Endoscopic treatment of Barrett's esophagus: why is it indicated?

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INTRODUCTION

Barrett's Esophagus (BE) is a change of the epithelium of the distal esophagus, of any extension, that can be recognized as columnar epithelium in an intestinal endoscopy and which can confirmed as intestinal metaplasia in a biopsy (1). BE is recognized as the principal risk factor for the development of esophageal adenocarcinoma. Its prevalence has been progressively increasing in the United States (1).

The diagnosis of high grade dysplasia and early cancer in patients with BE is not an easy task with conventional video endoscopy. The surface of the mucosa must be analyzed in detail. When irregularities such as discreet elevations or depressions of the mucosa or alterations in the coloration of epithelium are present, we must proceed with multiple biopsies. Currently, endoscopic monitoring of BE is performed according to the Seattle protocol. A series of biopsies is taken from the columnar epithelium, one from each quadrant, each measuring 1 to 2 cms (1, 2).

An esophagectomy is the only therapy that offers the security of removing all of the neoplastic epithelium. However, this treatment has the highest morbidity and mortality rates. With evidence of low incidence rates of ganglionary metastasis in tumors limited to the mucosa (3, 4), and with the development of new endoscopic techniques, endoluminal therapy has gained increasing acceptance for the initial approach to patients with high grade dysplasias or early tumors.

Endoscopic therapy for the treatment of BE can be divided into ablation procedures and resection procedures.

Ablation procedures include the use of multipolar electrocoagulation, Nd:YAG (neodymium-doped yttrium aluminum garnet) lasers, radio frequency, photodynamic therapy and cauterization with Argon Plasma. These use thermal or photochemical energy or radio frequency to ablate abnormal BE. After the ablation patients are maintained on high doses of proton pump inhibitors to help healing through the growth of squamous epithelium. These methods have two important limitations. The first is that they do not provide specimens for pathological tests required for staging of this illness. The second is that the damage caused by ablation is limited to the superficial mucosa. This leaves islands of columnar epithelium, or tumor nests, located below the epithelium even after the epithelium of the distal esophagus recovers through the growth of squamous epithelium. Such areas are not susceptible to endoscopic monitoring, and reports of neoplasia in this epithelium are not rare (5-9).

Among the resection procedures we find mucosectomy (either with the aid of a treatment hood or by submucosal injection), elastic band ligation of the following section of the esophagus, and, more recently, endoscopic submucosal dissection (ESD). Resection procedures provide specimens which allow for suitable histological analysis. Nevertheless, in patients with a long length of BE the resection of the complete injury is not always possible.

ABLATION PROCEDURES

Photodynamic Therapy (PDT)

Photodynamic therapy is based on the capacity of some photosensitizing agents to produce tissular damage when stimulated by a specific wavelength of luminous energy. In the case of BE, the active substance causes cellular damage and destruction of the columnar epithelium. When associated with antireflux therapy, recovery of the squamous epithelium is possible.

Porfimer Sodium (Photofrin®) is the most widely used photosensitizer in the USA, and is the only one approved by the FDA (Federal Drug Administration). After intravenous administration this agent is absorbed by most of the tissues of the body, but principally by the neoplastic tissues which, for unknown reasons, absorb this substance more readily than do other tissues (10). Porfimer Sodium does not only accumulate in the mucosa but also in deeper tissues of the esophageal wall. This can increase the efficiency of the treatment. (11). Nevertheless, it shows a high incidence of collateral effects such as fever and thoracic pain, but principally esophageal stenosis (up to 36%) (12). The patient should avoid prolonged exposure to the sunlight for up to 4 weeks after the injection because the photosensitizer can remain in the skin for as long as 30 days.

5-aminolevulinic acid (5-ALA) is a widely used photosensitizing agent in Europe which can be administered orally. 5-ALA shows great affinity for the epithelial tissue, thus decreasing the damage to deeper tissues (11) and therefore decreasing complications such as perforation and stenosis. In addition it remains photosensitive in the skin for only 24 to 48 hours.

A laser is used in endoscopy to activate the photosensitizing agent. Applied through a catheter, its application requires almost 30 minutes per 6-7cm segment.

