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Original article

**Treatment strategy and clinical outcomes of thoracoscopic endoscopic cooperative surgery for
submucosal tumors in the esophagus**

Running title: Strategy and clinical outcomes of TECS

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Abstract

Purpose: Recently, submucosal tumors (SMTs) of the esophagus have been treated with peroral endoscopic tumor resection (POET) and a new procedure called thoracoscopic endoscopic cooperative surgery (TECS). This study aimed to validate the treatment strategy for SMTs and determine whether TECS could be a viable option when POET is not feasible.

Methods: POET and TECS were performed on 12 patients between February 2020 and January 2024. Clinical characteristics and perioperative outcomes were retrospectively evaluated.

Results: Each group consisted of six patients, with most tumors located in the middle thoracic esophagus (75%). General anesthesia lasted significantly longer in the TECS group than in the POET group ($P<0.001$), and no significant differences in endoscopic procedure time, tumor mass index, oral intake date, and length of hospital stay were observed between the two groups. En bloc and R0 resections were achieved in all patients. One patient in the TECS group experienced a Clavien–Dindo grade 3a adverse event, and no tumor recurrence occurred during the median follow-up period of 33 months (range: 6–53 months).

Conclusion: TECS is a safe and feasible option for SMTs when POET is difficult to perform.

Keywords: POET, TECS, SMTs, treatment strategy

1 Introduction

2 Submucosal tumors (SMTs) in the esophagus are mostly found in the middle thoracic region.
3 Leiomyomas are the most common tumors found in the esophagus, followed by gastric gastrointestinal
4 stromal tumors (GISTs), schwannomas, cysts, and lipomas [1-5]. Although most esophageal SMTs do not
5 require surgery, their removal is sometimes necessary because of tumor growth or malignancy. Generally,
6 SMTs are treated with surgical resection. However, several issues arise when conventional thoracoscopic
7 or laparoscopic surgeries are performed. Intraluminal SMTs are difficult to enucleate, and partial
8 esophageal resection risks postoperative stricture unless the tumor is small, whereas total esophagectomy
9 is considered overly invasive for benign tumors such as leiomyoma.

10 Advances in endoscopic technology, such as peroral endoscopic tumor resection (POET) and
11 submucosal tunneling endoscopic resection (STER), which are types of third-space endoscopy [6, 7],
12 have enabled tumor resection, overcoming the disadvantages of surgery [1-5]. Several studies have
13 demonstrated the safety and feasibility of POET/STER in the esophagus [1-5, 8]. However, there are
14 several limitations in performing POET/STER. First, large tumors impair visibility and operability, often
15 requiring piecemeal or surgical resection [3]. Therefore, tumors with a minor axis greater than 30 mm or a
16 tumor mass index (TMI) [major axis diameter (mm) $\times$ minor axis diameter (mm)] greater than 1000
17 should be considered for surgical resection rather than POET/STER. Second, vital organs (aorta, heart,
18 trachea, and lungs) close to SMTs risk being damaged by electrical currents from endoscopic knives
19 because of the relatively thin muscularis propria layer of the esophagus [3]. Third, the incidence of
20 adverse events (AEs) remains unsatisfactory. Some studies have reported major AEs associated with
21 POET/STER at a rate of 5% [1]. Novel techniques have been proposed to overcome these limitations.

22 For gastric SMTs, including GIST, laparoscopic endoscopic cooperative surgery (LECS) was
23 introduced in 2008 and is now widely used [9]. LECS enables safer tumor resection with smaller margins
24 than surgical resection alone. Duodenal LECS was introduced to treat superficial non-ampullary duodenal
25 tumors and overcome the disadvantages of surgical or endoscopic resection alone [10]. Recently, this

concept, now called thoracoscopic endoscopic cooperative surgery (TECS), has been introduced in the treatment of esophageal tumors, though only a few reports have demonstrated its safety and feasibility, and all of these are case reports [11-15]. Therefore, this study aimed to validate the treatment strategy and clinical outcomes to determine whether TECS could be used in cases of esophageal SMTs where POET/STER is unsuitable.

