Communication from the ASGE Standards of Practice Committee

GUIDELINE

The role of endoscopy in subepithelial lesions of the GI tract

Prepared by: STANDARDS OF PRACTICE COMMITTEE

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This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. In preparing this guideline, a search of the medical literature was performed by using PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When little or no data existed from well-designed prospective trials, emphasis was given to results from large series and reports from recognized experts. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time the guidelines were drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence (Table 1).[1] The strength of individual recommendations is based on both the aggregate evidence quality and an assessment of the anticipated benefits and harms. Weaker recommendations are indicated by phrases such as "we suggest," whereas stronger recommendations are typically stated as "we recommend." This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and preferences and available resources and expertise. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from this guideline.

Subepithelial lesions (SELs) of the GI tract are tumors that originate from the muscularis mucosa, submucosa, or muscularis propria. The term *subepithelial lesion* is preferred to the term *submucosal tumor*, which should be reserved for those that originate from the submucosal layer. SELs are most commonly found in the stomach, as often as 1 in every 300 endoscopies.[2] They usually are identified during routine upper and lower endoscopy as rounded protuberances with normal overlying mucosa. The majority are small (<2 cm in diameter) and found incidentally; however, SELs can present with bleeding, obstruction, or metastases, depending on tumor size, location, and histopathology.[3]

Initial management of SELs centers on proper diagnosis and determination of any malignant potential of the lesion. The majority of these tumors are benign, with fewer than 15% found to be malignant at presentation.[4] Tumors with low malignant potential may appear endoscopically similar to those with a much higher risk for malignant transformation. Because of their subepithelial location, biopsies with endoscopic forceps often fail to provide diagnostic tissues. Thus, further imaging and sampling techniques (often with EUS) often are used to characterize these lesions.

EUS is the most accurate imaging test for evaluation of SELs of the GI tract[5-7] because of its ability to delineate individual histologic layers and, thus, the most likely site of tumor origin (Table 2). The 5 principal US layers seen on EUS include the following: first and second (mucosa including muscularis mucosa), third (submucosa), fourth (muscularis propria), and fifth (serosa or adventitia). EUS is superior to other imaging modalities (CT, magnetic

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TABLE 1. GRADE system for rating the quality of evidence for guidelines

Quality of evidence	Definition	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕◯
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕◯◯
Very low quality	Any estimate of effect is very uncertain.	⊕◯◯◯

Adapted from Guyatt et al.[1]

resonance imaging) in characterizing small (<2 cm) lesions.[8,9] It can accurately distinguish between extrinsic compression of the GI tract and an intramural growth; up to 30% of suspected intramural SELs are in fact extramural in origin (eg, compression from an adjacent organ).[10,11] EUS also permits measurement of lesion size and evaluation of any associated lymphadenopathy for further staging.[9,12] Finally, EUS-guided FNA (EUS-FNA) and fine-needle biopsy (FNB) allow tissue diagnosis to guide further management.

EUS has some technical limitations. Lower frequency EUS (<10 MHz) cannot reliably visualize the muscularis mucosa within the mucosal layer. Furthermore, compression of the lesion by the acoustic coupling balloon on radial and linear echoendoscopes may make lesion characterization difficult. These issues often can be overcome with instillation of water into the lumen or by the use of higher-frequency (20-30 MHz) miniprobes that can be advanced through the working channel of the endoscope.[13] At higher frequencies, visualization of subcentimeter SELs and more accurate assessment of the layer of origin may be possible. With miniprobes, evaluation of SELs also can be performed in regions inaccessible to most standard echoendoscopes, such as the proximal colon.

In this document, we discuss common types of SELs encountered in the GI tract, their endoscopic and clinical characteristics, and appropriate management. Indications and methods for tissue acquisition will be addressed as well as novel methods of endoscopic resection.

GI STROMAL TUMORS

GI stromal tumors are the most common mesenchymal neoplasms of the GI tract, with an incidence of approximately 4.3 per million per year in the United States.[14] They are characterized as sarcomas, with variable aggressiveness from benign and/or indolent to aggressive metastatic phenotypes. They are believed to originate from the interstitial cells of Cajal and can occur anywhere in the GI tract. They are most commonly found in the stomach (60%-70%) and less commonly in the small intestine (20%-30%), the colon (5%), and the esophagus (<5%).[15] They typically have a spherical or fusiform shape and arise from the muscularis propria or less commonly the muscularis mucosa.

These lesions often appear endoscopically as a smooth bulge with normal overlying mucosa (Fig. 1). The typical firm consistency of the lesion may be assessed by probing with biopsy forceps. Stacked or "bite-on-bite" pinch biopsies may be attempted, although diagnostic yield often is low.[16,17]

EUS generally demonstrates a hypoechoic, homogenous lesion, but GI stromal tumors can also appear heterogeneous with anechoic (cystic) spaces or shadowing foci (calcifications). Assessment for enlarged peritumoral adenopathy or involvement of additional wall layers should be performed. There are conflicting results from retrospective studies describing malignant EUS features of these lesions.[9,18-20] Some studies suggest that large tumor size (>3 cm) and irregular tumor margins are most consistently associated with a more aggressive phenotype.[18-21] Features such as echogenic foci, cystic spaces, heterogeneity, and ulceration were less-consistently associated with malignant risk. These findings have not been validated in prospective studies, and no true consensus has been made on which features best correlate with malignancy.

Histologically, GI stromal tumors are composed of spindle cells (70%), epithelioid cells (20%), or a mixture of both cell types (10%).[22] Immunohistochemical staining in 95% of tumors is positive for CD117, which corresponds to the presence of the c-tyrosine kinase receptor.[23] DOG1 (Discovered on GIST 1) is a newly discovered immunohistochemical marker for GI stromal tumors and can be useful if CD117 testing is negative. In addition, DOG1 can help differentiate GI stromal tumors from other mesenchymal lesions such as sarcomas and melanomas, which also can stain positive for CD117.[24]

GI stromal tumors should be stratified by malignant potential, and pathologic assessment of this risk involves description of tumor size, location, and mitotic count (Tables 3-4).[17] Tissue specimens acquired by EUS-FNA do not assess the mitotic rate accurately and are

TABLE 2. Characteristics of subepithelial mass lesions at endoscopy and EUS[12]

