

Diagnosis of subepithelial tumors in the upper gastrointestinal tract by endoscopic ultrasonography

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Abstract

Endoscopic ultrasonography (EUS) is the most accurate procedure for detecting and diagnosing subepithelial tumors, due to its higher sensitivity and specificity than other imaging modalities. EUS can characterize lesions by providing information on echogenic origin, size, borders, homogeneity, and the presence of echogenic or anechoic foci. Linear echoendoscopes, and recently also electronic radial echoendoscopes, can be used with color Doppler or power Doppler to assess the vascular signals from subepithelial masses, and thus permit the differentiation of vascular structures from cysts, as well as the assessment of the tumor blood supply. However, the diagnostic accuracy of EUS imaging alone has been shown to be low in subepithelial lesions with 3rd and 4th layers. It is also difficult to differentiate exactly between benign and malignant tumors and to gain an accurate picture of histology using EUS. On the other hands, EUS guided fine needle aspiration (EUS-FNA) can provide samples for cytologic or histologic analysis. Hypoechoic

lesions of the 3rd and the 4th EUS layers, more than in 1 cm diameter are recommended, and histologic confirmation using endoscopic submucosal resection or EUS-FNA should be obtained when possible. Therefore, EUS-FNA plays an important role in the clinical management of subepithelial tumors. Furthermore improvements in endoscopic technology are expected to be more useful modalities in differential diagnosis and discrimination between benign and malignant subepithelial tumors.

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Key words: Endoscopic ultrasonography; Submucosal tumor; Subepithelial tumor

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INTRODUCTION

Submucosal masses or lesions often referred to as 'submucosal tumors', represent a growth underneath the mucosa of the gastrointestinal (GI) tract whose etiology cannot be determined by GI endoscopy or barium studies^[1]. However, the term 'submucosal tumor' is inappropriate, because many of these lesions do not arise from the submucosa and many of them are not tumors^[2-5]. Thus, 'subepithelial' is a more appropriate term than 'submucosal'. Hence, other authors call these abnormalities subepithelial lesions, because they are covered by normal mucosa^[6]. These can

be caused by external compression by the neighboring organs or by intramural lesions. However, submucosal is still recognized and used.

The majority of subepithelial tumors do not cause symptoms and are discovered incidentally during endoscopic or radiologic examinations. The overlying mucosa usually appears smooth and normal at endoscopy. If symptoms do occur, they are nonspecific such as abdominal pain, obstruction, hemorrhage and intussusceptions^[7,8]. Large submucosal neoplasms may outgrow their blood supply, ulcerate through the mucosa, and present as GI bleeding. Firm subepithelial tumors may also present with obstructive symptoms, especially if they are located near the cardia or the pylorus. Subepithelial tumors obstructing the major or minor papilla may cause jaundice or pancreatitis. Pain and weight loss, often associated with large submucosal GI stromal tumors (GISTs), are symptoms that suggest malignancy^[7,9].

Endoscopic ultrasonography (EUS) is the most sensitive imaging procedure for the characterization of subepithelial tumors and it can also diagnose them, especially small ones^[10-14]. Linear echoendoscopes and electronic radial echoendoscopes can be used with color Doppler or power Doppler to assess the vascular signals from subepithelial masses, and thus permit the differentiation of vascular structures from cysts, as well as the assessment of the tumor blood supply^[11,12,15]. Furthermore, Catheter US (miniprbes), if available, may be particularly useful for evaluating subepithelial tumors because they permit sonographic examination of the tumor while the patient is having a diagnostic endoscopy^[16,17]. In addition to being convenient, catheter-type US probes are particularly useful for imaging small subepithelial tumors that are difficult to identify with dedicated echoendoscopes. They are also useful in imaging subepithelial tumors in the colon^[7], however, miniprbes are not useful if the subepithelial lesions are over 2 cm in diameter because of the limited penetrating depths. Therefore, EUS is performed as the second intervention following standard endoscopy^[14]. On the other hand, it is difficult to differentiate exactly between benign and malignant tumors and to gain an accurate picture of histology using EUS. EUS guided fine needle aspiration (EUS-FNA) can be used to provide samples for cytologic or histologic analysis. Therefore, EUS-FNA plays an important role in the clinical management of subepithelial tumors. This review will focus on EUS appearances of common subepithelial GI tract tumors, the diagnostic accuracy of EUS-FNA, and surveillance by EUS, highlighting their relative advantages and their complementary roles in clinical practice.

