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Endoscopic Submucosal Dissection for Esophageal Adenocarcinoma: A North American Perspective

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Abstract

Background Data are limited regarding the application of endoscopic submucosal dissection (ESD) in Western countries or for esophageal adenocarcinoma in any part of the world. We sought to review our experience employing ESD in patients with early esophageal cancer at a high volume North American esophageal cancer treatment center.

Methods A prospectively maintained database of all patients with esophageal cancer treated at the McGill University Health Center was used to identify ESDs performed for adenocarcinoma between 2012 and 2016. Patient demographics, pre-resection tumor characteristics, endoscopic resection technical variables, pathologic results, and short- and long-term outcomes were recorded.

Results Of 650 patients in the database, 26 underwent 27 procedures. The majority (67%) had pre-treatment EUS. There were no post-ESD bleeding events requiring re-intervention. Perforation occurred in 2/27 (7%), one of which required operative repair. Complete RO resection was achieved in 18/27(67%). Salvage laparoscopic esophagectomy was performed in six patients. At a median follow-up of 18.5 (7–35) months, cancer recurrence occurred in only one patient who subsequently underwent successful repeat ESD.

Conclusions Although technically challenging, ESD represents a safe and effective treatment of early esophageal adenocarcinoma and has the potential to become a more important tool in management of these early lesions in Western countries.

Keywords Esophageal cancer · Endoscopic submucosal dissection · Esophageal adenocarcinoma

Introduction

Esophageal adenocarcinoma is the fastest rising malignancy in North America.[1] For local/regional disease, esophagectomy remains the mainstay of curative intent treatment, either alone or in conjunction with neo-adjuvant therapy.[2–4] However, esophageal resection is associated with significant morbidity and mortality, representing one of the highest acuity procedures performed on a routine basis in North America.[5] Although the operative risk can be reduced in high-volume centers and by a minimally invasive approach, the morbidity of the procedure is still not trivial.[6–10] This high risk of surgery has prompted the development of endoscopic, organ sparing techniques to resect early esophageal cancer as long as two criteria integral to cancer surgery are respected: an acceptable (negligible) rate of lymph node metastasis and the ability to resect the lesion en bloc.

The ability to accurately predict risk of lymphatic invasion is critical to patient selection for endoscopic resection of any intestinal cancer. Early esophageal adenocarcinoma, as defined by the AJCC guidelines,[11] is associated with a significantly better prognosis than more advanced disease primarily due to the absence of lymph node involvement. Truly mucosal (T1a) lesions are associated with 0–7% risk of nodal involvement,[12–16] while deeper T1b lesions are associated with a substantial lymph node metastasis rate of 26 to 41%.[13–17]

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Aside from depth of invasion, other factors are associated with an elevated risk of nodal involvement.[17] Using data from 250 patients treated at five international centers, we previously published a risk nomogram for lymph node metastasis in early esophageal adenocarcinoma.[15] Increased tumor size, decreased differentiation, and presence of lymphovascular invasion were all found to independently and additively confer an elevated risk of lymph node metastases in addition to tumor depth. These features must be considered in choosing between endoscopic resection versus esophagectomy for early esophageal adenocarcinoma.

Endoscopic technologies and techniques have evolved through the years to enable increasingly complete and complex endoscopic resections. Endoscopic mucosal resection (EMR) was initially developed in East Asia and has been widely adopted in the West as the procedure of choice for endoscopic resection. Indeed, several centers, primarily in Europe, have demonstrated excellent outcomes with EMR for esophageal adenocarcinoma.[18, 19] EMR is a simpler technique limited by the size of tissue able to be resected at a time. This gives the possibility to resect en bloc small lesions of 1–2 cm. However, with larger tumors, the ability to resect the lesions en bloc is greatly diminished and requires piecemeal resection. This has been linked to a higher rate of local recurrence in some studies.[20] To address this issue, endoscopic submucosal dissection (ESD) was developed in Japan as a method for en bloc endoscopic resection of mucosal tumors.[21, 22] Although more technically challenging than EMR, and associated with a steep learning curve,[23] ESD results in a higher rate of en bloc resection of larger tumors with clear margins, allowing clear assessment of deep and circumferential margin status, as well as being linked to reduced local recurrence rates.[20]

