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EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Literature Review

Role of Mucosectomy in Treatment of Barret's Esophagus

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Abstract

Barrett's esophagus is a condition in which the stratified squamous epithelium in the distal esophagus is replaced by columnar epithelium abnormal. This change in this epithelium is prone to malignancy and it would be a consequence of the disease of chronic gastroesophageal reflux. The diagnosis of Barrett's esophagus is performed by endoscopy and histological dysplastic epithelium. Once a confirmed diagnosis is carried out periodic controls for the monitoring of injuries. Dysplasia's low degree only need monitoring because hardly progress to cancer. While high-grade lesions require invasive methods such as esophagectomy, endoscopic ablation, endoscopic mucosal resection or mixing methods. The esophagectomy has many postoperative complications why we prefer the methods endoscopic. The objective will be to review the current literature on the different endoscopic treatment options for Barrett's esophagus.

Keywords: *Barrett´s Esophagus; Endoscopic Submucosal Dissection; Endoscopic Mucosal Resection*

Introduction

Barrett's esophagus was established as a columnar metaplasia of the distal esophagus, associated with chronic GERD [1]. Barrett's esophagus mainly affects Caucasian and obese men, especially with central adiposity, as it predisposes to GERD by increasing intra-abdominal pressure [5]. Obesity is also associated with high serum levels of pro-proliferative hormones, such as insulin-like growth factor I (IGF I), and with decreased levels of the antiproliferative adiponectin hormone. All of these factors contribute to carcinogenesis in Barrett's esophagus [11].

There is also a lower prevalence of Barrett's esophagus in African Americans than in non-Hispanic whites, due to ethnic difference [17].

Studies suggest that *H. pylori* infection may protect against the development of Barrett's esophagus, due to decreased gastric acid secretion [5]. Other factors that protect the development of Barrett's esophagus are adenocarcinoma and use of aspirin (AAS) and non-steroidal anti-inflammatory drugs (NSAIDs) [15].

Barrett's esophagus can lead to esophageal adenocarcinoma, the overall incidence is 0.5% per year. Patients with non-neoplastic Barrett's esophagus developed low-grade neoplasia at a rate of 4.3% per year, and high-grade dysplasia at a rate of 0.9% per year. On the other hand, the risk of high-grade dysplasia developing cancer is 4% to 5% per year [11].

After the diagnosis of Barrett's esophagus, strict endoscopic surveillance is followed to detect the progression of epithelial lesions. Barrett's esophagus without changes is monitored every 2 to 3 years; in the case of low-grade lesions, follow-up should be performed every 6 months [9], but when a high-grade lesion is identified, invasive treatments are necessary, such as esophagectomy, endoscopic ablative therapies or endoscopic resections of the mucosa [9]. These measures create a neo epithelium, which is an epithelium similar to normal and does not have the alterations of Barrett's epithelium (Seewald., *et al*. 2008).

Esophagectomy has been the traditional therapy for high-grade dysplasia's and intramucosal cancers, as it can resect the lesion and the affected lymph nodes, but this greatly increases morbidity and mortality (often exceeds 2%) (Smith and Kahaleh, 2015).

New advances in endoscopy have provided less invasive therapies such as endoscopic mucosal resection (REM) and endoscopic submucosa dissection. These new endoscopic therapies (which remove lesions) combined with ablative treatments (which eliminates Barrett's epithelium) are an effective alternative for surgical treatment, when there is no metastatic lymph node (Smith and Kahaleh, 2015).

The ablative treatments can produce stenosis, perforation of the esophagus and persistence of foci of metaplasia under the re-epithelized mucosa of the esophagus [9]. However, modern techniques such as amniotic membrane grafting, endoscopic dilations and topical hemostatic powders are being used to prevent strictures with very promising results [4].

Literature Review

Barrett's esophagus is a situation in which the stratified squamous epithelium in the distal third of the esophagus is replaced by an abnormal columnar epithelium. This change in epithelium is associated with malignancy and would be a consequence of chronic gastroesophageal reflux disease (GERD) [11].

The diagnosis of Barrett's esophagus is performed through endoscopy and biopsies. In the endoscopic examination, an abnormal columnar type epithelium is seen lining the distal esophagus and through biopsies we show intestinal metaplasia in the distal esophageal epithelium [1].

Obesity, white race, age over 50, smoking, hiatal hernia and long-standing GERD are factors that increase the risk of Barrett's esophagus [6].

The classic presentation of Barrett's esophagus occurs when 3 cm or more, from the distal portion of the esophagus, are covered by a metaplastic mucosa, the pale pink color of the original squamous epithelium being contrasted with the salmon color of the new epithelium [1].

In 1994, several studies noted the presence of goblet or intestinal cells (goblet cells) at the esophagogastric junction of some patients with GERD, who do not have the 3 cm of columnar epithelium in the distal esophagus. (classic form of Barrett's esophagus). This condition was called the short Barrett [1].

