

# Endoscopic Ultrasound for Evaluating Subepithelial Duodenal Lesions

Martín Alonso Gómez Zuleta, MD.<sup>1</sup>

<sup>1</sup> Internist and Gastroenterologist at UGEC, Hospital El Tunal. Associate Professor of Gastroenterology at the National University of Colombia in Bogotá, Colombia

Received: 27-10-14  
Accepted: 06-04-15

## Abstract

Subepithelial lesions (SE) are rare. They are found in only one out of every 300 endoscopies (0.36%). Of these, only 10% are located in the duodenum. When endoscopy does detect a subepithelial lesion in the duodenum it is important to make an initial description of its size, shape, color, mobility, and consistency to touch. Next, a closed biopsy sample must be taken with pincers and analyzed to detect whether it is a cyst and whether it has a pillow sign which is highly suggestive of lipoma. When the lesion is neither a cyst nor a lipoma, endoscopic ultrasound is indicated, especially if the lesion is larger than one centimeter.

## Keywords

Subepithelial, duodenum, EUS, GIST, neuroendocrine.

Upper digestive tract subepithelial tumors (SETs) are so rare that only one in 300 endoscopies can find a SET (about 0.36%) (1). Recent studies have shown that finding these tumors is a qualitative indicator for early gastric cancer detection (2). The evidence available in the literature on SETs is very poor. Most studies are based on case series or expert opinions. One recent series looked at 129 subepithelial lesions of which 98 were located in the stomach, 14 in the esophagus and only 11 in duodenum (8.5%) (3). In general most SETs are considered to be asymptomatic. Sixty percent are located in the stomach, 30% in the esophagus, and 10% in the duodenum (4-6).

## HOW SHOULD THESE LESIONS BE APPROACHED?

As soon as duodenal SET is found during endoscopy, evaluation of the tumor should begin. Initially describe its size, shape, color, mobility and touch. Finally, describe its consistency. This can be evaluated with the closed biopsy forceps

allowing us to detect if it is cystic, firm or has the sign of the pillow which is highly suggestive of lipoma. If the lesion's mucosa has slight irregularities and a central depression, it is suggestive of an ectopic pancreas. Usually cysts or varices have smooth symmetrical mucosa while GISTs may have slight ulceration and are firm and mobile (7).

The next step is to use an imaging technique to evaluate the lesion. Endoscopic ultrasound (EUS) is the technique of choice which has replaced other techniques. This test is indicated only if the lesion measures more than one cm. If it is smaller, the patient should be scheduled for a follow-up endoscopy one year later (8). The accuracy of EUS to differentiate extraluminal compression of a subepithelial tumor is over 95% which is better than other imaging techniques such as conventional ultrasound and CT scans which are no longer mentioned in the literature (9, 10).

We propose evaluating duodenal lesions with EUS as follows: first locate the echoic layer which contains the lesion, then assess whether it is hypoechoic, isoechoic or hyperechoic.

## Second Echo Layer

The **Second Echo Layer** is the deepest part of the mucosa, lamina propria and muscularis mucosa. Lesions rarely originate in this layer, but those that do are usually hypoechoic.

### **Hypoechoic lesions**

Most tumors that originate in this layer are muscular, usually leiomyomas, however these tumors are most often located in the muscular layer (Fourth Echo Layer).

*Neuroendocrine tumors* (NETs) usually grow in the second layer and extend to the Third Echo Layer. These tumors typically appear to be or reticular or erythematous in the mucosa.

### **Anechoic lesions**

Specifically inclusion or retention cysts, can be seen in this layer.

## Third Echo Layer

The **Third Echo Layer** is a strip of tissue that appears to be hyperechoic to ultrasonography. Numerous tumors can originate in this layer.

