes con displasia de alto grado y adenocarcinoma intramucoso, aunque su aplicación debe complementarse con técnicas ablativas, como

*Author for correspondence.
E-mail address: pera@imas.imim.es (M. Pera).
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la radiofrecuencia, para eliminar la metaplasia de Barrett residual. La esofagectomía combinada con linfadenectomía es la opción de elección en pacientes con adenocarcinoma submucoso. El diagnóstico y el tratamiento de los pacientes con displasia de alto grado y adenocarcinoma precoz deben realizarlos equipos multidisciplinarios que evalúen cada caso de forma individualizada. Esta estrategia permitirá preservar el esófago en muchos pacientes con displasia de alto grado e indicar la esofagectomía en casos seleccionados.

Introduction

Barrett's oesophagus (BO) refers to the substitution of a squamous segment of epithelium from the distal oesophagus with columnar epithelium (metaplasia) as a consequence of chronic acid gastroesophageal reflux and duodenal content. Histologically, BO is defined by the presentation of intestinal metaplasia with characteristic goblet cells.[1,2] BO is the premalignant condition to oesophageal adenocarcinoma during the metaplasia-dysplasia-cancer sequence.[3]

The objective of this review is to present new advances in endoscopic diagnosis of dysplasia and early adenocarcinoma in BO patients, and also present different treatment options which are both endoscopic and surgical, and could be individualized options for the patient.

Dysplasia and difficulties with its histological diagnosis

BO dysplasia is histologically recognized by the combination of alterations which are both cellular and of epithelial architecture.[4,5] Dysplasia is classified by degrees of progressive severity according to the alterations observed. The pathologies are principally distinguished between low-grade dysplasia (LGD) and high grade dysplasia (HGD). Since the introduction of the Vienna classification for premalignant conditions of the digestive tract, some authors recommend that the term dysplasia be substituted for "intraepithelial neoplasia" (low-grade or high-grade intraepithelial neoplasia), with the objective of highlighting the tissue's neoplastic character.[6] The term carcinoma in situ is no longer used and would be a synonym for HGD. When neoplastic cells pass through the basal membrane and penetrate the lamina propria, we are faced with intramucosal carcinoma.

Intraobserver variations and variations among observers when diagnosing dysplasia is one of the main problems the gastrointestinal pathologists face. Among expert pathologists, the degree of consensus in diagnosing LGD is less than 50%.[7-9] In distinguishing HGD from other less severe epithelial conditions, consensus among pathologists is greater than (85%), but this is not the desired objective. It also may be difficult to distinguish HGD from intramucosal adenocarcinoma, especially in superficial biopsies.[10]

Early adenocarcinoma: classification and risk of lymph node involvement

Early invasive conditions are intramucosal cancers and neoplasias which penetrate the submucosa.[6,11] To better define the risk of metastasis in lymphatic ganglia, mucosa (m) and submucosa (sm) layers have each been divided into 3 sections. m1 refers to the epithelium being affected (high-grade intraepithelial neoplasia) without penetration of the basal membrane; m2, when there is infiltration of the lamina propria; and m3, when the infiltration reaches the muscularis mucosae (mm). Total thickness of the submucosa can only be evaluated in samples resected surgically, which allows for semiquantitative measurement of the depth of the tumoural infiltration and stratification of the submucosa into three equal layers: sm1, sm2, and sm3. Buskens et al[12] studied 77 oesophagectomy samples which contained HGD or T1 carcinoma. Lymph node metastasis was detected in 23% of the sm2 tumours and in 69% of the sm3 tumours, but not in m1, m2, m3, and sm1 lesions.

