Current endoscopic ultrasound-guided approach to incidental subepithelial lesions: optimal or optional?

Alexander J. Eckardt[a], Christian Jenssen[b]

DKD Helios Klinik Wiesbaden; Krankenhaus Märkisch Oderland, Strausberg, Wriezen, Germany

Abstract	Subepithelial lesions (SEL) are identified during endoscopic procedures on a regular basis. They can occur anywhere in the gastrointestinal (GI) tract and are located beneath the normal epithelial layer, which explains why a tissue diagnosis is difficult to obtain with routine biopsies. Endoscopic ultrasound (EUS) is used to further characterize these lesions. EUS can distinguish intramural lesion from extramural compression. Furthermore, it allows allocation of intramural lesions to a specific layer of the GI wall and offers additional information as to whether a lesion could be benign or malignant. EUS also assists in choosing the optimal means of tissue acquisition. The choice of tissue acquisition is based on a number of factors, such as tumor size, EUS features, and location within the GI tract or within a specific layer of the GI wall. Furthermore, local expertise and patient factors should be considered when deciding whether tissue acquisition, surgical intervention or follow up is recommended. In this review we offer an EUS-guided approach to the evaluation of incidental SEL based on current evidence and point out areas of uncertainty, which explain why the proposed algorithmic approach may be optional rather than optimal.

Keywords Endoscopic ultrasonography, fine needle aspiration, subepithelial lesions, gastrointestinal stromal tumor

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Introduction

Subepithelial lesions (SEL) are regularly encountered as incidental findings during endoscopic procedures with an estimated incidence of approximately 1 in 300 patients [1]. Only a minority of SEL presents with clinical symptoms and complications such as vomiting, anemia, dysphagia, and gastrointestinal (GI) bleeding [2]. As the name suggests, these lesions are located beneath the normal epithelial layer and can originate from anywhere within the GI wall or tract, with the stomach being the organ most frequently involved [2]. Many SEL are benign lesions, such as lipomas, pancreatic rests, leiomyomas, schwannomas or duplication cysts. However, up to 13% of upper GI tract lesions are malignant (e.g. metastases or lymphomas) and an additional 8% at least have malignant potential, such as GI stromal tumors (GIST) [3]. It is therefore important to further characterize and

Departments of [a]Gastroenterology and Hepatology, DKD Helios Klinik Wiesbaden (Alexander J. Eckardt); [b]Internal Medicine - Gastroenterology, Krankenhaus Märkisch Oderland, Strausberg-Wriezen (Christian Jenssen), Germany

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Correspondence to: Alexander J. Eckardt, MD, Department of Gastroenterology, DKD Helios Klinik Wiesbaden, Aukammallee 33, 65191 Wiesbaden, Germany, Tel.: +11 49 611 577 450, Fax: +11 49 611 577 460, e-mail: alexander.eckardt@dkd-wiesbaden.de; alexander.eckardt@helios-kliniken.de

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manage these lesions accordingly. A stepwise approach, using endoscopy, endoscopic ultrasound (EUS) and various forms of tissue acquisition has been recommended by most experts [2,4-8]. In this review, we describe an EUS-guided approach of incidental SEL based on the current evidence. As new techniques for endoscopic tissue acquisition evolve and information on varying success rates with endoscopic tissue acquisition is gained, such an approach must be viewed against the background of local expertise and patient factors. A 3-step algorithmic approach to incidental SEL (Fig. 1) is offered to help guide the reader through this review and areas of uncertainty are discussed.

Step 1: Endoscopic assessment

> **Check list – Step 1**
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> Patient history, localization, size, endoscopic appearance/ specific morphology, color, forceps palpation: consistency, gliding sign and pillow sign (suspected lipoma).
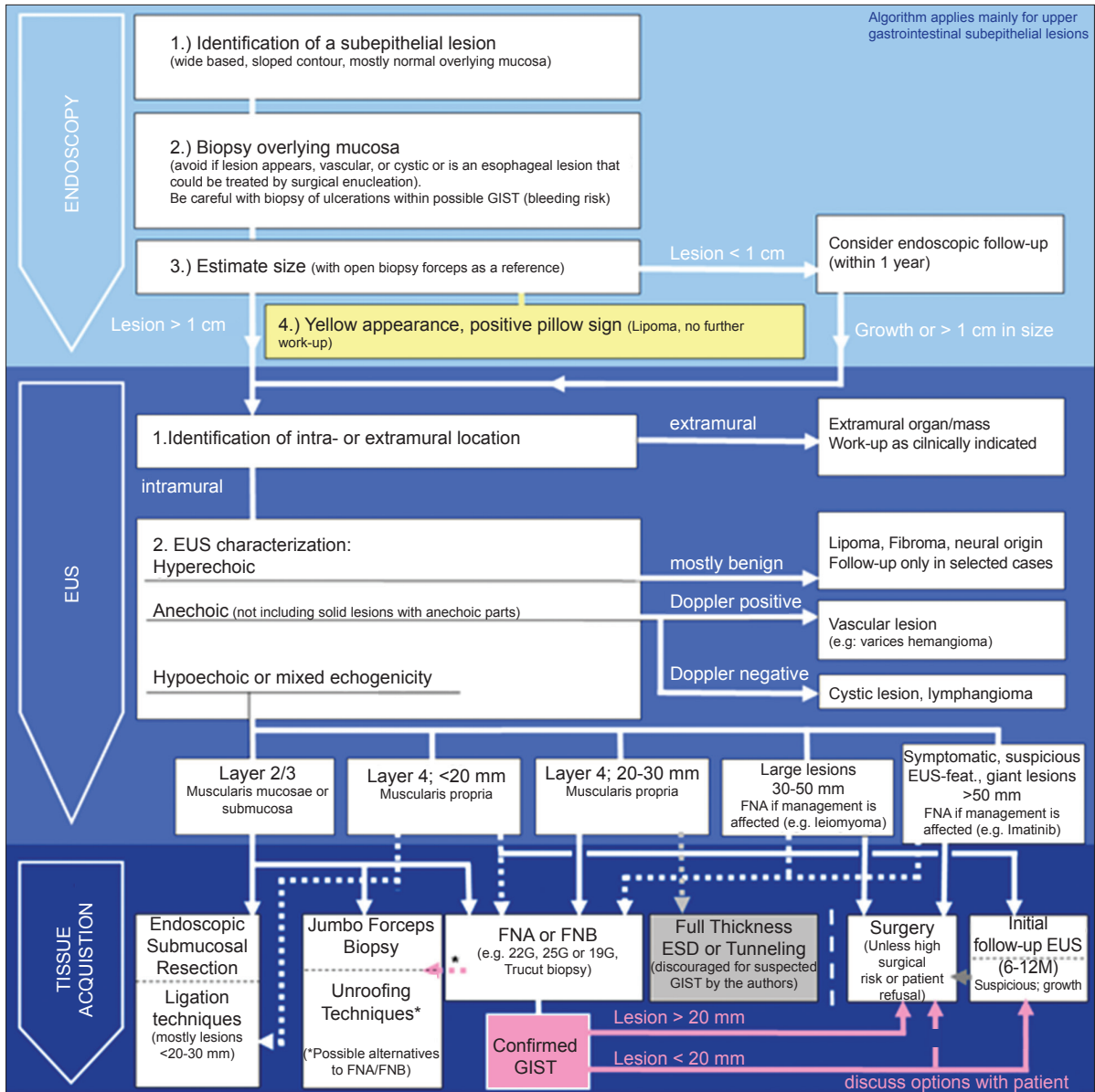
Endoscopy is the first diagnostic modality used to assess incidental SEL. Although endoscopy usually cannot distinguish between different types of SEL, it can offer important clues to the correct diagnosis and further management. As the first step, endoscopy is used to describe the appearance of a lesion and its location. The location of a lesion within the GI tract already
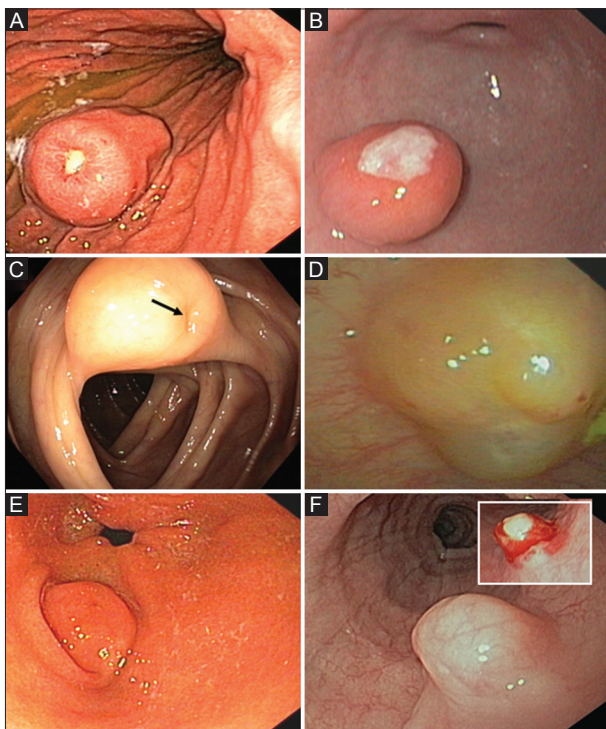
Figure 1 Stepwise algorithm for the work-up of an incidental upper gastrointestinal (GI) subepithelial lesion (SEL)
The diagnostic algorithm is explained in the manuscript. It applies mainly for upper GI-SEL. Exceptions, such as rectal lesions, small bowel lesions, suspected leiomyoma in the esophagus and suspected neuroendocrine tumors must be considered. Broken lines depict alternative options