*Hyperechoic lesions* are found in this layer. Lipomas are most frequently found (Figure 1). They are homogeneous hyperechoic lesions that usually have the pillow sign when pressed with endoscopic forceps. Hamartomas of Brunner's glands are also hyperechoic lesions in the Third Layer, but, unlike lipomas, they can also be found in the Second Layer. They are homogeneous and within them can be found an anechoic image like a dilated duct.

*Neurofibromas* are usually hyperechoic and originate in the submucosa or muscularis propria.



**Figure 1.** The typical endoscopic image of a subepithelial lesion, in this case a lipoma, can be seen in the lower right corner.

A *hypoechoic lesion* in this layer may be an ectopic or aberrant pancreas. Usually these lesions are heterogeneous, and you can occasionally see an anechoic ductal structure in the center that may be a duct. In the endoscopy you will see a lesion with a depressed center which may be in duodenum but most are in the antrum.

We can also find hypoechoic NETs although they are not subepithelial tumors themselves since they are not mesenchymal by nature, but rather are neuroendocrine tumors. They are usually small (less than one cm) hypoechoic (but more echoic than muscle) and settle in the deep mucosa (Second Echo Layer) which usually makes biopsies and histological study possible.

*Gastric lymphomas* may be hypoechoic or hyperechoic depending on the submucosa. Other less common lesions that are hypoechoic and depend on the Fourth Layer are neurofibromas and metastases which are very rare in the duodenum.

When *anechoic lesions* are observed in this layer, we must think about vascular structures or cysts. Doppler echo helps assess whether there is flow which helps differentiate them. Cysts seen in the wall of the gastrointestinal tract are usually benign and may be inclusion cysts, duplication cysts or retention cysts.

## Fourth Echo Layer

The **Fourth Echo Layer** is the muscularis, so most tumors in this layer are of muscular origin.

*Hyperechoic lesions* are rare in this layer but may be lymphomas, neurogenic tumors or metastases.

Most *hypoechoic lesions* in this layer are stromal tumors (GIST) which, although more common in the stomach, can also occur in the duodenum (Figures 2 and 3). Other lesions that may have this appearance are metastases (lung or breast), glomus tumors and schwannomas. Lymphomas can also be found in this layer but are usually associated with the outermost layers.

In our unit we use an alpha numeric descriptor for diagnosis when evaluating subepithelial lesions because the correlation of the endoscopic ultrasound image with the final histological result is not optimal (11). The first letter is C for *capa* (Spanish for layer) which is followed by the number of the layer in which the lesion is located (1 to 5). Next follows the letter E for echogenicity which is followed by an echogenicity rating from = to 3 (0; anechoic 1; hypoechoic 2; isoechoic, 3; hyperechoic). If, for example, a diagnosis includes the notation "C4E1", it means that the lesion is in the Fourth Layer and is hypoechoic. The differential diagnosis must now be made among GISTs, leiomyomas or even schwannomas.

The natural history of a SET depends on its histologic type. If it appears to be a benign lesion such as a lipoma,

Brunner hamartoma or ectopic pancreas, it will tend not to change over time and will not require monitoring. Nevertheless, for potentially malignant lesions such as GISTs, follow/up is a requirement. One study followed 49 patients with GISTs under 3cm for an average of 30 months and found that tumors increased 25% in size in only five patients. Those tumors were resected (11). On the other hand, NETs tend to grow and metastasize, so all of them should be resected regardless of size. A Japanese study evaluated tumors that had already metastasized and found that they measured only 14.5mm on average (12).



**Figure 2.** Ulcerated sub epithelium in the second portion of the duodenum which was referred for EUS.



**Figure 3.** EUS shows a hypoechoic lesion in Layer 4 corresponding to a GIST.

## WHEN SHOULD EUS GUIDED FINE NEEDLE ASPIRATION BE PERFORMED FOR SETS?

There is no consensus in the literature about puncturing a SET to obtain a biopsy sample, especially when the lesion is located in the duodenum. Although the risk is low, the results are not optimal especially with small lesions. Although there are no studies that specifically focus on EUS guided fine needle aspiration of duodenal lesions, a study by Brugge et al. has shown showed that the yield of EUS without fine needle aspiration of lesions smaller than 2cm is only 45% while EUS guided fine needle aspiration to allow histology is the gold standard (13).