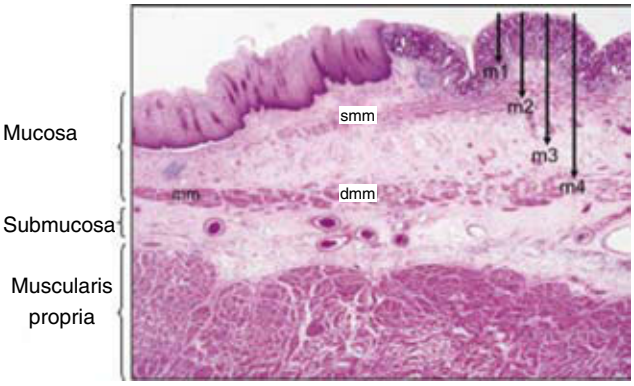

Figure 1 – Classification of Barrett's adenocarcinoma according to the grade of infiltration depth.[71] Splitting of the muscularis mucosae (mm) into 2 bundles is observed, one superficial (smm) and the other deep (dmm), from the area of squamous epithelium (left) toward the area of Barrett's columnar epithelium. m1: infiltration of the lamina propria; m2: infiltration of the superficial mm; m3: infiltration of the space between the 2 mm; m4: infiltration of the deep mm.

It has been confirmed as a characteristic histological fact of BO that there is a double mm.[13] Some pathologists could confuse the superficial mm with a single mm and interpret infiltration beyond this first mm as infiltration of the submucosa, when in reality, the tumour has not reached the deep mm. Vieth et al[14] have proposed a new classification of the different mucosa layers (Figure 1). When the tumour reaches the deep mm, there may be lymphatic invasion in 2.8%–10% of cases.[13,14] Pathological reports should precisely describe the degree of adenocarcinoma infiltration instead of using general descriptions such as invasion of the mucosa or submucosa.

Endoscopic diagnosis

Follow-up protocols in BO patients suggest periodic endoscopies with biopsy sampling in each quadrant of the oesophagus at 1 or 2 cm intervals and sampling of visible alterations such as nodes or ulcers (Seattle Protocol).[15] HGD and early adenocarcinoma are not normally visible in conventional endoscopies, and identifying them may be difficult despite following rigorous protocols in taking biopsies.

Various methods for more accurately identifying intestinal metaplasia, dysplasia and adenocarcinoma in BO have been evaluated or are in the process of being evaluated. Potential value of these diagnostic imaging techniques lies in the possibility of examining Barrett's segment in its totality, with the aim of identifying dysplasia without the need for biopsies, or with the aim of simplifying selective sampling in areas which probably contain dysplastic epithelium.

Endoscopic imaging techniques

Diagnostic imaging techniques can identify Barrett's epithelium both by the absorptive nature of its cells and by image magnification until reaching a resolution that displays glandular structure and minimal alterations may be detected in surfaces indicative of dysplasia.

Chromoendoscopy

The chromoendoscopy consists of the application of dyes on the oesophageal mucosa with the purpose of highlighting mucosa surface patterns and improving detection and limits of early neoplastic lesions. This method would make biopsies targeting suspicious areas possible instead of random selection.

Methylene blue reversibly dyes absorptive cells of intestinal metaplasia (Figure 2). HGD areas do not absorb the dye, while LGD areas do not respond in a homogeneous manner. Despite numerous articles dedicated to possible usefulness of methylene blue in diagnosing BO, results are controversial,[16,17] and diagnostic precision is reduced to patients with concomitant oesophagitis.[18,19] Methylene blue is less sensitive for detecting dysplasia than the Seattle Protocol.[20] Consequently, using chromoendoscopy with methylene blue does not seem to be recommendable in the BO follow-up. It has been described with particular concern that methylene blue binds with DNA, and when BO is exposed to white light, genetic alterations could be induced.[21]

Carmine dye is a blue dye which is not absorbed by the cells, but it highlights small irregularities of the mucosa surface. Its usefulness has been demonstrated when combined with magnification endoscopy.[22] Sharma et al[23] described 3 BO patterns: a ridged/villous pattern, a circular pattern, and an irregular/distorted pattern. The ridged/villous pattern was observed in non-dysplastic BO and in LGD. The irregular/distorted pattern was observed in HGD with a sensitivity and specificity of 100%.

