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Role of endoscopic therapy in early esophageal cancer

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Abstract

Esophageal carcinoma is a highly lethal cancer associated with high morbidity and mortality. Esophageal squamous cell carcinoma and esophageal adenocarcinoma are the two distinct histological types. There has been significant progress in endoscopic diagnosis and treatment of early stages of cancer using resection and ablation techniques, as shown in several trials in the recent past. Earlier detection of esophageal cancer and advances in treatment modalities have led to improvement in the 5-year survival from 5% to about 20% in the past decade. Endoscopic eradication therapy is the preferred modality of treatment in cancer limited to mucosal layer of the esophagus as there is very low risk of lymph node metastasis, leading to high cure rates, low risk of recurrence and with few adverse effects. The most common adverse events seen are strictures, bleeding and rarely perforation which can be endoscopically managed. In patients with recurrent advanced disease or invasive tumor, esophagectomy with lymph node dissection remains the mainstay of treatment. There is debate on post-endoscopic surveillance with some studies suggesting closer follow up with upper endoscopy every 6 mo for the first 1-2 years and then annually for the 3 years while others recommending the appropriate action only if symptoms or other abnormalities develop. Overall, the field of endoscopic therapy is still evolving and focus should be placed on careful patient selection using a multidisciplinary approach.

Key words: Endoscopic mucosal resection; Endoscopic submucosal dissection; Radiofrequency ablation; Argon plasma coagulation; Esophageal cancer; Photodynamic therapy; Cryotherapy

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Core tip: Endoscopic eradication therapy (EET) plays a pivotal role in the management of patients with early esophageal cancer who are at very low risk for lymph node metastases. The main advantage of EET over surgery is the lower morbidity and mortality rates with similar cure rates, five-year survival rates and better quality of life. These excellent outcomes are tempered by the need for multiple treatment sessions for complete eradication and risk of post eradication recurrences. Careful patient selection by a multidisciplinary approach and patient compliance are crucial for treatment success.

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INTRODUCTION

Esophageal carcinoma is the sixth most common cause of cancer death globally^[1]. Two histological forms exist: esophageal squamous cell cancer (ESCC) and esophageal adenocarcinoma (EAC). ESCC is the most common histological subtype globally, especially in areas of eastern Asia and Africa^[2] and is associated with heavy tobacco and alcohol use. The other histological form is EAC, seen more commonly in the Western world and associated with chronic gastroesophageal reflux disease^[3]. Esophageal carcinoma is a lethal cancer with a five-year survival rate of 19%^[4] due to the fact that more than 70% of cancers have spread beyond the esophagus by the time of diagnosis. In patients with cancer confined to the esophagus, the curative treatment is usually esophagectomy with or without chemoradiation therapy^[5]. These intensive treatment regimens lead to poor quality of life even after therapy and can be associated with recurrences. However, with the advent of organ sparing endoscopic interventions in the past two decades, cure rates of early cancer similar to those with surgery are reported with much better quality of life. There has been significant progress in endoscopic diagnosis and treatment of dysplastic tissue and early stages of cancer using resection and ablation techniques, as shown in several studies in the recent past. Detection of esophageal cancer at an earlier stage and better utilization of treatment modalities, mainly surgery, has lead to improvement in the 5-year survival from 5% to about 20% in the past decade^[4,6]. This editorial provides an understanding of the role of endotherapy in the treatment of early esophageal cancer, patient selection and the clinical outcomes of different modalities.

EARLY ESOPHAGEAL CANCER

Early esophageal cancer is defined as disease confined

to the mucosa or submucosa of the esophagus with no evidence of spread. About 20% of all the cases of esophageal cancers diagnosed constitute early cancer^[7]. Surgery with esophagectomy is considered the standard treatment with an estimated 5-year survival rates up to 90% in tumors which are confined to the mucosal layer^[8]. However, esophagectomy, being a surgical procedure, has its own pitfalls with an operative mortality rate of about 2% and morbidity rate of 10%^[8,9].