increases the pretest probability of certain lesions. For example, leiomyomas are the most common hypoechoic SEL in the 4th EUS layer in the esophagus, whereas in the stomach such lesions are likely to represent GIST. Brunner's gland hyperplasia is commonly found in the duodenal bulb and neuroendocrine tumors represent up to 40% of SEL found in the rectum [9]. With the few exceptions mentioned below, all solid appearing SEL should be biopsied to rule out an epithelial origin. Mucosal biopsies are usually insufficient to obtain an adequate tissue specimen, unless an ulcer of a lesion is targeted. Ulcerations occur in inflammatory or rapidly growing lesions and are a typical feature of large gastric GIST (Fig. 2A). However, ulcerations can also occur in other SEL, such as benign inflammatory fibroid tumors (Fig. 2B) [10]. Caution is necessary when a biopsy is

taken from an ulceration. Especially large ulcerated GIST can bleed severely with or without biopsy of the ulcer, because these lesions are often highly vascularized [11]. The closed biopsy forceps can be used to probe the lesion to assess its consistency (firm or soft). If the lesion has a yellow hue and can be easily indented with a closed biopsy forceps (positive pillow sign) the diagnosis of a lipoma can be made with an accuracy of >95% and no further evaluation is usually necessary (Fig. 1, 2C) [5]. In uncertain cases deep "bite on bite" biopsies or jumbo forceps biopsies are generally sufficient to unroof the lipoma and reveal the underlying tissue [4]. Biopsies should not be obtained if cystic or vascular lesions are suspected. Cystic lesions or lymphangiomas often appear slightly translucent and are easily compressible (Fig. 2D). Varices usually have a bluish tinge, are

often serpiginous and also easily compressible. However, in rare cases isolated varices can be mistaken for SEL [12]. If there is doubt, EUS should be performed prior to taking a biopsy to rule out a vascular lesion. Biopsies should also be avoided in lesions which are likely to undergo thoracoscopic surgical enucleation, such as probable esophageal leiomyomas or GIST. This recommendation is made by authors who have reported that scarring after biopsy might hinder surgical enucleation [13,14]. Pancreatic rests often have a classic umbilicated endoscopic appearance and are commonly located within the gastric antrum (Fig. 2E). A typical endoscopic feature of granular cell tumors is their yellowish appearance, but in comparison to lipomas they are rather firm and most commonly located in the distal esophagus (Fig. 2F). In addition to inspection and biopsy, the size of the SEL should be estimated. The open biopsy forceps (usually 7-8 mm) can be used as a reference standard. Lesions ≤1 cm in size are rarely symptomatic or malignant and therefore endoscopic follow up in 1 year is recommended. If the lesion grows or reaches a size >1cm, further characterization is required. Unless a definite diagnosis can be made by endoscopic criteria (e.g. lipomas or definite varices), all lesions >1 cm should be evaluated by EUS as the next step. An exception to this rule is potential neuroendocrine tumors in the duodenum and rectum, which have a high prevalence in these locations

and show potentially malignant behavior. Therefore, further work-up is recommended, even for subcentimeter SEL in these locations.

Step 2: EUS criteria and classification

> **Check list – Step 2**
>
> Mural versus extramural location, layer, size, contour, echogenicity (as compared with muscularis propria), echo-pattern (homogeneous, heterogeneous, specific features like halo or anechoic areas), vascularity (color Doppler, contrast enhancement).

EUS is the second step in the evaluation of SEL and adds valuable information to guide further management. EUS can distinguish intramural lesions from extramural compression with nearly 90% accuracy [15]. Extramural compressions are most commonly caused by normal organs, such as the spleen or splenic artery, pancreas, gallbladder and the left lobe of the liver, but can also represent pathologic structures, such as (pseudo-) cysts, enlarged gallbladder, splenic artery aneurysms or tumors [15,16]. Further work-up and treatment of pathologic extramural lesions should be performed as clinically indicated, but is beyond the scope of this review.

Figure 2 Endoscopic features of selected subepithelial lesions. (A) Gastric gastrointestinal stromal tumor with a central ulceration. (B) Inflammatory fibroid polyp with ulceration. (C) Lipoma in the transverse colon with a positive pillow sign after indentation with the closed biopsy forceps (arrow). (D) Lymphangioma with translucent appearance, the septated lesion appears lobulated on macroscopic inspection. (E) Pancreatic rest in the antrum with umbilication. (F) Granular cell tumor. A yellowish hue becomes particularly visible after superficial biopsy (small picture)
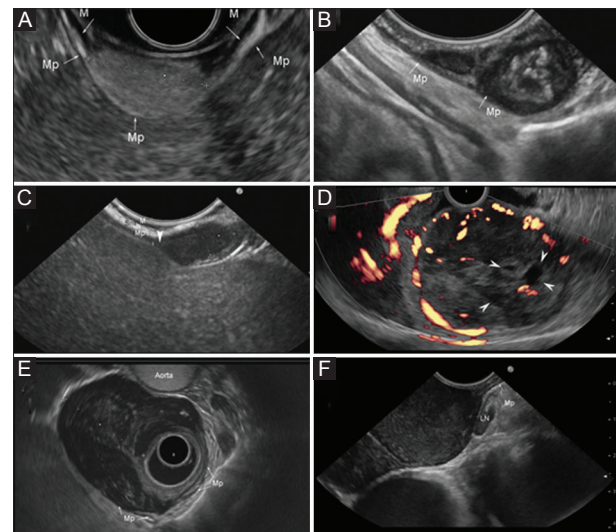

Figure 3 Endosonographic features of selected subepithelial lesions. (A) Hyperechoic gastric lipoma, arising from the 3rd endoscopic ultrasound layer (by courtesy of Prof. Dr. Uwe Will, Gera). (B) Small gastric leiomyoma with calcifications (atypical), arising from 4th hypoechoic layer. (C) Small gastric gastrointestinal stromal tumor (GIST), arising from 4th hypoechoic layer (arrowhead). (D) Large gastric GIST with distinct heterogeneity and small anechoic cavities (arrow heads), highly vascularized (contrast-enhanced power Doppler), arising from 4th hypoechoic layer. (E) Rare case of esophageal leiomyomatosis. The hypoechoic tumor nodules arise from the 4th hypoechoic layer. (F) Large esophageal leiomyoma arising from 4th hypoechoic layer
M, mucosa; SM, submucosa; Mp, muscularis propria; LN, lymph node

Table 1 Typical endosonographic features of benign and malignant subepithelial lesions

Subepithelial lesion	EUS layer	EUS features	Distribution in the GI tract	Malignant potential
Benign lesions and those with minimal malignant potential				
Leiomyoma	4th or 2nd	Differing sizes, hypoechoic (iso- or hypoechoic compared to muscle layer), homogeneous, sometimes calcifications Rarely multiloculated or diffuse – leiomyomatosis)	Mostly esophagus and stomach, but can occur anywhere in the GI tract	None (primary leiomyosarcoma: extremely rare)
Granular cell tumor	2nd, 3rd or 4th	Hypo- or isoechoic, oval, homogeneous, smooth margins	Mostly esophagus, colon and rectum	Very low risk of malignancy (2-4%), mostly in large lesions (>4 cm)
Ectopic pancreas	2nd, 3rd and/ or 4th/5th	Hypoechoic or mixed echogenicity, heterogeneous echotexture, umbilication, ductal structures, indistinct margins	Stomach (mostly antrum), duodenum (rare)	Extremely rare
Inflammatory fibroid polyp	2nd or 3rd (4th)	Hypoechoic, indistinct margin, homogeneous appearance	Anywhere in the GI tract (stomach and colon)	None
Schwannoma	3rd or 4th	Hypoechoic, round or oval, homogeneous, well demarcated	Stomach 70%, colon and rectum 15%	Extremely rare
Glomus tumor	3rd or 4th	Round, hypoechoic, homogeneous, may have a halo.	Anywhere in the GI tract	Rare
Endometriosis	4th or 5th	Hypoechoic, heterogeneous with irregular margins or homogeneous with regular margins.	Mostly colon and rectum; stomach	None
Varices	2nd or 3rd	Anechoic, serpiginous structure with Doppler signal	Esophagus, stomach (fundus), duodenum (rare)	None
Hemangioma	2nd or 3rd	Anechoic or heterogeneous, Doppler signal (low flow)	Anywhere in the GI- tract	None
Lymphangioma	2nd, mostly 3rd and 4th	Anechoic, occasionally multiloculated	Duodenum, colon, ileum, stomach	None
Duplication cysts	Any layer (mostly 3rd)	Anechoic, smooth, absent Doppler signal; duplication cysts can contain echogenic debris or septae	Anywhere in the GI tract: Jejunum, ileum up to 90%; esophagus, duodenum, stomach and colon	Extremely rare. If so, unusual EUS features (mixed lesion)
Lipoma	3rd	Hyperechoic, smooth margins, homogeneous, may be polypoid	Anywhere in the GI tract	None
Brunner's gland hyperplasia	2nd or 3rd	Hyperechoic, smooth margin, possibly hypoechoic dilated gland duct	Duodenum (Bulb)	None
Malignant lesions and those with malignant potential				
GIST ("benign"=very low risk, low risk)	4th or 2nd	Small (≤2 cm), oval or round, hypoechoic but relatively hyperechoic compared to muscle layer, homogeneous	Stomach 60%, small bowel 35%, esophagus 5%, rectum 5%	10-30% clinically malignant
GIST ("malignant"=intermediate, high and very high risk)		Large (>3-5 cm), irregular margins, heterogeneous echotexture, cystic spaces, hypervascularity, marginal halo, hyperechoic spots/echogenic foci (2 or more of these criteria increases sensitivity)		
Leiomyosarcoma	4th or 2nd	Hypoechoic, heterogeneous, irregular borders, infiltration of adjacent organs	Anywhere in the GI tract (very rare)	Always

