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Review article

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THERAPEUTIC OPTIONS IN PATIENTS WITH BARRETT'S ESOPHAGUS

SUMMARY

Barrett's esophagus (BE) is associated with an increased risk of developing adenocarcinoma. Cancer development is preceded by dysplastic changes. Management strategies for BE are based on a patient's dysplasia status. Advances in endoscopic treatment make early malignancies, for which surgical resection is the only accepted therapy, amenable for minimally invasive endoscopic treatment. Endoscopic mucosal resection (EMR) is a minimally invasive endoscopic technique that can be used in patients with circumscribed mucosal carcinomas. The technique is also useful as a diagnostic procedure by obtaining a full-thickness mucosal specimen for histologic examination. Photodynamic therapy (PDT) using the prodrug 5-aminolevulinic acid, is an ablative therapy that destroys the esophageal mucosa leaving the deeper layers of the esophageal wall intact. Cell damage is achieved by the action of light on the photosensitizing agent protoporphyrin IX in the mucosa, with skin photosensitivity of less than 48 hours. Such mucosal ablation, however, can also be accomplished with more common thermal techniques like Argon plasma coagulation (APC). In all these ablative procedures, squamous regeneratin is obtained by rigorous antacid therapy.

In selected patients these endoscopic ablation methods, although still experimental, might already offer an alternative to esophagectomy. The need for further improvement in conjunction with the lack of long-term follow-up data, however, limits the use of these techniques to expert centers.

Key words: **Barrett's esophagus, medical treatment, surgical treatment, endoscopic treatment**

INTRODUCTION

Barrett's esophagus (BE) is a complication of gastroesophageal reflux disease characterized by the presence of specialized columnar epithelium in the distal esophagus. The normal squamous lining of the distal esophagus is replaced with a metaplastic, intestinal columnar epithelium (1). BE is considered a premalignant condition with potential subsequent development of low-grade dysplasia, high-grade dysplasia and adenocarcinoma. The incidence of adenocarcinoma has been estimated to be 0.2% to 2.1% per year (2). The risk of developing cancer in BE ranges from 0.4 to 1.9%/year of follow-up. Early diagnosis and surveillance of BE and treatment of high grade dysplasia leads to improved survival (1). In view of this, endoscopic surveillance in patients with BE has been widely advised. Endoscopic surveillance is routinely performed by careful inspection with biopsies of any suspicious lesion, in con-

junction with random 4-quadrant biopsies with a large particle biopsy forceps at intervals of 2 centimeters (3).

The diagnosis of BE is made now when any length of columnar-lined epithelium (CLE) with intestinal metaplasia (IM) is present in the tubular esophagus. BE may be categorized into three groups: long-segment BE (LSBE; >3cm), short-segment BE (SSBE: <3cm) and intestinal metaplasia which may be associated with the cardia or the gastroesophageal junction. SSBE appears to be up to 10 times as common (1). The risk of esophageal adenocarcinoma appears to be greater in LSBE, but it is not negligible in SSBE.

Due to the potentially significant number of reflux patients at risk for BE, the American College of Gastroenterology has proposed practical guide-Jines for endoscopc screening and subsequent surveillance based on the presence and grade of dysplasia (3). Treatment recommendations in these guidelines offer antireflux therapy (medical or surgical) in patients with reflux symptoms and BE with no or low-grade dysplasia, and advise esophagectomy versus continued surveillance in patients with high-grade dysplasia (HGD).

A new treatment modality, endoscopic ablation, has recently been developed. Endoscopic ablation may cause regression or halt the progression of the metaplasia-dysplasia sequence in BE.

MEDICAL TREATMENT

The medical management of BE has been aimed at controlling the reflux of acid into the esophagus. This can be achieved by using proton pump inhibitors or histamine-receptor antagonist to control symptoms and heal esophagitis.

