Subepithelial Lesions

28

Christopher S. Huang and John R. Saltzman

Introduction

The term "subepithelial lesion" (or "submucosal lesion") is used to describe any gastrointestinal tract mass or polyp with normal-appearing overlying mucosa. These lesions are often incidentally detected during upper endoscopy or colonoscopy, and are identified by the presence of a smooth bulge protruding into the lumen. They can represent non-neoplastic intramural lesions, intramural neoplasms (both benign and those with malignant potential), as well as extrinsic compression from adjacent structures (normal and abnormal). Endoscopic ultrasound (EUS) is typically necessary to further evaluate subepithelial lesions and determine which ones require additional tissue sampling, follow-up, or resection. This chapter will cover the diagnosis and management of the most common subepithelial lesions likely to be encountered by practicing gastroenterologists.

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Case Presentation

A 54-year-old woman with a history of a T3N0M0 moderately differentiated mucinous adenocarcinoma of the sigmoid colon, status-post sigmoid colectomy 5 years ago, was referred for surveillance colonoscopy. The patient was asymptomatic, but had a mildly elevated CEA level. The most recent surveillance colonoscopy 3 years ago was unremarkable other than post-surgical changes. The current examination was notable for a prominent 3-cm bulge with smooth, normal-appearing overlying mucosa located 11 cm from the anal verge (Fig. 28.1).

What is the Differential Diagnosis of Subepithelial Lesions?

The differential diagnosis of subepithelial lesions encompasses a spectrum of processes, including non-neoplastic intramural lesions, a wide variety of benign and potentially malignant intramural neoplasms, and extrinsic compression from adjacent structures (Table 28.1). When encountering a subepithelial lesion, the endoscopist should be aware of the most common diagnoses based on the lesion's endoscopic appearance and location, placing them in the context of the patient's medical and surgical history. For example, a lobulated subepithelial lesion located in the gastric fundus in a patient with cirrhosis or prior bouts of acute pancreatitis should immediately raise the suspicion for gastric varices (Fig. 28.2).

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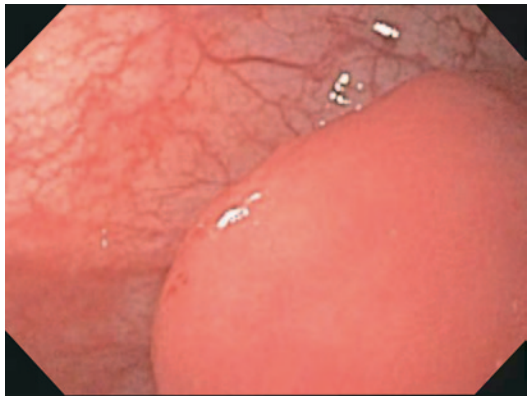

Fig. 28.1 A subepithelial lesion identified in the proximal rectum in a patient with a prior history of sigmoid colon cancer

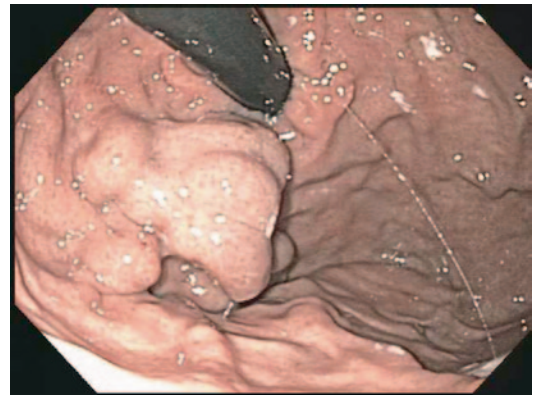

Fig. 28.2 Endoscopic appearance of gastric varices located in the fundus

The differential can be narrowed somewhat based on the location of the lesion [1–3]. The most common subepithelial lesions of the esophagus are leiomyomas, granular cell tumors, and cysts (duplication or bronchogenic). In the stomach, gastrointestinal stromal tumors (GISTs) and pancreatic rests are most common. Duodenal subepithelial lesions are encountered less commonly, but GISTs, carcinoids, lipomas, and duplication cysts can be found with similar frequency. In the colon and rectum, the most common lesions are carcinoids, lipomas, and GISTs. In women, one must also consider the possibility of endometriosis or even extrinsic compression of the rectum caused by a tampon in the vagina [4, 5].

A Stepwise Approach to the Evaluation of Subepithelial Lesions of the Gastrointestinal Tract

Initial Endoscopic Evaluation: What Endoscopic Techniques Diagnose Subepithelial Lesions?

The initial evaluation of subepithelial lesions can be performed using standard endoscopic equipment and techniques [6, 7]. The first step is to visually assess the following features: size, location, shape, color, surface characteristics, presence of pulsation, and change in appearance with patient repositioning and with air insufflation. Subepithelial lesions generally have normal-appearing overlying mucosa, but surface characteristics (e.g., focal ulceration or umbilication) and color

Table 28.1 Differential diagnosis of gastrointestinal subepithelial lesions

Benign intramural lesions	Malignant (or potentially malignant) intramural lesions	Extrinsic compression
Duplication cyst	Carcinoid	Normal intra-abdominal structures (pancreas, liver, spleen, gallbladder, etc.)
Granular cell tumor	Gastrointestinal stromal tumor	Abnormal intra-abdominal structures
Inflammatory fibroid tumor	Glomus tumor	(pancreatic/hepatic/renal cysts, aneurysms, lymph nodes, abscesses, tumors)
Leiomyoma	Lymphoma	
Lipoma	Metastatic carcinoma	
Lymphangioma		
Pancreatic rest		
Schwannoma		
Varices		

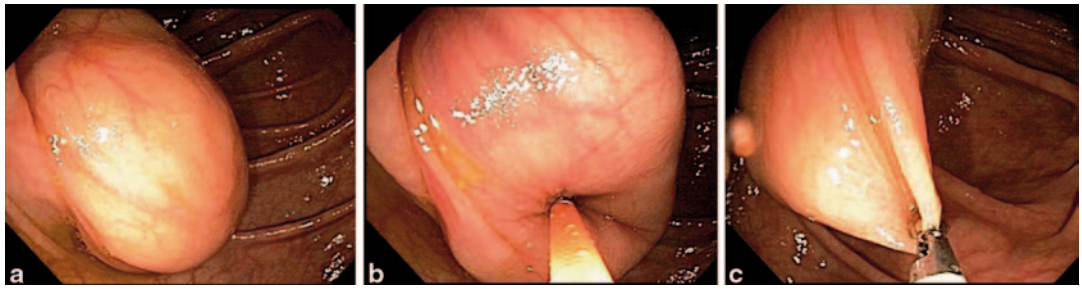

Fig. 28.3 Endoscopic features of lipomas. **a** Endoscopic appearance of a colonic lipoma in the ascending colon. **b** Positive "pillow" or "cushion" sign, characterized by indentation of the lipoma using a closed biopsy forceps. **c** Grasping the overlying mucosa and pulling it away from the underlying lipoma demonstrates the "tent sign"

(e.g., bluish, yellowish, translucent) should be evaluated, as these features may provide clues to the nature of the underlying lesion. Distinguishing intramural lesions from extrinsic compression can be difficult with endoscopy alone [8], but a significant change in the appearance of a lesion with alterations in patient position and degree of lumen distension suggests an extrinsic source.

A closed biopsy forceps can be used to probe the lesion, assessing its mobility and consistency. The presence of the "pillow/cushion" sign, characterized by the ability to indent the lesion with the biopsy forceps, is a feature that is highly specific for lipomas. Lipomas may also demonstrate the "tent sign," described as the ability to grasp the overlying mucosa with a forceps and easily pull the mucosa away from the underlying lesion (Fig. 28.3).

For lesions that do not appear vascular (bluish coloration) or cystic (translucent) and do not demonstrate the "pillow sign," biopsies may then be obtained to rule out an epithelial lesion as well as attempt to sample the underlying lesion. Unlike most other subepithelial lesions, carcinoid tumors can frequently be diagnosed using standard biopsy technique since they often arise from the deep mucosal layer. Areas of ulceration, if present, should be targeted to improve diagnostic yield [9]. "Stacked" (bite-on-bite, or tunneled) biopsies can be obtained using conventional, large-capacity, or jumbo biopsy forceps, although the reported yield of this technique is fairly low and variable depending on the forceps size (17%−42% for conventional and large-capacity, 67% for jumbo forceps) [10–13]. For jumbo forceps, significant bleeding occurred in nearly 35% of patients. Using jumbo forceps or a snare to "unroof" the overlying mucosa may expose the underlying lesion and allow for high-yield targeted biopsies, but also carries an increased risk for bleeding (Fig. 28.4) [13–16].