In an international randomized multicentric study (12) photodynamic therapy performed with porfimer sodium while reflux was inhibited with omeprazole was compared to the use of only omeprazole in 208 patients with BE who had high grade dysplasias. The high grade dysplasia was eliminated in 77% of the patients treated endoscopically (106/138) compared to only 39% of the proton pump inhibitor group (27/70). Progression to cancer occurred in both groups, but less often in the group subjected to photodynamic therapy (13% vs. 20%). The principal complications related to photodynamic therapy were photosensitivity (69%), esophageal stenosis (36%), vomiting (32%), non-cardiac thoracic pain (20%), fever (20%), dysphagia (19%), constipation (13%), dehydration (12%), nausea (11%) and hiccups (10%).

Ackroyd et al. (13) randomized 36 patients with BE and low grade dysplasias. 18 received photodynamic therapy with 5-ALA with inhibition of reflux using omeprazole while 18 were treated only with omeprazole. 16 of the photodynamic therapy group responded to treatment, with a mean decrease in the extension of the lesions of 30%. Meanwhile the placebo group showed a decrease of 10% in the extension of the lesions in only two patients. Dysplasia was not identified in any patient in the areas treated with photodynamic therapy while it persisted among 12 patients in the placebo group.

In a preliminary study of 32 randomized patients to receive photodynamic therapy with porfimer sodium or 5-ALA, patients who received 5-ALA showed a higher remission of BE with less complications such as stenosis and cutaneous photosensitivity (14).

The long term efficiency of photodynamic therapy has not yet been established. The few studies that exist have contradictory results (15, 16). In a study of 66 patients who have BE with high grade dysplasias (group A) or early cancer (group B) who were treated with photodynamic therapy, Pech et al. (15) showed good control of the disease. 89% of group A, and of 68% of group B, survived for 5 years free of disease and without mortality related to the method or to the tumor. On the other hand, Peters et al. (16) studied 20 patients with high grade dysplasias or residual neoplasia after endoscopic resection, subjecting them to photodynamic therapy. The initial success was observed in 15 patients (75%) and in the 30 months follow-up 4 relapses occurred (26%). The authors concluded that in this group of patients the rate of success of the photodynamic therapy is disappointing, it does not eliminates the metaplastic epithelium (residual in 100% of the cases) and it does not prevent the relapse. The authors advise against photodynamic therapy in this group of patients.

Photodynamic therapy should be seen as an alternative for those patients with high grade dysplasias that show a high surgical risk or reject the surgery, since this therapy can delay but not prevent, the progression to adenocarcinoma (17, 18).

Argon therapy

Argon plasma coagulation (APC) includes the application of a monopolar current taken to the tissue through a flux of

ionized Argon gas, allowing the ablation of the epithelium with limited penetration. It has the advantage of being an easily accessible technique and of easy execution (19).

Although studies show a decrease of BE extension, its full ablation is not always possible. Consequently the risk of residual epithelium under the newly formed squamous epithelium is worrisome, and there have even been reports of malignant transformations in these niches (7-9).

Some authors have suggested the use of greater potency Argon plasma (90W). They have achieved full regression of the columnar metaplasia in 96% to 98.6% of cases without reports of progression to cancer (20-22). However, this strategy is associated with a higher rate of complications such as retrosternal pain (22.5%), dysphagia (5%), fever (17.5%), stenosis (4.3%-9.1%) and perforation (0.7%) (19).

Bright et al. (23) carried out a randomized controlled study of 58 BE patients who had been subjected to surgical fundoplication. Their results were compared with the results of Argon ablation of columnar epithelium. Simple endoscopic surveillance was used to follow-up on these patients for an average of 68 months. Patients with high grade dysplasias were excluded from the study. In the beginning all the patients subjected to ablation with APC achieved regression of at least 95% of the columnar epithelium, which was maintained in 70% of the cases after 5 years. In the later stages of follow-up significant regression of columnar epithelium was observed among both groups. However, the decrease was higher in the APC group (5.9-0.8 cm vs. 4.6-2.2 cm). There were two cases of esophageal stenosis that required dilatation in the APC group, and two patients under endoscopic surveillance developed high grade dysplasia. The authors conclude that APC therapy is promising. Even so, more studies with a higher number of patients and a more prolonged monitoring will be necessary to determinate if there is decreased risk of cancer and longer survival times for these patients.

In our institution we used APC therapy on 19 BE patients who were subjected to video-laparoscopic fundoplication. We observed renewed growth of squamous epithelia in all the cases, with average follow-up times of 17 months. No cases evolved to dysplasia or cancer (24).