Despite its superiority to EMR for oncologic resection, and its extensive uptake in Asia for squamous cell carcinoma, data for esophageal ESD in adenocarcinoma are limited. Given the differences in biologic behavior, patterns of metastasis, and local invasion between squamous cell carcinoma and adenocarcinoma, there thus exists a gap in the literature on the utility of ESD for adenocarcinoma of the esophagus. Accordingly, we sought to review and describe our experience as an early North American adopter of ESD for esophageal adenocarcinoma.

Methods

Data Collection

A prospectively maintained gastric and esophageal cancer local database was reviewed for cases undergoing endoscopic resection from 2012 to 2016. Non-esophageal (i.e., gastric) resections, EMRs, and resections for pathology other than adenocarcinoma were excluded. Patient demographics, preresection tumor characteristics, endoscopic resection technical variables, pathologic results, and short- and long-term outcomes were recorded. Details from the database were corroborated against and supplemented from the hospital charts. En bloc resection is defined as the lesion being resected in a single complete specimen. Complete resection (R0) was defined as margins negative for malignancy. Esophageal stenosis was defined as a need for balloon dilation. Specimen with intestinal metatplasia at the margin of the ESD specimen was not considered as incomplete resection, as the goal of ESD in our series is treatment of invasive malignancy rather than complete Barrett's excision. Indeed, several patients underwent subsequent ablation for residual Barrett's after endoscopic resection of invasive cancer.

Staging and Patient Selection for ESD

All patients underwent gastroscopy and biopsy for tissue diagnosis and tumor characterization. Staging was generally completed with endoscopic ultrasound (EUS) and computed tomography (CT) of the chest, abdomen, and pelvis. Although EUS was routinely employed in the early stages of the ESD program, this form of investigation was found to be of limited utility in differentiating between T1a, T1b, and T2 lesions over the course of the study period and thus used only selectively in the latter phases of the study. After staging, patients were seen in the multidisciplinary upper gastrointestinal cancer clinic. If they were considered candidates for endoscopic resection based on the lesion characteristics (cT1a-T1bN0), they were offered ESD as an alternative to standard surgical resection with discussion on the risk associated with the procedure and potential need for salvage esophagectomy. The final decision was made by the patient.

ESD Technique

Most esophageal ESD cases were performed under general anesthesia with endotracheal intubation in an operating theater. A single thoracic surgeon/surgical endoscopist performed all procedures with a standard high definition gastroscope. Various attachments were used including an electrosurgical device with the insulated tip ITknife2 (KD-611 Olympus Co. Ltd., Japan), electrosurgical dual knife (KD650 L Olympus Co. Ltd., Japan), and/or Coagrasper (FD-410LR; Olympus Co. Ltd., Japan). Mucosal markings were made at 2-mm intervals around the lesion using the needle knife. Submucosal injection using 10% glycerol or hydroxyethyl starch solution mixed with indigo carmine and dilute epinephrine was performed to elevate the lesion. A small mucosal incision was made using a standard needle knife. From this opening, the insulated tip or dual knife was introduced and

used to complete the circumferential mucosal incision around the tumor, followed by submucosal dissection at the plane between the submucosa and muscularis propria. Most dissections were performed from distal to proximal, as this enhances visualization throughout the procedure. Specimens were extracted by the mouth and pinned on a specimen board before fixation. Patients were admitted for observation overnight. They were discharged on a progressive liquid and soft diet the following day, and treated with both proton pump inhibitors and sulcrafate orally for 8 weeks. Figure 1 details the steps of esophageal ESD used in this series. Patient underwent repeat endoscopy every 3 months for 1 year then yearly. Patients with moderate to high risk of occult metastasis additionally underwent EUS at the same interval and CT scan every 6 months for the first year.

