

## Advances in the therapy of Barrett's Esophagus

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### Abstract

The rising incidence of esophageal adenocarcinoma(EAC) in the world has led to continued interest in its precursor lesion, Barrett's esophagus(BE). This review endeavors to summarize the recent advances in the therapy of BE with an emphasis on novel endoscopic therapies.

*Key words:* Barrett's esophagus; Endoscopic therapy; Endoscopic

### INTRODUCTION

A dramatic increase in the incidence of esophageal adenocarcinoma(EAC) in recent years<sup>[1]</sup> has led to unprecedented attention being focused on its precursor lesion, namely Barrett's esophagus(BE). In China, a developing country, the morbidity of EAC is increasing<sup>[2]</sup>. BE is now a well recognized premalignant condition associated with a 30-50-fold increased risk of EAC<sup>[3]</sup>. Untreated, this can become Barrett's with dysplasia, in which cells start to transform to cancer cells<sup>[4-6]</sup>. The current review article endeavors to summarize the recent advances in the therapy of BE with an emphasis on novel endoscopic therapies.

### Medications

The most common cause of BE is longstanding acid reflux disease, called gastroesophageal reflux disease (GERD)<sup>[7]</sup>. In people with GERD, the esophagus is repeatedly exposed to excessive amounts of stomach acid and pepsin. In order to reduce the amount of acid produced by the stomach, a class of medications called proton pump inhibitors(PPI) is commonly recommended. Although multiple studies have proved that PPI therapy is associated with a significant reduction in the risk of developing dysplasia with BE<sup>[8,9]</sup>, it cannot alter the progression of genetically unstable cells(e.g.

p53 positive)<sup>[10,11]</sup>.

In the Chemoprevention for Barrett's Esophagus (CBET) trial, Heath and colleagues<sup>[12]</sup> evaluated the efficacy of celecoxib in decreasing cancer incidence when administered to patients with BE and dysplasia ( $n = 100$ ). This phase IIb randomized, multicenter, placebo-controlled trial was based on the premise that esophageal tumorigenesis is associated with COX2 overexpression and that selective COX2 blockade could decrease progression to cancer. After 48 weeks, no statistically significant difference was noted between the celecoxib and placebo groups in the proportion of biopsy samples containing dysplasia or cancer. Thus, celecoxib at a dose of 200 mg twice daily had no impact in preventing progression.

Reflux is the predominant risk factor for BE, and proximal gastric colonization by *H. pylori* seems to amplify this risk<sup>[13]</sup>. A few studies indicated that eradicating *H. pylori* can help reduce the morbidity of BE, but some more recent studies suggested that *H. pylori* infection may be protective against BE<sup>[14]</sup>. The most likely reason is that *H. pylori* infection can lead to gastric atrophy, in particular with the more virulent strains(CagA+). Gastric atrophy and reduced acid secretion should, in turn, lessen GERD risk. The link between *H. pylori* infection and BE is complex and it is debated whether or not eradicating *H. pylori* can help in the therapy of BE. Future research is required to

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resolve this question.

## ENDOSCOPIC THERAPIES

### Photodynamic therapy(PDT)

Photodynamic therapy(PDT) is a treatment that uses chemical agents, known as photosensitizers, to kill certain types of cells(such as Barrett's cells) when the cells are exposed to a laser of specific wavelength and power<sup>[15]</sup>. Patients are administered the photosensitizer medication intravenously, and then they undergo endoscopy. During the endoscopy, a laser light is used to activate the photosensitizer and destroy the Barrett's tissue. A recent study by Overholt *et al*<sup>[16]</sup> evaluated the long-term efficacy of PDT ablation for BE patients with high-grade dysplasia(HGD). This multicenter study randomized 208 patients in a 2:1 ratio to PDT with omeprazole versus omeprazole alone. As the primary outcome, patients in the PDT arm had a significantly higher rate of HGD elimination at 5 years of follow up (77% versus 39%,  $P < 0.001$ ). A secondary outcome was a slower and significantly lower rate of progression to cancer in the PDT group(15% versus 29%,  $P = 0.027$ ). Although the long-term efficacy has been confirmed, it's complication(e.g. narrowing of the esophagus) and the possibility of the untreated buried lesion should always be considered. A study by Mino-Kenudson *et al*<sup>[17]</sup> indicated that buried neoplasms are not common after PDT.

