American Journal of Gastroenterology Publish Ahead of Print

DOI: 10.14309/ajg.0000000000002530

Guidelines in Practice: The Diagnosis and Management of Gastrointestinal Subepithelial Lesions

Brian C. Jacobson, MD, MPH, FACG (Massachusetts General Hospital and Harvard Medical School, Boston, MA)
Vanessa M Shami, MD, FACG (University of Virginia, Charlottesville, VA)

Potential competing interests: None

The American College of Gastroenterology recently published a guideline on the diagnosis and management of gastrointestinal subepithelial lesions (SELs).[1] The recommendations within the guideline were developed using GRADE methodology and utilized a comprehensive literature search of EMBASE, PubMed, Cochrane Reviews, and the Cochrane Central Register of Controlled Clinical Trials from 2000 to December 31, 2020. The recommendations were accompanied by 'key concepts', or statements to which the GRADE process had not been applied but included guidance on clinical management based on expert opinion. What follows is a representative clinical case meant to familiarize the reader with the guidelines and demonstrate how they might be applied in practice.

Clinical Scenario:

A 60-year-old man undergoes EGD to investigate dyspepsia. His past medical history is significant only for an episode of gallstone pancreatitis complicated by a splenic vein thrombus, and subsequent cholecystectomy 10 years prior to this EGD. The endoscopy reveals antral gastritis and biopsies are taken. There is an incidentally noted 1.8 cm subepithelial lesion (SEL) at the gastroesophageal junction, noted to cross from esophagus to stomach (Figure 1).

Clinical Decision #1: Should the endoscopist take a bite-on-bite biopsy to diagnose the subepithelial lesion?

Bite-on-bite biopsy, where the endoscopist takes repeated biopsies from the same site in an effort to unroof the mucosa and sample an underlying subepithelial lesion, is commonly done in practice. Interestingly, the literature supporting this practice consists mainly of studies in which endoscopic ultrasound (EUS) was also performed, limiting the generalizability of this practice when EUS is not part of the evaluation.[2] Because of this, the guideline authors do not suggest bite-on-bite biopsies in the evaluation of SEL before EUS (a conditional recommendation based

on very low-quality evidence). In this particular case, EUS would be useful in excluding the possibility that the SEL is an isolated gastric varix as a result of the patient's splenic vein thrombus. Bite-on-bite of any lesion where the presence of a varix is a possibility should be avoided.

Clinical Decision #2: If not a varix, should the lesion be resected, or should a pre-resection diagnosis be rendered?

The guideline puts forth a 'key concept' that SELs causing symptoms or anemia can be resected without first obtaining a diagnosis as the diagnosis is unlikely to alter management. One potential exception cited was a large gastrointestinal stromal tumor (GIST) for which pre-resection neoadjuvant imatinib might be used to shrink the tumor. In this case, given the lack of symptoms, a diagnosis may better clarify management.

Clinical Decision #3: Should the patient undergo EUS or cross-sectional imaging (e.g. CT) for diagnosis?

Case series show EUS has greater accuracy than CT for making a pre-resection diagnosis of gastric SELs (64% vs 51%, respectively) and CT has difficulty even identifying small (e.g. <11mm) SELs.[3, 4] The data suggest that while cross-sectional imaging may detect lesions identified incidentally during EGD, there is little diagnostic gain over EUS. For this reason, the guideline suggests EUS be performed preferentially compared with endoscopy or contrast-enhanced cross-sectional imaging for the diagnosis of non-lipomatous SELs, a conditional recommendation based on very low-quality evidence. Lipomas represent a unique situation wherein EUS is not required for an accurate diagnosis. Lipomas can present anywhere within the GI tract, have a slightly yellow appearance, and demonstrate a "pillow sign", or indentation when pressed with a biopsy forceps. In one small prospective study, endoscopy alone had a 99% specificity for the diagnosis of lipomas based on the presence or absence of a pillow sign, although the sensitivity was low (40%).