Acetic acid (AA) eliminates the superficial layer of mucous and produces reversible denaturation of intracellular cytoplasmic protein which uncovers the mucous pattern and allows for identification of intestinal metaplasia. With this technique, Guelrud et al[24] distinguished 4 types of mucosa surface patterns and 2 of them (III: villous pattern; IV: distorted pattern) had a high predictive value (87% vs 100%, respectively) for intestinal metaplasia. Hoffman et al[25] demonstrated that magnification endoscopy combined with taking biopsies guided by previous dyeing with AA, was better than conventional video endoscopy with taking random samples of biopsies for diagnosing BO (78% vs 57%, respectively). Other authors have confirmed these observations in patients with short segments of BO (<3 cm).[26] There is no relevant information available on applying AA for the diagnosis of dysplasia and early adenocarcinoma in BO.

Narrow-band imaging

Narrow-band imaging (NBI) is a high-resolution endoscopic technique which uses additional optical filters which allow for

Figure 2 – Barrett's Oesophagus A: high-definition endoscopy. B: after dying with methylene blue. C: narrow-band imaging.

transmission of blue light, while these eliminate lights of other wavelengths. The depth of the light's penetration depends on its wavelength, and the 475 nm blue light only superficially penetrates the tissue and allows for, on the one hand, the best view of the mucosa's morphology without using dyes and, on the other, display of the vascular distribution when absorbed by the haemoglobin[27,31] (Figure 2).

Sharma et al[30,31] defined 3 mucosa patterns in BO patients: ridged/villous, circular, and irregular/distorted, and 2 vascular patterns: normal and abnormal. These authors also found that the ridged/villous pattern had a significant relationship with BO without HGD, and irregular/distorted and abnormal vascular patterns had a relationship with BO with HGD. Kara et al[28] have described that the irregular or destructured mucosal pattern, the irregular vascular pattern and abnormal blood vessels were independent predictive factors for HGD.

High-resolution endoscopy (HRE) followed by NBI is equivalent, in results, to the HRE followed by chromoendoscopy with carmine dye (86% vs 93%, respectively) for detecting HGD or early adenocarcinoma in BO.[32]

Autofluorescence

When tissues are exposed to a short wavelength light (ultraviolet or blue light), certain endogenous substances (fluorophores) absorb the light energy and reach a state of excitation. From the excitation state, the fluorophores emit a wavelength light which is longer than the light which produced the state of excitation. This phenomenon is called autofluorescence. The fluorophores which cause the autofluorescence of the tissues are the NADH in collagen, porphyrins and aromatic amino acids.[33,34] Variations in molecular composition and tissue microstructure produce differences in fluorescence, and in this manner, the conditions are established for distinguishing neoplastic tissues from the non-neoplastic ones. The application of autofluorescence through endoscopy as a source of exciter light waves is called light-induced fluorescence endoscopy.[35]

Despite its theoretical advantages and efforts for improving its efficacy (intravenous or topical administration of fluorophores, such as 5-aminolevulinic acid,[36] autofluorescence imaging (AFI) techniques which use high resolution endoscopies and imaging algorithms which incorporate reflectance,[37] combined AFI, and NBI,[38] and using the combination of HRE, NBI, and AFI in a single endoscopy),[39] the role of AFI in BO is still to be defined. Recent data show that this technique still lacks sufficient sensitivity and specificity to recommend its use in the follow-up of these patients. Some groups use AFI for initial detection of areas suspicious of dysplasia and later combine AFI and NBI for meticulous inspection. It has been demonstrated that NBI reduces false positives of AFI.[40]

Endoscopic mucosal resection in diagnosing dysplasia and early adenocarcinoma

Endoscopic mucosal resection (EMR) is both a diagnostic option and a treatment alternative for certain patients with superficial neoplastic lesions.[41] Among the most common EMR techniques are the following: strip biopsy, cap-assisted EMR, and suck-and-ligate technique. The size of samples taken in these procedures varies between 10 and 15 mm. EMR may be accompanied by complications, among which include haemorrhage and perforation (<1%).

