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MINIREVIEWS

Resection of early esophageal neoplasms: The pendulum swings from surgical to endoscopic management

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Abstract

Esophageal cancer is a highly lethal disease and is the sixth leading cause of cancer related mortality in the world. The standard treatment is esophagectomy which is associated with significant morbidity and mortality. This led to development of minimally invasive, organ sparing endoscopic therapies which have comparable outcomes to esophagectomy in early cancer. These include endoscopic mucosal resection and endoscopic submucosal dissection. In early squamous cell cancer, endoscopic submucosal dissection is preferred as it is associated with cause specific 5-year survival rates of 100% for M1 and M2 tumors and 85% for M3 and SM1 tumors and low recurrence rates. In early adenocarcinoma, endoscopic resection of visible abnormalities is followed by ablation of the remaining flat Barrett's mucosa to prevent recurrences. Radiofrequency ablation is the most widely used ablation modality with others being cryotherapy and argon plasma coagulation. Focal endoscopic mucosal resection followed by radiofrequency ablation leads to eradication of neoplasia in 93.4% of patients and eradication of intestinal metaplasia in 73.1% of patients. Innovative techniques such as submucosal tunneling with endoscopic resection are developed for management of submucosal tumors of the esophagus. This review includes a discussion of various endoscopic techniques and their clinical outcomes in early squamous cell cancer, adenocarcinoma and submucosal tumors. An overview of comparison between esophagectomy and endoscopic therapy are also presented.

Key words: Esophageal cancer; Submucosal tumors; Submucosal tunneling; Barrett's esophagus; Dysplasia; Adenocarcinoma; Endoscopic therapy; Radiofrequency ablation; Endoscopic mucosal resection

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Core tip: Advances in endoscopic therapies led to organ preserving endoscopic treatments for early esophageal cancer and submucosal tumors of the esophagus. These techniques include endoscopic mucosal resection, endoscopic submucosal dissection and submucosal tunneling endoscopic resection. Ablative techniques are useful for treatment of residual dysplasia.

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INTRODUCTION

Esophageal neoplasms are mostly malignant with benign tumors accounting for less than 1% esophageal tumors[1]. Globally, esophageal cancer was the seventh leading cancer with 572034 new cases (3.2% of all cancers) and the sixth leading cause of cancer related mortality with 508, 585 cancer related deaths (5.3% of all cancer mortality) in 2018[2]. In the United States alone, about 17650 new esophageal cancer cases will be diagnosed and 16080 deaths from esophageal cancer are estimated to occur in 2019[3]. The major histologic subtypes of esophageal cancer are squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). ESCC is the most common subtype globally accounting for over 88% of esophageal cancers[4]. In Australia, western Europe and United States, the incidence of EAC has increased steadily with a simultaneous decline in ESCC making EAC the predominant subtype[5]. Treatment of esophageal cancer depends on the stage of disease with esophagectomy being the main stay of treatment for localized disease with additional neoadjuvant therapy for regional disease. In the past three decades, endoscopic therapy is increasingly used for treatment of early stage cancers when there is minimal risk of lymph node metastases.

SURGICAL MANAGEMENT OF ESOPHAGEAL NEOPLASMS: ESOPHAGECTOMY

The conventional management of esophageal cancer is esophagectomy and lymph node dissection performed through a transhiatal or transthoracic approach[3]. Transhiatal approach includes laparotomy and left cervical anastomosis typically without a thoracotomy. Transthoracic approach involves either Ivor Lewis (right thoracotomy and laparotomy) or McKeown esophagectomy (right thoracotomy, laparotomy, and cervical anastomosis). Esophagectomy has high curative rates and five year survival rates in early stage cancers[6]. However, it is highly invasive with substantial morbidity and mortality. The overall incidence of adverse events varies between 20%-80% and include pulmonary complications such as pneumonia, respiratory failure and aspiration; myocardial infarction, atrial fibrillation; anastomotic leak and recurrent laryngeal injury[7]. Patients need prolonged hospitalization following esophagectomy with mean intensive care unit and hospital length of stay (LOS) of 3.35 and 13.54 d respectively[8]. Mortality rates after esophagectomy vary depending on where it is performed: low volume hospitals have higher rates of in-hospital mortality [8.48% *vs* 2.82%; pooled odds ratio (OR) = 0.29, $P < 0.0001$] and 30-d mortality (2.09% *vs* 0.73%; pooled OR = 0.31, $P < 0.0001$) compared with high volume hospitals[9].