Post-ESD Oncologic Management

In the case of negative margins, follow-up endoscopy with biopsy of the resection site was performed at 3–6 months. In the case of associated Barrett's esophagus, radiofrequency ablation of the flat metaplasia was performed. Patients with positive deep resection margins were offered minimally invasive salvage esophagectomy, as did good surgical candidates with negative margins but high risk of nodal involvement based on our published nomogram.[15] Poor surgical candidates or those refusing surgery were offered intensive surveillance with serial endoscopy and CT scans. In cases of positive circumferential margins, patients were offered repeat EMR/ESD of the involved margin or salvage esophagectomy. All resected patients underwent subsequent oncologic therapy according to the final pathology. Figure 2 details the post-ESD oncologic decision-making used at our institution.

Statistical Analysis

Descriptive statistics were calculated using median and interquartile range (IQR) for continuous variables, and proportion displayed as percentage for categorical variables. Calculations were performed using STATA version 12.

Results

Of a total of 650 patients in the database, 26 met inclusion criteria, in which 27 ESDs were performed. Median age was 67 (51–90) with most being male (77%: 20/26). The majority (67%) had pre-treatment EUS. Pre-resection tumor staging proportions were carcinoma in situ (11%), cT1a (44%), and cT1b (44%). Procedure time was 86 (50) min, and the majority (25/27; 93%) were performed en bloc. There were no post-ESD bleeding events requiring re-intervention or transfusions. Perforation occurred in 2/27 (7%) with one requiring operative repair. No post-procedure strictures requiring dilatation were found. All patients were admitted following the intervention with a median length of stay (LOS) of 1 (range 1–13) day (Table 1).

Final pathology revealed nodular HGD (4/27), pT1a (8/27), pT1b (11/27), and pT2 (3/27). Complete RO resection was achieved in 18/27 (67%). Of the nine R1 cases, all had deep positive margins (pT1b and pT2 lesions). Salvage laparoscopic esophagectomy was performed in five patients for positive deep margins and one for multifocal invasive cancer. All esophagectomies performed for positive margins had absence of nodal involvement (N0) on final pathology. Post-surgical staging was Tis (1), T1a (2), T2 (1), and one with no evidence disease (1). One patient underwent esophagectomy for long segment Barrett's (15 cm) with development of a

