Outcomes of endoscopic ultrasound and endoscopic resection of gastrointestinal subepithelial lesions: a single-center retrospective cohort study

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Abstract

Background Endoscopic resection (ER) is an emerging therapeutic alternative for subepithelial gastrointestinal lesions (SELs). We aimed to determine whether size, layer of origin, and histology based on endoscopic ultrasound (EUS) and EUS-guided sampling (EUS-GS) influenced the outcomes and selection of patients for ER.

Methods We performed a retrospective review of patients who underwent EUS, EUS-GS and resection of SELs from 2012-2019. Two pathologists reviewed the histology and layer of origin of all resected specimens, serving as the criterion for EUS accuracy.

Results Seventy-three patients were included, of whom 59 (81%) were gastric SELs. Per EUS, median lesion size was 21 mm (interquartile range 15-32), and 63 (86%) originated from the 4th layer. The overall accuracy of EUS and EUS-GS in predicting the layer of origin and histology was 88% (95% confidence interval [CI] 77-94%) and 96% (95%CI 87-98%), respectively. Based on EUS, 18 (25%) patients were referred for ER, 5 (7%) to laparoscopic-endoscopic cooperative surgery, and 50 (68%) to surgery. Size >20 mm was associated with the type of resection approach (P=0.005), while layer of origin and histology were not (P=0.06 and P=0.09, respectively). When SELs were inaccurately classified (n=4) there were no adverse events or revision of the resection approach.

Conclusions EUS plays an important role in the outcome of resection approach for SELs, with size significantly influencing the selection for ER. In patients undergoing ER, no revised resections were needed when EUS was inaccurate.

Keywords Endoscopic ultrasound, endoscopic resection, subepithelial lesion

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Introduction

Gastrointestinal tract subepithelial lesions (SELs) are often incidentally found during endoscopy or on radiologic examination. The true prevalence of SELs is unknown. A retrospective study reported a prevalence of 0.36% for gastric SELs after routine endoscopy [1]. Histologic types of SELs include benign entities, such as lipoma and pancreatic rest, and potentially malignant lesions, such as gastrointestinal stromal tumors. The reported diagnostic accuracy of endoscopic ultrasound (EUS) for SELs is 77%, which increases to 91% when EUS-guided sampling is performed [2].

SELs have traditionally been treated by surgical resection [3]; however, endoscopic resection is fast emerging as a therapeutic alternative. EUS is commonly undertaken to evaluate and diagnose SELs by identifying the layer of origin, echo features, size of the lesion and tissue sampling, in order

to guide management from surveillance to resection [4]. There remains a paucity of data on whether performing EUS and EUS-guided sampling actually impacts the outcome or the selection of the resection approach. Well-defined indications for endoscopic resection are yet to be established, and not all SELs are amenable to endoscopic resection. Therefore, the aims of this study were to assess whether lesion size, layer of origin, and histology of SELs, based on EUS and EUS-guided sampling, influence the outcomes and selection of patients for endoscopic resection.

Patients and methods

Study design and population

A retrospective review was performed of patients who underwent EUS, EUS-guided sampling, and endoscopic or surgical resection of gastrointestinal SELs from January 2012 to December 2019. Only lesions in sites that can be accessed and evaluated by EUS (esophagus, stomach, duodenum or rectum) were included. Data on patient demographics, EUS findings, tissue acquisition, pathology, resection technique and adverse events were obtained from electronic medical records and a procedural database (Provation Medical Inc., Minneapolis, MN). The study was approved by the Institutional Review Board (IRB# 19-006474).

EUS and EUS-guided sampling

All EUS procedures were performed by experienced endosonographers. Procedures were performed using Olympus (Olympus Medical Systems, Center Valley, PA) or Pentax (Pentax, Montvale, NJ) echoendoscope systems. Needles used for EUS-guided tissue acquisition were 19 G, 22 G or 25 G (EchoTip Ultra and Quick-Core, Cook Medical, Bloomington, IN; SharkCore, Medtronic, Minneapolis, MN) at the discretion of the endoscopist.

Resection

After EUS and EUS-guided sampling evaluation, patients were referred for endoscopic resection, laparoscopic-endoscopic cooperative surgery (LECS) or surgical resection. Two pathologists independently reviewed the histologic type and layer of origin of all resected specimens that served as the criterion standard to determine the accuracy of EUS.