EUS IMAGING

Optimal imaging of subepithelial lesions requires submersion under water, which sometimes requires repositioning of the patient after the GI lumen has been filled with water. Endosonographically, the wall of the GI tract consists of 5 layers of alternating echogenicity (Figure 1). The 1st

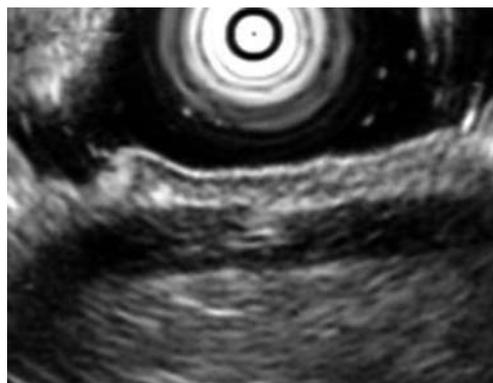


Figure 1 Normal structure of the gastric wall with five endoscopic ultrasonography layers present.

layer is hyperechoic and represents the superficial layer of the mucosa. The 2nd layer is hypoechoic and constitutes of the deep layer of the mucosa, including the muscularis mucosa. The 3rd, hyperechoic layer is the submucosa, the 4th hypoechoic the muscularis propria and the 5th hyperechoic is the serosa/adventitia^[18]. For subepithelial tumors that are intrinsic to the GI wall, it is important to characterize the layer(s) of origin or involvement, the echogenicity of the tumor, the smoothness of the border and any internal feature (Table 1). Inflation of the balloon covering the transducer with water may improve the ultrasonic contact. However, this may compress the GI tract wall and distort the EUS image. This is the reason why the esophagus and duodenum are sometimes visualized with only three layers, with the first hyperechoic layer corresponding to the balloon-mucosa-submucosa together with the submucosa-muscularis-propria interface.

Extrinsic compressions

An enlarged left atrium, left hepatic lobe, and spleen may commonly masquerade as a subepithelial tumor of the esophagus and stomach during endoscopy^[19-21]. A recent international multicenter study reported that the sensitivity and the specificity of extramural compression with endoscopy alone were 87% and 29%, respectively^[2]. The EUS characterization of these organs is useful in the evaluation of extraluminal organs which compress the GI tract lumen, 100% accurate for the differential diagnosis and superior to transabdominal ultrasound or CT scans (Figure 2). Pancreatic pseudocysts or tumors can also be identified when assessing subepithelial tumors by EUS.

Varices

Occasionally, large gastric varices may be polypoid^[3-5,22]. EUS imaging of gastric varices demonstrates characteristic anechoic serpiginous structures in the third hyperechoic layer. Flow within the varix can be demonstrated by Doppler examination.

Lipomas

Lipomas are generally soft, exhibiting a pillow sign when

Table 1 Endoscopic ultrasonography feature of subepithelial tumors

	EUS layer	Organ	EUS appearance
Varices	3rd	Fundus	Anechoic
Lipomas	3rd	Stomach, duodenum, rectum	Hyperechoic, smooth margins
Ectopic pancreas	3rd, 4th (2nd, 5th)	Antrum	Hypoechoic, heterogeneous (possible ductal structure)
Cysts	3rd	Esophagus, stomach, duodenum	Anechoic, compressible, round or oval (3rd or 5th layer are suggestive of duplication cyst)
Inflammatory fibroid polyp	2nd	Antrum, duodenum	Polypoid, hypoechoic, covered by a thin mucosa
Granular cell tumor	2nd, 3rd, 4th	Esophagus	Hypoechoic, oval, heterogeneous,
Leiomyoma	4th (2nd)	Esophagus, cardia	Hypoechoic, round or oval, well demarcated
Schwannoma	4th (3rd)	Stomach	Hypoechoic, round or oval, well demarcated
Gastrointestinal stromal tumor	4th (2nd, 3rd, 5th)	Stomach, small intestine	Hypoechoic, round (large tumors > 4 cm, homogeneous, irregular border, cystic areas of echogenic foci: borderline or malignant)
Leiomyosarcoma	2nd, 4th	Esophagus, stomach	Hypoechoic, heterogeneous, irregular extraluminal border or invasiveness of the neighbouring organs
Carcinoid	2nd, 3rd	Fundus, rectum	Hypoechoic
Lymphoma	2nd, 3rd, 4th	Stomach	Hypoechoic
Metastases	1st-5th or all	All	Hypoechoic, heterogeneous, irregular margin

EUS: Endoscopic ultrasonography.