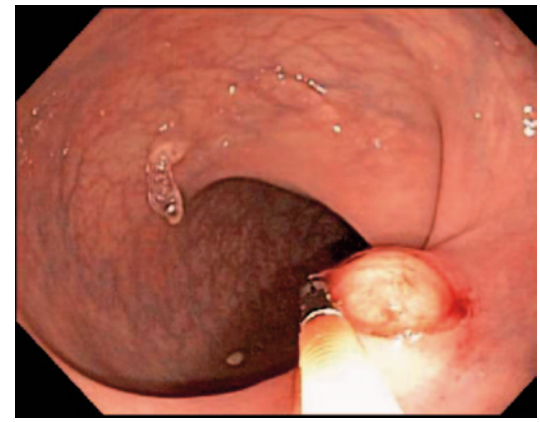

Fig. 28.4 Unroofing technique. The overlying mucosa was unroofed using a large capacity biopsy forceps, revealing the underlying lesion (lipoma)

At this stage of the evaluation, if the diagnosis has not been established, EUS should be performed.

EUS—Technical Tips to Enhance EUS Imaging

Subepithelial lesions can be imaged using radial scanning or linear array echoendoscopes,

as well as catheter ultrasound probes. Factors such as the size and location of the target lesion, its visibility from within the lumen, and the anticipated need to perform EUS-guided tissue acquisition may guide the selection of equipment to be used in any particular procedure. For example, catheter ultrasound probes may be more suitable for evaluating small (< 1 cm) subepithelial lesions due to the higher imaging frequency, which produces finer detail at the expense of depth of penetration. A radial echoendoscope may be preferred to initially localize a lesion that creates little-to-no visible bulge within the lumen. A linear array echoendoscope should be used initially if the lesion is readily localizable and EUS-guided tissue acquisition is definitely planned, obviating the need for radial examination and thereby reducing the number of endoscope insertions required.

When performing the EUS examination, the lumen of the gastrointestinal tract should be maximally deflated of air, and if possible, the target lesion should be submerged in water to achieve optimal imaging of the lesion. This may be impossible or unsafe due to lesion location and risk for aspiration (especially for lesions in the esophagus), in which case the balloon around the transducer should be filled with a very small volume of water to achieve acoustic coupling. The endoscopist should avoid overfilling the balloon, which may distort or compress very small lesions. Another approach to imaging small lesions in the esophagus is the "condom technique," whereby a condom is attached to the tip of a double-channel endoscope and filled with water, and the examination is performed with a catheter ultrasound probe advanced through the endoscope channel into the contained column of water [17].

Other locations can also introduce challenges during EUS examination, such as the gastric antrum, where it may be difficult to submerge the lesion in water. Repositioning the patient on to his or her back, and keeping the head of the bed elevated to at least 45° may allow for the safe instillation of more water into the gastric lumen. Lesions in the high gastric fundus or cardia may also be difficult to image, and it may be necessary to keep the endoscope tip in the distal esophagus and scan through multiple wall layers (from the outside-in). Slightly rotating the patient toward the prone position may help as well.

For colorectal lesions, the bowel should be prepared with enemas or oral purge, depending on the location of the lesion. In general, EUS of lesions proximal to the sigmoid colon should not be attempted with standard echoendoscopes given the technical difficulties of navigating an oblique-viewing scope through the colon. If available, a catheter ultrasound probe or a forward-viewing echoendoscope can be used in these situations.

At times, it can be challenging to accurately determine a lesion's layer of origin, particularly if the lesion is bulky. It may be helpful to carefully focus on the edges of the lesion where there is a transition from normal to abnormal tissue, rather than at the center. In addition, as in any EUS examination, it is important to make sure that the scanning is perpendicular to the target, as opposed to tangential scanning which can lead to distortion of the echolayers of the gut wall and misinterpretation of layer of origin.

How Accurate is EUS Imaging for Diagnosing Subepithelial Lesions?

Endoscopic ultrasound is the modality of choice for distinguishing intramural lesions from extrinsic compression and for diagnosing the nature of subepithelial lesions. Differentiating extrinsic compression from an intramural lesion by EUS is highly accurate at 100 % in one study [18]. For intramural lesions, EUS can determine the layer of origin and characterize the endosonographic features, which in some cases (e.g., lipomas) can establish a certain diagnosis even without the need to obtain tissue. Table 28.2 summarizes the typical EUS characteristics of the most commonly encountered subepithelial lesions. However, the diagnostic accuracy of EUS imaging alone is approximately 50 % overall, and only 30 % for lesions proven to be neoplastic in nature, with the majority of incorrect diagnoses occurring

Table 28.2 Endosonographic features of intramural subepithelial lesions

Subepithelial lesion	Echogenicity/appearance	EUS layer of origin
Carcinoid	Hypoechoic	2 or 3
Granular cell tumor	Hypoechoic	2 or 3
Varices	Anechoic, serpiginous structures	2 or 3
Inflammatory Fibroid Polyp	Hypoechoic, indistinct margins	2 or 3
Leiomyoma	Hypoechoic	2 or 4
Pancreatic rest	Hypoechoic/mixed; may contain anechoic tubular spaces	2, 3 or 4
Lipoma	Intensely hyperechoic	3
Gastrointestinal stromal tumor	Hypoechoic; may contain echogenic foci or anechoic spaces	4
Duplication cyst	Anechoic, compressible; 3- or 5-layer wall may be visible	Any, or extramural

Layer 2 = deep mucosa; layer 3 = submucosa; layer 4 = muscularis propria

with hypoechoic lesions arising from the third and fourth echolayers of the gut wall [8, 19, 20]. Interobserver variability also limits the accuracy of EUS imaging for lesions other than lipomas, cystic lesions, and extrinsic compression [21]. Therefore, tissue acquisition of hypoechoic lesions larger than 1 cm in size is generally recommended to establish a firm diagnosis, unless the lesion requires resection regardless of histology (e.g., patient is experiencing symptoms or complications related to the lesion such as gastrointestinal bleeding).

Tissue Acquisition: What Are the Pros and Cons of the Various Techniques?

There are several options for obtaining tissue from subepithelial lesions, including stacked biopsies/unroofing techniques (discussed above), EUS-guided fine needle aspiration (EUS-FNA), EUS-guided fine needle biopsy (EUS-FNB), endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). The choice of which technique to use depends on factors such as lesion size, location, layer of origin, as well as the availability of necessary equipment and expertise.

Endoscopic Ultrasound-Guided Fine Needle Aspiration

The technical aspects of EUS-FNA are covered in detail in Chap. 23.

Several studies have demonstrated that EUS-FNA is a safe and accurate means of diagnosing subepithelial lesions of the gastrointestinal tract, particularly GISTs, with overall accuracy rates ranging from 67 to 98 % (Video 28.1) [2, 9, 22–30]. In the largest relevant study published to date, comprising 141 patients with gastric subepithelial lesions, the overall accuracy rate of EUS-FNA was 96 % based on criterion standard (surgical histopathologic results, or follow-up course for inoperable cases) [23]. However, diagnostic yield of EUS-FNA may be somewhat limited with EUS-FNA being diagnostic in 43–68 % of cases [31].

Factors that may enhance the diagnostic yield of EUS-FNA include the presence of an on-site cytopathologist, higher number of needle passes (five are recommended), and availability of immunohistochemical staining. Needle diameter has not been definitively shown to significantly impact the diagnostic accuracy of EUS-FNA for subepithelial lesions [32, 33], but 25-gauge needles may more easily puncture small, mobile lesions, as well as those within or adjacent to the duodenum when the scope tip may be acutely angulated.

Endoscopic Ultrasound with Fine Needle Biopsy

In cases where tissue architectural details and immunohistochemical staining are required, obtaining a core-tissue specimen via EUS-FNB may be

advantageous [34]. Another potential advantage of obtaining tissue cores is that specimen adequacy can be determined by the endoscopist, whereas FNA samples require an on-site cytopathologist. Combining EUS-FNA with FNB may be superior to either tissue sampling technique alone, [35] although this approach has not been extensively studied in patients with subepithelial lesions.

Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection

In select cases, EMR or ESD of subepithelial lesions may be performed to simultaneously obtain a histologic diagnosis as well as provide definitive treatment. This approach may be considered for situations in which FNA or FNB is likely to be low yield (e.g., very small lesions, suspected symptomatic pancreatic rest) or when previous stacked biopsies were diagnostic for a lesion that warrants resection (e.g., carcinoid tumor, granular cell tumor). Although associated with an increased risk for complications, endoscopic resection of lesions arising from the submucosa and even muscularis propria is increasingly performed and has a high diagnostic yield (87–94 %) [10, 16, 36–41]. It is necessary to identify the layer of origin with EUS before attempting resection because the risks are directly related to the depth of the tumor. Traditional saline-assisted polypectomy and cap-assisted EMR may be used to resect lesions. A relatively simple and elegant way of resecting small lesions that arise from the deep mucosa or submucosa (without sonographic evidence of involvement of the muscularis propria) is endoscopic band ligation with snare polypectomy. This technique is frequently employed for the resection of rectal carcinoids smaller than 1 cm in diameter, and has been shown to be superior to conventional polypectomy in terms of achieving complete resection with negative margins [42, 43]. Band ligation with or without electrosurgical resection has also been employed as a promisingly safe and effective method of treating small subepithelial lesions arising from the muscularis propria, including GISTs [37, 44–46]. In the so-called "ligate and let-go" technique, snare resection is not performed at the time of band ligation, thereby avoiding the risks of bleeding and perforation. Rather, the lesion is allowed to undergo ischemic necrosis and spontaneously slough off over time. The long-term effectiveness of this technique as a treatment option remains to be shown and a downside to this technique is the lack of a complete specimen for histologic examination.

Case Continued

Rectal endoscopic ultrasound was performed to further evaluate the subepithelial lesion found during colonoscopy. A linear echoendoscope was selected for this examination because tissue sampling was anticipated. The examination demonstrated a hypoechoic, heterogeneous 3-cm lesion involving the submucosa, muscularis propria, and perirectal fat with an irregular outer border (Fig. 28.5). Fine needle aspiration was performed using a 22-gauge needle. Cytologic examination was positive for malignancy consistent with mucinous adenocarcinoma.

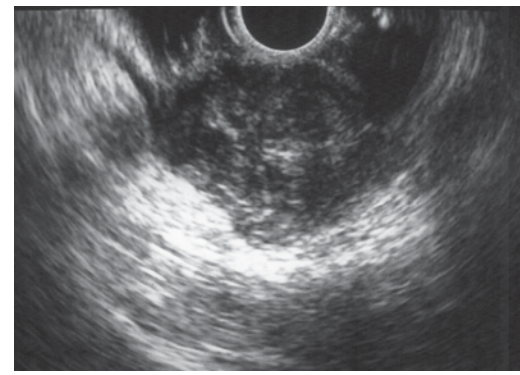

Fig. 28.5 Endoscopic ultrasound examination of a subepithelial lesion located in the proximal rectum of the patient with a prior history of sigmoid colon cancer.

Diagnosis and Management of Specific Gastrointestinal Subepithelial Lesions

Gastrointestinal Stromal Tumor (GIST): What EUS Features Predict Malignancy and How are Incidental GISTs Managed?

GISTs are the most common intramural subepithelial lesion encountered in the gastrointestinal tract, with approximately 4000–6000 new cases diagnosed each year and an estimated prevalence of 129 cases per million [47, 48]. They are most commonly located in the stomach (60–70%), followed by the small bowel (20–30%), colon and rectum (5%), and esophagus (<5%) [49]. GISTs may also arise from outside the gastrointestinal tract, in locations such as the mesentery, omentum, and retroperitoneum.

The clinical presentation of GISTs is quite variable, and related primarily to tumor size and location. Small GISTs are frequently asymptomatic, detected incidentally during endoscopic or radiographic studies performed for unrelated reasons. Symptomatic GISTs most commonly present with acute or chronic bleeding due to tumor ulceration. Other presenting signs or symptoms include abdominal pain, early satiety, dysphagia, gastric outlet obstruction, palpable masses, or acute abdomen (secondary to intra-abdominal hemorrhage) [50–52].

Endoscopic and Endosonographic Features

GISTs typically are round/oval, firm lesions with smooth contour and normal overlying mucosa, although ulceration may be present with larger tumors (Fig. 28.6). Endosonographically, GISTs are typically hypoechoic and most commonly originate from the fourth EUS layer (muscularis propria). Important features to assess by EUS include the size, regularity of the outer border, and presence of echogenic foci and cystic spaces. Large tumor size (>3 cm) and irregular border are the most reliable predictors of malignant behavior; other less consistent predictors include heterogeneous echotexture, cystic spaces, extraluminal growth, and hypervascularity [53–57].

Diagnosis and Management

GISTs were originally considered smooth muscle tumors, but are now known to arise from the interstitial cells of Cajal, which are the pacemaker cells of the gastrointestinal tract. Histologically, the majority of GISTs are composed of spindle cells arranged in interlacing, short fascicles or in a storiform pattern of growth (Fig. 28.6). A smaller proportion of GISTs are composed of epithelioid cells or a mixed cellular composition. The hallmark immunohistochemical feature of GISTs that distinguishes them from other mesenchymal/spindle cell tumors is positive staining for CD117 (c-KIT), which is expressed in over 90% of GISTs [58–60]. A novel marker known as DOG1 (discovered on gastrointestinal stromal tumors 1) is comparable to CD117 in terms of sensitivity and specificity, and may be especially useful in diagnosing cases of CD117-negative GISTs [61, 62]. Other markers that may be expressed include CD34 (60–80%), and less commonly smooth muscle actin (SMA) and S100. [58]. While these markers are generally unhelpful in confirming a diagnosis of GIST, they are useful in the diagnosis or exclusion of other gastrointestinal mesenchymal tumors [63].

Patients with GISTs should ideally be managed by a multidisciplinary team with expertise in sarcomas or tumors of the gastrointestinal tract [64, 65]. Gastroenterologists, working in conjunction with pathologists, are usually responsible for establishing the diagnosis and facilitating the appropriate referrals. Surgeons and medical oncologists are primarily responsible for developing a comprehensive treatment plan based on the resectability of the primary tumor, the aggressiveness of the tumor (Table 28.3), and the extent of any possible metastases.

Treatment of Localized GISTs

Surgical resection is the mainstay of therapy for patients with localized GIST, and should be the initial treatment if the tumor is technically resectable and the patient is a surgical candidate. However, the management of small, incidentally detected GISTs is controversial, and surgical resection of all such lesions may not be feasible or in the patient's best interest. The National