Minimally invasive esophagectomy (MIE) strategy was developed to decrease the morbidity and mortality associated with standard esophagectomy and to improve quality of life (QOL). MIE is performed *via* laparoscopy or *via* thoracoscopy with or without laparoscopy and simultaneous lymph node sampling or dissection. The operative mortality of MIE is about 1.68% and 30-d mortality is 2.1%[10]. When compared with open esophagectomy, MIE has shorter hospital LOS (14.9 *vs* 19.6 d) and intensive care unit LOS (4.5 *vs* 7.6 d) and fewer complications (relative risk 1.20,

95%CI: 1.08-1.34, P = 0.0009)[11]. MIE, however, requires longer operative time and higher costs compared to standard esophagectomy[12].

ENDOSCOPIC MANAGEMENT OF ESOPHAGEAL NEOPLASMS

Esophagectomy is associated with excellent outcomes in early esophageal cancer localized to mucosa but the risk of considerable morbidity and mortality and decreased QOL led to development of alternative techniques grouped under endoscopic eradication therapy (EET)[13]. In carefully selected patients such as those with T1a cancers, lymph node metastases are rare making EET feasible and curative while preserving the esophagus. The multiple EET modalities can be broadly classified into resection techniques [endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and submucosal tunneling endoscopic resection (STER)] and ablative techniques which include radiofrequency ablation (RFA), photodynamic therapy (PDT), cryotherapy and argon plasma coagulation (APC). With resection, abnormal areas are removed and assessed histologically for staging. With ablation techniques, the abnormal area is destroyed and hence not available for histological evaluation.

ENDOSCOPIC RESECTION TECHNIQUES

EMR

EMR was pioneered in Japan for the management of early gastric neoplasia and soon gained widespread use (Table 1). EMR in esophagus was first reported by Inoue in 1990[14]. EMR is used to remove sessile, flat or discrete mucosal lesions < 2 cm in size and involving less than two-thirds of the circumference of esophageal wall. EMR helps to determine local stage, degree of differentiation and lymphovascular invasion[15]. In injection-assisted EMR, saline or dilute epinephrine is injected in the submucosa of the visible lesion to lift the mucosa away from muscularis propria. This fluid cushion protects the deeper layer from injury during removal of the lesion by electrocautery. In cap-assisted EMR, a plastic cap (Olympus, Tokyo, Japan) is fitted over the tip of the endoscope along with a snare that is located along the internal circumferential groove of the cap. After submucosal injection, the mucosa is suctioned into the cap, the snare is closed around the target site and the lesion is resected using electrocautery. In ligation-assisted EMR, a band ligation device (Duette Kit, Cook Medical Inc., Winston-Salem, NC or Captivator EMR device, Boston Scientific, Marlborough, Mass) is fitted on the tip of the endoscope. The lesion is suctioned into the device and a band is deployed at the base of the tissue to create a pseudopolyp which is then resected using an electrocautery snare. Ligation allows multiple resections (up to 6) in single intubation. Focal EMR is removal of visible lesions only and is usually followed by ablation of remaining Barrett's esophagus (BE) tissue. Stepwise radical EMR is removal of entire BE segment in single or multiple sessions. EMR is safe, quick and has few complications (Table 2). In a study on 1000 patients who underwent EMR, major complications occurred in 1.5% which included major bleeding in 14 patients and perforation in 1 patient[13]. Minor complications included stenosis requiring endoscopic dilation in 13 patients. With stepwise radical EMR, early complications include perforation (1%) and bleeding(1.0%) which can be managed endoscopically[16]. Later, symptomatic stricture formation can occur in over 49.7% of patients and requires endoscopic dilation, stent placement or incision therapy[16].

ESD

ESD was introduced in 1988 in Japan to treat gastric neoplasia and subsequently, its use was extended to treat superficial esophageal cancer[17] (Table 1). ESD allows *en-bloc* resection of lesions irrespective of the size. Lugol's solution is applied to highlight abnormal areas and mucosal markings are made with a needle knife or with APC about 5 to 10 mm away in EAC and close to the margins in ESCC to avoid stenosis. An initial mucosotomy is made with a needle knife to expose the submucosal layer, and then the incision is extended circumferentially around the lesion with a needle knife or insulated tip knife about 5 mm outside of the marking leaving 10 mm of normal tissue between incision and tumor. Hydroxymethylcellulose is injected to lift the submucosa and then dissected with ESD knife parallel to the muscular layer to remove the tumor. ESD is a technically demanding and time consuming procedure. Complications include bleeding in 1.5% to 1.8%, perforation in 1.5% to 4.6% and