Subepithelial lesion	Endoscopic appearance	EUS layer	EUS appearance
Benign			
GI stromal tumor–low risk	No specific characteristics, lack ulcerations	4th (rarely 2nd or 3rd)	Hypoechoic, majority <3-5 cm, smooth margins, round, homogeneous, rare malignant GI stromal tumors were reported with size <3 cm
Leiomyoma	No specific characteristics	2nd, 3rd, or 4th	Hypoechoic, well-circumscribed
Lipoma	Yellow hue, pillow sign (high specificity, low sensitivity), usually isolated	3rd	Intensely hyperechoic, homogeneous, smooth margins, may be polypoid
Varices	Bluish tinge, tortuous, easily compressible	3rd	Anechoic, serpiginous, Doppler positive
Neural origin–schwannoma, neuroma, neurofibroma	No specific characteristics	3rd or 4th	Hypoechoic
Granular cell tumor	No specific characteristics, majority small (<4 cm) and solitary	2nd or 3rd	Hypoechoic, heterogeneous echotexture
Inflammatory fibroid polyp	Smooth, usually solitary, sessile polyp with ulceration of the overlying mucosa, 2-5 cm	3rd or 4th	Hypo- to hyperechoic, indistinct margin, homogeneous appearance
Duplication cyst	Smooth and regular appearance, slightly translucent, compressible	Any or extramural	Anechoic, 3-5 layer wall, round or oval, absent Doppler signal
Lymphangioma	Cyst-like bulging mass, easily compressed, more common in intestine	3rd	Anechoic with internal septa
Pancreatic rest	90% have umbilicated surface corresponding to a draining duct, >90% located in the antrum	2nd, 3rd, or 4th	Hypoechoic or mixed echogenicity (heterogeneous = acinous tissue, anechoic = ductal structures), indistinct margin, anechoic cystic or tubular structures within the lesions can be seen in 1/3 of cases
Brunner's gland hyperplasia	Duodenal bulb, usually single	2nd and 3rd	Hyperechoic, anechoic area due to duct, smooth margin
Malignant (potential)			
GI stromal tumor–low risk	Presence of ulcerations	4th (rarely 2nd or 3rd)	Hypoechoic, >3 cm, irregular extraluminal margins, cystic spaces, heterogeneous, echogenic foci
GI neuroendocrine neoplasm	No specific characteristics, may be yellowish in appearance; gastric carcinoid tumors often multiple. Types I and II usually are benign, and type III usually is malignant. Rectal and duodenal usually solitary.	2nd or 3rd	Mildly hypoechoic or isoechoic, homogeneous, oval or round, smooth margin
Lymphoma	No specific characteristics	2nd, 3rd, or 4th	Hypoechoic
Metastasis	No specific characteristics	Any or all	Hypoechoic, heterogeneous mass
Glomus tumor	No specific characteristics, mostly seen in the antrum	3rd and 4th	Hypo- or hyperechogenicity. More than half have internal hyperechoic spots that corresponded to calcifications. Doppler EUS shows a prominent vascular signal consistent with the hypervascular nature of the tumor.

SEL, Subepithelial mass lesion.

therefore insufficient to completely differentiate high-risk and low-risk lesions. Therefore, malignant potential is currently determined by final surgical pathology. Newer methods of endoscopic tissue acquisition, including new core biopsy techniques and endoscopic resection, are discussed in the tissue acquisition section of this document.

All GI stromal tumors have some malignant potential, and management often is dictated by size, location, and the presence of symptoms. GI stromal tumors in the small intestine may be more aggressive than those located in the stomach, as 40% to 50% of small intestine GI stromal tumors are malignant, compared with only 20% to 25% of lesions arising in the stomach.[22] Less is known about the

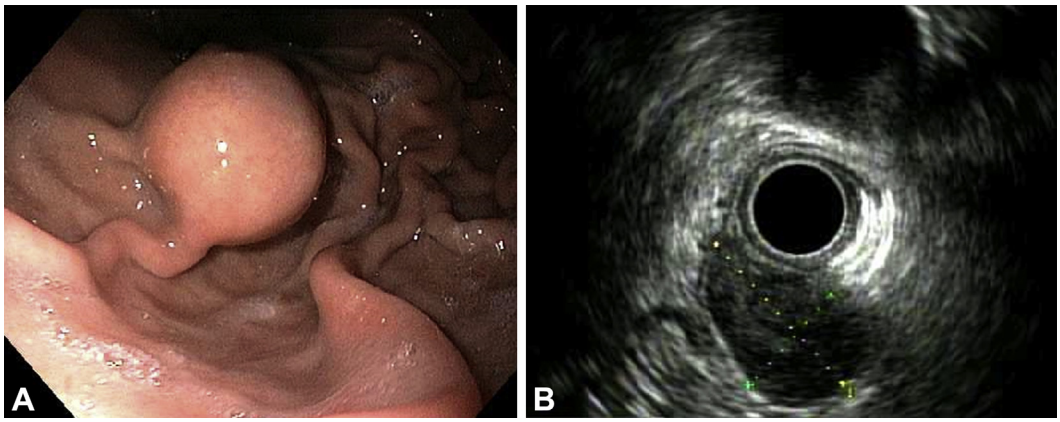

Figure 1. A, Subepithelial gastric lesion seen on standard EGD. **B,** EUS image revealing GI stromal tumor, deriving from the fourth layer of the gastric wall.

TABLE 3. Gastric GI stromal tumors: proposed guidelines for assessing the malignant potential[28]

Tumor size	Mitotic rate	Predicted biologic behavior
≤2 cm	≤5 mitoses/50 HPF >5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 0 metastasis rate or tumor-related mortality: <4%
>2 cm ≤5 cm	>5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 16%
>2 cm ≤10 cm	≤5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: <4%
>5 cm ≤10 cm	>5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 55%
>10 cm	≤5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 12%
>10 cm	>5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 86%

HPF, High-power field.

TABLE 4. Small-intestine GI stromal tumors: proposed guidelines for assessing the malignant potential[28]

Tumor size	Mitotic rate	Predicted biologic behavior
≤2 cm	≤5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 0
>2 cm ≤5 cm	<5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 2%
>2 cm ≤5 cm	>5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 73%
>5 cm ≤10 cm	≤5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 25%
>5 cm ≤10 cm	>5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 85%
>10 cm	>5 mitoses/50 HPF	Metastasis rate or tumor-related mortality: 50%-90%

HPF, High-power field.

malignant potential of GI stromal tumors found in other sites, so these should be treated similarly to those originating from the small intestine.[24] Surgical referral should be considered in patients with symptoms such as obstruction, pain, or GI bleeding, lesions with regional adenopathy, lesions >2 cm anywhere in the GI tract, or any tumors originating in the small bowel. One proposed management strategy for gastric GI stromal tumors <2 cm in size recommends surgical resection for lesions with high-risk EUS features, with EUS surveillance at 6-month to 12-month intervals for those without these features.[25] This strategy is supported by other retrospective data suggesting that GI stromal tumors <2 cm can be followed safely with EUS surveillance without operative management.[26,27] However, there are no large prospective studies that have evaluated the utility of routine interval surveillance of small GI stromal tumors. The National Comprehensive Cancer Network guidelines recommend that lesions >2 cm or smaller lesions with high-risk features (irregular borders, cystic spaces, ulceration, echogenic foci, heterogeneity) undergo resection. After resection, the risk of metastasis is best assessed by tumor size and mitotic rate, but also tumor location (gastric vs small bowel including colon and rectum).[28]

