American Gastroenterological Association Institute Technical Review on the Management of Gastric Subepithelial Masses

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See CME Quiz on page 2208.

Subepithelial mass lesions in the stomach are relatively common findings in patients undergoing upper gastrointestinal endoscopy. While such masses are often referred to as submucosal, these lesions are more correctly termed subepithelial because they may arise from layers of the gastric wall other than the histologic submucosa or from extrinsic compression of the stomach by a number of normal or abnormal intra-abdominal structures. In practice, the diagnostic evaluation and subsequent management of subepithelial masses varies considerably because approaches to these lesions are currently in evolution. The goal of the present review is to examine available evidence concerning the diagnosis and management of gastric subepithelial masses.

A literature review was conducted to identify all English-language articles relating to gastric subepithelial masses published between 1980 and 2005. A search of MEDLINE and PubMed was performed using the following key words: subepithelial tumor, subepithelial mass, submucosal tumor, or submucosal mass. The following terms were also searched to identify additional relevant articles: gastrointestinal stromal tumor, carcinoid, pancreatic rest, glomus tumor, inclusion cyst, duplication cyst, leiomyoma, leiomyosarcoma, lymphoma, lipoma, inflammatory fibroid polyp, and extraluminal compression. The reference lists of the articles identified in this manner were then manually searched to identify any additional references. References published only in abstract form were excluded. The present review concerns gastric subepithelial masses, and therefore articles concerned solely with subepithelial masses in other parts of the gastrointestinal tract were also excluded.

Epidemiology

The endoscopic appearance of a subepithelial lesion in the stomach is that of a mass, bulge, or impression visible within the gastric lumen that is covered by normal-appearing epithelium. While every endoscopist has encountered subepithelial lesions during endoscopy, the frequency of finding such lesions is likely to vary according to the size and location of the mass as well as the care taken during the endoscopic examination. The prevalence of subepithelial gastric masses on routine endoscopies is uncertain, although one retrospective study reported a prevalence of 0.36% during upper endoscopy performed between 1976 and 1984.[1] No recent studies have identified the prevalence of gastric subepithelial masses on a population basis.

Diagnostic Techniques

Endoscopy

The evaluation of subepithelial masses begins with the initial endoscopy. Features of subepithelial masses that can be assessed during endoscopy include an estimate of the size, shape, mobility, consistency (pillow sign, firm, cystic), pulsation, color, and mucosal appearance. In general, subepithelial masses have normal-appearing mucosa overlying the lesion, although erythema or inflammation on histologic examination of mucosal biopsy specimens unrelated to the underlying mass can be present. Furthermore, subepithelial lesions usually appear smooth with tapered margins along the edge of the lesion. However, it can be difficult to differentiate an intramural lesion from extramural compression with endoscopy alone. Two prospective studies have shown that the sensitivity and specificity of endoscopy to correctly differentiate an intramural lesion from extramural compression were between 89% and 98% and between 29% and 64%, respectively.[2,3]

Probing of the subepithelial mass can be performed with closed biopsy forceps to determine its consistency. If there is any concern that the lesion is vascular or cystic,

Abbreviations used in this paper: CT, computed tomography; ESD, endoscopic submucosal dissection; ESMR, endoscopic submucosal resection; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; GIST, gastrointestinal stromal tumor; MRI, magnetic resonance imaging.

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no biopsy specimens should be taken until the lesion has been evaluated with endoscopic ultrasonography (EUS). However, the consistency of the mass can suggest a diagnosis. For example, a mobile mass that is soft and indents when depressed using biopsy forceps (pillow sign) is highly suggestive of a lipoma.[2] Further evaluation is suggested for lesions that are firm and not consistent with either a cyst or a lipoma.

Endosonography

EUS can reliably differentiate intramural lesions from extrinsic compression. Furthermore, EUS will often result in a specific diagnosis, especially if the lesion is due to extrinsic compression. If an intramural lesion is identified, EUS can be used to ascertain the exact size and layer of origin, as well as additional morphologic features that can suggest the diagnosis. On EUS, the mass can be either homogeneous or heterogeneous and can be hyperechoic, hypoechoic, or anechoic. Anechoic masses can also be interrogated with Doppler to assess for blood flow. EUS is also used to evaluate the margins of the mass to determine if they are smooth or irregular and whether the mass disrupts or distorts adjacent layers or organs. Small, well-circumscribed lesions are typically benign, whereas a lesion with irregular margins that invades into other layers or structures is more likely to represent a malignant process.[4,5] The features identified on EUS can then be used to determine if further tests such as endoscopic resection, fine-needle aspiration (FNA), or core biopsies are required.

