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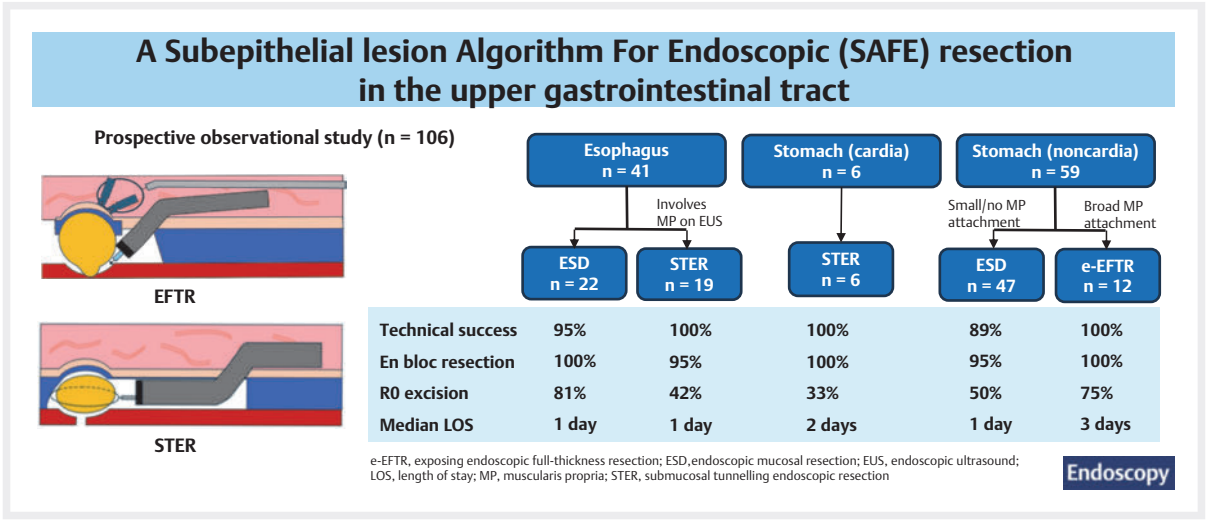
A subepithelial lesion algorithm for endoscopic (SAFE) resection in the upper gastrointestinal tract

GRAPHICAL ABSTRACT



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ABSTRACT

Background Complete excision of upper gastrointestinal subepithelial lesions (U-SELs) eliminates diagnostic uncertainty, obviates the need for surveillance, and may be necessary for definitive diagnosis and management. Current guidelines lack precision and cohesion, and surgery is associated with significant morbidity. We describe and report on the outcomes of our SEL algorithm for endoscopic (SAFE) resection.

Methods U-SELs were enrolled prospectively over 115 months until March 2023. All subjects underwent axial (computed tomography) imaging and endoscopic ultrasonography (EUS) to exclude a large exophytic component or invasion into local structures, and assess for muscularis propria (MP) involvement.

Results 106 U-SELs (41 esophageal, 65 gastric) were resected (mean patient age 60.6 [SD 13.4]; 51.9% male). Esophageal U-SELs underwent endoscopic submucosal dissection (ESD; n = 22) or submucosal tunneling endoscopic resection (STER) if MP involvement was suspected (n = 19). Gastric U-SELs underwent STER (n = 6 at cardia), ESD (n = 47), or exposing endoscopic full-thickness resection (e-EFTR; n = 12). Technical success rates were 97.6% and 92.3%, respectively. Among the noncardiac gastric U-SELs, five resections (9.6%) were completed laparoscopically owing to deep and broad full-thickness involvement; five

(9.6%) required laparoscopic gastrotomy and surgical retrieval after successful resection and closure owing to a large lesion size (mean 47 mm). There was no delayed bleeding, perforation, or recurrence at 13 months.

Conclusion U-SELs may be effectively and safely treated by endoscopic resection. The SAFE approach provides a framework that facilitates structured decision-making. Esophageal U-SELs suspected of involving the MP should undergo STER. Gastric SELs are best managed by ESD, with a view to proceeding to e-EFTR. A laparoscopic upper gastrointestinal surgeon should be available in case surgical retrieval of the specimen or laparoscopic completion is required.

Introduction

Subepithelial lesions of the upper gastrointestinal tract (U-SELs) are a heterogeneous and generally asymptomatic entity, detected incidentally at diagnostic gastroscopy in 2%–3% of individuals [1]. It is typically recommended that larger U-SELs (>3 cm) undergo surgical resection owing to their higher risk of malignant potential [1, 2, 3, 4, 5]. Where possible, minimally invasive surgery is used. This includes thoracoscopic excision or enucleation for esophageal SELs, and laparoscopic wedge resection for gastric SELs. To ensure technical success and prevent complications, these approaches generally require favorable lesion locations [6, 7]. For example, gastric stenosis is a well described following a wedge resection of the antrum. Moreover, U-SELs at the esophagogastric junction (EGJ) or on the posterior gastric wall generally require an esophagectomy or partial gastrectomy, respectively, for definitive management [6]. This is an important consideration as esophagectomy carries a 59% risk of immediate complications, including anastomotic leak, and a 2%–5% 30-day mortality [8, 9]. Long-term digestive morbidity is also frequent, with problems such as dumping occurring in upwards of 38% of patients following esophagectomy or gastrectomy [10].

Conversely, smaller U-SELs (<2 cm) are likely to remain static and carry minimal malignancy risk [11]. Although these may be monitored, this is resource intensive and not without a significant mental health burden, with over 50% of patients having borderline or pathologic anxiety-distress and carcinophobia [12]. Furthermore, surveillance programs are limited by patient compliance, biopsy sampling accuracy, and the burden of repeated procedures both in terms of cost and cumulative procedural risk [13].

Therefore, irrespective of size or location, complete minimally invasive endoscopic excision of U-SELs remains an attractive option. It eliminates diagnostic uncertainty, obviates the need for surveillance, and may be necessary for definitive diagnosis and management. Recently, there has been a growing body of evidence supporting the endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER), and endoscopic full-thickness resection (EFTR) techniques as effective treatment options for U-SELs. Moreover, they are organ-preserving procedures and may also treat U-SELs involving the muscularis propria (MP); however, current guidelines lack cohesion and evidence-based specificity. Critically, they do not distinguish the logical selection between these endoscopic techniques in their management algorithms (▶ **Fig. 1**) [1, 2, 3, 4, 5]. Owing to these shortcomings, we developed and followed an algorithm for U-SEL resection that delineates between the use of the ESD, STER, and EFTR techniques. Herein, we describe our algorithm and outcomes with respect to its effectiveness and safety.

