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Research article

How might recurrence of post-ablation Barrett's dysplasia be prevented?

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Abstract

Barrett's esophagus (BE) is characterized by a change of the normal stratified squamous epithelial lining of the esophagus to a metaplastic columnar epithelium with goblet cells. The spectrum of BE severity involves histologic changes ranging from non-dysplastic intestinal metaplasia (IM), indeterminate for dysplasia (IDD), low-grade dysplasia (LGD), high-grade dysplasia (HGD), intra-mucosal cancer (IMC), or invasive esophageal adenocarcinoma (EAC). While non-surgical management of HGD through control of gastric acidity and endoscopic esophageal photodynamic therapy (PDT) was an acceptable approach until the late 1990s, newer techniques including radiofrequency ablation (RFA) and cryoablation are now FDA approved for LGD, HGD, and IMC and have proven efficacy for down staging and eradication of dysplasia and IMC. However, even after endoscopic ablation, the risk of recurrent IM and dysplasia is significant, especially in patients with certain risk factors. While most post-ablation recurrences of BE or dysplasia occur within the first year, late recurrence can occur. A proper surveillance biopsy interval and pathologic evaluation by an expert GI pathologist are crucial for optimizing overall outcomes and prevention of dysplasia recurrence after ablation. Although there is growing enthusiasm about how to prevent recurrence of post-ablation BE, well-designed studies are lacking. In this review, we will briefly discuss the available data along with our experience on the role of various modalities in preventing post ablation recurrence of BE and dysplasia.

Introduction

Barrett's esophagus (BE) is characterized by a change of the normal stratified squamous epithelial lining of the esophagus to a metaplastic columnar epithelium with goblet cells. The prevalence of BE is estimated to be 1.5% in the general population and as high as 15% in patients with chronic gastroesophageal reflux (GERD). Other risk factors associated with BE are age more than 60 years, Caucasian race, male sex, central obesity, and smoking. There also appears to be a genetic predisposition among those with first degree relatives with BE [1,2].

The spectrum of BE ranges from histologic changes defined as the presence of non-dysplastic specialized intestinal metaplasia (IM), indeterminate for dysplasia (IDD), low-grade dysplasia (LGD), high-grade dysplasia (HGD), intra-mucosal cancer (IMC), or invasive esophageal adenocarcinoma (EAC). The risk of developing EAC is as high as 7% per year in those with HGD [3]. Major risk factors for progression of non-dysplastic IM to EAC include increasing degrees of dysplasia, older age, increasing BE segment length, male sex, and smoking. Controlling the gastric acidity with anti-reflux measures, proton pump inhibitors (PPI), and endoscopic photodynamic ablation therapy (PDT) in patients with BE and HGD were acceptable therapies until the late 1990s [4]. There are several additional FDA approved ablation options now available, including radiofrequency ablation (RFA) and cryoablation in patients with LGD, HGD, and IMC. Radiofrequency ablation is often a first line treatment of choice based on efficacy, safety, and minimal adverse events [5,6]. Cryoablation is another effective modality that delivers either carbon dioxide or liquid nitrogen to the dysplastic BE via a spray catheter. Recently, a

new cryobalation device using a self-contained, balloon-based delivery system with nitrous oxide has become available [7]. Although similar efficacy for dysplasia down staging and eradication has been observed with RFA and cryoablation [8,9], there is a need for ongoing randomized trials and direct comparisons of these two techniques. Patients with nodular BE have higher rates of malignancy so endoscopic mucosal resection (EMR) or submucosal dissection (ESD) are recommended as the initial ablation approach to determine not only depth of invasion, but also for curative purposes.

After complete eradication of IM and Barrett's dysplasia with RFA, the risk of recurrence is significant. A recent meta-analysis showed that the annual incidence of recurrent IM was 9.5%, 2% for LGD, and 1.2% for HGD and/or IMC 10]. The data suggest that the highest yield of detection of recurrence of IM or dysplasia in post-ablation patients is achieved via biopsy of the squamo-columnar junction and the cardia of the stomach [11]. Additional studies are needed to evaluate the effects of incorporating biopsies of the squamous columnar junction into routine practice. The recurrence rate of IM and dysplasia after achieving complete eradication with RFA was 29.1% and 2.2%/patient-year respectively, in a long term retrospective study of VA patients [12]. Most of the post-RFA recurrences of IM or dysplasia occurred within the first year and late recurrence was rare [13]. This suggests that the original eradication of IM or dysplasia may not have been complete.

