

Can contrast-enhanced harmonic endosonography predict malignancy risk in gastrointestinal subepithelial tumors?

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ABSTRACT

Background and Objectives: Contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) is a novel technology that can identify subepithelial tumors (SETs) by detecting the degree of enhancement, but whether CEH-EUS can predict the malignancy risk of gastrointestinal stromal tumors (GISTs) remains unclear. The aim of our study was to evaluate the diagnostic accuracy of CEH-EUS and its ability to discriminate among SETs and predict the malignancy risk of GISTs.

Materials and Methods: We retrospectively included patients with suspected subepithelial lesions who underwent CEH-EUS preoperatively. Thirty-five patients with histologically proven GISTs and benign neoplasms were enrolled in the study. The images of CEH-EUS were categorized in accordance with microvasculature, parenchymal perfusion, and nonenhancing spots. The diagnostic performance of CEH-EUS was evaluated by comparing these findings with the histological diagnosis.

Results: When we divided the enrolled patients into high- and low-grade malignancy and benign groups, nonenhancing spots on CEH-EUS were found more frequently in the high-grade malignancy group (63.6%), followed by the low-grade malignancy (46.7%) and benign groups (25.7%) ($P = 0.022$). However, based on the statistical validity of the CEH-EUS findings for the discrimination of SETs, the sensitivity was 53.8% for diagnostic performance and 63.6% for prediction of malignancy risk of GISTs. **Conclusions:** From our study results, it is unclear whether CEH-EUS alone has a diagnostic role in the discrimination of SETs and the prediction of malignancy risk of GISTs. Further studies with larger samples from multiple centers and use of other imaging analysis modalities are needed.

Key words: Contrast-enhanced harmonic endoscopic ultrasound, endoscopic ultrasound, gastrointestinal stromal tumor, subepithelial tumor

INTRODUCTION

Subepithelial tumors (SETs) are often found during upper gastrointestinal endoscopy and up to 20% of

these may be neoplastic.^[1-3] Gastrointestinal stromal tumors (GISTs) are the most commonly identified

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SETs in the upper gastrointestinal tract, particularly the stomach.^[4-6] Based on the National Institutes of Health (NIH) definition of aggressive risk, 10%–30% of GISTs can be malignant.^[7] This classification system requires a specimen obtained by surgical resection and makes it impossible to predict malignancy risk preoperatively.^[1] However, the absolute potential for malignancy appears to be very low, particularly for small GISTs (<3 cm).^[8] This has led to controversy over the benefit of surgical resection of GISTs with low potential for malignancy, regardless of the morbidity and mortality associated with surgery. Thus, alternative methods to predict malignancy risk preoperatively are needed.

Some retrospective studies showed that endoscopic ultrasound (EUS) features could be used to discriminate GISTs from other benign SETs and to assess the malignancy risk of GISTs.^[9,10] Unfortunately, in other studies, the diagnostic yield of EUS findings varied widely, even with tissue sampling by EUS-guided fine needle aspiration (EUS-FNA), core needle biopsy, and Tru-cut biopsy, particularly in the case of small GISTs.^[11-13]

Contrast-enhanced harmonic EUS (CEH-EUS) with microbubbles can differentiate SETs in the gastrointestinal tract according to the presence of fine vessels and slow blood flow, while EUS equipped with color and power Doppler modes can only identify large vessels.^[14] The contrast agent SonoVue (Bracco Imaging, Milan, Italy) does not diffuse into the extravascular compartment and remains within the blood vessels until the gas dissolves and is eliminated in expired air. Acoustic signals with low mechanical index ultrasound imaging techniques induce oscillation of the bubbles, and the flexible shell makes it possible to use low acoustic power, thus allowing imaging of parenchymal blood flow with continuous transmission.^[6,15,16] Recent studies have shown that this novel technique can differentiate subepithelial lesions on the basis of the pattern of contrast enhancement or by detecting intratumoral vessels, but whether or not CEH-EUS can predict the malignancy risk of GISTs remains unclear.^[6,8,12,14,17] The aim of our study was to evaluate whether CEH-EUS findings can identify SETs and predict the malignancy risk of GISTs, in comparison with surgical pathologic findings.