Methods

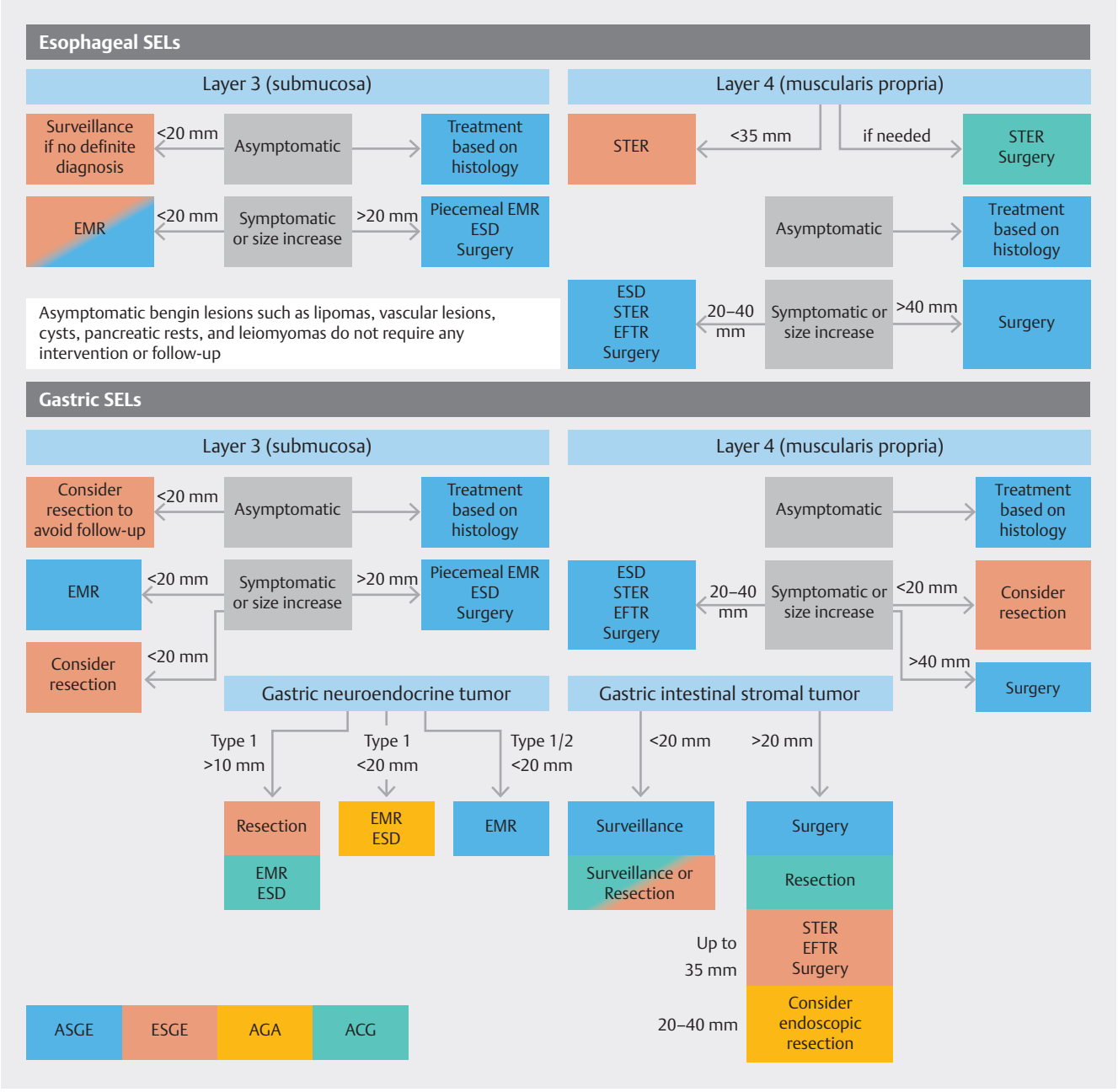
Study design

This manuscript was produced using guidance from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [14]. We conducted a single-center prospective observational study at a tertiary unit in Australia over 115 months until March 2023. All patients referred for U-SEL resection underwent axial (computed tomography [CT]) imaging to exclude an exophytic component and local invasion, and to establish the relationship with adjacent structures. Endoscopic ultrasonography (EUS) was performed in all patients to ascertain the features of the U-SEL and identify the layer of origin. After other factors such as lesion size, rate of growth, available histology, and patient age, co-morbidities, and preference had been considered, if deemed suitable, endoscopic resection (ER) was performed as per our algorithm for U-SEL resection (▶ **Fig. 2**). All patients provided informed consent. Approval to conduct this study was provided by our local research and ethics committee.

Endoscopic resection

All procedures were performed by a study investigator (accredited gastroenterologist with interventional endoscopy training and an established tertiary referral practice). Patients were under general anesthesia with endotracheal intubation, with their position changed to enhance the effect of gravity and to ensure that any fluid pool was located directly opposite the U-SEL to minimize the likelihood of contamination through a potential full-thickness mural defect.

A single-channel upper gastrointestinal (UGI) endoscope with a waterjet system was used. Carbon dioxide insufflation and a microprocessor-controlled generator (ERBE VIO 300D; ERBE, Tübingen, Germany) were used for all cases. The submucosal injectate consisted of succinylated gelatin with 0.4% indigo carmine and 1:100 000 epinephrine. STER was performed with a triangular tip knife (Olympus, Tokyo, Japan), while ESD was performed with a 1.5- or 2-mm Dual-J Knife (Olympus). Significant intraprocedural bleeding was treated with hemostatic forceps using soft coagulation (80 W, Effect 4; ERBE).



▶ **Fig. 1** Comparison of the various recommendations for the management of upper gastrointestinal subepithelial lesions made in guidelines of the American Society for Gastrointestinal Endoscopy (ASGE) [1], European Society of Gastrointestinal Endoscopy (ESGE) [3], American Gastroenterological Association (AGA) [5], and American College of Gastroenterology (ACG) [4].