Post-ablation surveillance is primarily aimed at the early detection of recurrent dysplasia. A proper biopsy protocol and evaluation of the biopsy specimens by an expert pathologist and utilization of appropriate surveillance intervals are important components of effective surveillance. We recommend performing endoscopic surveillance in post-ablation patients with a high-resolution white light endoscopy with adjunctive viewing techniques (narrow band imaging, i-scan) for better detection of mucosal lesions. In our experience and also in recent studies, confocal laser endomicroscopy and volumetric laser endomicroscopy have shown the ability to increase the yield of recurrent dysplasia with good accuracy [14-16]. We use a standard biopsy protocol for surveillance, which includes 4-quadrant biopsies every 1 cm in visible IM in addition to targeted sampling of focal mucosal abnormalities with EMR or ESD in selected cases. Our surveillance intervals are similar to those recommended by the American College of Gastroenterology practice guidelines [17].

Although there is a growing enthusiasm about how to prevent recurrence of post-ablation dysplasia, well-designed studies are lacking. We will briefly discuss the available data along with our own experience on role of various modalities in preventing the post-ablation recurrence of IM and dysplasia.

Chemoprevention

Most evidence regarding the benefit of chemoprevention of BE and prevention of progression of EAC is based on observational studies [18]. The outcome of prospective, randomized human chemoprevention trials for the reduction or prevention of recurrence of post-ablation IM or dysplasia are lacking. However, it is routinely recommended that all patients with IM should be treated with a once-daily proton pump inhibitor (PPI). Use of twice-daily PPI is not recommended, except in patients with refractory GERD and severe erosive esophagitis. Prolonged acid exposure time may lead to changes at the cellular level of the esophageal mucosa and ultimately initiate the metaplasia-dysplasia-carcinoma sequence. One meta-analysis showed a 71% risk reduction in the development of HGD or EAC in patients whose chronic GERD was controlled with the use of PPIs [19]. There was a trend toward a direct dose-response relationship with PPI use for more than 2 to3 years, but considerable heterogeneity was observed [19]. It has been shown that high-dose esomeprazole (40 mg twice a day) reduced inflammation and epithelial cell proliferation in patients with BE [20]. Other studies showed that high-dose PPI resulted in partial regression of IM and development of normal squamous epithelium in patients with BE [21-23]. It has also been reported that progression to neoplasia is reduced with a once-daily dose of PPI compared to no PPI therapy or with the use of H2 receptor blockers [23] and there is sufficient positive observational evidence to support the continued use of PPI to reduce acid exposure in patients with BE to prevent the progression of post-ablation dysplasia [19-24]. These medications have been shown to reduce chronic inflammation associated with cancer risk, decrease acid exposure associated with DNA damage and proliferation, and prevent the release of cancer-promoting cytokines by esophageal cells through acid-dependent mechanisms [18]. Therefore, we recommend long-term daily PPI to prevent recurrence of IM and dysplasia in all our patients with BE who have undergone ablation. The protective effect of PPI may be potentiated with the addition of aspirin for this scenario.

Long-term use of non-steroidal ant-inflammatory agents (NSAIDs), especially aspirin, has been associated (mostly in observational studies) with a decreased risk of EAC and a decreased risk of neoplastic progression in BE. A meta-analysis of 9 observational studies showed that the use of low-dose aspirin and non-aspirin COX inhibitors reduced the risk of EAC/HGD independent of the duration response [25]. Aspirin blocks IkB phosphorylation, nuclear translocation of p65, activation of CDX-2 promoter, and expression of CDX- 2 mRNA induced by acid and bile salts in esophageal mucosa. This mechanism may be important in the initiation of the SIM-dysplasia cycle [26]. The harmful adverse events of aspirin may be prevented with co-administration of a standard dose daily PPI. The AspECT trial [27] was a large randomized 5-year study which showed that the use of aspirin by itself had no significant role for chemoprevention in patients

with BE, however, the combination of high dose PPI with aspirin (300 or 325 mg) was effective for chemoprevention of BE. It is noted that the magnitude of the overall benefits observed in this trial were greater than expected and overall the treatment regimens were safe, with minimal serious adverse events [27]. Reduced PG-E2 concentrations have been shown in biopsies from patients with BE with no dysplasia or with LGD in patients treated with a PPI and 325 mg aspirin (but not 81 mg) [28]. There are no studies that have evaluated the role of aspirin alone or in combination with PPI in patients with recurrent dysplasia after ablation. It is feasible to use a 325 mg aspirin in combination with PPI in post-ablation patients to prevent recurrence of IM. However, in patients who are at high risk for GI bleeding, peptic ulcer disease, or hemorrhagic stroke, the risk-benefit ratio may not support the aspirin exposure.

