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Endoscopic Approach to Gastrointestinal Stromal Tumors

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The scenario is unfortunately all too common. Evaluating a patient for dyspepsia, the endoscopist is surprised to discover a submucosal mass in the stomach. It is obviously unrelated to the patient's complaint and probably benign—but then again, maybe not. The ensuing encounter with the patient ends unsatisfactorily amid confusion and alarm: Is it causing my symptoms? Is it cancer? Why don't you just take it out? Unrevealing CT scans and ambiguous surveillance endoscopies fuel rising frustration for patient and physician. When the curtain finally rings down on this drama—if it ever does—the plot is often left unresolved. Fortunately, a revision of this sad script is at hand because several recent developments have added considerably to our understanding of submucosal masses and the stromal cell tumors often lurking within them.

Evaluation of submucosal tumors

Background

Mesenchymal tumors of the gastrointestinal (GI) tract arise from the embryologic mesoderm and as such usually occupy a position within the wall of the GI tract. They often protrude into the lumen of the hollow viscus, where they can be seen on endoscopic or radiographic studies. Such an appearance is referred to as a “submucosal tumor,” which is a somewhat confusing term because not all such lesions arise within the submucosal layer. A large variety of lesions originating in several locations can present such an appearance, some of which are

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Table 1
Classification of submucosal tumors of the GI tract

	Non-neoplasms	Neoplasms
Extramural position	Cyst of adjacent organ (pancreas, liver) Organomegaly	Primary or metastatic neoplasm of adjacent organ including lymph nodes
Intramural position	Intramural cyst varices Pancreatic rest	GI stromal tumor Lipoma Granular cell tumor Glomus tumor Metastatic malignancy

listed in [Table 1](#). Whenever a submucosal tumor is encountered, the alert endoscopist bears in mind all the possibilities.

Prior studies of submucosal tumors (SMTs) have suggested that as many as half are extramural structures. These include normal organs such as the liver, spleen, gallbladder, and kidney; enlargement of these adjacent organs (organomegaly); abnormal structures such as aneurysms, cysts, and pseudocysts; and neoplasms of adjacent organs [1–3]. Among the intramural non-neoplastic lesions, varices are likely the most common but are easily recognized by endoscopic appearance and clinical circumstances. A few other non-neoplastic masses, such as pancreatic rests and duplication cysts, may occasionally be seen.

What are left, after these have all been excluded, are the mesenchymal neoplasms. This group comprises a confusing array of obscure and infrequent tumors, many of which are listed in [Table 2](#). GI stromal tumors (GISTs) are the most frequently encountered tumors on this list [4], and all GISTs contain potential for malignant behavior. For this reason, a discussion of SMTs almost always evolves promptly into a discussion of GIST.

Of lumps and bumps: initial characterization

When a submucosal tumor is encountered on visual endoscopy, the first step is to characterize it with respect to several parameters. The important considerations include location, size, shape, number, color, overlying mucosa, and compression characteristics. Other specific features, such as pedunculation, may occasionally be relevant. [Table 3](#) lists the parameters that may characterize each of these features.

Table 2
Mesenchymal tumors of the GI tract

Tumor type	Examples
Stromal tumor	GI stromal tumor, smooth muscle tumor (true leiomyoma or leiomyosarcoma), glomus tumor
Lipocytic tumor	Lipoma, liposarcoma
Vascular tumor	Hemangioma, hemangiosarcoma, Kaposi's sarcoma
Neural tumor	Neuroma/neurofibroma
Miscellaneous tumors	Granular cell tumor, inflammatory fibroid polyp, fibrovascular polyp

Table 3
Features of submucosal tumors and examples

Feature	Characterizations	Examples
Location	Organ, site	Granular cell tumors are typically esophageal.
Size	In two dimensions	Certain lesions, such as granular cell tumors, rarely exceed 1–2 cm.
Shape/contour	Smooth, lumpy, oval, irregular	GISTs are typically oval and smooth. Primary malignancies and metastases may be lumpy.
Color	Yellow, blue, pale, pink	Lipomas and granular cell tumors are often yellow. Vascular lesions are often blue.
Number	Single, multiple	Granular cell tumors are sometimes multiple.
Overlying mucosa	Ulcerated, dimpled, normal, erythematous	GISTs typically have normal mucosa but may be dimpled or ulcerated. Pancreatic rests are typically dimpled. Malignancies are often dimpled or ulcerated.
Compression characteristics	Firm, soft	Lipomas and vascular lesions are easily compressible. GISTs and pseudocysts are usually firm.
Miscellaneous	Sessile/pedunculated Bleeding Motion	Lipomas and varices are sometimes pedunculated. Extramural structures often move relative to the mucosa with respiration or pulse.