EUS imaging of the gastrointestinal tract wall typically exhibits 5 distinct layers but can also exhibit 7 or 9 layers, depending on the region of the gastrointestinal tract being examined and the frequency of the ultrasound transducer. Initial interpretation of the EUS images assumed direct correspondence of the layers seen on EUS to those seen on histology. However, it was later proven that this was an incorrect interpretation of the EUS images of the gastrointestinal tract wall.[6] In fact, it was shown that the 5 distinct layers seen on EUS imaging corresponded to the following: layer 1, interface echo between the superficial mucosa and the acoustic coupling medium; layer 2, deep mucosa; layer 3, submucosa plus the acoustic interface between the submucosa and muscularis propria; layer 4, muscularis propria minus the acoustic interface between the submucosa and muscularis propria; and layer 5, serosa and subserosal fat.

Cross-sectional Imaging (Computed Tomography/Magnetic Resonance Imaging)

Transabdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) findings in patients with subepithelial masses have been the subjects of case reports and small case series. These imaging studies are most useful for defining the origin and extent of large extramural masses. Large lipomas can be detected on both CT and MRI by the characteristic density and magnetic resonance properties of fatty tissue.[7] CT and MRI can image large gastrointestinal stromal tumors (GISTs) and are especially helpful in the evaluation for metastatic spread of malignant GISTs.[8,9] Unlike EUS, CT and MRI cannot identify the histologic layers of the gut wall and are therefore of limited value in distinguishing between the different causes of intramural masses.

Tissue Diagnosis

Initial evaluation of subepithelial lesions with EUS helps identify those lesions where tissue diagnosis may be necessary. If a subepithelial lesion is found to be a hypoechoic mass in the third or fourth echo layer on EUS examination, then tissue sampling should be strongly considered to establish the diagnosis because malignant or potentially malignant lesions are included in the differential diagnosis and EUS findings have been shown to be insufficient to correctly establish the diagnosis.[2] A preoperative tissue diagnosis may not be necessary for large and/or symptomatic lesions that require surgery irrespective of histology. The need to obtain tissue from small (<1 cm) hypoechoic masses of the gastric wall is controversial and has not been adequately studied but should be considered given the potential for malignant behavior of such lesions.

EUS-guided FNA. EUS-guided FNA is commonly used to confirm the presence of malignancy in lymph nodes or organs adjacent to the gastrointestinal tract. EUS-guided FNA (typically with a 22-gauge needle) can be used to obtain a specimen for cytologic examination, and occasionally core tissue specimens, by directing the needle into the area of interest under direct ultrasound guidance.[10,11] Complications from EUS-guided FNA are rare but include perforation, infection, or hemorrhage.[10,12–16] An exception may be cyst aspiration, where infection has been reported to occur in up to 15% of cases, justifying the use of preprocedural antibiotic prophylaxis.[17,18] In reports in which prophylactic antibiotics were administered before aspiration of cysts, fewer infectious complications have been reported.[14,19]

Cytology is most useful for distinguishing benign from malignant lesions but is less useful for determining the type of benign lesion present. Thus, the sensitivity, specificity, and accuracy of cytologic evaluation of intramural lesions are low.[11,12,20] The yield of EUS-guided FNA in the diagnosis of hypoechoic fourth-layer masses

such as GISTs may be improved with the application of immunohistochemical analysis.[11,21–23] Common markers used to evaluate hypoechoic intramural masses are CD117 (c-kit), CD34, smooth muscle actin, and S100.[23,24] The c-kit protein is a transmembrane receptor with tyrosine kinase activity that is highly sensitive and specific for GISTs. CD34 is also expressed in approximately 80% of GISTs. Positive staining for smooth muscle actin suggests the presence of a leiomyoma or glomus tumor, and the presence of S100 suggests a neural origin or Schwannoma. A preliminary study by Ando et al[21] suggested that immunohistochemical staining for Ki-67, a marker of cell proliferation, improved the ability to diagnose malignant GISTs. If this finding is confirmed, it would be a significant advance because the inability of EUS-guided FNA to accurately predict which GISTs have high potential for malignant behavior is currently a major limitation of this procedure.

EUS-guided core needle biopsy. EUS-guided core needle biopsy using a 19-gauge Trucut needle (QuickCore; Wilson-Cook, Inc, Winston-Salem, NC) has been proposed as a method for obtaining sufficient tissue for histologic evaluation.[25,26] The Trucut needle provides a core of tissue that can be examined histologically for changes in tissue architecture in addition to the individual cell morphology scrutinized in the cytologic evaluation of FNA specimens. Initial experience using the Trucut biopsy needle in intramural lesions yielded the correct diagnosis in 4 of 5 cases compared with 1 of 5 cases using EUS-guided FNA.[25] However, additional prospective studies are required to determine if EUS-guided core needle biopsy results in greater accuracy than EUS-guided FNA and to determine if complications are more frequent with this technique.

