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Endoscopic eradication therapy for Barrett's esophagus: Adverse outcomes, patient values, and cost-effectiveness

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ABSTRACT

Endoscopic therapy for Barrett's esophagus (BE) aims to replace dysplastic BE epithelium with neosquamous epithelium to prevent and reduce the risk of progression to esophageal adenocarcinoma (EAC) and treat early-stage EAC. Various modalities of endotherapy of dysplastic BE are described. Although endoscopic therapy is safe and effective in treating subjects with intramucosal carcinoma (IMCa), high-grade dysplasia (HGD), and confirmed low-grade dysplasia (LGD), challenges to successful treatment are being recognized. Though adverse outcomes of endotherapy such as bleeding, perforation, pain, and stricture formation are observed, they are not common and can usually be treated medically or endoscopically. Patient values and preferences toward endoscopic therapy and the cost-effectiveness of these endoscopic approaches also have crucial implications for the selection of appropriate treatment and subsequent outcomes in patients with BE.

1. Introduction

Barrett's esophagus (BE) is characterized by the replacement of squamous epithelium in the esophagus with specialized intestinal metaplasia and remains the strongest risk factor and only known precursor of esophageal adenocarcinoma (EAC) [1]. Endoscopic therapy for BE aims to replace dysplastic BE mucosa with neosquamous epithelium to reduce neoplastic risk. Although durable elimination of dysplasia and metaplasia is the immediate goal of endoscopic therapy, reduction in cancer risk is the long-term goal. Endoscopic therapy is safe and effective at achieving desired outcomes; however, adverse events have been described with the various modalities of endotherapy. Some of these adverse events include postprocedure pain, bleeding, perforation, and stricture formation.

Alternate approaches to endotherapy in the management of patients with BE include endoscopic surveillance, chemoprevention (particularly in patients without dysplasia and low-grade dysplasia), and surgery (in patients with carcinoma). Risk of progression to high-grade dysplasia (HGD) or EAC, patient preferences, costs of therapy, and resultant adverse effects have crucial implications in selection of therapy. For example, in patients with nondysplastic Barrett's esophagus (NDBE), recent data suggest lower rates of progression than previously reported [2–4]. Given the low rate of progression in these patients, the complications associated with endoscopic therapy, and the cost of endoscopic therapy, ablative therapy is not deemed to be an appropriate choice for patients with NDBE [5,6]. In some scenarios, such as individuals with low-grade dysplasia (LGD), shared decision-making between the patient and the physician may be needed in pursuing endoscopic intervention vs intense endoscopic surveillance. Only few studies exist in the literature that look into patient values and preferences for the treatment of BE. However, knowledge regarding patients' values and preferences for the treatment of BE with and without dysplasia is likely important in making management decisions [7–9].

In this article, we review and summarize data regarding some of these important variables such as adverse outcomes, cost-effectiveness, and patient values and preferences relevant to choosing management options in patients with BE.

2. Adverse outcomes of endoscopic eradication therapy

Various modalities of endoscopic therapy for Barrett's esophagus have been described, and they include tissue-acquiring techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) as well as ablative techniques such as radiofrequency ablation (RFA), argon plasma

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Table 1
Complications occurring with the various modalities of endoscopic therapy and their reported rates of occurrence (from review of literature).

Endoscopic therapy modality	Complication	Observed incidence rate
Endoscopic mucosal resection (EMR)	Bleeding	1%-45% [13–15,70]
	Stricture	12%-35% (c EMR)* [26,71]
		< 0.5% (f EMR)†[26,71]
	Perforation	< 1%-5% [72]
Endoscopic submucosal dissection (ESD)	Bleeding	11% [24–26]
	Stricture	5.6% [73]
	Perforation	6% [74]
Radiofrequency ablation (RFA)	Bleeding	< 2% [27–29]
	Stricture	6%-11% [34,35]
	Perforation	0.6% [41]
	Chest pain	5%-28% [27,75,76]
Photodynamic therapy (PDT)	Stricture	15%-58% [42–44]
	Perforation	rare
	Photosensitivity	10%-60% [49,53]
Cryotherapy	Stricture	4%-10% [47]
	Perforation	Rare [47]
Argon plasma coagulation (APC)	Bleeding	4% [77–79]
	Stricture	6% [77–79]
	Perforation	2% [77–79]

* c EMR—circumferential endoscopic mucosal resection.
† f EMR—focal endoscopic mucosal resection.

coagulation (APC), cryotherapy, and photodynamic therapy. All of the endoscopic therapies are safer (ie, have fewer adverse events and lower mortality rates) than surgery (ie, esophagectomy) and have the added advantage of being outpatient procedures with shorter recovery times [10,11]. Table 1 summarizes the complications that can occur with each modality of endoscopic therapy and their reported rates of occurrence based on available literature. Complication rates vary among different endoscopic techniques, and they can either be a direct result of the procedure or related to operator expertise.