Endoscopic eradication therapy (EET) has emerged as a popular method for treatment of early esophageal cancer with favorable outcomes. Studies have found comparable outcomes between EET versus surgery in terms of long term survival^[10,11]. A recent population based study utilizing the Surveillance, Epidemiology and End Results Program (SEER) database compared 2-year and 5-year overall survival and esophageal cancer specific mortality in patients undergoing EET and esophagectomy. They found no difference in cancer related mortality at 2-year (EET: 10.5% vs esophagectomy: 12.7%, $P = 0.27$) and 5-year (EET: 36.7% vs esophagectomy: 42.8%, $P = 0.16$) follow up^[7]. These results were found in patients with T0 (carcinoma *in situ*/high grade dysplasia) and T1a (limited to lamina propria or muscularis mucosa). It is imperative to understand that patients with cancer limited to the mucosa have a very low risk of lymph node metastasis (0% to 2%)^[11] and hence are candidates for EET. However, there are no randomized controlled trials that can provide definitive evidence comparing EET with surgery in terms of superiority.

PATIENT SELECTION

EET, which entails endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is increasingly used in the management of early esophageal cancer with expanding indications. It is not only used for treating precancerous lesions such as Barrett's esophagus (BE) with dysplasia, squamous dysplasia and intramucosal cancer (IMC) but also in selected cases of submucosal cancers (T1b)^[12]. Submucosal tumors are further classified into sm1 (involving one third of submucosa), sm2 (involving two thirds of submucosa) and sm3 (involving lower third of the submucosa). Since EET will address only disease confined to esophagus, the key factor is to exclude those patients who may have local or distant metastases. Therefore, patients should be evaluated with endoscopic ultrasound (EUS) and positron emission tomography (PET) scan for the spread of disease and have a multidisciplinary evaluation with oncologists, thoracic surgeons, pathologists and radiation oncologists before embarking on EET. Patients are to be counselled on the need for multiple treatment sessions and post eradication surveillance.

Candidates for EET in ESSC

According to the 2011 National Comprehensive Cancer Network (NCCN) guidelines, patients with squamous cell dysplasia (low-grade and high grade intra-epithelial neoplasm/carcinoma *in situ*) and T1a where the tumor

invades the lamina propria and muscularis mucosa without lymph node or vascular invasion are candidates for EET^[13]. In ESSC, the risk of lymph node metastases is 0% to 6% for IMC, 8% to 30% for sm1, 30% for sm2 and 60% to 70% for sm3 cancers^[11,14-16]. Therefore treatment differs between T1a and T1b with the latter being treated with esophagectomy. As per Japanese esophageal society guidelines for early SCC, indications for EET are IMC involving the epithelium and lamina propria occupying less than 2/3 of the lumen of the esophagus with relative indications being involvement of the muscularis mucosa or < 200 μ m invasion of the submucosa^[17]. For lesions larger than 15 mm, lesion with poor lifting and for better assessment of the depth of invasion in case of suspicion for submucosal invasion, ESD may be considered^[18].

Candidates for EET in EAC

In EAC, the rate of lymph node metastasis in T1a is 0% to 2% and for sm1, sm2 and sm3 cancers is 0% to 22%, 0% to 30% and 20% to 70% respectively^[11]. Therefore, EET is considered in high grade dysplasia, and IMC lesions with low risk of submucosal invasion. These include Type I (polypoidal), II a (slightly elevated), II b (flat) and II c (slightly depressed) based on Paris classification and smaller lesions (less than 20 mm), histological grades G1 and G2, or high grade dysplasia on biopsy^[19]. Lesions which are excavated, poorly/undifferentiated on biopsy or with lymphadenopathy detected on EUS are better managed by surgery.

Overall, the rate of lymph node metastasis is higher in submucosal invasion by SCC as compared to EAC^[20]. Therefore, stage T1b in ESSC is usually treated surgically with esophagectomy.

EET TECHNIQUES

EET involves endoscopic resection of the cancer followed by ablation of surrounding precancerous tissue to prevent recurrences. The widely used resection techniques are EMR and ESD.