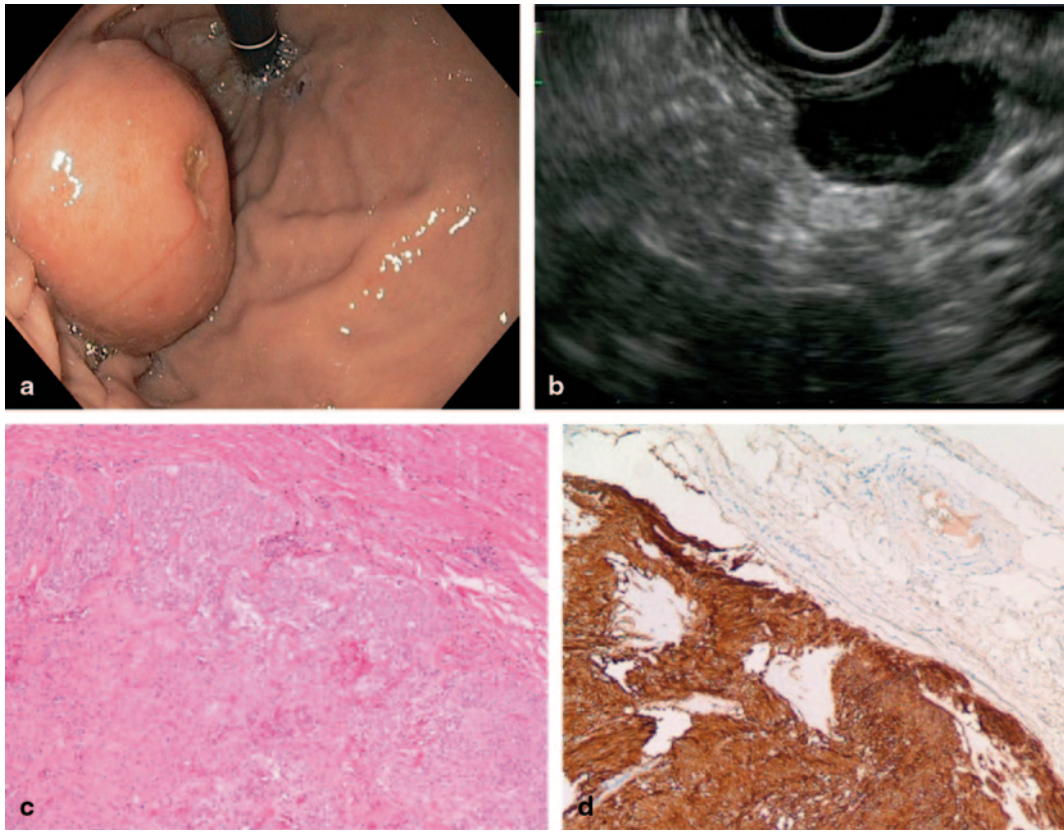

Fig. 28.6 Gastrointestinal stromal tumor (GIST). **a** Endoscopic appearance of a gastric GIST, featuring a focal surface ulceration. **b** Endosonographic appearance of a gastric GIST, characterized as a hypoechoic round lesion arising from the muscularis propria. **c** Histologic features of GISTs include spindle cells arranged in interlacing, short fascicles. **d** Immunohistochemical stain for CD117 (c-KIT) is strongly and diffusely positive

Table 28.3 Proposed modification of NIH consensus classification for assessing risk of aggressive behavior in gastrointestinal stromal tumors

Risk category	Tumor size (cm)	Mitotic index (per 50 HPF)	Primary tumor site/integrity
Very low	<2	≤5	Any site
Low	2–5	≤5	Any site
Intermediate	<5	6–10	Any site
	2–5	>5	Gastric
	5–10	≤5	Gastric
High	>10	Any mitotic rate	Any site
	Any size	>10	Any site
	>5	>5	Any site
	2–5	>5	Non-gastric
	5–10	≤5	Non-gastric
	Any size	Any mitotic rate	Tumor rupture

Adapted from Joensuu [123]

Comprehensive Cancer Network and the European Society for Medical Oncology recommend that all GISTs 2 cm or larger should be resected [64, 66], whereas the American Gastroenterolog-

ical Association's recommended size threshold for resection is 3 cm (as well as tumors < 3 cm with concerning EUS features) [7]. Studies examining the natural history of small, asymptomatic gastrointestinal subepithelial lesions arising from the muscularis propria suggest that the vast majority do not change significantly over time [67–71]. Therefore, surveillance may be a safe approach for the management of such lesions, provided they do not display suspicious EUS features. Surveillance may also be appropriate for patients with significant comorbidities, advanced age, or high surgical risk [72]. It is important that all patients being considered for surveillance understand the possible malignant potential of all GISTs, as well as the risks and benefits of serial EUS examinations versus surgical resection. The optimal surveillance interval has not been established, but 6- to 12-month intervals are generally considered appropriate [64, 72].

While not commonly performed, endoscopic resection of GISTs has been described using a variety of techniques, such as EMR, ESD, band ligation-assisted resection, and endoscopic enucleation/excavation [37, 40, 44, 46, 73, 74]. Because GISTs typically arise from the muscularis propria, endoscopic resection carries a considerable risk for complications, especially bleeding and perforation. In one of the largest published studies on this topic, 97 patients with gastric GISTs less than 3.5 cm in size underwent attempted resection using a technique termed "endoscopic excavation." In this technique, the overlying mucosa is incised in a cross pattern to expose the tumor, which is then separated from the surrounding tissue by injection of a solution of saline, indigo carmine, and epinephrine. After achieving adequate exposure, the tumor is excavated from the muscularis propria layer using a snare, insulated-tip knife or hook knife, and the gastric wall defect is closed using hemostatic clips. Using this modified ESD technique, resection was successful in 91 patients (94%), with a perforation rate of 24% [73]. Another option is the band "ligate and let-go" technique, which is technically simple and likely safe for resection of GISTs less than 1 cm in size, although the adequacy of resection remains questionable. Therefore, given the current concerns regarding safety and long-term efficacy, endoscopic resection of GISTs cannot be routinely recommended at this time.

Leiomyoma: What is the Recommended Management?

Leiomyomas are benign smooth muscle tumors that arise from either the muscularis mucosae or muscularis propria. Although quite rare, they are the most common mesenchymal tumor found in the esophagus, and can also occur infrequently in the colon (predominately in the rectum or sigmoid colon), stomach, or small bowel.

Leiomyomas are classically very slow growing, and as such are frequently asymptomatic. They can present at any age, with a peak incidence in the third to fifth decades. The most common symptoms of esophageal lesions are dysphagia or chest discomfort [75]. Rarely, leiomyomas may ulcerate and bleed. Malignant transformation is extremely uncommon.

Endoscopic and Endosonographic Features

Esophageal leiomyomas most commonly occur in the mid- to distal esophagus, correlating with the muscular composition of the esophagus. They usually appear as a solitary smooth flat or hemispheric bulge with intact overlying mucosa (Fig. 28.7) [76]. Some may be annular and encircle the esophagus. In the colon, they appear as smooth polypoid lesions that have a firm consistency. Endosonographically, leiomyomas appear hypoechoic, homogeneous, and well-circumscribed arising from the muscularis propria or muscularis mucosae.

Diagnosis and Management

Histologically, leiomyomas are characterized by fascicles of spindle cells, with low-to-moderate cellularity and absent or low mitotic activity (Fig. 28.7). On immunohistochemical testing, leiomyomas stain positive for smooth muscle actin (SMA) and desmin, but negative for CD117, CD34, and S100.

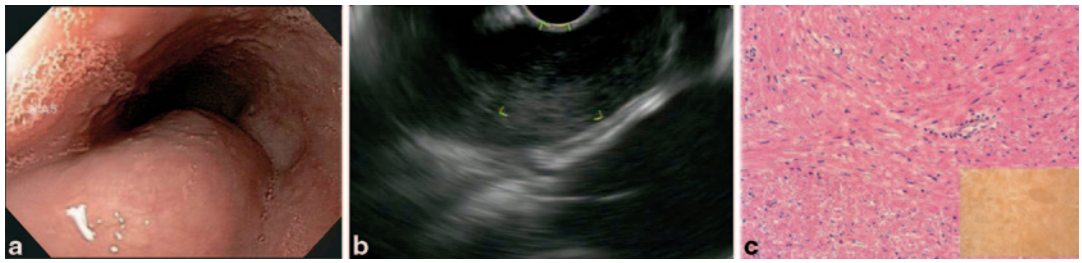

Fig. 28.7 Esophageal leiomyoma. **a** Endoscopic appearance of an esophageal leiomyoma resulting in mild compression of the esophagus. **b** Endosonographic examination demonstrates a homogenous, hypoechoic mass. **c** Histologic features include spindle cells arranged in fascicles with absent or low mitotic activity. Immunohistochemical stain for smooth muscle actin (inset lower right corner) is diffusely positive

Asymptomatic leiomyomas generally do not require intervention, but rather expectant observation and periodic surveillance by radiography, endoscopy, or EUS [77]. The natural history of most asymptomatic esophageal leiomyomas is usually benign, with most tumors remaining stable in size for many years; thus, a non-surgical approach is justified. Indications for resection include unremitting symptoms, increase in tumor size, large size, mucosal ulceration, and the need to obtain definite histopathologic diagnosis. Surgical resection is the traditional treatment of choice for esophageal leiomyomas, most commonly via thoracotomy (or more recently, thoracoscopy) with transthoracic extramucosal enucleation. Endoscopic resection via EMR or ESD techniques can be considered for small lesions that arise from the muscularis mucosae [78]. As with GISTs, there is growing experience with endoscopic resection of leiomyomas arising from the muscularis propria [38, 40, 45, 73, 74, 79], but this approach has not been widely embraced in the United States.

Lipoma: What Endoscopic and EUS Features are Diagnostic?

