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REVIEW

Barrett's esophagus with high-grade dysplasia: Focus on current treatment options

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Abstract

High-grade dysplasia (HGD) in Barrett's esophagus (BE) is the critical step before invasive esophageal adenocarcinoma. Although its natural history remains unclear, an aggressive therapeutic approach is usually indicated. Esophagectomy represents the only treatment able to reliably eradicate the neoplastic epithelium. In healthy patients with reasonable life expectancy, vagal-sparing esophagectomy, with associated low mortality and low early and late postoperative morbidity, is considered the treatment of choice for BE with HGD. Patients unfit for surgery should be managed in a less aggressive manner, using endoscopic ablation or endoscopic mucosal resection of the entire BE segment, followed by lifelong surveillance. Patients eligible for surgery who present with a long BE segment, multifocal dysplastic lesions, severe reflux symptoms, a large fixed hiatal hernia or dysphagia comprise a challenging group with regard to the appropriate treatment, either surgical or endoscopic.

INTRODUCTION

In the era of minimally invasive therapies, numerous treatment options for Barrett's esophagus (BE) with high-grade dysplasia (HGD) are available. Nevertheless, since therapy is individualized, the standard of care remains debatable for a large number of patients without clear-cut guidelines. The aim of this review is to briefly present and compare current therapeutic modalities with an emphasis on endoscopic approach, outline factors that can aid in the choice of the appropriate treatment (medical, endoscopic or surgical) and underline the lack of a properly designed study so far that compares the outcomes of these therapies.

BE is the result of chronic gastroesophageal reflux disease (GERD) and represents the end stage of the natural course of this disease. It has been estimated that 20% of the population in the United States suffers from gastroesophageal reflux[1] and that about 10% of

these patients are diagnosed with BE[2]. Commonly, BE is discovered during endoscopy for the evaluation of GERD symptoms. The severity of GERD symptoms is not considered an indicator of BE presence, whereas the chronicity of GERD symptoms may be related to the possibility of BE transformation[3]. It is documented that longstanding exposure of esophageal mucosa to gastric acidity results in cellular damage of the stratified squamous epithelium and creates an abnormal environment, which stimulates repair in the form of intestinal epithelial metaplasia[4,5]. Moreover, BE is related to a serious mechanical insufficiency of the lower esophageal sphincter, a functional derangement of the esophageal body, as well as an insufficient esophageal clearance[6-8].

In BE it is possible to encounter three histologic types of columnar epithelium: (1) the specialized intestinal metaplasia type, in which the epithelium exhibits a villous surface and intestinal-type crypts lined by columnar cells that secrete mucous and goblet cells containing mucin; (2) the gastric fundus epithelial type; and (3) the junctional type. Among these three histological types, only the intestinal type represents an important premalignant state.

In BE, the stratified squamous epithelium, which physiologically lines the esophageal mucosa, is replaced by a pathological, specialized columnar epithelium which is neither of cardiac nor of stomach type, but exhibits features of the intestinal type of epithelium[4]. This pathological type of epithelium usually demonstrates DNA alterations that predispose to malignancy[2,9,10]. The alterations in BE are histologically classified into three categories, depending on whether or not they exhibit dysplasia: (1) BE without dysplasia; (2) BE with low-grade dysplasia; and (3) BE with HGD[11-13]. In BE with HGD, dysplasia is confined to the mucosa without crossing the basement membrane. If dysplasia extends beyond the basement membrane into the lamina propria through the in-coming lymphatic network, it is defined as intramucosal (superficial) adenocarcinoma, whereas if it invades the muscularis mucosa layer it becomes invasive adenocarcinoma. Thus, BE with HGD is considered a precursor of invasive adenocarcinoma. Six to twenty percent of patients with BE and HGD are at greatest risk of developing adenocarcinoma within a short period of time, ranging from 17 to 35 mo at follow-up[14]. Esophagectomy specimens from patients with BE and HGD revealed invasive adenocarcinoma in 30%-40% of cases[15]. A recent meta-analysis demonstrated that patients with BE and HGD developed esophageal adenocarcinoma with an average incidence of 6 every 100 patients per year, during the first 1.5 to 7 years of endoscopic surveillance[16]. Furthermore, the majority of esophageal adenocarcinoma is thought to have evolved from cells that have undergone Barrett's metaplasia[17].