MATERIALS AND METHODS

Patients

We conducted a retrospective analysis and included patients with suspected subepithelial lesions, who were referred to our hospital for EUS examination from April 2012 to June 2015. All patients had been examined with B-mode EUS and CEH-EUS to analyze the characteristics of the respective subepithelial lesions. All patients provided informed consent before undergoing procedures. The Institutional Review Board of our hospital approved this study.

Endosonographic evaluation

Standard B-mode EUS was performed for all patients with suspected subepithelial masses. EUS was performed with a radial echoendoscope (GF-UE260-AL5; Olympus Medical Systems, Tokyo, Japan) and a Prosound Alpha 10 processor (Aloka Co., Ltd., Tokyo, Japan). If indeterminate masses were found, size, location of layer, echogenicity, homogeneity, and existence of echogenic spots were documented.

For CEH-EUS, the extended pure harmonic detection mode was used, which combines the filtered fundamental and second harmonic component frequencies with a mechanical index of 0.17.^[12] When a subepithelial lesion was detected by fundamental B-mode EUS, the setting was changed to the extended pure harmonic detection mode. All patients with solid subepithelial lesions received 2.4 mL of SonoVue as an ultrasound contrast agent into the antecubital vein through a catheter, followed by a 10 mL saline flush. The CEH-EUS images were categorized in accordance with the pattern of microvasculature (no, regular, or irregular vessels), parenchymal perfusion (homogeneous or heterogeneous), and nonenhancing spots (presence or absence). We also evaluated diagnostic performance using real-time CEH-EUS findings, including characteristics of the microvasculature, by examining continuous, 0–20 s microvessel images and patterns of parenchymal perfusion with 20–60s perfusion images [Figures 1 and 2 and Videos 1 and 2]. All B-mode EUS and CEH-EUS image clips were stored on the hard disk of the scanner and were reviewed by a single experienced endosonographer (C.C.) who was blinded to the final diagnosis.

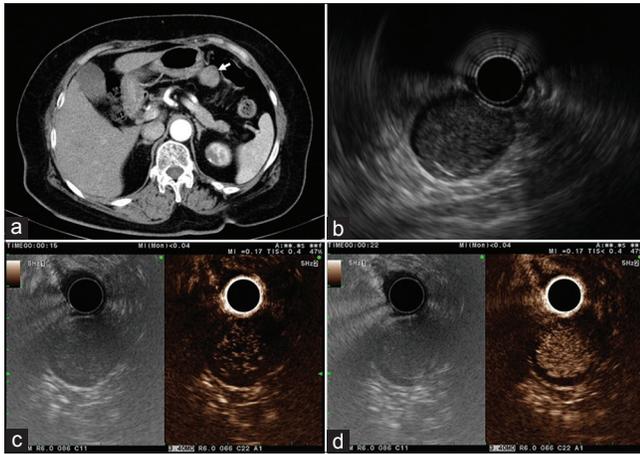


Figure 1. Images of low-grade malignancy gastrointestinal stromal tumor of the stomach in a 66-year-old woman. (a) Contrast-enhanced computed tomography showing homogeneous enhancement of a 21 mm diameter tumor in the stomach wall (arrow). (b) Endoscopic ultrasound showing homogeneous appearance and a well-demarcated margin in the submucosal layer without local invasion. (c) Vessel image of contrast-enhanced harmonic endoscopic ultrasound showing regular vessels flowing from the periphery to the center of the tumor. (d) Perfusion of contrast-enhanced harmonic endoscopic ultrasound showing homogeneous appearance within the tumor

Histopathological evaluation

Among patients with subepithelial lesions who received standard B-mode EUS and CEH-EUS preoperatively, we enrolled those with histologically proven GISTs or benign neoplasms confirmed by surgical resection. Each pathologic report was evaluated to confirm the diagnosis and to determine the NIH classification if the lesions were GISTs. The GISTs were defined as SETs composed of spindle cells that stained positive for c-kit and CD34. We categorized three groups on the basis of the pathologic reports: a benign group, a low-grade malignancy group that included very low- and low-risk GISTs, and a high-grade malignancy group that included intermediate- and high-risk GISTs.