In the years 1997 and 1998, many publications showed intestinal metaplasia in the region of the squamous columnar junction in patients who underwent endoscopy due to various symptoms (not just GERD), so small irregularities in the "z" line were called "Ultra-short Barrett" [2].

In 2006, a new systematization was proposed, based on the Prague consensus, in which the terms classic, short and ultra-short Barrett's esophagus would be replaced by the "C" and "M" criteria that measure the circumferential (C) and cephalic extension (M of maximum) of the columnar epithelium above the esophagogastric transition. However, this proposal was not widely adopted [2].

Pathogenesis

Dysplasia are architectural and cytological abnormalities that favor unregulated cell growth. Dysplasia's are classified as high grade or low grade, depending on the degree of histological abnormalities [9].

The most accepted hypothesis is that the metaplastic epithelium appears when chronic GERD damages the esophageal native squamous epithelium. Barrett's epithelial cells appear to be better than native epithelial cells for resisting reflux-induced esophageal injury. Unfortunately, Barrett's epithelium is also predisposed to neoplasia [1].

Dysplasia treatments

In patients with low-grade dysplasia, invasive treatments are not recommended since in these patients the progression to cancer is low. However, in patients with high-grade dysplasia, we can count on several methods such as esophagectomy, endoscopic ablative therapies and endoscopic mucosal resection [11].

Esophagectomy

Esophagectomy is the most definitive treatment, however, it has high operative mortality and high long-term morbidity, such as weight loss, dysphagia, quality of life decreases substantially [11]. It is reserved for lesions with invasion of the sub-mucosa and lymph nodes at risk of metastasis [6].

Endoscopic therapies

There are two types of endoscopic therapies:

- Ablative endoscopic therapy: using thermal energy e.g. Leisure, electrocoagulation, argon plasma coagulation, HALO system, BARRX Medical, Sunnyvale, Calif., Cold nitrogen gas. Or photochemical energy (photodynamics) for ablation of the barrett epithelium [9].

- Endoscopic mucosal resection (REM): in which a diathermic loop or endoscopic scalpel are used to remove a segment of Barrett's esophagus (below the submucosa) [11].

The ablative treatments destroy the altered tissue, so they do not provide a pathology sample that can define the depth of the invasion in the tissue. However, REM offers large samples of tissue that can define the depth of dysplasia [11].

A disadvantage of ablative therapies is that they can bury metaplastic tissue with its neoplastic potential and hide it from the endoscopist. Thus, the neo-squamous epithelium (ENE) would cover the dysplastic epithelium and allow the progression of cancer (Odze and Lauwers, 2008).

Without histological examination of the esophagus or the duration of follow-up greater than 5 years, we cannot say that the dysplasia or cancer was eliminated by ablation [11].

Endoscopic mucosal resection

Endoscopic resection of the mucosa has the advantage that it can be used for the diagnosis and treatment of injuries (Odze and Lauwers, 2008). Generally, the "suck and cut" method is used, in which the endoscopist raises and aspirates the mucosa. Another variation is the "band and loop" method, as it uses an endoscopic ligation device, to implant elastic bands around the aspirated segment without the need for prior injection of liquid into the sub-mucosa, afterwards the segment with the band is removed using a polypectomy loop [11].

The survival rate with REM is high (98%), but recurrent or killer cancers were found in 11% of patients over an average period of 37 weeks [11].

Endoscopic mucosal resection is a lower risk alternative to treat high-grade intra-epithelial lesions and intra-mucous cancers. Two approaches are being used, localized resection and total resection of Barrett's mucosa [8].

The total resection of the mucosa exceeds the localized resection as it removes the entire mucosa with risk of dysplasia [8]. Currently, mucosal resection is being performed mainly through the peacemeal technique [8]. Although this resection has recently been attempted through block resection [8].

Circumferential esophageal resection of the submucosa en bloc offers better histological assessment of the mucosa when compared to piecemeal mucosectomy for high-grade dysplasia, however, it has not yet been released due to frequent mucosal constrictions [3]. Although these constrictions are easily treated with endoscopic dilations [7].

Due to the improvement in diagnostic methods and advances in endoscopic surgical programs, more and more superficial esophageal cancers are found, which, due to their limited metastatic potential, are easy to treat [14]. Endoscopic ultrasound, endoscopic mucosal resection and endoscopic submucosal dissection are among the new modalities used to diagnose and treat superficial esophageal cancers [14].

Esophageal stenosis is a complication when we use REM to remove the entire circumferential extension of Barrett's epithelium in a single endoscopic session [11].

Esophageal stenosis is a common complication and is the major cause of post-dissection endoscopic submucosal morbidity. However, corticosteroids showed the best results. Both the systemic and the local routes have their advantages and disadvantages for each group of patients [14]. No other method such as esophageal stents, autologous leaf cell transplantation, polyglycolic acid and tranilast have shown promising results, but experience with these methods is limited [14].