LEIOMYOMAS

Leiomyomas are benign smooth muscle tumors of the GI tract that originate from the muscularis mucosa or the muscularis propria. Most tumors are located in the esophagus, although they can be found rarely in other parts of the GI tract. The vast majority of spindle-cell neoplasms in the esophagus are leiomyomas, accounting for roughly two thirds of all benign tumors of the esophagus.[29] GI stromal tumors are uncommon in this location (<5% of all GI stromal tumors).[22,30] Ninety percent of all esophageal leiomyomas are found in the lower (56%) and middle third (34%) of the esophagus and only rarely in the upper third. This correlates with the muscular composition of the esophagus, because the lower third is composed predominantly of smooth muscle, with a mixture of smooth and skeletal muscle in the mid-esophagus.[29] Leiomyomas also can be found in the stomach, and the EUS appearance can be indistinguishable from a GI stromal tumor. However, the 2 tumors can be differentiated histologically, because leiomyomas stain negative for CD117 and CD34 and positive for desmin and α-smooth muscle actin.[3] Surgical resection is required only for tumors with associated symptoms such as dysphagia, intestinal obstruction, bleeding, or perforation.[31,32]

LIPOMAS

Lipomas are common subepithelial lesions found throughout the GI tract, most commonly in the colon and gastric antrum. They are collections of adipose tissue, which often display a yellowish hue on endoscopy and are soft on forceps probing. Demonstration of a "pillow sign" or indentation on probing is 98% specific for the diagnosis, although it is not a very sensitive feature.[7] Characteristic EUS imaging demonstrates a homogeneous, well-defined hyperechoic lesion arising from the submucosal layer (Fig. 2). Tissue sampling is not required when endoscopic imaging is characteristic. Lipomas generally are asymptomatic but may cause hemorrhage and obstruction in rare cases of larger lesions.[33] Lipomas have negligible malignant potential. Therefore, unless tumors are symptomatic, resection or surveillance are not required after diagnosis.

GI NEUROENDOCRINE NEOPLASMS

GI neuroendocrine neoplasms, formerly known as carcinoid tumors, are the most common neoplasm of the small intestine and arise from the enterochromaffin-like cells of the GI tract. Although some GI neuroendocrine neoplasms may produce hormones that cause well-described clinical syndromes, most are found incidentally in the rectum, stomach, or duodenum during routine endoscopy and do not produce any clinically meaningful hormonal syndrome.

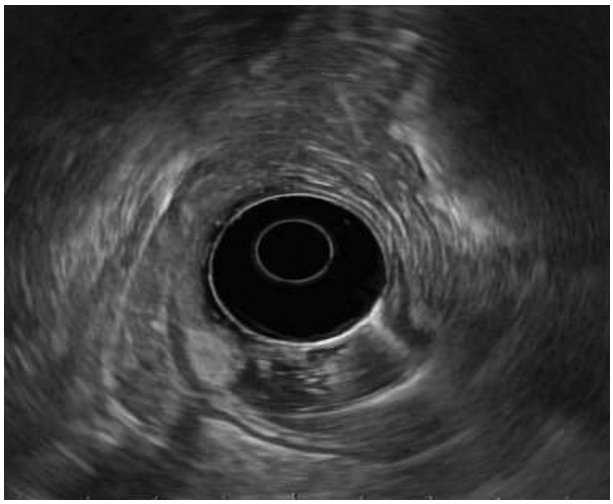

Figure 2. EUS image of a gastric lipoma.

GI neuroendocrine neoplasms usually originate from the mucosal layer of the GI tract and penetrate into the submucosa. Therefore, a diagnosis usually is made by using standard mucosal biopsy techniques. Endoscopy typically reveals a polypoid or a smooth and rounded subepithelial lesion, which may have a central depression or erosion. They may appear red or yellow. EUS imaging characteristically shows a hypoechoic, uniform round, well-defined lesion within the deep mucosal and submucosal layers.[34] GI neuroendocrine neoplasms are classified histologically by grade and differentiation (based on mitotic rate and Ki-67 index) as well-differentiated grade 1 (low grade), grade 2 (intermediate grade), and grade 3 (poorly differentiated) tumors.[35]

Gastric GI neuroendocrine neoplasms

Gastric GI neuroendocrine neoplasms are commonly diagnosed on routine EGD, and their incidence has increased 10-fold over the past 30 years.[36] They are classified into 3 subtypes.[37] Type I gastric GI neuroendocrine neoplasms (multifocal, well-differentiated) are associated with chronic atrophic gastritis, hypergastrinemia, and pernicious anemia and have low potential for metastasis. Five-year and 10-year survival for these tumors is equivalent to that of the general population.[38-40] Type II gastric GI neuroendocrine neoplasms (multifocal, well-differentiated) are associated with Zollinger-Ellison syndrome or multiple endocrine neoplasia type1, and they have an intermediate potential for metastasis. In patients with tumors >2 cm in size, lymph node metastases are found in 10% to 30%, and the 5-year survival rate is 60% to 75%.[41] Type III (solitary, well-differentiated) gastric GI neuroendocrine neoplasms are sporadic tumors not associated with hypergastrinemia and often are metastatic at the time of diagnosis. Overall

5-year survival with type III tumors is <50%.[42] An alternate classification scheme has been proposed, with 4 subtypes, separating enterochromaffin-like–predominant GI neuroendocrine neoplasms (types I-III) from those not enterochromaffin-like–predominant (type IV). Type IV are poorly differentiated neuroendocrine carcinomas and tend to be solitary, rare gastric tumors found most commonly in older men (age >60 years).[43,44] These tumors often are diagnosed at an advanced stage, and 1-year survival is only 50%. The ASGE has recently published guidelines on the role of endoscopy in the management of premalignant conditions of the stomach, and further discussion of management of gastric GI neuroendocrine neoplasms can be found in that document.[45]

Appropriate classification of gastric GI neuroendocrine neoplasms at the time of diagnosis is critical to triage-appropriate management and for determination of the overall prognosis. EMR may be considered for types I and II gastric lesions <2 cm in size.[34] Lesions <1 cm may not require removal; however, surgical resection often is warranted for larger lesions.[35] After endoscopic or surgical resection, surveillance endoscopy may be indicated, although optimal surveillance intervals are unknown. Some experts suggest surveillance imaging every 1 to 2 years.[41] Type I and II gastric lesions should be re-evaluated every 6 to 12 months for the first 3 years, then annually per the National Comprehensive Cancer Network guidelines.[35] Type III GI neuroendocrine neoplasms should be managed surgically, based on the high incidence of lymph node metastases, although small (<1 cm), well-differentiated lesions may be considered for endoscopic removal.[39-41]

Rectal GI neuroendocrine neoplasms

There has been a dramatic increase in the diagnosis of rectal GI neuroendocrine neoplasms because of widespread use of colonoscopy for colorectal cancer screening.[46-48] The prevalence of rectal GI neuroendocrine neoplasms in adults is approximately 0.05% to 0.07% during screening colonoscopy.[48,49] Because of the lack of controlled prospective studies, the optimal management of rectal GI neuroendocrine neoplasms remains somewhat controversial.