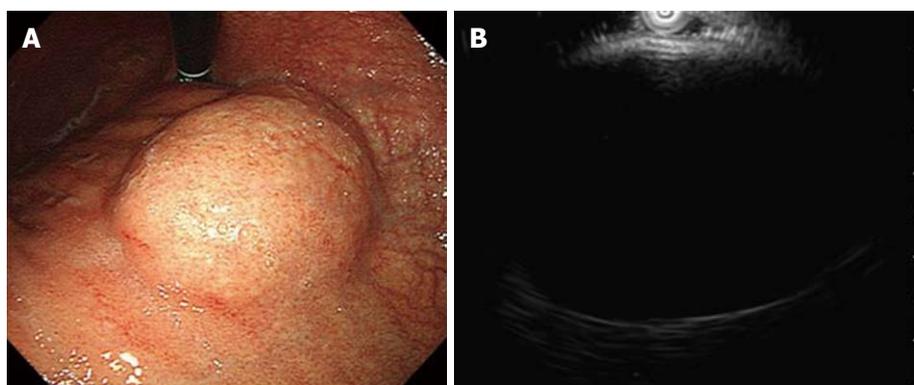


Figure 2 Endoscopic and endoscopic ultrasonography finding of extrinsic compression. A: Endoscopic view of subepithelial lesion of the gastric angle; B: Endoscopic ultrasonography shows an extramural compression by a liver cyst.

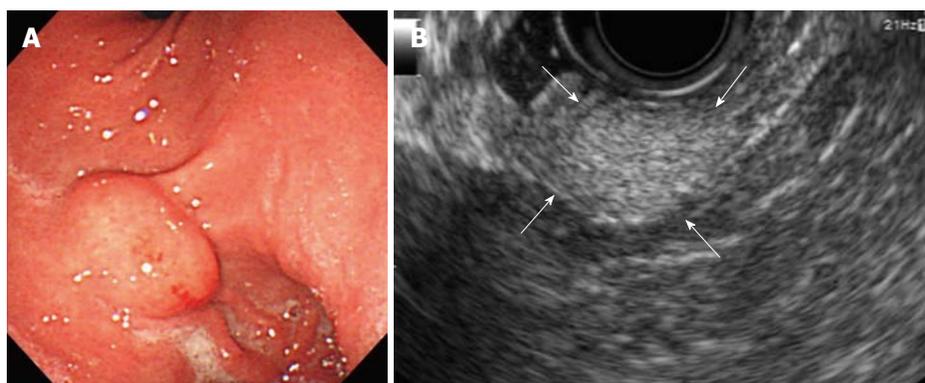


Figure 3 Endoscopic and endoscopic ultrasonography finding of lipomas. A: Endoscopic view of 1.5 cm subepithelial lesion of the anterior part of the gastric angle; B: Endoscopic ultrasonography shows a typical aspect of an 1.6 cm lipoma of the gastric angle (arrows).

probed, and have a yellowish hue. EUS demonstrates lipomas as hyperechoic, homogeneous, well-circumscribed ovoid masses in the 3rd layer (Figure 3)^[3-5].

Cysts/duplication cyst

Cysts typically appear as round or ovoid, smooth anechoic

compressible structures located within the 3rd layer. The wall of the duplication cyst may appear as a three or a five layer structure^[23,24].

