



Outcomes of endoscopic submucosal dissection in esophageal adenocarcinoma staged T1bN0 by endoscopic ultrasound in non-surgical patients

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Abstract: Patients with esophageal adenocarcinoma (EAC) invading submucosa (T1b) are traditionally treated with esophagectomy and with chemoradiotherapy in poor surgical patients. Endoscopic submucosal dissection (ESD) has emerged as an alternative treatment in these patients. In this case series, we analyzed the outcomes of ESD in EAC staged T1bN0 by endoscopic ultrasound (EUS). Patients with EAC staged T1bN0M0 by EUS and PET scan who underwent ESD by a single operator (MS) between 2014 and 2017 at our institution were included. They were deemed as poor surgical candidates and ESD was considered as the most appropriate treatment option after a multi-disciplinary evaluation. There were 8 patients (male =5; female =3) with average age of 70.5 years old (range, 53–84 years old). ESD was completed in 7 and aborted in 1 patient due to tumor invasion into muscularis propria. *En bloc*, R0 and curative resection rates were 86% (6/7), 86% (6/7) and 71% (5/7) respectively. Final histology was intramucosal (T1a) in 4 and submucosal (T1b) in 3. One patient (14%) developed stricture requiring balloon dilation. Mean follow-up duration was 10 months (range, 3–15 months) and 71% (5/7) remain in clinical remission. Two patients required CRT, one with T1a who developed recurrence and another with T1b with lymphovascular invasion. In poor surgical candidates, ESD was associated with accurate staging and favorable outcomes in EAC staged T1bN0 by EUS. We suggest considering ESD in EAC staged T1bN0 for accurate histological staging, curative potential and also to help determine further course of treatment.

Keywords: Endoscopic submucosal dissection (ESD); endoscopic mucosal resection (EMR); endoscopic ultrasound (EUS); early esophageal adenocarcinoma (early EAC)

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Introduction

Endoscopic resection (ER) is considered as a preferred treatment for early esophageal adenocarcinoma (EAC) and has been shown to be curative in certain submucosal cancers which are confined to the outer third of the submucosa (sm1). ER can be accomplished by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). ESD is associated with higher *en bloc* and curative resection rates and it may be preferred over EMR in

selected cases such as lesions larger than 20 mm, poorly lifting tumors, and lesions at risk for submucosal invasion (1). In this study, we present the outcomes in patients diagnosed as T1bN0 EAC on EUS who underwent ESD by one of the authors (MR Sanaka).

All the cases were discussed at a multi-disciplinary tumor board meeting involving representatives from medical oncology, radiation oncology, thoracic surgery and gastroenterology where ESD was deemed as an appropriate