Abbreviation: GIST, gastrointestinal stromal tumor.

It is difficult to overstate the importance of this type of basic endoscopic characterization. Because mucosal pinch biopsies rarely yield diagnostic material, the endoscopic appearance and clinical circumstances usually determine which such lesions deserve further evaluation. It may be necessary to use special techniques: Compression with a biopsy forceps is often helpful even when no biopsies are intended, and side-viewing endoscopy using a duodenoscope is regularly needed to fully characterize duodenal SMTs. A few extra minutes of study while peristalsis changes the perspective can be invaluable.

Endoscopic ultrasound (EUS) is usually the next diagnostic step. Although not every lump and bump deserves such examination, several features can be suggested to identify those that need further testing, including size >1 cm, dimpled or ulcerated surface, lumpy or irregular shape, multiple lesions, a hard or firm texture, and a personal history of malignancy. Lesions that are obviously lipomas (small, soft, yellow, smooth) or granular cell tumors (small, esophageal, yellow, round) usually do not need further diagnostic testing. Lesions with obvious mucosal involvement, as may be indicated by an adenomatous surface, are not truly submucosal tumors; these are typically best managed by aggressive efforts to obtain diagnostic tissue by conventional biopsy before EUS.

The role of endoscopic ultrasound

Having determined that a given SMT deserves further attention, what should be done? New CT imaging methods are able to identify lesions as small as 1 cm, but further useful characterization has not been described [5]. Nevertheless, CT is

Table 4
Endoscopic ultrasound characterization of intramural tumors

Characteristic	Descriptors
Size	Cross-sectional diameters
Shape	Round, oval, triangular, irregular
Margin definition	Well defined (distinct), poorly defined (indistinct)
Margin contour	Smooth, irregular
Wall layer	relative to five-layer wall structure
Background echogenicity	Anechoic, hypoechoic, hyperechoic
Focal echogenicity	Hypoechoic foci, anechoic foci, hyperechoic foci

a reasonable next step for large lesions (2–3 cm or bigger) not least because, if nothing abnormal is seen, extrinsic compression by extraluminal organs becomes a strong consideration.

EUS has become the most important next step in evaluating submucosal tumors. Normal and abnormal extramural structures and organs are readily identified as the cause of extrinsic compression into the GI lumen [6]. More importantly, EUS can characterize intramural lesions with respect to a number of features helpful in suggesting pathologic diagnoses (Table 4). In addition, for tumors that are invasive, the degree of invasion (tumor T stage) can be described.

The accuracy of such characterizations and their relationship to various pathologic types has been examined. Rosch et al [4], in a study that included 102 intramural lesions, described the appearance of stromal tumors, lipomas, varices, and other entities. Yasuda [7] also described such findings in 210 submucosal tumors. Rosch [4] reported diagnostic accuracy figures ranging from 80% to 90% for various types of lesions.

Fig. 1 shows the typical appearance of an esophageal granular cell tumor. These benign lesions are usually found in the distal esophagus and are characteristically under 2 cm in size. Most are asymptomatic, although dysphagia may occasionally be present. Multiple lesions are not uncommon. They may be of Schwann cell origin, although the pathogenesis is uncertain. The endoscopic

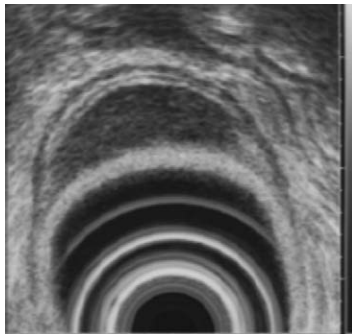


Fig. 1. EUS appearance of a granular cell tumor. The tumor is located within the submucosa, and the muscularis propria layer is intact.

appearance is of a flattish pale yellow oval submucosal lesion without overlying mucosal abnormality. Endosonographically, they appear as hypoechoic round or oval masses arising within the submucosal layer. The ground glass echostructure usually does not contain internal features. Because they do not seem to have a malignant form, they may be safely left in situ unless they are symptomatic.

Fig. 2 shows the typical EUS appearance of a submucosal lipoma. In this case, the neoplasm is pedunculated. Lipomas consist of clustered adiposites and seem to arise from the submucosa. They are most common in the stomach, duodenum, and colon but can be found anywhere in the GI tract. Although they are usually asymptomatic, they may cause obstruction if located at a narrow area, especially if they are large. Ulceration with chronic GI blood loss is occasionally seen. Endoscopically, lipomas are soft yellowish masses that deform easily on palpation with an instrument. They are typically round or oval and have normal overlying mucosa. On EUS examination, lipomas are brightly echogenic structures arising from the third echo layer (the submucosa). They have well-defined and smooth margins and have an oval shape. Almost all are benign. A malignant form (the liposarcoma) has been described, but the EUS appearance of such a lesion has not been reported. Unless the lesion is large, symptomatic, or shows unusual alarming features, it may be safely left in situ.