Statistical analysis

Statistical analyses of the differences in size, microvasculature, parenchymal perfusion, and nonenhancing spots (presence or absence) among the three groups were conducted using one-way analysis of variance and linear-by-linear association tests. The sensitivity, specificity, positive and negative predictive values, and accuracy for differentiation of the three groups were also calculated and compared. $P < 0.05$ was considered statistically significant. Statistical calculations were performed using SPSS version 18.0 for Windows software (SPSS Inc., Chicago, IL, USA).

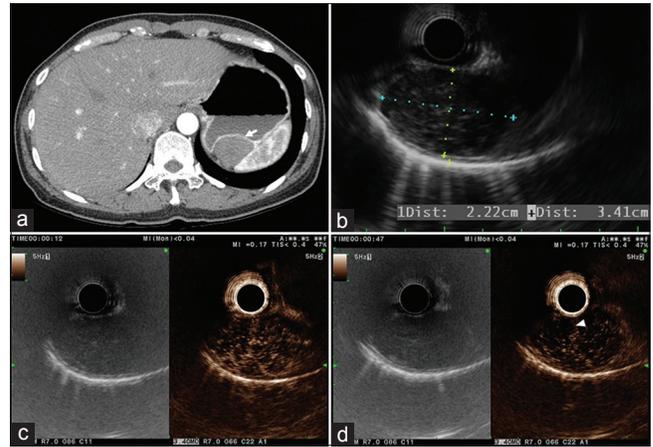


Figure 2. Images of high-grade malignancy gastrointestinal stromal tumor of the stomach in a 50-year-old woman. (a) Contrast-enhanced computed tomography showing heterogeneous enhancement of a 34 mm diameter tumor in the stomach wall (arrow). (b) Endoscopic ultrasound showing heterogeneous appearance and a well-demarcated margin located in the muscularis propria layer. Contrast-enhanced harmonic endoscopic ultrasound showed irregular vascular pattern in the early vascular phase (c) and heterogeneous perfusion with nonenhancing spots (arrowhead) during parenchymal perfusion (d)

RESULTS

Baseline characteristics

A total of 35 patients were enrolled in this study; all patients underwent surgery, and their baseline characteristics are shown in Table 1. Based on the histologic reports of surgical specimens, nine had benign neoplasms including leiomyoma in five, glomus tumor in two, schwannoma in one, and ectopic pancreas in one. Twenty-six patients were diagnosed with GISTs including 15 in the low-grade malignancy group and 11 in the high-grade malignancy group. The median age was 57 years (range: 36–84) and the male:female ratio was 18:17. The most common site of SET was the stomach (74.3%, 26 of 37), followed by the esophagus, duodenum, and rectum. Most GISTs were also located in the stomach (76.9%, 20 of 26).

Comparison of endoscopic ultrasound and contrast-enhanced harmonic endoscopic ultrasound features in the benign, low-, and high-grade malignancy groups

Subepithelial lesions had an average size of 32.5 ± 12.5 mm in standard B-mode EUS. Among the three groups, the mean size of SETs on EUS was larger in the high-grade malignancy group (43.27 ± 14.49 mm) than in the low-grade malignancy group (28.0 ± 6.15 mm) and the benign group (26.88 ± 10.34 mm) ($P = 0.001$). However, there was no significant difference in other EUS features among the three groups [Table 2].

In CEH-EUS findings, there were significant differences in the microvasculature and nonenhancing spots. The presence of nonenhancing spots among the CEH-EUS features was most common in the high-grade malignancy group (63.6%, 7 of 11), followed by the low-grade malignancy (46.7%, 7 of 15) and benign groups (25.7%, 1 of 9) ($P = 0.022$). There were no significant differences in the presence of irregular vessels and parenchymal perfusion among the three groups [Table 2].