It is generally considered that EUS guided fine needle aspiration may be indicated for lesions of the muscularis propria, especially if they are hypoechoic or larger than two cm in size. Since it has been seen that lesions in other layers and lesions that are not hypoechoic are unlikely to be malignant, yet another article by the same author has shown that EUS guided fine needle aspiration of GISTs in the duodenum produce much poorer sample quantities than does the same procedure in the stomach (14).

EUS guided fine needle aspiration's performance in subepithelial lesions varies from 43.3% to 78.4% (15, 16). In terms of biopsy samples, subepithelial lesions produce 17% to 38% (17). The aforementioned series by Buscaglia et al. compared performance of jumbo biopsy to EUS guided fine needle aspiration for 129 subepithelial lesions and reported that the jumbo biopsies have a yield of 58.9% and that the yield of EUS guided fine needle aspiration was 45.1%. Results for jumbo biopsies were better than those of EUS guided fine needle aspiration biopsies for Third Layer lesions (65.1% vs 35.5%) and worse for Fourth Layer lesions (40.0% vs. 57.1%) (3). Unfortunately, 34.9% of the patients had significant bleeding from the biopsies. This work suggests that jumbo biopsies should be used for Third Layer lesions and that fine needle EUS guided fine needle aspiration should be used for the Fourth Layer. Another recent work by the group of Costamaña performed fine needle aspiration guided by a new frontal endoscope with ultrasound on 121 patients with subepithelial lesions. Thirteen lesions were in the esophagus, 96 in the stomach 96, 10 in the duodenum, and two in the rectum. The performance was excellent even for the lesions in the duodenum. Sensitivity was 93.4% (113/121) and specificity was 100% (18). This suggests that EUS guided fine needle aspiration for duodenal lesions could be improved with this equipment because it allows a better approach than does conventional equipment.

EUS guided fine needle aspiration is very safe and has low risks. Prophylactic antibiotics are recommended only for cystic lesions. The patient should be under observation for at least one hour following the procedure. One study has collected 1,135 patients who had aspiration biopsies taken of SETs at 219 hospitals. Of the total number of lesions, 73.5% were located in the stomach, 13.4% in the esophagus, 8.2% in the duodenum, and 4.9% elsewhere. There were 93 duodenal lesions of which six were GISTs. This work showed that only five patients (0.44%) had severe bleeding requiring transfusion or endoscopic treatment. Only one of the five was a duodenal lesion. There were no perforations, and only one patient (0.09%) died within 30 days of EUS guided fine needle aspiration, but the death was not associated with bleeding or perforation (19).

### **WHEN SHOULD SETS BE TREATED? FOR WHOM SHOULD THEY BE TREATED? AND, HOW SHOULD THEY BE TREATED?**

SETs should be treated if there is suspicion of malignancy or if the lesions are symptomatic. Duodenal lesions such as lipomas, ectopic pancreas, and Brunner's hamartomas that are considered to be benign do not require treatment if they are not producing symptoms such as bleeding or obstruction. Lesions with malignant potential such as NETs, lymphomas and GISTs require treatment. Patients with duodenal NETs under 1 cm can be treated with endoscopic resection with great effectiveness and safety. This can be done with one loop or placement of a band. Lesions which are one to 2 cm can be resected with advanced surgical techniques such as wedge resection which limits the extent of the surgery or dissection to the submucosa. Use of these techniques depends on the experience of personnel at the medical center (22). Lesions larger than 2 cm should be managed surgically with lymphadenectomy. The technique will depend on location and experience (20-23).