The exact mechanism for the use of statins in the prevention of BE progression is not well understood, but it is assumed that statins inhibit proliferation, induce apoptosis, and inhibit growth factor signaling in esophageal squamous cells. Observational studies suggest that statin use may reduce the development of dysplasia in patients with IM in a VA based case-control study [29]. This study showed that the risk of IM was lower with statin use among obese patients. Another meta-analysis of pooled data showed statin use was associated with a significantly lower incidence of IM compared to control groups and more pronounced when used in combination with aspirin or for longer duration [30]. Although bile acids may be a contributing factor for the development of IM and even dysplasia, more convincing studies regarding the effects of statins on these outcomes are needed. Moreover, there is no study focusing on the role of statins alone or in combination with PPI and/or aspirin in patients with dysplasia after ablation.

Population studies have demonstrated an inverse relationship between green tea consumption and mortality rates for a variety of cancers, including EAC, and there is a large amount of preclinical literature demonstrating the anticancer activity of several green tea compounds [18]. A phase 1b, randomized, double-blinded, placebo-controlled study using green tea extract (polyphenon E) was well tolerated and preliminary results suggest that green tea-derived compounds may be used in chemoprevention in patients with IM [31].

Surgery

A recent meta-analysis and systematic review showed that the presence of a large hiatal hernia (HH) increases the risk of BE of any length by nearly four times, and the risk goes up to 12 times for developing long-segment BE [32]. Multiple other surgical studies showed that the presence of a large HH (>3 cm) results in an increased risk of BE [33-36]. A small study of 33 patients with IM showed that the width of the opening in the diaphragm also results in higher rates of BE [35]. Increased numbers of RFA sessions (> 3) are required to achieve complete eradication of SIM in patients with large HH [36]. These studies highlight an important question of whether pre- or post- ablation HH repair may impact the outcomes of ablation and reduce the recurrence rate of IM. A surgical study of 56 patients undergoing RFA for BE followed by daily PPI versus laparoscopic fundoplication found that the recurrence of BE was about 20% in the PPI users compared to 9.1% in the surgery group after 2 years of follow-up [37]. The US RFA registry study showed that prior laparoscopic fundoplication was not associated with improved efficacy or reduced number of RFA sessions compared to PPI management alone [38]. There is a desperate need for prospective studies in this important area. If a BE patient with dysplasia and large HH (>3 cm) continues to have refractory GERD after successful ablation, we recommend surgical management of the HH to prevent the recurrence of IM in our center.

Gastric bypass in selected patients with morbid obesity may be an effective anti-reflux procedure, because no acid is produced at the small proximal gastric pouch and no duodenal reflux is present due to the long Roux-en-Y limb. Csendes and his team have a long-time leadership in this topic and showed that disappearance of GERD symptoms, healing of endoscopic esophagitis, and an important regression of SIM [39,40]. We and others [41,42] have used this approach successfully in selected cases to prevent or reduce the progression of post-ablation dysplasia. However, long-term follow-up for these patients according to standard surveillance protocols is still lacking. For patients with morbid obesity and IM or dysplasia, sleeve gastrectomy is not a good surgical option [43].

Endoluminal Therapy

Although multiple minimally invasive endoscopic modalities have been investigated over the last 2-3 decades, they have not widely used in clinical practice due to procedure related complications and limited effectiveness [44]. Recently, transoral incisionless fundoplication (TIF), Stretta, and the Medigus ultrasonic surgical endostapler (MUSE) have been approved by the FDA for the treatment of patients with chronic GERD. We have a large experience with the first two of these procedures. There are no studies focusing on the effects of endoluminal therapy in recurrence of IM or dysplasia after ablation. We are conducting a prospective investigation with Stretta evaluating its impact on recurrence after RFA treatment in BE patients with dysplasia at our center.

Conclusions

We strongly recommend anti-reflux measures and lifestyle changes, tobacco cessation (inhaled or smokeless), and discontinuation of excessive alcohol intake to reduce the risk of recurrent IM or dysplasia in patients who have undergone successful ablation. Proton pump inhibitors should be continued at least daily in this popu-

lation and the addition of aspirin, if not contraindicated, may provide additional protection from recurrence. Continued surveillance is essential after ablative treatment and well-designed studies are needed to evaluate these and alternative methods to prevent or minimize post-ablation dysplasia recurrence.

