Ablative Therapies in Barrett's Esophagus

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Introduction

Barrett's esophagus (BE) is a condition in which the stratified squamous epithelium that normally lines the distal esophagus lumen is replaced by metaplastic columnar epithelium that has both gastric and intestinal features. It is usually caused by persistent damage to the esophageal mucosa due to long-standing gastroesophageal reflux disease (GERD) and predisposes patients to esophageal adenocarcinoma (EAC), a cancer with a significantly increasing incidence over the past 40 years. While there are several risk factors for EAC, including smoking and obesity, GERD is the most significant one. Patients with BE have an estimated 30–125-fold greater chance of developing EAC compared to the general population [1]. The prevalence of BE has been estimated at 1–2% in all patients undergoing endoscopy for any indication and anywhere from 5% to 15% in patients receiving endoscopy for GERD symptoms [2]. While the incidence of EAC is higher in patients with BE, only a small fraction of patients with BE develop cancer with an annual risk of 0.1–0.5% [3, 4].

Epidemiology of Barrett's Esophagus

Barrett's esophagus most commonly affects older adults in developed countries, with a Caucasian male predominance [5]. The age at diagnosis varies widely but the majority of patients are diagnosed in the sixth or seventh decade of life [6]. The true prevalence is challenging to determine because many individuals with BE are

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asymptomatic and are not diagnosed. In fact, one of the first estimates of BE was through an autopsy study. Cameron and colleagues estimated that the prevalence of long-segment BE (LSBE) was approximately 0.4% and that only a small fraction of cases was clinically evident [7]. Studies out of tertiary endoscopy centers have attempted to quantify the true prevalence of BE. In one study, investigators performed upper endoscopy on 961 patients undergoing routine screening colonoscopies and found BE in 65 patients, which translates to an overall prevalence of 6.8%, with 1.2% having LSBE. In patients with symptomatic heartburn, the prevalence was higher at 8.3% but most patients with BE on endoscopy were asymptomatic [8].

Risk Factors

Gastroesophageal Reflux Disease

GERD is the major risk factor for the development of BE. Several case-control studies demonstrate that patients with GERD are six to eight times more likely to have BE. Additionally, it has been shown that longer duration of symptoms is associated with an increased risk of developing BE [9–11]. A systematic review found no association between reflux symptoms and short-segment BE (SSBE) but found increased odds of LSBE in patients with reflux symptoms [12]. Patients with BE have been found to have significant evidence of abnormal acid exposure, such as longer periods of acid exposure, lower pH, weaker peristaltic contractions, and lower esophageal sphincter (LES) tone [13, 14]. While some data exist that suggest that the use of proton pump inhibitors (PPI) may decrease the risk of developing cancer, the effects that these medications have on the development of BE is unclear [15].

Management

The goal of treatment of BE is to prevent the progression to high-grade dysplasia (HGD) and ultimately EAC, which carries a dismal prognosis. Management has traditionally focused on mitigating insult to the esophagus by treating the GERD symptoms, preventing erosive injury, and performing surveillance endoscopy to monitor for evidence of dysplasia [16–18]. Studies have demonstrated that non-dysplastic BE has the potential to progress to HGD and to EAC, with the rate of progression 0.9% and 0.5%, respectively [19–26].

Endoscopic Ablative Therapies

The treatment of BE has evolved over the last decade. Historically, patients with BE, specifically those with dysplasia, were treated with an esophagectomy, a procedure that is associated with significant morbidity and mortality. However, endoscopic therapies have gained acceptance and have replaced esophagectomy as the mainstay of treatment. Patients with non-dysplastic BE are managed with surveillance endoscopy

with biopsies to look for dysplasia and adenocarcinoma [27]. Endoscopic procedures fall into two main categories: endoscopic mucosal resection (EMR), which will be discussed in the next chapter, and ablation techniques, such as radiofrequency ablation (RFA), argon plasma coagulation (APC), or cryotherapy [28].

Radiofrequency Ablation

RFA involves using radiofrequency energy and applying it directly to the Barrett's epithelium. 350–500 kHz is typically used and the high-frequency energy is thought to limit the damage to the mucosa and does not involve the submucosa or muscularis propria, which decreases the subsequent risk of stricture formation. The energy is delivered either circumferentially using a balloon-based 360 degree catheter or focally using an endoscopic-mounted probe [29]. One study, which compared these two techniques, found that treatment with the focal device resulted in a greater reduction in length of the BE segment compared to the balloon device [30].