In a comparative study of BE treatments, Hage et al. (5) showed one year remission rates of metaplastic epithelium of 67% for APC therapy and 86% for photodynamic therapy using 5-ALA. Islets of columnar epithelium were found under the newly formed squamous epithelia in 50% of the patients subjected to APC therapy and in 4% of the patients treated with photodynamic therapy. Collateral effects such as pain, nausea and fever were more common in patients subjected to photodynamic therapy.

The principal advantages of APC therapy are its easy application, its greater availability, the possibility of ambulatory use, the low rate of complications and the lower price compared to the photodynamic therapy (6).

Its principal disadvantages are the great number of sessions needed and the possibility that focal points of intestinal metaplasia will remain under the newly reformed squamous epithelium.

Radio frequency

Ablation with radiofrequency consists of a system composed of an energy generator and an ablation catheter (HALO system®). There are two types of catheters, a circumferential (HALO 360) usually used in the first session and a focal (HALO 90) used in the following sessions. The generator produces an energy density at a pre-determined radiofrequency (approximately 10 J/cm) which is transmitted through ablation catheter in a pulse that lasts less than 1 second. This destroys the epithelium to a limited depth thus minimizing the risk of stenosis.

Sharma et al. (25) studied this method in 70 BE patients without dysplasias who were monitored for 12 months. They observed complete responses in 70% of the patients with no reports of stenosis or intestinal metaplasia under the recently formed squamous epithelium.

In a multicentric study of 127 BE patients with low and high grade dysplasias radio frequency (84 patients) was compared with a simulated procedure (43 patients) (26). BE completely disappeared in 77.4% of the patients subjected to radiofrequency and in 2.3% of the control patients. The dysplasias completely disappeared in 90.5% of the patients with low grade dysplasia and in 81% of the patients with high grade dysplasia in the group subjected to radiofrequency, versus 22.7% and 19% respectively in the control group. Progression to esophageal cancer was more frequently observed in the control group (9.3%) than in the treated group (1.2%). Three patients subjected to radio frequency presented serious adverse effects: one case of high digestive hemorrhage, one case of thoracic pain and one case of thoracic pain and nausea. Five patients presented esophageal stenosis. There were no serious side effects seen in the control group. Only 5.1% of the patients subjected to radio frequency presented islets of intestinal metaplasia under the new epithelium.

Although radio frequency ablation has been presented as a promising therapy for treatment of BE, more randomized studies with a more prolonged monitoring are still needed to determine the impact on decreasing risks of evolution to dysplasia or cancer.

RESECTION PROCEDURES

There are diverse modalities of endoscopic resection of esophageal lesions. The choice of technique depends a great deal on the characteristics, size and location of the lesion, as well as upon the experience of the endoscopist and the equipment available.

The principal advantage of resections is that fragments are obtained for histological analysis. The resected fragment allows for a better analysis of the grade, size and depth of the dysplasia than do fragments obtained in conventional biopsies. In one study with 75 patients subjected to mucosectomy for endoscopic resection of BE, Moss et al. (27) showed changes in histological classifications of lesions in 48% of the patients after resection.

However, in cases with great extension of BE it is not possible to resect the entire lesion. In these cases the areas with elevated, irregular or depressed visible lesions of the mucous, which might indicate high grade dysplasia or early cancer, are resected. Ablation is applied to the remaining BE (28).

Resection with monofilament loop

Resections with monofilament loops require the least resources (29). The loop is located around the area that is going to be resected. Then it is slowly closed while suction is applied to help fully imprison the lesion which is then resected a coagulation current. If it is necessary, the procedure is repeated to ensure full removal (piecemeal resection). It is not necessary to elevate the lesion with an injection of solution into the mucous.

In a study of twelve patients, Seewald et al (30) achieved the resection of the entire extension of BE in all patients (average extension 5 cm) with this technique. Four patients presented minor bleeding during the procedure and two developed stenoses. In 9 months of follow-up none of the patients presented relapses.

Strip-Biopsy Technique

The strip-biopsy technique consists of applying traction with biopsy forceps to the lesion followed by the resection with a polypectomy loop. It is necessary to use dual channel equipment and to elevate the submucosal lesion with saline solution.

In a study with 21 patients with BE and either high grade dysplasia or early cancer, Giovanini et al. (31) achieved full resections of BE in 18 patients, of whom two presented late relapses. None of the patients developed stenoses.