Ectopic pancreas

Ectopic pancreas, also called heterotopic or aberrant pan-

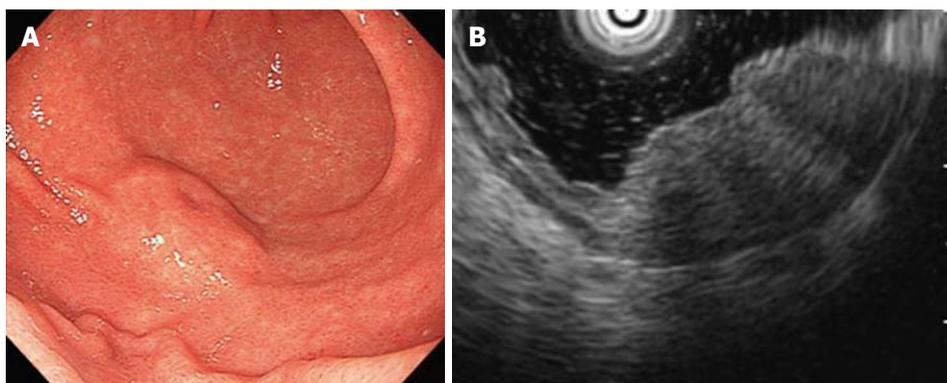


Figure 4 Endoscopic and endoscopic ultrasonography finding of ectopic pancreas. A: Endoscopic view of a subepithelial lesion of the greater curvature of the gastric antrum, covered with normal mucosa, with a central depression; B: Endoscopic ultrasonography shows indistinct margin, hypoechoic tumor developed within the 4th layer.

creas, is defined as pancreatic tissue lying outside its normal location and lacking anatomic or vascular connection with the pancreas. Ectopic pancreas, which usually does not cause symptoms, is found incidentally in the stomach, duodenum, and small intestine. Gastric lesions are discovered in the antrum in 85%-90%, either on the posterior or anterior wall, being more common along the greater curvature. The frequency of ectopic pancreas has been estimated as 1 case per 500 explorations of the upper abdomen or 0.6% to 13.7% of autopsies. The endoscopic appearance of a pancreatic rest is usually that of a firm, slightly irregular nodule in the stomach or elsewhere in the GI tract (Figure 4A). The mucosa over the nodule may have a central depression or dimpling, and ducts may empty into the lumen at this site. Usually, the characteristic EUS demonstrates an indistinct margin, hypoechoic or mixed echogenicity, a heterogeneous lesion, and most locations are within either the 3rd or 4th layers or only in the 3rd layer (Figure 4B)^[3-5].

Granular cell tumor

Granular cell tumors are benign neoplasms. Typically they are located in the distal part of the esophagus with a yellowish appearance; EUS demonstrates a heterogeneous mass with smooth borders located in the 3rd layer^[25,26].

Submucosa cancer/metastases

Subepithelial primary carcinoma, lymphoma or metastases may rarely involve the submucosa. EUS show a hypoechoic, heterogeneous lesion in any or all of the EUS layers^[1,7]. The most frequent primary tumors that result in GI metastases are breast cancer, melanoma and lung cancer^[18].

Gastric inflammatory fibroid polyp

Inflammatory fibroid polyp (IFP) appears as a 2 cm almost-pedunculated polyp on the antrum when analysed using endoscopy. The polyp is covered mostly by normal mucosa, with whitish exudates. The appearance of IFPs on EUS is characterized by an indistinct margin, hypoechoic homogeneous lesion and location within the 2nd and/or 3rd layer with an intact 4th layer^[27].

Mesenchymal tumor

Mesenchymal tumors of the GI tract are classified in three type tumors, GIST, leiomyoma, and schwannoma. Pathologically, most of these tumors are completely or partly composed of spindle cells and have a light microscopic appearance suggestive of smooth muscle or nerve sheath differentiation. These tumors therefore have been presumed to be of smooth muscle origin and often labeled as leiomyomatous or Schwann cell tumors^[28,29]. In recent years, with the advance of immunohistochemical^[30,31] and ultrastructural^[32] studies, it has been shown that most gastric and small intestinal mesenchymal tumors are neither leiomyoma nor schwannoma but GIST derived from the interstitial cells of Cajal. GISTs are the most common GI mesenchymal tumors, now defined as KIT-positive mesenchymal tumors. Leiomyoma tumors demonstrate α -smooth muscle actin, desmin protein on immunohistochemistry, but not KIT expression. Schwannoma tumors demonstrate S100 protein on immunohistochemistry, but not KIT expression^[30-32].