Stacked forceps biopsy. Standard biopsy forceps are designed to sample primarily the mucosa, although submucosa is sometimes obtained. By taking multiple biopsy specimens of the same site using a jumbo forceps (interchangeably referred to as stacked, bite-on-bite, or tunneled biopsies), tissue from deeper layers of the gastric wall can be obtained. This technique appears to be safe with a relatively low risk of bleeding, although the diagnostic yield also appears to be limited. In one study, the diagnostic yield of stacked biopsies was 42% (15/36 lesions) and the complication rate was 2.8% (1/36 cases complicated by bleeding).[27]

Endoscopic submucosal resection and dissection. The use of endoscopic submucosal resection (ESMR) or endoscopic submucosal dissection (ESD) to resect submucosal lesions is another technique to obtain tissue specimens for accurate histologic diagnosis.[27–31] This technique provides greater yield than stacked biopsies but has not been compared with either EUS-guided FNA or EUS-guided core needle biopsy. ESMR and ESD are usually reserved for lesions that are confined to the submucosal or deep mucosal layers due to the increased risk of perforation associated with endoscopic resection of lesions from the muscularis propria; however, there are some small case series in the literature of endoscopic resection of lesions arising from the muscularis propria with no associated perforations.[27,28] Given that the perforation rate for ESMR of submucosal lesions is reported to be 2%–3%, it is likely that endoscopic resection of lesions from the muscularis propria will be similar if not higher.[22] Bleeding, both during the procedure and delayed, is a significant complication that can occur with all endoscopic resection techniques.

Differential Diagnosis

The differential diagnosis of a gastric subepithelial mass depends on whether the lesion represents compression from a normal or abnormal structure adjacent to the gastric wall or if it originates from the wall itself. A brief description of lesions in the differential diagnosis of subepithelial lesions is presented with a description of the corresponding findings on EUS examination and additional methods that can be used to obtain tissue to establish the diagnosis. The differential diagnoses for intramural causes of gastric subepithelial masses are presented as benign lesions or lesions that are malignant or have malignant potential (Table 1).

Extramural Lesions

The most common source of extraluminal compression in the stomach is from the spleen and splenic vessels.[2,3,32] Other sources of extraluminal compression include normal abdominal structures such as the left lobe of the liver, gallbladder, colon, and pancreas. In addition, pathologic lesions such as tumors, abscesses, pancreatic pseudocysts, renal cysts, aneurysms, and enlarged lymph nodes can appear as gastric subepithelial lesions on endoscopy.

Benign Intramural Lesions

The differential diagnosis for intramural causes of gastric subepithelial masses can be divided into benign lesions or lesions that are malignant or have malignant potential.

Lipoma. Gastric lipomas are a rare cause of gastric subepithelial masses, accounting for <1% of gastric intramural lesions.[33] Gastric lipomas are benign, slow-growing lesions; however, they can cause significant clinical symptoms such as bleeding caused by ulceration, obstruction

Table 1. Differential Diagnosis of Intramural Gastric Subepithelial Masses Based on EUS Features

Subepithelial lesion	EUS layer[a]	Echogenicity
Benign		
Leiomyoma	2, 3 or 4	Hypoechoic
Neural origin tumors		
Schwannoma	3 or 4	Hypoechoic
Neuroma		
Neurofibroma		
Lipoma	3	Intensely hyperechoic
Duplication cyst	Any or extramural	Anechoic
Pancreatic rest	2 or 3	Hypoechoic
Inflammatory fibroid polyp	3 or 4	Hyperechoic
Granular cell tumor	2 or 3	Hypoechoic
Varices	2 or 3	Anechoic
Malignant or with malignant potential		
GIST	4 (rarely 2 or 3)	Hypoechoic
Lymphoma	2, 3 or 4	Hypoechoic
Carcinoid	2 or 3	Hypoechoic
Metastatic carcinoma	Any	Hypoechoic
Glomus tumor	3 or 4	Hypoechoic

[a]Layer 1 is the interface of luminal fluid and mucosa, layer 2 represents the deep mucosa, layer 3 is largely due to the submucosa, layer 4 represents the muscularis propria, and layer 5 is adventitia or serosa with adjacent fatty or fibrous tissue.

from intussusception into the pylorus or duodenal bulb, and abdominal pain.[7,33,34] Lipomas present typically as solitary lesions; however, multiple lipomas of the stomach and duodenum have been reported.[35] On endoscopy, lipomas can have a yellow hue, often exhibit a pillow sign when probed with closed biopsy forceps, and may also exhibit some mobility. A recent study showed that the pillow sign had 98% specificity but only 40% sensitivity in identifying lipomas.[2] The finding of an intensely hyperechoic well-circumscribed mass arising from the submucosal wall layer on EUS examination is essentially diagnostic for a lipoma, and no further evaluation is needed in such cases.