BE is also classified into two categories according to the extent of intestinal metaplasia above the gastroesophageal junction: (1) long segment BE, if the extent of the intestinal epithelium is greater than 3 cm; and (2) short segment BE, if it is less than 3 cm[18]. Among patients who undergo endoscopy for symptoms of GERD, the incidence of long segment BE is 3%-5%, whereas short segment BE occurs in 10%-15%[4]. Whether long and short segment BE share the same pathogenetic alterations or the same predisposition to malignancy still remains unclear; however, both conditions are currently treated in the same manner[19].

ENDOSCOPIC SURVEILLANCE IN PATIENTS WITH BE

Concerning the therapeutic management of BE, endoscopic follow-up of the patient at regular intervals, so-called endoscopic surveillance, plays a pivotal role. There is great difference of opinion when dealing with the problems of therapeutic management of BE. The value of endoscopic surveillance in patients with BE represents one of the many controversies that exist amongst gastroenterologists.

As aforementioned, BE represents a strong risk factor for developing adenocarcinoma, which is a particularly lethal malignancy[19]. In order to diminish the risk of cancer development, the American College of Gastroenterology introduced the application of a surveillance protocol that is, in summary, as follows[20]: (1) patients who are diagnosed with BE at two consecutive endoscopies should undergo endoscopy every 3 years; (2) if Barrett's dysplasia is diagnosed, it should be confirmed by a second specialized pathologist; (3) patients who are definitely diagnosed with low-grade dysplasia after examination of sufficient biopsy specimen should undergo endoscopic surveillance every year; (4) patients diagnosed with HGD should undergo a new endoscopy with a second adequate biopsy specimen, to check the possible presence of invasive cancer; (5) if the results are positive, the biopsy specimen should be examined by a second specialized pathologist; and (6) if multiple HGD foci are confirmed, then the patient should undergo either surgical therapy (esophagectomy) or endoscopic surveillance every 3 mo.

This protocol, concerning high-risk patients, is considered strict in various aspects. Many authors believe that surveillance is not justified in a cost-effectiveness analysis[21-23]. Others compare endoscopic surveillance of patients with BE with the endoscopic follow-up of patients with ulcerative colitis for early detection of malignancy or mammography for early diagnosis of breast cancer and conclude that the former is lacking, in terms of cost-effectiveness, compared to the other two[24,25].

Furthermore, many studies have shown that the survival of patients with BE is not different from that of the general population[26]. This observation, as paradoxical as it may appear, can be explained by the low absolute number of adenocarcinoma cases in patients with BE[19]. Current data demonstrate that patients with BE develop adenocarcinoma at a low rate of 0.5% which is, nevertheless, 30-40 times higher than that of the general population[27,28]. The subgroup of patients with BE and HGD

develop esophageal adenocarcinoma at a higher rate of 6.58 per 100 patient-years, as shown in a recent meta-analysis[16]. Moreover, survival studies in patients with BE primarily include elderly individuals, for whom the risk of death from other lethal co-morbid conditions is much higher than the annual 0.5% risk of death from esophageal adenocarcinoma[29]. Apart from the above, a long-term prospective study involving young patients with BE demonstrating a decreased life span in these patients has not yet been published[19].

Concerning the endoscopic surveillance of patients with BE, this is not a risk-free procedure. It is estimated that the risk of development of adenocarcinoma is one in every 200 or 300 patients with BE, whereas the risk of a major complication from an endoscopic procedure is one in 1000 esophagogastroscopies[28-30]. The program of the American College of Gastroenterology also differs from that of the British Society of Gastroenterology[31] and the NHS Technology Review[32] in the value of endoscopic surveillance as a screening tool. Despite the previously mentioned contradictory views, many authors indicate a benefit of endoscopic surveillance in cost-effectiveness analyses for the early diagnosis of cancer[33-36].

