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Endoscopic treatment of Barrett's esophagus: From metaplasia to intramucosal carcinoma

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Abstract

The annual incidence of adenocarcinoma arising from Barrett's esophagus (BE) is approximately 0.5%. Through a process of gradual transformation from low-grade dysplasia to high-grade dysplasia (HGD), adenocarcinoma can develop in the setting of BE. The clinical importance of appropriate identification and treatment of BE in its various stages, from intestinal metaplasia to intramucosal carcinoma (IMC) hinges on the dramatically different prognostic status between early neoplasia and more advanced stages. Once a patient has symptoms of adenocarcinoma, there is usually locally advanced disease with an approximate 5-year survival rate of about 20%. Esophagectomy has been the gold standard treatment for BE with HGD, due to the suspected risk of harboring occult invasive carcinoma, which was traditionally estimated to be as high as 40%. In recent years, the paradigm of BE early neoplasia management has recently evolved, and endoscopic therapies (endoscopic mucosal resection, radiofrequency ablation, and cryotherapy) have entered the clinical forefront as acceptable non-surgical alternatives for HGD and IMC. The goal of endoscopic therapy for HGD or IMC is to ablate

all BE epithelium (both dysplastic and non-dysplastic) due to risk of synchronous/metachronous lesion development in the remaining BE segment.

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INTRODUCTION

The annual incidence of adenocarcinoma arising from Barrett's esophagus (BE) is approximately 0.5%^[1-3]. Through a process of gradual transformation from low-grade dysplasia (LGD) to high-grade dysplasia (HGD), adenocarcinoma can develop in the setting of BE^[4]. The clinical importance of appropriate identification and treatment of BE in its various stages, from intestinal metaplasia (IM) to intramucosal carcinoma (IMC) hinges on the dramatically different prognostic status between early neoplasia and more advanced stages. Once a patient has symptoms from adenocarcinoma, there is usually locally advanced disease with an approximate 5-year survival rate of about 20%^[5,6].

Esophagectomy has been the gold standard treatment for BE with HGD, due to the suspected risk of harboring occult invasive carcinoma, which has been estimated to be as high as 40%^[7,8]. Our previous analysis of the pub-

lished literature demonstrated that the true prevalence of submucosal invasive carcinoma in the setting of HGD was actually 12%, which was much lower than the pooled reported historical rate of 40%^[9]. Esophagectomy has also been routinely performed for BE with IMC, despite a low incidence of lymph node metastasis of < 1% that is associated with non-invasive T1a disease^[10]. Additionally, esophagectomy is associated with significant morbidity and mortality even in high-volume centers^[11,12].

With these issues in mind, the paradigm of BE early neoplasia management has recently evolved, and endoscopic therapies have entered the clinical forefront as acceptable non-surgical alternatives for HGD and IMC. The goal of endoscopic therapy for HGD or IMC is to ablate all BE epithelium (both dysplastic and non-dysplastic) due to risk of synchronous/metachronous lesion development in the remaining BE segment^[10]. Endoscopic therapies can be further subdivided into tissue-acquiring and non-tissue-acquiring modalities. Tissue acquisition can be achieved through endoscopic mucosal resection (EMR), while photodynamic therapy (PDT), radiofrequency ablation (RFA), and cryotherapy all ablate tissue without the benefit of histological specimen retrieval. A brief technical review and pertinent available efficacy/safety data are summarized for these various modalities in treating stages of early BE neoplasia that ranges from IM to IMC. Modalities such as argon plasma coagulation, multipolar electrocoagulation, and laser therapies are not be discussed as current mainstay therapies due to high BE relapse rates, infrequent usage, or significant risk of buried gland development^[13].