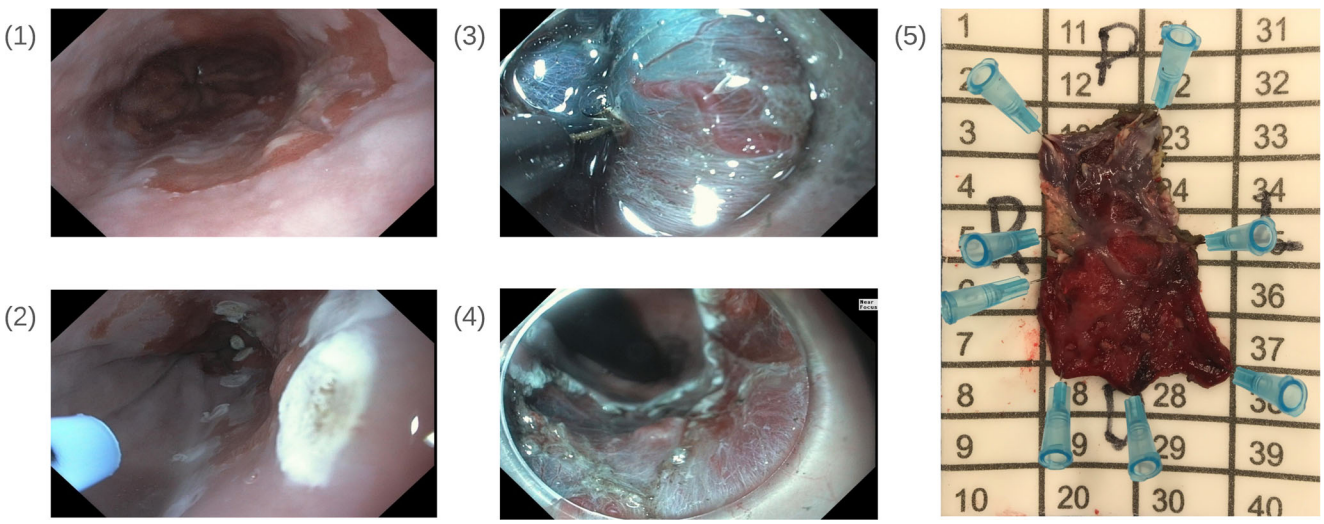

Fig. 1 Esophageal endoscopic submucosal dissection. (1) Initial lesion. (2) Marking of the resection margins. (3) Mucosal injection and submucosal dissection. (4) Post-resection. (5) Specimen pinned before fixation to allow accurate assessment of margins