Methods

Patients

Twelve patients with SMTs in the esophagus and esophagogastric junction (EGJ) were retrospectively enrolled in the study between February 2020 and January 2024. All patients underwent endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) to identify the layer of origin and for histological diagnosis after esophagogastroduodenoscopy (EGD) and contrast-enhanced computed tomography (Figure 1 and Figure 2). The treatment plan was determined preoperatively in consultation with the endoscopists and surgeons, based on the Japanese Clinical Practice Guidelines for Gastrointestinal Stromal Tumors and a previous report (Figure 3) [3, 15]. Three inclusion criteria were used for treating SMTs of the esophagus and EGJ—(i) tumors with a major axis ≥ 2 cm, (ii) positive symptoms, and (iii) rapid tumor growth. POET was selected for SMTs without ulcerative lesions, with TMI < 1000 , tumor minor axis < 3 cm, and the tumor was not adjacent to the aorta, bronchus, or azygos vein. TECS was performed when POET was not feasible. If creating a submucosal tunnel is anticipated to be difficult (such as in cases of cervical esophageal tumors, after radiotherapy, post-endoscopic submucosal dissection [ESD], or post-peroral endoscopic myotomy [POEM]), POET and TECS are not deemed feasible, and esophagectomy should be considered. However, no such case was noted in this study. All study participants provided informed consent, and the study design was approved by the Ethics

Review Board of Konan Medical Center, following the tenets of the 1995 Declaration of Helsinki (2019-12, 2023-23).

Patient positioning

All patients were treated under general anesthesia. For POET alone, patients were placed in the supine position. For TECS, the procedure began with the patient in the left lower half lateral decubitus position. During the thoracoscopic procedure, the operating table was rotated to the right such that the patient was in a prone position. During the POET procedure, the operating table was rotated to the left such that the patient was in the left lateral decubitus position (Figure 4).

Endoscopic procedures for POET and TECS

The preparation for TECS was almost similar to that for POET, except for the patient's position. Endoscopic procedures were performed using a tapered-tip transparent cap-fitted endoscope and an electrosurgical generator (VIO3; Erbe, Tübingen, Germany) under carbon dioxide insufflation. (i) After injecting saline into the submucosal layer, a longitudinal mucosal incision was made with a Flush Knife BTS 1.5 mm (Fujifilm Medical, Tokyo, Japan), approximately 2–3 cm proximal to the tumor (Figure 1c and Figure 2e). In cases of TECS, the vital organs were protected using thoracoscopy before starting the endoscopic procedure (described below). (ii) Submucosal dissection was performed to create a tunnel from the mucosal entry, 1–2 cm distal to the tumor, and expose the tumor. (iii) The intraluminal SMT was resected from the inner circular muscle, preserving the outer longitudinal muscle if possible. If detaching the tumor from the outer longitudinal muscle was difficult, full-thickness myotomy was performed for margin-negative (R0) resection (Figure 1d and Figure 2f). In contrast, extraluminal SMT in the TECS group was resected thoracoscopically after ESD around the tumor. (iv) The tumor was extracted orally (Figure 1e and Figure 2g), and the mucosal incision was closed using endoscopic closure clips or purse-string sutures with an endoloop and clips (Figure 1f and Figure 2h). If the tumor was too large for

endoscopic removal, it was extracted thoracoscopically after an extension of the wound incision in the TECS group.

Operative procedure for TECS

Thoracoscopic exfoliation

The patients were placed in the supine position. The camera port was inserted into the 9th intercostal space, a 12 mm port into the 8th intercostal space, and a 5 mm port into the 7th and 5th intercostal spaces. Pneumothorax was induced at 8 mmHg. The location of the tumor was confirmed endoscopically, and markings were made on the esophageal adventitia (Figure 2c). If the azygos vein arch obstructed the surgical field, it was exfoliated circumferentially and dissected using an auto-suture device. The aorta, left main bronchus, and azygos vein were exfoliated from the esophageal wall around the tumor, and the esophageal branch of the thoracic aorta was preserved. A gauze was placed in the exfoliated space around the esophagus to prevent damage to these organs during the endoscopic procedure (Figure 2d).

Tumor extraction

Tumors were extracted either orally or intercostally. If oral retrieval was difficult because of the sheer size, it was retrieved through the intercostal space. Approximately 4 cm skin incision was made along the intercostal space, followed by an intercostal muscle incision. The tumor was placed in a plastic bag and extracted through the intercostal space.