Lipomas are benign tumors composed of mature adipocytes. In the gastrointestinal tract, they are most commonly found in the colon, and only rarely in the upper gastrointestinal tract or small bowel. Gastrointestinal tract lipomas are usually asymptomatic, but depending on size and location, may result in complications or symptoms such as abdominal pain, change in bowel habits, bleeding or obstruction from intussusception.

Endoscopic and Endosonographic Features

Endoscopically, lipomas are characterized by a yellowish hue and soft consistency with a positive "pillow/cushion sign" which is 98 % specific, but only 40 % sensitive for lipomas [8]. In addition, grasping the overlying mucosa with a biopsy forceps easily pulls the mucosa away from the underlying lesion ("tent sign"). Stacked biopsies may occasionally produce an extrusion of fatty tissue ("naked fat sign"). Lesions that lack these characteristic endoscopic features should be investigated further with EUS. The finding of an intensely hyperechoic, well-circumscribed mass arising from the submucosal layer is diagnostic, making further diagnostic testing or tissue acquisition unnecessary (Fig. 28.8).

Diagnosis and Management

The diagnosis of lipomas can be made based on the characteristic endoscopic and EUS features. Asymptomatic lipomas require no treatment, whereas symptomatic lipomas should be resected, traditionally via surgery. Endoscopic resection can be considered in circumstances when the clinical situation allows for elective resection. Although endoscopic resection of lipomas larger than 2 cm was initially discouraged

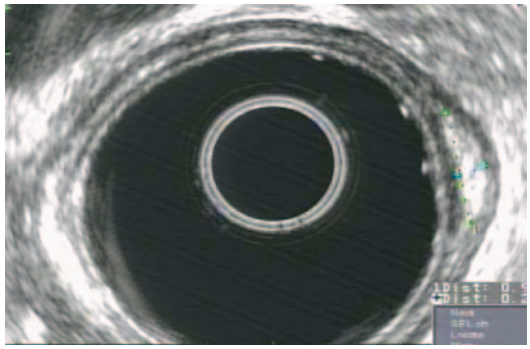

Fig. 28.8 Endosonographic appearance of a small gastric lipoma, characterized by an intensely hyperechoic lesion within the submucosa

due to increased risk of perforation, several case reports have described safe resection techniques even for large lesions. The spectrum of techniques includes saline/epinephrine-lift with snare resection, ligation of the base with a detachable loop prior to snare resection or as a stand-alone therapy to induce ischemic necrosis and spontaneous separation from the wall ("loop and let go"), and unroofing techniques [80–85]. On a practical note, endoscopists who endeavor to perform snare resection of large lipomas should be aware that fatty tissue conducts electrosurgical current inefficiently, so careful assessment of snare placement is necessary to avoid inadvertent application of cautery through the tumor itself.

Carcinoid Tumor: When is Endoscopic Resection Indicated?

Carcinoid tumors constitute a heterogeneous group of tumors that arise from neuroendocrine cells of the gastrointestinal tract. They can arise in any portion of the gut, most commonly in the small intestine and in the rectum [86–88]. Gastric carcinoids, which represent approximately 6% of all carcinoids, are categorized into three types: (1) Type I carcinoids (most common) are associated with chronic atrophic gastritis, achlorhydria, hypergastrinemia and often pernicious anemia; (2) Type II carcinoids occur in the setting of Zollinger–Ellison syndrome and MEN-I; and (3) Type III carcinoids (sporadic) are usually solitary, large tumors that develop in normal gastric mucosa without hypergastrinemia; these tend to display aggressive local behavior and have a high incidence of metastasis.

Most carcinoids are non-functioning tumors and do not create symptoms from excess hormone production and release. Presenting features may include non-specific symptoms such as pain, nausea, and vomiting from local invasion, bowel obstruction, or mesenteric ischemia. The carcinoid syndrome, characterized by the well-known features of flushing, wheezing, and diarrhea, occurs in approximately 20–30% of well-differentiated midgut carcinoids (small bowel to the proximal colon), but rarely, if ever, occurs with foregut and hindgut tumors. Carcinoid syndrome is usually due to release of vasoactive compounds such as serotonin and tachykinins from hepatic metastases, but may also occur if there is direct retroperitoneal involvement, with venous drainage that bypasses the liver.

Endoscopic and Endosonographic Features

Endoscopically, carcinoids usually appear smooth, round, and yellowish. They tend to have a firm consistency, and may have a central depression or ulceration (Fig. 28.9) [89]. On EUS, carcinoids appear as hypoechoic, homogeneous lesions with smooth margins, typically arising from the deep mucosa or submucosa.

Diagnosis and Management

Unlike most other subepithelial lesions, carcinoids can usually be diagnosed using standard biopsy forceps because they often originate from the deep mucosal layer. Histologically, they are characterized by small, round, or polygonal, uniform cells arranged in nests, trabecular, or gyriform patterns. Immunohistochemical stains for synaptophysin and chromogranin are strongly and diffusely positive, establishing the diagnosis (Fig. 28.9).

The treatment of widespread disease and syndromes associated with hormonal hypersecretion is beyond the scope of this chapter. The

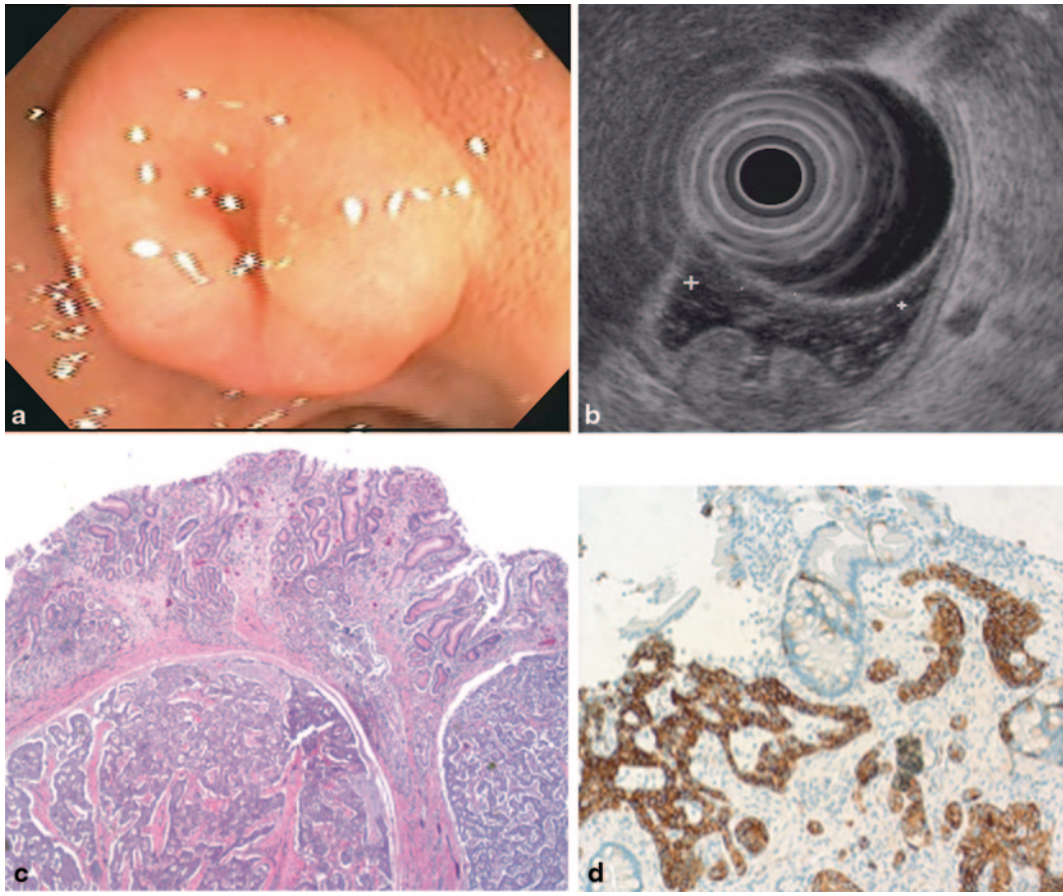

Fig. 28.9 Duodenal carcinoid tumor. **a** Endoscopic appearance of a carcinoid in the duodenal bulb, demonstrating a central depression. **b** Endosonographic appearance of a duodenal carcinoid. **c** Histologic features of gastric carcinoid. **d** Immunohistochemical stains for chromogranin A are positive

management of localized carcinoids depends on tumor location and size. Surgical resection of the primary tumor and local lymph nodes is considered the only potentially curative treatment [87, 90, 91]. Type I and II gastric carcinoids that are smaller than 1 cm in size may be managed by annual endoscopic surveillance alone given their extremely low risk of local invasion and metastasis. Endoscopic resection can be considered for type I and type II gastric carcinoids that are 1–2 cm in size and do not invade the muscularis propria on EUS imaging [7, 92, 93]. Whenever possible, surgical resection and lymph node dissection should be performed for Type III gastric carcinoids given their more aggressive nature. Rectal carcinoids smaller than 1 cm in size can also be adequately treated by endoscopic resection, with little risk for local or distant recurrence (Fig. 28.10) [94]. There is debate concerning the adequacy of endoscopic resection of rectal lesions 1–2 cm in size, and rectal carcinoids larger than 2 cm should be resected surgically [87]. Both small intestine and colon carcinoids should be surgically resected due to their more aggressive nature.