Author Contributions

Dedania B contributed to this paper with conception of the format, literature review, and drafting, Thosani N, Tozlu M, and Cash B contributed to this paper by doing critical revision, and proof reading and Ertan A contributed to this paper by adding his personal experience and final approval of the article.

Conflict of Interest Statement

No potential conflicts of interest.

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References:

1. Eluri S, Shaheen N. Barrett's esophagus: diagnosis and management. GIE. 2017; 85: 889-903.
2. Spechler SJ. Clinical practice: Barrett's esophagus. N Engl J Med. 2002; 346:836-42.
3. Rastogi A, Puli S, El-Serag HB, et al. Incidence of adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. GIE. 2008; 67:394-8.
4. Lightdale CJ. "Photodynamic Therapy: A New Light on Barrett's Esophagus." Gastrointest Endosc. 1995; 42:96-8.
5. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009; 360:2277-88.
6. Kroep S, Heberle CR, Curtius K, et al. Radiofrequency ablation of Barrett's esophagus reduces esophageal adenocarcinoma incidence and mortality in a comparative modeling analysis. Clin Gastroenterol Hepatol 2017; 15:1471-4.
7. Scholvinck DW, Kunzli HT, Kestens C, et al. Treatment of Barrett's esophagus with a novel focal cryoablation device: a safety and feasibility study. Endoscopy. 2015; 47:1106-12.
8. Ghorbani S, Tsai FC, Greenwald BD, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's dysplasia: results of the National Cryospray Registry. Dis Esophagus. 2016; 29:241-7.
9. Verbeek RE, Vleggaar FP, Ten Kate FJ, et al, Cryospray ablation using pressurized CO2 for ablation of Barrett's esophagus with early neoplasia: early termination of a prospective series. Endosc Int Open. 2015; 3:107-12.
10. Guarner-Argente C, Buoncristiano T, Furth EE, et al. Long-term outcomes of patients with Barrett's esophagus and high-grade dysplasia or early cancer treatment with endoluminal therapies with intention to complete eradication. Gastrointest Endosc. 2013; 77:190-9.
11. Cotton CC, Wolf WA, Pasricha S, et al. Recurrent intestinal metaplasia after radiofrequency ablation for Barrett's esophagus: endoscopic findings and anatomic location. Gastrointest Endosc. 2015; 81:1362-9.
12. Tan MC, Kanthasamy KA, Yeh AG, et al. Factors associated with recurrence of Barrett's esophagus after radiofrequency ablation. Clin Gastroenterol and Hepatol. 2019; 17: 65-72.
13. Badreddine RJ, Prasad GA, Wang KK, et al. Prevalence and predictors of recurrent neoplasia after ablation of Barrett's esophagus. Gastrointest Endosc. 2010; 71:697-703.
14. Sharma P, Meining AR, Coron E, et al. Real-time increased detection of neoplastic tissue in Barrett's esophagus with probe base confocal laser endomicroscopy: final results of an international, multicenter, prospective, randomized, controlled trial. Gastrointest Endosc. 2011; 74: 465-72.
15. Bertani H, Frazzoni M, Dabizzi E, et al. Improved detection of incident dysplasia by probe base confocal laser endomicroscopy in a Barrett's esophagus surveillance program. Dig Dis Sc. 2013;58: 188-93.
16. Canto MI, Anandasabapathy S, Brugge W, et al. In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter, international randomized controlled trial (with video). Gastrointest Endosc. 2014; 79: 211-21.
17. Nicholas JS, Falk GW, Iyer PG, et al. ACG clinical guideline: Diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2015; 111.1: 30-50.
18. Bresalier RS. Chemoprevention of Barrett's esophagus and esophageal adenocarcinoma. Digest Dis Sci. 2018;63: 2155-62.
19. Singh S, Garg SK, Singh PP, et al. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut. 2014;63: 1229-37.
20. Abu-Sneineh A, Tam W, Schoeman M, et al. The effects of high-dose esomeprazole on gastric and oesophageal acid exposure and molecular markers in Barrett's oesophagus. Aliment Pharmacol Ther. 2010;32: 1023-30.
21. Sampliner RE. Effect of up to 3 years of high-dose lansoprazole on Barrett's esophagus. Am J Gastroenterol. 1994;89: 1844-8.
22. Krishnan K, Pandolfino JE, Kahrilas PJ, et al. Increased risk for persistent intestinal metaplasia in patients with Barrett's esophagus and uncontrolled reflux exposure before radiofrequency ablation. Gastroenterology 2012;143: 576-81.
23. Kastelein F, Spaander MC, Steyerberg EW, et al. Proton pump inhibitors reduce the risk of neoplastic progression in patients with Barrett's esophagus. Clin Gastroenterol Hepatol. 2013;11: 382-8.
24. Kia L, Komanduri S. Care of the postablation patient: surveillance, acid suppression, and treatment. Gastrointest Endosc Clin N Am. 2017; 27: 515-29.
25. Zhang S, Zhang XQ, Ding XW, et al. Cyclooxygenase inhibitors use is associated with reduced risk of esophageal adenocarcinoma in patients with Barrett's esophagus: a meta-analysis. Br J Cancer. 2014;110: 2378-88.
26. Huo X, Zhang X, Yu C, et al. Aspirin prevents NF-kB activation and CDX2 expression stimulated by acid and bile salts in oesophageal squamous cells of patients with Barrett's esophagus. Gut. 2018;67: 606–15.
27. Jankowski JAZ, de Caestecker J, Love SB, et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomized factorial trial." The Lancet. 2018;392: 400-8.
28. Falk G, Buttar NS, Foster NR, et al. A combination of esomeprazole and aspirin reduces tissue concentrations of prostaglandin E2 in patients with Barrett's esophagus. Gastroenterology. 2012;143: 917-26.
29. Nguyen DM, Richardson P, El-Serag HB. Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma. Gastroenterology. 2010;138: 2260-66.
30. Beales ILP, Dearman L, Vardi I, et al. Reduced risk of Barrett's esophagus in statin users: case-control study and meta-analysis. Dig Dis Sc. 2016; 61:238-46.
31. Joe AK, Scnoll-Sussman E, Bresalier RS, et al. Phase 1b randomized, double-blinded and placebo-controlled, dose escalation study of polyphenon E in patients with Barrett's esophagus. Cancer Prev Res. 2015;8: 1131-37.
32. Andrici, J, Tio M, Cox MR, et al. Hiatal hernia and the risk of Barrett's esophagus. J Gastroenterol Hepatol. 2013: 28: 415-31.
33. Pasricha S, Bulsiewicz WJ, Hathorn KE, et al. Durability and predictors of successful radiofrequency ablation for Barrett's esophagus. Clin Gastro-