Asymptomatic GISTs less than 2 cm should be endoscopically observed every six to twelve months and examined with EUS once a year. Alternately, EUS guided fine needle aspiration biopsy can be used to establish whether there is a risk of malignancy if there are irregularities or cystic spaces within the GIST. According to the pathology results, the patient should either undergo surgery or continue to be monitored. A GIST over 2cm should be resected because of the risk of malignancy (24, 25).

### **WHAT IS THE FOLLOW-UP FOR SETS?**

Suspicious asymptomatic GIST lesions less than 2 cm should be examined endoscopically every 6 months and annually with endoscopic ultrasound. If a lesion has

irregular borders, or cystic spaces within it, it should be punctured to establish the prognosis (24). All duodenal NETs should be resected. Benign lesions do not warrant monitoring since they are unlikely to change.

The decision to manage SETs surgically or endoscopically depends on the type of lesion and its size. If the lesion is a NET, it should be resected endoscopically when it is less than one cm. If it is between 1 and 2 cm, submucosal dissection may be feasible (26), or laparoscopic wedge resection may be the best option (22). Lesions larger than 2 cm should be resected by surgery with lymphadenectomy (23).

On the other hand, GISTs that are smaller than 2cm may be observed or punctured. Puncture allows determination of proliferation index Ki 67 which can establish the prognosis. Lesions larger than 2cm must be resected because of the risk of malignancy (24). Every day additional studies of GIST lesions located in the Fourth Layer or muscularis that have been endoscopically resected appear. This may become a very good treatment option in the future (27).

In short, subepithelial lesions less than one cm do not warrant echoendoscopy but should rather be followed-up endoscopically once a year. If the lesion is larger, it is mandatory to perform endosonography. If the lesion is small and is located in the first, second or third layer, it can be followed up in one year. If the lesion is large (2-3cm) especially if it is hypoechoic or is located in the Fourth Layer, it is ideal to EUS-guided puncture. If it is established that it is a benign lesion, it should be observed again in 6 months without EUS guided fine needle aspiration. If it has not grown, further follow-up is not needed, but if it is malignant or has malignant potential, treatment is recommended. If the lesion is larger than 3 cm, it should be resected endoscopically or surgically without the necessity of EUS guided fine needle aspiration.

### **REFERENCES**

1. Sonnenberg A, Amorosi SL, Lacey MJ, et al. Patterns of endoscopy in the United States: analysis of data from the Centers for Medicare and Medicaid Services and the National Endoscopic Database. *Gastrointest Endosc.* 2008;67(3):489-96.
2. Park CH, Kim B, Chung H, Lee H, Park JC, Shin SK, et al. Endoscopic quality indicators for esophagogastroduodenoscopy in gastric cancer screening. *Dig Dis Sci.* 2015;60(1):38-46.
3. Buscaglia J, Nagula S, Jayaraman V, Robbins D, 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;75:1147-52.
4. Papanikolaou IS, Triantafyllou K, Kourikou A, et al. Endoscopic ultrasonography for gastric submucosal lesions. *World J Gastrointest Endosc.* 2011;3(5):86-94.