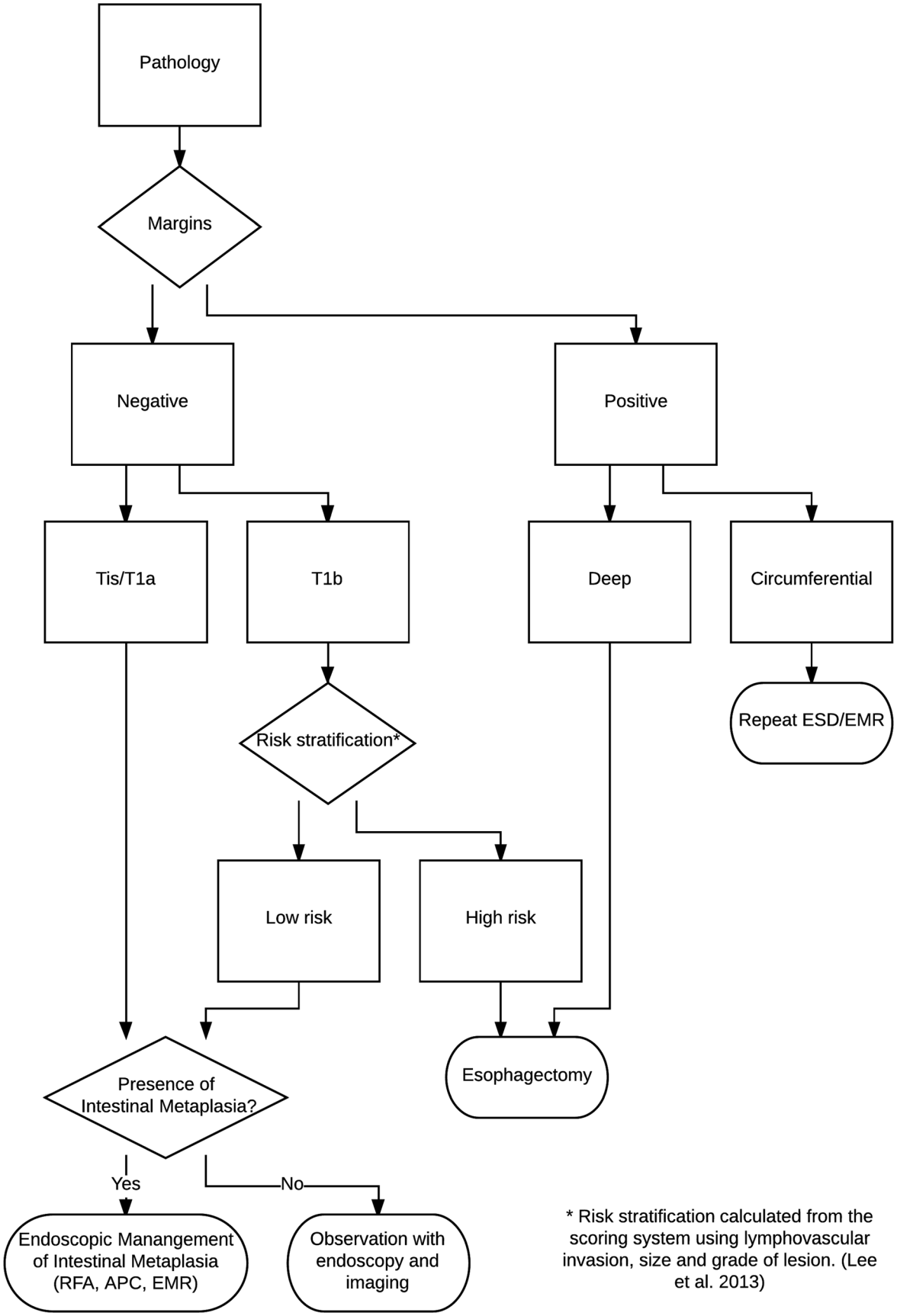

Fig. 2 Post-ESD management pathway

Table 1 Patient and tumor characteristic

	Frequency	Percentage
Sex[a]		
Male	19	73
Female	7	27
Age at time of resection[b]		
Median (range)	67 (51–90)	
Initial pathology		
High-grade dysplasia	2	7
Intra-mucosal carcinoma	4	15
Adenocarcinoma	21	78
Tumor location		
Esophageal	9	33
Gastroesophageal junction	18	67
Preoperative staging EUS	18	67
Tis[c]	2	11
T1a[c]	8	44
T1b[c]	8	44
N0	18	100
Pathological tumor staging		
High-grade dysplasia	2	7
Tis	2	7
T1a	8	30
T1b	11	41
T2	3	11
Absence of residual disease	1	4

[a] Percentage referring to number of patient (26)

[b] Percentage referring to number of ESD (27)

[c] Percentage referring to number of EUS (18)

Table 2 Outcomes and complications

	Frequency	Percentage
Resection		
En Bloc	25	93
R0	18	67
R1	9	33
Procedure time (min)		
Mean (IQR)	80 (50)	
Length of stay (days)		
Mean (IQR)	1 (1)	
Early complication		
Perforation	2	7
Bleeding	0	0
Late complication		
Recurrence of adenocarcinoma	1	4
Bleeding	0	0
Stricture	0	0
Follow-up length (months)		
Median (range)	18.5 (7–35)	
Subsequent procedures		
Salvage esophagectomy	6	22
RFA	3	11
APC	2	7
EMR	1	4
ESD	1	4
Planned ablations	3	11

second nodule of adenocarcinoma away from the initial ESD scar. Intestinal metaplasia was reported in 16/27 (59%) of patients at the time of excision or follow-up endoscopy. Of the nine patients with residual Barrett's esophagus post-ESD who did not undergo esophagectomy, four (40%) underwent ablation with a mix of RFA, APC, and/or EMR with three more planned for RFA (Table 2). One patient was not a candidate for RFA given a tight proximal stenosis following radiotherapy for oropharyngeal cancer.

Of the patients who underwent preoperative EUS (18), depth of invasion was accurately predicted in nine (50%) and overestimated in three (17%). In the other six (33%) cases where EUS underappreciated the invasion of the lesion, it led to five cases of positive margins on final pathology.

At mean follow-up of 18.5 (7–35) months, recurrence of cancer occurred in only one patient. This recurrence occurred after positive deep margins on initial resection in a high surgical risk patient who was followed with intensive surveillance. Local recurrence occurred 6 months later and was treated successfully with repeat ESD. There is no evidence of further recurrence in this patient after more than 2.5 years (Table 2).

Discussion

Over the past several years, interest in ESD has increased substantially in all portions of the gastrointestinal tract as an attractive organ-sparing alternative to operative resection for early malignancy.[24, 25] Originally developed in Japan,[26] ESD provides the ability to resect superficial tumors of the esophagus in an oncologically sound en bloc manner, allowing for complete margin analysis and some reports of reduced local recurrence rates. Furthermore, the technique of ESD, in which the submucosa is precisely dissected off the muscularis propria, enables resection of deeper T1b lesions that may not be technically feasible with other methods of endoscopic resection such as EMR.[20]

Despite the superiority of ESD to EMR and its widespread use in Asia, use of this technique has yet to become widespread in North America. This is likely due to the increased technical difficulty of this approach over EMR, and thus the long learning curve needed to safely adopt this technique.