CURRENT MANAGEMENT OF BE WITH HGD

Controversy is also perpetuating between surgeons and gastroenterologists. BE with HGD carries a high risk of developing esophageal adenocarcinoma, at a rate of 6%-20%, within a short period of time (17-35 mo)[14,16]. Therefore, in the presence of such risk, the traditional standard therapy was en bloc esophagectomy with regional lymph node dissection. This approach has been supported by the fact that invasive adenocarcinoma was previously diagnosed in patients with HGD at a rate of 30%-40%[15], although more recent data have revealed a significantly lower incidence (12%)[27]. Nevertheless, en bloc esophagectomy carries a high mortality (4%-19%)[37], high postoperative morbidity (20%-47%)[38] and unacceptable late postoperative quality of life[39].

During the last few years, while surgeons try to improve their surgical technique and the results of esophageal resection (esophagectomy without lymph node dissection and/or without thoracotomy, esophagectomy with vagal preservation or laparoscopic esophagectomy), endoscopists have been developing minimally invasive therapeutic methods for the management of BE with HGD. It should be noted that the problem of GERD persists with these endoscopic methods and endoscopic surveillance is necessary for all endoscopic treatment options.

Management of gastroesophageal reflux disease

The therapeutic goal in patients with BE is similar to that of patients with GERD, i.e., relief of symptoms and reversal of the epithelial damage caused by increasing gastric reflux. In cases of BE with HGD, the question is whether medical or surgical management of GERD can have beneficial effects on the dysplastic lesions. Therefore, the following questions come into play:

Can either surgical or medical antireflux therapy achieve regression of the epithelium in BE?

Evidence clearly indicates that medical therapy of GERD does not lead to acceptable results, with regard to the regression of dysplastic epithelial lesions[40]. Surgical therapy may have better results than conservative therapy in terms of regression, but is far from being considered adequate. In a series of five publications that included 151 patients submitted to surgical management of gastroesophageal reflux (fundoplication), surgical therapy achieved full regression of these lesions in 6 patients only, whereas in 31 patients only a decrease in the length of BE lesions was observed and 6 patients developed invasive adenocarcinoma. Furthermore, other published data corroborate that antireflux surgery does not decrease the rate of adenocarcinoma in patients with gastroesophageal reflux[41-43]. Data from the subgroup of patients with BE are also conflicting and pose an unsettled issue[44].

Does antireflux surgery prevent the metaplastic evolution of the mucosa in BE?

Evidence suggests that surgery is superior to conservative therapy as it can abolish, at high rates, the progression of metaplastic mucosal lesions in BE[45,46] and therefore protect from dysplasia and malignancy. On the other hand, systematic review indicates that antireflux surgery in patients with BE is associated with regression of BE lesions and/or dysplasia, but evidence supporting the assertion that surgery decreases the rate of adenocarcinoma comes from non-controlled studies[47]. In a study from the Mayo Clinic in 118 patients who underwent antireflux surgery and follow-up for 18.5 years, it was stated that only 3 patients developed adenocarcinoma within the first three years postoperatively[48]. This outcome suggested that the lesion probably existed during the operation[49,50]. Encouraging data come from patients with low-grade dysplastic mucosa and antireflux surgery who, at endoscopic surveillance, showed conversion from a dysplastic to a non-dysplastic mucosa at a rate of about 70%[51]. Concerning the endoscopic antireflux interventions (Stretta procedure, Bard EndoCinch, Wilson-Cook Endoscopic Suturing Device, NDO Plicator, Enteryx, Gatekeeper Reflux Repair System and Plexiglas), these are currently under evaluation and evidence is lacking to support their role in the therapy of BE with HGD[52].

Should antireflux therapy accompany other treatment modalities when confronting metaplasia or dysplasia of BE epithelium?

The combination of medical or surgical antireflux therapy with endoscopic mucosal ablation has yielded promising results[53,54]. These early observations concluded that the resected mucosa undergoes re-epithelialization by normal squamous epithelium and is preserved with the aid of antireflux therapy; usually proton pump inhibitors. Further research is nevertheless needed in this field.