Leiomyoma. Leiomyomas are smooth muscle tumors that arise from either the muscularis mucosae or muscularis propria within the wall of the gastrointestinal tract and are benign tumors composed of well-differentiated smooth muscle cells. True leiomyomas are rarely found in the stomach, although case reports are abundant in the older literature because tumors that are now classified as GISTs were often misclassified as leiomyomas or leiomyosarcomas. With new immunohistochemical methods, it is clear that tumors of smooth muscle origin, as identified by positive staining for α–smooth muscle actin and desmin and negative staining for CD117, CD34, and S100 protein, are rare in the stomach. A recent study that examined archived histologic slides of more than 500 gastrointestinal mesenchymal tumors previously classified as smooth muscle tumors showed that most were actually GISTs with the exception of masses in the esophagus, where true leiomyomas were more common.[36] In this relatively large study, no gastric leiomyomas were identified. In another retrospective study of gastric spindle cell tumors, 2 of 17 tumors were identified as leiomyomas.[21] Leiomyomas appear as hypoechoic, well-circumscribed masses arising from the muscularis propria or the muscularis mucosae on EUS examination.

Varices. Gastric varices can have the appearance of a subepithelial mass or large gastric fold on endoscopy.[37] Gastric varices should be suspected in patients with portal hypertension (end-stage liver disease, Budd–Chiari syndrome, portal vein thrombosis, and so on) and in patients with splenic vein thrombosis, typically due to pancreatitis, that result in isolated gastric varices. Endoscopic examination may reveal the presence of portal hypertensive gastropathy, and probing with closed biopsy forceps may reveal a soft consistency to the lesion. Closely examining the color of the lesion for a blue hue can also suggest that the lesion may be a varix. If these features are present, biopsy specimens should not be obtained and EUS examination should be performed to confirm that the lesion is a varix. EUS examination will show a round or tubular hypoechoic or anechoic structure located in the submucosa (third layer), and Doppler examination will demonstrate flow within the structure.

Pancreatic rest. A pancreatic rest or heterotopic pancreatic tissue is the presence of ectopic pancreatic tissue within the wall of the stomach, typically in the gastric antrum, and usually within the submucosal layer.[38] Although they generally do not cause symptoms, pancreatic rests have been reported to present with nausea, epigastric pain, weight loss, hematemesis, and gastric outlet obstruction.[38,39] In addition, there are rare case reports of heterotopic pancreatic tissue that have undergone malignant change.[40–44] On endoscopy, a pancreatic rest commonly exhibits an umbilication on the surface of the nodule, although the specificity of this finding is not known. On EUS examination, a pancreatic rest will appear hypoechoic relative to the surrounding submucosal layer with a heterogeneous echotexture. Because the differential diagnosis for hypoechoic third-layer lesions includes potentially malignant lesions, tissue sampling to establish the diagnosis is necessary. Cap-assisted ESMR has been reported as a potential endoscopic method of obtaining an adequate histologic sample to diagnose a pancreatic rest.[45]

Duplication cyst. Gastrointestinal duplication cysts are benign lesions that result from an error in the embryonic development of the foregut and are primarily diagnosed in the pediatric population.[46,47] Duplication cysts in adults are often found incidentally and are usually asymptomatic. The cysts are located either within or adjacent to the wall of the gastrointestinal tract and are lined with gastrointestinal epithelium.[48] Because duplication cysts generally do not communicate with the gastrointestinal lumen, they can enlarge, resulting in mass effect, rupture, or bleeding.[46,49,50] The diagnosis of a gastric duplication cyst can easily be made using EUS, which will show an anechoic, smooth, spherical, or tubular structure with a well-defined wall.[51,52] If the cystic structure is adjacent to the pancreas, EUS/FNA can be performed to sample the fluid contents of the cyst to rule out a pancreatic pseudocyst or a pancreatic cystic neoplasm.[53]

Inflammatory fibroid polyp. Gastric inflammatory fibroid polyps are rare benign lesions in the stomach that are characterized histologically by fibrous tissue that is not encapsulated. In addition, there are commonly many small blood vessels and an eosinophilic inflammatory infiltrate.[54,55] On EUS examination, the polyps are located in the deep mucosal or submucosal layers without involvement of the muscularis propria.[55] They are typically hypoechoic with a homogeneous echotexture and indistinct margins. Occasionally they will appear slightly hyperechoic, which corresponds histologically with multiple small penetrating vessels within the fibrous stroma of the polyp.[55]