Reports indicate a number of at least 30 to 50 cases needed in order to achieve proficiency.[23, 27] Furthermore, ESD requires more specialized endoscopic tools than EMR, and the long operative time may necessitate intubation and thus access to the operating room.[28, 29] All these factors have coalesced to reduce widespread adoption of this approach outside of Asian centers. Our report confirms that this technique is both safe and oncologically sound in North American patients and represents one of the largest series of ESD for esophageal cancer outside of Asia.

In our experience, several factors were instrumental in the adoption of ESD at our center. A dedicated foregut surgeon, with a high-volume esophageal cancer practice and considerable interventional endoscopy experience, spent 6 weeks in Japan learning ESD first-hand from several world-renowned experts. This same surgeon then initially started performing ESD only in gastric cancer cases, which have a shorter learning curve, a lower risk of serious complications, and allowed for increased operative volume. Finally, institutional and leadership support for the ESD program allowed for the eventual construction of and regular access to a dedicated therapeutic endoscopy operating room, such that long cases could be performed under anesthesia and rapid access to surgical intervention could be offered in the eventuality of a major complication. Finally, close collaboration with dedicated upper GI pathologists led to a change in sectioning technique such that ESD specimens are sectioned every 2 mm and depth of submucosal invasion is accurately measured and reported, allowing clinical decisions to be made according to standards applied for ESD in large Asian centers.[30] These factors together have allowed for the safe and reliable adoption of this new technique into our standard practice.

If ESD is to be used for esophageal cancer in North America, it must be oncologically sound for use in adenocarcinoma, the most commonly encountered histologic subtype in this region.[1] However, although numerous series have reported successful ESD for esophageal cancer, the vast majority are limited to the histology most often encountered in Asia, namely squamous cell carcinoma.[31, 32] Use of ESD for adenocarcinoma may differ in several manners to that for squamous cell carcinoma, chief of which include the frequent association of Barrett's esophagus as well as a higher rate of submucosal spread, potentially impacting the ability to achieve complete resection. The present series represents one of the largest reported single institution experiences using ESD for esophageal adenocarcinoma in the world and confirms this approach can achieve excellent oncologic outcomes for this increasingly frequent histologic subtype of esophageal malignancies. Similar studies in Western settings are summarized in Table 3.

This series also confirms the efficacy of ESD as not only a therapeutic but also a diagnostic tool for staging esophageal cancer depth. Direct visualizations by endoscopy and EUS are

Table 3 Western studies for esophageal ESD for Barrett's esophagus and adenocarcinoma

Study name and type	Country	Number of centers	Number of patients	Follow-up Mean (median) months	EMR/ESD	Final pathology	R0 (for cancer)	Perforation
Neuhaus et al. 2012[33] Prospective	Germany	1	30	[27]	ESD	HGD 2 (6.9%), T1a 21 (72.4%) T1b 3 (10.3%)	10/26 (38.5%)	0
Probst et al. 2014[34] Prospective	Germany	1	87 (subset)	24.3	ESD	T1a 74 (84.1%), T1b 14 (15.9%)	73/87 (83.9%)	0
Höbel et al. 2014[35] Retrospective	Germany	1	22	(19.2)	ESD	T1a 20 (90.9%), T1b 2 (9.1%)	18/22 (81.8%)	1 (4.5%)
Chevaux et al. 2015[36] Retrospective	Belgium	1	75	[20]	ESD	LGD 6 (8.3%), HGD 11 (15.3%), T1a 48 (66%) T1b (9.7%)	40/73 (54.8%)	0
Lang et al. 2015[37] Retrospective	USA	1	4 (subset)	13	ESD	HGD 1 (25%), adenocarcinoma 3/4 (75%) (T-staging N/A)	3/4 (75%)	0
Yang et al. 2016[38] Retrospective	USA	5	43	(11.3)	ESD	HGD 14 (30.4%), IMC 17 (37%), T1b+ 15 (32.6%)	35/46 (76.1%)	1 (2.1%)
Terheggen et al. 2016[39] RCT	Germany	1	20 (ESD arm only)	22.6	ESD	LGD 2 (10%), T1a 10 (50%), T1b 7 (35%)	10/17 (58.8%)	2 (10%)
Holmes et al. 2016[40] Retrospective	USA	1	11	–	ESD/EMR	LGD 2 (18%) HGD 1 (9%), T1a 5 (45%), T1b 3 (27%)	–	0