EMR

EMR can be performed through a variety of techniques: free-hand, lift-and-cut, cap-assisted, or band-assisted. Injection of saline with a sclerotherapy needle is performed to create a submucosal fluid cushion, and a snare is used to entrap directly the mucosal tissue in the free-hand method. In the lift-and-cut approach, a dual channel endoscope is used to introduce simultaneously a grasping forceps and snare for resection. The cap technique uses a clear distal attachment with an inner rim around which a crescent-shaped snare is carefully fitted. The target area is injected for submucosal lift, then suction is applied through the cap, and tissue is entrapped by the snare for subsequent mucosal excision. Band-assisted techniques are modifications of the variceal band ligation device that allows for injection and then deployment of bands for mucosal pseudopolyp creation. A snare is then introduced and the mucosa is resected either above or below the band^[14].

Focal EMR can be performed for endoscopically visible lesions that are suspicious for malignancy. However, several previously published studies on focal resection have demonstrated a high rate of synchronous and recurrent lesion development, which ranged from 14% to 47%, and increased with longer observation times^[15-22]. As a

result of this limitation of focal EMR, complete Barrett's eradication EMR (CBE-EMR) has been advocated and performed in select centers, with the intent to remove all BE epithelium curatively, to reduce the potential risk of synchronous or metachronous lesion development. Complete responses have ranged from 76% to 100%. The complication profile of EMR includes stricture formation, with an incidence rate that approaches 50%, bleeding and perforation. Of note, most esophageal stenoses and bleeding are amenable to endoscopic treatment^[23-26].

When evaluating the effect of EMR on final histopathological staging, our center long-term results with CBE-EMR have revealed that initial EMR upstaged seven of 49 (14%) and down-staged 15 of 49 (31%) final pathology results when compared to pre-EMR biopsy results. Among the upstaged group, four patients had advanced pathology that was found after index EMR (either submucosal carcinoma or IMC with lymphatic channel invasion). All four of these patients had visible lesions upon endoscopy^[26]. This is the crucial point that distinguishes EMR from all other non-tissue-acquiring modalities that would have inadvertently attempted ablation of advanced pathology in the setting of presumed BE HGD treatment.

PDT

The goal of PDT is destruction of tissue through a light-sensitizing reaction sequence. A photosensitizer is first administered which accumulates in esophageal malignant and pre-malignant tissue before light activation therapy. Porfimer sodium is the most common photosensitizer, and this is delivered intravenously 72 h before the procedure. Alternatively, oral 5-aminolevulinic acid (ALA) and intravenous m-tetrahydroxyphenyl chlorine (mTHPC) can be used. Activation of the photosensitizing agent occurs upon exposure to either bare cylinder or balloon-based diffusing light fibers that are placed alongside the target tissue via an endoscopic approach. The resulting molecular excitation reacts with oxygen to create radical oxygen species that cause eventual cell apoptosis^[27].

A multicenter trial by Overholt *et al*^[28] randomized BE HGD patients to receive twice daily oral omeprazole (20 mg) with or without porfimer sodium PDT administration. The study found that, at 5 years, PDT was significantly more effective than proton pump inhibition (PPI) alone, in elimination of HGD (77% *vs* 39%, $P < 0.0001$). Prevention of cancer progression was a secondary outcome that also showed a significant difference, with the PDT/PPI group demonstrating half the likelihood of developing cancer and longer time to cancer progression.

Overholt *et al*^[29] have conducted another porfimer PDT study of 103 patients with LGD, HGD, or IMC with a mean follow-up of 50.65 mo (SD 20.57) (range: 2-122 mo). Intention to treat success rates were 92.9%, 77.5%, and 44.4% for the respective LGD, HGD, and IMC groups. Three patients (4.6%) developed sub-squa-

mous adenocarcinoma. Strictures occurred in 18% with one session of PDT, 50% with two treatments, and 30% in the overall group.

ALA PDT has shown 97% and 100% complete response rates for treatment of BE with HGD and IMC, respectively, in a median follow-up period of 37 mo (interquartile range: 23-55 mo). Disease-free survival of HGD patients was 89%, and 68% in patients with IMC. The calculated 5-year survival was 97% for HGD and 80% for IMC, but no deaths were related to Barrett's neoplasia^[30].