Treatment of BO with dysplasia and early adenocarcinoma

The oesophagectomy, with complete dysplastic epithelium removal, has been the standard treatment for HGD and early adenocarcinoma in BO patients, with a 5-year survival rate above 90%–95%.[42] However, this technique has a significant morbidity and 3%–5% mortality in referral centres. Intramucosal adenocarcinomas have a very low risk of lymph node involvement, and this would allow for its local treatment. Different endoscopic techniques have been developed for treating dysplasia and early adenocarcinoma.

Endoscopic treatment

The objective of endoscopic treatment is to eliminate dysplastic BO, and facilitate recovery of the squamous epithelium. Among the methods used for eliminating HGD are photodynamic therapy (PDT), argon plasma coagulation (APC), and radiofrequency (RF), such as EMR (Table 1). After these procedures, it is necessary to maintain prolonged control of gastroesophageal reflux.

Endoscopic mucosal resection as treatment: indications and results

EMR, contrary to ablative techniques (PDT, APC, and RF), allows for histological evaluation of the lesion and defines both the lateral infiltration margin and the depth of the tumour. Conio et al[43] and Mino-Kenudson et al[44] observed a change in the histological diagnosis in 26% and 37%, respectively, of BO patients who had an EMR (Table 2).

Different studies indicate that EMR can successfully eliminate early adenocarcinomas with a low rate of complications, but it is recognized that EMR has recurrence rates of 25%–30% in the first 3 years when it is the only treatment used for patients with HGD or with intramucosal adenocarcinoma.[45] This information indicates a disadvantage of this technique; a reason why a very strict endoscopic follow-up is necessary after an EMR or treatment of residual BO through ablative techniques.

Ell et al[46] carried out 144 EMRs on 100 patients with low-risk oesophageal adenocarcinomas (macroscopic types I [polypoid], IIa [elevated], IIb [flat], and IIc [depressed]; diameter no greater than 20 mm, mucosa lesion without evidence of lymphatic and venous invasion, and G1 and G2 histological grades) without significant complications. The authors achieved complete local remission in 99 patients after a maximum of 3 resections. During an average follow-up of 36.7 months, 11% of patients developed recurrences or metachronous lesions and were again successfully treated with EMR. Ablation of the remaining mucosa was carried

Table 1 – Treatment options for early adenocarcinoma in Barrett's oesophagus

Treatment	Advantages	Disadvantages	Result
EMR	Histological evaluation. Excision of circumferential BO up to 4 cm	Incomplete treatment of occult foci of HGD in long segments of BO	Favourable in intramucosal adenocarcinoma[a]
PDT	Easy to carry out	Absence of an adequate histological exam. Photosensitivity and oesophageal stenosis. Incomplete treatment of residual IM. Occult islets of IM below the new squamous epithelium	Favourable in intramucosal adenocarcinoma[b]
(HALO®) radiofrequency	Easy to carry out. Circumferential ablation. Without complications	Incomplete treatment of residual IM (in less proportion than PDT)	Favourable in HGD. Favourable in intramucosal adenocarcinoma (without long-term results)[b]
Surgery	Complete excision of BO. Histological evaluation of lymphatic ganglia	Negligible morbidity and mortality. Worsening of quality of life	Radical treatment

BO indicates Barrett's oesophagus; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; IM, intestinal metaplasia; PDT, photodynamic therapy; RF, radiofrequency.
[a]Should combine with PDT or RF in Barrett's segments >4 cm.
[b]EMR should always be done before ablation to eliminate visible lesions.