### Argon plasma coagulation(APC)

Argon plasma coagulation(APC) is one of the several endoscopic approaches that have been proposed in order to reverse BE and to induce squamous re-epithelialization. This technique allows ablation of large areas of specialized intestinal metaplasia with a limited depth of injury that minimizes the risk of stricture and perforation<sup>[18]</sup>. Pereira *et al*<sup>[19]</sup> used argon beam coagulation at a power setting of 65-70 W for the therapy of BE. In their study, complete restoration of squamous mucosa took place in all 33 cases(mean age: 55.2 yr, range:21-84 yr; 21 men and 12 women) after a mean of 1.96 sessions(range, 1-4). Endoscopic results were histologically confirmed. After a mean follow-up of 10.6 months there was one endoscopic, as well as histological, recurrence of Barrett's mucosa in a patient with an ineffective laparoscopic fundoplication. A study by Pedrazzani and colleagues<sup>[18]</sup> evaluated the effectiveness of 90 W APC for the ablation of BE. The ablation treatment was completed in all 25 patients but one(96%). The mean number of APC sessions needed to complete ablation was 1.6(total number: 40). Successful eradication was obtained in the majority of cases(60%) with only one session. Two sessions were required in 24% of the cases, and three or more in 16%. The follow-up

was accomplished in all the patients for a mean period of 26.3 mo, and in 20 patients(84%) with a follow-up period longer than 24 mo. Only one patient relapsed with a recurrence of metaplastic mucosa 12 mo after the completion of ablation. The most frequent symptoms after APC was retrosternal pain(22.5%) and fever (17.5%).

Surprisingly, there has been a recent report of a high recurrence rate(14/21) of Barrett's epithelium in a long-term follow-up after APC<sup>[20]</sup>. The different recurrence rates reported in published studies may be due to technical differences and different PPI schedules. We suggest that optimal conditions for this procedure must be defined before further studies are undertaken.

### Endoscopic mucosal resection(EMR)

Endoscopic mucosal resection(EMR) can be considered therapeutic when the lesion is confined to the mucosa and clear margins of resection are obtained<sup>[21]</sup>. A recent non-blinded and nonrandomized, single-center, prospective study by Ell and colleagues<sup>[22]</sup> evaluated the efficacy of EMR in a total of 100 consecutive patients with low risk EAC(defined as macroscopic types I, II a, II b and II c with lesion diameter < 20 mm, absence of lymphatic invasion and early histologic grade G1 and G2). Complete local remission was achieved in 99 of the 100 patients after 1.9 months and a maximum of three resections. Although 11% developed metachronous lesions during a mean follow-up period of 36.7 months, all could be successfully re-treated endoscopically. No major complications were reported and the 5-year survival rate was 98%. The most common complications of EMR are bleeding, perforation and stenosis<sup>[23]</sup>.

EMR provides large tissue specimens that can be examined by the pathologist to determine the character and extent of the lesion and these can also be used to determine if an adequate amount of tissue was removed. Therefore, this procedure can both help confirm the initial diagnosis and completely treat the abnormality (if the abnormal tissue is removed completely).

### Radiofrequency ablation(RFA)

Radiofrequency ablation(RFA) is an exciting new tool that has proven to be effective in eliminating intestinal metaplasia<sup>[24]</sup>. Its role in ablating dysplasia is currently being evaluated. The radiofrequency balloon(Halo 360 system) contains a tightly packed array of multipolar electrodes capable of delivering a high-energy pulse in a fraction of a second. In a recent report of 70 patients with nondysplastic BE who underwent circumferential balloon based ablation at 10 J/cm<sup>2</sup>, repeat post-treatment endoscopies with biopsies were performed at 1, 3, 6 and 12 months. A second ablation was performed if BE was detected at 1 or 3 months. At 1 year, the

group reported complete elimination of BE in 70% ( $n = 48$ ) of patients with no major complications<sup>[25]</sup>.