Diagnostic performance of contrast-enhanced harmonic endoscopic ultrasound for discrimination among subepithelial tumors and prediction of malignancy risk of gastrointestinal stromal tumors
Based on the validated results in Table 2, we also analyzed the diagnostic performance

(sensitivity, specificity, positive and negative predictive value, and accuracy) of the CEH-EUS images, which were divided into two categories by histology: one compared the benign group with the GIST groups, and the other compared the low- and high-grade malignancy groups. However, neither category showed high sensitivity, specificity, or accuracy for the CEH-EUS findings of nonenhancing spots. The same was true for the presence of at least 1, 2, or 3 of the CEH-EUS findings [Table 3].

DISCUSSION

GISTs arise most commonly from the muscularis propria and are asymptomatic. To determine the malignancy risk of GISTs, surgical resection is generally needed to detect the tumor size and mitotic count. However, some studies have shown that the absolute potential of malignancy in small GISTs appears to be very low and that only 1.9% of patients with very low risk had disease progression during follow-up.^[8,18] Therefore, whether surgical resection should be performed to confirm malignancy of low-risk GISTs has been unclear. This has prompted a search for alternative studies to predict malignancy risk preoperatively.

EUS is one of the most common imaging tests for the determination of tumor size, shape, tumor border, and internal composition of SETs,^[1,19] but some studies had conflicting opinions about the diagnostic role of EUS in the prediction of malignancy risk of SETs. Chak *et al.* reported relatively high sensitivity and specificity over 80% using their diagnostic criteria for EUS.^[10] In contrast, Hwang *et al.* reported diagnostic accuracy with EUS as low as 43% and Okai *et al.* also showed that the criteria described above

Table 1. Baseline characteristics of enrolled patients

Enrolled patients	N=35
Mean age (years)	56.9±11.9
Sex (male:female)	18:17
Location (%)	
Esophagus	3 (8.6)
Stomach	26 (74.3)
Duodenum	3 (8.6)
Rectum	3 (8.6)
Mean size (mm)	32.5±12.5
Histology (%)	
Benign	9 (25.7)
Leiomyoma	5 (14.3)
Glomus tumor	2 (5.7)
Schwannoma	1 (2.9)
Ectopic pancreas	1 (2.9)
GIST	26 (74.3)
Very low risk	4 (11.4)
Low risk	11 (31.4)
Intermediate risk	8 (22.9)
High risk	3 (8.6)

GIST: Gastrointestinal stromal tumor

Table 2. Univariate analysis for risk stratification according to standard B-mode endoscopic ultrasound and contrast-enhanced harmonic endoscopic ultrasound features

	Number of cases (%)			P value
	Benign (n=9)	Low-grade malignancy (n=15)	High-grade malignancy (n=11)	
Standard B-mode EUS findings				
Lesion size (mm)	26.88±10.34	28.00±6.15	43.27±14.49	0.001 [†]
Heterogeneity	4 (44.4)	6 (42.9)	9 (81.8)	0.084
Irregular margin	1 (12.5)	2 (13.3)	3 (30.0)	0.323
CEH-EUS findings				
Irregular vessels	2 (22.2)	7 (46.7)	7 (63.6)	0.070
Heterogeneous perfusion	1 (11.1)	4 (26.7)	4 (36.4)	0.209
Nonenhancing spots	1 (25.7)	7 (46.7)	7 (63.6)	0.022 [*]

[†]One-way ANOVA, *Linear by linear association. EUS: Endoscopic ultrasound, CEH-EUS: Contrast-enhanced harmonic endoscopic ultrasound, ANOVA: Analysis of variance

Table 3. Diagnostic performance of contrast-enhanced harmonic endoscopic ultrasound images according to risk stratification of subepithelial tumors