Multiple studies have demonstrated that acid suppression which effectively controls symptoms can lead to the appearance of squamous islands within columnar-lined epithelium but does not cause regression of BE, i.e. a decrease in the overall length (4,5). It has been showed, in the study of Sharma et al., that despite the increase in the number of squamous islands, the length of BE did not change after the average of 5.7 years follow-up (6). Sampliner and coworkers convincingly snowed that treatment with high-dose proton pump inhibition does nqt markedly decrease Barrett's metaplasia (7). This suggests that metaplasia itself may not be reversible or that elements other than acid may play a role in the development and maintenance of columnar metaplasia.

Many patients with BE may be found incidentally and have no symptoms of reflux. The use of acid-suppressive medication in asymptomatic reflux with BE cannot be recommended at present (8). The role of acid suppression in BE should be symptom based (3).

SURGICAL MANAGEMENT OF BARRETT'S ESOPHAGUS

Antireflux Surgery

The current indication of antireflux surgery is to provide long-term control of reflux symptoms. Its effectiveness in reducing acid in the esophagus is equivalent to acid-suppressive medications. Although it offers the added physiologic benefit of reducing esophageal exposure to the nonacid components of gastric refluxate, antireflux surgery has not been shown to cause regression of BE. However, some studies suggest that it may play a role in altering or delaying the malignant progression of BE (8).

Esophagectomy

Until recently, esophagectomy has been the standard of therapy for patients with Barrett's epithelium containing HGD or carcinoma in situ. This approach is based on surgical data demonstrating that esophagectomy specimens harbored unsuspected foci of cancer and even lymph node involvement in approximately 50% of the patients with HGD (9-12).

Surgical therapy still caries a mortality rate of 3 to 10% and a long-term morbidity in the range of 45-75%. Since submucosal invasion of Barrett's carcinoma already carries a 35% risk of lymph node metastasis, esophagectomy is the treatment of choice. Mucosal cancer, dysplasia, and nondysplastic Barrett's metaplasia are the only appropriate candidates for nonsurgical — endoscopic approach (8).

ENDOSCOPIC TREATMENT OF BARRETT'S ESOPHAGUS

The clinical significance of endoscopic therapy lies in the potential to reverse the development of neoplasia. Sampliner and coworkers showed that to restore the native squamous epithelium, injury to the metaplastic epithelium was needed in addition to normalization of acid exposure (13). Therefore, clinical studies predominantly focus on eradicating dysplasia in Barrett's.

Current endoscopic ablative therapies include endoscopic mucosal resection (EMR), thermal coagulation (e.g. multipolar electrocoagulation, laser coagulation, argon plasma cogulation), and photodynamic therapy (PDT). Overall, all of these

methods should be considered as complementary techniques, and a combined therapeutic strategy which seems to be the most successful (14).

Endoscopic mucosal resection

The esophageal wall essentially consists of an inner mucosal layer and an outer muscle layer. These two components are separated by the loose connective tissue. In EMR these layers are separated by injection of saline into the submucosa. Since the gastrointestinal wall is only 4 to 6 mm in full thickness, separation of these layers is extremely important to avoid perforation. A variety of techniques exist to subsequently resect the mucosal layer from inside the gastrointestinal tract (15). These resection techniques can be divided in two categories, techniques with and without suction. Endoscopic mucosectorny can be performed en bloc for lesions up to 20 mm, or in a piecemeal fashion for larger lesions. Since EMR is the only endoscopic treatment of Barrett's that provides a specimen for histologic investigation, it can also be applied diagnostically.

Makuchi et al. began applying the "lift-and--cut" technique with a snare for treatment of early esophageal carcinoma using a suction technique with a transparent plastic overtube equipped with a snare device. Using the same techniques, Inoue reported the first experience of resection of an early Barrett's carcinoma (16). A transparent cup fitted at the tip of the endoscope subsequently replaced the tube, a modification called capped mucosectorny or EMR-C (17). Currently, a standard variceal band ligator is also used ("band-and-snare") for small lesions, as an alternative for the specially designed EMR cap.

Up to the preset moment, a large number of reports of EMR in the esophagus exists in the literature, showing it to be a safe and effective diagnostic and therapeutic procedure. Kodama encountered a complication rate (perforation, bleeding, stenosis) of 6.8% (18). Inoue reportedly encountered only 3 major complications, 1 perforation and 2 stenosis, at removing 175 early esophageal cancers (19). The group from Rochester published a series of 23 patients with no complications (20).