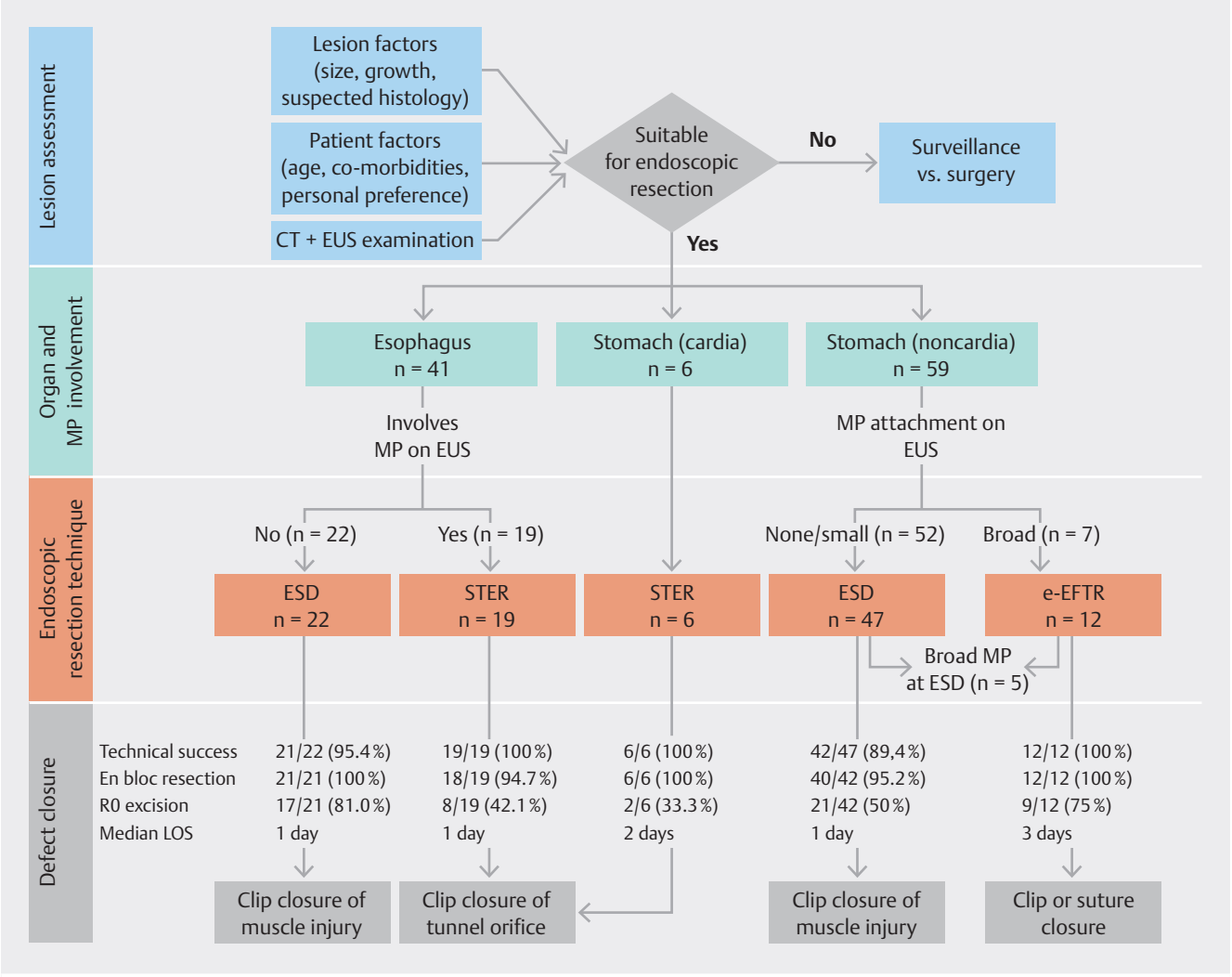
Algorithm for U-SEL resection

Esophageal

The growth of esophageal U-SELs tends to be along the organ's longitudinal axis. Therefore, in our experience, luminal diameter does not typically preclude ER or specimen retrieval. In this location, EFTR techniques were avoided to prevent a full-thickness defect into the mediastinum. Therefore, our algorithm used either STER or ESD. STER was performed if MP involvement was suspected on the basis of tumor pathobiology and the EUS examination (▶ **Fig. 3**; ▶ **Video 1**). The remaining U-SELs underwent ESD.

Gastric

U-SELs in the gastric cardia, located within 3 cm of the EGJ, underwent STER by tunneling from the esophagus. The simplicity of the linear approach and mucosal closure in the esophagus, along with a stable scope position within the tunnel made this technique more appealing than ESD, which itself may be precluded by challenging access, particularly in lesions located towards the fundus. STER was avoided in noncardia gastric U-SELs because, in this location, they were typically spherical and large (>40 mm). In this setting, we believed that scope angulation within a wide tunnel lumen would invariably lead to tearing of



▶ **Fig. 2** A simplified algorithm for the endoscopic management of upper gastrointestinal tract subepithelial lesions (U-SELs).
CT, computed tomography; e-EFTR, exposing endoscopic full-thickness resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasonography; LOS, length of stay; MP, muscularis propria; STER, submucosal tunneling endoscopic resection.

the tunnel orifice. Additionally, nonexposing EFTR devices were not considered as they can be limited by lesion size (<20 mm) and may capture unintended extramural tissue [2].

Therefore, the options used for ER in the stomach included ESD or exposing EFTR (e-EFTR). Lesions that involved the MP underwent upfront e-EFTR, while the remainder underwent ESD with a view to progression to e-EFTR if significant MP involvement was unexpectedly encountered during resection (▶ **Fig. 4**; ▶ **Video 2**). This was important because the accuracy of EUS in the stomach with regard to determining MP involvement may be limited [15]. For all cases, a laparoscopic UGI surgeon was available to assist on the same day if required.

