

# Endoscopic ultrasound with tissue sampling is accurate in the diagnosis and subclassification of gastrointestinal spindle cell neoplasms

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## ABSTRACT

**Background and Objectives:** Mesenchymal (spindle cell) neoplasms (SCN) of the gastrointestinal (GI) tract are an important subtype of subepithelial lesions that need subclassification to assess their malignant potential. Reported success rates of accurate subclassification with endoscopic ultrasound (EUS)-guided biopsies are variable. Our goal was to analyze our experience using EUS-guided TruCut biopsy (EUS-TCB) in the majority of patients. **Methods:** Retrospective analysis in patients who underwent EUS with biopsies for suspected SCN at our tertiary referral center between 2004 and 2013. **Results:** A total of 146 patients with suspected SCN underwent EUS with tissue acquisition. Thirteen patients were excluded from analysis because tissue acquisition established a definite diagnosis other than SCN. In the remaining 133 patients, tissue acquisition was diagnostic of SCN in 118 (88.7%) and nondiagnostic in 15 (11.3%). Subclassification based on immunohistochemistry (IHC) was possible in 109 of the 133 cases (81.9%). The final diagnosis was GI stromal tumor in 64, leiomyoma in 39, and schwannoma in 6 cases. The percentage of patients who were subclassified by the various EUS-guided techniques together was 72.18%, and the percentage of patients who were subclassified specifically with EUS-TCB was 61.65%. Tissue specimens that enabled a specific diagnosis based on histological or cytological characteristics in conjunctions with IHC were obtained with EUS core biopsy in 83 (TCB in 82 and ProCore needle biopsy in 1), fine-needle aspiration in 13, mucosal resection in 10, and forceps biopsies (bite-on-bite) in 3 cases. **Conclusion:** EUS with endoscopic tissue acquisition is accurate in the diagnosis and subclassification of SCN. In experienced hands, the EUS-TruCut needle is a valuable tool with a high success rate for this indication.

**Key words:** Endoscopic ultrasound, fine needle aspiration, gastrointestinal stromal tumors, spindle cell neoplasms, TruCut biopsy

## BACKGROUND

Subepithelial lesions (SEL) constitute a spectrum of lesions that are located within the gastrointestinal (GI) wall below an endoscopically intact epithelium. These lesions are generally found incidentally during

endoscopy with an estimated incidence of 0.3% on upper endoscopy.<sup>[1]</sup> SELs include mesenchymal neoplasms, epithelial lesions without overt mucosal

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involvement, and a variety of nonneoplastic lesions including pancreatic rests, endometriosis, and inflammatory lesions. If epithelial lesions are excluded, the vast majority of SEL are benign with the reported rate of malignancy of <15%.<sup>[2]</sup>

Among SELs, an important subgroup is made up of mesenchymal neoplasms which are commonly lumped together based on morphologic similarity as spindle cell neoplasms (SCNs). These lesions include GI stromal tumors (GISTs), schwannomas, and leiomyomas. GISTs are by far the most common mesenchymal tumors of the GI tract and have the potential for malignant behavior and distant metastases.<sup>[3]</sup> The risk of malignant transformation in leiomyomas and schwannomas is extremely low.<sup>[4,5]</sup>

Because of the malignant potential of GISTs and the indolent behavior of schwannomas and leiomyomas, it is important to correctly diagnose and subclassify SCN. Although endoscopic ultrasound (EUS) can typically distinguish mesenchymal lesions from other SEL based on sonographic appearance, subclassification of these SCN into GIST, leiomyoma, and schwannoma requires tissue sampling so that immunohistochemistry (IHC) can be performed.

We, therefore, conducted a retrospective study to test our hypothesis that endoscopy with EUS and tissue acquisition using TruCut biopsy (TCB) in a majority of the patients is accurate in the diagnosis and subclassification of SCN.