Statistical analysis

Descriptive statistics are reported as frequencies and percentages for categorical variables, and as mean ± standard deviation or median and interquartile range (IQR), as appropriate, for continuous variables. For the inferential analysis, t-tests were used to compare continuous data and chi-square tests were used to compare categorical data. Lesion size on EUS and cross-sectional imaging was correlated by calculating the Spearman correlation coefficient (rho, ρ). All analyses were 2-tailed and statistical significance was set at P<0.05. All statistical tests were performed using the software package JMP Pro 14, SAS Institute Inc. Cary, North Carolina, United States.

Results

Study population and EUS

A total of 73 patients met the study inclusion criteria (mean age 63±14 years, 51% male.) EUS was indicated after abnormal computed tomography scan (CT) in 34 (47%) patients and for suspected SEL found during endoscopy in 39 (53%). Indications for CT and/or endoscopy that resulted in EUS included evaluation and surveillance of tumors unrelated to SEL: e.g., renal cancer (n=13, 17.8%), dyspepsia (n=10, 13.7%), abdominal pain (n=10, 13.7%), iron deficiency anemia and overt gastrointestinal bleeding (n=10, 13.7%), gastroesophageal reflux disease (n=8, 11%), and miscellaneous reasons, such as bloating (n=22, 30.1%).

The majority of SELs were located in the stomach (81%). The median size of SELs was 21 mm (IQR 15-32), while 44 (60%) lesions were >20 mm. Sixty of the 73 patients (82%) had cross-sectional imaging (CT=58, magnetic resonance imaging=2) with a median lesion size of 26 mm (IQR 17.5-42). There was a positive strong correlation in size between EUS and cross-sectional imaging, which was statistically significant (ρ=0.88, P<0.001). Per EUS, 63 (86%) SELs originated from the 4th layer (*muscularis propria*) of the gastrointestinal tract and 71 (97%) were hypoechoic. Fine needle aspiration (FNA), fine needle biopsy (FNB), and FNA + FNB were performed in 29%, 48%, and 23% of cases, respectively. The overall diagnostic yield of EUS-guided sampling was 92%, with no significant difference in yield between FNA and FNB techniques (P=0.86). Lymphadenopathy was reported in 5 (7%) patients. There were no adverse events related to EUS and EUS-guided sampling. Detailed information is displayed in Table 1.

Resection

Based on EUS and EUS-guided sampling, 50 (68%) patients were referred for surgical resection, 18 (25%) for endoscopic resection and 5 (7%) for LECS. There were no significant differences in age (P=0.97), body mass index (P=0.32) or SEL location (P=0.26) between the resection approaches.

Methods for endoscopic resection included endoscopic full thickness resection (EFTR) in nine (50%) patients, submucosal tunneling endoscopic resection (STER) in 4 (22%), endoscopic

Table 1 Patient baseline characteristics and EUS features of gastrointestinal subepithelial lesions

Patients' characteristics	n=73
Male sex	37 (51%)
Age (years; mean±SD)	63±14
EUS	
SEL location	
Stomach	59 (81%)
Duodenum	8 (11%)
Esophagus	4 (5%)
Rectum	2 (3%)
SEL size (mm; median [IQR])	21 (15-32)
Layer of origin	
4th *(Muscularis propria)*	63 (86%)
3rd *(Submucosa)*	6 (8%)
2nd *(Deep mucosa)*	4 (6%)
Regional lymphadenopathy	
No	68 (93%)
Yes	5 (7%)
Echogenicity	
Hypoechoic	71 (98%)
Hyperechoic	1 (1%)
Anechoic	1 (1%)
Tissue acquisition	
FNB	35 (48%)
FNA	21 (29%)
FNA+FNB	17 (23%)
Needle gauge	
22 G	70 (96%)
19 G	2 (3%)
25 G	1 (1%)

SD, standard deviation; IQR, interquartile range; EUS, endoscopic ultrasound; SEL, subepithelial lesion; FNB, fine needle biopsy; FNA, fine needle aspiration

Table 2 EUS and EUS-guided sampling agreement with resected specimen

Pathology	N=73 (%)	Layer of origin agreement	Histologic type agreement
GIST	45 (62%)	92%	100%
Leiomyoma	11 (15%)	86%	100%
NET	5 (7%)	40%	80%
Pancreatic heterotopia	4 (5%)	100%	0%
Lipoma	2 (3%)	100%	100%
Neural neoplasm	2 (3%)	50%	100%
Others	4 (5%)	100%	100%

EUS, endoscopic ultrasound; GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor

In univariate analysis, lesion size >20 mm measured by EUS significantly influenced the selection of resection approach (P=0.005). Layer of origin and histologic type did not influence resection approach (P=0.06 and P=0.09, respectively).