Closure

The mucosal incision was closed using an endoscopic clip or a purse-string suture. The extent of muscle damage outside the tumor resection site was evaluated using a thoracoscope. Thoracoscopic suturing of the esophageal adventitia and muscular layer was performed using a manual intracorporeal knotted 3–0 vicryl suture (Ethicon GmbH; Norderstedt, Germany) (Figure 2i).

Postoperative management

All patients underwent EGD on postoperative day 1. Oral fluid intake was initiated if the EGD findings were favorable. A soft diet was initiated the day after water intake. All AEs were graded according to the Clavien–Dindo classification.

Statistical analysis

Data are presented as frequencies and percentages, means ($\pm$ standard deviation) or medians (range) where appropriate. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Twelve patients were enrolled in this study. Six patients underwent POET, whereas the other six underwent TECS (Supplemental Figure 1 and 2). Patient backgrounds and characteristics are presented in Table 1 and Supplemental Table 1, respectively. The mean age of patients was 51.8 ± 14.2 years in the POET group and 53.7 ± 4.9 years in the TECS group. The POET group comprised four male and two female patients, whereas the TECS group comprised three male and three female patients. The tumors in the POET group were located in the middle thoracic esophagus (Mt) in four patients and at the EGJ in two, whereas the tumors in the TECS group were located in the upper thoracic esophagus (Ut) in one patient and in the Mt in five. All patients underwent EUS-FNA before POET/TECS. All six patients were diagnosed with leiomyoma in the POET group. Conversely, five patients were diagnosed with leiomyoma, and one patient was diagnosed with schwannoma in the TECS group preoperatively. The mean TMI for the POET and TECS groups were 382.7 ± 25.1 and 505.6 ± 360.1 , respectively.

The perioperative outcomes are presented in Table 2. The mean duration of general anesthesia for POET and TECS were 140.5 ± 50.5 min and 327.5 ± 78.9 min, respectively ($P < 0.001$). Moreover, no significant difference was observed between the mean endoscopic procedure time for POET and TECS, with 97.0 ± 44.6 min and 104.4 ± 61.1 min, respectively. All tumors originated from the inner circular muscle, as diagnosed preoperatively using EUS. All the patients underwent en-bloc resection with negative margins. Endoscopic resection and oral retrieval were successfully performed in all patients in the POET group. In the TECS group, endoscopic resection was successfully completed in four cases, whereas two cases were converted to thoracoscopic resection according to the preoperative plan. Tumors were extracted orally in four patients and intercostally in two patients. All patients in the TECS group underwent reinforcement of the esophageal adventitia and muscle layer. The median postoperative hospital stay for POET and TECS was 5 (range: 4–6) days and 6.5 (range: 5–14) days, respectively. An oral diet was initiated on postoperative day 2, except in one patient with mucosal necrosis after TECS. In the TECS group, delayed mucosal necrosis was observed in one patient with the largest tumor, showing a preoperative TMI of 1140 (postoperative TMI: 1350). EGD performed the day after TECS showed only a change in mucosal color; however, EGD conducted 4 days later revealed delayed mucosal necrosis. Intraoperative thoracoscopic sutures prevented perforation, with no signs of mediastinitis or mediastinal emphysema. Polyglycolic acid sheets and fibrin glue were used to promote mucosal healing. Another patient in the TECS group had a submucosal hematoma and subcutaneous emphysema, which resolved without treatment.

Histopathological examination revealed four cases of leiomyoma, one case of schwannoma, and one case of c-KIT-negative GIST in the POET group. In contrast, all the tumors in the TECS group were leiomyomas. The median major tumor axes for POET and TECS were 20 (range: 10–49) mm and 19.5 (range: 15–45) mm, respectively. The TMI for POET and TECS were 289 (range: 70–1225) mm and 313.5 (range: 170–1350) mm, respectively. R0 resection was achieved in all cases. During the median

1 follow-up period of 33 (range: 6–53) months, no recurrence was observed in either group. A summary of
2 these two procedures is provided in Supplemental Table 2.

4 Discussion

5 Esophageal SMTs have a low incidence, and the limited number of cases requiring treatment has
6 prevented the establishment of guidelines in Japan. This study evaluated the clinical outcomes of POET
7 and TECS for esophageal SMTs and assessed the suitability of these treatment strategies. Although a few
8 case reports have described TECS for esophageal SMT, no comprehensive studies have compared it with
9 POET [11-13]. Some reports have described TECS for gastric tube cancer; however, these involve
10 thoracoscopically assisted ESD and should not be compared with TECS using the submucosal tunneling
11 technique [14, 15].