## METHODS

This study was performed at the University of Iowa Hospitals and Clinics under a protocol approved by the Institutional Review Board. We reviewed all patients who underwent EUS for evaluation of an SEL at our institution from 2004 to 2013. Endosonographic characteristics and results from EUS-guided biopsies or other types of endoscopic tissue acquisition were reviewed for the ability to diagnose SCN and to perform IHC for subclassification into GIST, leiomyoma, and schwannoma. EUS procedures were performed by three experienced endosonographers (Henning Gerke, Rami El-Abiad, and Adrian N. Holm). A linear echoendoscope (GF-UCT140 and GF-UC140P, Olympus America Medical, Center Valley, PA, USA) was used to delineate SELs. At the discretion of the endosonographer, tissue acquisition

was attempted by one of the methods outlined in Table 1. EUS-guided TCB (EUS-TCB) was performed using a 19-gauge TruCut needle (Quick-Core, Cook-Medical, Bloomington, IN, USA). Before sending the tissue cores for histology, they were touched on glass slides; air-dried and stained using the Diff-Quik (American Scientific Products, McGraw Park, IL, USA) method to obtain touch imprint cytology (“touch prep”) in the majority of the cases. The TCB tissue core was then placed into formalin for fixation and sent to pathology for routine paraffin-embedded tissue processing with hematoxylin and eosin staining. EUS-guided fine-needle aspiration (FNA) was performed with a 22-gauge FNA needle (EchoTip; Cook Medical Inc., Bloomington, IN, USA). After advancing the needle tip into the target lesion, either no suction was used or suction of 5 mL–10 mL achieved with a 10 cm<sup>3</sup> syringe and the needle tip was moved back and forth within the target lesion in fast strokes before being removed. Typically, two smears were made for each pass and either air-dried or fixed in alcohol. Any remaining aspiration material was placed in RPMI for cell block preparation. Cell blocks were prepared using the collodion bag technique with subsequent formalin fixation. Diff-Quik stains were done on air-dried smears for on-site assessment. Alcohol-fixed smears were stained with Toluidine blue for on-site assessment and with Papanicolaou for final assessment. Our group has described some of these techniques in detail previously.<sup>[6,7]</sup> In some cases, tissue acquisition was performed using an EchoTip ProCore needle (Cook-Medical, Bloomington, IN, USA). An onsite cytopathologist was present in all cases. All patients were closely monitored for any immediate complications. Data were collected on demographic

**Table 1. Technique of tissue acquisition**

Sampling technique	Frequency	Percentage
FNA	14	9.6
FNA, EMR	1	0.7
FNA, bite-on-bite biopsy	2	1.4
FNA, TruCut	49	33.6
FNA, TruCut, EMR	1	0.7
FNA, TruCut, bite-on-bite biopsy	2	1.4
EMR	14	9.6
Bite-on bite biopsy	3	2.0
EMR, bite-on-bite biopsy	3	2.0
TruCut	50	34.2
TruCut, bite-on-bite biopsy	2	1.4
TruCut, ProCore	5	3.4
<b>Total</b>	<b>146</b>	<b>100</b>

FNA: Fine needle aspiration, EMR: Endoscopic mucosal resection

characteristics, location of the lesion, method of tissue acquisition, endoscopically suspected diagnosis, IHC, final diagnosis, and complications. Final diagnosis was based on diagnostic histology, cytology or surgery or a follow-up without treatment. The final decision to perform surgery was made by the surgeon after a thorough assessment of the clinical situation in each referred case.

### Statistical analysis

Frequencies, percentages, means, and standard deviations were used, as appropriate, for descriptive analysis. All statistical analyses were conducted using SPSS software for Windows, release 11 (SPSS Inc., Chicago, Ill, USA).

## RESULTS

From 2004 to 2013, a total of 310 patients underwent 350 EUS procedures for a total of 313 SEL. Based on the EUS findings, 146 (47%) patients were suspected to have SCN. Patients with typical findings of lipoma, duplication cyst, hemangioma, malignancy, pancreatic rest, or varices were excluded from the study. There were 65 (44.5%) males and 81 (55.5%) females. The mean age at the time of procedure was  $61.6 \pm 14.8$  years for males and  $63 \pm 14.3$  years for females. The mean size of the lesion was  $26.5 \pm 15.9$  mm in greatest dimension.

The most common presentation was incidentally discovered SEL on upper or lower endoscopy (65, 44.5%) followed by abdominal pain (23, 15.8%), gastroesophageal reflux disease (19, 13.0%), dysphagia (17, 11.6%), and GI bleeding (16, 11.0%). The most frequent location of the lesion was stomach (90, 61.6%) followed by esophagus (28, 19.2%) and duodenum (11, 7.5%). Ten (6.8%) lesions were located at the gastroesophageal junction and 7 (4.8%) in the colorectum [Table 2]. Tissue could be obtained in 139 cases (95.2%), and it was inadequate or could not be obtained in 7 cases (4.8%) because of the location of the lesion or needle failure. For the duodenal lesions, 6 out of 7 had EUS-TCB performed. It delivered diagnostic immunostains in 2 and a nonspecific diagnosis in 2. FNA in the same patients was diagnostic for SCN in 2 but did not achieve diagnostic IHC in any.