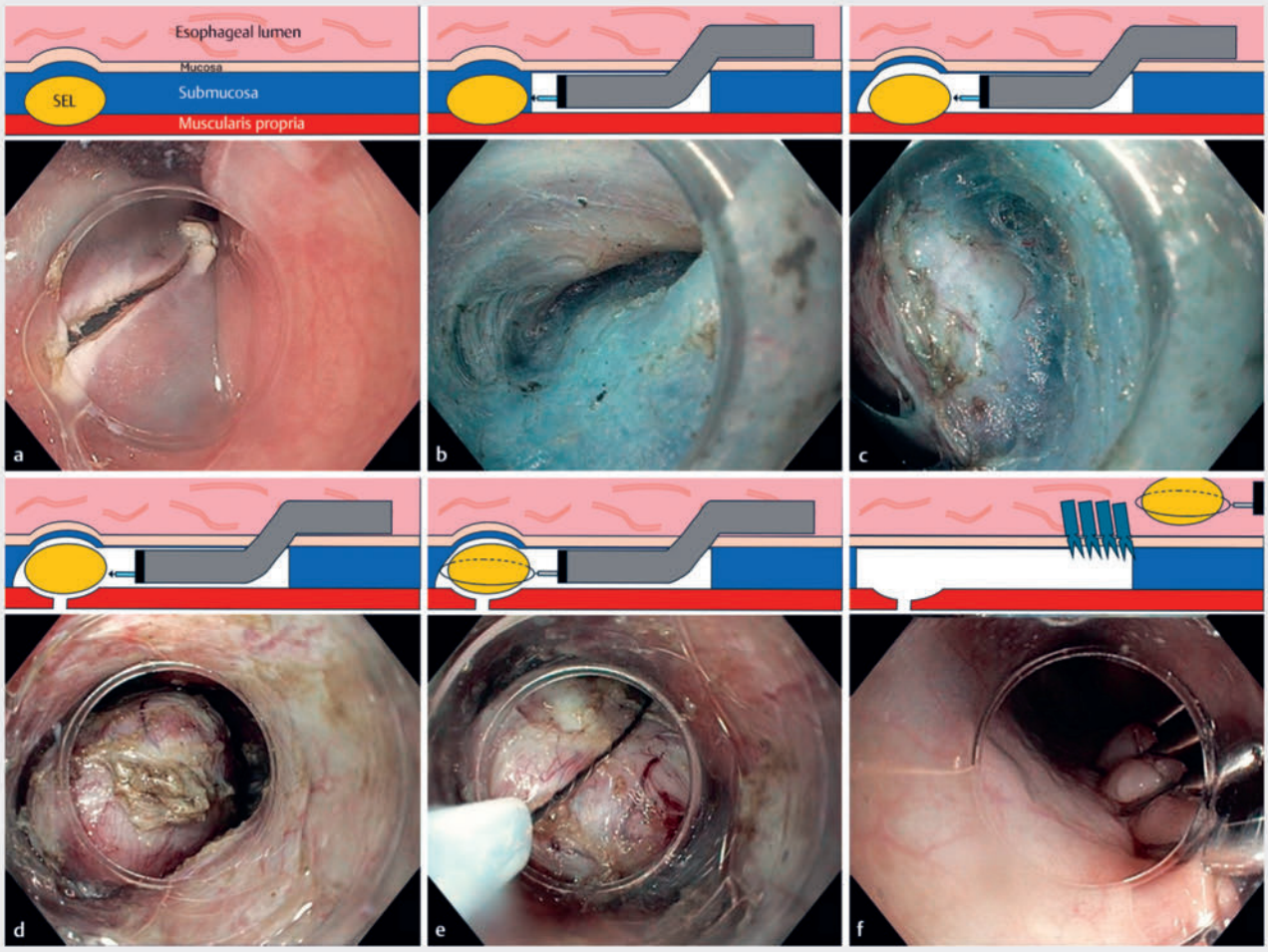
In cases of e-EFTR, where necessary owing to increased end-tidal pressures or tense abdominal distension, transabdominal needle decompression was performed to assist with venting of the associated capnoperitoneum (▶ **Video 3**). A leak test was subsequently performed, with cessation of bubbling indicating successful closure.

Histologic evaluation

Once retrieved, the U-SEL was fixed in 10% formalin. Following serial sectioning, the resected specimens were assessed histologically by two experienced GI pathologists. The histologic type, macroscopic appearance, tumor size, depth of invasion, lymphatic and vascular involvement, and horizontal and vertical margins were assessed.

Follow-up

Post-resection, patients were kept fasted and observed in hospital overnight on intravenous fluids and a continuous intravenous proton pump inhibitor (PPI) infusion. The following morning, patients were commenced on clear fluids. Patients were discharged if stable, afebrile, pain free, and tolerating fluids. All patients were prescribed twice daily oral PPI therapy for 2 months. At follow-up gastroscopy 6 months post-resection, if there was endoscopic concern of recurrence, biopsies were tak-



▶ **Fig. 3** The stages involved in submucosal tunneling endoscopic resection (STER) of an esophageal upper gastrointestinal subepithelial lesion (SEL) including: **a** submucosal injection, followed by a longitudinal mucosal incision of 2–3 cm approximately 3–4 cm proximal to the U-SEL; **b** submucosal tunnel with a width of 20–30 mm created down to the U-SEL, using a combination of dry cut current (80 W, Effect 3; ERBE) and swift coagulation (50 W, Effect 2; ERBE); **c** careful dissection of the submucosa towards the mucosal aspect of the U-SEL until it is independent of the overlying mucosa, then dissection of the submucosa towards the muscularis propria (MP) to expose the U-SEL's point of attachment to the MP; **d** careful dissection of the lesion from the MP, including a full-thickness extramural dissection of the attachment if required; **e** retrieval of the U-SEL with a snare once liberated; **f** endoscopic clip closure of the tunnel orifice.

en to assess for histologic evidence of recurrence. A CT scan was obtained at 12 months.

Definitions and outcomes

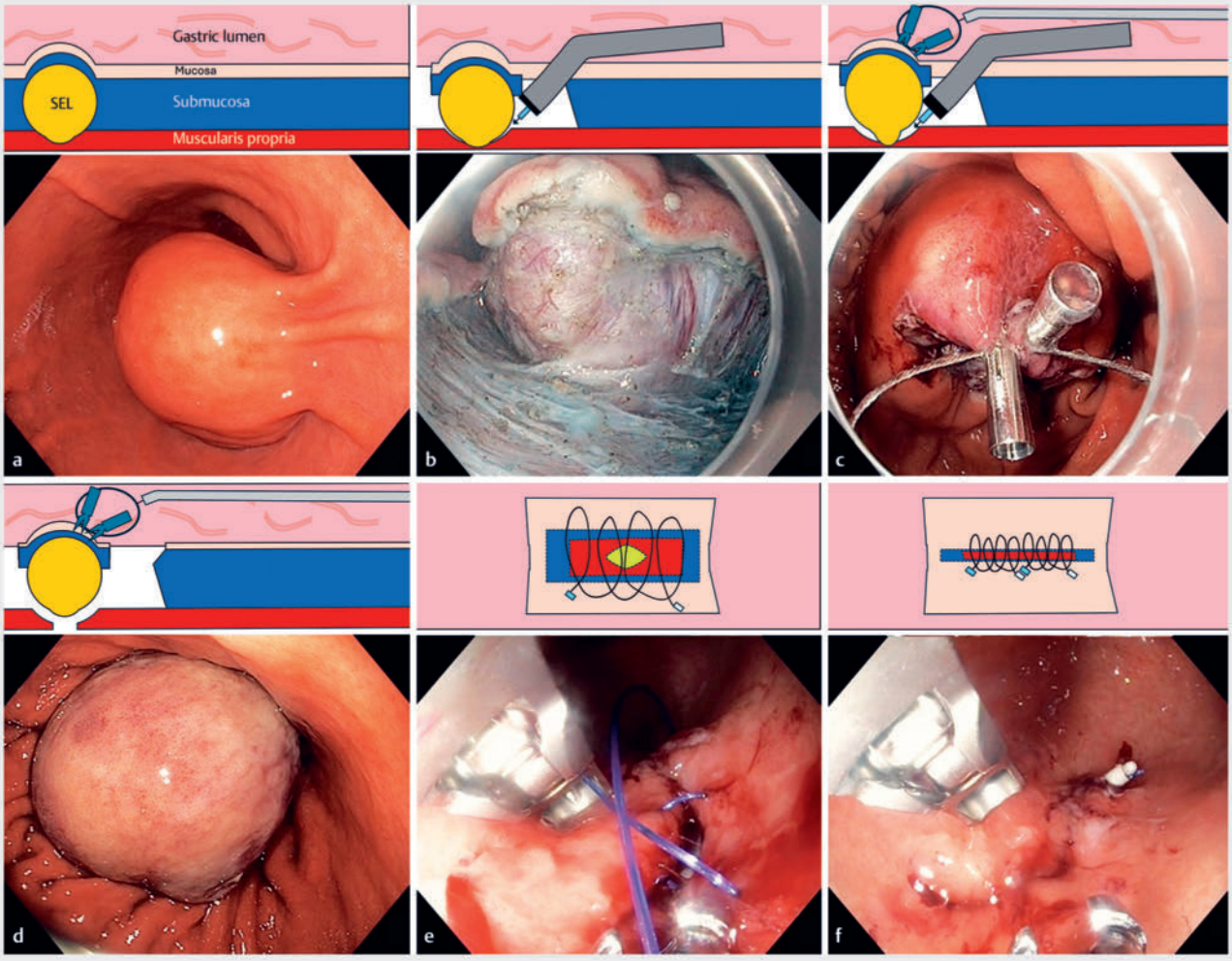
Technical success was defined as completion of the procedure with liberation of the U-SEL. If the U-SEL was liberated, but laparoscopic retrieval was required, the procedure was still deemed to be technically successful; however, if laparoscopic excision of the U-SEL was required, the procedure was not considered technically successful. En bloc resection was defined as resection of the lesion in a single piece with no endoscopically visible residual tumor. R0 resection was defined as en bloc resection with histologically clear horizontal and vertical margins.