Table 2 – Selected studies of endoscopic resection of the mucosa in high-grade dysplasia and early adenocarcinoma in Barrett's oesophagus

Author	Patients, No.	Size of the lesion, median, cm	Pre-EMR histology	Post-EMR histology	Complications	Surgery	Follow-up, average, mo	Recurrence
Peters et al,[67] 2005	28/33 (EMR)	1.5	9 HGD; 10 HGD/AC; 14 AC	8 HGD; 15 IMC; 7 SMC; 3 without dysplasia	Mild haemorrhage, 54% (15/28); stenosis, 3.5% (1/28)	5 4 SMC, (1 IMC)	19[a]	19% (5/26)
Mino-Kenudson et al,[44] 2005	18	1.1	10 HGD; 7 IMC; 2 SMC	2 LGD; 5 HGD; 10 IMC; 2 SMC	0	1 AC	NDA	47% (8/17)
Conio et al,[43] 2005	39	1.5	35 HGD; 4 IMC	5 LGD; 27 HGD; 2 IMC; 5 SMC	Haemorrhage 10% (4/39); stenosis, 3% (1/39)	3 (1 HGD, 2 SMC)	35[a]	
Giovannini et al,[48] 2004	21	1.6	12 HGD; 9 IMC	12 HGD; 9 IMC	Haemorrhage, 19% (4/21)	1 (IMC)	18	0
Seewald et al,[50] 2003	12	NDA	3 HGD; 2 HGD/IMC; 7 IMC	BO; 1 LGD; 2 5 HGD; 4 IMC	Haemorrhage, 33% (4/12); stenosis, 17% (2/12)	0	9[a]	0
May et al,[45] 2002	80	NDA	7 HGD; 73 EA	7 HGD; 62 IMC; 11 SMC	Haemorrhage, 6% (5/80); stenosis, 4% (3/80)	0	34	30% (24/80)
Buttar et al, 2001[68]	17	NDA	7 IMC; 10 iAC	7 IMC; 10 iAC	Haemorrhage, 6% (1/17); stenosis, 30% (5/17)	1	13	0
Nijhawan et al,[69] 2000	25	NDA	2 BO; 8 LGD; 5 HGD; 9 AC; 1 other	2 BO; 3 LGD; 5 HGD; 7 IMC; 6 SMC; 2 others	0	2/13 (AC)	14.6	31% (4/13)
Ell et al,[70] 2000	35	0.9	3 HGD; 32 IMC	3 HGD; 32 IMC	Haemorrhage, 20% (7/35)	NDA	12	11% (4/35)

AC indicates adenocarcinoma; BO, Barrett's oesophagus; EA, early adenocarcinoma; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; iAC, invasive adenocarcinoma (probably submucosal invasion); IMC, intramucosal cancer; LGD, low-grade dysplasia; NDA, no data available; SMC, submucosal cancer.
[a]Median.

out on 49 patients, with APC or PDT for short and long BO segments, respectively.

Circumferential mucosectomy (stepwise radical endoscopic resection) is a step forward in resective technique which would allow for complete and radical excision of the metaplastic epithelium, with optimal histological evaluation, and it avoids the persistence of residual foci of BO. However, carrying this out is not easy and it would only be indicated in BO segments with a length <5 cm[47-51] (Figure 3). The incidence of complications (haemorrhage and perforation) is low (2%), but the incidence of stenosis is high (20%–50%).

Ablation of Barrett's epithelium

During recent years, endoscopic treatments using thermal energy (argon plasma coagulation, laser, radiofrequency, multipolar electrocoagulation) or photochemistry (PDT) have been proposed as an alternative to oesophagectomy for destroying BO with dysplasia. After epithelial ablation, control of gastroesophageal reflux is necessary by using antisecretory drugs and antireflux surgery, and in theory, all of this creates conditions for the restitution of the area destroyed by squamous epithelium.

The most used technique is PDT. Patients receive a photosensitizing drug (porfimer or 5-aminolevulinic acid) which the dysplastic epithelial cells take up. The application of laser light on the oesophageal mucosa produces activation of the drug and generation of oxygen free radicals which selectively destroy the tissue. 5-aminolevulinic acid accumulates in the mucosa, while the porfimer accumulates in the submucous and causes a deeper necrosis.