Thirteen patients (8.9%) were found to have a definitive diagnosis other than SCN despite EUS features suggestive of SCN (neuroendocrine tumor in 4, pancreatic heterotopia in 2, hyperplastic/inflammatory

polyp in 3, endometriosis in 1, adenocarcinoma in 1, and Brunner's gland hamartoma in 2).

Of the remaining 133 patients, EUS with tissue acquisition established a definite diagnosis of SCN in 118 (88.7%) whereas 15 remained without definite tissue diagnosis. Subclassification into GIST, leiomyoma, or schwannoma based on adequate tissue acquisition for IHC was possible in 109 of the 133 cases (81.9%). Further characterization of SCN was not possible in 9 cases due to inadequate tissue samples for IHC. The final diagnosis was GIST in 64, leiomyoma in 39, and schwannoma in 6 cases [Table 3].

The percentage of patients who were subclassified by the various EUS-guided techniques together was 72.18%, and the percentage of patients who were subclassified specifically with EUS-TCB was 61.65%. The diagnosis based on histological or cytological characteristics in conjunctions with IHC was made on EUS core biopsy specimen in 83 (TCB in 82 and ProCore needle biopsy in 1), FNA in 13, endoscopic mucosal resection (EMR) in 10, and forceps biopsies (bite-on-bite) in 3 cases. Of 15 patients with nondiagnostic endoscopic sampling, the final diagnosis was made on surgically resected specimens in 7 [Figure 1]. Eight patients remained without a definite final diagnosis.

**Table 2. Baseline demographics**

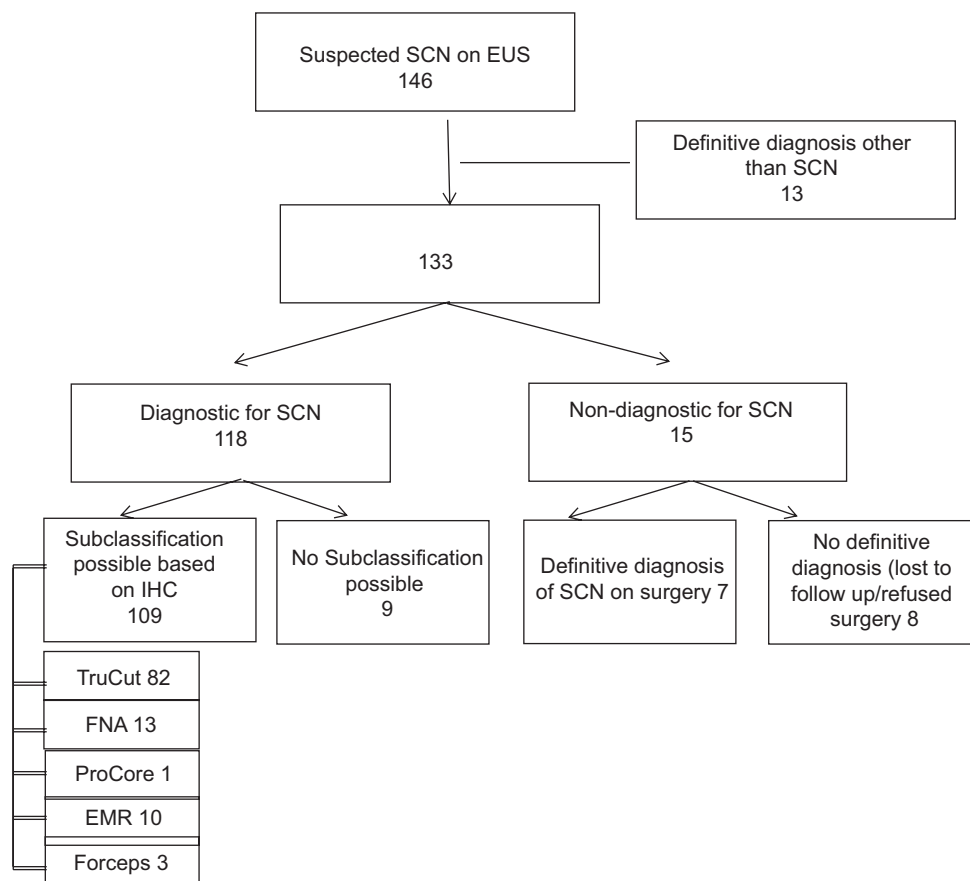
Variable	n (% or $\pm$ SD)
Number of patients	146
Sex, n (%)	
Males	65 (44.5)
Mean age $\pm$ SD (years)	62.33 $\pm$ 14.45
Mean size of the lesion (mm)	26.5 $\pm$ 15.9
Location, n (%)	
Stomach	90 (61.6)
Esophagus	28 (19.2)
Duodenum	11 (7.5)
GE junction	10 (6.8)
Colorectum	7 (4.8)