12 Since histological diagnoses of gastrointestinal SMTs are often difficult to obtain via endoscopic
13 biopsies [16, 17], EUS-FNA/fine needle biopsy (FNB) has become increasingly common for diagnosing
14 SMTs [18-20]. However, Verloop et al. reported that the diagnostic accuracies for SMTs were only 74.6%
15 and 84.2% for EUS-FNA and FNB, respectively [21]. Three cases (25%) in our study had different
16 histological diagnoses between the EUS-FNA and resected specimens. Therefore, large or rapidly
17 growing SMTs should be actively considered for resection using minimally invasive procedures to
18 confirm the diagnosis. En-bloc resection is desirable because GIST cannot be completely ruled out.
19 Enucleation of esophageal and EGJ SMTs with POET is the least invasive and most effective procedure;
20 however, the rate of AEs is not necessarily low [1, 3, 5]. Additionally, patients with a TMI exceeding
21 1000 or a minor axis greater than 30 mm are more likely to experience difficulties achieving complete en
22 bloc resection with POET [3]. Given these considerations, a modified technique is anticipated to
23 overcome the limitations of POET and expand its indications. TECS could be an effective alternative for
24 certain SMTs where POET is unsuitable.

Risk factors for serious AEs with POET include the incisional distance to the tumor, piecemeal resection, extraluminal location, mucosal injury, operative time, and duration of the POET procedure [1]. Mucosal injuries and prolonged exposure of the mediastinum with full-thickness resection can lead to severe AEs, such as pneumomediastinum and mediastinitis. Although these complications are rarely observed with POEM [22, 23], which is also a submucosal tunneling technique, they are more common with POET [1, 3]. This is likely owing to the thinness of the mucosa and muscle layer (as many patients with esophageal achalasia undergoing POEM often have thicker layers [24]) and poor visibility caused by large tumors. POET for extraluminal SMTs is also considered to carry a higher risk of complications owing to poor visibility and longer procedure time near the mediastinum.

We believe that TECS is well-suited for the treatment of high-risk cases. Although thoracoscopy allows for reliable determination of resection margins in cases with extraluminal SMTs, thoroscopic enucleation without endoscopic resection has been associated with mucosal injury that may lead to severe AEs in over 20% of cases [25]. TECS prevents mucosal injury during thoroscopic procedures by creating a submucosal tunnel and performing submucosal dissection around the tumor endoscopically in advance. In one patient with an extraluminal SMT in our study, this approach enabled safe en bloc resection, followed by thoroscopic resection according to the preoperative plan.

Although aortic injury-related esophageal endoscopic procedures include aorto-esophageal fistulas caused by esophageal foreign bodies or esophageal stent placement [26-29], no such injuries have reported owing to electrocautery resection of esophageal tumors with endoscopy. However, the risk of aortic wall damage during SMT resection near the aorta cannot be completely ruled out because POET sometimes involves full-thickness myotomy. Periesophageal exfoliation and placement of gauze between the esophagus and vital organs can prevent damage. This protection method did not increase the technical difficulty of the endoscopic procedure; hence, the mean endoscopic procedure time did not differ significantly between the POET and TECS groups.

1 Additionally, thoracoscopic intraoperative suturing of the esophageal adventitia and muscle layer
2 may prevent severe AEs, even if mucosal damage occurs. In another case of SMT with a TMI greater than
3 1000 in our study, delayed mucosal necrosis occurred; however, mediastinitis or mediastinal emphysema
4 complications were avoided because of reinforcement of the muscle layer. The use of polyglycolic acid
5 sheets, fibrin glue, and a prolonged fasting period prevented complications. The tumor was successfully
6 resected en bloc and retrieved through the intercostal space without division. Without thoracoscopy,
7 POET may have led to incomplete resection or tumor fragmentation during extraction, based on prior
8 reports.