Clinical Scenario Continued

The patient's gastric biopsies reveal Helicobacter pylori and his dyspepsia resolves with eradication therapy. He subsequently undergoes EUS which reveals a 1.8 cm hypoechoic mass in the muscularis propria of the distal esophagus/cardia of the stomach (Figure 2).

Clinical Decisions #4 and #5: Should the lesion be sampled for pathologic diagnosis, and if so, how?

The guideline suggests EUS be coupled with tissue acquisition to improve the diagnostic accuracy of SELs, a conditional recommendation based on very low-quality evidence. EUS appearance alone is not sufficient to render a diagnosis in non-lipomatous lesions. The addition of tissue acquisition increases the diagnostic accuracy from a range of 30%–50% to a range of 73%–84%. One study found that interobserver agreement was good to excellent for cysts and lipomas but only poor to fair for other SELs including leiomyomas and vascular lesions.[5]

Tissue acquisition can be done by fine needle aspiration (FNA) or fine needle biopsy (FNB); the difference being the size of the specimen and how samples are processed. FNA samples are typically

processed as smears by cytological methods while FNB samples are processed as core biopsies by histopathological methods. FNA may be coupled with rapid on-site evaluation (ROSE) where cytology personnel can advise in real time on whether a sample is adequate to ultimately render a diagnosis or whether further FNA samples should be obtained. The guideline suggests EUS-FNB alone or EUS-FNA with ROSE sampling of solid non-lipomatous SELs compared with EUS-FNA without ROSE as a conditional recommendation based on low-quality evidence.

A meta-analysis of 10 studies (including 6 randomized trials) with a total of 669 patients compared EUS-FNA with FNB of SELs.[6] FNB yielded higher rates of adequate samples and histologic cores, yielded greater diagnostic accuracy, and required fewer numbers of needle passes. However, when ROSE was available in these studies, no significant differences between FNA and FNB were noted. Therefore, FNA without ROSE may be associated with need for repeat EUS and should be avoided.

Clinical Scenario Continued

The EUS is performed at a facility where rapid on-site evaluation (ROSE) by cytopathology is not available. Fine needle biopsy is performed with a 22-guage forked-tip needle (Figure 3). The diagnosis of GIST is made based on pathology and immunohistochemical staining. No features suggesting aggressive tumor behavior is noted. The patient asks if surveillance of the lesion is an option instead of resection.

Clinical Decision #6: Is surveillance an option for small GISTs?

Based on the available data, there is insufficient evidence to recommend surveillance vs resection of GISTs <2 cm in size. However, owing to their malignant potential, the guideline suggests resection of gastric GISTs >2 cm and all non-gastric GISTs. The metastatic rate of gastric GISTs <2cm approaches 0% regardless of the mitotic rate. The National Comprehensive Cancer Network guidelines agrees that surveillance is reasonable if EUS shows no high-risk features such as irregular borders, cystic spaces, ulceration, echogenic foci, or heterogeneity.[7] In the presence of high-risk features, resection should be strongly considered. For GISTs >2 cm, the rate of metastatic spread increases with the size of the lesion and may be as high as 86% for lesions greater than 10 cm with a high mitotic rate. It should be noted the guideline also recommends, as a key concept, that patients with any SEL lacking a diagnosis should be entered into some form of a surveillance protocol.

Clinical Scenario Continued

The patient undergoes surveillance EUS annually for two years with no interval growth. He was to have an EUS two years later but declined further imaging. Six years after initial diagnosis, he presents with dysphagia to solid food. EUS reveals the GIST is now 2.8 cm. Complete work up fails to reveal an alternate cause for dysphagia and a barium tablet takes more than a minute to pass the site of the GIST. Resection of the GIST is desired.

Clinical Decision #7: Is surgery required or is there a therapeutic endoscopic option?