(*Contd...*)

Table 1 (*Continued...*)

Subepithelial lesion	EUS layer	EUS features	Distribution in the GI tract	Malignant potential
Neuroendocrine Tumor/ Carcinoid	1st, 2nd and/ or 3rd layer	Oval to round, hypo- or isoechoic, homogeneous, regular margins, "salt and pepper" appearance	Rectum, stomach duodenum	Depending on type, size and location
Metastasis (e.g. lung, breast, malignant melanoma)	Any layer	Heterogeneous or hypoechoic	Anywhere in the GI tract; stomach	Always
Lymphoma	2nd, 3rd or 4th	Hypoechoic	Mostly stomach	Always

EUS, endoscopic ultrasound; GIST, gastrointestinal stromal tumor; GI, gastrointestinal

Intramural SEL should be further characterized by EUS. The EUS layer, location within the GI tract and echo features can provide valuable information to establish the possible diagnosis of these lesions (Table 1, Fig. 3). In an algorithmic approach, hyperechoic and anechoic lesions are initially differentiated from hypoechoic, isoechoic or mixed echogenic lesions. Hyperechoic lesions are generally benign and most often represent lipomas. If there are no unusual (mixed) features within a hyperchoic lesion, no further work-up is needed. Anechoic lesions are fluid-filled structures which can represent vascular lesions (e.g. varices or hemangioma) or "cystic" lesions (e.g. duplication cysts, lymphangioma). Vascular lesions and "cystic" lesions are easily distinguished by a positive or negative Doppler signal, respectively. Mixed lesions with partially solid appearing components require further work-up, as these lesions can represent solid (mesenchymal) lesions with cystic degeneration, complicated cystic lesions or intramural abscesses. In the case of attempted fine needle aspiration (FNA) of such lesions, prophylactic antibiotics should be given and the cyst or cystic part should be aspirated completely to avoid septic complications [17-19].

For hypoechoic, isoechoic or mixed SEL, a specific diagnosis is required, because of their possible malignant potential [3,20-23]. The accuracy of EUS to distinguish benign from (pre-)malignant lesions is suboptimal [24,25]. GIST present a particular challenge in this regard. GIST are mesenchymal tumors that originate from the interstitial cells of Cajal and are most commonly found in between the proper muscle layers (4th EUS layer) of the GI wall (Table 1). Although most small GIST (≤2 cm) behave in a benign fashion and are frequently found as incidental findings on autopsy series and surgical specimen, all GIST are thought to have at least malignant potential [26,27].Efforts have been made to identify EUS features that distinguish benign mesenchymal SEL (e.g. leiomyoma and Schwannoma) from GIST and benign from malignant GIST [28-31].

One retrospective study demonstrated that 4 EUS features (echogenicity compared with the muscularis propria, homogenicity, hyperechoic reflexes or a hypoechoic halo) may differentiate gastric GIST from gastric leiomyomas with a sensitivity and specificity of 89% and 86%, respectively [20]. Moreover, digital image analysis was able to differentiate GIST from leiomyoma with 91% accuracy [21].

Chak *et al* identified 4 criteria, namely size >4 cm, irregular extraluminal border, echogenic foci (>3 mm) and cystic spaces as independent predictors for malignancy of gastric SEL [28]. In another study, Palazzo *et al* confirmed a high positive predictive value for malignancy when extraluminal irregular margins, cystic spaces and also lymph nodes were present [29]. The latter is surprising because lymphatic spread is rare in malignant GIST. Despite the poor sensitivity of this finding, advanced disease can be expected, when it occurs [32,33]. Sepe and Brugge pointed out that large size of a SEL and irregular margins are the most consistent findings to suggest malignancy [34]. The sensitivity for the diagnosis of a malignant GIST increases if 2 or more of the above features occur simultaneously [28,29]. Although EUS criteria can give important clues to the etiology and risk of malignancy of a lesion, their accuracy is insufficient and therefore a tissue diagnosis is usually required. Although new EUS methods for tissue characterization, such as digital image analysis, real-time elastography and contrast-enhanced EUS, may be helpful in the differential diagnosis of SEL in the future, these are not validated yet [21,35,36]. Preliminary data suggest that contrast- enhanced EUS may visualize the strong neovascularization of intermediate and high-risk GIST and, therefore, may be used to predict the malignant potential of GI SEL [37,38].

The strength of EUS prior to tissue acquisition is its capability to guide the physician to the choice of an optimal tool of tissue acquisition (Fig. 1, 4). For example, small lesion within the 2nd or 3rd EUS layer can be completely resected by endoscopic (sub-) mucosal resection, whereas large lesions with EUS criteria for malignancy are best referred to surgery. Which tool for tissue acquisition is used depends on EUS criteria, location of the lesion within the GI tract, local expertise and patient preference.

Step 3: Tissue acquisition

Check list – Step 3:

Means of tissue acquisition depends on: Preliminary diagnosis, layer, specific localization, size, ulceration, vascularity, local expertise and patient factors.

Tools of tissue acquisition: Forceps biopsy (bite-on-bite), unroofing techniques, endoscopic resection techniques, EUS-FNA / fine needle biopsy (FNB), surgery.
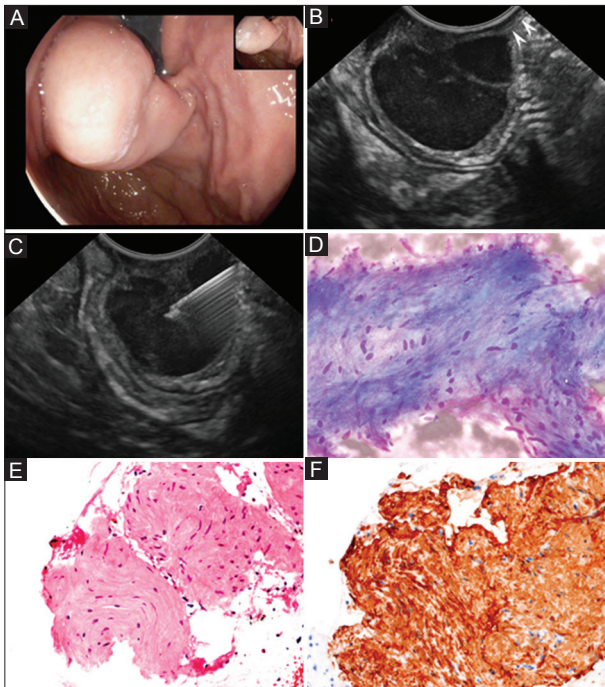
Figure 4 Endoscopic ultrasound (EUS)-guided fine-needle aspiration of a gastric subepithelial tumor. (A) Endoscopic image of an incidental medium-sized subepithelial lesion (SEL) arising from the gastric cardia. (B) EUS reveals a 2 cm, hypoechoic, homogeneous, lobulated SEL with distinct margins, arising from the 4th EUS layer (M. propria, arrow heads). Leiomyoma is suspected. (C) EUS fine needle aspiration using a 22G aspiration needle. (D) Smear cytology (May-Grünwald-Giemsa, x200) and (E) Histology of core particles (Hematoxylin-Eosin, x200) show fascicles of spindle-shaped tumor cells, suggestive of a mesenchymal tumor. (F) Immunohistochemistry (Desmin, x 200: strongly positive; CD117: negative, not shown here) confirms benign leiomyoma. Surgery is not necessary (Photomicrographs D-F by courtesy of Dr. Stephan Wagner, Königs Wusterhausen, Germany)

Tissue acquisition is required to establish the correct diagnosis of hypo-, iso- or mixed-echoic SEL, to predict their malignant potential and to guide further management. Ideally, a histological specimen of sufficient size to perform immunohistochemistry (IHC) is obtained. IHC is an essential tool for further characterization of a lesion. This is especially important to distinguish between completely benign leiomyomas (positive stain for desmin and actin), Schwannoma (positive stain for S100) and potentially malignant GIST (positive stain for cluster of differentiation (CD) 117, CD 34, Platelet derived growth factor receptor/PDGFR-α or Diagnosed on GIST/DOG-1), when a hypoechoic lesion is identified in the 4th EUS layer [39]. Because SEL are located deep under the epithelial layer, tissue acquisition remains challenging. The options for sampling SEL include FNA, FNB techniques, such as 19G Trucut biopsy (TCB), endoscopic submucosal resection (ESMR) or dissection (ESD), jumbo forceps or bite-on-bite biopsies, unroofing techniques, endoscopic ligation, resection and tunneling techniques, and surgery. The diagnostic yield, possible challenges and risk of complications of each method are discussed below.