Leiomyoma

Leiomyomas are benign tumors without malignant potential which arise from the muscularis mucosa or the muscularis propria. They are found in the esophagus, but are rare in the stomach and small intestine. EUS demonstrates a hypoechoic, well-circumscribed, homogeneous lesion, developed in the 2nd or 4th layer (Figure 5A).

Schwannoma

The GI schwannoma to GISTs (the most frequent GI SMTs) ratio is approximately 1:50-100^[33]. Therefore, GI schwannomas are rare. The schwannoma appearance is similar to that of leiomyoma or GISTs (Figure 5B)^[34-36].

GIST

GISTs occur most frequently in the stomach (65%) and in the small bowel (25%), rarely in the rectum and the colon. They are exceptional in the esophagus (1%)^[1,7,33-36]. Approximately 10%-30% of GISTs are clinically malignant, although the fact that all GISTs are considered to have some degree of malignant potential should be kept

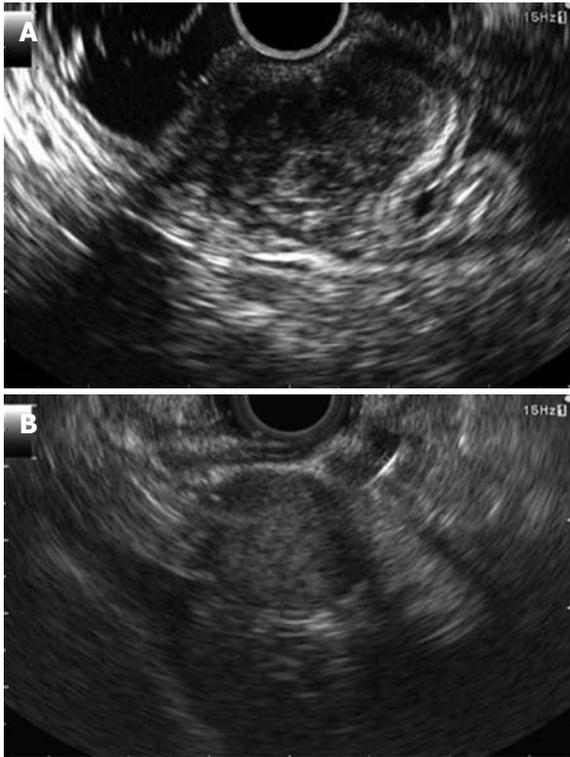


Figure 5 Hypoechoic tumor developed within the 4th layer. A: Leiomyoma of the esophagus (30 mm); B: Schwannoma of the stomach (22 mm).

in mind. GISTs in the small intestine are more aggressive than those located in the stomach^[37]. EUS demonstrates a hypoechoic tumor contiguous with the 4th layer and well-delineated lesion (Figure 6). However recent reports also indicate the presence of GISTs in the 3rd layer^[1-7,34] contiguous with the muscularis mucosa^[38-41].

Differentiation between leiomyomas, schwannomas and GISTs is extremely difficult by imaging modalities, even EUS. Recently, Okai *et al.*^[42] tried to differentiate between 19 GISTs, 3 leiomyomas, and 2 schwannomas by EUS. A complete or incomplete marginal hypoechoic halo was found in more than half of the patients with GISTs and schwannomas, whereas a distinct marginal halo was not seen in leiomyomas. It was also demonstrated that the echogenicities of GISTs were generally low but slightly higher than that of the normal surrounding proper muscle layer, whereas the level of leiomyomas was nearly equal to that of the surrounding normal proper muscle layer and that of schwannoma was extremely low. Accordingly, the difference in echogenicities among the three mesenchymal tumors might reflect the pathologic differences of cellularity and structural components of the tumor. Although the number of patients enrolled in their study was too small to make a comparison, these EUS findings may be helpful for differentiation between these gastric mesenchymal tumors.