9 In this study, no TECS procedures were performed for SMTs of the EGJ. In our cases, there was
10 no contact with vital organs, and the TMI and minor axis were within the applicable ranges for POET.
11 Even if the SMT at the EGJ exceeds the applicability for POET, laparoscopic assistance would likely be
12 more appropriate than thoracoscopic assistance owing to its location. In cases where en bloc resection is
13 necessary for such SMTs, the optimal choice among LECS with full-thickness resection, including the
14 mucosa, intragastric surgery, laparoscopy-assisted endoscopic full-thickness resection or proximal
15 gastrectomy remains controversial [30-34]. The submucosal tunneling technique with laparoscopic
16 assistance may be a minimally invasive surgical option for SMTs of the EGJ that is unsuitable for POET;
17 however, further investigation is necessary. In our cases, safe en bloc resection was achieved with POET
18 alone, without laparoscopy.

19 Finally, whether enucleation procedures, such as POET or TECS, are appropriate for GIST
20 remains controversial. Although subtotal esophagectomy ensures secure negative margins, it is highly
21 invasive. Lv et al. reported in their meta-analysis that no recurrence occurred in previous STER (POET)
22 cases, which included a large number of GIST cases [5]. Currently, POET and TECS are not absolute
23 indications for GIST but should be considered as treatment options based on the patient's clinical
24 background and preferences.

1 This study has several limitations. First, this was a single-center, retrospective study with a small
2 sample size. Second, we performed TECS in all cases where POET was not feasible. Therefore,
3 comparing POET and TECS under the same conditions is difficult. Finally, we could not confirm whether
4 reinforcement of the esophageal adventitia and muscle layer reduces the incidence of AEs because of the
5 small sample size in this study. Despite these limitations, we believe that TECS is a viable and effective
6 treatment option for esophageal SMTs where POET is challenging. Furthermore, our treatment strategy
7 for SMTs in the esophagus and EGJ, based on tumor size, location, and histology, appears reasonable.
8 Further studies with larger sample sizes are needed to validate our results.

9 In conclusion, TECS is a safe and feasible procedure for SMTs in the esophagus, where POET is
10 not feasible. Treatment strategies for SMTs in the esophagus and EGJ should be based on tumor size,
11 location, and histology, with thorough preoperative discussions between endoscopists and surgeons.

13 **Conflict of interest**

14 The authors have no conflict of interest to declare.

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Figure Legends

Figure 1.

Here is a representation of step-by-step approach in POET for the enucleation of esophageal SMT. Endoscopic findings showed the SMT in the esophagus (a). The SMT was detectable on CT (yellow arrow) (b). Longitudinal mucosal incision and submucosal dissection were performed to create a tunnel from the mucosal entry to the tumor (c). The SMT was excised from the surrounding submucosa and muscle within the tunnel (d). The SMT was resected and extracted per-orally (e), and the mucosal incision was closed using endoscopic clips (f).

Figure 2.

Here is a representation of step-by-step approach in TECS for the enucleation of esophageal SMT. Endoscopic findings showed the SMT in the esophagus. An intraluminal growth-type SMT was seen on the posterior wall, opposite the compression by the left main bronchus (red arrow) and the transmitted light of the thoracoscope (white arrowhead) (a). The SMT was detectable on CT (yellow arrow). The tumor was adjacent to the left main bronchus (red arrow) and aorta (red arrowhead) (b). The location of the tumor was confirmed endoscopically, and markings were made on the esophageal adventitia (yellow arrow) with thoracoscopy (c). The aorta, left main bronchus, and azygos vein were exfoliated from the esophageal wall around the tumor, and the esophageal branch of the thoracic aorta was preserved. A gauze was placed in the exfoliated space around the esophagus to prevent damage to these organs during the endoscopic procedure (d). Longitudinal mucosal incision and submucosal dissection were performed to create a tunnel from the mucosal entry to the tumor (e). The SMT was excised from the surrounding submucosa and muscle within the tunnel. The gauze was slightly visible after tumor resection (f). The SMT was resected and extracted per-orally (g), and the mucosal incision was closed using endoscopic clips (h). Thoracoscopic suturing of the esophageal adventitia and muscular layer was performed (i).

Figure 3.

Therapeutic strategy for treating SMTs in the esophagus and EGJ.

Figure 4.