From a practical standpoint, band-ligation EMR is probably the most technically simple, safe, and effective approach to resection of suitable carcinoid tumors [95]. Endoscopic submucosal dissection may also be considered, depending on local expertise and experience.

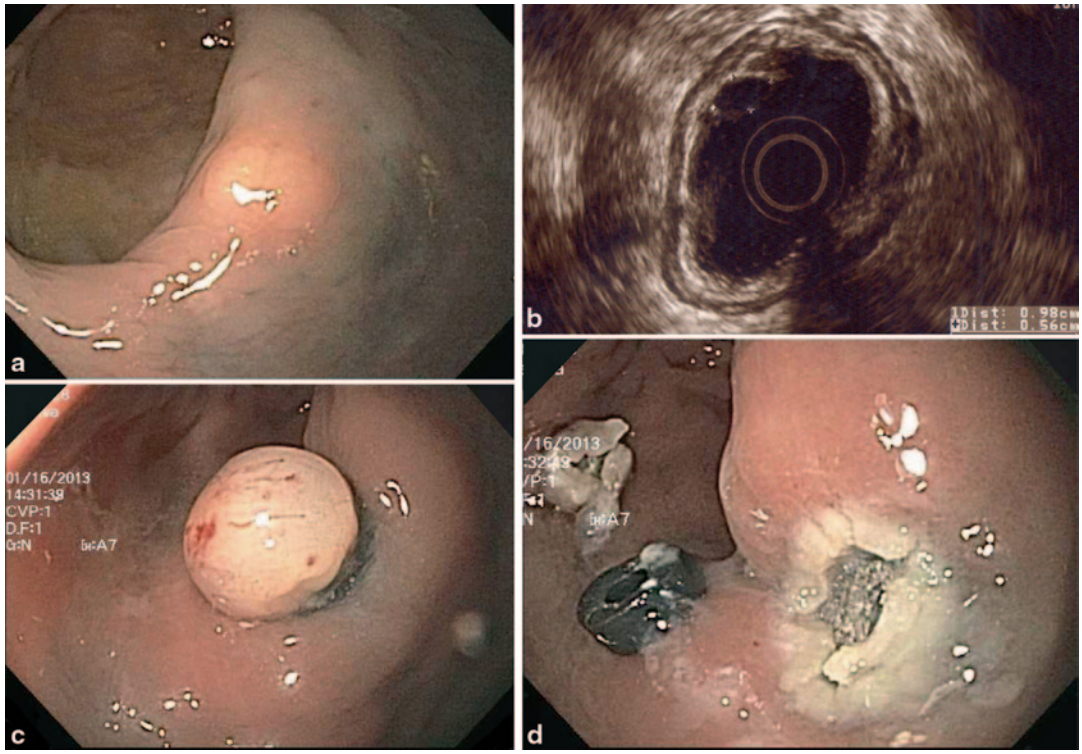

Fig. 28.10 Band ligation-endoscopic mucosal resection of a small rectal carcinoid. **a** Endoscopic appearance of rectal carcinoid. **b** Endosonographic examination of the rectal carcinoid confirms the absence of involvement of the muscularis propria, and size under 1 cm. **c** Band ligation of the rectal carcinoid. **d** Complete resection of the rectal carcinoid achieved by endoscopic resection

Pancreatic Rest: What Endoscopic and EUS Features Are Characteristic?

Pancreatic rests represent ectopic pancreatic tissue within the wall of the gastrointestinal tract. They are most commonly detected in the gastric antrum, but also may occur in the duodenum or proximal jejunum. The majority of these lesions are asymptomatic with no clinical significance, but rare complications have been reported, including ulceration, bleeding, gastric outlet obstruction, pancreatitis, and even malignancy [96].

Endoscopic and Endosonographic Features

Endoscopically, pancreatic rests typically are soft, malleable round/oval subepithelial nodules, often with a central umbilication that represents the orifice of a draining duct (Fig. 28.11). They are most commonly located in the 3 o'clock to 7 o'clock position of the antrum along the posterior wall of the greater curvature. On EUS, they usually appear hypoechoic or heterogeneous with indistinct margins, and may contain anechoic tubular areas (duct structures), and localize within the second, third, or fourth echolayers [97, 98].

Diagnosis and Management

The diagnosis of pancreatic rest can usually be confidently established based on the endoscopic and EUS features. Histologic confirmation, although not usually necessary, may occasionally be obtained by inserting biopsy forceps within the central umbilication, or most effectively by band-ligation EMR or cap-assisted EMR techniques [10, 36, 99]. Histologic examination of resected specimens would be expected to reveal

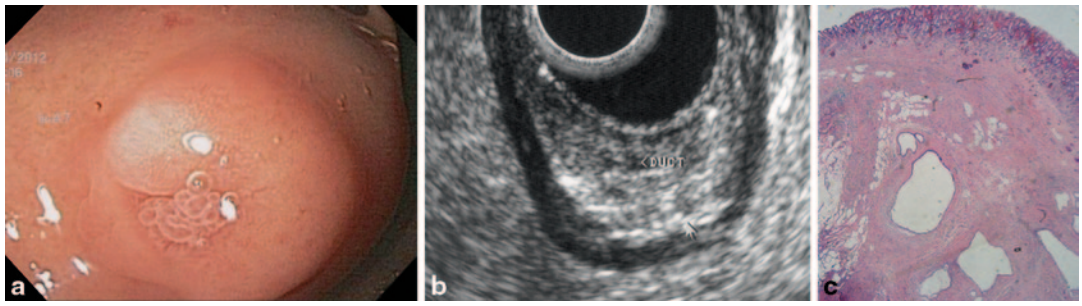

Fig. 28.11 Pancreatic rest. **a** Endoscopic appearance of a pancreatic rest in the stomach, featuring a pseudopapilla. **b** Endosonographic examination demonstrates a heterogeneous "salt-and-pepper" appearance typical of pancreatic parenchyma within the submucosa, including small anechoic spaces corresponding to ductal structures. **c** Histologic features of an endoscopically resected pancreatic rest

submucosal lobules of pancreatic acinar tissue with associated ducts (Fig. 28.11). These resection techniques may also be employed for treatment of symptomatic pancreatic rests, provided the muscularis propria is not involved based on EUS examination. No specific management other than expectant observation is necessary for asymptomatic, incidentally detected pancreatic rests.

Granular Cell Tumor: What is the Role of Endoscopy in Diagnosis and Management?

Granular cell tumors (GCTs) are rare tumors of Schwann cell origin with a predilection for the upper digestive tract, skin, and soft tissue. They are relatively rare in the gastrointestinal tract, where they are most commonly found the lower third of the esophagus and can be multifocal [100]. These tumors are usually asymptomatic and found incidentally, but rarely can ulcerate, bleed, or obstruct. They are generally considered benign, although rare occurrences of malignant transformation have been reported in large GCTs (>4 cm size) or tumors that exhibit rapid recent growth and/or rapid recurrence after excision [101–103].

Endoscopic and Endosonographic Features

Endoscopically, GCTs appear as a slightly elevated, firm nodule, with a whitish-gray or yellowish hue (Fig. 28.12). On EUS, they appear as hypoechoic lesions with smooth margins, usually confined to the second or third echolayer (deep mucosa or submucosa, respectively) [104, 105].