DIFFERENTIAL DIAGNOSIS

We have described the EUS appearance of each subepithelial tumor. Determination of the histologic layer and the echotexture of the lesion can significantly narrow the

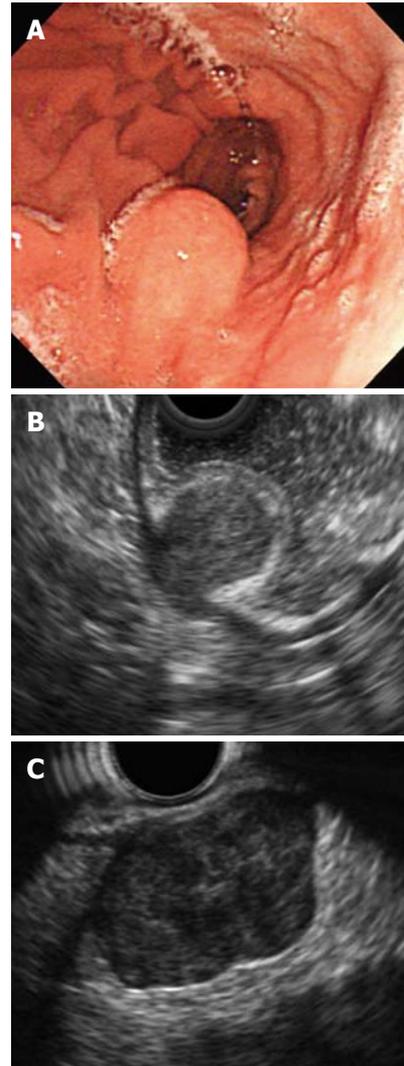


Figure 6 Endoscopic and endoscopic ultrasonography finding of gastrointestinal stromal tumor. A: Endoscopic view of subepithelial lesion of the posterior side of the greater curvature of the gastric body; B: Endoscopic ultrasonography shows hypoechoic, homogeneous 2 cm tumor developed within the 4th layer (low risk gastrointestinal stromal tumor of the stomach); C: 35 mm hypoechoic, heterogeneous, lobulated submucosal lesion with exogastric growth developed within the 4th layer (high risk gastrointestinal stromal tumor of the stomach).

differential diagnosis. However, the differential diagnosis of a hypoechoic 4th layer lesion is broad and includes benign, premalignant, and malignant lesions^[43]. EUS performs better than other modalities in evaluating GI subepithelial lesion, but the diagnostic accuracy of EUS imaging alone has been shown to be as low as 43% in subepithelial lesions with 3rd and 4th layers^[2]. Hwang *et al.*^[2] prospectively evaluated the performance characteristics of EUS in the diagnosis of GI subepithelial masses. Most incorrect EUS diagnoses occurred with hypoechoic 3rd and 4th layer masses with two of the cases demonstrating malignancies. One case was an invasive squamous cell carcinoma invading the esophagus that on EUS coincided with the 4th EUS layers and was hypoechoic with internal hyperechoic foci, and had an irregular appearing margin. The 2nd case was a gastric adenocarcinoma with EUS demonstrating the lesion coincided with the 3rd EUS layers and was

hypoechoic with internal hyperechoic foci, with smooth margins. Therefore, hypoechoic lesions of the 3rd and the 4th EUS layer were considered. Histologic confirmation by using endoscopic submucosal resection or EUS-FNA should be obtained when possible.

DIFFERENTIAL DIAGNOSIS BETWEEN BENIGN AND MALIGNANT TUMORS

In 1992, Rösch *et al.*^[10] compared the EUS features of benign with malignant tumors in SMT of the upper GI tract, and concluded there was no single reliable criterion that would enable a differential diagnosis. However, they proposed larger, echo-inhomogeneous masses with irregular outer borders are suggestive of malignancy whereas smaller (< 3 cm) echo-homogeneous subepithelial tumors with a smooth margin are likely to be benign. Chak *et al.*^[16] found that features predictive of malignant subepithelial tumors were diameter > 4 cm, irregular extraluminal border, echogenic foci, and cystic space. When the presence of at least two of the following three features were used as malignancy determinants, sensitivity ranged from 80% to 100%, depending on the endosonographer. Recently, it has been considered that subepithelial tumors are mostly gastric GISTs, and there are some reports that assess EUS characteristics for predicting the malignant potential of GISTs^[44]. Tumor size (more than 3 to 5 cm depending on the study) was the most the important. The predictive value of other features, such as irregular borders, echogenic foci, cystic spaces, ulcerated mucosae, lymph nodes and exogastric growths with malignant pattern, is unclear (Figure 6C)^[1,7,34,36,42]. However, those studies are retrospective and included small numbers of tumor samples, thus somewhat conflicting results that have not been validated in prospective series have been obtained. Therefore, larger study numbers and prospective multicenter studies are needed.