The efficacy of RFA has been studied comprehensively. The seminal study addressing this topic is the Ablation of Intestinal Metaplasia (AIM) trial. This landmark study was the first randomized controlled trial to examine RFA as the treatment for dysplastic BE. In this trial, 127 patients with BE dysplasia, divided evenly between HGD and LGD, were randomized to receive either RFA or a sham procedure. The results demonstrated that in the LGD and HGD groups, there was eradication of the neoplasia in 90.5% and 81%, respectively, compared to 22.7% and 19%, respectively, in the sham arm. Additionally, 77.4% had complete eradication of intestinal metaplasia (CE-IM) compared to 2.3% in the sham group [31]. Other studies followed this landmark trial and reinforced the efficacy of RFA. A retrospective analysis looked at 244 patients with BE-related neoplasia who were treated with RFA and found that 80% achieved CE-IM and 87% achieved complete eradication of dysplasia (CE-D). Four patients progressed to cancer despite RFA [32]. A large meta-analysis reinforced these results. This analysis consisted of 18 studies in the USA, the UK, and Europe with over 3000 patients and demonstrated CE-IM in 78% of patients and CE-D in 91% of patients treated with RFA [33].

After these initial landmark studies were conducted and showed promising results, the next step was to demonstrate durability and examine long-term outcomes. The AIM trial conducted a 3 year follow-up and found that of the patients available for follow-up, 98% had CE-D and 91% had CE-IM [34]. Orman et al. reported data from 262 patients with 155 patient-years who had received RFA and found on follow-up that the recurrence rate was 5.2%/year with a progression rate of 1.9%/year [33]. In a series of 592 patients over 8 years, Gupta et al. showed that 33% of patients who achieved successful eradication experienced a recurrence after 2 years [35]. In evaluating the UK RFA registry, the recurrence rate of intestinal metaplasia was 5.1%, 19 months after treatment [36]. This elaborate collection of data demonstrates that while RFA provides high short-term success rates, there is still a risk of recurrence and surveillance must continue following treatment.

RFA is not without complications. A large meta-analysis examined 37 studies with over 9000 patients and demonstrated an adverse event rate of 8.8%, the most

common being stricture formation at 5.6%, followed by less common issues such as bleeding at 1% and a very low rate of perforation at 0.6%. Risk factors for complications include increasing BE length and RFA performed in conjunction with endoscopic mucosal resection [37].

Cryotherapy

This technique involves using extremely cold temperature to destroy the aberrant tissue. The two main cryogens used are liquid nitrogen and carbon dioxide [28].

The efficacy of cryotherapy has been examined in several studies. One multicenter prospective registry reported that in patients with LGD, rates of CE-D and CE-IM were 81% and 65%, respectively, and in patients with HGD, CE-D and CE-IM rates were 81% and 65%, respectively. This study also examined short-segment BE and demonstrated that in these patients, CE-D was accomplished in 97% and CE-IM in 77% of patients [38]. A retrospective, non-randomized study looked at patients who received cryotherapy as a salvage treatment following failed RFA. At 1 year, the response rate was 77% for cancer, 89% for dysplasia, and 94% for HGD [39].

A single-center retrospective study evaluated the recurrence rates at 3 and 5 years. The recurrence rates per person-year follow-up of intestinal metaplasia, dysplasia, and HGD were 12.2%, 4%, and 1.4%, respectively. Adenocarcinoma was very uncommon and most recurrences were successfully managed [40].

Cryotherapy has a reasonable safety profile. Complications are minimal and the procedure appears to be well tolerated. When the national cryospray registry was examined, the results showed that none of the patients had a perforation and there were no mortalities. Only one patient developed a stricture, but it did not require dilatation [41].

Argon Plasma Coagulation (APC)

APC uses a non-contact thermal energy to ablate tissue. A probe is used to ionize argon gas and an electric current is conducted through the jet of ionized argon, which coagulates the tissue. In order to mitigate the risk of stricture, hybrid APC is used and consists of injecting saline in the submucosa, which protects the deeper esophageal layers during the procedure [28].

The efficacy of APC has been examined in several studies. The APE trial was a randomized study that compared APC with surveillance after EMR of neoplastic BE lesions. It included 63 patients and showed a significant decrease in secondary lesions in the APC-treatment arm, 3% versus 36.7%, respectively ($p = 0.005$) [42].

Studies that examined the long-term outcomes of APC have showed variable results. One of the first studies, which was done by Kahaleh et al., had a median follow-up of 36 months and showed that over 50% of the 39 patients who underwent

APC had a relapse on either endoscopy or histological analysis [43]. However, in another small study of 19 patients treated with APC, 70% had complete reversal of BE at 2 years [44]. These studies are small and more research is needed to evaluate the long-term outcomes and durability of APC. Additionally, long-term outcomes for hybrid APC have not been examined to date.

Conclusion

Endoscopic ablative therapies have replaced esophagectomies for dysplastic BE and have become the standard of care. However, it is an evolving and dynamic field and more long-term data are needed. While EMR is the most utilized method for visible nodular dysplastic lesions in BE, ablative therapies have emerged as the standard treatment for flat BE mucosa. Among these therapies, RFA is the most extensively studied with its high-efficacy data that has been demonstrated in several large studies. While cryotherapy has been shown to be promising and has an excellent safety profile, the data are limited and many patients receive it as a salvage treatment after failing RFA. APC is also promising but is most safe when used with the hybrid technology, and long-term data on the efficacy of this combined technique are lacking at this time. Regardless of which ablative technique is used, it is paramount that surveillance endoscopy continues to be used as follow-up since recurrence remains a possibility.

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