Treatment of rectal GI neuroendocrine neoplasms varies based on the size of the lesion, because tumor size impacts the likelihood of lymph node metastases and overall survival. Classification of rectal GI neuroendocrine neoplasms generally is divided as tumors ≤1 cm, 1 to 2 cm, and >2 cm in diameter. Typically, rectal GI neuroendocrine neoplasms discovered during screening colonoscopy are <13 mm in size,[50] and often are removed endoscopically by using conventional polypectomy techniques. Tumors <10 mm confined to the submucosa tend to be well-differentiated and generally have a benign disease course if no lymphovascular invasion is present.[51] These small lesions may be managed by local endoscopic or transanal excision. Node-negative rectal carcinoid tumors <1 cm in size and without lymphovascular invasion or invasion of the muscularis propria have a 98.9% to 100% 5-year survival rate.[52,53] Aggressive surveillance after resection of small lesions without metastatic disease may be unnecessary, because recurrence rates are extremely low.[54-57] There are no widely accepted guidelines for endoscopic surveillance, but 1 proposed protocol uses EUS at 3 months after resection, followed by EUS every 6 months for 3 years.[58] National Comprehensive Cancer Network guidelines propose that follow-up is not required for rectal carcinoid tumors <1 cm that are fully resected either endoscopically or transanally with negative margins.[35]

Endoscopic or transanal excision may be considered for medium-sized rectal tumors (1-2 cm in diameter). Before resection of lesions >1 cm, EUS should be performed to assess for invasion into the muscularis propria or for the presence of nodal metastasis.[59] However, EUS is not required before removal of lesions <1 cm because of the negligible risk of metastatic adenopathy or invasion of deeper layers. Tumors with regional adenopathy or invasion of the muscularis propria should be referred for surgical resection. The incidence of lymph node metastases of tumors 11 to 19 mm in diameter ranges from 17% to 81%.[42,48,51-53] After resection, surveillance strategies are based on tumor stage at diagnosis. The North American Neuroendocrine Tumor Society guidelines[59] suggest that long-term endoscopic or radiologic surveillance is not required for stage I disease (tumor <2 cm, submucosal, node-negative). Patients with stage II or III tumors (invading muscularis propria or node-positive) may warrant radiographic surveillance beyond 5 years because metastatic spread can occur many years after diagnosis. National Comprehensive Cancer Network guidelines suggest that tumors between 1 and 2 centimeters should undergo evaluation with rectal magnetic resonance imaging or EUS at 6 and 12 months after primary therapy and then as clinically indicated.[35] In a recent retrospective study, 50% of patients with initial well-differentiated tumors 11 to 19 mm in size were found to have metastatic disease within 6 years of diagnosis,[51] emphasizing the importance of follow-up after resection.

Rectal GI neuroendocrine neoplasms >2 cm in diameter should be managed surgically, including lymph node dissection, because up to 80% of these patients will have nodal disease at the time of diagnosis.[46,60]

Small-intestine GI neuroendocrine neoplasms

As for rectal GI neuroendocrine neoplasms, there has been a dramatic increase in the diagnosis of duodenal GI neuroendocrine neoplasms over the past 4 decades,[47] attributed to the increase in the use of both cross-sectional imaging and EGD.[61] The majority of patients present with duodenal tumors that have a low risk for regional nodal metastases, especially for tumors ≤2 cm that do not involve the muscularis propria (2% and 4.7%

for tumors <1 cm and 1-2 cm, respectively).[62] For tumors >2 cm in diameter, the risk of nodal disease increases to 20%.

There are no specific guidelines for the management of duodenal GI neuroendocrine neoplasms; however, these often are managed similarly to rectal carcinoid tumors. Small (<1 cm), well-differentiated lesions can be removed endoscopically by polypectomy or EMR.[63,64] After removal, patients with angioinvasion, invasion of the muscularis propria, or grade 2 and/or grade 3 histology, should be referred for surgical resection.

Surgical resection is recommended for GI neuroendocrine neoplasms identified in the jejunum and ileum, because metastatic mid-gut disease is incurable.[65] With the exception of small, well-differentiated GI neuroendocrine neoplasms of the appendix, GI neuroendocrine neoplasms of the mid-gut have a substantial risk of relapse after resection and require clinical follow-up for at least 7 years.[65]

PANCREATIC RESTS

A pancreatic rest is heterotopic pancreatic tissue often found incidentally along the greater curve of the gastric antrum during endoscopy. Autopsy series show an estimated prevalence of 2% to 14%.[66] These lesions often appear as rounded subepithelial lesions with normal overlying mucosa and a central umbilication. Most are asymptomatic but may present with GI bleeding, abdominal pain, or intestinal obstruction. Rarely, manifestations of acute or chronic pancreatitis may occur with lesions 3 cm or larger.[66,67] Malignant transformation also has been reported.[68-70]

A firm SEL with central umbilication along the greater curve of the distal stomach is considered diagnostic for a pancreatic rest, and therefore EUS is not required. However, differentiation of a pancreatic rest from other gastric SELs, such as a GI stromal tumor or carcinoid tumor may be difficult when these features are not present.[9,66,71] When performed, EUS typically demonstrates heterogeneous and hypoechoic echotexture and may involve any subepithelial layer.[72,73]

GRANULAR CELL TUMORS

Granular cell tumors are rare nerve sheath tumors that arise from Schwann cells. They usually are found incidentally during endoscopy and can involve any part of the GI tract, although most are found in the esophagus.[74,75] Patients can present with symptoms such as dysphagia or retrosternal pain, which often are related to the size of the tumor. They appear as grayish-yellow, firm SELs, often described as a "submucosal pill."[76] Granular cell tumors are considered to be benign lesions, although malignant transformation has been reported, generally only in lesions >4 cm in size.[77,78] Histologic criteria for malignancy have been proposed,[79] but the only consensus criterion for malignancy is the presence of metastases.[80]

On EUS, these lesions originate from the mucosal or submucosal layer and appear hypoechoic and homogeneous, with smooth margins.[81] Diagnosis often can be made with standard biopsy. Immunochemical staining is positive for S-100 and negative for staining patterns more typical of a GI stromal tumor or leiomyoma.[76] A surveillance approach to subcentimeter granular cell tumors appears to be safe. Goldblum et al[82] reported that 12 of 13 patients with subcentimeter granular cell tumors followed an average of 5 years (range 7 months to 11 years) developed no evidence of metastatic disease.