Fig. 3 shows the EUS appearance of a GIST. Endoscopically, stromal tumors appear as rounded firm smooth masses. The overlying mucosa is usually normal, although dimpling or even frank ulceration is common. GISTs are most common in the stomach but have been described throughout the GI tract. On EUS evaluation, these lesions usually seem to arise from the fourth echo layer (the muscularis propria) and to be contiguous with it. They may appear within the second echo layer. Regardless of the origin layer, the surrounding layers are usually well preserved (unless the tumor is malignant) and can be demonstrated by careful imaging. The parenchyma of GISTs are hypoechoic but not anechoic,

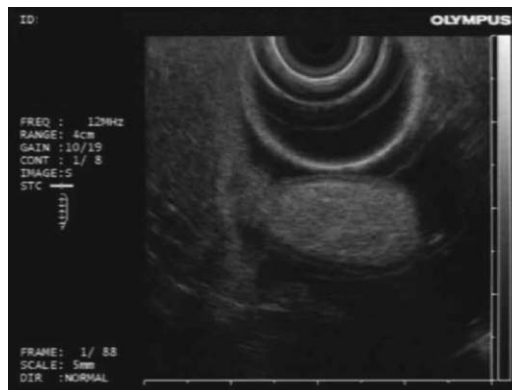


Fig. 2. EUS appearance of a pedunculated duodenal lipoma. The tumor is brightly echogenic due to the fat content, but the first two echo layers are preserved.

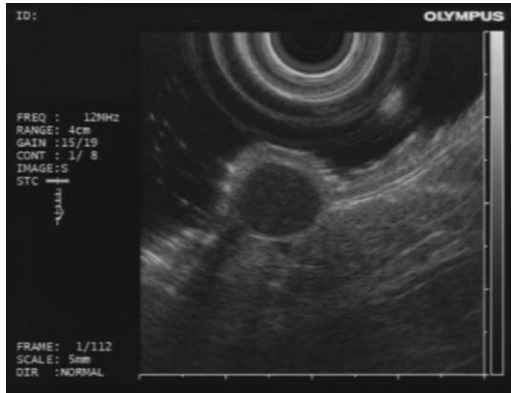


Fig. 3. A benign GIST of the stomach. Note the small size, round shape, and well-defined and smooth margins. This lesion contains no internal hyperechoic or hypoechoic foci.

appearing as a “ground glass” echodensity. Foci within this background are often seen and may be hypoechoic, anechoic, or hyperechoic (Fig. 4).

Although GISTs are the largest category of lesions demonstrating this appearance, several other entities can do so. Granular cell tumors are oval hypoechoic masses; so are carcinoids, lymphomas, pancreatic rests, and metastatic malignancies. Clinical setting and endoscopic appearance usually allow these to be distinguished.

Several features have been examined that may provide clues about benign versus malignant pathology when GISTs are seen. Large size and irregular or knobby margins are alarm signs (Fig. 5), and these are relatively objective fea-



Fig. 4. A hypoechoic intramural tumor showing hypoechoic and hyperechoic internal foci. This lesion proved to be a carcinoid tumor on resection.



Fig. 5. A GIST showing signs for possible malignancy. Note the large size, irregular shape, and lumpy (although well-defined) margins.

tures [8]. Internal hyperechoic, hypoechoic, and anechoic (“cystic”) foci have been proposed as features of malignant risk, but validation of these features has been much more difficult. Although Tsai et al [9] demonstrated that such features were statistically associated with malignancy, the diagnostic accuracy was sub-optimal. Chak et al [10], in a retrospective videotape study, found good association of these features with malignancy. However, a recent large, multicenter, prospective study of 198 tumors could validate only the association of size >3 cm, surface ulceration, non-oval shape, and irregular or indistinct margins with malignancy. Hypoechoic and hyperechoic internal foci were unassociated with pathology [11]. In this same study, one or more of the associated features was present in all lesions that were malignant or had significant malignant potential; however, the specificity was relatively low. Surface ulceration and EUS characterization of size, shape, and margin features should be considered valid indicators of malignant risk, whereas internal hyperechoic or hypoechoic foci should not, by themselves, prompt resection.