Table 1 Summary of the history and role of all endoscopic therapies

Technique	History	Indications/role
EMR	EMR was introduced in Japan to treat early gastric cancer and its use in esophagus was first reported by Inoue in 1990[14]. EMR use determines local stage, degree of differentiation and lymphovascular invasion[15]	EMR is indicated to remove sessile, flat or discrete mucosal lesions < 2 cm in size and involving less than two-thirds of the circumference of esophageal wall[14] Focal EMR is removal of visible lesions only. Stepwise radical EMR is removal of entire Barrett's segment in single or multiple sessions
ESD	ESD was introduced in 1988 in Japan to treat gastric cancer and subsequently, its use was extended to treat superficial esophageal cancer[17]	ESD is indicated for *en-bloc* resection of lesions irrespective of the size. ESD is a technically demanding and time consuming procedure
STER	STER was introduced in 2011 and is based on the principles of peroral endoscopic myotomy and ESD[21]	STER is used to resect submucosal tumors[21]. The advantage of STER is preservation of mucosal integrity that lowers adverse outcomes[23]
RFA	RFA was introduced in 2005 and is now a well-established modality for early esophageal cancer which utilizes high frequency alternating electrical current to generate thermal energy for ablation[25]	RFA is the standard of care in flat mucosal lesions[25]. In RFA, a circumferential catheter is used to ablate ≥ 3 cm Barrett's segment or a focal catheter for shorter segments
PDT	PDT was one of the first techniques described for treatment of Barrett's associated neoplasia	PDT is associated with many complications and is not commonly used in the United States any more
Cryotherapy	Cryotherapy was introduced in 1851 by James Arnott to freeze tumors[27]. The application of Cryotherapy was extended to the esophagus in 1997 using an endoscope	Cryotherapy circumvents the need for mucosal contact making ablation of an uneven or nodular surface feasible[27]. CbFAS uses cryogenic fluid and overcomes the challenges of unequal distribution and need for decompression tube
Hybrid-APC	APC was introduced in the early 1990s to perform thermal coagulation of tissue[25]. More recently, Hybrid APC in which a submucosal cushion is created before APC is being used[28]	Hybrid APC is indicated in Barrett's esophagus up to 3-5 cm in length and the cushion controls the depth of ablation[28]

APC: Argon plasma coagulation; CbFAS: Cryoballoon focal ablation system; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; PDT: Photodynamic therapy; RFA: Radiofrequency ablation; STER: Submucosal tunneling endoscopic resection.

strictures in 6.5% to 11.6% that is treated endoscopically without long-term complications[18,19] (Table 2). Prophylactic use of steroids has been suggested to decrease the stricture rate and frequency of endoscopic balloon dilations[20].

STER

STER was introduced in 2011 and is based on the principles of peroral endoscopic myotomy and ESD[21]. STER is used to resect gastrointestinal submucosal tumors (SMT) by creating a tunnel between submucosa and muscularis propria. About 3-5 cm proximal to the tumor, a submucosal cushion is raised[22]. The mucosa is incised to create an entrance to the tunnel and the submucosa is dissected to form a tunnel advancing towards the tumor. Then the tumor along with its capsule is dissected and removed. Endoscopic clips are used to close the tunnel. The advantage of this process is that the mucosal integrity is maintained which lowers adverse outcomes[23] (Table 2). The most common complications are subcutaneous emphysema and pneumomediastinum in 14.8%, pneumothorax in 6.1% and pneumoperitoneum in 6.8%[24]. Less common complications include pleural effusion (16.9%), mucosal injury (5.6%), esophageal fistula and diverticulum[24]. Majority of STER-related complications can be treated conservatively.

ABLATION TECHNIQUES

Ablation is performed to eradicate abnormal tissue either by thermal injury (heat in RFA and cold in cryotherapy) or photochemical injury (PDT). The underlying principle is that the destruction abnormal neoplastic tissue leads to regrowth of normal squamous epithelium in an environment of maximum acid suppression either by proton pump inhibitors or antireflux surgery. Optimal dosimetry (number of applications and time of exposure) aims to limit tissue damage beyond the mucosal layer to avoid complications.

RFA

RFA is a well-established ablation modality which utilizes high frequency alternating electrical current to generate thermal energy[25] (Table 1). Commercially available RFA