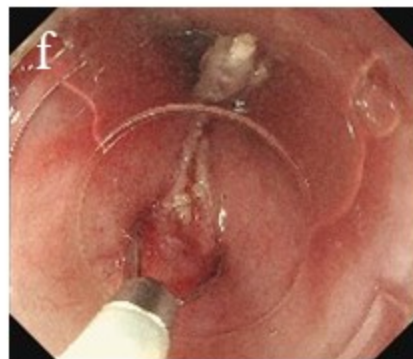
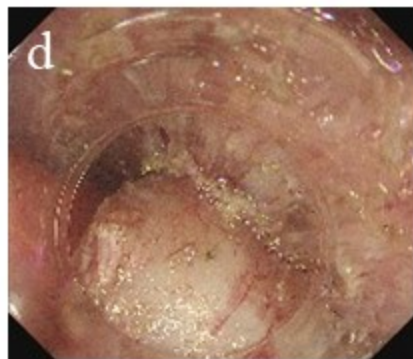
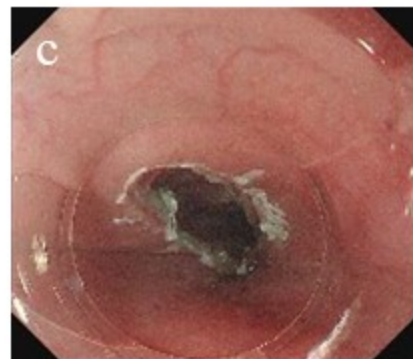
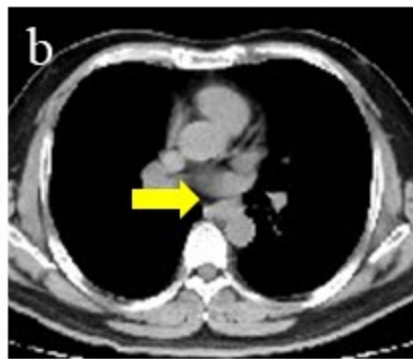
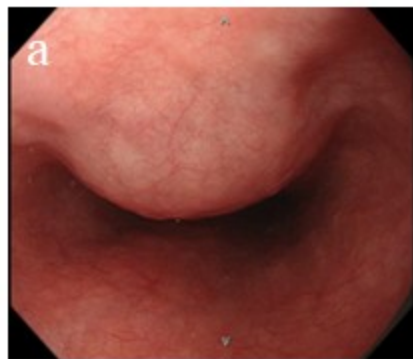
In TECS, the surgery starts with the patient in the left lower half of the lateral decubitus position. The operating table is rotated to the right during the thoracoscopic procedure and left during the endoscopic procedure.

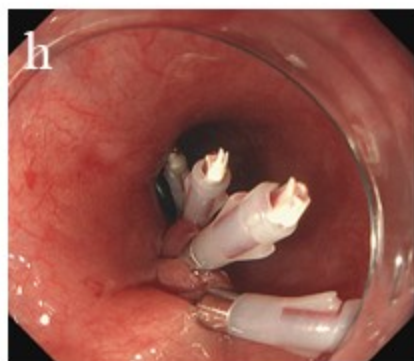
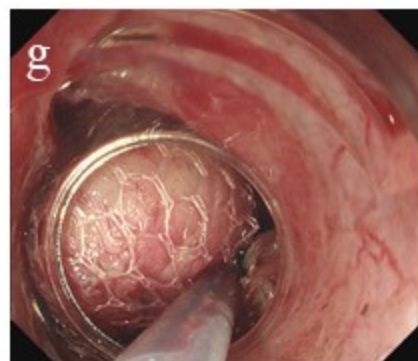
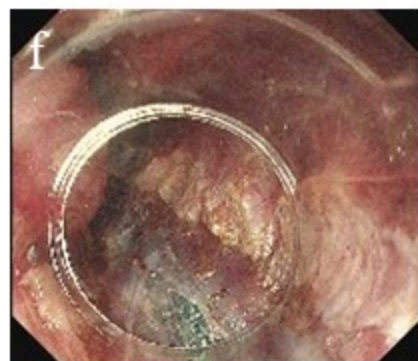
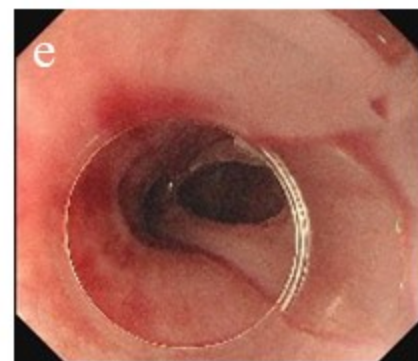
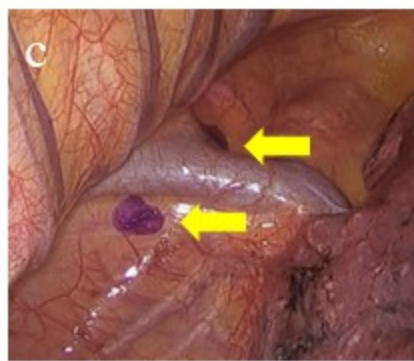
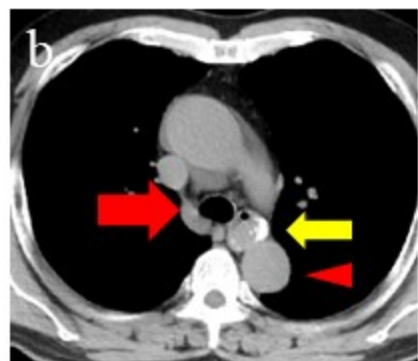
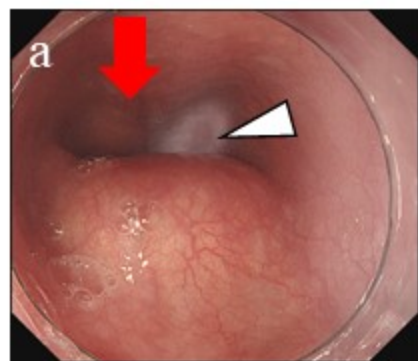
Supplemental Figure 1.