Endoscopic resection of small granular cell tumors may be considered, possibly obviating the need for further surveillance.[83,84] Removal often can be accomplished by snare excision or EMR.[83,85,86] It is unknown whether small, unresected granular cell tumors or larger lesions resected endoscopically should undergo surveillance.

DUPLICATION CYSTS

Duplication cysts are congenital anomalies that arise during early embryonic development and are most commonly attached to the GI wall or in direct communication with the GI lumen.[87] They are lined with GI epithelium and contain a mucoid fluid secreted from the epithelium, which can cause enlargement of the cyst. These cysts are typically asymptomatic, although symptoms of dysphagia, pain, bleeding, or obstruction may occur depending on location.[88-90] Rarely, malignant transformation of foregut duplication cysts has been reported.[91,92]

On EGD, duplication cysts often appear as a bulge in the GI lumen, with overlying normal mucosa; however, they are most commonly diagnosed by cross-sectional imaging.[93,94] The typical EUS appearance is a smooth, well-defined tubular to round, hypoechoic or anechoic lesion arising from the submucosa or extrinsic to the gut wall.[12] Hypoechoic features can be seen secondary to mucinous material within the cyst. A "duplication" of GI tract wall layers may be noted within the cyst. When the lesion is clearly anechoic, FNA should be avoided. EUS-FNA of cysts in the mediastinum can be considered if the diagnosis is unclear (evidence of solid component, hypoechoic), but use of prophylactic antibiotics should be considered because of the risk of infection.[95-98] Resection of esophageal duplication cysts is rarely performed unless the cyst becomes symptomatic. The management of small-bowel duplication cysts remains somewhat controversial because there may be an increased risk of malignant transformation.[99,100] Successful endoscopic management

of symptomatic duplication cysts has been reported.[101-105] There are no data to support surveillance of these patients.

OTHER SUBEPITHELIAL LESIONS

Metastasis to the GI tract occurs most often in the stomach and can present as a SEL. Overall, this appears to be a rare event, with a prevalence of 0.2% to 5.4% in an autopsy series of patients with known malignancy.[106] Metastases to the stomach are most commonly found in the body and fundus and have a central depression. Solid tumors most likely to metastasize to the stomach include breast, lung, esophagus, renal cell, and malignant melanoma. Endoscopic biopsies are diagnostic in over 90% of cases, therefore further investigation is rarely required because the primary malignancy is generally clinically apparent. On EUS examination, metastases to the GI tract typically appear as hypoechoic and/or heterogeneous lesions and usually can be diagnosed with FNA if standard biopsies are nondiagnostic.[107]

Varices in the esophagus and stomach are diagnosed easily in the appropriate clinical setting, but they may present incidentally during routine endoscopy.[108] Varices can be found in more atypical locations such as the duodenum and rectum, even when absent in the esophagus and stomach. On endoscopy they appear as a bulge and are soft to forceps probing. The diagnosis can be confirmed by EUS or a through-the-scope Doppler probe as an anechoic round or tubular submucosal lesion with Doppler flow. EUS may be able to delineate the anatomy of varices and communication with other vessels. EUS-guided injection of cyanoacrylate and deployment of intravascular coils have been used for treatment of gastric varices.[109,110]

Glomus tumors are rare neoplasms that are most often found in the skin. These also can be located in the GI tract, most notably the stomach.[111] Endoscopically they appear as an ulcerated SEL, most often in the antrum.[112] On EUS, they typically originate from the muscularis propria, but can be found in the submucosal or mucosal layers. They can be hyperechoic or hypoechoic and have internal hyperechoic foci, with a prominent Doppler signal consistent with the vascular nature of these tumors. Glomus tumors can be difficult to distinguish from other subepithelial lesions (such as GI stromal tumors and carcinoid tumors). EUS-FNA immunostaining is positive for actin and vimentin and negative for CD117, chromogranin A, carcinoembryonic antigen, and neuron-specific enolase.[112]

DIAGNOSIS AND MANAGEMENT

For some SELs, such as a lipomas, duplication cysts, and ectopic pancreas, endoscopic and EUS appearances are considered diagnostic, and tissue sampling is not required. However, hypoechoic and heterogeneous lesions from the submucosal and muscularis propria layers such as GI stromal tumors, leiomyomas, and carcinoid tumors have a wide differential diagnosis, and tissue sampling or removal is recommended to diagnose and determine the malignant potential of these lesions. Immunohistochemical staining is mandatory to further characterize these lesions, and thus tissue adequacy is essential.

Because SELs usually are located deep to the epithelial layer and most often originate from the submucosa or muscularis propria, tissue acquisition can be challenging. Various techniques have been described to facilitate the diagnosis of these lesions. These include standard biopsy, jumbo biopsy, unroofing techniques, bite-on-bite biopsy, endoscopic ligation, FNA, FNB, endoscopic submucosal resection (ESMR), endoscopic submucosal dissection (ESD), submucosal tunneling with endoscopic resection (STER), and surgery.

Standard biopsy

Open biopsy forceps can be used to assess the size of a SEL. Probing with closed biopsy forceps may demonstrate a soft (ie, varix or lipoma) or firm (ie, GI stromal tumor or carcinoid tumor) lesion. Pinch biopsies done by using a standard biopsy forceps (jaw volume 5-6 mm^3) alone rarely are sufficient for diagnosing SELs from the submucosal and muscularis propria layers.[113] Tunnel or bite-on-bite biopsies involve using a biopsy forceps to create a defect in the mucosa overlying the SEL to obtain 2 to 8 deeper biopsy specimens.[2] This technique can allow for sampling of submucosal lesions; however, diagnostic yield is only 30% to 40%.[114]

Jumbo biopsy and unroofing techniques

Jumbo biopsy forceps (jaw volume 12-13 mm^3) may obtain tissue from the submucosal layer of the GI tract, which can aid in diagnosing SELs. A retrospective study of 129 patients with SELs in the upper GI tract and colon (average size 15 mm ± 9.3 mm) that compared jumbo biopsy and EUS-FNA reported a definitive diagnosis in 59% and 45%, respectively ($P = .18$).[115] However, significant bleeding was seen in 35.7% of patients after jumbo forceps biopsy, and 34.9% of patients required some form of endoscopic therapy for achieving hemostasis. Jumbo biopsy had a higher diagnostic yield for lesions arising from the submucosal layer, whereas there was a trend for a higher diagnostic yield with FNA for lesions arising from the muscularis propria. Bite-on-bite jumbo biopsy of SELs with on-site touch preparation cytology evaluation has been reported to obtain a definitive diagnosis in 82% (18 of 22) of SELs.[116] However, a prospective comparative study of lesions from the submucosal layer found the yield of jumbo forceps biopsies with the bite-on-bite technique to be only 17% and significantly less than ESMR (87%; $P = .001$).[117] Jumbo forceps biopsy of ulcerated GI stromal tumors can have a high diagnostic yield and can be considered if there has been no recent bleeding from the lesion.[118]

Unroofing of a SEL for diagnostic evaluation was first described by Mimura et al[119] in 1997. This technique removes the overlying mucosa and possibly permits partial resection of the lesion, thereby improving access to the deeper layers. Unroofing can be performed with a needle-knife, snare, cap, or banding device. These techniques significantly increase the diagnostic yield when compared with that of forceps biopsies.[117]

Recently, the single-incision needle-knife (SINK) technique has been described for tissue sampling of SELs. In this method, a needle-knife creates a 6 to 12 mm linear incision over the highest convexity of the lesion, after which standard biopsy forceps are used to obtain tissue from the deeper layers. In a series of 14 patients, tissue obtained by using the SINK technique was adequate for diagnosis in 93% of cases, without adverse events.[120] Mitotic counts also could be determined in 5 of 7 GI stromal tumors.