Table 2 Summary of the efficacy and complications of all endoscopic therapies

Technique	Efficacy	Complications
Focal EMR and ablation	CE in EAC: 96.3%[13] and ESCC: 90%[54]	Major bleeding: 1.4%[13] Perforation: 0.1% Strictures: 1.3%
Stepwise radical EMR	CE-N: 94.9%[42] CE-IM: 79.6%	Bleeding: 1.0%[16] Perforation: 1.0% Strictures: 49.7%
ESD	*En-bloc* resection rate in EAC: 92.9%[18] and ESCC: 90%-100%[55-57] Complete resection rate in EAC: 74.5%[18] Curative resection rate in EAC: 64.9%[18] and ESCC: 88%-97%[55-57]	Bleeding: 1.5%-1.8%[18,19] Perforation: 1.5%-4.6% Strictures: 6.5%-11.6%
STER	Complete Resection rates in SMTs: 100%[24]*En-bloc* resection rates in SMTs: 98.6%	Subcutaneous emphysema and pneumomediastinum: 14.8%[24] Pleural effusion: 16.9% Pneumoperitoneum: 6.8% Pneumothorax: 6.1% Mucosal injury: 5.6%
RFA	CE-D: 81%[44] CE-IM: 77.4%[44] CE in ESCC: 84%[61]	Strictures: 6%[25] Chest pain: 2% Bleeding: 1%
PDT	Discontinued in the United States	Photosensitivity reactions: 69%[25] Esophageal strictures: 36% Chest pain: 20%
Cryotherapy	CE-HGD: 98%[46] CE-D: 94% CE-IM: 82%	Abdominal pain: 19.3%[27] Dysphagia: 10.2% Sore throat: 9% Chest pain: 8% Strictures: 0-12.5%
Hybrid-APC	CE-IM:78%[28]	Strictures: 2%[28]

APC: Argon plasma coagulation; CE-D: Complete eradication of dysplasia; CE-HGD: Complete eradication of high grade dysplasia; CE-IM: Complete eradication of intestinal metaplasia; EAC: Esophageal adenocarcinoma; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; ESCC: Esophageal squamous cell carcinoma; PDT: Photodynamic therapy; RFA: Radiofrequency ablation; SMT: Submucosal tumors; STER: Submucosal tunneling endoscopic resection.

devices include the Barrx™360 express RFA balloon catheter, Barrx™ RFA 90 catheter, Barrx™ 60 RFA focal catheter, Barrx™ ultra long RFA focal catheter Barrx™ and channel RFA endoscopic catheter (Medtronic, Sunnyvale, CA, United States)[25]. Circumferential catheter is used for ablation of BE segments ≥ 3 cm whereas focal catheters are used for ablation of shorter segments. Before performing circumferential RFA, the mucosa is sprayed with 1% N-acetyl cysteine to remove the mucus and balloon catheter is introduced over a guidewire. The balloon is inflated and energy is delivered by one application of 10 J/cm^2 followed by cleaning and second application. Focal catheters are mounted on the endoscope or passed through the accessory channel and 2 applications of 12 J/cm^2 are delivered followed by cleaning and second application. RFA is safe with very rare complications making direct RFA the standard of care in flat mucosal lesions (Table 2). Stricture formation is reported in 6% after RFA alone and in 13% when RFA is preceded by EMR[25]. Additionally, chest pain requiring hospitalization (2%), bleeding (1%), esophageal mucosal tears and perforation were reported[25].

PDT

PDT was one of the first techniques described for treatment of BE associated neoplasia (Table 1). In PDT, a photosensitizing drug such as porfimer sodium intravenously or 5-aminolevulinic acid orally is administered. It localizes to the esophagus and is activated by a certain wavelength of light. A photochemical reaction then leads to the generation of oxygen radicals which induce neoplastic tissue damage. Complications were many including photosensitivity reactions (69%), esophageal strictures (36%) and chest pain (20%)[25] (Table 2). Even though effective, PDT was largely replaced by RFA in view of severe adverse effects.

Cryotherapy

In cryotherapy, the esophageal mucosa is exposed to repeated cycles of rapid freezing and slow thawing which cause tissue damage of the cells and their organelles by apoptosis (Table 1). Commercially available cryotherapy options include cryospray and cryoballoon. In cryospray (CryoSpray Ablation Medical, Lexington, Mass, United States), the cryogen (liquid nitrogen) is sprayed onto the mucosa at low pressure (2-4 PSI) for 10 to 20 s. A decompression tube is used to evacuate large quantities of expanded gas released into the stomach. This is followed by thawing of mucosa and repeating the freezing for 2-3 cycles at each site. Cryospray circumvents the need for mucosal contact making ablation of an uneven or nodular surface feasible. Recently, cryoballoon focal ablation system (CbFAS) was introduced in which the cryogenic fluid (liquid nitrous oxide) is delivered by direct mucosal contact through an inflated balloon catheter (Pentax Medical, Montvale, NJ, United States)[25,26]. CbFAS overcomes

the challenges of cryospray such as unequal distribution and need for decompression tube. Cryotherapy is generally safe and well tolerated[27]. Abdominal pain (19.3%), dysphagia (10.2%), sore throat (9%), chest pain (8%) and strictures (0-12.5%) are the most common post-procedural side effects[27] (Table 2). Cryotherapy allows deeper ablation than RFA with fewer complications; hence cryotherapy is often considered when RFA cannot be used.