SD: Standard deviation, GE: Gastro-esophageal

**Table 3. Final diagnosis**

Diagnosis	n
GIST	64
Leiomyoma	39
Schwannoma	6
Spindle cell neoplasm	9
Definitive diagnosis other than SCN	13
Nondiagnostic	15
Total	146

GIST: Gastrointestinal stromal tumor, SCN: Spindle cell neoplasm

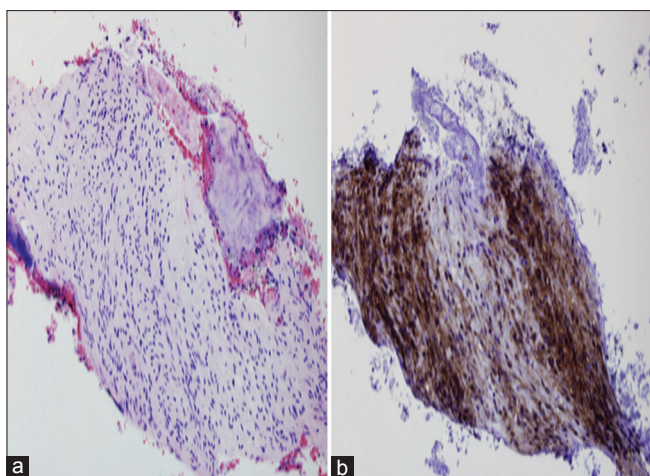


**Figure 1.** Different types of techniques used for tissue acquisition and associated success rate

## DISCUSSION

SCN is a subtype of SEL and includes most commonly GIST, leiomyomas, and schwannomas. They can be suspected with EUS based on the layer of the origin and the endosonographic appearance although lipomas, fibromas, pancreatic rests, duplication cysts, and carcinoid tumors may occasionally be confused with SCN due to overlapping features.<sup>[4,8]</sup> The typical sonographic findings on EUS for mesenchymal or SCN are round, hypoechoic lesion with a homogeneous to ground glass echotexture arising from the muscularis propria. While the characterization as a mesenchymal neoplasm can usually be made based on characteristic ultrasound features alone, accurate subclassification requires tissue acquisition for IHC. This can be accomplished through EUS-guided FNA or core biopsy. Core biopsies offer the potential advantage of providing larger tissue samples. However, they require special needles or modified biopsy techniques that may make tissue acquisition more cumbersome. In addition, it remains controversial, if histologic core samples offer a relevant diagnostic advantage

over cytology specimens obtained with traditional FNA. The EUS-TruCut needle is a dedicated core biopsy needle. Its main drawbacks are the stiffness and delicate mechanics, which make it prone to fail, if excessive endoscope tip angulation is required to access the biopsy target, especially during the transduodenal approach.<sup>[6]</sup> However, if a short and straight endoscope position can be achieved, transduodenal EUS-TCB can be attempted. In a randomized trial comparing TCB to a modified FNA technique to sample a variety of lesions, TCB resulted in a higher rate of histologic specimens but not in greater diagnostic accuracy because cytologic assessment alone enabled a diagnosis in most cases.<sup>[6]</sup> In the subset of patients with known or suspected SCN, core biopsy remains appealing because these larger histologic samples facilitate IHC for subclassification. Alternatively, IHC can be done on cell block preparations from FNA specimens [Figure 2]. However, the fibrotic nature of some mesenchymal lesions may prevent aspiration of sufficiently cellular material in some cases. Similarly, we have observed that rapid on-site assessment of touch preparations from tissue cores commonly