EMR

EMR was initially started in Japan for management of gastric cancer^[21], however, it is now being increasingly used for carcinomas of gastrointestinal tract confined to mucosa and submucosa not only for therapeutic benefits but also for its diagnostic value in staging and ascertaining the depth of invasion as well as degree of differentiation and lymphovascular invasion^[22-25].

EMR technique: The commonly used techniques can be categorized as cap- and ligation-assisted. The simplest technique available is based on snare resection after lifting the submucosa with a saline-epinephrine injection. This is rarely performed in the esophagus now as this is restricted to pedunculated lesions only.

The cap-assisted technique, first described by Inoue and Endo, involves attaching a specially developed trans-

parent plastic cap to the end of the endoscope^[26]. After submucosal injection under the target lesion, the lesion is sucked into the cap and resected using a diathermy loop that has previously been loaded onto a specially designed groove on the lower edge of the cap. This is often referred to as the "suck and cut" technique. Preloading of the loop is easily done in the gastric antrum by applying slight suction to the mucosa and carefully advancing the snare until it is placed exactly in the rim at the distal margin of the cap. The borders of the lesion are marked with electrocautery, before the submucosal injection as it is difficult to identify the borders following the injection.

Another alternative to cap-assisted technique is using a ligation device, based on the same principle of "suck and cut"^[27]. This is the commonest technique performed in the United States. After the target lesion is sucked into the cylinder of the ligation device, there is creation of pseudo-polyp using a rubber band which is released simultaneously at the base of this polyp. The band is subsequently released in a few seconds following the prolapse of the mucosa and submucosa into the cylinder. Following this, the ligation device is removed after withdrawing and re-introducing the endoscope and introducing the loop. The main advantage of this method in comparison with cap resection, is that previous submucosal injection is not necessary. The ligation devices come in both single use and reusable forms^[28]. Recently, newer ligation cylinders have been developed with multiple rubber bands and a facility for advancing a snare through the working channel of a regular endoscope enabling the endoscopist to perform multiple resections without having to withdraw and reintroduce the endoscope^[29].

Both the above described techniques have shown similar efficacy and safety in terms of resection of early esophageal cancers. In a prospective randomized study, 100 consecutive endoscopic resections were performed in 72 patients with early stage esophageal cancer^[30]. There were no significant differences in terms of the maximum diameter of the resection specimen, resection area and the complication rate. Stepwise endoscopic resection technique (SRER) entails resection of BE in multiple sessions with an eventual complete removal of the segment^[24]. Eligible candidates are those with BE length of 5 cm or less, a histological diagnosis of high grade intraepithelial neoplasia or invasive cancer without poor differentiation, lymphovascular spread or positive resection margins^[24].

Outcomes of EMR: EMR, as an effective treatment modality for early EAC was first reported by Ell *et al*^[27] in 2000, where complete remission was seen in 97% of the patients with low risk EAC versus 59% in high risk EAC. However, recurrent carcinomas developed in 14% and 17% in high risk and low risk groups respectively at a mean follow up of 1 year^[27]. To reduce the risk of recurrences, SRER was described by Pouw *et al*^[24], which led to sustained eradication of neoplasia in 95.3% but

Table 1 Comparison of various modalities of endoscopic resection techniques for esophageal cancer

Technique	Focal EMR with ablation	SRER	ESD
Efficacy in ESCC	Curative resection rate 58.6% ^[34]	Curative resection rate 92.3% ^[36]	Curative resection rate 99% to 100% ^[46]
Efficacy in EAC	Eradication of neoplasia 93.4% and eradication of metaplasia 73.1% ^[75]	Eradication of neoplasia 94.9% and eradication of metaplasia 79.6% ^[75]	95% to 97% curative resection rate ^[44,45]
Recurrence	11% for ESCC ^[34] , 1.4% for EAC ^[75]	0.7% for EAC ^[75] 6.9% at one year for ESCC ^[36]	0.9% to 9.8% for ESCC ^[58] , 0.17% for EAC ^[56]
Adverse events	Stricture (5% to 14%) ^[25,61,62] , bleeding (1.1%) ^[75] and perforation (0.2%) ^[75]	Strictures (33% to 88%) ^[24,37] , bleeding (2.4% to 25%) ^[24] and perforation (1.3%) ^[75]	Stricture (15% to 60%) ^[52] , bleeding (0.9% to 6.7%) ^[52,53] and perforations (3%) ^[55]

ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; EMR: Endoscopic mucosal resection; SRER: Stepwise radical endoscopic resection; ESD: Endoscopic submucosal dissection.

found to be associated with strictures requiring repeated dilations in 49% of patients. Therefore focal EMR with ablation of residual mucosa has been described with equivalent outcomes but low rate of strictures compared to SRER^[25,31]. A recent study of 1000 patients with IMC undergoing EMR, showed excellent long term outcomes with 96% of the patients achieving complete response with 10-year survival rate of 75%^[32]. Other studies have also shown 5-year survival in upto 95% to 98% patients with both early SCC and EAC^[27,33]. The long-term outcomes of EMR for SCC are less reported. In a Japanese study of 204 patients with early SCC treated with EMR followed by ablation in the presence of positive margins, 11% of patients experienced recurrence during a median follow of 36 mo^[34]. All patients were able to be treated with subsequent endoscopic therapy. Another study of patients undergoing EMR for ESCC involving muscularis propria or submucosa showed no significant difference in 5-year survival when compared to the surgical group (95.0% and 93.5% respectively)^[35].

Adverse events after EMR: EMR is generally a safe procedure with a low risk of complications. With focal EMR, strictures and bleeding are seen in about 2% respectively^[36]. SRER or extensive EMR can cause bleeding in 2.4% to 25% cases^[24]. The rate of stricture formation is also higher as compared to focal EMR, with rates as high as 33%-88% as shown in some studies^[24,37]. Perforations are rare with EMR and seen in 0-5% of patients^[38]. Focal EMR is associated with high recurrence rate up to 25% to 33% in BE during follow up if the residual BE is left untreated^[39-41]. Therefore, focal EMR should always be followed by ablation of residual BE.

ESD

Similar to EMR, the technique of ESD was first attempted in 1988 in Japan for early gastric cancers^[42] before being applied for treatment of early esophageal cancers. The procedure involves three steps. After marking the resection borders of the lesion using argon plasma coagulation (APC) or ESD knife, a submucosal cushion is created by injecting normal saline or diluted sodium hyaluronate solution. Finally, dissection of the submucosal

layer is achieved after a circumferential incision around the lesion with stripping of the lesion from the muscularis propria. This allows *en bloc* resection of the lesion, irrespective of the size and shape. A carbon dioxide insufflation system is usually used in order to prevent mediastinal emphysema^[43].

Outcomes of ESD: Multiple studies have been published in the literature to look at long term outcomes of ESD. Curative *en bloc* resection rates have been reported to be as high as 100% in ESCC and 95% to 97% in EAC^[44,45]. Resection with tumor free lateral and basal margins (R0 resection) rate was 90% in lesions involving muscularis layer (M3) and about 70% if lesion extends beyond M3 in BE^[44]. More recently, a meta-analysis of 21 studies on ESD for ESCC, the pooled *en bloc* resection rate was 99% to 100% for the tumors and R0 resection rate 90% to 92%. Larger tumors with diameter greater than 2.5 cm achieved lower curative resection rates as compared to the smaller tumors^[46].

Overall, ESD has led to excellent *en bloc* resection rates and curative resection rates in Asian countries^[47,48]. Studies conducted in Europe have shown high *en bloc* resection rates up to 95% and curative resection rates up to 72% with a recurrence rate of 2.5%. Disease specific survival was 97% with an overall survival of about 96%^[44]. Ishihara *et al*^[49] in their retrospective study on 136 patients in Japan, showed that ESD was associated with high curative resection rates irrespective of the size of the lesion.