The endoscopic images (a-f) and CT scans (g-l) of six cases in which POET was performed. The yellow arrows indicate the tumors. The SMT of the case 4 patient (j) could not be detected by CT scan.

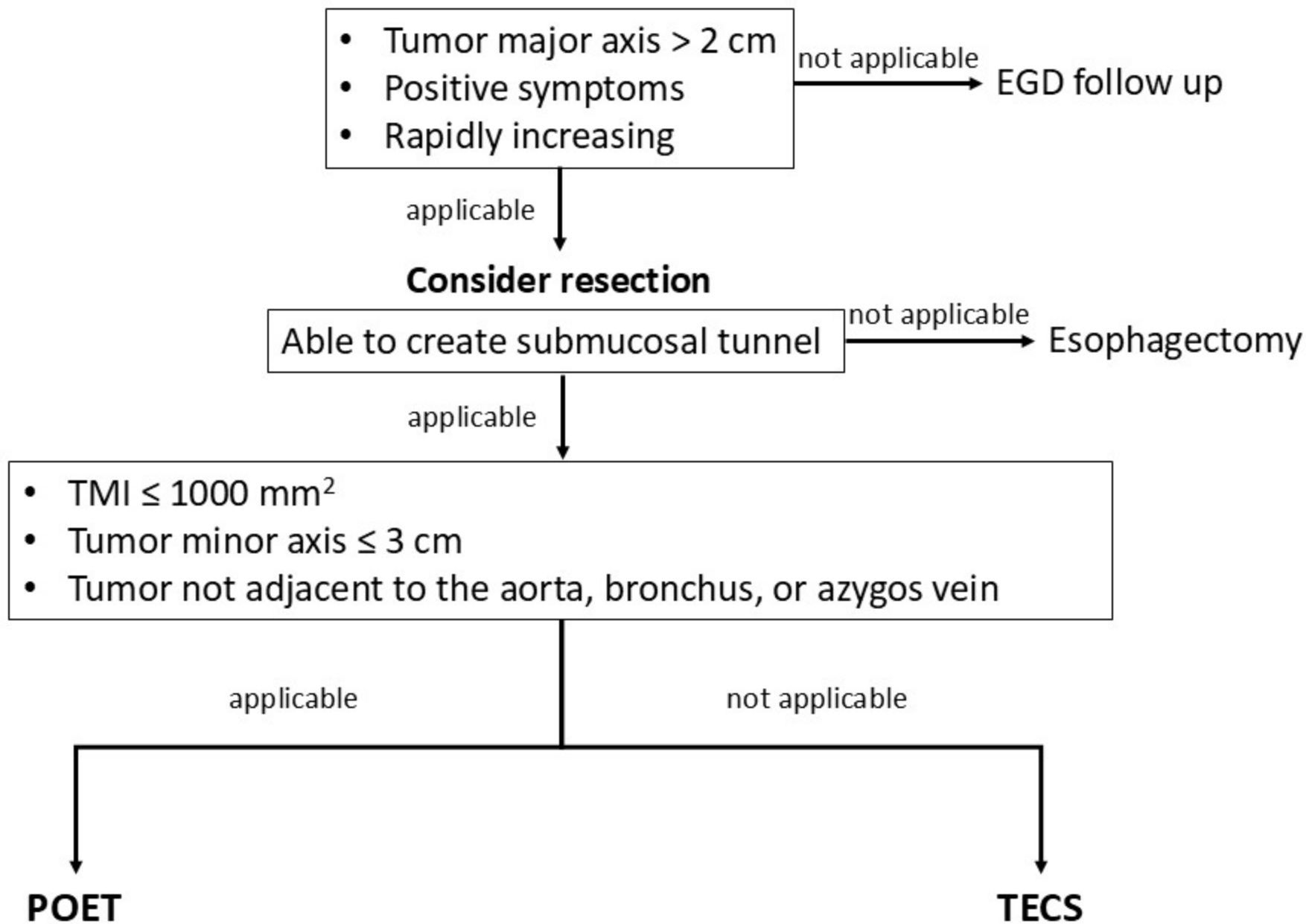
Supplemental Figure 2.