Endoscopic resection with cap

In Europe, endoscopic resection using a cap is the most frequently used technique for resecting precocious neoplasias associated with BE. First, a solution with adrenaline (1:10.000) is injected into the submucosa to elevate the lesion which will be sucked into a cap connected to the tip of the endoscope. (32). The pseudo-polyp formed is linked to the polypectomy loop and is resected with electrocoagulation.

In a study conducted by Peters et al. (33), endoscopic resection with cap was used for 216 patients. Full resection was possible in all patients: 25% were resected in a single block of tissue, and 75% in several fragments (piecemeal resection). Bleeding occurred immediately in 23% of the cases. These were endoscopically treated with success through the placement of hemoclips, electrocoagulation or sclerotherapy. Two perforations occurred (1%). They were conservatively treated with gastric drainage, antibiotic therapy and endoscopic application of metallic agraffes. It is worth emphasizing that, after the initial endoscopic resection using a cap, 72 patients required ablation of residual columnar epithelium ("stepwise radical endoscopic resection") which contributed to the high rate of "piecemeal" resection.

Elastic band technique

This technique does not need submucosal injections. An elastic ligature system is connected to the end of the endoscope. Then the lesion is sucked into and imprisoned by the elastic band. Afterwards the ligature system is removed and a conventional polypectomy loop is inserted to resect the pseudo-polyp (34).

In order to facilitate the process of ligature and resection, especially for more extensive lesions, the Duette mucosectomy system (Cook Ireland Ltd) was recently developed. It consists of a system of conventional elastic ligature which allows the insertion of the polypectomy loop through a catheter for injections of colorants so that there is no need to remove and disassemble the endoscope to use the technique (35).

May et al. (36) carried out a prospective randomized study of 72 patients with early esophageal cancer which compared endoscopic resection with cap and submucosal injections to the system of ligature without submucosal injections. No significant differences were observed between the groups regarding the size of the specimen removed (ligature 164x11mm vs. Cap 15.5 x10, 7mm). There was only one report of bleeding in each group. Both were

endoscopically controlled. There were no important complications.

Endoscopic Submucosal Dissection (ESD)

The endoscopic submucosal dissection is the most recently developed technique for resection of gastrointestinal tumors. Widely used in Japan, this method allows for higher rates of resection in only one block with similar complications rates to endoscopic mucosal resection (EMR). However, to master this technique it is necessary to have a long learning curve. This has limited its use in western centers, where detection of early tumors is lower. Due to the low incidence of BE in Japan the use of ESD in these cases is still limited.

Yoshinaga et al. (37) retrospectively analyzed 24 patients with esophagogastric junction tumors who underwent a total of 25 ESDs between 2001 and 2006 in the Hospital of the National Cancer Center in Tokyo. Resection in a single block was possible in all cases (100%). The only complication was stenosis, which occurred in two cases (8%) and was treated through endoscopic dilatation. Therapeutic resections (defined as lateral and deep resections with borders free of lesions, without submucosal invasion greater than 500 micrometers, and without vascular or lymphatic invasion) were possible in 18 cases (72%). They presented no local relapses or metastases, and average follow-up time was 30.6 months. Seven lesions were classified as incurable. Two patients were subjected to surgical resection. No residual tumor was found in the resected piece removed from one of them. A patient with a deeply compromised border who rejected surgery presented pulmonary metastasis after 3 years.

Conclusion

When facing a lesion macroscopically indicative of malignant degeneration in a patient with Barrett's esophagus, endoscopic resection is suitable for diagnostic purposes (diagnostic macrobiopsy) if conventional biopsies are not conclusive. On the other hand, when faced with short and non-circumferential Barrett's esophagus with a low or high grade dysplasia, we support the use of endoscopic resection of all of the metaplastic area since this provides material for definitive histological study without risk of stenosis. Finally, for large metaplasias (>3 cm) of circumferential extension and with a high grade dysplasia, we think that esophagectomy is a suitable point of reference if the patient has the clinical conditions to endure such procedure. Otherwise, radiofrequency ablation is a promising treatment in this situation. It should be emphasized that this is a method not yet available in our environment. As a result, when confronted with this type of patient (with precarious clinical conditions, long circumferential Barrett's Esophagus, and high grade dysplasia), our tendency is to diagnose the condition with optical chromoendoscopy (e.g. narrow band imaging) and magnification, then endoscopically resect the area of dysplasia/superficial neoplasia, and follow up with endoscopic monitoring (also with optical chromoendoscopy and magnification) for the residual metaplastic segment.

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