Thermal coagulation

Thermal coagulation includes multipolar electrocoagulation (MPEG), KTP laser destruction, and argon plasma coagulation (APC). Larger areas of mucosa can be readily destroyed by thermal coagulation. Complete squamous re-epithelialization is often achieved, and the risk of perforation, bleeding and stenosis is limited. Thermal coagulation of a larger segment of Barrett's is usually time consuming, on average 2-4 treatment sessions are necessary. The frequent finding of remaining metaplastic mucosa underneath the newly developed squamous epitelium, so-colled sub-squamous, is of particular concern. Barrett encountered it in 0-30% of patients during follow-up. This may well be due to uneven in-depth destruction.

MPEC is a contact method requiring direct apposition of probe and mucosa for delivery of energy. The practical advantages of this method are the low cost of utilization, its widespread availability, and familiarity of most endoscopists with the MPEC technique.

KTP laser ablation is a noncontact technique, which allows a free hand, paintbrush-like manner. The KTP laser has several advantages over other types of lasers (argon and Nd:YAG); it offers superficial coagulation and variable depth effect when the pulse duration is adjusted.

APC is a technique that delivers controlled monopolar electrocoagulation via a stream of ionized argon gas ignited by a high voltage discharged at the tip of a specialized flexible probe. It is a noncontact ablative method with a predetermined depth of injury (approximately 2 mm) that is most often used for coagulation of bleeding surface lesions such as arteriovenous malformations.

Photodynamic therapy

PDT is a noncontact nonthermal ablative therapy involves the in situ photoactivation of an otherwise nontoxic drug, a photosensitizer, which has accumulated in tumor and normal tissues following oral or intravenous administration. The photosensitizer is activated by a wavelength of light that matches the absorption spectrum of the drug. Each photosensitizer has an optimum wavelength of light to be activated. The light, generated by a laser, is applied through a cylindrical diffuser fiber that is centered in the esophagus by a balloon catheter. The resultant photochemical reaction gives rise to highly active singlet oxygen species capable of causing cell death directly and a necroinflammatory cascade indirectly. Ideally, this effect selectively destroys only abnormal cells because the photosensitizer accumulates preferentially in the dysplastic or neoplastic cells and because only the target mucosa is illuminated during a treatment session. Both the photosensitizer and the light can be applied to the tissue with some degree of selectivity.

The most commonly used photosensitizers for the esophagus are the hematoporphyrin derivative *pot firmer sodium,* and the protoporphyrine IX precursor *5-aminolevulinic acid* (5-ALA). These photosensitizers differ considerably in the depth of tissue destruction and the associated side effects.

PDT using *porfimer sodium* will generate deep tissue destruction through vascular damage, ischemia, and apoptosis. It can be used for treatment or palliation of invasive esophageal carcinoma. The drug induces a skin phototoxicity lasting 4 to 6 weeks; perforations have occurred and stricture formation is a relatively common late complication. Overholt published a series of 100 patients with neoplasia in Barrett's, including 13 with invasive cancers (21). In all patients conversion to squamous epithelium of more than 75% of the surface area occurred. Dysplasia was eliminated in 78 patients, but recurred during follow-up in 11. Ten of 13 malignancies were ablated. Esophageal strictures occurred in 34%.

PDT using *5-ALA* seems better suited for treating esophageal dysplasia and intramucosal carcinomas. After oral administration, the pro-drug is rapidly converted in the gastrointestinal mucosa to the photosensitizer protoporphyrin IX. Because of its mucosa specificity, no deep destruction of the esophageal wall occurs. Therefore, perforation and stricture formation are not likely to occur. Furthermore, skin phototoxicity is relatively mild and limited to 48 hours after ingestion. However, since mucosal ablation is intrinsically limited to the mucosa, 5-ALA PDT is not suitable for treatment of cancers invading into the submucosa or deeper layers. Gossner and coworkers published their series of 32 patients treated with 5-ALA PDT in 10 patients with high-grade dysplasia and 22 early cancers (22). In 68% of patients a partial re-epithelization by normal squamous epithelium occurred. Sub-squamous Barrett's epithelium was encountered in the follow-up biopsies in 2 patients (6%). In this series, high grade dysplasia is eradicated in all 10 patients, whereas 17 of 22 early cancers (77%) were eliminated.