Endoscopic treatment of BE with HGD

It is documented that BE with HGD or intramucosal adenocarcinoma constitute diseases amenable to cure in most cases. Data from high volume centers of esophageal surgery have indicated rare lymph node metastasis, ranging in incidence between 2%-6%[36,49,55,56]. Newer, less invasive treatment modalities such as endoscopic therapies or less aggressive surgical operations are currently being evaluated in an effort to achieve the least postoperative morbidity and the best quality of life.

Current endoscopic methods include two major therapeutic categories: (1) endoscopic ablation of Barrett's mucosa that can be achieved by thermal, photodynamic and/or radiofrequency energy; and (2) endoscopic mucosal resection.

Thermal therapy

In methods implementing thermal energy, the endoscopic elimination or destruction of the diseased superficial esophageal mucosa is achieved by the administration of heat with one of the following specialized devices: (1) electrocoagulation; (2) argon plasma coagulation (APC); (3) heat probe; and (4) Nd: neodymium-doped yttrium aluminium garnet laser. Another version of thermal therapy consists of cryospray ablation, but experience with this method is limited[57].

The more widely used first two methods of thermal therapy, probably due to greater availability in endoscopy units, provoke a superficial mucosal injury with a low rate of serious complications. APC has been evaluated at twelve independent centers in 444 patients with BE, making this technique by far the most commonly applied method[55]. However, the significant variation in the regression of intestinal metaplasia and the formation of new squamous epithelium, together with the complications of this method, resulted in dismissal of APC as the method of choice[55]. In published series, full regression of BE has ranged from 36%[58] up to 98%[59] in an average time frame of 36 and 12 mo, respectively.

Two studies have focused on the effect of APC on intestinal metaplasia in association with the amount of administered energy. In one, no recurrence of BE was noted, while in the other, recurrent disease occurred in 30% of cases. It is noted that in the patients of the first study (n = 70) a higher energy device (90 W) was utilized and higher doses of omeprazole (40 mg three times a day) were administered. In 69 patients (98.6%) complete BE eradication with associated squamous regeneration was achieved after a median of two APC sessions (range 1-5). During a median follow-up of 12 mo (range 2-51 mo) with continuous acid suppression, no case of dysplasia relapse was noted. Of these patients, only 3 developed stenosis (4.3%), for whom dilatation was advocated for therapy[59]. In the second study, where low energy was administered in 27 patients, 70% showed regeneration of squamous epithelium with no persistent intestinal metaplasia and in 30%, areas of intestinal metaplasia were present under the new squamous epithelium, after a median follow-up of 9 mo (range 6-18 mo). Overall, two cases of perforation were reported, one of which was fatal[60]. In a third study of 33 patients treated with APC energy between 65 W and 70 W and 60 mg omeprazole daily, complete restoration of the normal squamous epithelium was noted in all cases after 1.96 sessions (range 1-4). Esophageal stenosis occurred in 3 patients, for whom dilatation was deemed necessary, 5 patients developed mediastinal syndrome (high fever and pleural effusion) and one patient pneumomediastinum. After a follow-up period of 10.6 mo, only one recurrence of BE was observed[61]. Accordingly, the amount of energy administered with APC seems to be directly related to the recurrence rate of BE, favoring the use of high energy devices for a median follow-up of 9 to 12 mo, although data for long-term effectiveness are still lacking. It should be stated that the emergence of APC-related complications depends not only on the amount of energy, but also on other parameters such as mucosal contact at different pressures and repetitive therapy in the same area[55].