FNA and FNB techniques

A number of needles are available for EUS-guided tissue acquisition, such as FNA (e.g. 25G, 22G or 19G caliber needles), FNB with new reverse bevel 25G, 22G, and 19G needle systems and TCB (19G) [40]. Tissue acquisition with such methods, primarily FNA, has become the method of choice in the work-up of SEL in the majority of cases, especially if a lesion arises from the 4th EUS layer (Fig. 1). FNA/FNB or TCB is not recommended in large lesions (>3-5 cm) with malignant features, because these should be referred to surgery, unless FNA alters management decisions (e.g. neoadjuvant imatinib therapy for advanced GIST) [41]. Enough tissue should be obtained to perform IHC, which can best distinguish between different types of SEL, especially those originating from the 4th EUS layer. Ideally, a histological core specimen is obtained for IHC (Fig. 4 C-F). All needle systems are generally able to provide cytology and/or histology, although large bore (19G) needles are specifically designed to deliver larger core specimen [42]. FNA is performed by advancing the needle into the SEL under EUS guidance. Most investigators use a stylet for the initial puncture, but whether this improves sampling is still a matter of debate [43,44]. A recent randomized trial has shown no difference in the diagnostic yield, whether a stylet was used or not [45]. After removing the stylet, the FNA needle is advanced back and forth, preferably in a fanning technique [44]. Given the strong cohesiveness of mesenchymal tissue, suction should be applied to the syringe in the case of suspected mesenchymal tumors. The number of needle passes depends on the adequacy of the obtained tissue. Rapid onsite evaluation of the specimen by a cytologist has been shown to improve the yield of FNA by up to 10-30% [43].

Retrospective studies report yields between 64-100% for small (22 or 25G) needles (Table 2) [46-56]. However, the two largest studies only report a yield of 43-62% when "suspected" diagnoses (based on morphologic criteria without IHC) were excluded [52,54]. Furthermore, the highest yields were observed in the smallest studies with no more than 17 patients [47,51]. One prospective study by Akahoshi *et al* showed a diagnostic yield of 82% in 53 patients with the use of 22G FNA (Table 3) [57]. Likewise, diagnostic yields of 79-100% were observed in retrospective studies, which used 19G FNA needles. Again the highest yield was observed in a case series of 6 patients [56,58-60]. In prospective investigations by our group and Philipper *et al* (Table 3), 19G FNA had a yield of a definite IHC-based diagnosis of 52% and 34%, respectively [18,61]. Only one study by Larghi *et al*, which used a new forward-viewing EUS technique in some cases, reported a high yield of 82% with 19G FNA in a small subgroup of SEL (n=17) [62]. The same group used the same forward-viewing echoendoscope and a 19G aspiration needle in a retrospective study of 121 consecutive patients with GI SEL. Histologic examination of specimens including immunostaining was possible in 93.4% of patients [63].

19G TCB is another large-bore technique, designed to deliver a histological core specimen. This type of needle has a spring-loaded mechanism in the handle that permits

Table 2 Retrospective studies: Yield of EUS FNA with small and large-bore needles

Publication	N	Examined lesions	Diagnostic yield (%)	Technical aspects
Retrospective studies with small-bore needles (22 or 25G)				
Ando et al [46]	23	SEL in the 4th EUS layer (mostly stomach)	91.8	22G FNA, (FNA without sufficient material were excluded)
Kinoshita et al [47]	10	SEL (stomach)	100	22G FNA
VanderNoot et al [48]	62	Intra- and extramural lesions (esophagus, stomach, duodenum), including 19 GIST	94.4	22G FNA with ROSE
Okubu et al [49]	18	Retrospective analysis of FNA in resected GIST	78	Selected patients with gold standard (surgery) tissue diagnosis
Arantes et al [50]	10	SEL (anywhere in the GI tract)	80	FNA
Chatzipantelis et al [51]	17	SEL (stomach)	100	FNA
Hoda et al [52]	112	SEL (stomach)	62% diagnostic 22% suspicious	22G FNA
Sepe et al [53]	37	Retrospective analysis of FNA in resected GIST	78.4	Selected patients with gold standard (surgery) tissue diagnosis
Mekky et al [54]	141	SEL (stomach)	43% diagnostic 39% suspicious	22G FNA
Suzuki et al [55]	47	SEL in the 4th EUS layer (stomach)	74.5	22G FNA
Retrospective studies with large bore needles (19G FNA or 19G TCB)				
Storch et al [60]	6	"accessible" SEL stomach (n=6)	67	19G TCB (total n=41; including other lesions)
Hoda et al [52]	15	SEL (stomach)	47	19G TCB Only applied in a minority of total patients (n=112)
Chu et al [58]	6	SEL (GIST)	100	19G FNA lesions >2 cm
Iglesias-Garcia et al [59]	109	Intra-and extraintestinal mass lesions and lymph nodes; SEL (n=11)	85.9; SEL 81.8	19G reverse bevel FNA
Watson et al [56]	65	SEL of the upper GI tract	68 (diagnostic) 12 (suspicious)	22G FNA (64% diagnostic) 19G FNA (79% diagnostic) ROSE+ (74% diagnostic) ROSE- (58% diagnostic)
Rong et al [112]	170	Extraluminal solid lesions and SEL (n=46; esophagus, stomach, duodenum)	Accuracy for GIST 83.3 and for leiomyoma 78.6, similar accuracy for 25G and 22G FNA	22G FNA 25G FNA 19G FNA
Larghi et al [63]	121	SEL (esophagus, stomach, duodenum, rectum)	93.4%	19G FNA,

Diagnostic: cases with definite diagnosis, based on IHC; Suspicious: Cytologic features suggestive of a diagnosis.
EUS, endoscopic ultrasound; GIST, gastrointestinal stromal tumor; FNA, fine needle aspiration; G, gauge, TCB, trucut biopsy; SEL, subepithelial lesion; ROSE, rapid onsite cytologic evaluation

automated specimen procurement. The needle assembly is first advanced into the lesion under EUS guidance. Then the cutting needle is advanced to its limit (2 cm) and the spring is released. This causes the cutting sheath to deploy over the tissue tray, generating a core biopsy. 19G TCB has a yield of 47-67% in "accessible" gastric SEL in retrospective studies (Table 2) [52,60]. In prospective studies the diagnostic yield of 19G

TCB was 55-63% for "accessible" lesions [17,64,65]. Technical failures of the 19G TCB occurred in up to 14% in the study by Lee *et al* and were mostly related to difficulty with advancing the relatively stiff needle because of acute angulation of endoscope [65]. One concern using large bore needles in SEL with necrotic or cystic components is septic complications [17,18]. It is therefore our routine to administer prophylactic antibiotics in

Table 3 Prospective studies: Yield of FNA or TCB (22G-, 19G FNA and 19G TCB)

Publication	N	Examined lesions	Diagnostic yield (%)	Technical aspects
Prospective studies (22G FNA)				
Akahoshi *et al* [57]	53	SEL (stomach)	82	22G FNA
Prospective studies (19G FNA)				
Philipper *et al* [61]	47	SEL, (upper GI tract, only those that were subsequently resected)	58 (19G FNA suspicious) 71 (22G FNA suspicious) 34 (diagnostic)	19G FNA versus 22G FNA (Crossover-study with histological gold standard)
Larghi *et al* [62]	17	Gastrointestinal lesions SEL subgroup (n=17)	82 19G FNA 88 (diagnostic in SEL subgroup)	19G FNA (Forward-viewing" EUS, including other etiologies than SEL n=120)
Eckardt *et al* [18]	46	SEL (stomach)	52 (diagnostic) 7 (suspicious)	19G FNA without ROSE (19G FNA needle intended in 71% of all SEL)
Prospective studies (19G TCB)				
Polkowski *et al* [17]	49	SEL (stomach)	63 (diagnostic) 14 (suspicious)	19G TCB
Fernandez-Esparach *et al* [64]	40	SEL (stomach)	55 (diagnostic 19G TCB) 53 (diagnostic 22G FNA)	19G TCB versus 22G FNA (Randomized crossover-study with ROSE) 70%yield for 22G FNA when suspected diagnosis based on cytology were included
Lee *et al* [65]	120	SEL (stomach)	57 (diagnostic)	19G-TCB without ROSE (19G-TCB intended in 54% of all SEL)

Diagnostic: cases with definite diagnosis, based on IHC; Suspicious: Cytologic features suggestive of a diagnosis.
EUS, endoscopic ultrasound; FNA, fine needle aspiration; G, gauge, TCB, trucut biopsy; SEL, subepithelial lesion; ROSE, rapid onsite cytologic evaluation

such cases. In contrast, risk of relevant hemorrhage or tumor seeding appears almost negligible [18,66,67]. Another limitation of all EUS needles including the 19G needles is the fact that mitotic counts, a factor for predicting the malignant potential of GIST, cannot be reliably assessed [18,67]. In a recent study the authors were able to establish a mitotic count on 50 HPF in 40.6% of biopsies but these counts were lower than those of the subsequent surgical specimen [63]. These limitations and the results of two prospective, comparative studies by Philipper *et al* and Fernandez-Esparach *et al*, question the superiority of large-bore needles over 22G FNA for the diagnosis of SEL and the former even suggests that 22G FNA may have a higher diagnostic yield [61,64]. Whether new large bore biopsy needles, such as the ProCore reverse bevel technology (Cook Endoscopy Inc, Limerick, Ireland) will deliver better results remains to be seen. One study has shown high accuracy for diverse GI lesions with this needle, with a yield of 82% in a subgroup of 11 SEL. However, technical difficulties were observed in 18% of all cases [59]. Therefore, the choice of the needle is still largely determined by the operator's preference and technical aspects.