Periprocedural adverse events (AEs), including bleeding and perforation, were recorded. Delayed bleeding was defined as hematemesis or melena that required an additional endoscopic procedure and necessitated the use of hemostatic forceps or endoclips within the first 2 weeks post-resection. Perforation was subdivided into intraprocedural and delayed. Intraprocedural perforation was defined as Sydney deep mural injury (DMI) grade III, IV, or V, for procedures other than e-EFTR [16]. Delayed perforation was diagnosed when a patient presented with fevers or pain and was noted to have peritoneal or retroperitoneal free air on CT imaging, in the absence of intraoperative perforation.

Outcomes included the rates of technical success, en bloc resection, R0 excision, AEs, and recurrence.

Statistical analysis

SPSS version 26.0 (IBM, Armonk, USA) was used for data analysis. Continuous variables were summarized using mean (SD) where normally distributed, or median and interquartile range



▶ **Fig. 4** The stages involved in endoscopic submucosal dissection (ESD) and exposing endoscopic full-thickness resection (e-EFTR) including: **a** marking of the lesion and submucosal injection; **b** complete circumferential dissection of the upper gastrointestinal subepithelial lesion (U-SEL) to expose its point of attachment to the muscularis propria (MP); **c** snare and clip-based traction, with the attachment placed on the intact mucosal surface of the U-SEL, with gentle traction applied externally by an assistant to lift up the U-SEL to further expose its point of attachment to the MP; **d** careful dissection of the lesion away from the muscle; **e,f** for e-EFTR procedures with a full-thickness hole, closure performed with clips or an endoscopic suturing device (in U-SELs completely resected by ESD without MP injury, defects were not routinely closed).

(IQR) where non-normally distributed. Categorical values were summarized as relative frequencies and percentages. To test for association between categorical variables, Fisher's exact tests were used. To assess for differences in continuous data between two groups, Student's *t* tests were used. All statistical analyses were two-tailed tests, with a 5% significance level used throughout.

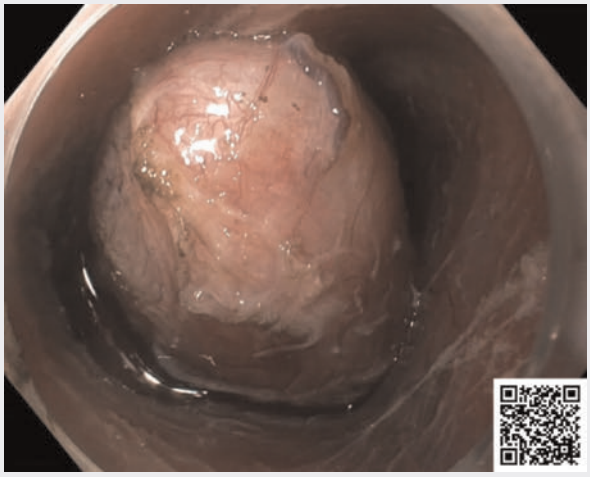
Results

A total of 106 U-SELs (41 esophageal, 65 gastric) were resected in 106 patients (mean age 60.6 [SD13.4] years; 55 men [51.9%]). Co-morbidities included cardiovascular disease in 41 patients (38.7%), diabetes in 26 (24.5%), and pulmonary disease in 14 (13.2%). The median length of stay was 1 day (IQR 1–1) and there were no cases of delayed bleeding or delayed perforation. There were no cases of recurrence at a median follow up of 13 months (IQR 6–29.5).

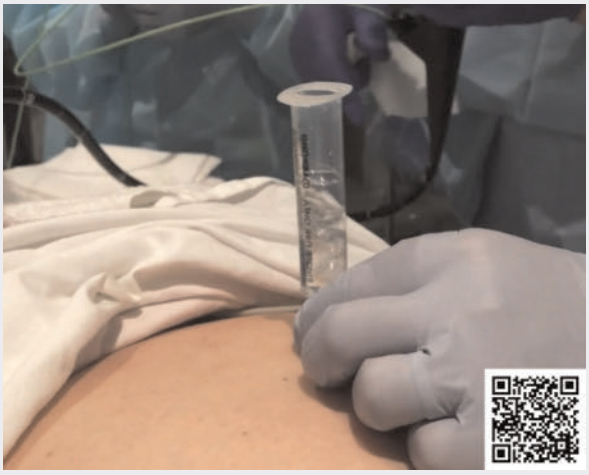
Pre-resection EUS-guided fine-needle aspiration (FNA) histology was available in 42 patients, which was accurate in 29 (69.0%). Minor AEs occurred in four patients (3.8%), including aspiration pneumonia (n = 2), mild acute kidney injury (n = 1), and hypophosphatemia (n = 1). All were treated during the inpatient admission and there were no sequelae.

Esophageal U-SELs

Esophageal U-SELs were managed by either ESD (n = 22) or STER (n = 19) (▶ **Table 1**). Overall technical success was achieved in 40 (97.6%). Of these, the rates of en bloc resection for ESD and STER were 100% (21/21) and 94.7% (18/19), respectively (P = 0.90). R0 resection was higher with ESD (81.0% [17/21] vs. 42.1% [8/19]; P = 0.01).