In a pilot study of PDT using mTHPC for seven patients with HGD and 12 patients with IMC, Lovat *et al*^[31] found that treatment results were variable based on red versus green light usage. Successful ablation was achieved in four out of six mucosal carcinoma and three out of four HGD patients who received red light. However green light exposure failed to achieve successful disease eradication or long-term remission. Significant complications such as death occurred after premature biopsy performance after treatment. This limited sample size study demonstrated that although mTHPC can destroy BE epithelium, the optimal light and drug dosimetry are still unknown^[31].

To date, no randomized, controlled prospective trials have been conducted to compare PDT and surgery for BE neoplasia management. However, a retrospective data analysis of HGD patients who received PDT ($n = 129$) or esophagectomy ($n = 70$) has revealed no statistically significant differences in mortality or long-term survival based on choice of treatment modality^[32].

The major side effects of PDT include photosensitivity that requires patients to avoid post-procedure skin sunlight exposure, non-cardiac chest pain, and symptomatic stricture formation. Risk factors for post-PDT stricture development include history of prior esophageal stricture, performance of EMR before PDT, and more than one PDT treatment in a single session^[33]. Another concern about PDT is development of sub-squamous BE glands that could harbor neoplastic potential. The clinical significance of this finding is still not fully understood. However, reports of adenocarcinoma arising from sub-squamous BE glands after PDT therapy have been described^[29,34]. For these reasons, PDT usage has gone out of favor in recent years, with the availability of other endoscopic ablative options.

RFA

Using either a balloon-based catheter or a focal device, RFA of BE tissue can be achieved in either a circumferential or localized fashion. After initial insertion of a sizing balloon into the esophagus, the optimal size of the circumferential balloon is selected based on various pressure measurements in different locations. The ablation process is a series of two separate applications of direct thermal energy with the electrodes embedded in either the circumferential or focal device. Scraping of treated tissue is performed between the first and second ablation

to ensure adequate and uniform thermal contact. The most common complications associated with RFA include non-cardiac chest pain, non-transmural lacerations, and stricture formation (lower stricture rate when compared to EMR).

After thermal dose-escalation animal testing and pre-esophagectomy human experiments^[35,36], the first larger clinical evaluation of RFA was performed on BE patients without dysplasia in the Ablation of intestinal metaplasia (AIM) study from 2003 to 2005. This multicenter trial demonstrated a 70% complete remission of BE in the circumferential-balloon-treated group at 1 year follow-up, without evidence of subsequent stricture formation or buried BE among 4306 biopsy fragments evaluated^[37]. A subsequent AIM II study reported 98% complete remission of IM after stepwise circumferential therapy with additional focal ablative therapy of remaining BE^[38].

RFA was also studied in 142 patients with BE HGD. At 1 year follow-up, complete remission of HGD was achieved in 90.2%, complete remission of dysplasia in 80.4%, and complete remission of IM in 54.3% of patients^[39]. In a recent landmark multicenter, sham-controlled trial, 127 patients with dysplastic BE were randomly assigned to receive either RFA or a sham procedure. The measured primary outcomes at 1 year included complete eradication of dysplasia and intestinal metaplasia. Based on an intention-to-treat analysis, in patients with LGD, complete eradication of dysplasia occurred in 90.5% in the ablation group, compared to only 22.7% in the control group ($P < 0.001$). In the HGD sub-group, complete eradication occurred in 81% of ablated patients as compared with 19% of the control group ($P < 0.001$). Overall, 77.4% of ablation patients demonstrated complete eradication of IM, as compared to 2.3% in the control group ($P < 0.001$). There was less disease progression in patients in the ablation group (3.6% *vs* 16.3%, $P = 0.03$) and fewer cancers developed (1.2% *vs* 9.3%, $P = 0.045$). There were more reports of chest pain after ablation than after sham procedures, and a 6% esophageal stricture rate was reported in the treated group^[40]. This stricture rate is markedly lower than that commonly reported for EMR, which confers a significant advantage for RFA in treatment of BE with flat HGD.