enterol Hepatol 2014;12: 1840-7.
34. Yasuda K, Choi SE, Nishioka NS, et al. Incidence and predictors of adenocarcinoma following endoscopic ablation of Barrett's esophagus. Dig Dis Sci 2014; 59(7):1560-6.
35. Cameron, A.J. Barrett's esophagus: prevalence and size of hiatal hernia. Gastroenterology 1998;114: A83.
36. Akiyama, J, Chun CL, Aulakh S, et al. Large hiatal hernia and long segment Barrett's esophagus are associated with delayed response to radiofrequency ablation. Gastroenterology 2012;142; A 109.
37. Skrobic O, Simic A, Radovanovic N, et al. Significance of Nissen fundoplication after endoscopic radiofrequency ablation of Barrett's esophagus. Surg Endosc 2016;30: 802-7.
38. Shaheen NJ, Kim HP, Bulsiewicz, et al. Prior fundoplication does not improve safety or efficacy outcomes of radiofrequency ablation: results from the U.S. RFA registry. J Gastrointest Surg 2013;17: 21-9
39. Csendes A, Burgos AM, Smok G, et al. Effect of gastric bypass on Barrett's esophagus and intestinal metaplasia of the cardia in patients with morbid obesity. J Gastrointest Surg 2006; 10: 259-64.
40. Braghetto I, Korn O, Csendes A, et al. Laparoscopic treatment of obese patients with gastroesophageal reflux and Barrett's esophagus: a prospective study. Obes Surg. 2012;22: 764-7.
41. Parikh K, Khaitan L. Radiofrequency ablation coupled with Roux-en-Y gastric bypass: a treatment option for morbid obese patients with Barrett's esophagus. J Surg Case Rep. 2016;3: 1-6.
42. Andrew, B., Alley, J., Aguilar, C., & Fanelli, R. (2018). Barrett's esophagus before and after Roux-en-Y gastric bypass for severe obesity. Surgical Endoscopy, 32(2), 930-6.
43. Braghetto I, Csendes A. Prevalence of Barrett's esophagus in bariatric patients undergoing sleve gastrectomy. Obes Surg. 2016; 26: 710-4.
44. Dugan J, Thosani N, Ertan A. Bridging gap with endoscopic (endoluminal) therapies for gastroesophageal reflux disease. J Gastroenterol Pancreatol Liver Dis. 2016;3: 1-6.

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