Gastrointestinal stromal tumors: new insights

Several developments during the last decade have provided significant insights which improve our understanding of GISTs.

The pathology problem: new diagnostic criteria

A major stumbling block regarding GISTs has been the problem of characterizing benign and malignant tumors. In most other neoplasms, benign is benign, malignant is malignant, and that’s that: Benign adenomatous colon polyps, once removed, are no longer a problem, whereas colon cancer, untreated, will promptly

kill you. It has long been known, however, that for GISTs the histology only imperfectly predicts clinical behavior: Tumors with frightening histology do not always locally invade or metastasize, whereas histologically “benign” tumors are occasionally described as showing these malignant behaviors. Under such circumstances, the meanings of the terms “benign” and “malignant” are vague.

One reflection of this problem was the difficulty in identifying and validating the specific pathologic and histologic parameters useful in characterizing benign and malignant GIST. One of the heretofore most widely used systems relied on size plus six other histologic features as risk factors; those lacking all the features were benign, those with two or more were malignant, and those with one were of “indeterminate” malignant risk [12]. Many resected tumors fell into the vague “indeterminate” category; moreover, many of the features, such as epithelioid pattern or pleomorphism, were fairly subjective, limiting the usefulness of this system.

A recent NIH consensus conference has developed new guidelines for GIST histologic classification (Table 5) [13,14]. The guidelines incorporate two innovations. First, only two criteria are used: size and mitotic index, the latter defined as the number of mitotic figures seen in 50 high-power fields. These criteria are objective and are reasonably well validated with respect to malignant behavior compared with the other histologic features previously used. The second innovation is that tumors are no longer classified as “benign” or “malignant” but rather according to four levels of risk for malignant behavior, ranging from “very low risk” to “high risk.” This system emphasizes that, for even the most innocent GIST, the malignant risk is low but not zero, whereas even the ugliest histology is not a guarantee of malignant behavior. The consensus group agreed that smaller size thresholds are probably justified for lesions arising in locations other than the stomach but did not specify such sizes. These criteria do not apply to GISTs, which are already locally invasive or metastatic; these are definitely malignant. The system does retain the troublesome “intermediate” category, but further improvement in GIST pathologic characterization will likely require the emergence of new knowledge about the tumor, probably requiring biochemical markers.

Table 5
NIH criteria for malignant risk in gastrointestinal stromal tumors

Risk level	Size (cm)	Mitoses/50 HPF
Very low risk	<2	<5
Low risk	2–5	<5
Intermediate risk	<5	6–10
	5–10	<5
High risk	>5	>5
	>10	Any rate
	Any size	>10

Abbreviation: HPF, high-power field.

Proto-oncogenes in the genesis of gastrointestinal stromal tumors

Other recent work has shed light on the pathogenesis of GISTs. Originally, the tumors were thought to be of smooth muscle origin, in part because they arise predominantly from the muscle layers of the GI tract wall and in part because, microscopically, the sheets of uniform eosinophilic spindle cells resemble muscle tissue. For this reason, the terms “GIST” and “leiomyoma” were sometimes used interchangeably. In 1998, Sarlomo-Rikala et al [15] reported that the majority of GISTs express a specific tyrosine kinase receptor (KIT). This receptor, originally also called CD117, mediates several cellular growth functions. In the GI tract, it is normally expressed by the interstitial cells of Cajal (ICC), giving rise to the current prevailing theory that GISTs arise from or are related to ICC. When stimulated by stem cell factor, KIT stimulates a variety of cellular proliferative mechanisms, including antiapoptotic pathways, transcription proteins, and other cascades. The result is cellular proliferation, inhibition of apoptosis, and other growth functions [16]. The interesting feature of KIT expression in GISTs is that the receptor has a gain-of-function abnormality resulting from a mutation in the corresponding gene [17]. The abnormal KIT expressed in GISTs allows initiation of the cell proliferative pathways without stimulation by stem cell factor, resulting in unregulated growth—an obvious step in the development of a neoplastic tumor. Several gene mutations, usually acquired, have been identified in GISTs, and all seem to be capable of initiating the cell-proliferative cascades, although to different degrees. More recent research has identified a second tyrosine kinase receptor mutation present in many malignant GISTs that are KIT negative. The abnormal platelet-derived growth factor alpha (PDGF- α) receptor present in these tumors also contains a gain-of-function mutation and is capable of initiating many of the same cell proliferation pathways as KIT [18].

The current theory of the pathogenesis of GISTs is that a mutation (acquired as a result of unidentified factors) to ICC or ICC progenitor cells results in expression of gain-of-function tyrosine kinase receptors associated with cell proliferation. A variety of mutations in genes for at least two such receptors, KIT and PDGF- α , are known. The abnormal receptor promotes unregulated cell proliferation resulting in tumor formation. Additional unknown factors concurrently or subsequently promote frank malignant behavior in at least some such tumors.