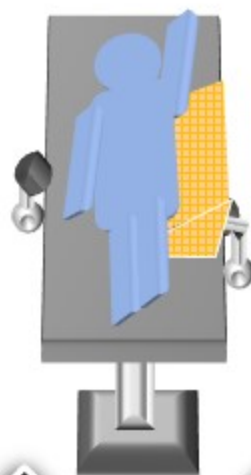
The endoscopic images (a-f) and CT scans (g-l) of six cases in which TECS was performed. Yellow arrows represent SMTs, red arrows represent the bronchi, yellow arrowheads represent the azygos veins, and red arrowheads represent the aortae. The tumor is adjacent to the aorta (g). The tumor is adjacent to the left bronchus, aorta, and azygos vein (h). The tumor is huge and adjacent to the main bronchus and the aortic arch (i). The tumor is adjacent to the left bronchus and aorta (j). The tumor is adjacent to the aorta (k). The tumor is adjacent to the left subclavian artery (l).





SMTs of the esophagus





Thoracoscopic procedure

Endoscopic procedure



Table 1. Characteristics of the patients

	POET (n=6)	TECS (n=6)	P value
Age (SD)	51.8 (14.2)	53.7 (4.9)	0.77
Gender			
Male/ Female	4/ 2	3/ 3	1.00
Location			
Ut/ Mt/ EGJ	0/ 4/ 2	1/ 5/ 0	0.46
EUS-FNA	6	6	1.00
TMI (SD)	382.7 (250.1)	505.6 (360.1)	0.52

Ut; Upper thoracic esophagus, Mt; middle thoracic esophagus, EGJ; esophagogastric junction, EUS-FNA; endoscopic ultrasonography-fine needle aspiration, TMI; tumor mass index

Table 2. Operative characteristics and postoperative outcomes

	POET (n=6)	TECS (n=6)	P value
Operation time, min, mean (SD)	140.5 (50.5)	327.5 (78.9)	<0.001
Endoscopy time, min, mean (SD)	97.0 (44.6)	104.4 (61.1)	0.82
En bloc resection	6	6	1.00
Tumor resection			
Endoscopy/thoracoscopy	6/0	4/2	0.46
Tumor extraction			
oral/intercostal	6/0	4/2	0.46
Adverse event			
All	0	2	0.46
CD grade 3a ≤	0	1	1.00
Oral intake date, median (range)	2 (2)	3.2 (2-9)	0.34
Length of stays, days, median (range)	5 (4-6)	6.5 (5-14)	0.06
Histology			
leiomyoma/ schwannoma/ GIST	4/ 1/ 1	6/ 0/ 0	0.46
Major tumor axis, mm, median (range)	20 (10-49)	19.5 (15-45)	0.87
TMI, median (range)	289 (70-1225)	313.5 (170-1350)	0.52
Recurrence			
yes/no	0/6	0/6	1.00

CD; Clavien Dindo, GIST; gastrointestinal stromal tumor, TMI; tumor mass index