Photodynamic therapy

Photodynamic therapy requires previous administration of a photosensitizer and selection of a specific wavelength of light that stimulates a specific target area or the whole of BE. As a result, singlet oxygen is formed that causes damage to the esophageal mucosa. 5-aminolevulineic acid (5-ALA) is an oral photosensitizing agent that incites severe superficial injury in the patients with HGD and superficial cancer. In the United States, intravenous porfimer sodium, which causes deeper injury, is used. Overholt *et al*[62] applied a technique of introducing a cylindrical inflatable balloon through which light was administered in 101 patients with HGD. After a follow-up of at least 4 years, the analysis of the therapeutic effect showed that in 54% of cases there were no residual BE lesions. Successful eradication of low- or high-grade dysplasia or cancer reached 93%, 78% and 48%, respectively. It is thus suggested that HGD and cancer exhibit the greatest resistance to therapy. The total rate of stenosis reached 30%, reflecting the effect of this therapy in deeper esophageal layers.

Great value to this type of therapy is attributed by a large multicentric, semi-blinded, randomized study by Overholt *et al*[62] in 208 patients with HGD. Patients were randomly divided, in a 2:1 ratio, into a study group treated with photodynamic therapy and omeprazole and a control group receiving only omeprazole. A statistically significant difference ($P < 0.0001$) regarding the complete eradication of HGD was noted in favor of photodynamic therapy (106/158, 77%), compared to the control group (27/70, 39%). The therapeutic response persisted even after 5 years of follow-up. It should be noted that endoscopic ablation was combined with a long-term follow-up and was, thus, more costly. Nevertheless, this approach has proved to be a better treatment option in terms of cost-effectiveness, compared to the standard follow-up and radical surgery for the treatment

of dysplasia, although clinical trials directly comparing these strategies are warranted[63]. Additionally, esophagectomy provided 11.82 quality adjusted life years (QUALYs) compared to photodynamic therapy with 12.31 QUALYs and long-term follow-up[63]. Furthermore, anecdotal time-life analysis of several cases has revealed that many patients with HGD and even early cancer could be controlled with ablative techniques and careful follow-up for 5-10 years[39].

Radiofrequency energy ablation

This method is a novel therapeutic approach employing (1) energy emitted from a controlled radiofrequency (RF) source [Halo360 or Halo90 RFA (where A stands for ablation), BARRX Medical Inc, Sunnydale, CA]; (2) a sizer balloon catheter, that is introduced into the esophagus and measures esophageal width; and (3) an EFA balloon catheter. The controller of the RFA source is preset to deliver energy of 12 J/cm^2 which causes complete destruction beyond the lamina propria[64]. The RFA balloon is 3 cm long and consists of 60 narrowly spaced electrode rings in a bipolar fashion. After the esophageal diameter is measured by the sizer balloon, the RFA balloon catheter is introduced in the esophagus and placed in its position. The balloon is then inflated and the RFA source releases energy circumferentially on the esophageal surface for 300 ms. The whole procedure is performed under general anesthesia[65].

The use of radiofrequency for the ablation of the dysplastic epithelium in BE is more effective, posing less risk for damage beyond the desired limits, while also controlling the depth of the damage[66]. In contrast to photodynamic therapy, radiofrequency mucosal ablation is not associated either with the development of esophageal strictures or with recurrent disease resulting from buried Barrett's glands. According to current opinion, the development of strictures after photodynamic or thermal therapy has been attributed to the circumferential destruction of the mucosa. Despite the fact that during RFA therapy destruction is also circumferential, no strictures are observed, as a result of better control of the depth of ablation attained by this method[65,66]. In order to safely evaluate this method and its long-term effects, studies with larger series, longer duration of follow-up and endoscopic surveillance are expected, so as to document the recurrent dysplasia-free interval.

Recently, endoscopic radiofrequency ablation was evaluated in a study as the definitive treatment of 25 patients with ultralong-segment (≥ 8 cm) BE, using balloon- and/or plate-based devices (BARRX Medical Inc., Sunnydale, CA). Complications for all 25 patients included hemorrhage in one, stricture in two, and nausea and vomiting in two cases. The time from the initial procedure was such that 15 patients underwent at least one post-ablation biopsy. One patient was elected to undergo esophagectomy based on biopsies. Of these patients, 78.5% (11/14) had a complete response. The number of ablations in this group was 2-3 (median 2.5). The authors concluded that the method is safe and feasible in patients with ultralong-segment BE and can be applied to the entire length of intestinal metaplasia during one session[67]. Radiofrequency ablation has also been recommended as a single-modality therapy for flat type mucosa, or as a supplementary therapy after endoscopic resection of visible lesions. The treatment protocol consists of initial circumferential ablation, using a balloon-based electrode, followed by focal ablation of residual Barrett's epithelium. The authors believe that radiofrequency is less frequently associated with stenosis and buried glandular mucosa, in contrast to other ablation techniques. This method has been shown to be safe and effective in the treatment of patients with BE and early cancer[68].

Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) with a curative intent, beyond the scope of mucosal resection for biopsy, is being investigated more than any other endoscopic method for the treatment of HGD in BE. Since the first publication in 2000[69], several other similar reports have emerged in the United States as well as in Europe[56,70-76].

The landmark study by Ell *et al*[69] included 35 low-risk patients with superficial cancer and well or moderately differentiated BE less than 2 cm in diameter who underwent EMR. With an average of 1.3 interventions and an average follow-up time of 1 year, complete regression was observed at a rate of 97% and local recurrence or metachronous cancer at a rate of 17%, with only one case of hemorrhage that was controlled endoscopically. In another study, a group of 70 patients with HGD or early cancer similarly underwent EMR, with an average follow-up interval of 34 mo, and demonstrated regression of lesions in 98% of cases, with a complication rate of 9.5%. Metachronous or recurrent disease occurred in 30% of cases[77].

EMR has demonstrated satisfactory rates of complete regression; up to 82.5% in 550 patients with HGD or Barrett carcinoma, at an average follow-up interval of 12 mo. The best results were documented in patients with HGD and small (< 20 mm), well or moderately differentiated Barrett carcinomas, at a rate of 97%[78]. Recently, in a retrospective, single center study from the University of Chicago, 49 patients, 33 with high-grade dysplasia and 16 with early carcinoma, underwent complete Barrett's eradication with the aid of EMR. The rate of stenosis was significant, but it resolved easily with endoscopic dilatation. The authors noticed the presence of Barrett's epithelium underneath the squamous resection margin (Z line) in 13 of 47 patients (28%) at initial mucosectomy. Based on their findings and surveillance biopsies, they concluded that ablative therapy should extend to 1 cm proximal to the endoscopically determined squamocolumnar junction. They also concluded that EMR, with close endoscopic surveillance, is an effective treatment modality for BE with HGD and intramucosal carcinoma[79]. Another recent study, originating from two Australian academic hospitals, involved 75 patients; 89% with Barrett's HGD

and 11% with early esophageal cancer, who were treated by EMR over a 7-year period. The treatment resulted in complete Barrett's excision in 94% of cases with short segment BE. During the mean follow-up of 31 mo (range, 3-89) there was no recurrence although 11% developed metachronous lesions. Five patients underwent esophagectomy because the endoscopic resection specimen demonstrated submucosal invasion. The complications were one aspiration and six strictures, which were managed with endoscopic dilatation. This study concluded that EMR alters histological grade or local T stage in 48% of patients and dramatically reduces esophagectomy rate, thus providing a safe and effective therapy[80].

The development of EMR allows full eradication of the neoplastic mucosal lesions and simultaneous accurate staging. Nevertheless, the greatest value of this method is focused on the ability to detect a metachronous lesion, in 50% of cases, in the residual portion of BE. From a therapeutic approach, EMR is promising but has been associated with persistent HGD, persistent Barrett's epithelium and serious recurrence rates of dysplasia or neoplasia in the residual Barrett's epithelium, thus necessitating endoscopic surveillance after resection. It is, therefore, obligatory to completely extirpate intestinal metaplasia at its whole extent, a target that can be accomplished with the combination of EMR with other therapeutic modalities. Combinations of EMR and photodynamic therapy with porfimer sodium, 5-ALA, or meta-tetrahydroxyphenylchlorine[73,76,77] have been applied in selected patients and have yielded successful results with regard to the eradication of dysplastic lesions[55].