Some centers combine both methods, (REM and ablative), apparently improving the appearance of dysplastic epithelium and cancer. The squamous neo-epithelium (SEN) is histologically similar to normal and does not have the molecular aberrations of Barret's epithelium (Seewald., *et al*. 2008).

Endoscopic resection and ablation are the new gold standard treatments for patients with Barrett's esophagus neoplasia [12]. And after successful treatment, strict monitoring is necessary, as recurrences are not rare [12].

Data on the effectiveness of ablation in Barrett's esophagus has excellent results. Risk factors for ablation failure include: wide segments of Barrett's esophagus and gastroesophageal reflux [10]. Metastatic lymph nodes in intramucosal adenocarcinomas are rare (~ 2%), which is why endoscopic resections are performed [10].

Endoscopic dissection of the submucosa offers a higher cure rate and better histological evaluation than endoscopic resection of the mucosa [8]. This technique is easy and safe, but it is not risk-free, so it has not yet been recommended on the piecemeal technique [16].

Currently, new techniques are being developed to prevent esophageal strictures after endoscopic treatments, with very promising results such as the application of hemospray [7], or the use of amniotic membrane graft after circumferential submucosal resections [4].

Through a meta-analysis carried out in 2014 that involved several retrospective studies, the safety and effectiveness of DES and REM were evaluated. The cure rate in the DES group was 92.3% (362/392) versus 52.7% (337/639) in the EMR group. The bleeding rate was the same in the 2 groups. Surgical time and perforations were longer in the DES group than in the EMR group, and finally there is a lower recurrence rate in the DES group (0.3% 1/398) than in the EMR group (11.5% 80/695) [13]. When the size of the lesion was less than 20 mm, the recurrence rate was the same in both groups [13].

A	Endoscopic dissection of the submucosa		Endoscopic resection of the mucosa			Probability ratio
Study/subgroup	Events	Total	Events	Total	Occurrence	M-H, 95% CI
Ishihara 2008	31	31	110	140	13.9%	17.39 [1.03, 292.42]
Jung 2008	36	37	12	32	7.6%	60.00 [7.26, 495.86]
Konishi 2012	56	56	53	105	7.1%	110.89 [6.68, 1841.77]
Kubota 2010	29	36	3	131	5.5%	176.76 [43.10, 724.94]
Takahashi 2010	116	116	98	184	7.1%	204.61 [12.53, 3340.41]
Teoh 2010	21	22	9	13	11.2%	9.33 [0.91, 95.57]
Urabe 2011	77	79	57	83	30.6%	17.56 [4.00, 77.03]
Yamashita 2011	69	71	25	56	17.1%	42.78 [9.53, 191.98]
Total (95% CI)		448		744	100.0%	52.76 [25.57, 108.84]
Total de eventos	435		367			

Heterogeneity: $x^2 = 8.93$, df = 7(P = 0.26); $I^2 = 22\%$						
Overall effect for the test: Z = 10.73 (P < 0.00001)						
B	**Endoscopic dissection of the submucosa**		**Endoscopic resection of the mucosa**			**Probability ratio**
Study/subgroup	**Events**	**Total**	**Events**	**Total**	**Occurrence**	**M-H, 95% CI**
Ishihara 2008	30	31	81	140	11.7%	21.85 [2.90, 164.79]
Jung 2008	32	37	17	32	16.3%	5.65 [1.75, 18.21]
Kubota 2010	23	36	2	131	14.2%	114.12 [24.14, 539.48]
Takahashi 2010	113	116	144	184	16.2%	10.46 [3.16, 34.70]
Teoh 2010	18	22	11	13	12.5%	0.82 [0.13, 5.23]
Urabe 2011	77	79	57	83	14.6%	17.56 [4.00, 77.03]
Yamashita 2011	69	71	25	56	14.5%	42.78 [9,53, 191.98]
Total (95% CI)		392		639	100.0%	13.90 [4.84, 39.95]
Total de eventos	1		80			
Heterogeneity: $Tau^2 = 1.42$; $x^2 = 20.96$, df = 6 (P=0.002); $I^2 = 71\%$						
Overall effect for the test: Z = 4.89 (P < 0.00001)						

Table: *Comparison of block resection (A) and cure rates (B) between endoscopic submucosal dissection and mucosal endoscopic resection. DES: Submucosal Endoscopic Dissection; REM: Mucous Endoscopic Resection (Source: [13]).*

Conclusion

Currently, mucosectomies are preferred when compared to esophagectomies, due to the lower number of surgical and postoperative complications; the results are very similar for high-grade lesions and carcinoma in situ. New mucosectomy techniques are being developed with very promising results, such as en bloc resection of the submucosa. Endoscopic dissection of the sub-mucosa offers a higher cure rate and better histological evaluation than endoscopic resection of the mucosa. Rates of post-surgical stenosis are improving due to modern techniques to prevent narrowing of the esophagus such as dilation sessions, powdered hemostatics to promote epithelial reepithelization or amniotic membrane graft, widely used in ophthalmology today.

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