Even though various studies have described the viability of this technique for eliminating neoplastic epithelium,[52] its clinical benefit as a single technique for treating HGD and intramucosal adenocarcinoma has not been well established. PDT is a costly technique which has risks, such as stenosis (25%–30%), and disadvantages. Along with the persistence of Barrett's epithelial areas after using this technique, intestinal epithelial islets have also been detected below the new squamous epithelium. The persistence of histological and cellular alterations has also been shown in residual Barrett's epithelium after PDT ablation.

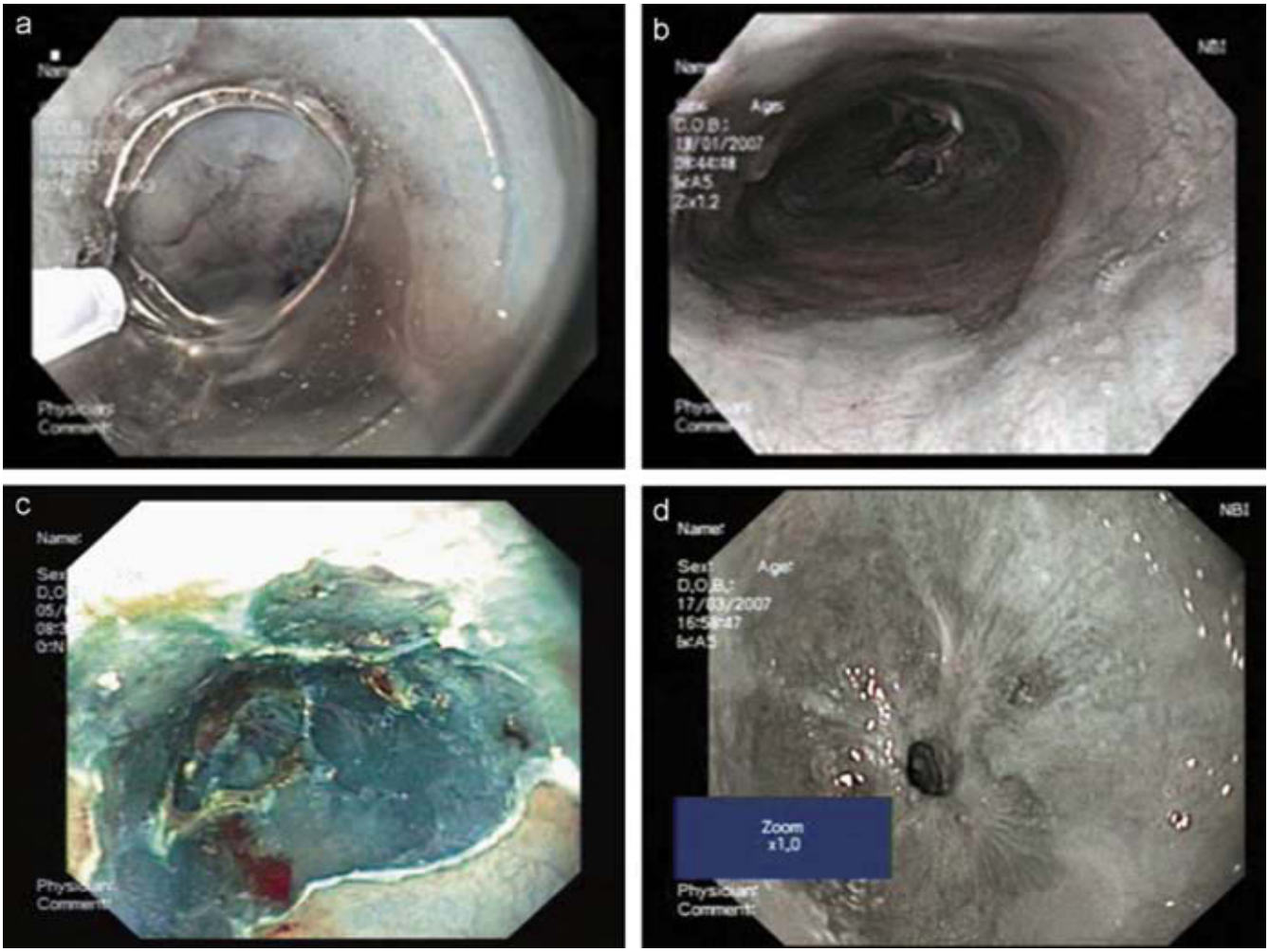

Figure 3 – Circumferential endoscopic resection of Barrett's mucosa. A: alteration of mucosa (intramucosal adenocarcinoma) before endoscopic resection of the mucosa. B: resection of the visible lesion in the lower oesophagus. C: complete circumferential resection of Barrett's oesophagus has already been done. D: benign stenosis 3 weeks later.

The application of PDT as an auxiliary treatment to EMR is a more desirable treatment option for patients with HGD and intramucosal adenocarcinoma. EMR allows for extirpation of visible lesions and other suspicious areas with the subsequent histological study. If a submucosal adenocarcinoma has been ruled out and the resection of intramucosal adenocarcinoma has been radical, then residual Barrett's epithelium may be treated by PDT. A recent retrospective cohort study carried out in the Mayo Clinic did not find differences in overall mortality between a group of patients with HGD treated by PDT in combination with EMR and another group with HGD treated by oesophagectomy (9% vs 8.5%).[53] The median follow-up time in both groups was longer than 5 years. Operative mortality was 1.4% and occult adenocarcinoma was found in 12.8% of the samples from the oesophagectomy. During the follow-up of the patients treated with PDT, 8 (6.2%) developed adenocarcinoma, and 5 of these were intramucosal. These results come from a centre which is particularly specialised in the multi-disciplinary treatment of this disease, and these results are not easily extrapolated and should be confirmed by other prospective studies.