Malignant and Potentially Malignant Intramural Lesions

GIST. GISTs are the most commonly identified intramural subepithelial mass in the upper gastrointestinal tract, and some controversy exists regarding the diagnosis and management of these tumors. It is believed that 5000–6000 new cases of GIST are diagnosed each year, with 10%–30% being malignant.[56] Most patients are in their fifth or sixth decade of life at the time of diagnosis, and the most common location of GISTs is the stomach.[24,56] GISTs were once believed to represent smooth muscle tumors (leiomyomas and leiomyosarcomas); however, they are now believed to arise from the interstitial cells of Cajal and can be identified using immunohistochemistry for expression of CD117, which is also known as c-kit protein (a cell membrane receptor with tyrosine kinase activity). Due to this recent change in classification, the older literature may be confusing and must be considered in light of this new information. A study of archived histologic slides of masses previously classified as smooth muscle tumors showed that most were actually GISTs with the exception of masses in the esophagus, where true leiomyomas were more common.[36]

GISTs most commonly arise from the muscularis propria and are usually asymptomatic until the tumor becomes large or ulcerates, resulting in bleeding. EUS examination of a GIST shows a hypoechoic mass with a homogeneous echotexture that is contiguous with the muscularis propria (fourth EUS layer). Findings on EUS of a mass diameter >3 cm, irregular extraluminal border, cystic spaces, echogenic foci (heterogenous echotexture), and adjacent malignant-appearing lymph nodes are features that can suggest malignancy[4,5]; however, even small GISTs have malignant potential and have been reported to metastasize.[57–59] Unfortunately, EUS findings do not accurately predict the malignant potential of a small GIST and histologic examination is necessary. There are reports of new techniques using EUS-guided FNA or core needle biopsies that may be helpful in determining the malignant potential of a GIST without having to perform surgical resection; however, studies examining their clinical utility in large numbers of patients have yet to be reported.[10,21,60]

Carcinoid tumor. Gastric carcinoid tumors are neuroendocrine tumors that originate from enterochromaffin-like cells located in the gastric mucosa. Carcinoid tumors can be solitary or multiple, the latter usually occurring in the setting of hypergastrinemia due to gastrinoma or autoimmune atrophic gastritis. Carcinoid tumors originate in the mucosal layer and can invade into deeper structures of the gastrointestinal tract wall.[61] The biologic behavior appears to be different between solitary gastric carcinoids and multiple gastric carcinoids due to hypergastrinemia; solitary gastric carcinoids exhibit a greater potential for malignancy and metastasis to local lymph nodes and the liver.[62–64] On endoscopy, carcinoids typically appear as polypoid lesions with normal-appearing overlying mucosa.[65] EUS examination of a carcinoid tumor will show a hypoechoic lesion, typically originating from the deep mucosa or submucosa (second or third EUS layer), and can be useful in identifying the depth of invasion of the carcinoid tumor.[66] Furthermore, EUS can be used to assess for possible local lymph node metastasis.

Lymphoma. Primary gastric lymphomas are typically either diffuse large B-cell lymphomas or low-grade B-cell mucosa-associated lymphoid tissue lymphomas.[67,68] In addition, disseminated nodal disease can secondarily involve the gastrointestinal tract.[69] Endoscopically, gastric lymphomas can present as an ulcerated polypoid mass, thickened gastric folds, or subepithelial

mass. Because gastric lymphomas typically involve the deep mucosa, standard biopsy specimens usually provide sufficient tissue to make the diagnosis. EUS of primary gastric lymphoma typically shows a hypoechoic lesion that can be localized to the second and third layers of the gastric wall or extend through the entire wall.[70] EUS can also be used to assess for local lymph node involvement, and EUS-guided FNA can be used to obtain tissue for flow cytometry to establish the diagnosis.[71,72]

Glomus tumor. Glomus tumors originate from modified vascular smooth muscle cells and usually occur in peripheral soft tissue but can also occur in the gastrointestinal tract, typically the stomach.[73,74] These lesions are usually benign, but they have potential for malignant behavior and can also present with ulceration and hemorrhage. In a retrospective study of 31 gastric glomus tumors, Miettinen et al reported that all but one tumor exhibited benign behavior; however, one patient died due to liver metastases of the glomus tumor.[73] EUS will show a hypoechoic, well-circumscribed mass located in the third and/or fourth EUS layer; however, EUS findings are insufficient to establish the diagnosis and cannot be used to predict the malignant potential of the tumor.[75] EUS-guided FNA has been reported to successfully diagnose glomus tumors using cytologic and immunohistochemical analysis. Immunohistochemical staining will show positivity for smooth muscle actin and vimentin while being negative for CD117 (c-kit) staining, which helps to differentiate these lesions from GISTs.[73,76]

Metastasis. Metastatic spread of malignancies to the gastric wall is extremely rare; however, various malignancies have potential to metastasize to the gastric wall, including malignant melanoma as well as carcinomas of the breast, lung, kidney, and ovaries.[77–82] EUS examination of most metastatic lesions will show a hypoechoic lesion that can be in any layer of the gastric wall. EUS-guided FNA can be performed to obtain tissue to establish the diagnosis of metastasis to the gastric wall.[81]