Compared to esophageal resection, all currently developed endoscopic therapy for BE have favorable mortality and morbidity rates. Accurate staging and control of acid reflux are paramount to the success of Barrett's ablation. Photodynamic therapy appears to be the most promising ablative agent. Again, all three methods should be considered complimentary and a combined therapeutic strategy seems the way to go. However, none of the current endoscopic therapies or the combination of these, guarantees complete elimination of metaplastic and dysplastic epithelium. Esophageal cancer represents an aggressive disease. Invasive carcinoma limited to the mucosa already carries a 4% risk of lymph node metastasis. Due to the preservation of the esophagus, the risk of local recurrences and metachronous cancer will remain.

The most troubling hypothesis regarding endoscopic ablation is that the malignant potential in the neosquamous mucosa is preserved, as it is derived from the same pluri-potent stem cell. There are already anecdotal reports of squamous cell carcinoma arising in newly formed squamous epithelium within a year after Barrett's ablations.

CONCLUSION

Although a number of ablative treatment options for BE have appeared, the long-term effectiveness of these modalities and the unclear natural history of this condition precludes the recommendation of any one specific treatment modality. Management strategies for BE from 1999 are based on a patient's dysplasia status (8):

Barrett's without dysplasia

- Symptom control (medical or surgical) and surveillance biopsies

Low-grade dysplasia

- Symptom control (medical or surgical) and surveillance biopsies.
- Endoscopic ablation, antireflux surgery, sur veillance biopsies (in research trials only)

High grade dysplasia ladenocarcinoma confined to mucosa (stage Tl)

- Esophagectomy
- Endoscopic ablation, antireflux surgery, sur veillance biopsies in the nonsurgical candidate (in research trials only).

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TERAPIJSKE OPCIJE U PACIJENATA SA BARETT-OVIM EZOFAGUSOM

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SAŽETAK

Barett-ov ezofagus (BE) je udružen sa porastom rizika za razvoj adenokarcinoma. Razvoju karcinoma prethode displastične promene sluzokože jednjaka. Strategije tretmana BE se baziraju na stepenu displazije. Napredak u endoskopskom tretmanu čini rane malignitete, za koje je hirurška resekcija bila jedini prihvaćeni tretman, dostupnim za minimalno invazivni endoskopski tretman. Endoskopska mukozna resekcija (EMR) je minimalno invazivna endoskopska tehnika koja se može koristiti u bolesnika sa cirkumskriptnim mukoznim karcinomima. Ova tehnika je takode korisna kao dijagnostička procedura za uzimanje uzoraka mukoze pune debljine za histolosko ispitivanje. Fotodinamska terapija (PDT) korišćenjem 5-aminolevulinske kiseline je ablativna terapija za destrukciju ezofagealne mukoze, pri čemu dublji slojevi ezofagealnog zida ostaju intaktni. Oštećenje ćelija se postiže delovanjem svetlosti na fotosenzitivni agent protoporphyrin IX u mukozi, sa fotosenzitivnošću kože trajanja manjeg od 48 sati. Mukozna ablacija može se uraditi i termalnim tehnikama kao što je argon plasma koagulacija (APC). Kod svih ovih ablativnih procedura, skvamozna regeneracija se postiže i igoroznom antacidnom terapijom. U selektiranoj grupi bolesnika, ove endoskopske ablacione metode, iako još eksperimentalne, mogu biti alternativa ezofagektomiji. Korišćenje ovih tehnika je ograničeno na pojedine ekspertne centre zbog potrebe daljeg usavršavanja i nedostatka podataka dugotrajnog praćenja bolesnika.

Ključne reči: **Barettov ezofagus, medikamentozni tretman, hirurški tretman, endoskopski tretman**