In patients who demonstrate visible lesions in the setting of HGD, a combination of EMR and RFA has recently been studied. Pouw and colleagues have reported on performance of EMR for visible lesions with subsequent ablation of the remaining segment^[41]. Complete histological eradication of all dysplasia and IM was achieved in 43 patients (98%). Post-ablation complications included mucosal laceration at prior EMR sites ($n = 3$) and transient dysphagia ($n = 4$). No dysplasia recurred after a 21-mo follow-up period^[41]. A more recent multicenter European trial involved EMR of visible lesions, followed by serial RFA. Focal escape endoscopic resection was utilized in cases of BE persistence despite RFA. The study included 24 patients, and achieved neoplasia and IM eradication in 95% and 88% of patients, respectively. These

rates improved to 100% and 96%, respectively, following escape EMR in two patients. No neoplasia recurred within a median 22-mo follow-up period^[42]. Neo-squamous epithelium rigorous EMR and biopsy evaluation in a group of 22 post-RFA patients with baseline BE with IMC or HGD showed no evidence of persistent genetic abnormalities or buried BE glands^[43]. To date, as far as we are aware, no published studies exist on outcomes of sole RFA therapy of BE with IMC.

CRYOTHERAPY

Cryotherapy is the latest modality to arrive on the endoscopic horizon of ablative options. This technology utilizes sprayed liquid nitrogen freeze-thaw cycles that result in tissue destruction by intracellular disruption and tissue ischemia, with relative preservation of the extracellular matrix to promote less fibrosis formation^[44,45]. The procedure requires placement of an orogastric decompression tube to allow for adequate excess nitrogen gas expulsion to prevent inadvertent gastrointestinal viscus perforation. Repeat treatment sessions can be conducted every 4-6 wk as needed to ensure complete remission of the target area.

In a prospective open-label trial, Dumot *et al*^[46] enrolled patients with BE and HGD or IMC who were not deemed surgical candidates or who refused esophagectomy. EMR was used for pathological staging of nodular areas before cryoablation and focal residual areas during the follow-up period. Patients with prior ablation therapy were not excluded. Twenty-seven of 30 patients had pathological downgrading post-treatment. After a median follow-up of 1 year, elimination of cancer or downgrading of HGD was achieved in 80% of IMC and 68% of HGD patients. A perforation occurred in a patient with Marfan syndrome, with the prototype system. Of six patients who showed a complete response, three had recurrence of dysplasia or cancer in the gastric cardia.

The efficacy and safety of liquid nitrogen cryotherapy has been demonstrated in a four-center study of 23 patients (17 with HGD, four with IMC, and three with early-stage adenocarcinoma). Complete response to HGD was found in 94% with HGD, and 100% with IMC and cancer. Complete response to IM was noted in 53% with HGD, 75% with IMC, and 67% with cancer. No symptoms were reported in 48% of 323 procedures. Esophageal strictures developed in three patients, but all were successfully treated by dilation. Other complications included chest pain, dysphagia, sore throat, and the gastric perforation noted in the Marfan patient as above^[47].

CONCLUSION

BE early neoplasia treatment has undergone transition from radical esophagectomy to endoscopic organ-preserving options. The key to successful endoscopic management hinges on appropriate selection of candidate patients and detection of visible lesions through careful white light, high-definition endoscopy and ancillary

imaging techniques such as narrow-band imaging and/or endomicroscopy. All visible lesions must be removed by EMR for definitive histopathological staging and to ensure adequacy of resection margins. Total eradication of the entire BE segment must occur to protect against synchronous/metachronous lesion development.

As a result of the higher risk of stricture development associated with EMR, our center currently employs a hybrid approach to treatment of BE early neoplasia that is based on segment length. For BE segments that measure ≤ 5 cm and harbor HGD or IMC, a CBE-EMR approach is used. For patients with BE segments > 5 cm, all focal lesions are resected, and the remaining flat BE is ablated using RFA to decrease the rate of stricture formation.

The critical research issues that still remain unanswered for endoscopic BE management center on: long-term survival and remission rates of both treated neoplasia and IM; development and significance of buried BE glands; quality of life and cost assessments for the various modalities compared to surgical cohorts; the role of these therapies for LGD or non-dysplastic BE; and the clinical impact of post-endoscopic therapy surveillance.

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