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Number of positive findings ≥ 1					
Benign versus GIST	73.1	66.7	86.4	46.2	71.4
Low-grade versus high-grade malignancy	90.9	40.0	52.6	85.7	61.5
Number of positive findings ≥ 2					
Benign versus GIST	42.3	88.9	91.7	34.8	54.3
Low-grade versus high-grade malignancy	54.5	66.7	54.5	66.7	61.5
Number of positive findings ≥ 3					
Benign versus GIST	23.1	100	100	31.0	42.9
Low-grade versus high-grade malignancy	18.2	73.3	33.3	55.0	50.0

PPV: Positive predictive value, NPV: Negative predictive value, GIST: Gastrointestinal stromal tumor

had very low sensitivity for the differentiation of GISTs from other SETs.^[9,19] In our study, a significant difference was seen in tumor size, using standard B-mode EUS. The mean size of SETs was larger in the high-grade malignant GIST group (43.27 mm) than in the benign and low-grade malignant GIST groups. However, no significant differences were observed in other EUS findings for heterogeneity and irregular tumor margins. Based on these results, we were skeptical about the value of EUS used alone in the diagnosis of SETs. EUS-FNA, core needle biopsy, and Tru-cut biopsy are additional methods that can improve the value of the diagnostic performance of EUS. However, some studies reported that the diagnostic yield of EUS-guided FNA varied widely. In addition, because these procedures provide small tissue samples, no histological tests are able to determine the mitotic index.^[11-13]

Although EUS equipped with color and power Doppler modes can identify a large vessel, it is unable to detect vessels with slow flow or demonstrate parenchymal perfusion.^[14] However, the development of contrast-enhanced harmonic imaging and ultrasound contrast agents has enabled better assessment of vascular morphology and enhancing patterns.^[20-22] Based on this technological improvement, some studies evaluated the role of CEH-EUS in characterizing SETs. Sakamoto *et al.* showed that CEH-EUS can predict the malignancy risk of GISTs.^[12] All 16 high-risk patients with GISTs had irregular vessels and heterogeneity, and only 5 of 13 low-risk patients with GISTs showed these features on CEH-EUS. The authors in this study suggested that CEH-EUS might play an important role in predicting the malignancy risk of GISTs, with a sensitivity and specificity of 100% and 63%, respectively. Yamashita *et al.* also suggested that intratumoral vessels observed in GISTs on CE-EUS

are correlated with a higher degree of angiogenesis, resulting in higher malignant potential.^[17] In this study, among 6 of 13 patients with surgically proven GISTs with intratumoral vessels observed on CE-EUS and 5 had intermediate- or high-risk GISTs. With regard to the discrimination of GISTs from benign SETs, some studies also reported the important role played by the enhanced features of CEH-EUS. They observed that GISTs showed primarily hyperenhanced features on CEH-EUS, while benign SETs such as leiomyoma and lipoma showed hypo-enhanced features.^[6,23] In contrast, Sakamoto *et al.* reported that low-grade GISTs and all benign neoplasms, including leiomyomas and schwannomas, demonstrated regular vessels and homogeneous enhancement with CE-EUS, indicating the limitation of CE-EUS in the differentiation of low-risk GISTs from benign neoplasms. These studies suggested that high-risk malignant GISTs tend to have irregular vessels and hyperenhancement in CEH-EUS findings but were not able to show the diagnostic performance of CEH-EUS for the risk stratification of GISTs, except in the study by Sakamoto *et al.*^[12] The results of our study partially corresponded to those of previous studies mentioned above. The presence of nonenhancing spots in CEH-EUS findings tended to discriminate GISTs from benign SETs but could not discriminate malignancy risk among GISTs. We also evaluated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for 3 of the CEH-EUS findings, by comparing two categories: benign SETs versus GISTs and high-grade versus low-grade malignant GISTs. In our study, CEH-EUS had low sensitivity, specificity, and accuracy in the discrimination of the malignancy risk of SETs.

There were some limitations in this study. First, the number of cases enrolled was small, and this was a single-center study. Second, there might be a difference

in the interpretation of images of CEH-EUS, based on the experience of the endoscopist and equipment used.