Another novel therapeutic approach with the intent to eliminate local recurrence involves the use of circumferential mucosal resection with complete excision of the visible Barrett's epithelium[81]. High success rates in eradication of Barrett's epithelium with a low rate of complications have been demonstrated[82,83]. These findings suggest that this method could be beneficial for all patients with BE and HGD or intramucosal cancer. Larghi *et al*[84] have used the technique of cylindrical mucosal excision in 26 patients with BE and HGD as a way to achieve complete excision of Barrett's mucosa. The technique utilized either endoscopic cap suction or endoscopic snare mucosectomy or a combination of both methods. The method of endoscopic cap suction was applied as previously described[80,84], with the aid of commercially available kits (K001 and K002, Olympus America Inc.). The method of endoscopic snare mucosectomy was performed in the way described by Soehendra *et al*[85], in which a single-channel therapeutic endoscope (type GIF-IT, Olympus America Inc.) and a single-channel mucosectomy snare (type D3422161 M-C, Endo-Flex GmbH, Voerde, Germany) were used. From the follow-up of 23 patients over an average period of 28 mo, complete eradication of lesions occurred in 21 patients (87.5%), whereas in one patient Barrett's epithelium developed underneath the neo-squamous epithelium three mo after excision, and in another an HGD nodule was detected and excised at twelve mo during follow-up. Finally, many authors appreciate this method owing to its high therapeutic yield, but also stress the need for additional larger cohort studies, with longer duration of follow-up and endoscopic surveillance, in order to deduce definitive conclusions. It is also suggested that new equipment will aid in the en bloc resection and possibly prove more effective in completely excising the mucosa along with eliminating the possibility of residual Barrett's epithelium. Improvement in the skills needed to perform such techniques with optimal results is expected to accompany technological advances[84,86,87].

CHOICE OF THERAPEUTIC APPROACH

The classical therapy of BE with HGD has been based on the well renowned, *en bloc* esophagectomy with thoracotomy, vagotomy and lymph node dissection; an operation that, as already mentioned, carries high perioperative mortality, morbidity and a poor quality of life. Considering these disadvantages, many patients are considered unfit for such an operation, whereas others fail to accept it as an option. Additionally, studies from high volume centers in esophageal surgery have demonstrated rare lymph node metastasis, in the region of about 5%, rendering lymph node dissection unnecessary[36,88,89]. The above data have led surgeons as well as gastroenterologists to in-depth research regarding less invasive endoscopic procedures and operations with decreased mortality, morbidity and an acceptable quality of life, such as laparoscopic vagal-sparing esophagectomy. However, the decision for the appropriate therapeutic approach is often difficult and currently there is considerable controversy over which method is better, i.e., surgery or endotherapy (techniques involving endoscopy). Nevertheless, it must be noticed that a number of other parameters may affect the choice of the therapeutic method.

The histopathological diagnosis of HGD, or even the distinction between low- and high-grade dysplasia, remains alarmingly subjective. The kappa values for intra-observer and inter-observer variability are 0.64 and 0.45[90] and the accordance for the diagnosis of dysplasia attains a rate of 94% and 88%, respectively. Furthermore, agreement between specialized and non-specialized pathologists as to the definition and the histopathological characteristics of HGD exists in only 50% of cases[88]. When the need to distinguish HGD from intramucosal carcinoma arises, agreement is even poorer. It is also common knowledge that the natural course of dysplasia differs from patient to patient. Thus, some researchers announce cancer development in 60% of patients at 8 mo, while others report a cumulative cancer rate of 9% at 5 years and only 16% over a 15.9-year period, as documented by endoscopic surveillance[91].

The presence of esophageal cancer in BE represents yet another diagnostic problem. With meticulous examination of esophagectomy specimens in an effort to detect invasion through the submucosal layer, the kappa values for intra-observer and inter-observer variability

are 0.56 and 0.42, respectively[92]. There is also significant discrepancy between the prevalence of carcinoma in esophagectomy specimens of patients who are operated for HGD (0% up to 75%)[93-95] and that of invasive adenocarcinoma in patients with HGD who are under endoscopic surveillance (16% up to 60%)[88,93,95]. Further disagreement exists as to the presence of occult cancer in patients with BE and HGD. Cameron *et al*[94] histologically mapped esophagectomy specimens from patients operated for early adenocarcinoma and depicted areas with occult cancer that are extremely small and can easily evade attention.