Circumferential and/or focal ablation of BO through RF with the HALO system is a new and promising technique. Primary circumferential ablation is carried out with a bipolar electrode coupled to a balloon, while secondary treatment of BO residual areas is carried out with a bipolar electrode which is at the end of the endoscope. Recent data from clinical trials which included BO patients without dysplasia, with LGD or HGD, and with intramucosal adenocarcinomas after its elimination with EMR, show that ablation with RF, in combination or not with EMR, is safe and effective for eliminating dysplasia and intestinal metaplasia.[54-56] Pouw et al[55] treated 44 BO patients with LGD, HGD or intramucosal adenocarcinoma with RF. In 31 cases, an EMR was carried out before the ablation. The authors describe, after an average follow-up of 21 months, complete elimination of dysplasia and intestinal metaplasia in 98% of the cases. The key point when this technique is compared with PDT is the absence of occult foci of intestinal metaplasia below the new squamous epithelium.[55,56] Furthermore, RF ablation preserves oesophageal functionality without causing stenosis. Studies with a long follow-up period are needed to confirm that BO elimination is maintained over time.

The role of surgery

For patients with HGD, oesophagectomy has been the treatment of choice for many years. The arguments put forward are: the high risk of progression from dysplasia to adenocarcinoma, resection of all the esophageal segment with columnar epithelium without the possibility that Barrett's epithelium and adenocarcinoma reappear in the future, and data from surgical series which confirm T1a or T1b occult carcinomas after an oesophagectomy in up to 50% of patients initially diagnosed with HGD.[57-59]