A variation of the SINK technique has been described for sampling of SELs <3 cm arising from the muscularis propria in the stomach and esophagus. In this technique, the mucosa overlying the lesion was resected by using a snare, and once the lesion was exposed the upper half of the lesion was grasped and resected. This procedure had a diagnostic yield of 94% in a series of 16 patients.[121] Minor hemorrhage was seen in 56% of cases, but hemostasis was achieved in all cases with argon plasma coagulation, and no perforations were reported.

A potential disadvantage of the jumbo biopsy and partial resection techniques is development of perilesional fibrosis that may render subsequent attempts at endoscopic resection difficult or even impossible.[122,123]

EUS-FNA

EUS evaluation of a SEL can guide the endoscopist to the optimal tissue acquisition technique. When available, EUS-FNA is the most widely used method for obtaining tissue from SELs arising from the submucosal or muscularis propria layer. However, the diagnostic accuracy of EUS-FNA ranges widely from 46% to 93% in the evaluation of GI stromal tumors.[124]

Several factors that may impact the diagnostic yield of EUS-FNA of SELs have been evaluated, including lesion size, type and size of needle used, biopsy technique, the availability of on-site cytology review, and whether or not a stylet or suction are used. The diagnostic yield for EUS-FNA in small lesions is low, thus, various other endoscopic techniques described earlier have been used to obtain tissue for histologic evaluation, immunohistochemical staining, and risk stratification (especially for GI stromal tumors).

Some of the factors to consider while performing FNA for SELs for maximizing tissue acquisition for immunohistochemical staining include the FNA needle and the needle gauge.

Needle. Various EUS-FNA needles (19G, 22G, 25G) may be used for tissue acquisition. For most SELs, it is essential to acquire sufficient material for both cytology evaluation and cell block preparation to permit immunohistochemical staining. Under certain circumstances, a small core biopsy can be obtained with a 22G or 25G needle. Larger needles (19G) may acquire more tissue but biopsy in some locations (ie, proximal stomach or duodenum) may not be possible because of the needle size and stiffness of the device.[125] Small, mobile lesions may be easier to puncture with smaller 25G needles.[126] A single prospective study reported no difference in the diagnostic yield of SELs between 22G and 25G needles (22G 80% vs 25G 60%; P = not significant).[127]

Stylet and suction. Initial lesion puncture with a stylet may prevent contamination or clogging of the needle, yet it is not clear that this increases diagnostic yield. A prospective randomized trial evaluating EUS-FNA of solid lesions (including SELs) found that the use of a stylet did not improve the diagnostic yield or frequency of inadequate samples.[128] The additional utility of suction or slow stylet withdrawal to improve sampling during FNA of SELs is also unknown.

Needle pass and fanning. Accuracy of FNA in SELs has been shown to increase gradually with a plateau reached after the fourth pass.[129] Using the up-down knob on the endoscope or the elevator to move the needle in a fan-like fashion may help sample multiple areas within the lesion. However, there are no data that fanning increases diagnostic accuracy of these lesions.

On-site cytopathology evaluation. Real-time evaluation by a trained cytotechnician or cytopathologist of the specimen adequacy from a direct smear of FNA samples may decrease the number of FNA passes required and nondiagnostic specimens acquired. However, there are currently insufficient data to recommend its routine use for evaluation of SELs.

Core biopsy needles. Histologic specimens may aid in the diagnosis and further characterization of SELs. Standard FNA needles may obtain histologic specimens; however, samples are often insufficient for immunohistochemical staining, which is critical for differentiating SELs. New needles specifically designed to acquire core biopsy specimens are available in different gauges (19G, 22G, and 25G). Kim et al[130] reported that the yield of FNB by using a 22G core biopsy needle (75%) was significantly greater than the yield of a 22G FNA needle (20%) for the evaluation of SELs. EUS-FNB can be used as a salvage technique when FNA results in a nondiagnostic or inadequate specimen.

ENDOSCOPIC RESECTION AND/OR LIGATION AND TUNNELING TECHNIQUES

ESMR

ESMR adapts techniques used for EMR to facilitate removal of lesions up to 20 mm in size that arise from the mucosal and submucosal layers. ESMR involves

resection with a standard snare (with or without a grasping forceps using a double channel endoscope)[131] or by using a transparent cap (ESMR-C) or ligation device (ESMR-L).[131-133]

In ESMR-C, the lesion is suctioned into a clear cap with or without a submucosal injection. Commonly, a submucosal injection is performed, the lesion is suctioned into a clear cap, a preloaded snare is then closed, and the lesion is resected by using electrocautery. When this technique is used, small lesions (mean maximal diameter of 15.6 mm) limited to the submucosa in the esophagus, stomach, duodenum, and sigmoid colon have been resected successfully with a diagnostic yield of 87%.[117] Bleeding was reported in 3 of 23 cases, 2 of which required endoscopic intervention. Because of the risk of perforation, caution should be used while applying these techniques in the duodenum.

ESMR-L involves initial ligation of the base of a small SEL (<20 mm) by using a band or endoloop.[133,134] The overlying mucosa of the lesion could then be unroofed, and a biopsy could be taken alone without resection, or the tissue could be resected completely by using snare electrocautery. Sufficient tissue for immunohistochemical diagnosis was obtained with the suck-ligate-unroof-biopsy technique in all the patients in a series of 24 cases of SEL, with a median size of 10 mm, arising from various layers of the stomach, small bowel, colon, and rectum.[135] ESMR-L reportedly produced spontaneous sloughing of 95% of leiomyomas arising from the fourth layer in the esophagus, stomach, and duodenum within 3.6 to 4.5 weeks after banding without perforation.[136] A limitation of this approach is the inability to retrieve the surgical specimen, and thus tissue diagnosis should be obtained before, or at the time of, ligation. Successful band ligation and complete histologic resection in 96% (24/25) of cases, with SELs of the esophagus limited to the muscularis mucosa or submucosa and measuring <13 mm, have been reported with no major adverse events.[134] ESMR-L by using a band has been used successfully for resection of small carcinoid tumors (usually <10 mm) in the stomach, duodenum, and rectum that are limited to the submucosa, with no involvement seen of the muscularis propria on EUS and without lymph node metastasis.[63,137,138]

ESMR not only excises submucosal lesions but also has been shown to have a significantly higher diagnostic yield for various lesions arising from the submucosa when compared with the bite-on-bite technique using jumbo biopsy forceps.[117] These techniques should be used with caution for lesions arising from the muscularis propria because of the risk of perforation, tumor spillage, and incomplete resection.[139] ESMR may be complicated by bleeding in up to 9% of cases.[140,141] However, this usually can be controlled endoscopically.[140] ESMR also has a risk of perforation, and, thus, ESMR techniques should be considered for lesions limited to the muscularis mucosa or submucosa, and caution should be used when these techniques are used in the duodenum.