EUS-related outcomes of endoscopic resection

In patients who had endoscopic resection of SELs, the accuracy of EUS and EUS-guided sampling in predicting the layer of origin and histologic type was 71% (95%CI 45-88%) and 100% (95%CI 81-100%), respectively. In patients in whom SELs were inaccurately classified based on layer of origin (n=4) there were no adverse events reported or need for a revised resection approach, such an example is depicted by Fig. 1A-F.

Discussion

Gastrointestinal SELs are traditionally resected with surgery. Endoscopic resection is fast emerging as an alternative approach; however, the indications for endoscopic treatment of SELs are not well-established. Our study evaluated the role of EUS in selecting the resection approach for SELs, and found that lesion size assessed by EUS significantly influenced the decision on mode of resection.

EUS evaluation and EUS-guided sampling of SELs provide information on lesion size, layer of origin and histologic type [5,6]. EUS is frequently recommended as the modality of choice to characterize SELs. Studies have shown that the overall accuracy of EUS alone in differentiating SELs ranges from 43-77%. In a study by Akahoshi *et al*, the diagnostic yield was related to the size of SEL: 71%, 86% and 100% for lesions measuring <20 mm, 20-40 mm and >40 mm, respectively [7]. The use of endosonographic criteria such as lesion size (>20 mm), irregular margins, inhomogeneous pattern or presence of lymph nodes (>10 mm) can improve differentiation
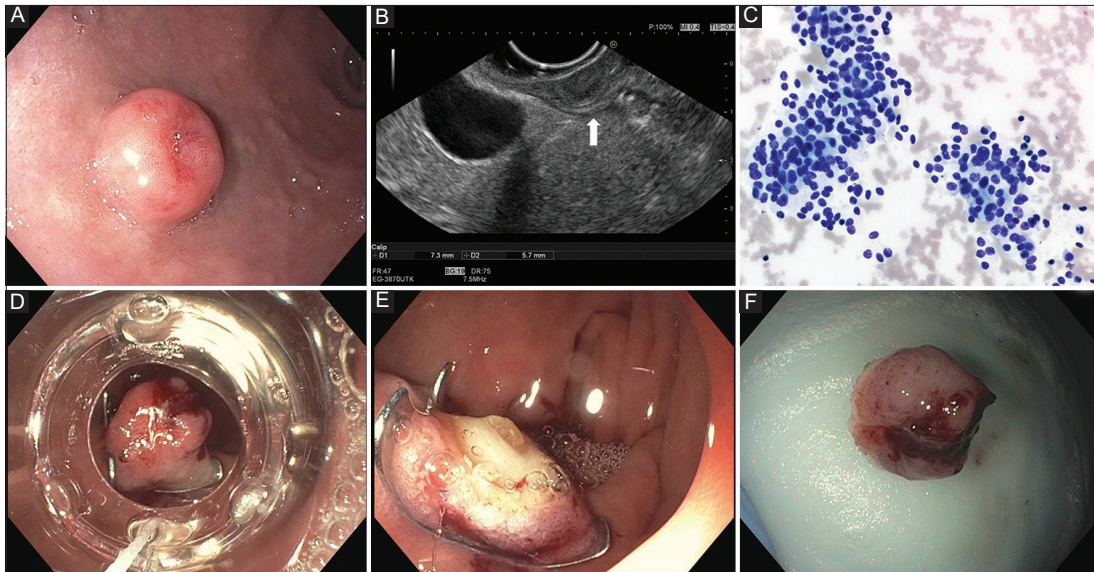
submucosal dissection (ESD) in 4 (22%), and endoscopic mucosal resection (EMR) in 1 (6%). Endoscopic resection success rate was 94%, with adverse events reported in 2 (3%) patients. Both occurred during peroral lesion extraction: an esophageal tear and an esophageal perforation managed with endoscopic clips and surgery, respectively.

Role of EUS in selection of resection approach

Gastrointestinal stromal tumor was the most common definitive diagnosis (46, 62%). The overall accuracy of EUS and EUS-guided sampling in predicting the layer of origin and histologic type were 88% (95% confidence interval [CI] 77-94%) and 96% (95%CI 87-98%), respectively. The highest and lowest agreements between EUS and layer of origin of resected specimens were for gastrointestinal stromal tumors and neuroendocrine tumors, respectively, while pancreatic heterotopia had the lowest agreement between EUS-guided sampling and the pathology of the resected specimen (Table 2). There were no malignant lesions seen in our cohort of patients.