With the use of EUS, subepithelial lesions can be further characterized by demonstrating the location of the mass, size, and echogenicity^[8,20,21]. Furthermore, if a lesion is intramural, EUS can demonstrate the histologic layer of origin within the GI wall. Determination of the histologic layer and the echotexture of the lesions can significantly narrow the differential diagnosis and may be diagnostic in some cases.

In addition, studies have shown interobserver agreement to be poor, and the diagnostic accuracy to depend heavily on the experience of the endosonographer^[45].

EUS-FNA

EUS-FNA is a safe and effective technique for obtaining samples for cytologic or histologic examinations either as a primary procedure or in cases where biopsy techniques have failed (Figure 7). Williams *et al.*^[46] reported that the overall sensitivity, specificity and accuracy of EUS-FNA for the diagnosis of malignancy were 85%, 100% and 89%, respectively, for lymph nodes; 82%, 100%, and 85%,

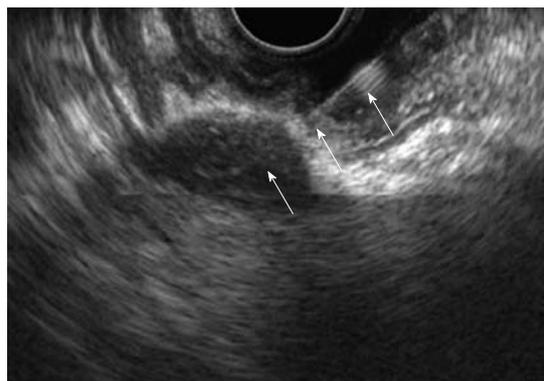


Figure 7 Endoscopic ultrasonography-guided fine needle aspiration of a 20 mm hypoechoic subepithelial tumor of the stomach, using a 25-gauge (arrows).

respectively, for pancreatic lesions; 88%, 100%, and 90%, respectively, for perirectal masses; and 50%, 25%, and 38%, respectively, for intramural lesions. They suggested that when providing accurate diagnosis of pancreatic and perirectal malignancies, the technique is less useful for intramural lesions. Similarly, Wiersema *et al.*^[47] reported that EUS-FNA sensitivity, specificity, and accuracy were 92%, 93%, and 92%, respectively, for lymph nodes, 88%, 95%, and 90%, respectively, for extraluminal masses, and 61%, 79%, and 67%, respectively, for GI wall lesions. Therefore, from those previous reports, EUS-FNA for subepithelial tumors has not had high reliability and sufficient diagnostic accuracy. Recently, there are some reports that the diagnostic yield of EUS-FNA depends on site, size and characteristics of the tumor as well as technical and procedural factors (type of needle, biopsy technique and material processing). Other weighting factors include expertise, training and interaction between the endosonographer and cytopathologist^[41,44]. Another factor that appears to affect the accuracy of EUS-FNA is the presence of an on-site pathologist since, in most studies that reported high levels of EUS-FNA diagnostic accuracy, a cytopathologist was present during the procedure to ensure that adequate cytological specimens were obtained^[48,49]. When a cytopathologist is present during EUS-FNA, it appears that the diagnostic yield increases by 10%^[50,51]. Vander Noot *et al.*^[52] reported that the sensitivity, specificity, and diagnostic accuracy of EUS-FNA on-site cytological evaluation during FNA procedure in diagnosing GI tract neoplastic lesions were 89%, 88%, and 89%, respectively. When specimens with suspicious cytologic diagnoses were classified as being positive for malignancy the sensitivity and specificity became 96% and 81%, respectively, and the diagnostic accuracy improved to 92%. It is noteworthy that the results of this study were better than those reported in the literature. They suggested that one possible explanation is a cytopathologist is always present on site to assess specimen adequacy and to determine whether additional material should be obtained for ancillary studies, such as flow cytometric and immunocytochemical analyses. Klapman *et al.*^[53] observed that an EUS center with on-site cytologic

interpretation had significantly lower rates of unsatisfactory specimens and a higher rate of positive or negative cytologic diagnoses for malignancy compared with an EUS center without on-site cytologic interpretation. False-positive diagnosis of malignancy in EUS-guided biopsy is also rare. Jenssen *et al*^[54] reported that the high prognostic and therapeutic relevance of the cytopathological diagnoses resulting from EUS-guided biopsy calls for a shared responsibility of an endosonographer and a cytologist.