ESD has been studied in BE related neoplasia in studies described from western world, with lesions with high risk for submucosal invasion, size more than 15 mm and poorly lifting in nature. The resection rates were not sufficiently high enough to warrant its use over piecemeal EMR. When performed with ablation, it achieved complete remission in 96% of patients^[50]. A European study showed comparable resection rates in BE neoplasia with both EMR and ESD with complete remission, however, ESD was associated with more adverse events and was more time consuming^[51].

Adverse events after ESD: ESD is a technically demanding procedure with a learning curve and has

adverse events similar to, but more frequent, than in EMR. The most common complications are bleeding and stricture formation. In patients with BE undergoing ESD, bleeding rates are 0.9% to 6.7%^[52] and strictures are reported in 15% to 60% of patients^[52,53]. In patients undergoing ESD for ESCC, the rates of strictures may be higher if the entire circumferential esophagus is dissected and > 5 cm of longitudinal mucosal defect length is present^[54]. Perforation rates of 3.3% have been reported after esophageal ESD in Japan of which, over half the patients required open thoracotomy for repair^[55]. A lower hospital volume and female sex were factors associated with a higher occurrence of complications. In a meta-analysis of ESD in BE related neoplasia, the pooled estimates for perforation and bleeding were 1.5% and 1.7% respectively with a stricture rate of 11.6%^[56]. Incidence of recurrence after curative resection was 0.17% (95%CI: 0%-0.3%) at a mean follow-up 22.9 mo (95%CI: 17.5-28.3)^[56].

Comparison between EMR and ESD

In patients with BE-related neoplastic lesions larger than 15 mm, lesions with poor lifting and to better assess depth of invasion if submucosal invasion is suspected, ESD is considered superior to EMR^[18,57]. However, EMR is preferred in BE associated neoplasia as ESD has not been proven to be superior to EMR in terms of clinical outcomes in a randomized controlled trial^[51]. Ishihara *et al.*^[49] in their retrospective study, showed that in lesions smaller than 15 mm, both the techniques are comparable in achieving complete resection. In patients with ESCC, higher R0 resection rates (100% vs 53%) and lower recurrence (0.9% vs 9.8%) has been associated with ESD as compared to EMR as shown in a large retrospective study^[58]. Similar results were seen in a more recent meta-analysis in Asian population undergoing ESD versus EMR for early esophageal cancer^[38]. Strictures are frequently encountered in both EMR and ESD. In a meta-analysis of eight studies, the rates of stricture formation were comparable in both groups^[38]. A comparison of both techniques are presented in Table 1.

ABLATION TECHNIQUES

Ablative treatment mainly implies destruction of the neoplastic tissue by thermal injury in the form of heat through burning, coagulation and necrosis or freezing. Following EMR or ESD, radiofrequency ablation (RFA) or argon plasma coagulation (APC) are performed typically after 8-12 wk to eradicate the remaining BE or squamous dysplasia^[59]. It is important to confirm the absence of any residual cancer by pathological staging of the specimen. Other ablative techniques such as cryotherapy and photodynamic therapy (PDT) have been used for in patients with early stage cancer independent of EMR.

RFA

This is the most widely used ablation technique, primarily

for ablation of dysplastic tissue after resection of cancer. It should not be used as the sole treatment modality for early esophageal cancer. This technique uses a radiofrequency generator and balloon/focal ablation catheters which deliver radiofrequency energy waveform to the epithelium, leading to water vaporization, protein coagulation and subsequent tissue necrosis^[60].

Combination of focal resection of cancer followed by ablation of residual BE with RFA showed a complete eradication of dysplasia and intestinal metaplasia of 91% and 78%, respectively at one year follow up^[31]. Recurrence of metaplasia is usually seen in the distal part of esophagus or at the gastro-esophageal junction with rates between 13% and 33%, necessitating the need for lifelong surveillance^[31]. Complications seen with RFA are strictures and rarely, bleeding. Strictures can develop in 5% to 14% patients with comparable rates in patients with prior EMR^[25,61,62].