Diagnosis and Management

In the majority of cases, stacked biopsies using standard forceps will yield the diagnosis [104]. Endoscopic resection using band-ligation EMR or cap-assisted EMR can also be performed for small GCTs to establish the diagnosis and provide definitive treatment. Histologically, they are characterized by sheets or nests of large polygonal cells with granular cytoplasm and small round nuclei. Immunohistochemical stains will be positive for S100, indicative of neural origin.

There is no consensus on the optimal management of small, incidentally detected GCTs of the gastrointestinal tract. Small GCTs (<2 cm) limited to the mucosa and submucosa can be resected via band-ligation EMR or cap-assisted EMR, provided there is available endoscopic expertise [104, 106]. Alternatively, endoscopic/EUS surveillance every 1–2 years may be appropriate, given the low-malignant potential of small gastrointestinal tract GCTs. Patients with large GCTs should be referred for consideration of surgical resection.

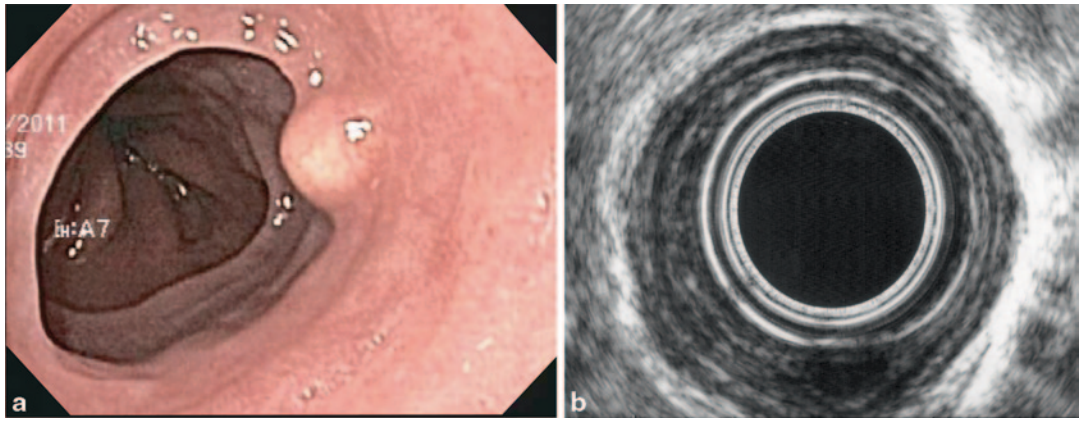

Fig. 28.12 Esophageal granular cell tumor. **a** Endoscopic examination reveals a small, firm nodule with a yellowish hue located in the distal esophagus. **b** Endosonographic appearance of a small esophageal granular cell tumor

Duplication Cysts: What is the Role of EUS/EUS-FNA in Diagnosis?

Duplication cysts arise during embryonic development, possibly related to errors of recanalization and fusion of longitudinal folds. They may occur at any level from oral cavity to rectum, with the small bowel being the most common site. Duplication cysts are usually asymptomatic, but can rarely result in symptoms due to mass effect (dysphagia, gastric outlet or bowel obstruction, pancreatitis), as well as bleeding, intussusception, and even perforation. Instances of malignant transformation (mainly adenocarcinoma arising within gastric duplication cysts) have been reported, although this is a very rare event [107].

Endoscopic and Endosonographic Features

Endoscopically, duplication cysts are rounded or tubular in morphology, with smooth contours. In the esophagus, they may mimic the appearance of esophageal varices, but without the bluish coloration. They are usually compressible and soft in consistency. On EUS imaging, duplication cysts usually appear as anechoic structures within the submucosal layer, or adjacent to the wall of the gastrointestinal tract. A 3- or 5- layer wall may be visible, and fluid levels and internal echogenic foci from mucinous material or debris may be present (Fig. 28.13) [108–111].

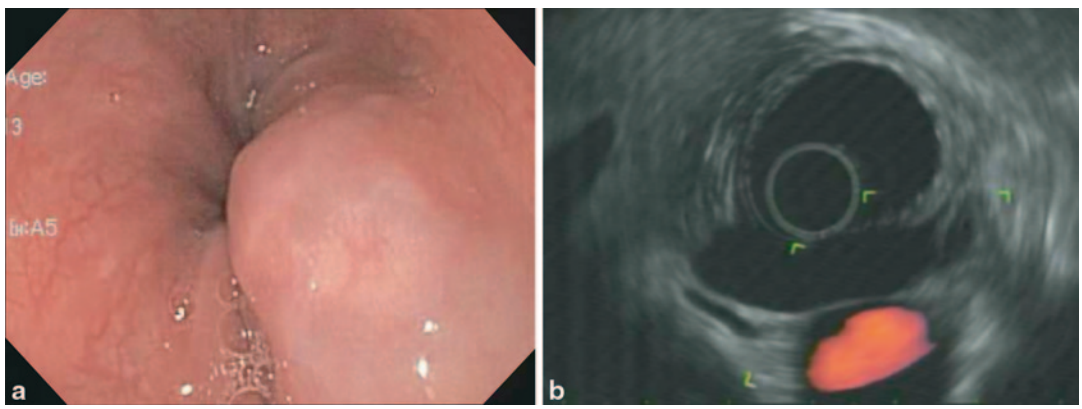

Fig. 28.13 Esophageal duplication cyst. **a** Endoscopic appearance, featuring a shiny, translucent appearance. **b** Endosonographic examination reveals a Doppler-negative anechoic structure

Diagnosis and Management

The diagnosis can be established by EUS-FNA to sample the cyst fluid although this is not always required and the information obtained by FNA must be weighed against the high risk of infection. EUS-FNA is recommended when diagnostic uncertainty remains for atypical-appearing lesions following EUS evaluation. The use of prophylactic antibiotics and smaller gauge needles (22-gauge) is recommended if cyst aspiration is performed [108]. The aspirated fluid may have a thick, gel-like consistency, and cytologic examination may reveal pseudostratified columnar-ciliated epithelium in a background of proteinaceous debris, mucin, and histiocytes [108, 112].

Management of asymptomatic duplication cysts is usually expectant observation, with the option of periodic EUS surveillance. The treatment of symptomatic or enlarging cysts has traditionally been surgical resection or marsupialization. Endoscopic treatments that have been described in case reports include snare resection, endoscopic incision, and marsupialization [113–116].

Inflammatory Fibroid Polyps: What Endoscopic and Histologic Findings are Characteristic?

Inflammatory fibroid polyps (IFPs), also known as Vanek tumors, are rare, benign mesenchymal tumors that can occur throughout the gastrointestinal tract. They are most commonly found in the colon and stomach (although only representing < 0.1 % of all gastric polyps) [117]. The etiology of these lesions is uncertain, but a high frequency of platelet-derived growth factor receptor alpha (PDGFR-A) mutation points to an underlying clonal, neoplastic pathogenesis [118].

The clinical presentation of IFPs largely depends on the location of the lesion. Gastric IFPs may cause abdominal pain, gastric outlet obstruction, or bleeding. Small intestinal lesions frequently present with intussusception [119].

Endoscopic and Endosonographic Features

Endoscopically, IFPs are usually firm, solitary, semi-pedunculated, and often ulcerated or with an erythematous central depression (Fig. 28.14) [120]. Gastric IFPs are usually located in the antrum or pyloric region. On EUS imaging, they appear as hypoechoic, homogenous lesions with indistinct margins, located in the deep mucosa or submucosa, without the involvement of the muscularis propria [121].

Diagnosis and Management

Histologically, IFPs consist of submucosal proliferations of spindle cells, small vessels, and a striking inflammatory infiltrate predominated by eosinophils (Fig. 28.14). Another characteristic finding is the presence of concentric cuffing of vessels by the spindle cells, referred to "onion skinning" [119]. Immunohistochemical staining for CD34 is diffusely and strongly positive in the majority of IFPs, but negative for CD117.

IFPs may be safely resected using standard electrosurgical snare polypectomy, with or without the use of a detachable loop. As most IFPs do not recur after resection, no surveillance is necessary [122].