Imatinib: hope for the hopeless

The incidence of frankly malignant GISTs is fortunately low because, although the tumor is slow growing, it is relentlessly progressive and has been resistant to all conventional treatment regimens. Progress in this area has been made during the last decade, and effective treatment for even this hopeless cancer is now emerging. The pathophysiology centering on disordered tyrosine kinase receptor function has led to the development of an agent that specifically inhibits this activity. Imatinib (Gleevec; Novartis, Basel, Switzerland) is a selective com-

petitive inhibitor of the KIT receptor and downregulates the abnormal cell proliferative activity caused by the oncogene expression. Two clinical studies have shown impressive results. In a European study of 36 subjects, 32 halted tumor progression while on the drug, and 25 showed tumor regression. Similar findings were seen in an American study of 147 patients. Over half of patients showed tumor regression (more than 50% reduction in tumor bulk), and in most of the remainder of patients no further progression occurred on therapy. Although no complete regression (ie, cure) was seen, these results are nevertheless highly meaningful.

Additional work has shown correlation between imatinib response and the specific mutations involved. The most common mutation in the c-KIT oncogene was also the phenotype that responded best to imatinib, and other c-KIT mutations responded less well. Tumors associated with mutations in PDGF- α receptor also responded less well, although the response was suggested to vary depending on the specific mutation. Tumors that had mutations of neither c-KIT nor PDGF- α receptor responded poorly to imatinib.

The management of hypoechoic intramural tumors

The question usually confronting the endoscopist and patient with a hypoechoic intramural tumor not obviously malignant is less “Where did it come from?” and more “What to do about it?” The choices are two: ignore it, or resect it. A third choice—watch it (by surveillance examinations)—ultimately results in one of the two primary choices. How to go about deciding?

Specific EUS criteria (size, shape, ulceration, and margins), although incompletely validated, seem to be capable of identifying lesions suspicious for malignancy or malignant risk. Although the sensitivity of these criteria is probably high, the specificity may be low. The prospective study of 198 tumors suggested that well over half of hypoechoic intramural tumors will meet at least one of these criteria and merit resection [11]. Part of the problem is that the exact risk of malignant behavior in “indeterminate risk” GISTs is unknown, and there is not even a consensus about whether all such lesions deserve resection. If one assumes that the prudent physician (and patient) would want such a tumor out, then a specificity figure of around 50% might be ascribed to the EUS criteria. This figure, combined with sensitivity exceeding 90% is, if not optimal, at least not unreasonable. Mollifying the distaste of resection with such an indifferent degree of discrimination is the emergence of laparoscopic approaches that have been shown to be technically successful and safe in several case series [19,20].

For lesions that do not clearly require resection, surveillance examination (by, presumably, EUS) seems attractive. However, the evidence suggests that this middle-ground management strategy is almost certainly unsatisfactory. In the Hypoechoic Intramural Tumor Study, approximately half of enrolled subjects were assigned to annual surveillance EUS spanning a 3-year period. At follow-

up, fewer than one third could be persuaded to return for even a single surveillance examination [11]. Moreover, the surveillance examinations that were performed yielded not a single additional malignant-risk lesion in the series. The disappointing surveillance rate is commensurate with other recent data indicating poor compliance with surveillance endoscopy. In a study of patients with Barrett's esophagus, only 42% were compliant with a surveillance program [21], and in a study of colorectal cancer screening, similarly low compliance rates were documented [22]. Although surveillance may be appropriate in highly selected circumstances, these findings suggest that, on an intention-to-treat basis, the sensitivity of surveillance as a management strategy is unlikely to be satisfactory when cancer is on the line.

The decision to dismiss a submucosal tumor without resection or further follow-up takes courage. Yet, it is neither wise clinical practice nor prudent stewardship of medical resources to refer every bump for EUS, and little is to be gained by further examination of those meeting clinical and endoscopic criteria for benign appearance. When EUS is performed, trust should be invested in the findings, and the clinician should rest secure that the criteria as we understand them seem to be sufficiently conservative that little dangerous pathology will slip through the net.

The last decade has seen remarkable progress in nearly all areas related to SMTs and GISTs: new diagnostic modalities, new pathophysiologic understanding, and new treatments. Much work remains, and the script contains several unfinished scenes. Nevertheless, we have reason to hope that the unfortunate theater we witnessed at the opening of this article will, with the new plot outline now available, eventually vanish from the medical stage.

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