Several non-randomized studies have compared surgical and endoscopic resections, finding good outcomes regardless of approach. However, in many of those studies, the endoscopic approaches were performed in patients with smaller GISTs (typically around 2 cm). The guideline suggests either submucosal tunneling endoscopic resection (STER) or surgical resection for the management of SELs originating from the muscularis propria layer of the esophagus and gastroesophageal junction when resection is necessary, a conditional recommendation based on very low-quality of evidence. One

retrospective study found comparable technical success rates among patients who underwent STER (n=91) or thoracoscopic enucleation (TE; n=75) for large (mean size >5 cm) symptomatic SELs in the esophagus and gastroesophageal junction.[8] En bloc resection rates in that study were 85% with STER and 87% with TE. With smaller SELs, STER was associated with shorter procedure times and hospital length of stay and a similar rate of adverse events. However, for SELs >3.5 cm or with irregular borders, STER was associated with more technical difficulties, piecemeal resections, and adverse events. A key concept in the guidelines is that for GISTs <2 cm, if the clinical decision is to resect, endoscopic methods may be considered as acceptable alternative therapies compared with surgery. There is insufficient data to suggest any one endoscopic method as superior.

Clinical Scenario Continued

The patient undergoes STER with successful resection of the lesion (Figure 4). He is discharged following an overnight hospital stay for observation. He advances rapidly from a liquid diet to a normal diet and has no further dysphagia. Pathology confirms a 2.8 cm GIST with a low mitotic rate. EUS one year later shows no residual tumor in the region of the gastroesophageal junction.

Conclusion

SELs are commonly identified in the gastrointestinal tract during standard endoscopy and the latest ACG Guideline represents an attempt to provide a practical approach to their diagnosis and management. This *Guidelines in Practice* is not meant to be comprehensive, and readers are directed to the full guideline to learn about additional topics including the diagnosis and management of neuroendocrine tumors, the use of unroofing techniques to yield a diagnosis when FNA/FNB fails to provide one, and appropriate settings for the use of endoscopic mucosal resection.

Figure Legends

Figure 1. Endoscopy reveals an incidental 1.8 cm subepithelial lesion at the gastroesophageal junction.