APC

APC was introduced in the early 1990s and employs high frequency current for thermal coagulation of tissue carried through ionized argon gas[25] (Table 1). Heat generated in the process desiccates and shrinks the tissue to a limited depth that depends upon the application time and operative distance between the probe and tissue. A power setting of 30-90 W is used. In Hybrid APC, a submucosal cushion is created before APC is delivered to the mucosa to control the depth of ablation and this leads to decreased stricture formation (2%)[28] (Table 2).

OUTCOMES: EET VERSUS ESOPHAGECTOMY

Standard esophagectomy, MIE and EET have been employed for the management of early esophageal cancer and have similar survival outcomes that are sustained over long term follow up. However, EET is associated with lower morbidity, mortality and costs and easier availability making the pendulum swing from surgical to endoscopic management in early esophageal neoplasms. In a Surveillance, Epidemiology and End Results database study of 2661 patients with early esophageal cancer treated by either esophagectomy or EET, no significant difference in overall survival [hazard ratio (HR) = 1.216, 0.854-1.731, P = 0.279] or esophageal cancer specific survival (HR = 0.692, 0.404-1.184, P = 0.179) was noted between the two groups[29]. In another study on 114 patients with T1a EAC, complete eradication was achieved in 100% patients who underwent esophagectomy (n = 38) and in 98.7% who underwent EET (n = 75) and these rates were maintained even after about 4-years follow up[30]. Despite the comparable survival rates, esophagectomy is associated with major complications (32%) and high 90-d mortality (2.6%) compared to EET (0% for both). Esophagectomy also carries the risk of substantial morbidity, high overall mortality (> 2%) and higher costs ($53849 *vs* $22640 for EET, $P < 0.001$)[31,32]. While EET is associated with a higher recurrence rate of 6.6%, recurrences can be treated endoscopically[30]. To overcome the drawbacks of standard esophagectomy, MIE was introduced which had comparable outcomes to EET. One study compared the two treatment modalities and found similar rates in the treatment of early esophageal cancer (R0 resection rate 94.9% *vs* 97.5%, $P > 0.05$), 3-year survival (96.6% *vs* 97.5%, $P > 0.05$), 4-year survival (91.5% *vs* 90%, $P > 0.05$) and local recurrence ($P > 0.05$)[33]. However, EET was superior with fewer complications (11.8% *vs* 32.5%, $P > 0.05$), shorter operative time (74 ± 23 min *vs* 298 ± 46 min), hospital LOS ($P < 0.001$) and recovery time compared to MIE[33]. Therefore, EET is increasingly used as it is cost effective, has minimal morbidity and mortality with excellent long-term survival comparable to esophagectomy.

ROLE OF ENDOSCOPIC ULTRASOUND IN EARLY ESOPHAGEAL CANCER

Staging of the tumor is an essential step before determining the approach to management. Staging includes establishing the extent of the tumor by depth of invasion (T-staging), lymph node invasion (N-staging) and metastases (M). The imaging modalities used for staging include computerized tomography/positron emission tomography and endoscopic ultrasound (EUS). EUS is the most accurate tool for evaluating locoregional spread with accuracy of T-staging varying from 81.6% to 92.4%[34]. In a meta-analysis of studies involving EUS-based staging of pre-operative ESCC compared with pathological staging, the pooled sensitivity for T1a was 84%, T1b was 83% and T4 84%[35]. The overall accuracy of EUS for T-staging in ESCC was 79%, and for N-staging was 71%. However, it's utility in management of superficial EAC has been questioned as it is suboptimal in differentiating T1a and T1b cancers[36]. In a recent meta-analysis of 895 patients with BE associated neoplasia, the false positive rate for advanced disease was 9.1% and false negative rate was 9.2% with an overall accuracy of 74.6%[37]. This implies that about 1 in 4 patients will be misstaged with EUS. Rather, careful inspection and endoscopic therapy has been proposed for accurate staging as this approach provides histological specimen for examining depth of invasion and features of lymphovascular spread. For N-staging of regional lymph

nodes, EUS helps in identifying abnormal nodes and by facilitating fine needle aspiration (FNA). The sensitivity and specificity of EUS for N- staging is 84.7% and 84.6% respectively which increased to 96.7% and 95.5% respectively with the addition of FNA[34].

EET IN BE AND EAC

Patient selection

EET is indicated in early EAC with negligible risk of lymph node metastases. T1a cancers are associated with low risk of lymph node metastasis (< 2%) and hence amenable for EET[31]. The risk of lymph node metastases increases with depth of tumor infiltration, lymphatic vessel infiltration, tumor differentiation (well differentiated or moderately differentiated versus poorly differentiated) and vascular infiltration[38]. In T1b cancers, surgical resection is preferred as lymph node metastases have been reported in up to 50% of patients[39]. However, recent studies show that in well differentiated T1b tumors with submucosal invasion ≤ 500 μm and lack of lymphovascular invasion, the risk of lymph node metastasis is 0% to 2% and hence, EET can be safely employed[40]. The indications for esophageal ESD include visible lesions ≥ 15 mm (not amenable to enbloc resection by EMR) and patients with BE with the following features: Large or bulky area of nodularity, equivocal preprocedure histology, T1a tumors, suspected superficial submucosal invasion, recurrent dysplasia or EMR specimen showing invasive carcinoma with positive margins[41].