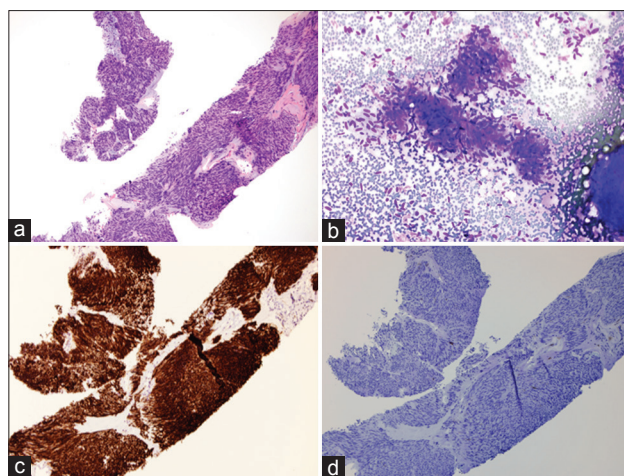
**Figure 2.** (a and b) Gastrointestinal stromal tumor. Cell block preparation of aspiration material shows a proliferation of bland spindle cells and stroma (H and E,  $\times 200$ ) (a) and diffuse positive staining for *c-kit*/CD117 within the tumor cells (*c-kit*/CD117 Immunoperoxidase,  $\times 200$ ) (b)

remains nondiagnostic in SCN because the cells do not “touch off” well.

When comparing EUS-FNA and TCB in the diagnosis of gastric stromal tumors in a randomized crossover study, EUS-TCB was not found to be superior to EUS-FNA in GISTs because of the high rate of technical failure of TCB. The overall diagnostic accuracy of EUS-FNA was 52% and that of EUS-TCB was 55% ( $P =$  not significant). This study, however, reported that when an adequate sample was obtained with EUS-TCB, IHC was almost always possible.<sup>[9]</sup> Similarly, we found that EUS-TCB, if technically possible, allowed an accurate diagnosis in most cases. This may offer an advantage over traditional FNA if the nature of the lesions inhibits obtaining sufficient material for cell block preparation.

In our series, EUS-TCB enabled IHC for accurate subclassification in 61.7% of patients with SCN [Figures 3 and 4]. When other methods of endoscopic tissue acquisition were included, an accurate diagnosis was achieved in 81.9%.

Table 4 shows published results of diagnostic immunostaining on tissue obtained through FNA or TCB. The largest study included 141 patients with GIST and EUS-FNA (22 G) achieved diagnostic immunostaining in 45.6%. In other series, the rates of diagnostic immunostaining range from 20% to 100% with FNA (19, 22, or 25 G) and from 55% to 79% with TCB (19 G).



**Figure 3.** (a-d) Core biopsy and corresponding touch prep of a gastrointestinal stromal tumor demonstrating uniform spindle cells (H and E,  $\times 100$  [a], Diff-Quik,  $\times 200$  [b]). The tumor cells are strongly and diffusely positive for CD117 (c) and negative for S100 (d)

A different type of EUS core biopsy needle (ProCore, Cook Endoscopy) has recently been designed to overcome some of the technical limitations of the EUS-TruCut needle. Although this needle has been studied in pancreatic lesions, no large series of its use in SCN is available.<sup>[28-30]</sup> Further, some technical difficulties may still be encountered when performing transduodenal passes with a 19-gauge ProCore needle due to its stiffness. In our study, a total of 5 patients underwent tissue acquisition by ProCore needle in addition to FNA and/or TCB. It was nondiagnostic in 4 cases and diagnostic in 1. Others report that tissue cores can be obtained with conventional 19-gauge FNA needles and even with 22-gauge FNA needles, but this has not been confirmed in SCNs.

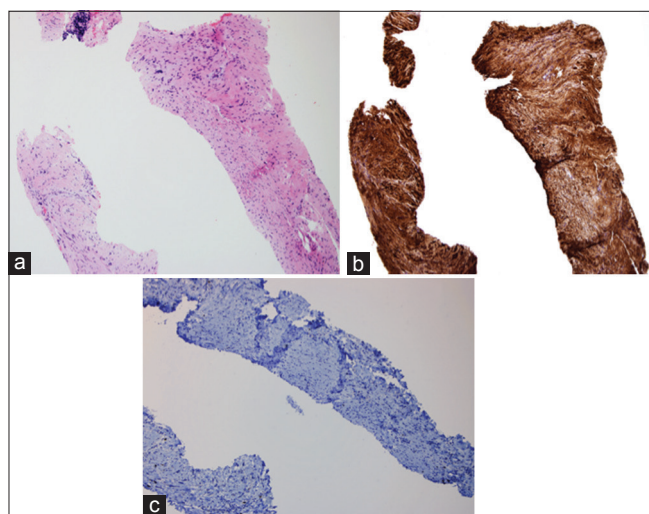
For GI SELs, bite-on-bite technique of two to eight bites using conventional-sized forceps yielded diagnostic samples in 38% (54% in the esophagus and 28% in the stomach and duodenum;  $P < 0.019$ ).<sup>[31]</sup> In another study by Cantor *et al.*, bite-on-bite biopsies were compared to endoscopic submucosal resection (ESMR) in 23 patients with SELs. The diagnostic yield of bite-on-bite biopsy was 17% versus 87% seen with ESMR ( $P = 0.0001$ ).<sup>[32]</sup> In our study, only a few patients were successfully diagnosed through bite-on-bite biopsy, EMR, or snare resection, primarily because of the low number of attempted biopsies and the high rate of tissue acquisition with other techniques.