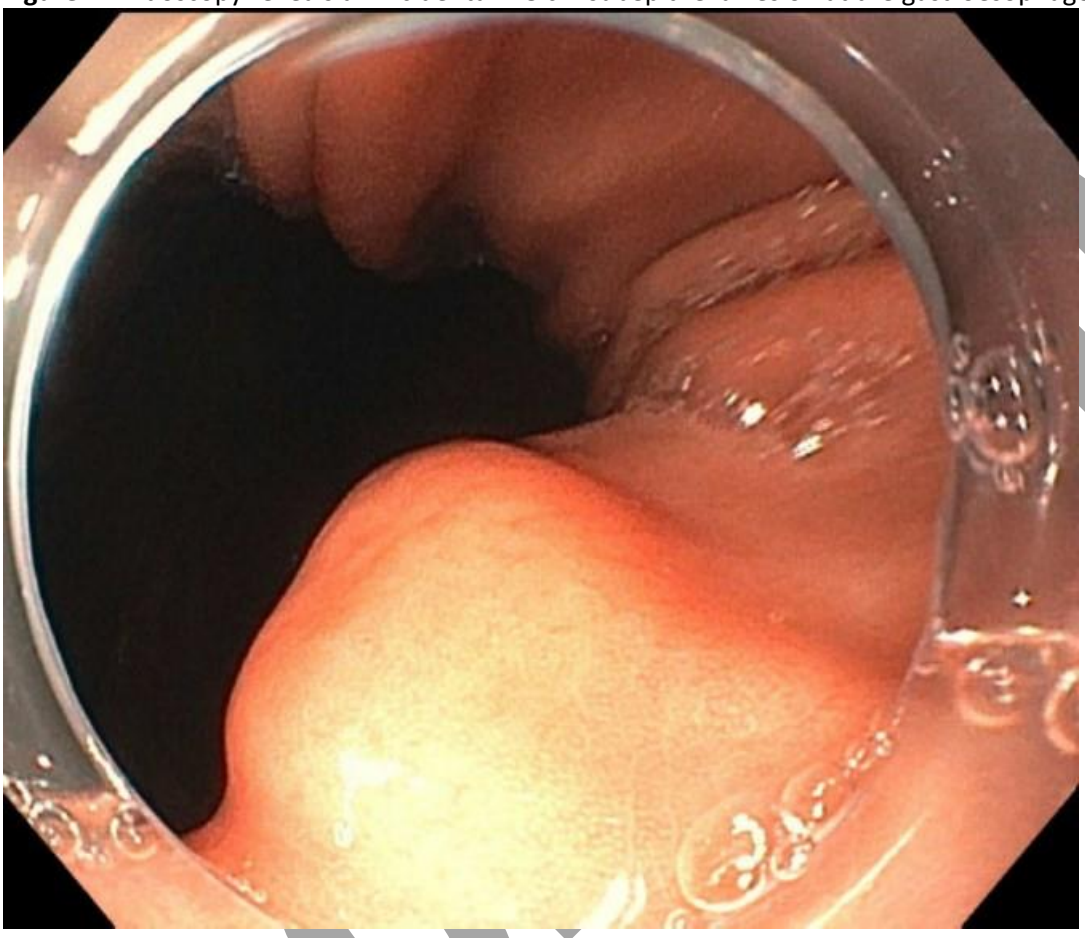


Figure 2. Endoscopic ultrasound demonstrates a 1.8 cm hypoechoic mass (arrow) arising from the muscularis propria (fourth wall layer) of the gastroesophageal junction.