Figure 1 (A) Duodenal bulb subepithelial lesion. (B) EUS demonstrates the subepithelial lesion originated from the second layer (arrow). (C) Cells from FNA show pale cytoplasm, round nucleus with salt and pepper chromatin, suggesting a well-differentiated neuroendocrine tumor (Pap stain. 400× original magnification). (D) Over-the-scope clip-assisted endoscopic full thickness resection with the neuroendocrine subepithelial lesion above the deployed clip. (E) Post-resection site. (F) *En bloc* resected specimen, which on pathology showed clear margins and the layer of origin of the neuroendocrine tumor to be from the submucosa (layer 3)
EUS, endoscopic ultrasound; FNA, fine needle aspiration

for malignant lesions with a specificity of 80%, but with a relatively low sensitivity of 64% [8,9]. EUS-guided sampling improved the diagnostic yield to >80% [5,10-16]. In our cohort there were no differences in diagnostic accuracy between FNA and FNB; however, a recent meta-analysis favored FNB over FNA in patients with SELs [17].

Information about the accuracy, outcomes and role of EUS in the selection of patients undergoing endoscopic vs. surgical resection of SELs is scarce. In our study cohort, the overall accuracy of EUS in predicting the layer of origin was 88%, while the accuracy of EUS-guided sampling in identifying histologic type was 96%, similar to previous studies [18]. In a subgroup analysis of patients who underwent endoscopic resection, the accuracy of EUS and EUS-guided sampling in predicting the layer of origin and histologic type was 71% and 100%, respectively. This highlights the challenges in identifying the layer of origin, particularly with ill-defined lesions arising from the third layer of the gut wall [11]. Based on EUS findings, 32% of SELs were considered suitable candidates for endoscopic resection and LECS, while 68% were referred for surgical resection. In the univariate analysis, only size >20 mm was significantly associated with the resection approach. The low number of endoscopic resections in our cohort (n=18) precluded a multivariate analysis to identify independent factors associated with endoscopic resection. Layer of origin and histologic type did not significantly influence the resection approach in our cohort of patients; however, they did allow the differentiation of benign from malignant entities and provide a roadmap for the choice of endoscopic technique (e.g., EMR for superficial lesions and EFTR for deeper lesions). Layer of origin was inaccurately assessed by EUS in 4 patients who underwent

endoscopic resection, with no adverse clinical outcomes or need for a revised resection approach. At present, there are no guidelines or standardized criterion based on size for referral of gastrointestinal SELs for surgery vs. endoscopic resection. Even though some authors suggest endoscopic removal of lesions <3-4 cm [19], in most studies the mean size of lesions treated by endoscopic resection is close to 20 mm [20]. This is in keeping with our study, in which most lesions >20 mm were referred for surgery.

Endoscopic resection techniques for SELs include EFTR, STER and ESD, with reported success rates ranging from 90-100% [19,21-23]. In our study, the most common endoscopic technique was EFTR and the overall success rate of endoscopic resection was 94%. Adverse events were reported in 3% of our patients undergoing endoscopic resection. Complication rates related to endoscopic resection are heterogeneous among different series in the literature, with reports of bleeding ranging from 0-24% and perforation from 0-5% [24,25].

Although EUS is commonly used to diagnose SELs in clinical practice, its role in determining the optimal type of resection is unclear. This study highlights the merits and benefits of EUS when selecting gastrointestinal SELs for endoscopic resection. The study is limited by the small sample size, single-center experience, inherent limitations of a retrospective study and potential selection bias based on physician referral.

Based on our study, EUS should be considered prior to selecting a resection approach for gastrointestinal SELs, with size significantly influencing the selection for endoscopic resection. In our cohort of patients undergoing endoscopic resection, no revisions of resection or adverse events occurred when EUS was inaccurate.

Summary Box

What is already known:

- Endoscopic resection is emerging as a therapeutic alternative to surgery for gastrointestinal subepithelial lesions (SELs)
- Indications for endoscopic resection of SELs are not yet established
- There are limited data on the role and outcomes of endoscopic ultrasound (EUS) in the selection of patients for endoscopic vs. surgical resection

What the new findings are:

- Lesion size assessed by EUS influences the selection mode for resection of SELs
- The accuracy of EUS in predicting the layer of origin was 88%; in patients undergoing endoscopic resection, no revision of resection or adverse events occurred when EUS was inaccurate
- EUS should be considered prior to selecting a resection approach for gastrointestinal SELs

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