Outcomes

EMR is very effective in the management of T1a tumors. The largest experience of EMR in esophageal cancer comes from a series of 1000 patients with T1a tumors[13]. After a mean follow up period of 56.6 mo, 963 patients (96.3%) achieved a complete response and surgery was necessary in 12 patients (3.7%) after EET failed (Table 2). Metachronous lesions developed during the follow up period in 140 patients (14.5%) but endoscopic retreatment was successful in 115, resulting in a long term complete remission rate of 93.8%. The calculated 10-year survival rate of patients who underwent EET of T1a tumors was 75%. In a meta-analysis, focal EMR followed by RFA and stepwise radical EMR were found to be equally effective for the treatment of BE-high grade dysplasia (HGD) and T1a tumors[42]. Focal EMR followed by RFA showed complete eradication of neoplasia in 93.4% of patients and complete eradication of intestinal metaplasia (CE-IM) in 73.1% of patients. The recurrence rates of EAC, dysplasia and IM were 1.4%, 2.6% and 16.1% respectively. Stepwise radical EMR showed CE of neoplasia in 94.9% of patients and CE-IM in 79.6% of patients with recurrence rates for EAC, dysplasia and IM of 0.7%, 3.3% and 12.1% respectively (Table 2).

Studies also found ESD to be effective in the management of early EAC with high resection rates and low recurrence rates. A meta-analysis evaluated the efficacy of ESD in early BE neoplasia[18]. The pooled estimate for enbloc resection was 92.9%, complete resection rate was 74.5% and curative resection rate was 64.9% respectively (Table 2). Recurrence after curative resection was 0.17% at a mean follow up 22.9 mo. In a randomized control trial comparing ESD to EMR, R0 resection was achieved more frequently with ESD (10/17 *vs* 2/17, $P = 0.01$), but there was no difference in complete remission from neoplasia at 3 mo (ESD 15/16 *vs* EMR 16/17, $P = 1.0$)[43]. ESD is, however, more time consuming and may cause severe adverse events and hence should be reserved for larger lesions which are amenable for EMR.

The goal of EET in EAC is enbloc resection of cancer with negative margins followed by ablation of residual BE. Therefore, CE-IM is the goal. RFA is the most widely used ablation technique. The efficacy of RFA to eradicate dysplastic BE was evaluated in a multicenter, randomized sham-controlled trial[44]. Complete eradication of dysplasia (CE-D) occurred in 81% of patients with HGD (*vs* 19% in sham arm) and CE-IM in 77.4% of patients with HGD (*vs* 2.3% in sham arm) (Table 2). RFA also lowered the risk of progression to EAC (1.2% *vs* 9.3%, $P = 0.045$). In a comparative model analysis, RFA treatment for BE-HGD decreased the incidence of EAC by 51%, EAC mortality by 44% and the number of treatments needed to avert one EAC death was 44[45]. The strategy was resource intensive with an incremental cost effectiveness ratio of $182093-$422256/quality adjusted life year (QALY) that is above a $100000/QALY willingness-to-pay threshold[45].

In a study evaluating the outcomes of cryotherapy on patients with BE-HGD and T1a tumors, initial CE-HGD, CE-D and CE-IM occurred in 98%, 90% and 60% of the patients respectively[46] (Table 2). This effect was durable with overall CE-HGD, CE-D and CE-IM of 96%, 94%, 82% respectively at 3 years and 93%, 88% and 75%

respectively at 5 years[46]. After initial eradication, the recurrence rates of IM, dysplasia and HGD/EAC per person-year of follow up was 12.2%, 4.0% and 1.4% per person-year for the 5-year cohort. In a study on patients with BE associated dysplasia or T1a tumors who underwent cryotherapy or RFA, CE-IM was achieved in 52.6%, CE-D in 86.4% and persistent dysplasia or cancer in 12.3%[47]. Compared to cryotherapy, patients who underwent RFA had 3-fold higher CE-IM (OR 2.9, 1.4-6.0, P = 0.004) but the odds for CE-D was similar between the two treatments (OR 1.7, 0.66-4.3, P=0.28). CbFAS is effective for primary or rescue therapy for BE-HGD or IM. In a recent study evaluating the efficacy of CbFAS in 41 patients with BE associated neoplasia, the overall 1-year CE-D and CE-IM were 95% and 88% respectively[26].