5. Muenst S, Thies S, Went P, et al. Frequency, phenotype, and genotype of minute gastrointestinal stromal tumors in the stomach: an autopsy study. *Hum Pathol.* 2011;42(12):1849-54.
6. Jenssen C, Dietrich CF. Endoscopic ultrasound in subepithelial tumors of the gastrointestinal tract. En: Dietrich CF, editor. *Endoscopic ultrasound: an introductory manual and atlas.* New York: Thieme; 2006. p. 121-54.
7. Souquet JC, Bobichon R. Role of endoscopic ultrasound in the management of submucosal tumours in the esophagus and stomach. *Acta Endoscop.* 1996;26:307-12.
8. 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(2):202-8.
9. Boyce GA, Sivak Jr. MV, Rosch T, et al. Evaluation of submucosal upper gastrointestinal tract lesions by endoscopic ultrasound. *Gastrointest Endosc.* 1991;37:449-54.
10. Caletti G, Zani L, Bolondi L, et al. Endoscopic ultrasonography in the diagnosis of gastric submucosal tumor. *Gastrointest Endosc.* 1989;35:413-8.
11. Bruno M, Carucci P, Repici A, Pellicano R, Mezzabotta L, Goss M, et al. The natural history of gastrointestinal subepithelial tumors arising from muscularis propria: an endoscopic ultrasound survey. *J Clin Gastroenterol.* 2009;43(9):821-5.
12. Soga J. Early-stage carcinoids of the gastrointestinal tract: an analysis of 1914 reported cases. *Cancer.* 2005;103:1587-95.
13. Karaca C, Turner BG, Cizginer S, Forcione D, Brugge W. Accuracy of EUS in the evaluation of small gastric subepithelial lesions. *Gastrointest Endosc.* 2010;71(4):722-7.
14. Sepe PS, Moparty B, Pitman MB, Saltzman JR, Brugge WR. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. *Gastrointest Endosc.* 2009;70(2):254-61.
15. Mekky MA, Yamao K, Sawaki A, et al. Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors. *Gastrointest Endosc.* 2010;71:913-9.
16. Hoda KM, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. *Gastrointest Endosc.* 2009;69:1218-23.
17. Sepe PS, Moparty B, Pitman MB, et al. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. *Gastrointest Endosc.* 2009;70:254-61.
18. Larghi A, Fuccio L, Chiarello G, Attili F, Vanella G, Paliani GB, et al. Fine-needle tissue acquisition from subepithelial lesions using a forward-viewing linear echoendoscope: *Endoscopy.* 2014;46(1):39-45.
19. Hamada T, Yasunaga H, Nakai Y, Isayama H, Horiguchi H, Matsuda S, et al. Rarity of severe bleeding and perforation in endoscopic ultrasound-guided fine needle aspiration for submucosal tumors. *Dig Dis Sci.* 2013;58(9):2634-8.
20. Waisberg J, Joppert-Netto G, Vasconcellos C, Sartini GH, Miranda LS, Franco MI. Carcinoid tumor of the duodenum: a rare tumor at an unusual site. Case series from a single institution. *Arq Gastroenterol.* 2013;50(1):3-9.
21. Tai WP, Yue H. Endoscopic mucosa resection of a duodenum carcinoid tumor of 1.2 cm diameter: a case report. *Med Oncol.* 2009;26:319-21.
22. Tsujimoto H, Ichikura T, Nagao S, Sato T, Ono S, Aiko S, et al. Minimally invasive surgery for resection of duodenal carcinoid tumors: endoscopic full-thickness resection under laparoscopic observation. *Surg Endosc.* 2010;24:471-5.
23. Zyromski NJ, Kendrick ML, Nagorney DM, Grant CS, Donohue JH, Farnell MB, et al. Duodenal carcinoid tumors: how aggressive should we be? *J Gastrointest Surg.* 2001;5:588-93.
24. Iorio N, Sawaya RA, FriedenberG FK. Review article: the biology, diagnosis and management of gastrointestinal stromal tumours. *Aliment Pharmacol Ther.* 2014;39(12):1376-86.
25. Chok AY, Koh YX, Ow MY, Allen JC Jr, Goh BK. A systematic review and meta-analysis comparing pancreaticoduodenectomy versus limited resection for duodenal gastrointestinal stromal tumors. *Ann Surg Oncol.* 2014;21(11):3429-38.
26. Matsumoto S, Miyatani H, Yoshida Y, Nokubi M. Duodenal carcinoid tumors: 5 cases treated by endoscopic submucosal dissection. *Gastrointest Endosc.* 2011;74:1152-6.
27. Huang ZG, Zhang XS, Huang SL, Yuan XG. Endoscopy dissection of small stromal tumors emerged from the muscularis propria in the upper gastrointestinal tract: Preliminary study. *World J Gastrointest Endosc.* 2012;4(12):565-70.