For EUS-guided biopsy predictors of malignancy GIST, several factors have been studied in an effort to provide preoperative cytologic risk assessment. Ando *et al*^[55] reported that the presence of mitoses in specimens collected by fine-needle aspiration was associated with malignant GISTs. However, mitoses are seldom seen on smears. The same study also found that a high Ki-67 labeling index, a protein marker of cell proliferation, was significantly associated with malignant lesion. Okubo *et al*^[56] reported that the presence of an MIB-1 labeling index of more than 5% indicated a high-grade malignancy, with a diagnostic accuracy of 85.7%. KIT and PDGFRA mutation analysis has been proven possible using EUS-guided cell block specimens^[57-59]. As KIT mutation analysis has prognostic importance and can be predictive of response to treatment^[60-63], its preoperative determination may help to guide the approach to treatment in locally advanced and metastatic disease. The clinical role of such testing is currently being investigated.

EUS-FNA is a safe and precise non-invasive procedure for the diagnosis of subepithelial upper GI tract tumors. Furthermore, utilization of sampling material by EUS-FNA has been expected to improve treatment and management in clinical practice. However, recently, two cases of tumor seeding after percutaneous biopsy for malignant GIST were reported^[48,49]. Although there have been no reports of seeding after EUS-FNA for malignant subepithelial tumors, obtaining samples by EUS-FNA from small tumors and from tumors with exogastric growth may result in high peritoneal seeding risk because the FNA needle may easily penetrate not only the tumor but also the whole gastric wall, reaching the peritoneal side and seeding tumor cells along the way. Therefore, during sampling by EUS-FNA in such cases we must pay attention to the needle in order not to penetrate the tumor.

SURVEILLANCE BY EUS

For management of subepithelial tumors, EUS is recommended for subepithelial tumors more than 1 cm in diameter, and histologic evaluation, such as EUS-FNA, is recommended for hypoechoic subepithelial tumors less than 3 cm in diameter. Surgery is recommended for subepithelial tumors more than 3 cm in diameter^[64]. Although these procedures are helpful in a categorizing a lesion, they cannot absolutely determine the type of lesion or determine if a lesion is benign or malignant^[7]. The American Gastroenterological Association recommends periodic endoscopic or endosonographic follow-up or surgical re-

section for small (less than 3 cm), hypoechoic, 3rd and 4th layer masses, which are most likely GISTs^[22]. GISTs are most commonly identified intramural subepithelial tumors in the upper GI tract^[7]. Small GISTs (less than 2 cm) have very low malignant potential according to the classification system proposed by the National Institutes of Health Consensus Conference^[65]. The recommended duration of follow-up is very variable. Hwang *et al*^[43] suggested a 1 year follow-up interval and suggested that the interval between surveillance examinations be extended if the lesion remained unchanged for 2 consecutive follow-up EUS. Guidelines in Japan recommended endoscopic examination once or twice per year for subepithelial lesions less than 2 cm in diameter^[66].

CONCLUSION

EUS imaging is essential for the evaluation of subepithelial tumors, because EUS performs better than other modalities in evaluating GI subepithelial lesions. However, the diagnostic accuracy of EUS imaging alone has been shown to be low in subepithelial lesions with a 3rd and 4th layer. In the case of hypoechoic lesions of the 3rd and the 4th EUS layers that are more than in 1 cm diameter, histologic confirmation by using EUS-FNA should be obtained when possible. Although EUS-FNA is a safer and more accurate non-invasive method than other methods of getting samples of the subepithelial tumor, even EUS-FNA is not always accurate enough to determine malignancy, especially determination of malignant GISTs. Furthermore improvements in endoscopic technology are expected to be more useful modalities in differential diagnosis and discrimination between benign and malignant subepithelial tumors.

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