Recent studies have provided information which could modify medical recommendations for the oesophagectomy in select cases. There are data which indicate that the most accurate estimate of adenocarcinoma incidence in patients diagnosed with HGD would be 6.6/100 patients/year of follow-up, as long as the endoscopic evaluation is rigorous.[60] Konda et al[61] recently determined the prevalence of invasive adenocarcinomas (submucosal), with a high prevalence of lymph node involvement, in patients with HGD treated by oesophagectomy. From a total of 14 studies analyzed, only 12.7% of patients had submucosal adenocarcinoma, a much lower prevalence compared to the 40%–50% frequently described in the literature. A lack of strict protocol in taking biopsies, inadequate inspection for detecting minute changes in the mucosa and the pathologists' experience can influence these results. At a time when endoscopic techniques (EMR combined with RF or PDT), which are still experimental, show promising results, the information provided by this study is relevant because it demonstrates the low prevalence of submucosal adenocarcinomas (suggesting oesophagectomy), and it establishes a platform on which the distinction between submucosal adenocarcinoma and invasive adenocarcinoma is a critical point when considering different treatment options with the patient.[61]

Currently, oesophagectomy results in patients with HGD and Barrett's early adenocarcinoma should be considered the standard to which other treatment modalities are compared. Data from the literature show cancer-free survival in more than 90% of patients with HGD and intramucosal adenocarcinoma.[62]

Results from oesophagectomies for tumours which infiltrate the submucosa depend on there being lymph node involvement or not. In absence of lymph node involvement, probability of survival at 5 years is above 90%, while in cases of lymph node involvement it is 40%–60%. Despite these excellent oncological results, the main disadvantages are morbidity (20%–45%) and the low but significant mortality (1%–5%), which accompany this procedure when carried out in excellent centres.

Recent interest has focused on developing less-invasive surgical interventions as an effort to decrease morbidity and mortality figures even more and to level off the new challenge which endoscopic techniques undertake. Absence of lymph node involvement and micrometastasis in patients with HGD and intramucosal adenocarcinoma would support this proposal.

The first option would consist of a very limited distal oesophagectomy with resection of the cardia, followed by jejunum interposition to reconstruct the intestinal transit (Merendino operation). Stein et al[63] published results from a series of 70 patients who were treated with this technique who had uT1 tumours, without lymph node involvement and after an endoscopic evaluation. In the histopathological study of the tissue sample, lymph node involvement was not observed. After a median follow-up of 69 months, probability of survival at 5 years was 83.4%. The quality of life evaluation did not detect gastroesophageal reflux and assessed deglutition as good-excellent in 92% of patients.

A second option for patients with HGD or intramucosal adenocarcinoma without a visible endoscopic lesion consists of subtotal oesophagectomy with preservation of the vagus nerves and reconstruction with the stomach or colon. In a series of 15 patients, Banki et al[64] described the absence of

diarrhea and a significantly lower incidence of *dumping* (6.6%) in comparison to standard resections with colon or stomach interposition (30% and 60%).

A third option consists of an oesophagectomy done by thoracoscopy or laparoscopy, followed by gastric tubulization and oesophagogastric anastomosis at the cervical level. In a series of 222 patients treated by this method, mortality at 30 days was 1.4%.[65] Survival at 40 months in a group of 45 patients with HGD was 96%, and for patients in stage I, it was 70%. Some authors question this technique because of the lack of adequate lymphadenectomy and an insufficient extension study, which would lead to a greater risk of recurrence. This concern is specifically focused on patients with submucosal adenocarcinoma, and for whom recurrence has been described in 50% after a transhiatal oesophagectomy.[66]

Conclusions

Diagnosis and treatment of HGD and early adenocarcinoma in BO should be done in a multidisciplinary manner. For optimal detection of these lesions, high-resolution endoscopic methods and expert histological evaluation are required. EMR is fundamental as it improves assessment of the stage of these lesions and allows for individualized decisions to be made. The detection of a submucosal adenocarcinoma suggests an oesophagectomy. In the case of intramucosal adenocarcinoma, with minimal risk of lymph node involvement, EMR may become a treatment of choice, because excision is always radical and assumes the need for additional treatment of residual BO with ablative techniques such as radiofrequency. Radiofrequency ablation may become the treatment of choice for HGD, but always when all suspicious adenocarcinoma lesions have been previously evaluated by EMR.

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