Obviously, current data are not sufficient to dictate clear-cut therapeutic indications for this specific patient population. The question in doubt is whether to choose endoscopic therapy, particularly EMR, over esophagectomy. Nevertheless, this does not apply to patients who reject surgical intervention or are considered unfit to undergo a major operation. The therapeutic indication for these patients is limited to the choice of an appropriate endoscopic method. Additionally, it must be pointed out that endoscopic therapy should probably be precluded for a group of patients with BE and HGD who are young (about 55 years old), otherwise healthy without significant co-morbidities, with a high risk of developing invasive adenocarcinoma[95]. Therefore, the selection of the appropriate treatment is questionable for older patients who are eligible for esophagectomy.

Proponents of endoscopic treatment, even in the absence of comparative studies between surgical units and endoscopic departments, advocate that endoscopic therapy carries lower morbidity and mortality than esophagectomy. They also raise the argument that the FDA has already approved porfimer sodium for the photodynamic eradication of premalignant lesions in patients with BE who do not undergo esophageal resection. It seems that even technology works in favor of the endoscopic therapy argument. Recently, in the field of optical spectroscopy, a technique that allows detection of molecular degeneration and minute dysplastic alterations in real time was developed. This technique is expected to allow simultaneous detection and destruction in a single endoscopic session[79,80].

On the other hand, surgeons argue that the patient is subject to the risk of being lost during the follow-up with endoscopic surveillance and may reappear later with inoperable disease. Moreover, the techniques of endoscopic destruction of the lesion may not provide adequate samples for histological examination. At EMR, residual foci of dysplastic cells remain deeper in the regenerated squamous epithelium; however, HGD is often multifocal and early reports of endoscopic excision have documented an unacceptably high rate of positive excision margins. The majority of studies evaluating endoscopic treatment of BE with HGD were neither randomized nor controlled, included small numbers of patients and the duration of follow-up was relatively short, thus unreliable for extraction of safe conclusions. From a surgeon's point of view, before choosing a therapeutic approach, the severity of GERD as well as the gravity of symptoms should be taken into account. Thus, avoiding esophagectomy and implementing an endoscopic therapy should be considered for patients with few symptoms, normal esophageal function and short segment BE, with associated low risk of intramucosal cancer. Accordingly, esophagectomy is reserved for patients with BE and HGD or intramucosal cancer who present with severe symptoms of GERD or dysphagia, long segment BE, a large hiatal hernia and poor function of esophageal body[96].

Currently, the optimal therapy of BE with HGD is, at best, controversial, despite the vast number of emerging new techniques in the fields of both surgery and endoscopy. No properly designed prospective randomized controlled trial, comparing the various therapeutic modalities, has yet been conducted, rendering the undertaking of such a study mandatory in order to elucidate the ideal therapy[97].

CONCLUSION

The modern era surgeon is confronted with multiple dilemmas concerning the best therapeutic management of patients with BE and HGD, which represents an area of dispute between esophagogastric surgeons and gastroenterologists. The ideal therapy for BE with HGD is further perplexed by the unclear natural history of the disease, the discordance of histopathologic diagnosis and its relation to malignancy, i.e., coexistent disease or subsequent development of esophageal adenocarcinoma. When considering the best therapeutic approach for these patients, multifocality, extent and pretreatment staging of the disease, as well as patient's preference and performance status, should all be taken into account. Therefore, the ideal therapy should be individualized. Many advocate esophagectomy as the gold standard therapy for BE with HGD. Nevertheless, new and emerging minimally invasive, endoscopic and ablative techniques have more recently yielded significant results and gained popularity. Randomized controlled trials are still required to properly define their optimal role in the armamentarium against BE with HGD and current research is expected to lead to the incorporation of these techniques in standard clinical practice.

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