Published data on complications following endoscopic therapy are highly variable [12–17], and the expertise of those performing these techniques is not disclosed in most studies. Several studies have assessed the effect of learning curve assessment on safety and efficacy outcomes in advanced endoscopic procedures [18–22], and they have shown that the experience and level of training of the endoscopist are associated with a decrease in complication rate and procedure time [20–22]. Case volume is another factor affecting outcomes in endoscopic eradication therapies with higher volumes positively correlating with complete eradication of intestinal metaplasia (CRIM) rates [23].

2.1. Bleeding

Bleeding (both major and minor) is a significant adverse outcome that has been observed with endoscopic eradication therapies particularly the tissue-acquiring techniques (EMR and ESD). Patients with major bleeding are usually defined as those with a significant drop in hemoglobin (> 2 g/dL), requiring a blood transfusion, needing endoscopic or surgical treatment for hemostasis, or requiring hospital admission while patients with minor bleeding fulfilling none of the above requirements. Bleeding can occur from exposed vessels at the resection site base or from the resection site margins. Bleeding can be intraprocedural or delayed and may be dependent on various factors such as, use of anticoagulation or NSAIDS prior to or after the procedure, extent of EMR, and electrocautery settings (with cutting current more associated with immediate bleeding and coagulation current more associated with delayed bleeding).

Reported post-EMR bleeding rates are quite varied (1%-45%) and often limited by small patient numbers [12–15]. In a large BE cohort of 681 patients undergoing EMR, Tomizawa et al reported an overall rate of bleeding after EMR as 1.2% with all 8 patients having developed acute post-EMR bleeding [11]. Post-ESD bleeding is the most frequent adverse event associated with ESD. Post-ESD bleeding rates as high as 11% have been reported [24–26]. Bleeding is infrequently associated with ablative techniques such as RFA, because of the fact that the depth of ablation is limited to the mucosa without injury to the submucosa which is more vascular. Post-RFA bleeding requiring endoscopic therapy has been reported in less than 2% of procedures [27–29].

Further, Qumseya et al in their recent meta-analysis of 37 studies on adverse events occurring after RFA in BE patients reported a pooled bleeding rate of 1% from 26 studies. This provides the strongest evidence to date that bleeding after RFA is more than likely a rare occurrence after RFA therapy [41].

Management of bleeding usually involves either injection of epinephrine solution, electrocautery, or placement of endoscopic clips to achieve hemostasis. Occasionally, patients may need a blood transfusion, especially if associated with significant bleeding or drop in hemoglobin (> 2 g/dl). Techniques to reduce the incidence of delayed bleeding include the application of prophylactic hemostatic clips or cauterization of exposed vessels after the resection is completed (Figure 1).

2.2. Stricture

Stricture formation is a significant complication that occurs with endoscopic eradication therapy (with both ablative and tissue-resective techniques). A symptomatic stricture is defined as an endoscopically identified narrowing or stenosis producing patient complaints of dysphagia necessitating endoscopic dilation. Stricture formation appears in part relating to the inflammatory process that develops after the application of thermal or photochemical energy as part of resection or ablation. Animal models have demonstrated lack of epithelization and a chronic active inflammatory infiltrate that appears to have both polymorphonuclear cells and disorganized fibrotic collagen deposition [30]. Strictures typically present 3-4 weeks after resection or ablation with persistent or worsening dysphagia to solids.

Rates of stricture occurrence after the EMR are variable and studies have reported rates as high as ~37% in those who underwent circumferential EMR (cEMR) [31,32]. Resection of at least 50% of the esophageal mucosal circumference has been reported to be strongly associated with stricture formation by retrospective analysis of EMR monotherapy for BE [33]. Another predictor for stricture occurrence following EMR seems to be the resection of multiple lesions during the procedure [34]. Studies have also shown increased stricture rates in those who undergo ESD, particularly when more than 50% of the esophageal circumference is resected given the narrower lumen in the esophagus than other organs [35,36]. The use of prophylactic steroid injections (into the margins or base of the resection site) or oral steroids following esophageal ESD has been shown to decrease the risk of stricture formation [37,38].

Ablative techniques have also been associated with esophageal stricture formation. The most common adverse outcome of RFA therapy is stricture formation, with rates ranging between 6% and 11% [34,35]. There is conflicting data on stricture rates between patients who underwent RFA alone vs those who underwent RFA after EMR, with some studies showing no difference in the rate of complications between the 2 groups [39,40]. However, Qumseya et al found that the relative risk for adverse events due to RFA was