Jumbo forceps (bite-on-bite) biopsies and unroofing techniques

Large capacity ("jumbo") forceps biopsies or bite-on-bite biopsies can be used for unroofing of the epithelial layer, allowing to dig into the submucosa (or deeper) in order to obtain tissue biopsies from a SEL. This technique can be particularly useful in those cases, in which SEL are located in the 2nd or 3rd EUS layer. One study performed jumbo forceps biopsy (Radial jaw 4, Boston Scientific Corp., Natick, MA, USA) followed by ESMR in lesions limited to the submucosa (3rd EUS layer) and found diagnostic yields of 17% and 87%, respectively [68]. Interestingly, all 23 lesions were benign lesions without malignant potential. Another study used the same jumbo forceps and aimed at clear visualization of the gastric SEL after unroofing it with the forceps [69]. Twenty-nine percent of the lesions were located in the submucosa and 71% in the muscularis propria. The authors reported a much higher yield of 92% with jumbo forceps biopsy compared to 58% with EUS FNA. A benefit of forceps biopsy was the fact that mitotic indices were reliably assessed in 89% all GIST in the study (29/33 GIST). In a multicenter, retrospective study, Buscaglia *et al* found mixed results with jumbo forceps biopsies, depending on the layer in which the lesion was located [70]. Jumbo forceps had a yield of 65% for lesion in the submucosa (2nd and 3rd EUS layer) but only of 40% in the muscularis propria (4th EUS layer), whereas the reverse was true for EUS FNA with yields of 38% and 57%, respectively. The large range in the diagnostic yield between 17% and 92% might be related to the type, size and location of the lesions or to differences in technique. For best biopsy results, it seems of particular importance that the SEL is thoroughly unroofed to ensure an adequate tissue diagnosis, especially in those lesions

that are located in the 4th EUS layer. In a small retrospective series, Serna-Higuera *et al* used a 6-12 mm needle-knife incision with subsequent deep introduction of a jumbo forceps in a "button hole" technique to obtain tissue. They reported a histological diagnosis in 93% of the 14 retrospectively analyzed patients. Mitotic counts were determined in 71% of GIST with sufficient material (5/7 GIST). Recently, Tae *et al* used a similar technique in a prospective study, in which biopsies were taken after unroofing the SEL with a needle-knife. They reported a yield of 90% with a change in treatment plan in 35% of their cases [71]. To gain optimal access to small upper GI SEL (<2 cm), Lee *et al* used a snare for an endoscopic partial resection unroofing technique in a case series of 16 patients [72]. The diagnostic yield of the endoscopic partial resection unroofing technique was 94%, although oozing of blood occurred in 56% of these patients. Fortunately, successful hemostasis was achieved by using argon plasma coagulation in all cases.

Endoscopic ligation, resection and tunneling techniques

Endoscopic techniques to excise SEL in the submucosa include traditional ESMR with a snare or newer approaches using a transparent cap (ESMR-C) or ligation device (ESMR-L), which are most commonly used for small SEL (<2 cm) [73]. Initially, ESMR with a regular snare or a cap-fitted endoscopic snare device was proposed as a technique to completely excise strictly submucosal or pedunculated lesions, originating from the EUS layers 2 or 3 [74]. As mentioned above, ESMR has a high diagnostic yield for lesions in the submucosa, as it delivers a tissue specimen rather than biopsy fragments and it has the potential to completely excise the lesion [69]. A grasp-and-snare technique has recently been reported to perform full thickness resection of deeper lesions and closure with an over the scope clip (OTSC). The reported rate of complete resection was 86% and the procedure was performed under laparoscopic control [75]. However, this study has been criticized, because grasping the tumor with a tissue anchor can cause rupture, resulting in the inability to ensure the integrity of the tumor. Furthermore, there is potential risk of contamination to the peritoneal cavity and peritoneal infection and finally the OTSC technique cannot treat leaks larger than 2.5cm [76].

ESMR-C uses a crescent-shaped snare that is placed in the distal ridge of a transparent cap. The lesion is usually lifted with a combination of dilute epinephrine (1:100,000) in a saline solution, mixed with indigo-carmine dye. The lifted lesion is then sucked into the cap, creating a pseudopolyp, captured by closing the snare and removed by electrocautery. This technique can remove small lesions completely in 87% of cases and has a high diagnostic yield of 95%, but is associated with a bleeding risk of 5% [77].

ESMR-L uses a ligation device with a cap to deploy an elastic band or loop around the base of an SEL after it is lifted and aspirated into the cap of the device. The lesion is subsequently decapitated and biopsied or completely removed with a snare using electrocautery. This technique mainly applies to small lesions that can be aspirated into the cap (<15-20 mm) [78,79]. Sun *et al* reported spontaneous sloughing of the lesion after

banding in up to 95% of small gastric and 100% of duodenal GIST within 3-4 weeks [80,81]. Recently, Binmoeller *et al* used a modification of this technique, in which small SEL (<20 mm) are sucked into a transparent cap and ligated with a detachable loop, the so-called suck-ligate-unroof-biopsy technique. After ligation the SEL is unroofed with a needle-knife and biopsies are taken. When GIST were biopsied, the authors were able obtain enough tissue to analyze the mitotic count/50 HPF. Follow-up endoscopy at 3 and 6 months revealed no residual tumor in the 9 lesions examined. However, there is some concern of delayed bleeding approximately 7 days after the procedure when the lesions slough off and also of possible incomplete microscopic margins or spillage, especially when GIST are removed [80-82].

Lately, a plethora of mostly Asian studies have reported the successful removal of esophagogastric or gastric SEL in the muscularis propria by ESD [82-92]. Successful resection varies from 64-100% in these studies. Most of them are small retrospective case series. The 2 largest studies by Li *et al* and He *et al* reported complete resection in 92-94% of their patients with a perforation rate of 4-14%. The most recent studies even report ESD in lesions with a size of up to 5 cm. However, this approach had a high risk of perforation in 19% of cases. The high perforation rate and the risk of incomplete resection or tumor spillage which will turn potentially curable lesions into metastatic disease are a major concern with this technique. A recent analysis by Chun *et al* suggested that smaller tumor size ≤ 2cm and a positive "rolling sign" (a mobile mass under the mucosa) correlate significantly with complete resection and perforations seem to occur mostly within fixed lesions [93].

Submucosal tunneling techniques are the latest endoscopic innovation, aiming at complete resection of the SEL. A number of small case series have been published using this method [94-96]. The method was adapted from the peroral endoscopic myotomy procedure, which was recently inaugurated for the treatment of achalasia [97]. Using this technique the mucosa is lifted and incised a few centimeters proximal to the lesion to create an entry point into the submucosal layer for the endoscope. Then a submucosal tunnel is created using the ESD technique and the tumor is enucleated using electrocautery knives (triangle-tip or insulated-tip knives). Finally, the enucleated SEL is suctioned into a transparent cap on the endoscope and removed via the tunnel. The proximal entry site is subsequently closed with the use of endoclips. The reported success rates in small case series are 70-100%. Pneumoperitoneum occurred in 13-16% of cases, but patients were treated conservatively. In another retrospective study, a tunneling technique was used for esophageal leiomyomas [98]. Here, hemorrhage was reported in 3 of 18 patients. Again, an additional major concern with this method is incomplete resection, especially in the case of larger GIST, removed in a narrow working-space, such as the submucosal tunnel. These studies do not explicitly mention how large tumors of up to 4 cm can be safely retrieved *en bloc* after enucleation [97]. Certainly, such treatments are only possible by trained experts in specialized centers and cannot be recommended for broad application. Larger studies and comparisons with surgical procedures are necessary to establish the role of these new endoscopic procedures.

Surgery

An in-depth discussion of the surgical management of SEL is beyond the scope of this review. However, some basic principles to guide the endoscopist in the decision which patients to refer for surgery, are herein mentioned. The main indication for surgery is the removal of symptomatic lesions or (pre-) malignant lesions, most of which are GIST in the upper GI tract or neuroendocrine (carcinoid) tumors in the rectum and duodenum. The difficulty in deciding which patients should be directly referred for surgery lies in the fact that EUS criteria and means of tissue acquisition have the above-mentioned limitations and a definite tissue diagnosis before surgery is not always possible or desirable. For example, surgical enucleation of esophageal leiomyomas could be difficult after previous biopsy or other tissue acquisition, such as unsuccessful tunneling or EMR procedures.