Risk of recurrence after EET in EAC

The recurrence rates after EET for IM, dysplastic BE, and HGD/EAC are 7.1% (95%CI: 5.6-8.6), 1.3% (95%CI: 0.8-1.7), and 0.8% (95%CI: 0.5-1.1) per patient-year, respectively[48]. After RFA alone, the recurrence rates of IM, dysplastic BE, and HGD/EAC after RFA are 9.5% (95%CI: 6.7-12.3), 2.0% (95%CI: 1.3-2.7), and 1.2% (95%CI: 0.8-1.6) per patient-year, respectively[48]. Any persistence of IM is associated with an increased risk of recurrence; therefore, CE-IM is the goal. Recurrence after EET is treated by repeat EET until complete eradication and infrequently may require surgical intervention.

EET IN ESSC

Patient selection

ESSC is a more aggressive cancer compared to EAC and the risk of lymph node metastases according to the depth of invasion is higher in ESSC. In ESCC, the risk of lymph node metastasis is 0% for M1 (disease confined to epithelium), 3.3% for M2 (disease confined to lamina propria mucosa), 10.2% for M3 (tumors involving muscularis mucosae) and 26.5% for SM1 (disease extending to superficial third of submucosa)[49]. However, lymph node involvement is absent in M3 and SM1 lesions if depth of invasion is < 200 μm, tumors are well to moderately differentiated and there is no lymphovascular invasion[50]. Absolute indications for EET are high grade intraepithelial neoplasms, including M1 and M2 without lymphovascular infiltration, lymph node or distant metastases[51]. Relative indications for EET includes lesions at a depth of invasion < 200 μm in the submucosa (M3 and SM1). ESD is preferred over EMR in tumors large enough to prevent enbloc resection by EMR such as those ≥ 15 mm or for lesions with poor lifting and for better assessment of the depth of invasion in case of suspicion for submucosal invasion[52].

Outcomes

EET in ESCC is associated with excellent outcomes but carries a minimal risk of recurrence. In a Japanese study on 204 patients with early ESCC treated by EMR, the 5-year survival was 75.9% with recurrence of 11% when followed for median of 36 mo[53]. In a European study on 39 patients with superficial ESCC, EMR was curative in 90% patients[54] (Table 2).

ESD in ESCC has enbloc resection rates of 90% to 100% and curative resection rates of 88% to 97%[55-57] (Table 2). In a study on 102 patients treated by ESD, there was no local recurrence when followed over 21 mo[58]. The cause specific 5-year survival rates after ESD are 100% for M1 and M2 tumors and 85% for M3 and SM1[57]. Perioperative mortality following ESD in T1a and T1b ESCC tumors was lower (0.3%) when compared with esophagectomy (1.5%, P = 0.186) and morbidity was also lower (15.2% *vs* 27.7%, P = 0.001)[59]. After a median follow up of 21 mo, there was no significant difference between treatments in all-cause mortality (7.4% *vs* 10.9%, P = 0.209) or rate of cancer recurrence or metastasis (9.1% *vs* 8.9%, P = 0.948).

In a meta-analysis that compared the efficacy of ESD with EMR in ESCC[60]. ESD was found to have higher enbloc resection rates when compared to EMR (314/319 lesions *vs* 299/476 lesions, OR 27.3) and higher complete resection rates (289/297 lesions with ESD *vs* 307/463 lesions with EMR, OR 18.4). The local recurrence rate was also lower with ESD compared to EMR (1/306 lesions *vs* 31/459 lesions, OR 0.13). In view of higher curative rates and lower risk of recurrences, ESD is preferred over EMR for treated of ESSC. Use of RFA for treatment of squamous dysplasia and early ESCC have been reported with over 84% complete response over 12 mo[61] (Table 2). However, even in flat ESCC, there is a chance of lymphovascular invasion and undertreatment with RFA, hence, ESD is preferred.

EET IN RARE ESOPHAGEAL CANCERS

Rare histological types of esophageal cancer include epithelial tumors such as mucoepidermoid carcinoma, adenoid cystic carcinoma, small cell carcinoma, undifferentiated carcinoma, carcinoid and non-epithelial tumors such as leiomyosarcoma, rhabdomyosarcoma, Kaposi sarcoma and malignant melanoma[62]. Treatment depends on the size of the lesion, depth of invasion and presence or absence of metastases. Small cell carcinoma or neuroendocrine tumors account for 0.3% to 3.8% of all esophageal cancers[63]. EET may be considered when tumor size is < 1.0 cm, pathology is not poorly differentiated and in the absence of local lymph node metastasis, lymphovascular invasion or perineural invasion and tumor is completely resectable as the survival rate is high without recurrence on long-term follow up[63]. One case is reported on the successful use of ESD to remove esophageal submucosal NET that showed no recurrence on 22 mo follow up[64].