ESD

Various terms have been used to describe the application of ESD for diagnostic or therapeutic removal of SELs, including endoscopic enucleation, endoscopic submucosal excavation, or endoscopic muscularis dissection.

ESD has been applied for resection of carcinoid tumors, granular cell tumors, and also SELs arising from the muscularis propria. Lu et al[83] reported en-bloc resection of esophageal granular cell tumors by using ESD in 92.9% (13/14) of cases. Procedure time ranged from 25 to 60 minutes, and no adverse events were seen. ESD of type I gastric carcinoid tumors and colorectal carcinoid tumors <2 cm has been reported, with complete resection performed successfully in >90% of cases.[142,143]

He et al[144] reported ESD of 145 gastric SELs arising from the muscularis propria with a mean diameter of 15 mm (range 3-50). Complete resection was obtained in 92% of lesions. Perforation was seen in 14% of cases, but all were managed endoscopically with clips or nylon bands. No local recurrence or distant metastases were seen during the mean follow-up of 19 months (range 3-51 months). The mean time required for these procedures has been reported to be 71 minutes (range 40-105 minutes).[145] A higher risk of perforation occurs in nonmobile fixed lesions and in lesions in which the underlying muscularis layer could not be identified on EUS.[146,147]

Although ESD may provide complete resection of SELs, there are limitations to this technique. ESD is technically challenging, time consuming, and has limited application for large tumors (>5 cm) because of a reported perforation rate of up to 19% for larger lesions.[145] Additional risks include positive resection margins, bleeding, and tumor spillage because of a disrupted lesion capsule. Therefore, despite studies reporting low recurrence rates with ESD of SELs up to 5 cm, its widespread application for this indication remains controversial.

STER

Submucosal tunneling was first described in an animal model for access in natural orifice transluminal endoscopic surgery and subsequently used in the esophagus for per-oral endoscopic myotomy for the management of achalasia.[148,149] It has been applied for endoscopic resection of SELs arising from the muscularis propria in the esophagus and gastric cardia.[150] Submucosal tunneling with endoscopic biopsy of SELs to obtain tissue for histologic assessment also has been reported.[151]

The STER technique involves creating a mucosal incision at least 5 cm proximal to the lesion, and through this incision the endoscope is advanced into the submucosal space. Submucosal dissection is performed until the lesion is seen in the tunnel. Then the lesion is enucleated by using ESD techniques, taking care that the overlying mucosa is not breached. Once the tumor is completely resected, it is retrieved through the tunnel, and the mucosal incision site is closed.

The potential advantage of STER over ESD is maintenance of the integrity of the mucosa, which promotes wound healing and reduces risk of peritonitis and mediastinitis. Multiple case series have reported en-bloc resection rates of 78% to 100% with this technique and an adverse event rate of 11% to 33%.[150,152-156]

In the largest reported experience to date of STER, complete resection was performed in all 85 small (≤3 cm) upper GI SELs arising from the muscularis propria.[157] The overall rate of adverse events was 9.4%, including pneumothorax in 7.1%, subcutaneous emphysema in 9.4%, and pneumoperitoneum in 4.7%. All adverse events were managed conservatively.

Larger prospective studies and comparison with surgery are needed to further evaluate the safety and efficacy of this technique. Incomplete resection, resection of lesions in difficult locations such as the fundus, and resection of larger lesions remain challenges with this method. The application of these techniques requires clinical expertise and specialized centers, thereby limiting their broad adoption.

Endoscopic full-thickness resection

For SELs arising or infiltrating the muscularis propria, especially GI stromal tumors, a full-thickness resection is required to ensure reliable and complete removal. Two different techniques for endoscopic full-thickness resection (EFTR) are (1) full-thickness resection followed by endoscopic closure of the defect and (2) initial creation of a serosa-to-serosa approximation followed by EFTR.

Hybrid EFTR is a combined endoscopic and laparoscopic technique especially used for lesions such as small GI stromal tumors that do not require lymphadenectomy and can be treated by radical tumor enucleation. The use of the submucosal tunneling technique has been reported for performing EFTR of gastric SELs. Because EFTR results in a GI wall defect, reliable and effective defect closure is mandatory. Endoscopic closure of defects created by these techniques has been performed by using standard clips, over-the-scope clips, endoscopic suturing, and endoloops.[157-159]

Zhou et al[157] reported EFTR of 26 gastric SELs arising from the muscularis propria by using ESD techniques with closure of the defect by using endoclips. Complete resection was obtained in 100% of cases. The mean tumor size was 2.8 cm (1.2-4.5 cm), and no major adverse events were reported.

It has been postulated that securing the luminal wall patency before resection may potentially decrease the risk of intra-abdominal infections related to EFTR. Thus, the concept of application of an over-the-scope clip over GI SELs in various locations (esophagus, stomach, duodenum, and rectum) followed by snare resection above the clip has been developed. Complete (R0) resection with this technique was possible in 87.5% (7/8) of cases, and full-thickness resection was achieved in 25% of cases.[160] There were no adverse events, but a drawback of this technique is that the size of the cap limits the size of the lesion that can be resected (mean size 13.4 mm). To mitigate this limitation, a novel full-thickness resection device has been used to resect larger lesions.[161] Because of the large outer diameter of 21 mm, per-oral passage is difficult, and this limits it use to colon lesions.

Potential advantages of EFTR include applicability to large tumors (up to 4 cm), ability to perform complete resection of lesions arising from the muscularis propria, and performance in difficult-to-access locations such as the fundus and proximal body. However, secure and effective closure of the defect is of utmost importance.

MANAGEMENT ALGORITHM

Management of subepithelial GI lesions depends on the etiology, location, size, symptoms, and patient-related factors such as age, comorbidities, life expectancy, preference, compliance with follow-up, and need for surveillance examinations (Fig. 3). The principal indications for surgery include SELs that are symptomatic or malignant or those with a risk of metastases such as larger carcinoid tumors in the duodenum or rectum. Thus preoperative characterization of the size and type of SEL is critical. However, EUS and all tissue acquisition techniques discussed earlier have limitations. The goals of surgery are complete resection, avoiding tumor rupture and spillage, intraoperative staging, and lymph node resection when metastasis is suspected.