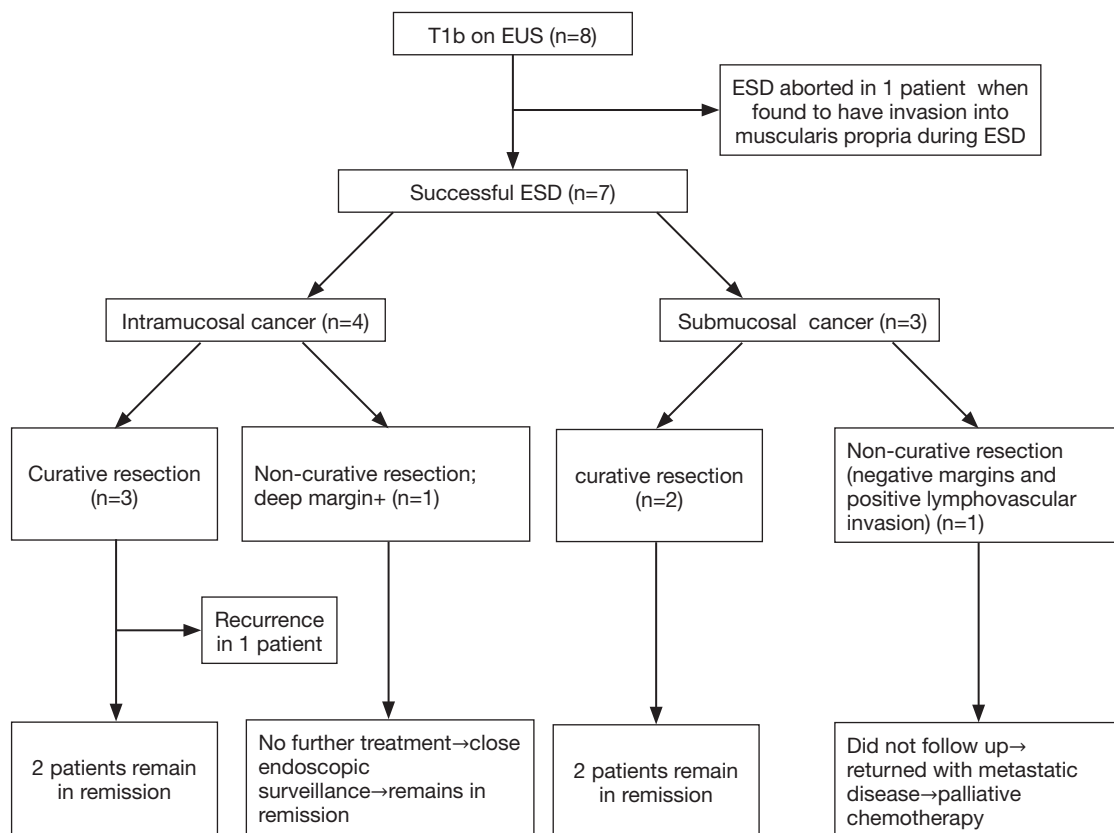


Figure 1 Flow chart showing study method and outcomes. ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound.

treatment option. Patients were explained the non-negligible risk of lymph node involvement and need for additional surgery, radiation or chemotherapy based on the results of the ER. Detailed flowchart is outlined in *Figure 1*.

ESD procedure

All ESD procedures were performed by a single operator (MR Sanaka) under general anesthesia and carbon dioxide insufflation through the endoscope. Standard ESD technique of circumferential marking, incision and submucosal dissection was performed. Methylene blue stained Voluven was used as sub-mucosal injection solution. Devices used were Dual knife, IT Nano knife and Coagraspers (Olympus USA). All patients were admitted post-procedure for observation. An esophagram was performed on post-operative day one and patients were started on clear liquid diet if no leak was detected. Diet was advanced and if patients were stable, they were discharged home on oral proton pump inhibitors for at least 2 months.

Definition of outcomes

En bloc resection: defined as excision of the targeted lesion in a single specimen.

Piecemeal resection: defined as excision of the targeted lesion in more than one piece.

R0 resection: defined as histologically complete resection with deep and lateral margins negative for malignancy irrespective of the presence of high-grade dysplasia (HGD) or intestinal metaplasia (IM).

R1 resection: defined as histologically incomplete resection with positive deep or lateral margins.

Curative resection: patients with R0 resection, with well to moderately differentiated histology, absence of LVI and absence of invasion beyond superficial submucosa (sm1) were considered to have curative resection.

Results

Eight patients met the inclusion criteria during the study

Table 1 Individual patient outcomes

Patient	Final histological degree of invasion	<i>En bloc</i> resection	R0 resection	Deep margin	Horizontal margin	Lymphovascular invasion	Degree of differentiation	Curative resection
1	T1a	Yes	No	Positive	Negative	No	G1	No
2	T1a	Yes	Yes	Negative	Negative	No	G2	Yes
3	T1a	Yes	Yes	Negative	Negative	No	G2	Yes
4	T1a	Yes	Yes	Negative	Negative	No	G2	Yes
5	T1b	No	Yes	Negative	Negative	Yes	G3	No
6	T1b	Yes	Yes	Negative	Negative	No	G1	Yes
7	T1b	Yes	Yes	Negative	Negative	No	G2	Yes
8	T2					ESD aborted		

ESD, endoscopic submucosal dissection.

period (male =5; female =3). All patients were Caucasians with an average age of 70.5 years (range, 53–84 years). Seven patients were classified as American Society of Anesthesiology (ASA) classification III and one patient was ASA class IV. EUS staging was T1bN0 and Paris classification was 0–Is + IIa in 4 patients, 0–IIa+IIb in 3 patients and 0–IIa + IIc in 1 patient. ESD was successfully completed in 7 patients and aborted in 1 patient, in whom the tumor was noted to invade the muscularis propria layer (T2) at the time of ESD. Average procedure duration (time from endoscope in to endoscope out) was 190.8 minutes (range, 105–352 minutes). Average diameter of the resected specimen was 32.3 mm (range, 16–50 mm) and average diameter of the resected tumor was 15.14 mm (range, 4–40 mm).