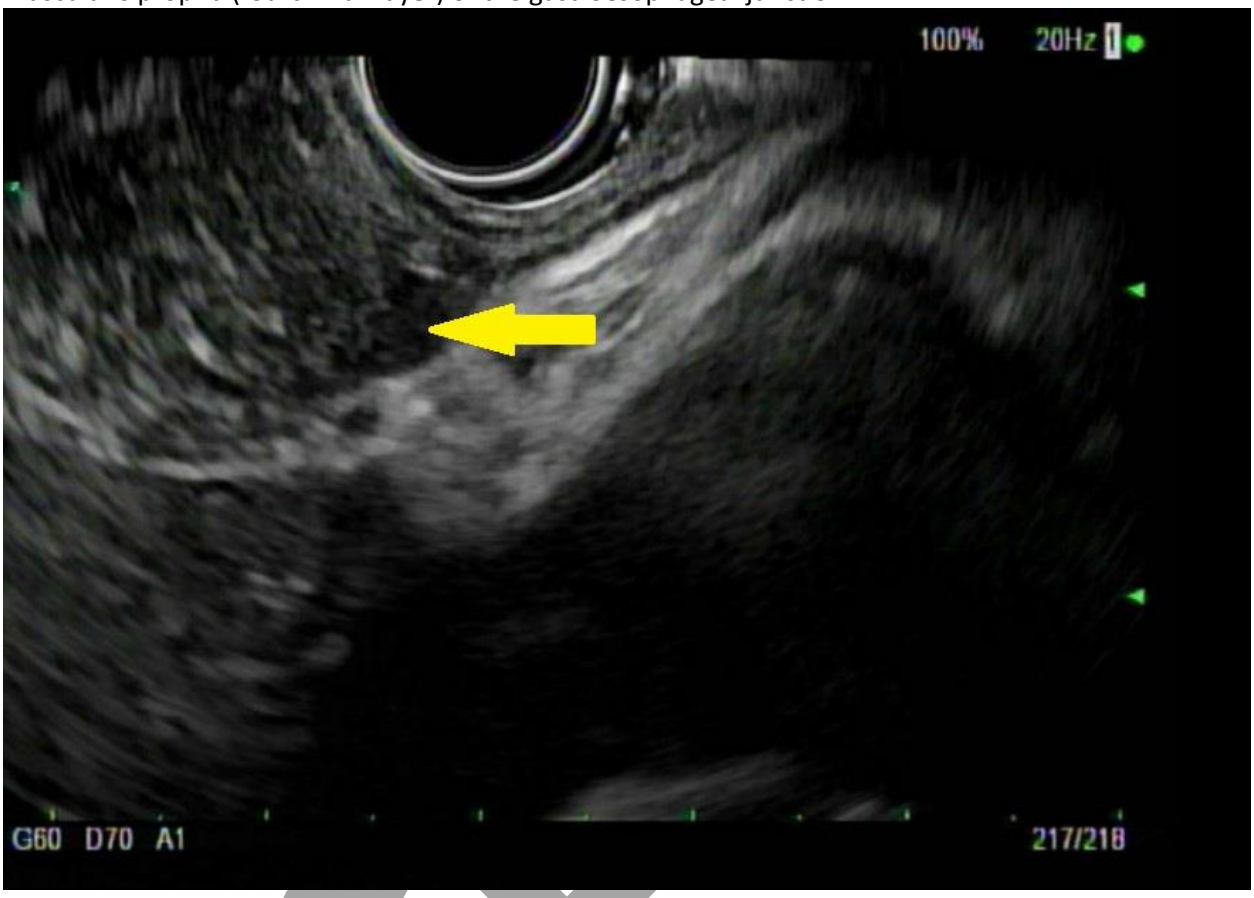
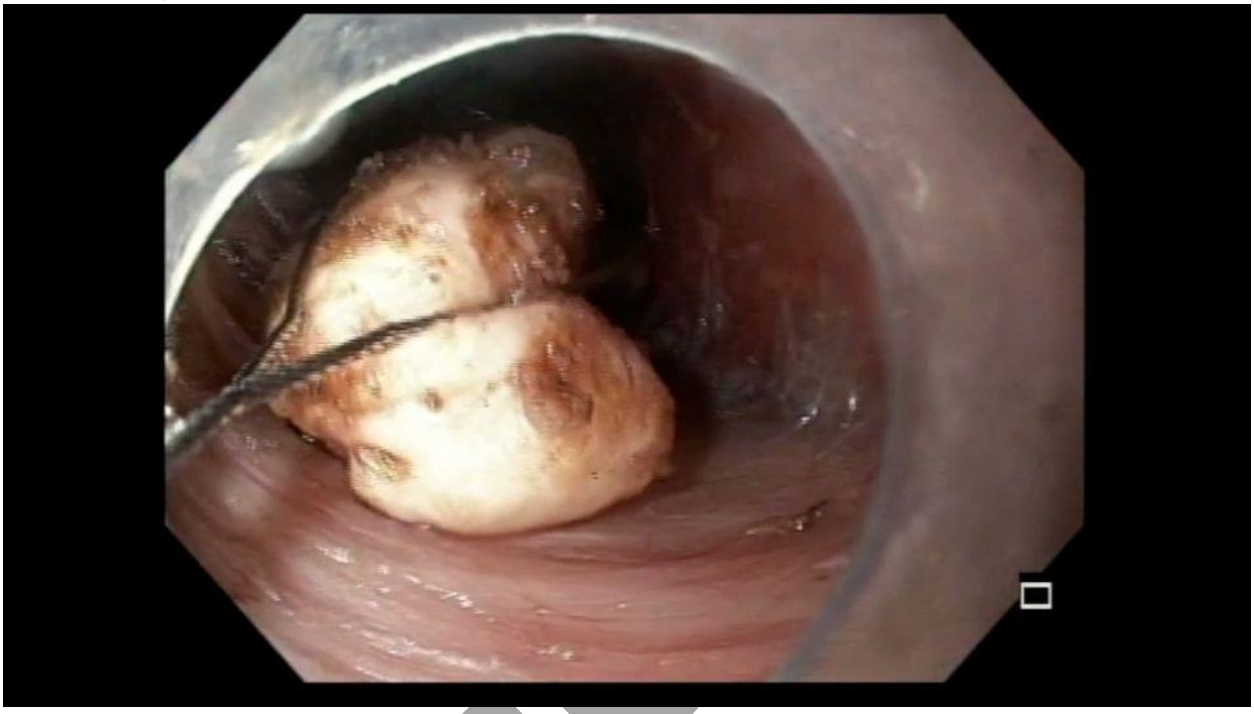


Figure 3. Fine needle biopsy (FNB) of the 1.8 cm hypoechoic mass.