Asymptomatic benign lesions such as lipomas, vascular lesions, cysts, pancreatic rests, and leiomyomas do not require any intervention or follow-up. Lesions with malignant potential should be resected either endoscopically or surgically, based on patient preference; lesion type, size, and location; and available expertise in endoscopic resection techniques or surgery. Laparoscopic resection for malignant lesions remains the standard of care.[162,163]

RECOMMENDATIONS

1. We suggest that EUS be used to further characterize indeterminate SELs. ⊕⊕⊕◯
2. We suggest surveillance EUS for gastric GI stromal tumors <2 cm in size. ⊕⊕◯◯
3. We recommend surgery for gastric and colorectal GI stromal tumors >2 cm in size and those with high-risk features. ⊕⊕⊕◯
4. We recommend that rectal GI neuroendocrine neoplasms <1 cm in size may be managed by local endoscopic or transanal excision. ⊕⊕⊕◯
5. We suggest EUS for staging of rectal GI neuroendocrine neoplasms >1 cm. Endoscopic or transanal excision may be considered for rectal tumors 1 to 2 cm in

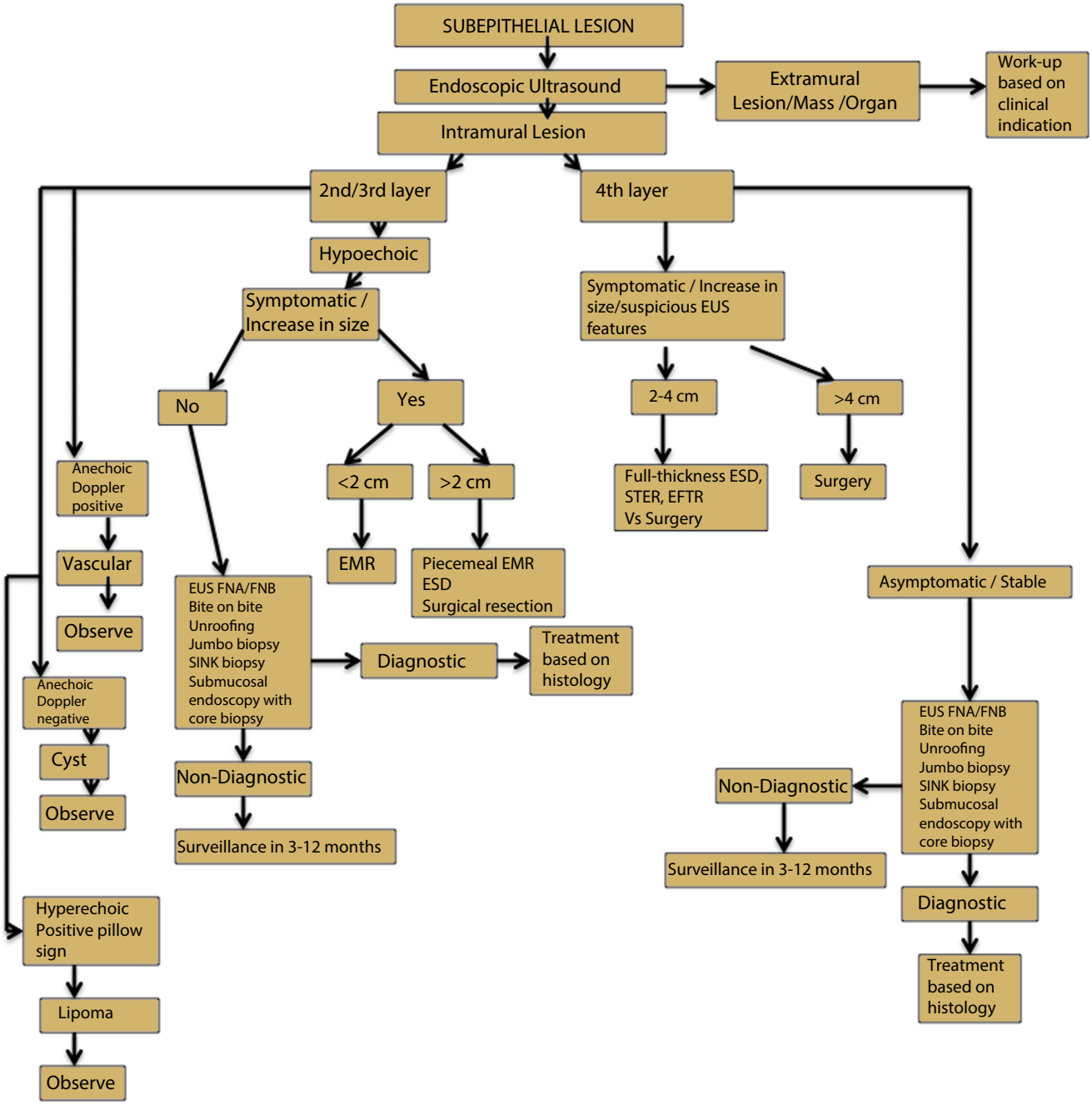

Figure 3. Management algorithm of subepithelial GI lesions. *ESD,* endoscopic submucosal dissection; *STER,* submucosal tunneling with endoscopic resection; *EFTR,* endoscopic full-thickness resection; *FNB,* fine-needle biopsy; *SINK,* single-incision needle-knife; *EUS-FNA,* EUS fine-needle aspiration.

diameter that do not invade the muscularis propria. ⊕⊕◯◯

6. We recommend surgical resection for GI neuroendocrine neoplasms identified in the jejunum and ileum. ⊕⊕⊕◯
7. We recommend that asymptomatic leiomyomas do not require endoscopic surveillance or therapy unless symptomatic. ⊕⊕⊕◯
8. We recommend that GI lipomas do not require follow-up or therapy unless symptomatic. ⊕⊕⊕◯
9. We suggest that lesions arising from the muscularis propria be sampled with FNA or fine-needle biopsy for histologic evaluation. ⊕⊕◯◯
10. We suggest that a firm, round subepithelial lesion with central umbilication along the greater curve of the antrum of the stomach be considered diagnostic for a pancreatic rest. Further investigation with EUS and follow-up is not required. ⊕⊕◯◯
11. We suggest that lesions with malignant potential requiring treatment can be removed either

endoscopically or surgically based on the type of lesion, size, location, patient preference, and available expertise. ⊕⊕○○

DISCLOSURE

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Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; EFTR, endoscopic full-thickness resection; ESD, endoscopic submucosal dissection; ESMR, endoscopic submucosal resection; ESMR-C, ESMR done with a transparent cap; ESMR-L, ESMR done with a ligation device; EUS-FNA, EUS-guided FNA; FNB, fine-needle biopsy; SEL, subepithelial lesion; SINK, single-incision needle-knife; STER, submucosal tunneling with endoscopic resection.

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