Management

The management of gastric subepithelial lesions depends on the diagnosis determined using the findings at endoscopy, EUS, and biopsy. Many benign gastric subepithelial masses, including lipomas, varices, pancreatic rests, duplication cysts, and extramural compression from normal structures, require no further evaluation or follow-up. The management of frankly malignant lesions is also straightforward in that all such lesions require complete removal by either surgical or endoscopic resection. However, many gastric subepithelial masses, including GISTs and some carcinoid tumors, may not be malignant at diagnosis but have potential for malignant behavior. The management of this category of gastric subepithelial lesions is controversial and often based on limited data and/or clinical experience. While a comprehensive review of the management of all the lesions that can present as a gastric subepithelial mass is beyond the scope of this review, strategies for observation versus surgical or endoscopic resection are discussed, with particular attention to GISTs and carcinoid tumors.

Management of GISTs

The clinical behavior of GISTs is quite variable and can be difficult to predict on the basis of available clinical and histologic features. Nonetheless, a consensus conference has proposed a strategy for predicting malignant behavior of GISTs based on size (<2 cm, 2–5 cm, 5–10 cm, >10 cm) and mitotic count on histology (<5, 6–10, or >10 per 50 high-power field), with the understanding that no GIST can be defined as benign on the basis of currently available diagnostic testing.[24] It should be noted that this method for predicting the malignant potential of GISTs requires a surgical specimen to determine the mitotic count and therefore cannot be determined preoperatively. EUS criteria, including size (>3 cm), irregularity of the extraluminal border, and the presence of cystic spaces, echogenic foci, and heterogeneity, have also been associated with an increased likelihood of malignant behavior of GISTs, although the sensitivity and specificity of these criteria are imperfect and there is also considerable interobserver variability in interpretation of these findings.[4,5] Moreover, the natural history of GISTs is incompletely defined, and the potential for malignant behavior of even small lesions exists.[21,57–59]

The optimal management of these lesions remains controversial. All GISTs have malignant potential according to the classification system proposed by the National Institutes of Health Consensus Conference[24]; however, the absolute potential for malignancy and metastasis appears to be very low, especially for small (<3 cm) lesions. Because surgery is the current standard of care for resecting GIST lesions, there is debate as to whether the potential morbidity and mortality associated with surgical resection are acceptable for removing a lesion with low potential for malignancy. Given the lack of sufficient evidence to guide management, we recommend that this decision be made on an individual basis, taking into consideration the clinical presentation (eg, symptoms, comorbidities), endoscopic and EUS evaluation, histologic evaluation (if obtained), and patient preference. Only prospective studies with long-term fol-

low-up will identify the appropriate management strategy for GISTs.

Management of Carcinoid Tumors

Gastric carcinoids are believed to arise from enterochromaffin-like cells in the gastric mucosa, and clinical behavior can vary considerably. On the basis of clinical behavior and pathologic features, 3 distinct types of gastric carcinoids have been proposed.[63] Type 1 carcinoids are the most common, encompassing approximately 65% of gastric carcinoids, and are associated with hypergastrinemia in the setting of chronic atrophic gastritis.[83] Type 2 carcinoids arise in the setting of hypergastrinemia associated with a gastrinoma in patients with Zollinger–Ellison syndrome and multiple endocrine neoplasia type 1. Gastric carcinoids that arise in the setting of hypergastrinemia (type 1 and type 2) are generally believed to have a favorable prognosis and rarely become locally invasive or metastatic. This is particularly true for type 1 lesions, where 5-year survival exceeds 95%.[83] Type 3 or sporadic carcinoids are less frequently identified (21% of gastric carcinoids) and arise in the setting of normal serum gastrin levels.[63] In contrast to type 1 carcinoids, up to one half of type 3 carcinoids will become locally invasive or metastatic. While the risk of metastasis is believed to be associated with size, there are reports of even small gastric carcinoids metastasizing to lymph nodes.[84] Therefore, recommended management of type 3 carcinoids in an otherwise healthy individual is aggressive surgical resection.[83] More conservative management of type 1 and 2 carcinoids can be considered, although many authorities recommend endoscopic excision of small (<1–2 cm) gastric carcinoids if feasible followed by endoscopic surveillance.[85] Others have reported that reduction in antral G-cell mass via antrectomy can result in regression of carcinoids associated with hypergastrinemia and may be the optimal treatment for multiple large carcinoids that are symptomatic due to bleeding or obstruction.[86]

Management Strategies

Surveillance. When a subepithelial lesion is believed to be neither benign nor clearly malignant or premalignant or if a patient with a premalignant lesion is deemed to be at excessive operative risk, surveillance may be indicated. This is often the case with third- and fourth-layer hypoechoic masses where tissue sampling (ESMR or FNA) is not technically feasible or is not diagnostic. Such lesions are most likely GISTs. Moreover, if such lesions are small (<3 cm) and no concerning endosonographic features are present, such as irregularity of the extraluminal border or presence of cystic spaces, echogenic foci, or heterogeneity, then surveillance may be considered with the understanding that no GIST can be confirmed to be benign. Only one small series of endosonographic follow-up in this setting has been published.[87] In this series, which included follow-up for a mean of 19 months, 24 of 25 lesions (96%) remained stable with regard to both size and echo features, whereas one lesion increased from 30 to 38 mm and became irregular and inhomogeneous during follow-up. This lesion was subsequently identified to be a GIST with high malignant potential at resection. Therefore, if surveillance of a premalignant lesion is undertaken, it should be done so after thorough discussion with the patient.