Carroll and colleagues of Georgetown University Hospital are planning to begin a study to see if it is worth doing Barrx treatment even earlier-in patients whose BE has not yet developed precancerous spots.

### Cryoablation therapy

A new method, called cryoablation therapy, is available to damage cells in the esophagus by freezing them, preventing them from turning cancerous. The FDA has recently approved using this technique in the treatment of BE. The method employs a special catheter and liquid nitrogen to freeze the damaged tissue in the superficial lining of the esophagus. The treated tissue eventually sloughs off, allowing normal cell replacement in about six to eight weeks. This is the same technology that has been in place and used by dermatologists for years to treat skin irregularities. However, it is a completely novel technique for treating BE, and more studies are required to confirm its efficacy and safety.

### Others

Many more techniques for destroying the Barrett's lining have been studied, including lasers<sup>[26]</sup>, a heat probe<sup>[27]</sup> and combination therapy with chemicals and others<sup>[28,29]</sup>. As of yet, it is not clear which patients would benefit from these approaches, particularly since they may be associated with side-effects (such as narrowing of the esophagus or creation of a penetrating lesion in the esophagus during treatment).

### Surgery

Prior to the development of the potent acid-reducing medications described above, surgery was used for severe cases of GERD that were not resolved with medical treatment. Because of the effectiveness of medical therapy, the role of surgery has become more limited. In general, anti-reflux surgery involves repairing a hiatal hernia and strengthening the lower esophageal sphincter.

The most common surgical treatment is the laparoscopic Nissen fundoplication. This procedure involves wrapping the upper part of the stomach around the lower end of the esophagus, thus minimizing reflux. Patients in whom surgery is being considered typically require esophageal manometry and endoscopy to confirm the diagnosis and decide which surgical treatment will be most effective. Although the outcome of surgery is usually good, complications can occur. Examples include persistent difficulty swallowing (occurring in about 5 percent of patients), a sense of bloating and gas (known as "gas-bloat syndrome"), breakdown of the repair (1 to 2 percent of patients per

year), and uncommonly, diarrhea due to inadvertent injury to the nerves leading to the stomach and intestines. Comparably, endoscopic therapies result in fewer complications.

The question remains, is esophagectomy inferior to endoscopic therapies for the treatment of HGD? There are no prospective studies addressing this issue but a recent single center retrospective cohort study compared survival among 129 BE patients treated with PDT plus EMR with 70 patients treated with esophagectomy<sup>[6]</sup>. Despite the fact that patients in the endoscopic therapy group were older and had a higher comorbidity index, the overall survival as well as tumor-free survival were comparable in both groups (mortality in the PDT group was 9% [11/129] and in the surgery group was 8.5% [6/70] over a median follow-up period of  $59 \pm 2.7$  months for the PDT group and  $61 \pm 5.8$  months for the surgery group). Survival was comparable when adjusted for age, BE length and comorbidity index. This review<sup>[6]</sup> makes a powerful argument in favor of endoscopic therapy, but obviously results from this high-volume center with broad expertise in endoscopy, pathology and surgery cannot be generalized to all clinical settings. While esophagectomy might not be the best procedure, we believe it can be an alternate choice available for the treatment of BE.

## CONCLUSION

The rising incidence of EAC in the world has led to continued interest in its precursor lesion, BE. Significant advances have been seen in the past years and we now have many treatment options available, as indicated above. But, which is the best one? When should we use these approaches? There is no certain answer, because none of the approaches above is perfect enough to treat every patient without some risk of complications. Despite the uncertainties surrounding the therapy of BE, there is consensus on one matter: The available options should be tailored to the individual patient.

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