the two most commonly utilized staging tools for early esophageal cancer. However, direct visualization is poor at gauging depth for anything but very superficial lesions, and EUS often has difficulty differentiating between T1b and T2 lesions, with under or over staging occurring about 10% and 46%, respectively, of T2 lesions in some series,[41] and a 33% rate of overstaging seen in our study. Given the high morbidity of esophagectomy,[6] we advocate for diagnostic ESD in patients with c/uT1bN0 lesions before proceeding directly to surgical resection. Furthermore, in the case of R0 resection for T1b lesions, ESD has the potential to be curative if the risk of lymph node metastases is acceptably low. To determine this, we discuss with the patient the risk of occult lymph node metastases according to our previously published nomogram,[15] and balance this against the individualized risk of surgical morbidity and mortality before proceeding to esophagectomy. In our series, 50% of patients with cT1b lesions underwent curative ESD and were thus able to avoid esophagectomy. However, in pathologically confirmed T1b lesion excised by ESD, an esophagectomy was strongly recommended unless the patient was deemed to have high surgical risk. In this series, the T1b lesions who did not undergo esophagectomy had a mean age of 79 years old and comorbidities such as advanced cirrhosis, heart failure, and postpneumonectomy.

Central to the utilization of ESD for early esophageal adenocarcinoma is the management of concomitant Barrett's esophagus. Not surprisingly, intestinal metaplasia was present in the majority of patients in this series. These patients were managed in a multimodality fashion according to the ACG guidelines for dysplastic Barrett's Esophagus, namely endoscopic resection of nodular lesions (EMR or ESD) for both curative and diagnostic purposes, followed by radiofrequency ablation of the flat area. Early in our experience, some patients underwent argon plasma coagulation of islands of intestinal metaplasia—this no longer reflects preferred and recommended practice. Given the short follow-up time, we are unable to comment on the Barrett's esophagus remission rate after treatment and the number and type of procedures performed. Patients agreeing to undergo endoscopic management of their esophageal adenocarcinoma and dysplastic Barrett's esophagus should be well informed of the proportion of cases who will require further therapeutic modalities, may it be salvage esophagectomy, radiofrequency ablation, or repeat endoscopic resection, all of which are demonstrated in our series.

The main limitations of this study come from the retrospective design and the absence of a control group of similar cases undergoing esophagectomy. We suspect the presence of selection bias towards older and more comorbid patients with diagnosis such as cirrhosis (9%, $n = 3$) and coronary artery disease (25%, $n = 7$). Several of these patients would not have been considered candidates for surgical resection given their high perioperative risk and therefore underwent this endoscopic procedure. However, this limits mainly the generalizability of these finding and not the internal validity regarding the safety of this procedure. As this is a new technique, this study is also limited in its follow-up time and lacks long-term data. Long-term recurrence rate and disease-free survival will become available when greater time elapses.

Conclusions

In this single institution North American study, we have found that ESD, although technically challenging, represents a safe and effective treatment of early esophageal adenocarcinoma, even in many T1b lesions. Longer follow-up data is, however, needed to assess the oncological outcome of the more advanced lesion. ESD should be more widely adopted as an important tool in the therapeutic armamentarium for the treatment of early esophageal adenocarcinoma in Western countries, especially in patients at high perioperative risk for esophagectomy.

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