Malignant lesions in the GI tract should always be treated by oncologic standards. The most common pre-malignant SEL are GIST and comprehensive guidelines are available for their management [99-101]. A Korean guideline strictly discourages endoscopic enucleation if a GIST is suspected [39]. Surgical resection is considered the primary approach of GIST management and should be performed in all GIST >2 cm [41]. GIST ≤2 cm in the stomach have a very low risk of malignancy and follow up can be discussed with the patient [59,102]. Conversely, GIST in the rectum have a high risk of malignancy and should be excised, even if they are smaller than 2 cm [39]. The goals of surgery include complete resection, avoidance of tumor rupture, and intra-operative staging to exclude metastatic disease [103]. Because GIST rarely metastasize to lymph nodes, lymphadenectomy is only warranted if suspicious nodes are present. Laparoscopic (wedge-) resection of gastric GIST is feasible if intra-abdominal tumor rupture or seeding is unlikely, but discouraged for large tumors with high risk of rupture [39,101].

Algorithmic approach

Multiple algorithms have been proposed for the stepwise assessment of SEL or suspected GIST by experts in the field [4,5,7-9,34,41,104]. All algorithms follow a stepwise EUS-guided approach, similar to our suggested 3-Step algorithm (Fig. 1). Most experts agree that endoscopic assessment of the lesion (Step 1; Fig. 1) is the first step to evaluate the SEL and that most lesions ≤1 cm can be followed annually, unless they grow [4,5,7-9]. Because small GIST ≤2 cm (in the stomach) are considered to have very low risk of malignant behavior, few authors even consider a size cut-off ≤2 cm appropriate for follow up [105-107]. It must be stressed that this size cut-off does not apply for rectal SEL, because these often represent GIST with high malignant potential or neuroendocrine tumors, which should be resected. It is also broadly accepted that the next step in the evaluation of SEL is EUS (Step 2; Fig. 1). EUS can clearly identify benign lesions, such as most hyperechoic (e.g. lipoma) or completely anechoic lesions (e.g. vessel, hemangioma, cysts or lymphangiomas) and it is used to determine the layer of origin.

The main difficulty with any algorithm for SEL is that all methods of tissue acquisition (Step 3; Fig. 1) have limitations. It is not surprising that, although FNA is considered the method of choice for tissue acquisition by the vast majority of EUS practitioners in the United States and Germany, only a minority will perform EUS FNA regularly when GIST are suspected [108,109]. We suggest an approach to tissue acquisition guided by the size of the lesion, layer of origin and location in the GI tract. Because rectal SEL have a higher risk of representing a malignant lesion, complete endoscopic or surgical resection is usually performed in these lesions. SEL in the small bowel, located distal to the duodenum, are also surgically removed, as they cannot be easily accessed by endoscopic interventional techniques. Longitudinal endoscopes, used for FNA-guided biopsy, have an oblique-viewing optic, which limits the applicability within the large bowel. This might change in the future, as front-viewing, forward-array endoscopes give better access to proximal colonic lesions [110]. Therefore, the algorithm should be considered mainly for SEL of the upper GI tract. Here, duodenal lesions might pose another exception as FNA or TCB have limited applicability in some locations in the duodenum and EMR or surgery might be preferred for lesions that cannot be clearly identified as benign lesions [111]. As shown in the algorithm (Step 3; Fig. 1), we follow an approach that considers symptoms, EUS layer, EUS features of malignancy and size in choosing the tool for tissue acquisition. Tissue acquisition in the 2nd or 3rd EUS layer can be performed by endoscopic resection techniques, unroofing/ jumbo biopsy technique or FNA depending on the size and suspected EUS diagnosis (Table 1). SEL in the 4th EUS layer of the esophagus more frequently present leiomyomas and if surgical enucleation is considered, they should not be biopsied or partially resected prior to surgery. In the stomach, GIST are the most common entity in the 4th EUS layer. FNA/TCB is still considered the primary means of tissue acquisition in suspected GIST, unless the tumor is very large, symptomatic, has malignant features or is resected, regardless of FNA results. FNA best applies for 4th layer-lesions between 20-30 mm in size and possibly for those up to 50 mm if the presence of a non-GIST histology (e.g. leiomyoma) is likely, because this would change management. Very large suspected GIST should undergo FNA/TCB if neoadjuvant treatment with tyrosine kinase inhibitors is considered. Any lesion that grows during the follow up must be re-evaluated according to the algorithm. Although all confirmed GIST have potential for malignant transformation, the risk in gastric GIST ≤2 cm is considered to be very low and follow up is an option, especially in patients of advanced age or those with high surgical risk. We discourage endoscopic resection with ESD or tunneling procedures in suspected GIST, as these procedures carry a risk of tumor rupture and might turn a curable lesion into metastatic disease. Special consideration must always be given to the local availability of technique, operator expertise, surgical risk and patient wishes.

Concluding remarks

SEL are commonly identified during endoscopic procedures. These lesions can occur anywhere in the GI tract and EUS-guided tissue acquisition is used for further characterization. EUS cannot only distinguish intramural from extramural lesions, but also helps distinguish benign from potentially malignant lesions, even before tissue acquisition. The choice of tissue acquisition is based on a number of factors, such as tumor size, EUS features, tumor location within the GI tract or within a specific EUS layer. Furthermore, local expertise and patient factors must be considered when deciding whether tissue acquisition, surgical intervention or follow up is recommended. An algorithmic approach of the management of SEL is offered. However, the outlined challenges of all diagnostic methods explain why any algorithmic approach to SEL should be considered optional rather than optimal.

References

1. Hedenbro JL, Ekelund M, Wetterberg P. Endoscopic diagnosis of submucosal gastric lesions. The results after routine endoscopy. *Surg Endosc* 1991;**5**:20-23.

2. Jenssen C, Dietrich CF. Endoscopic ultrasound of gastrointestinal subepithelial lesions. *Ultraschall Med* 2008;**29**:236-256.

3. Polkowski M. Endoscopic ultrasound and endoscopic ultrasound-guided fine-needle biopsy for the diagnosis of malignant submucosal tumors. *Endoscopy* 2005;**37**:635-645.

4. Menon L, Buscaglia JM. Endoscopic approach to subepithelial lesions. *Therap Adv Gastroenterol* 2014;**7**:123-130.

5. Eckardt AJ, Wassef W. Diagnosis of subepithelial tumors in the GI tract. Endoscopy, EUS, and histology: bronze, silver, and gold standard? *Gastrointest Endosc* 2005;**62**:209-212.

6. Hwang JH, Rulyak SD, Kimmey MB. American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. *Gastroenterology* 2006;**130**:2217-2128.

7. Humphris JL, Jones DB. Subepithelial mass lesions in the upper gastrointestinal tract. *J Gastroenterol Hepatol* 2008;**23**:556-566.

8. Landi B, Palazzo L. The role of endosonography in submucosal tumours. *Best Pract Res Clin Gastroenterol* 2009;**23**:679-701.

9. Caplin M, Sundin A, Nillson O, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. *Neuroendocrinology* 2012;**95**:88-97.

10. Matsushita M, Hajiro K, Okazaki K, Takakuwa H. Endoscopic features of gastric inflammatory fibroid polyps. *Am J Gastroenterol* 1996;**91**:1595-1598.

11. Seya T, Tanaka N, Yokoi K, et al. Life-threatening bleeding from gastrointestinal stromal tumor of the stomach. *J Nippon Med Sch* 2008;**75**:306-311.

12. Tio TL, Kimmings N, Rauws E, et al. Endosonography of gastroesophageal varices: evaluation and follow-up of 76 cases. *Gastrointest Endosc* 1995;**42**:145-150.

13. Lee HJ, Park SI, Kim DK, Kim YH. Surgical resection of esophageal gastrointestinal stromal tumors. *Ann Thorac Surg* 2009;**87**:1569-1571.

14. Blum MG, Bilimoria KY, Wayne JD, et al. Surgical considerations for the management and resection of esophageal gastrointestinal stromal tumors. *Ann Thorac Surg* 2007;**84**:1717-1723.

15. Hwang JH1, Saunders MD, Rulyak SJ, et al. A prospective study comparing endoscopy and EUS in the evaluation of GI subepithelial masses. *Gastrointest Endosc* 2005;**62**:202-208.

16. Motoo Y, Okai T, Ohta H, et al. Endoscopic ultrasonography in the diagnosis of extraluminal compressions mimicking gastric submucosal tumors. *Endoscopy* 1994;**26**:239-242.

17. Polkowski M, Gerke W, Jarosz D, et al. Diagnostic yield and safety of endoscopic ultrasound-guided trucut biopsy in patients with gastric submucosal tumors: a prospective study. *Endoscopy* 2009;**41**:329-334.

18. Eckardt AJ, Adler A, Gomes EM, et al. Endosonographic large-bore biopsy of gastric subepithelial tumors: a prospective multicenter study. *Eur J Gastroenterol Hepatol* 2012;**24**:1135-1144.

19. Sato M, Irisawa A, Bhutani MS, et al. Gastric bronchogenic cyst diagnosed by endosonographically guided fine needle aspiration biopsy. *J Clin Ultrasound* 2008;**36**:237-239.

20. Kim GH, Park DY, Kim S, et al. Is it possible to differentiate gastric GISTs from gastric leiomyomas by EUS? *World J Gastroenterol* 2009;**15**:3376-3381.

21. Kim GH, Kim KB, Lee SH, et al. Digital image analysis of endoscopic ultrasonography is helpful in diagnosing gastric mesenchymal tumors. *BMC Gastroenterol* 2014;**14**:7.