EET IN BENIGN ESOPHAGEAL TUMORS

Benign esophageal tumors are rare and account for < 1% of esophageal tumors[1]. According to the WHO Classification, benign epithelial tumors are squamous papilloma and non-epithelial tumors are leiomyoma, lipoma, gastrointestinal stromal tumor (GIST) and granular cell tumors[62]. The most common SMT in esophagus are leiomyoma (95%) followed by GIST (4.2%) and granular cell tumors (0.8%)[22]. Esophageal GISTs mimic the appearance of leiomyomas, but can be differentiated following EUS-guided FNA[65]. GIST is KIT-positive with immunohistochemical staining while leiomyomas are KIT-negative and positive for smooth muscle actin, desmin, and h-caldesmon.

Benign tumors are encountered during routine endoscopy as they are usually asymptomatic and are managed by periodic surveillance[66]. Removal is indicated when they become symptomatic or have a risk for malignant transformation (large diameter or origin from muscularis propria). Removal should be attempted in leiomyomas ≥ 2 cm and all granular cell tumors and GIST in view of malignant potential[67]. EMR is performed in SMT ≤ 50 mm. Other endoscopic alternatives include ESD and more recently, STER.

Outcomes

EET can be safely performed in small SMTs. In a study with 36 patients and mean tumor size of 0.6 mm, the overall enbloc and complete resection rates were 100% and 80.6% respectively[68]. There was no local recurrence during follow up of 6 to 82 mo. Some studies evaluated ESD for SMTs and found that an optimal size of 1 to 2 cm and submucosal location instead of muscularis propria or deeper made ESD feasible[69]. In these studies, complete resection rate of ESD was 93% and of STER about 100%. The use of STER for esophageal SMT was also studied in a meta-analysis of 16 studies[24]. Complete resection and enbloc resection rates were 100% and 98.6% respectively (Table 2). STER was most effective in tumors < 3 cm. A study on 180 patients with SMTs of which 69% (n = 124) were esophageal in location with a median tumor size of 2.6 cm, STER had an enbloc resection rate of 90.6%. No recurrence or distant metastasis was noted on median follow up of 36 mo[70]. STER requires longer procedure time than ESD but is relatively safe and preserves mucosal integrity[22,23].

For esophageal GIST, molecular targeted therapy and surgical resection are the main stay of treatment. However, EET is being increasing utilized. The available data on GIST comes from small, retrospective studies with limited follow up[71,72]. In a study of 224 patients with SMTs of which 34.4% were GIST and 41.1% werelocated in esophagus, 92.9% were successfully treated with ESD[71]. The mean size was 13.6 mm and no recurrence was reported during 12 mo follow up. STER was successfully employed in a 69 year old male patient with 4 cm GIST in the lower esophagus who was not a surgical candidate and no recurrence, dysphagia or reflux was reported on 1 month follow up[72].

PALLIATIVE THERAPY

Palliative therapy is considered in patients with esophageal cancer when curative therapy is not achievable[73]. The goals of care at this stage are improved QOL by restoration of the ability to swallow and adequate control of pain and bleeding if any, from the cancer. Dysphagia is treated with endoscopic stent placement or tumor destruction by APC, PDT, Nd:YAG laser therapy, brachytherapy or cryotherapy.

Cryotherapy has been shown to improve mean dysphagia score from 2.4 to 1.7 with lower scores indicating better swallowing function[74]. Bleeding can be controlled by endoscopic hemostatic methods such as injection of epinephrine clipping or APC. Locally advanced esophageal cancer may sometimes lead to tracheoesophageal fistulas that can be covered with an esophageal stent.

CONCLUSION

The role of esophagus preserving EET in management of esophageal tumors is ever expanding. EET is the standard of care in early esophageal cancers with minimal risk of lymph node metastases and low risk features. In ESSC, ESD is preferred over EMR due to low risk of recurrence. In EAC, focal EMR is followed by ablation of residual BE mucosa to prevent recurrences. RFA is suitable for ablation of flat mucosa in esophagus whereas lesions with scarring and distorted anatomy are better approached with cryoablation. In general, the use of PDT has declined because of its side effects. Multidisciplinary assessment and determination of a treatment plan involving endoscopists, pathologists, medical oncologists, radiation therapists and surgeons are necessary for decision making in management of esophageal cancer. Treatment plans depend on clinical tumor stage, subsite, and histology of tumor, performance status, physical fitness and co-morbidities. Currently, studies are undergoing to assess role of second generation PDT and ESD followed by chemoradiation therapy in patients at risk for lymph node metastases. The technologic advances are likely to increase the application of the endoscopic management and high quality studies will guide appropriate candidate selection.

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