If surveillance is selected, there may be alternatives to performing EUS to evaluate for a change in the lesions. Several articles have reported on the use of transabdominal ultrasonography for the examination of lesions arising in the gastric wall.[88–90] While transabdominal ultrasonography is less invasive than EUS, it must be emphasized that not all lesions arising in the gastric wall can be visualized by transabdominal ultrasonography; published series have reported that rates of adequate visualization for surveillance range from 69% to 93%. Polkowski et al have reported than visualization with transabdominal ultrasonography in this setting is inversely proportional to the size of the mass in the gastric wall, with only 61% and 50% visualization for lesions <30 mm and <10 mm, respectively.[90] Therefore, those lesions that are most likely to be considered for surveillance are also those that may be most difficult to visualize with transabdominal ultrasonography. Another alternative to surveillance with EUS may be to follow lesion size alone using gastroscopy with comparison to a size reference such as a biopsy forceps. Hwang et al have reported good correlation between endoscopic evaluation of size with a standard reference (open biopsy forceps) compared with EUS measurement of size.[2] This may have particular utility in settings where EUS is not readily available.

Surgical resection. Treatment of GISTs >3 cm, selected gastric carcinoids, and other malignant or premalignant lesions should be complete removal of the lesion. In addition, lesions in which the malignant potential cannot be determined by less invasive means may also require surgical excision for diagnosis. While a complete review of surgical approaches to subepithelial masses in the stomach is beyond the scope of this review, indications and an overview of techniques are briefly discussed.

For GISTs, local resection with clear margins appears to be adequate and neither wide histologic margins nor lymph node dissection appear to be necessary.[91] Simi-

larly, local excision appears to be adequate for removal of type 1 and type 2 carcinoid tumors, although the need for resection of these lesions is somewhat uncertain.[83,85] In contrast, type 3 gastric carcinoids appear to have much greater potential for aggressive behavior, and partial or total gastrectomy with lymph node dissection is required in such cases.[85]

Traditionally, surgical resection of most malignant and premalignant subepithelial gastric masses has been accomplished by complete local resection using an open surgical approach. However, there are now numerous case series describing the use of laparoscopic[92–98] or combined laparoscopic/endoscopic[99,100] approaches for resection of gastric subepithelial lesions. These series report high success rates usually in excess of 90% among well-selected patients with low rates of complications and shorter hospital stays compared with traditional open resections. However, it must be noted that the length of follow-up in many of the studies of laparoscopic resection is limited, and rates of local recurrence in reported case series of laparoscopic resection of GISTs range from 0% to 30%. Whether the rate of local recurrence differs between minimally invasive and open approaches cannot be determined with certainty from the available literature because no prospective, randomized comparison has been published to date. Despite this, minimally invasive approaches are becoming the standard of care for the surgical resection of GISTs and other mass lesions arising in the gastric wall.

Endoscopic resection. Endoscopic resection of mucosal lesions is a common practice among gastroenterologists, but resection of lesions arising in deeper layers of the gastric wall is less commonly practiced owing to the more technically demanding nature of such procedures and the higher rate of complications, including bleeding and perforation.[27] However, endoscopic resection of lesions arising in both the submucosa and muscularis propria has been described and is increasingly performed, particularly in Asian centers. It must be emphasized that characterization of the layer of origin with EUS is necessary before proceeding with attempted endoscopic resection because the risk of the procedure is directly related to the depth of the tumor within the gastric wall.