Video 1 Submucosal tunneling endoscopic resection (STER) is performed.
Online content viewable at:
https://doi.org/10.1055/a-2369-7854



Video 3 Transabdominal needle decompression is performed to assist with venting of a capnoperitoneum.
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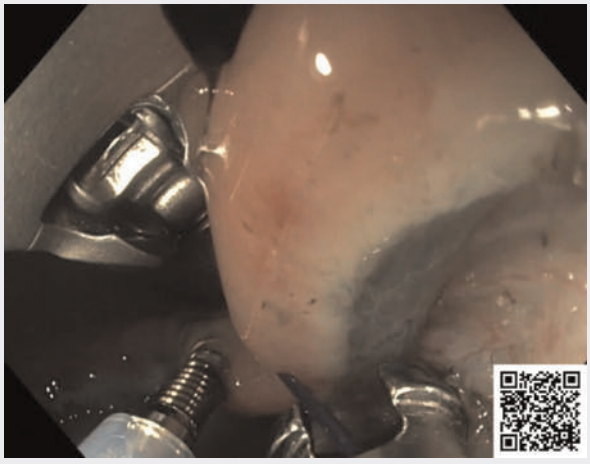

Video 2 Exposing endoscopic full-thickness resection (e-EFTR) is performed.
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Of the 19 U-SELs excised by STER, involvement of the MP was accurately predicted by EUS in 16 (84.2%). Of the 22 excised by ESD, exclusion of the MP was accurately predicted in 20 (90.9%). In the two incorrectly predicted ESD cases, one was aborted owing to extensive MP involvement and instead underwent serial surveillance, while the other had a small MP attachment that could be resected without causing a full-thickness defect. All specimens were endoscopically retrieved.

The histology was found to be leiomyoma (n = 28), granular cell tumor (GCT; n = 7), gastrointestinal stromal tumor (GIST; n = 3), neuroendocrine tumor (NET; n = 1), and submucosal Warthin's tumor (n = 1). U-SELs that underwent STER were larger (mean 29.5 [SD 8.4] mm vs. 18.6 [11.4]; $P<0.001$) and took longer to resect (mean 102.6 [SD 84.8] minutes vs. 41.5 [28.7]; $P<0.001$). A median of five clips (IQR 4.8–7) were required to close the tunnel orifice in the STER cases. In the ESD cases, DMI occurred in two cases, requiring a median of two clips (IQR 2–2) to close.

Gastric U-SELs

Gastric U-SELs were managed by STER (n = 6), ESD (n = 47), or e-EFTR (n = 12) (▶ **Table 2**). Technical success was achieved in 92.3% (60/65). All six gastric cardia U-SELs were successfully resected by STER. EUS under-reported MP involvement in 27.3% of cases.

Of the 52 noncardia U-SELs that began as ESD cases, five (9.6%) were converted to e-EFTR owing to a broader MP attachment than expected, and five (9.6%) were aborted and completed laparoscopically owing to deep and broad full-thickness involvement that was not amenable to e-EFTR and would have precluded endoscopic closure. Therefore, the technical success rate of ESD (not requiring surgery) was 89.4% (42/47). Of the five cases that required surgery, four underwent same-day surgical resection and one resection on the following day.

Of the 54 successfully resected noncardia cases, the rates of en bloc resection by ESD and e-EFTR were 95.2% (40/42) and 100% (12/12), respectively ($P = 0.68$). The rates of R0 resection were 50% (21/42) and 75% (9/12), respectively ($P = 0.12$). Five U-SELs (7.7%) required laparoscopic gastrotomy and surgical retrieval after successful ER owing to lesion size (one ESD, four e-EFTRs; mean size 47 mm). Of the nine U-SELs ≥40 mm that were successfully resected, four (44.4%) required laparoscopic retrieval.

▶ **Table 1** Comparison of lesion characteristics, outcomes, complications, and recurrence for the different endoscopic resection techniques in the esophagus.

	ESD (n = 22)	STER (n = 19)	*P* value (ESD vs. STER)
Size, mean (SD), mm	18.6 (11.4)	29.5 (8.4)	<0.001
Location, n (%)			0.94
▪ Mid-esophagus	7 (31.8)	6 (31.6)	
▪ Lower esophagus	15 (68.2)	13 (68.4)	
MP involvement, n (%)	2 (9.1)	16 (84.2)	<0.001
Technical success, n (%)	21 (95.4)	19 (100)	0.91
En bloc resection, n (%)[1]	21 (100)	18 (94.7)	0.90
R0, n (%)[1]	17 (81.0)	8 (42.1)	0.01
Histology, n (%)[1]			N/A
▪ Leiomyoma	12 (57.1)	16 (84.2)	
▪ Gastrointestinal stromal tumor	0 (0)	3 (15.8)	
▪ Granular cell tumor	7 (33.3)	0 (0)	
▪ Neuroendocrine tumor	1 (4.8)	0 (0)	
▪ Submucosal Warthin's tumor	1 (4.8)	0 (0)	
Intraprocedural bleeding, n (%)	11 (50.0)	13 (68.4)	0.23
Procedure duration, mean (SD), minutes	41.5 (28.7)	102.6 (84.8)	<0.001
Delayed bleeding, n (%)	0 (0)	0 (0)	N/A
Delayed perforation, n (%)	0 (0)	0 (0)	N/A
Length of stay, median (IQR), days	1 (1–1)	1 (1–1)	>0.99
Recurrence, n (%)	0 (0)	0 (0)	N/A

ESD, endoscopic submucosal dissection; IQR, interquartile range; MP, muscularis propria; STER, submucosal tunneling endoscopic resection.
[1] Percentage of lesions with technical success.

There were no predictors of technical failure. Laparoscopic retrieval was most associated with a larger lesion size (mean 47 [SD 13] mm vs. 22.9 [15] mm; $P = 0.001$) and e-EFTR (33% [4/12] vs. ESD 2.1% [1/47]; $P = 0.005$).

The histology was found to be GIST (n = 21), NET (n = 17), leiomyoma (n = 10), inflammatory fibroid polyp (n = 7), lipoma (n = 4), and plexiform angiomyxoid myelofibroblastic tumor (n = 1). U-SELs that underwent e-EFTR trended towards being larger (mean 31.3 [SD 13.3] mm vs. 22.3 [15.0]; $P = 0.06$), more likely to involve the MP (100% [n = 12] vs. 27.6% [n = 13]; $P<0.001$), and took longer to resect (mean 155.0 [SD 84.2] vs. 59.7 [47.5] minutes; $P<0.001$).

In ESD cases, DMI occurred in 12 cases (27.9%), requiring a median of three clips (IQR 2–9) to close the injury. In two of these cases, the DMI was more extensive and required endoscopic suturing to close. The median length of stay was longer in patients who underwent e-EFTR (3 days[IQR 1.8–4.3] vs. 1 day [1]–[1]; $P<0.011$).