22. Onishi M, Tominaga K, Sugimori S, et al. Internal hypoechoic feature by EUS as a possible predictive marker for the enlargement potential of gastric GI stromal tumors. *Gastrointest Endosc* 2012;**75**:731-738.

23. Kim MN, Kang SJ, Kim SG, et al. Prediction of risk of malignancy of gastrointestinal stromal tumors by endoscopic ultrasonography. *Gut Liver* 2013;**7**:642-647.

24. Rösch T, Kapfer B, Will U, et al. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: A prospective multicenter study. *Scand J Gastroenterol* 2002;**37**:856-862.

25. Karaca C, Turner BG, Cizginer S, et al. Accuracy of EUS in the evaluation of small gastric subepithelial lesions. *Gastrointest Endosc* 2010;**71**:722-727.

26. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med* 2006;**130**:1466-1478.

27. Kawanowa K, Sakuma Y, Sakurai S, et al. High incidence of microscopic gastrointestinal stromal tumors in the stomach. *Hum Pathol* 2006;**37**:1527-1535.

28. Chak A, Canto MI, Rösch T, et al. Endosonographic differentiation of benign and malignant stromal cell tumors. *Gastrointest Endosc* 1997;**45**:468-473.

29. Palazzo L, Landi B, Cellier C. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. *Gut* 2000;**46**:88-92.

30. Shah P, Gao F, Edmundowicz SA, et al. Predicting malignant potential of gastrointestinal stromal tumors using endoscopic ultrasound. *Dig Dis Sci* 2009;**54**:1265-1269.

31. Jeon SW, Park YD, Chung YJ, et al. Gastrointestinal stromal tumors of the stomach: endosonographic differentiation in relation to histological risk. *J Gastroenterol Hepatol* 2007;**22**:2069-2075.

32. Tokunaga M, Ohyama S, Hiki N, et al. Incidence and prognostic value of lymph node metastasis on c-Kit-positive gastrointestinal stromal tumors of the stomach. *Hepatogastroenterology* 2011;**58**:1224-1228.

33. Al-Thani H, El-Menyar A, Rasul KI, et al. Clinical presentation, management and outcomes of gastrointestinal stromal tumors. *Int J Surg* 2014;**12**:1127-1133.

34. Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. *Nat Rev Gastroenterol Hepatol* 2009;**6**:363-371.

35. Dietrich CF, Jenssen C, Hocke M, et al. Imaging of gastrointestinal stromal tumours with modern ultrasound techniques - a pictorial

essay. *Z Gastroenterol* 2012;**50**:457-467.

36. Kannengiesser K, Mahlke R, Petersen F, et al. Contrast-enhanced harmonic endoscopic ultrasound is able to discriminate benign submucosal lesions from gastrointestinal stromal tumors. *Scand J Gastroenterol* 2012;**47**:1515-1520.

37. Sakamoto H, Kitano M, Matsui S, et al. Estimation of malignant potential of GI stromal tumors by contrast-enhanced harmonic EUS (with videos). *Gastrointest Endosc* 2011;**73**:227-237.

38. Yamashita Y, Kato J, Ueda K, et al. Contrast-enhanced endoscopic ultrasonography can predict a higher malignant potential of gastrointestinal stromal tumors by visualizing large newly formed vessels. *J Clin Ultrasound* 2015;**43**:89-97.

39. Kang YK, Kang HJ, Kim KM, et al; Korean GIST Study Group (KGSG). Clinical practice guideline for accurate diagnosis and effective treatment of gastrointestinal stromal tumor in Korea. *Cancer Res Treat* 2012; 44:85-96.

40. Webb K1, Hwang JH. Endoscopic ultrasound-fine needle aspiration versus core biopsy for the diagnosis of subepithelial tumors. *Clin Endosc* 2013;**46**:441-444.

41. Faigel DO, Abulhawa S. Gastrointestinal stromal tumors: the role of the gastroenterologist in diagnosis and risk stratification. *J Clin Gastroenterol* 2012;**46**:629-636.

42. Jenssen C, Dietrich CF. Endoscopic ultrasound-guided fine-needle aspiration biopsy and trucut biopsy in gastroenterology - An overview. *Best Pract Res Clin Gastroenterol* 2009;**23**:743-759.

43. Polkowski M, Larghi A, Weynand B, et al. European Society of Gastrointestinal Endoscopy (ESGE). Learning, techniques, and complications of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline. *Endoscopy* 2012;**44**:190-206.

44. Salah W, Faigel DO. When to puncture, when not to puncture: Submucosal tumors. *Endosc Ultrasound* 2014;**3**:98-108.

45. Wani S, Early D, Kunkel J, et al. Diagnostic yield of malignancy during EUS-guided FNA of solid lesions with and without a stylet: a prospective, single blind, randomized, controlled trial. *Gastrointest Endosc* 2012;**76**:328-335.

46. Ando N, Goto H, Niwa Y, et al. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. *Gastrointest Endosc* 2002;**55**:37-43.

47. Kinoshita K, Isozaki K, Tsutsui S, et al. Endoscopic ultrasonography-guided fine needle aspiration biopsy in follow-up patients with gastrointestinal stromal tumours. *Eur J Gastroenterol Hepatol* 2003;**15**:1189-1193.

48. Vander Noot MR 3rd, Eloubeidi MA, Chen VK, et al. Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine-needle aspiration biopsy. *Cancer* 2004;**102**:157-163.

49. Okubo K, Yamao K, Nakamura T, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy for the diagnosis of gastrointestinal stromal tumors in the stomach. *J Gastroenterol* 2004;**39**:747-753.

50. Arantes V, Logroño R, Faruqi S, et al. Endoscopic sonographically guided fine-needle aspiration yield in submucosal tumors of the gastrointestinal tract. *J Ultrasound Med* 2004;**23**:1141-1150.

51. Chatzipantelis P, Salla C, Karoumpalis I, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy in the diagnosis of gastrointestinal stromal tumors of the stomach. A study of 17 cases. *J Gastrointestin Liver Dis* 2008;**17**:15-20.

52. Hoda KM, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. *Gastrointest Endosc* 2009;**69**:1218-1223.

53. Sepe PS, Moparty B, Pitman MB, et al. EUS-guided FNA forthediagnosis of GI stromal cell tumors: sensitivity and cytologic yield. *Gastrointest Endosc* 2009;**70**:254-261.

54. Mekky MA, Yamao K, Sawaki A, et al. Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors.

55. Suzuki T, Arai M, Matsumura T, et al. Factors associated with inadequate tissue yield in EUS-FNA for gastric SMT. *ISRN Gastroenterol* 2011;**2011**:619128.

56. Watson RR, Binmoeller KF, Hamerski CM, et al. Yield and performance characteristics of endoscopic ultrasound-guided fine needle aspiration for diagnosing upper GI tract stromal tumors. *Dig Dis Sci* 2011;**56**:1757-1762.

57. Akahoshi K, Sumida Y, Matsui N, et al. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. *World J Gastroenterol* 2007;**13**:2077-2082.

58. Chu YY, Lien JM, Ng SC, et al. Endoscopic ultrasound-guided tru-cut biopsy for diagnosis of gastrointestinal stromal tumors. *Hepatogastroenterology* 2010;**57**:1157-1160.

59. Iglesias-Garcia J, Poley JW, Larghi A, et al. Feasibility and yield of a new EUS histology needle: results from a multicenter, pooled, cohort study. *Gastrointest Endosc* 2011;**73**:1189-1196.

60. Storch I, Jorda M, Thurer R, et al. Advantage of EUS trucut biopsy combined with fine-needle aspiration without immediate on-site cytopathologic examination. *Gastrointest Endosc* 2006;**64**:505-511.

61. Philipper M, Hollerbach S, Gabbert HE, et al. Prospective comparison of endoscopic ultrasound-guided fine-needle aspiration and surgical histology in upper gastrointestinal submucosal tumors. *Endoscopy* 2010;**42**:300-305.

62. Larghi A, Verna EC, Ricci R, et al. EUS-guided fine-needle tissue acquisition by using a 19-gauge needle in a selected patient population: a prospective study. *Gastrointest Endosc* 2011;**74**:504-510.

63. Larghi A, Fuccio L, Chiarello G, et al. Fine-needle tissue acquisition from subepithelial lesion using a forward-viewing linear echoendoscope. *Endoscopy* 2014;**46**:39-45.

64. Fernández-Esparrach G, Sendino O, et al. Endoscopic ultrasound-guidedfine-needle aspiration and trucut biopsy in the diagnosis of gastric stromal tumors: a randomized crossover study. *Endoscopy* 2010;**42**:292-299.

65. Lee JH, Choi KD, Kim MY, et al. Clinical impact of EUS-guided Trucut biopsy results on decision making for patients with gastric subepithelial tumors ≥2 cm in diameter. *Gastrointest Endosc* 2011;**74**:1010-1018.

66. Hamada T1, Yasunaga H, Nakai Y, et al. Rarity of severe bleeding and perforation in endoscopic ultrasound-guided fine needle aspiration for submucosal tumors. *Dig Dis Sci* 2013;**58**:2634-2638.

67. Polkowski M, Bergman JJ. Endoscopic ultrasonography-guided biopsy for submucosal tumors: needless needling? *Endoscopy* 2010;**42**:324-326.