CONCLUSIONS

High-grade malignancy GISTs tend to show nonenhancing spots on CEH-EUS compared with findings for low-grade malignancy GISTs and benign SETs. However, this finding was insufficient for discrimination of malignancy risk among GISTs. Moreover, whether CEH-EUS alone has a diagnostic role in discriminating GISTs from benign SETs remains unclear because of low sensitivity and specificity. Further large-scale studies in multiple centers and use of additional imaging analysis modalities are required to evaluate differentiation of SETs and risk stratification among GISTs.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Hwang JH, Rulyak SD, Kimmey MB; American Gastroenterological Association Institute. American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. *Gastroenterology* 2006;130:2217-28.
- Min YW, Park HN, Min BH, et al. Preoperative predictive factors for gastrointestinal stromal tumors: Analysis of 375 surgically resected gastric subepithelial tumors. *J Gastrointest Surg* 2015;19:631-8.
- Eckardt AJ, Wassef W. Diagnosis of subepithelial tumors in the GI tract. Endoscopy, EUS, and histology: Bronze, silver, and gold standard? *Gastrointest Endosc* 2005;62:209-12.
- Hwang JH, Kimmey MB. The incidental upper gastrointestinal subepithelial mass. *Gastroenterology* 2004;126:301-7.
- Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: An analysis of 1,458 cases from 1992 to 2000. *Am J Gastroenterol* 2005;100:162-8.
- 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;47:1515-20.
- Palazzo L, Landi B, Cellier C, et al. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. *Gut* 2000;46:88-92.
- Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol* 2002;33:459-65.
- Okai T, Minamoto T, Ohtsubo K, et al. Endosonographic evaluation of c-kit-positive gastrointestinal stromal tumor. *Abdom Imaging* 2003;28:301-7.
- Chak A, Canto MI, Rösch T, et al. Endosonographic differentiation of benign and malignant stromal cell tumors. *Gastrointest Endosc* 1997;45:468-73.
- Polkowski M, Gerke W, Jarosz D, et al. Diagnostic yield and safety of endoscopic ultrasound-guided trucut [corrected] biopsy in patients with gastric submucosal tumors: A prospective study. *Endoscopy* 2009;41:329-34.
- 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;73:227-37.
- Philipp 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;42:300-5.
- Kitano M, Sakamoto H, Kudo M. Contrast-enhanced endoscopic ultrasound. *Dig Endosc* 2014;26 Suppl 1:79-85.
- Sanchez MV, Varadarajulu S, Napoleon B. EUS contrast agents: What is available, how do they work, and are they effective? *Gastrointest Endosc* 2009;69 2 Suppl: S71-7.
- Cosgrove D. Ultrasound contrast agents: An overview. *Eur J Radiol* 2006;60:324-30.
- 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.
- Miettinen M, Lasota J. Gastrointestinal stromal tumors: Pathology and prognosis at different sites. *Semin Diagn Pathol* 2006;23:70-83.
- Hwang JH, Saunders MD, Rulyak SJ, et al. A prospective study comparing endoscopy and EUS in the evaluation of GI subepithelial masses. *Gastrointest Endosc* 2005;62:202-8.
- Ding H, Kudo M, Onda H, et al. Hepatocellular carcinoma: Depiction of tumor parenchymal flow with intermittent harmonic power Doppler US during the early arterial phase in dual-display mode. *Radiology* 2001;220:349-56.
- Park BK, Kim B, Kim SH, et al. Assessment of cystic renal masses based on Bosniak classification: Comparison of CT and contrast-enhanced US. *Eur J Radiol* 2007;61:310-4.
- Xia Y, Kitano M, Kudo M, et al. Characterization of intra-abdominal lesions of undetermined origin by contrast-enhanced harmonic EUS (with videos). *Gastrointest Endosc* 2010;72:637-42.
- Fusaroli P, D'Ercole M, Ceroni L, et al. Contrast Enhanced-Endoscopic Ultrasonography (Ch-EUS) in the Differential Diagnosis of Gastrointestinal Submucosal Tumors (SMTs). In: Abstracts of the 19th National Congress of Digestive Diseases/Digestive and Liver Disease 45S; 2013.