High risk lesions

A total of 42/106 U-SELs (24 GISTs and 18 NETs) were deemed to be high risk lesions based on their final histology (▶ **Table 3**).

Resected GISTs had a mean (SD) size of 31.1 (14.4) mm, and the majority were located within the noncardia portion of the stomach (n = 18; 75.0%). The ER techniques used included STER (n = 6), ESD (n = 8), and e-EFTR (n = 10). Technical success was achieved in 22 cases (91.7%), with the two failures the result of broad involvement of the MP. Where technical success was achieved, the resection was en bloc resection in 22 cases (100%) and R0 in 15 (68.2%). There were no signs of recurrence at follow-up.

Resected NETs had a mean (SD) size of 19.1 (12.4) mm, and the majority were located within the noncardia portion of the stomach (n = 16; 88.9%). All resections were performed by ESD, with technical success achieved in 17 (94.4%), with the one failure due to broad involvement of the MP. Where technical success was achieved, resection was en bloc in 17 cases (100%) and R0 in 12 (70.6%). There were no signs of recurrence at follow-up.

▶ **Table 2** Lesion characteristics, outcomes, complications, and recurrence for the different endoscopic resection techniques in the stomach.

	STER (n = 6)	ESD or e-EFTR (n = 59)	ESD (n = 47)	e-EFTR (n = 12)	*P* value (ESD vs. e-EFTR)
Size, mean (SD), mm	36.7 (19.7)	23.6 (15.3)	22.4 (15.0)	32.0 (13.3)	0.01
Location n (%)					0.91
▪ Cardia	6 (100)	0 (0)	0 (0)	0 (0)	
▪ Fundus	0 (0)	3 (5.1)	2 (4.3)	1 (8.3)	
▪ Proximal body	0 (0)	33 (55.9)	26 (55.3)	7 (58.3)	
▪ Distal body	0 (0)	9 (15.3)	6 (12.8)	3 (25.0)	
▪ Angularis	0 (0)	2 (3.4)	2 (4.3)	0 (0)	
▪ Antrum	0 (0)	12 (20.3)	11 (23.4)	1 (8.3)	
MP involvement, n (%)	4 (66.7)	25 (42.4)	13 (27.6)	12 (100)	<0.001
Technical success, n (%)	6 (100)	54 (91.5)	42 (89.4)	12 (100)	0.37
En bloc resection, n (%)[1]	6 (100)	52 (96.3)	40 (95.2)	12 (100)	0.68
R0, n (%)[1]	2 (33.3)	30 (68.2)[2]	21 (50.0)	9 (75.0)	0.12
Histology, n (%)[1]					NA
▪ Leiomyoma	3 (50)	7 (13.0)	6 (14.3)	1 (8.3)	
▪ Gastrointestinal stromal tumor	3 (50)	18 (33.3)	7 (16.7)	11 (91.7)	
▪ Neuroendocrine tumor	0 (0)	17 (31.5)	17 (40.5)	0 (0)	
▪ Inflammatory fibroid polyp	0 (0)	7 (13.0)	7 (16.7)	0 (0)	
▪ Plexiform angiomyxoid myelofibroblastic tumor	0 (0)	1 (1.9)	1 (2.4)	0 (0)	
▪ Lipoma	0 (0)	4 (9.3)	4 (9.5)	0 (0)	
Intraprocedural bleeding, n (%)	6 (100)	40 (83.3)[3]	33 (78.6)	12 (100)	0.37
Procedure duration, mean (SD), minutes	134.3 (49.7)	78.8 (67.6)	59.7 (47.5)	155.0 (84.2)	<0.001
Delayed bleeding, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Delayed perforation, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Length of stay, median (IQR), days	2 (1.3–5)	1 (1–2)	1 (1–1)	3 (1.8–4.3)	<0.001
Recurrence, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	NA

e-EFTR, exposing endoscopic full-thickness resection; ESD, endoscopic submucosal dissection; IQR, interquartile range; MP, muscularis propria; STER, submucosal tunneling endoscopic resection.
[1] Percentage of lesions with technical success.
[2] Only 44 cases for R0 resection.
[3] Only 48 cases for intraprocedural bleeding.

Discussion

We show that the endoscopic en bloc excision of U-SELs is effective and safe. In contrast to contemporaneous guidelines, once a decision has been made to embark upon U-SEL resection, our algorithm specifies the preferred resection modality based upon simple parameters such as location and suspected MP involvement. When the algorithm is followed, ESD, STER, and e-EFTR all achieve excellent technical success rates in the esophagus (97.6%) and stomach (92.3%). Therefore, our algorithm is extremely useful as a decision-making tool when planning U-SEL resection and may also aid in the consent process.

Current guidelines pertaining to the management of U-SELs are incomplete, lack cohesion, and do not advocate for one ER technique over another (▶ **Fig. 1**). Taking the example of an esophageal U-SEL involving the MP, the American Society for Gastrointestinal Endoscopy (ASGE) recommend ESD, EFTR, STER, or surgery for symptomatic lesions between 20 and 40 mm in size [1], whereas the European Society of Gastrointestinal Endoscopy (ESGE) recommend STER for lesions <35 mm in size [3] and the American College of Gastroenterology (ACG) recommend STER or surgery [4]. In contrast, we provide a simple algorithm, in which only ESD or STER are recommended in the esophagus; the choice being based on suspected MP involvement; we do not recommend EFTR in the esophagus, as this

▶ **Table 3** Lesion characteristics, technical success, complications, and recurrence for gastrointestinal stromal tumors (GISTs) and neuroendocrine tumors (NETs).

	GIST (n = 24)	NET (n = 18)
Size, mean (SD), mm	31.1 (14.4)	19.1 (12.4)
Location n		
▪ Esophageal	3	1
▪ Gastric cardia	3	1
▪ Gastric noncardia	18	16
Type of procedure, n		
▪ STER	6	0
▪ ESD	8	18
▪ e-EFTR	10	0
Muscularis propria involved, n	20	16
Endoscopic success, n	22	17
En bloc resection, n	22	16
R0, n	15	12
Intraprocedural bleeding, n	17	13
Procedure duration, mean (SD), minutes	127.6 (71.8)	49.7 (14.1)
Delayed bleeding, n	0	0
Delayed perforation, n	0	0
Hospital stay, median (IQR), days	2 (1.5–3.5)	1 (1.0–1.8)
Recurrence at latest follow-up, n	0	0

e-EFTR, exposing endoscopic full-thickness resection; ESD, endoscopic submucosal dissection; IQR, interquartile range; STER, submucosal tunneling endoscopic resection.

has the potential to cause a direct full-thickness defect into the mediastinum. The utility of our selective approach is corroborated by the excellent rates of technical success achieved and the absence of significant AEs in this study.