68. Cantor MJ, Davila RE, Faigel DO. Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. *Gastrointest Endosc* 2006;**64**:29-34.

69. Komanduri S, Keefer L, Jakate S. Diagnostic yield of a novel jumbo biopsy "unroofing" technique for tissue acquisition of gastric submucosal masses. *Endoscopy* 2011;**43**:849-855.

70. Buscaglia JM, Nagula S, Jayaraman V, et al. Diagnostic yield and safety of jumbo biopsy forceps in patients with subepithelial lesions of the upper and lower GI tract. *Gastrointest Endosc* 2012;**75**:1147-1152.

71. Tae HJ, Lee HL, Lee KN, et al. Deep biopsy via endoscopic submucosal dissection in upper gastrointestinal subepithelial tumors: a prospective study. *Endoscopy* 2014;**46**:845-850.

72. Lee CK, Chung IK, Lee SH, et al. Endoscopic partial resection with the unroofing technique for reliable tissue diagnosis of upper GI subepithelial tumors originating from the muscularis propria on EUS (with video). *Gastrointest Endosc* 2010;**71**:188-194.

73. Kim GH. Endoscopic resection of subepithelial tumors. *Clin Endosc* 2012;**45**:240-244.

74. Kawamoto K, Yamada Y, Furukawa N, et al. Endoscopic

submucosal tumorectomy for gastrointestinal submucosal tumors restricted to the submucosa: a new form of endoscopic minimal surgery. *Gastrointest Endosc* 1997;**46**:311-317.

75. Schlag C, Wilhelm D, von Delius S, et al. EndoResect study: endoscopic full-thickness resection of gastric subepithelial tumors. *Endoscopy* 2013;**45**:4-11.

76. Qin Z, Linghu E. The EndoResect study: endoscopic full-thickness resection of gastric subepithelial tumors. *Endoscopy* 2013;**45**:590.

77. Kajiyama T1, Hajiro K, Sakai M, et al. Endoscopic resection of gastrointestinal submucosal lesions: a comparison between strip biopsy and aspiration lumpectomy. *Gastrointest Endosc* 1996;**44**:404-410.

78. Wehrmann T, Martchenko K, Nakamura M, et al. Endoscopic resection of submucosal esophageal tumors: a prospective case series. *Endoscopy* 2004;**36**:802-807.

79. Huang WH, Feng CL, Lai HC, et al. Endoscopic ligation and resection for the treatment of small EUS-suspected gastric GI stromal tumors. *Gastrointest Endosc* 2010;**71**:1076-1081.

80. Sun S, Ge N, Wang C, et al. Endoscopic band ligation of small gastric stromal tumors and follow-up by endoscopic ultrasonography. *Surg Endosc* 2007;**21**:574-578.

81. Sun S, Ge N, Wang S, et al. EUS-assisted band ligation of small duodenal stromal tumors and follow-up by EUS. *Gastrointest Endosc* 2009;**69**:492-496.

82. Park YS, Park SW, Kim TI, et al. Endoscopic enucleation of upper-GI submucosal tumors by using an insulated-tip electrosurgical knife. *Gastrointest Endosc* 2004;**59**:409-415.

83. He Z, Sun C, Wang J, et al. Efficacy and safety of endoscopic submucosal dissection in treating gastric subepithelial tumors originating in the muscularis propria layer: a single-center study of 144 cases. *Scand J Gastroenterol* 2013;**48**:1466-1473.

84. Shi Q, Zhong YS, Yao LQ, et al. Endoscopic submucosal dissection for treatment of esophageal submucosal tumors originating from the muscularis propria layer. *Gastrointest Endosc* 2011;**74**:1194-1200.

85. Chu YY, Lien JM, Tsai MH, et al. Modified endoscopic submucosal dissection with enucleation for treatment of gastric subepithelial tumors originating from the muscularis propria layer. *BMC Gastroenterol* 2012;**12**:124.

86. He Z, Sun C, Zheng Z, et al. Endoscopic submucosal dissection of large gastrointestinal stromal tumors in the esophagus and stomach. *J Gastroenterol Hepatol* 2013;**28**:262-267.

87. Li QL, Yao LQ, Zhou PH, et al. Submucosal tumors of the esophagogastric junction originating from the muscularis propria layer: a large study of endoscopic submucosal dissection (with video). *Gastrointest Endosc* 2012;**75**:1153-1158.

88. Lee IL, Lin PY, Tung SY, et al. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. *Endoscopy* 2006;**38**:1024-1028.

89. Liu BR, Song JT, Qu B, et al. Endoscopic muscularis dissection for upper gastrointestinal subepithelial tumors originating from the muscularis propria. *Surg Endosc* 2012;**26**:3141-3148.

90. Białek A, Wiechowska-Kozłowska A, Pertkiewicz J, et al. Endoscopic submucosal dissection for treatment of gastric subepithelial tumors (with video). *Gastrointest Endosc* 2012;**75**:276-286.

91. Hwang JC, Kim JH, Kim JH, et al. Endoscopic resection for the treatment of gastric subepithelial tumors originated from the muscularis propria layer. *Hepatogastroenterology* 2009;**56**:1281-1286.

92. Zhou PH, Yao LQ, Qin XY, et al. Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria. *Surg Endosc* 2011;**25**:2926-2931.

93. Chun SY, Kim KO, Park DS, et al. Endoscopic submucosal dissection as a treatment for gastric subepithelial tumors that

originate from the muscularis propria layer: a preliminary analysis of appropriate indications. *Surg Endosc* 2013;**27**:3271-3279.

94. Inoue H, Ikeda H, Hosoya T, et al. Submucosal endoscopic tumor resection for subepithelial tumors in the esophagus and cardia. *Endoscopy* 2012;**44**:225-230.

95. Xu MD, Cai MY, Zhou PH, et al. Submucosal tunneling endoscopic resection: a new technique for treating upper GI submucosal tumors originating from the muscularis propria layer (with videos). *Gastrointest Endosc* 2012;**75**:195-199.

96. Gong W, Xiong Y, Zhi F, et al. Preliminary experience of endoscopic submucosal tunnel dissection for upper gastrointestinal submucosal tumors. *Endoscopy* 2012;**44**:231-235.

97. Inoue H, Santi EG, Onimaru M, Kudo SE. Submucosal endoscopy: from ESD to POEM and beyond. *Gastrointest Endosc Clin N Am* 2014;**24**:257-264.

98. Wang L, Ren W, Zhang Z, Yu J, Li Y, Song Y. Retrospective study of endoscopic submucosal tunnel dissection (ESTD) for surgical resection of esophageal leiomyoma. *Surg Endosc* 2013;**27**:4259-4266.

99. Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. *J Natl Compr Canc Netw* 2007;**5**(Suppl 2):S1-29; quiz S30.

100. ESMO / European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;**23**(Suppl 7):vii49-55.

101. Nishida T, Hirota S, Yanagisawa A, et al. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. *Int J Clin Oncol* 2008;**13**:416-430.

102. Landi B, Bouché O, Guimbaud R, et al. Management of gastrointestinal stromal tumours of limited size: proposals from a French panel of physicians. *Dig Liver Dis* 2011;**43**:935-939.

103. Yeh CN, Hwang TL, Huang CS et al. Clinical practice guidelines for patients with gastrointestinal stromal tumor in Taiwan. *World J Surg Oncol* 2012;**10**:246.

104. Akahoshi K, Oya M. Gastrointestinal stromal tumor of the stomach: How to manage? *World J Gastrointest Endosc* 2010;**2**:271-277.

105. Lim YJ1, Son HJ, Lee JS, et al. Clinical course of subepithelial lesions detected on upper gastrointestinal endoscopy. *World J Gastroenterol* 2010;16:439-444.

106. Gill KR, Camellini L, Conigliaro R, et al. The natural history of upper gastrointestinal subepithelial tumors: A multicenter endoscopic ultrasound survey. *J Clin Gastroenterol* 2009;**43**:723-726.

107. Nishida T, Kawai N, Yamaguchi S, Nishida Y. Submucosal tumors: comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors. *Dig Endosc* 2013;**25**:479-489.

108. Ha CY, Shah R, Chen J, et al. Diagnosis and management of GI stromal tumors by EUS-FNA: a survey of opinions and practices of endosonographers. *Gastrointest Endosc* 2009;**69**:1039-1044.

109. Eckardt AJ, Barreiros AP, Will U, et al. A nationwide German survey on EUS-guided diagnosis and management of suspected gastrointestinal stromal tumors (GIST) – The gap between evidence and "Gut Feeling". *Ultraschall Med* 2013;**34**(S01):WS_SL17_03.

110. Nguyen-Tang T, Shah JN, Sanchez-Yague A, Binmoeller KF. Use of the front-view forward-array echoendoscope to evaluate right colonic subepithelial lesions. *Gastrointest Endosc* 2010;**72**:606-610.

111. Pavlovic Markovic A, Rösch T, Alempijevic T, et al. Endoscopic ultrasound for differential diagnosis of duodenal lesions. *Ultraschall Med* 2012;**33**:E210-E217.

112. Rong L, Kida M, Yamauchi H, et al. Factors affecting the diagnostic accuracy of endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) for upper gastrointestinal submucosal or extraluminal solid mass lesions. *Dig Endosc* 2012;**24**:358-63.