Figure 4a. Dissection of the mass by submucosal tunnel endoscopic resection (STER). Image courtesy of Amit Bhatt, MD

Figure 4b. Extraction of the resected mass through the submucosal esophageal tunnel. Image courtesy of Amit Bhatt, MD



REFERENCES

1. Jacobson BC, Bhatt A, Greer KB, et al. ACG Clinical Guideline: Diagnosis and Management of Gastrointestinal Subepithelial Lesions. Am J Gastroenterol 2023;118:46-58.
2. Komanduri S, Keefer L, Jakate S. Diagnostic yield of a novel jumbo biopsy "unroofing" technique for tissue acquisition of gastric submucosal masses. Endoscopy 2011;43:849-55.
3. Kim SY, Shim KN, Lee JH, et al. Comparison of the Diagnostic Ability of Endoscopic Ultrasonography and Abdominopelvic Computed Tomography in the Diagnosis of Gastric Subepithelial Tumors. Clin Endosc 2019;52:565-573.
4. Goto O, Kambe H, Niimi K, et al. Discrepancy in diagnosis of gastric submucosal tumor among esophagogastroduodenoscopy, CT, and endoscopic ultrasonography: a retrospective analysis of 93 consecutive cases. Abdom Imaging 2012;37:1074-8.
5. Gress F, Schmitt C, Savides T, et al. Interobserver agreement for EUS in the evaluation and diagnosis of submucosal masses. Gastrointest Endosc 2001;53:71-6.
6. Facciorusso A, Sunny SP, Del Prete V, et al. Comparison between fine-needle biopsy and fine-needle aspiration for EUS-guided sampling of subepithelial lesions: a meta-analysis. Gastrointest Endosc 2020;91:14-22 e2.
7. Shah MH, Goldner WS, Halfdanarson TR, et al. NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. J Natl Compr Canc Netw 2018;16:693-702.
8. Chen T, Lin ZW, Zhang YQ, et al. Submucosal Tunneling Endoscopic Resection vs Thoracoscopic Enucleation for Large Submucosal Tumors in the Esophagus and the Esophagogastric Junction. J Am Coll Surg 2017;225:806-816.

ACG Patient Care Summary

Information for Patients, Parents, and Caregivers: Understanding the ACG Clinical Guidelines

The diagnosis and management of gastrointestinal subepithelial lesions

Published: January 2023

Overview: The wall of the GI tract is comprised of several layers. Subepithelial lesions are growths that originate from one of these layers other than the most superficial one. Sometimes organs can push on the GI tract and mimic lesions during endoscopy. Most subepithelial lesions are found incidentally during endoscopy or imaging done for other reasons. Diagnosis is essential because these lesions can range from entirely harmless to cancerous. Factors that influence the treatment of these lesions include the size, location in the GI tract, whether they are causing symptoms (pain, trouble swallowing, anemia, etc.), and tissue diagnosis.

Questions for your doctor

What are the next steps in the diagnosis of this lesion?

Does this lesion have anything to do with my symptoms?

What are my treatment options if the lesion is either precancerous or cancerous?

What would happen if I left the lesion alone?

ACG Treatment Guidelines

If the subepithelial lesion is consistent with fatty growth or lipoma and is not causing symptoms, it is safe to leave it alone.

If the lesion is inconsistent with a lipoma, an endoscopic (internal) ultrasound is recommended to characterize it further.

If the mass is not comprised of large blood vessels, a biopsy with a needle during the endoscopic ultrasound is recommended to obtain tissue and diagnose the lesion.

No further treatment is needed if the lesion is noncancerous and not causing symptoms.

Removal is recommended if the lesion is precancerous or causes symptoms.

The decision to remove precancerous lesions during endoscopy or surgery depends on several factors, including the size, location, and type of lesion.

Not every gastroenterologist has the training to remove these lesions, so you may need to be referred to a subspecialist.