Limitations of our study include the retrospective design with potential for selection bias. However,

**Table 4. Studies showing diagnostic immunostaining on endoscopic ultrasound with fine-needle aspiration/core biopsy in subepithelial lesions**

Study	Number of patients	Lesion	Diagnostic immunostaining on FNA (%)	Size of needle used (G)	Diagnostic immunostaining on TCB (%)	Size used (G)	Type
Ando <i>et al.</i> <sup>[10]</sup>	23	GI SEL	91	22			Prospective
DeWitt <i>et al.</i> <sup>[11]</sup>	38	GI SEL	36	22	79	19	Retrospective
Fernández-Esparrach <i>et al.</i> <sup>[9]</sup>	40	G SEL	52	22	55	19	Prospective
Mekky <i>et al.</i> <sup>[12]</sup>	141	G SEL	45.6	22		NA	Retrospective
Hoda <i>et al.</i> <sup>[13]</sup>	112	Upper GI SEL	61.3	22		NA	Retrospective
Arantes <i>et al.</i> <sup>[14]</sup>	10	GI SEL	30	22		NA	Retrospective
Chatzipantelis <i>et al.</i> <sup>[15]</sup>	17	G SEL	100	22		NA	Retrospective
Gu <i>et al.</i> <sup>[16]</sup>	12	G SEL	91.7	22		NA	Retrospective
Ito <i>et al.</i> <sup>[17]</sup>	23	G SEL	84.6	22		NA	Retrospective. 11/23 got FNA so low number
Watson <i>et al.</i> <sup>[18]</sup>	65	Upper GI SEL	68	19/22		NA	Retrospective
Kim <i>et al.</i> <sup>[19]</sup>	22	GI SEL	20	22	75	22 (ProCore)	Randomized
Larghi <i>et al.</i> <sup>[20]</sup>	121	GI SEL	93.4	19		NA	Retrospective
Eckardt <i>et al.</i> <sup>[21]</sup>	46	G SEL	52	22		NA	Retrospective
Lee <i>et al.</i> <sup>[22]</sup>	65	G SEL	NA		57	19	Retrospective
Sepe <i>et al.</i> <sup>[23]</sup>	37	GI SEL	78.4	19/22/25		NA	Retrospective
Akahoshi <i>et al.</i> <sup>[24]</sup>	51	GI SEL	82	22		NA	Prospective
Philipper <i>et al.</i> <sup>[25]</sup>	47	Upper GI SEL	46	22		NA	Prospective
Polkowski <i>et al.</i> <sup>[26]</sup>	49	G SEL			63	19	Prospective
Yoshida <i>et al.</i> <sup>[27]</sup>	49	GI SEL	81.9	22		NA	Retrospective

G SEL: Gastric subepithelial lesion, GI SEL: Gastrointestinal subepithelial lesion, FNA: Fine needle aspiration, TCB: TruCut biopsy, NA: Not available



**Figure 4.** (a-c) Core biopsy of a schwannoma demonstrating spindle cells embedded in dense collagen (H and E,  $\times 100$  [a]). The tumor cells are strongly and diffusely positive for S100 (b) and negative for CD117 (c)

our diagnostic yield of EUS-TCB remains high even if we conservatively define all cases as TCB failures where tissue was acquired through alternative methods. Despite the high success rate of TCB to subclassify SCN in our study, the uncontrolled study design does not allow us to prove that TCB

is superior to FNA. Further controlled studies are needed.

## CONCLUSION

EUS with endoscopic tissue acquisition is accurate in the diagnosis and subclassification of SCN. In experienced hands, the EUS-TruCut needle is a valuable tool with a high success rate. Traditional FNA with cell block, other needle designs, or alternative methods of endoscopic tissue acquisition can be considered if sharp angulation of the echoendoscope tip prevents the successful use of the EUS-TruCut needle.

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### *Conflicts of interest*

There are no conflicts of interest.

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