En bloc, R0 and curative resection rates were 86% (6/7), 86% (6/7) and 71% (5/7) patients respectively. Focal positive deep tumor margin and LVI were present in one patient each. On histopathological assessment, 57% (4/7) tumors were intra-mucosal (T1a), whereas only 43% (3/7) had submucosal invasion (T1b). Well-differentiated, moderately differentiated and poorly differentiated tumor were present in 29% (2/7), 57% (4/7) and 14% (1/7) cases respectively. Average length of stay (LOS) was 1.8 days (range, 1–3 days). There were no intra-procedural adverse events. One patient (1/7: 14%) developed an esophageal stricture in the post-operative period requiring esophageal balloon dilatation. Of the 4 patients with only mucosal invasion (T1a) on final histology, 3 patients had curative resection and 1 patient had non-curative resection due to focally positive deep margin. Out of 3 patients with curative resection, 1 patient developed recurrence of cancer during follow-up period and underwent radiation therapy

and is currently in remission. The fourth patient with T1a tumor with non-curative resection was noted to be negative for malignancy on follow-up EGD with biopsies and is currently tumor-free and under close endoscopic surveillance. Of the 3 patients with submucosal invasion (T1b, sm1), 2 patients had curative resection and 1 patient had non-curative resection due to presence of LVI. Both the patients with curative resection remain in remission on endoscopic follow up. One Patient with non-curative resection was subsequently noted to have distant metastasis and is undergoing palliative chemotherapy. Average follow-up duration was 10 months (range, 3–15 months) and 71% (5/7) patients remain in clinical remission at the last follow up. Individual patient outcomes are shown in *Table 1*.

Discussion

Endoscopic therapy for EAC is gaining gradual acceptance in the United States. ER is a less invasive alternative to esophagectomy in patients with mucosal cancer associated with Barrett's esophagus (BE). Recent studies have shown that certain lesions with superficial submucosal invasion ($\leq 500 \mu\text{m}$, sm1) and low risk features (well or moderately differentiated tumor (G1–2), without LVI (L0 and V0), and smaller size ($< 3 \text{ cm}$) may also be amenable to ER, as they harbor low risk of lymph node metastasis (2–4). EMR is the treatment of choice for resection of visible lesions in patients with BE. ESD enables *en bloc* resection of the lesions regardless of the tumor size, allowing for a detailed histopathological analysis, high curative rates and low rates of local recurrences and may be preferred for larger lesions (1,5). ESD is extensively performed in Japan and other

eastern countries and is considered the first line treatment for the superficial squamous cell esophageal cancer (SQEC) (1). Studies from eastern hemisphere on ESD for EAC have reported high rates of *en bloc* resection (81–100%), R0 resection (38% to 97%), curative resection (64% to 86%) and mean procedure times of 70–145 minutes (3–9). In our study, the *en bloc* resection rate, R0 resection rate and curative resection rate were 86%, 86% and 71% respectively, which are comparable to above studies. However, the average procedure time was much longer in our study (190 minutes), since ESD was only recently started in our institution and it is associated with significant learning curve.

EUS was reported to be inaccurate to differentiate between mucosal (T1a) and submucosal tumors (T1b) (10–14). Recent studies indicate that EUS under-staged 15–25% of cases and over-staged 4–12% cases, as compared to staging by EMR (15,16). Even in our study, EUS accurately staged T1b tumor in only 37.5% (3/8), over-staged 50% (4/8) cases and under-staged in 12.5% (1/8) cases. Relying on EUS as a “T” staging method in early carcinomas might result in some potentially endoscopically resectable tumors being subjected to esophagectomy. Therefore, EUS is not routinely recommended by some experts prior to EMR/ESD for superficial cancers. On the contrary, EUS provides more accurate staging for advanced ECs and it is better than PET and CT for evaluation of both T and N staging (17). Therefore, EUS may be used for nodal staging and staging of high risk lesions as they have a greater risk of invasiveness.

Our study has some limitations. This is a retrospective study performed by a single operator at a single center with a very small number of patients. Even the ESD procedures performed during the early part of the learning curve were also included (within initial 25 ESD cases). This could have impacted the ESD outcomes including procedure length. Currently ESD is performed in only a few select centers in the US and our study findings may not be generalizable. Also, our outcomes are reported based on a short-term follow up and long-term outcomes are not known. Strengths of this study include a thorough and complete multi-disciplinary evaluation and careful selection of patients. This is one of the very few reports on outcomes of ESD in T1b EAC, especially from the US.

Conclusions

In conclusion, ESD is safe and is associated with favorable

outcomes in EAC staged T1bN0 by EUS in poor surgical candidates. In addition, ESD led to a more accurate histological staging than EUS. In patients with early EAC, definitive treatment decisions should not be made solely on the basis of EUS because of its inability to accurately differentiate between mucosal and sub-mucosal involvement. After confirming the absence of loco-regional and distant metastasis, ESD with or without additional treatments may be considered as an alternative to definitive CRT in T1b lesions among poor surgical candidates. ESD would be both diagnostic and therapeutic in some cases and helps to determine further course of treatment. Prospective trials are warranted in western world to assess the efficacy of ESD plus/versus CRT in non-surgical candidates with invasive T1b EAC.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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