In contrast to EAC, there is sparse literature on the use of RFA in early ESCC. In a study of 13 patients with ESCC who underwent EMR and subsequent circumferential RFA, complete eradication was seen after a median of two RFA sessions^[63]. Three patients developed stenosis and none had recurrence at 17 mo follow up. Similarly, in a bigger cohort study on 29 patients undergoing EMR and RFA for either moderate grade, high grade or flat type early SCC, 97% patients had complete response at 12 mo with no further progression^[64]. Results from a United Kingdom registry study on early SCC, showed some contrasting results with 50% patients achieving complete eradication at 1 year follow up and 30% progressing to invasive cancer eventually^[65]. Flat ESCC may be under-staged as it is based on endoscopic appearance only, hence endoscopic resection therapies should be preferred over ablation as there might be a higher risk for tumor progression with failure to completely eradicate them.

APC

This is a focal noncontact method of thermal ablation which uses argon gas to conduct electrical current to the target tissue and causes tissue necrosis. Its utility in the management of ESCC is mainly limited to T1a and T1b lesions which are not amenable to endoscopic therapy due to underlying comorbidities. It has shown to be somewhat successful in achieving curative rates with less recurrences. Min *et al.*^[66] in their study on 19 patients with ESCC who underwent APC, showed that 95% patients achieved complete response at 1 year follow up. However, it is less effective in improving long term survival in patients with early esophageal cancer^[67]. APC has shown promising results in the treatment of flat BE lesions which recur or are residual after EMR, ESD or RFA^[68]. However, its use is fairly limited to pre-cancerous lesions of the esophagus and indications should be carefully considered in management of early cancer. There are limited studies on the role of APC in the treatment of BE lesions. No studies have reported the

use of APC in EAC.

PDT

This involves the use of laser therapy which is used to activate a photosensitizer, administered either orally or intravenously, to the target lesion leading to ischemia and cell necrosis. Main indication of PDT is palliative treatment in advanced cancers and after failure of chemotherapy and high grade dysplasia in BE. However, some studies supported the use of this technique in treatment of early esophageal cancer. Overholt *et al*^[69] reported use of PDT in 13 patients with T1-T2 EAC with eradication of 77% of cancers. In a case series of 14 patients with T1 cancers, 13 patients had complete eradication of cancer^[70]. Tanaka *et al*^[71] in their retrospective study of 38 patients with early SCC lesions which were too large for endoscopic treatment, showed complete remission in 87% patients after undergoing PDT. Similar rates have been observed in patients with carcinoma *in situ* or T1a ESSC lesions^[72]. Main complications of the procedure are stricture formation and photosensitivity. They can develop in about 30% and 70% of patients respectively^[69,70].

Cryotherapy

This method involves the use of liquid nitrogen to deliver thermal energy at -196 degrees Celsius causing repeated cycles of freezing and thawing target tissue which leads to immediate as well as delayed necrosis. In a multicenter study of 88 patients with EAC (39 with T1a, 25 with T1b, 9 with unspecified T1, and 15 with T2), complete response of intraluminal disease was seen in 55.8% of the patients^[73]. The complete response rates were 76.3% for T1a, 45.8% for T1b, 66.2% for all T1, and 6.7% for T2 during a mean follow-up was 18.4 mo. There were no deaths or perforations related to spray cryotherapy. Strictures developed in 12 of 88 patients (13.6%) but were present before spray cryotherapy in 3 out of 12 patients. Use of a new cryoballoon system using nitrous oxide has been developed and its use was reported in 9 patients with squamous dysplasia and one with ESCC. All patients were disease free at last visit, with a median follow-up time of 10.7 mo^[74].

CONCLUSION

EET plays a pivotal role in the management of patients with early esophageal cancer who are at a very low risk for lymph node metastases. The main advantage of EET over surgery is the lower morbidity and mortality rates with similar cure rates, five year survival rates and better quality of life. These excellent outcomes are tempered by the need for multiple treatment sessions for complete eradication and risk of post eradication recurrences. Careful patient selection by a multidisciplinary approach and patient compliance are crucial for treatment success.

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