Interestingly, for gastric U-SELs, some guidelines advocate for endoscopic mucosal resection (EMR) for lesions of <20 mm in size and without MP involvement. We would caution against this approach, as this may inadvertently result in piecemeal or incomplete resection. Similarly, nonexposing EFTR devices may be limited by lesion size (<20 mm), are relatively uncontrolled, may not capture the entire lesion, or may injure other organs. As demonstrated in our study, the mean size of noncardia gastric U-SELs undergoing e-EFTR was 32 mm, and therefore such devices would have hindered en bloc resection and left residual tissue behind [2]. Furthermore, we did not perform STER in the noncardia parts of the stomach because, in our experience, U-SELs here are typically spherical and may become very large (>40 mm). In this setting, there is a risk of the tunnel orifice tearing because of scope angulation in the stomach. Moreover, in our algorithm, noncardia gastric lesions were effectively managed with ESD with a view to performing e-EFTR if required.

The importance of en bloc resection in the management of U-SELs cannot be understated. The excellent rates achieved in this study are underscored by the absence of recurrence during surveillance. Of note, rates of en bloc resection without R0 excision were much lower, being achieved in 55.6% (30/54) of gastric and 62.5% (25/40) of esophageal U-SELs. Despite this, there were no cases of recurrence at a median follow up of 13 months. This remains the case when considering only higher risk U-SELs (GISTs and NETs) in our study. This is because, unlike ESD for early esophageal or gastric cancers, where clear peripheral and deep margins are oncologic necessities, U-SEL resection only requires excision of the lesion itself. In such cases, the status of "clear margins" depends on the integrity of the U-SEL's pseudocapsule, which may not be feasible to achieve owing to its proximity to the plane of dissection. However, as others have demonstrated [17], the lack of R0 excision does not translate to recurrence. Rather, en bloc resection is the key, and therefore techniques that carry a high risk of resulting in piecemeal and incomplete resection should be avoided.

In our algorithm, we rely on a U-SEL's location and suspected MP involvement to determine the preferred resection modality. In the esophagus, STER is preferred if EUS findings suggest MP involvement, with the remaining lesions undergoing ESD. In this location, EUS had a favorable positive predictive value (PPV) of 84.2% and negative predictive value (NPV) of 90.9% with regard to MP involvement. This is likely because, in contrast to the stomach, the esophagus is a tubular structure that facilitates better apposition of the EUS probe to the mucosal lining. It is therefore not surprising that, while EUS had a PPV of 100% in the noncardia stomach, the NPV for detecting MP involvement was lower at 72.7%. Therefore, in the setting of noncardia gastric U-SELs, it imperative that cases flagged for ESD are performed with a view to progression to e-EFTR if significant MP involvement is unexpectedly encountered.

Our study does not specifically address whether a U-SEL should be resected or surveilled. While surveillance could be recommended in some cases, compliance can be poor and repeated procedures carry a cost and a cumulative procedural risk [13]. We acknowledge that a large proportion of resected U-SELs were benign on final histology; however, the decision to resect them was nuanced and based upon the results of CT/EUS examinations, the availability of FNA/fine-needle biopsy (FNB) results, lesion size, growth, and patient age, co-morbidities, preference, and symptoms. It is important to note that the accuracy of pre-resection histology was limited in our study (69%) and therefore excision eliminated diagnostic uncertainty and obviated the need for surveillance. This approach is not without merit, as over 50% of patients suffer from significant mental health burden, including borderline or pathologic anxiety-distress and carcinophobia [12]. This also partly explains why some guidelines recommend consideration of resection for asymptomatic nondiagnostic gastric U-SELs <20 mm [3]. Therefore, while we do not suggest that all U-SELs should be resected, given the excellent results obtained when using our algorithm, complete excision of U-SELs remains an attractive op-

tion to eliminate diagnostic uncertainty, obviate the need for surveillance, and provide a definitive diagnosis and management plan.

The use of our algorithm also results in the safe resection of U-SELs. There were no cases of delayed perforation or delayed bleeding. DMI was more common in the stomach; however, it was readily treated with either clip closure or endoscopic suturing, with no short or long-term sequelae. In cases of e-EFTR, snare and clip-based traction was used, as this enabled the U-SEL to be lifted out of the MP. This facilitated controlled dissection, leaving a small full-thickness defect that was easily closed. While all guidelines consider surgery as an option for U-SEL management, this should be performed only in cases of technical failure. As we have demonstrated, the technical success rate with ER is over 90%, which therefore avoids the morbidity and mortality associated with surgery. It is however important to remember that a laparoscopic UGI surgeon should be available to assist on the same day if required. This is crucial in the case of large (>40 mm) noncardia U-SELs undergoing ESD or e-EFTR, as 44.4% of such U-SELs required laparoscopic retrieval in our study. Although surgical assistance was required in these cases, the alternative would have been to perform a wedge resection or partial gastrectomy, which both carry additional risks.

Our study is not without limitations. This algorithm was developed and validated in an expert tertiary center. The ER of U-SELs is highly specialized and should be performed only in such settings and with surgical support available. Selection bias may have been introduced as we do not have data on lesions that were not referred for ER (i. e. those referred directly for surgical resection). Furthermore, surgical assistance was required in some cases, so it is important for such support to be available. In our center, all procedures were performed in the endoscopy unit and, in cases where surgery was required, patients were transported anesthetized to the operating room, which is co-located with our unit. A formalized and structured approach to this situation is important to establish, particularly as it will vary between centers because of differences in unit structures and the availability of surgical teams and equipment.

The endoscopic management of U-SELs is a dynamic field and becoming increasingly accessible with growth in the scale and complexity of ER for the definitive treatment of neoplasia. As techniques are refined over the next decade, one could envisage that the majority of patients with U-SELs, after a fully informed discussion on the treatment and surveillance options, will choose ER over the burden and comparative uncertainty of surveillance. Although this study is not an expert consensus, it serves as a framework upon which to logically move forward in the management of this endoscopically defined UGI entity, with its variable underlying pathology and anatomy.

In conclusion, although many U-SELs are asymptomatic and detected incidentally, they confer diagnostic and therapeutic imperatives and potential surveillance requirements. Upfront ER is attractive to attenuate this burden, particularly given its safety, comparatively low cost, definitive nature, and minimal sequalae. The SAFE approach provides endoscopists with a simple and logical approach when selecting between possible ER modalities. While this approach is safe and effective, further studies are required to validate our findings.

Conflict of Interest

M.J. Bourke has received research support from Olympus, Cook Medical, and Boston Scientific. S. Gupta, J. Gauci, T. O'Sullivan, O. Cronin, A. Whitfield, A. Craciun, H. Awadie, J. Yang, V. Kwan, E.Y.T. Lee, and N. G. Burgess declare that they have no conflicts of interest.

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