Case reports of endoscopic resection of lesions in the submucosal layer date back to the early 1990s.[101,102] Early series of endoscopic submucosal resection primarily included esophageal, small intestinal, and colonic lesions, although more recent series have included increasing numbers of gastric lesions. One early series consisted of 62 patients with esophageal submucosal lesions ranging in size from 0.6 to 7.5 cm.[28] In this series, lesions <2 cm in diameter were removed by standard snare polypectomy and those ≥ 2 cm were removed by stripping of the overlying mucosa followed by enucleation with a snare and electrocoagulation electrode. The investigators reported complete excision of the esophageal submucosal lesions with no perforations and 3 patients who required endoscopic therapy for bleeding. Another series included 45 patients with submucosal tumors in various parts of the gastrointestinal tract that were resected with a polypectomy snare with or without assistance of a grasping forceps using a double-channel endoscope. This series reported complete resection of all lesions with no perforations and only 5 patients with mild or moderate bleeding that was controlled endoscopically.[103] Kojima et al reported their experience with endoscopic submucosal resection of 31 submucosal tumors (14 gastric) with snare electrocautery and a grasping forceps via double-channel endoscope with no perforations and a 9% bleeding rate.[29] In this same series, forceps biopsy of lesions arising in the submucosa was accomplished following resection of the overlying mucosa and submucosa by the same technique. Another series included 27 submucosal lesions (4 gastric) in which attempted removal with either snare and grasping forceps technique or cap-assisted technique was successful in 93% of cases with no complications.[30] One case report has reported the adjunctive use of band ligation before submucosal resection.[104]

Endoscopic resection of lesions arising in the muscularis propria has also been reported in several small case series. Spinelli et al reported on the endoscopic resection of 7 gastric leiomyomas using a polypectomy snare with no major complications.[105] Sun et al reported a series of endoscopic resections of subepithelial lesions, including several lesions arising in the muscularis propria.[31] In this series, EUS was first used to inject saline into the submucosa. Lesions arising in the submucosa were then directly removed with a polypectomy snare, whereas tumors arising in the muscularis propria were removed via enucleation with a polypectomy snare after the overlying mucosa and submucosa were removed with a needle knife. Six submucosal tumors and 9 tumors in the muscularis mucosae were removed, with no perforations and 2 patients requiring endoscopic hemostasis for bleeding. Most lesions removed in this series were classified as leiomyomas, with no distinction made between GISTs and leiomyomas.

One recent study has also reported the use of band ligation for the treatment of lesions arising in the muscularis propria after EUS with FNA or stacked forceps biopsy specimens were used to make a histologic diagnosis.[106] In this study of 64 upper gastrointestinal leiomyomas (14 gastric), bands were placed and lesions

allowed to slough over time with success rates of 100% in the esophagus and duodenum and 75% in the stomach. It should be noted that this study did not evaluate these fourth-layer hypoechoic masses for c-kit, although it is likely that many of these lesions were GISTs. Most of the lesions treated in this series were small (<1–2 cm), and a disadvantage of this technique is that complete histologic evaluation of the lesions was not possible because the masses were not removed but rather allowed to slough into the lumen and pass through the gastrointestinal tract.

A newer technique for endoscopic resection of subepithelial tumors involves the use of an insulated-tip electrosurgical knife, which was initially developed for the endoscopic resection of early-stage gastric cancer. Park et al reported the use of the insulated-tip electrosurgical knife for the resection of 5 esophageal and 10 gastric tumors, including 11 cases in which the tumor arose from the muscularis propria.[107] Complications included bleeding in one patient and perforation in one patient, both of which were managed with placement of endoscopic clips. Rösch et al have recently reported their experience with the combined use of suction cap ESMR and insulated-tip electrosurgical knife resection in 12 patients with tumors localized to the submucosa by EUS.[108] In this series, the complete removal rate was reported to be 79%, with one perforation and one clinically significant bleeding event occurring in these patients.

In all case series of endoscopic resection of gastric subepithelial lesions, it must be emphasized that follow-up was limited and studies have not included examination of surgical or autopsy specimens to confirm completeness of resection. The clinical importance of complete resection of gastric subepithelial masses is currently unknown, although the premalignant nature of many of these lesions should warrant complete removal until data to the contrary are available. Moreover, while reported complication rates are relatively low, they are significantly greater than the risks associated with other endoscopic procedures such as polypectomy and complication rates are likely to be higher among less experienced operators.

Ablation. A single case report has described the use of 95% ethanol to ablate a gastric GIST.[109] In this report, injection of ethanol into a 4-cm GIST under EUS guidance resulted in successful ablation of the tumor with no evidence of residual GIST at follow-up EUS 2 years after treatment. Whether the use of ethanol or other ablative therapies can be used for successful ablation of premalignant subepithelial lesions requires prospective study.

Conclusions

Identifying a subepithelial mass during endoscopy is common. Further evaluation with EUS allows for improved characterization of subepithelial lesions, aiding the clinician in narrowing the differential diagnosis; however, the specificity of EUS imaging findings alone has been disappointing. It must be emphasized that despite the lack of specificity of EUS in diagnosing the etiology of subepithelial lesions, it remains the best test for determining the need for further evaluation, endoscopic resection, or surgery. Obtaining tissue using EUS-guided FNA or endoscopic submucosal resection is often necessary to establish the diagnosis and direct further patient management. The literature is abundant with case reports on endoscopic management of subepithelial masses; however, further investigation is needed to better define the optimal management of patients with GISTs and those with indeterminate lesions.

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