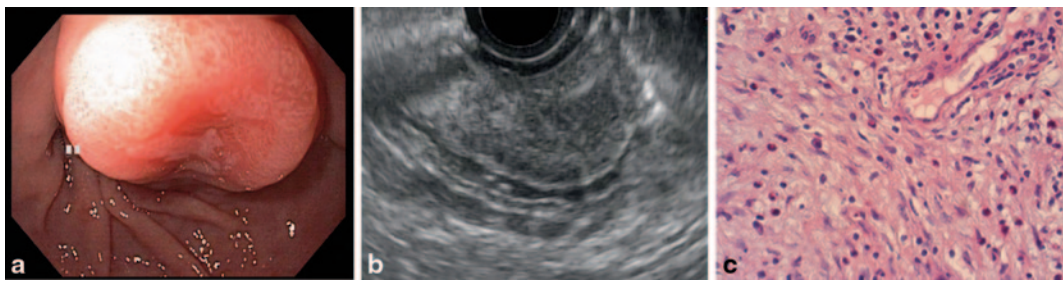

Fig. 28.14 Gastric inflammatory fibroid polyp (Vanek tumor). **a** Endoscopic appearance, characterized by central depression/ulceration and location in the antrum. **b** Endosonographic appearance. **c** Histologic features characterized by prominent eosinophilic infiltrate

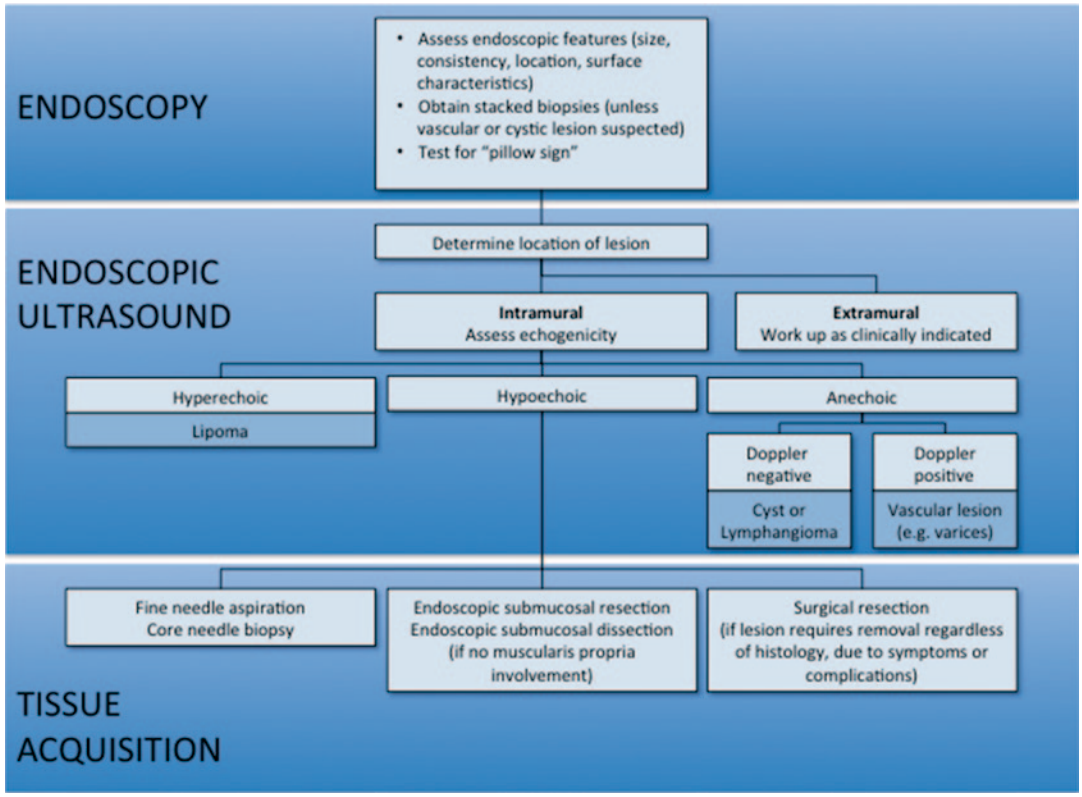

Fig. 28.15 An algorithmic approach to the evaluation of subepithelial lesions of the gastrointestinal tract

Case Continued

The patient underwent laparotomy with low anterior resection of the recurrent tumor. Surgical pathologic examination revealed a 3.5 cm x 3 cm x 2 cm well-to-moderately differentiated mucinous adenocarcinoma located mainly in the muscularis propria, extending to the serosal surface. The patient completed adjuvant chemotherapy and has had no evidence of residual or recurrent disease after 3 years of follow-up since the operation.

Conclusion

Subepithelial lesions of the gastrointestinal tract can represent a wide variety of processes, including congenital abnormalities, extrinsic compression from adjacent structures, and intramural neoplasms. Gastroenterologists should be familiar with the diagnostic features and management of the most commonly encountered subepithelial lesions discussed in this chapter. A stepwise evaluation (Fig. 28.15) including careful endoscopic examination followed by EUS with or without tissue acquisition will lead to the correct diagnosis in the majority of cases.

Key Points

- Subepithelial lesions can occur throughout the gastrointestinal tract, and warrant careful evaluation given the possibility of underlying malignancy or premalignant pathology.
- Routine endoscopic examination and stacked biopsies are useful first steps in evaluation of many subepithelial lesions, but endoscopic ultrasound is the best diagnostic modality and should be performed in the majority of cases.

- Endoscopic ultrasound-guided fine needle aspiration or fine needle biopsy should be performed to achieve a definitive cytologic or histologic diagnosis when there is diagnostic uncertainty or concern for malignancy.
- Tissue acquisition by endoscopic submucosal resection or dissection can be considered for definitive diagnosis and therapy in selected cases, after endosonographic examination excludes involvement of the muscularis propria.

Video Caption

Video 28.1 This video demonstrates the endoscopic and endosonographic appearance of a gastric GIST, as well as two methods for tissue acquisition: stacked biopsies using forceps and fine needle aspiration. In this case, both methods confirmed the diagnosis of GIST

References

1. Landi B, Palazzo L. The role of endosonography in submucosal tumours. Best Pract Res Clin Gastroenterol. 2009;23(5):679–701.
2. Polkowski M. Endoscopic ultrasound and endoscopic ultrasound-guided fine-needle biopsy for the diagnosis of malignant submucosal tumors. Endoscopy. 2005;37(7):635–45.
3. Polkowski M, Butruk E. Submucosal lesions. Gastrointest Endosc Clin N Am. 2005;15(1):33–54.
4. Brullet E, Campo R, Fontanet M, Puig M. False submucosal rectal tumor. Gastrointest Endosc. 2000;52(6):752.
5. Suzuki R, Bhutani MS. Vanishing rectal subepithelial mass. Gastrointest Endosc. 2013;77(4):663.
6. Eckardt AJ, Wassef W. Diagnosis of subepithelial tumors in the GI tract. Endoscopy, EUS, and histology: bronze, silver, and gold standard? Gastrointest Endosc. 2005;62(2):209–12.
7. Hwang JH, Rulyak SD, Kimmey MB. American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. Gastroenterology. 2006;130(7):2217–28.
8. Hwang JH, Saunders MD, Rulyak SJ, Shaw S, Nietsch H, Kimmey MB. A prospective study comparing endoscopy and EUS in the evaluation of GI subepithelial masses. Gastrointest Endosc. 2005;62(2):202–8.
9. Hoda KM, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. Gastrointest Endosc. 2009;69(7):1218–23.
10. Cantor MJ, Davila RE, Faigel DO. Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. Gastrointest Endosc. 2006;64(1):29–34.
11. Hunt GC, Smith PP, Faigel DO. Yield of tissue sampling for submucosal lesions evaluated by EUS. Gastrointest Endosc. 2003;57(1):68–72.
12. Ji JS, Lee BI, Choi KY, Kim BW, Choi H, Huh M, et al. Diagnostic yield of tissue sampling using a bite-on-bite technique for incidental subepithelial lesions. Korean J Intern Med. 2009;24(2):101–5.
13. Buscaglia JM, Nagula S, Jayaraman V, Robbins DH, Vadada D, Gross SA, et al. Diagnostic yield and safety of jumbo biopsy forceps in patients with subepithelial lesions of the upper and lower GI tract. Gastrointest Endosc. 2012;75(6):1147–52.
14. Keswani RN, Nayar R, Mahajan A, Komanduri S. Touch preparation of jumbo forceps biopsies allows rapid adequacy assessment of subepithelial GI masses. Gastrointest Endosc. 2011;74(2):411–4.
15. Komanduri S, Keefer L, Jakate S. Diagnostic yield of a novel jumbo biopsy "unroofing" technique for tissue acquisition of gastric submucosal masses. Endoscopy. 2011;43(10):849–55.
16. Lee CK, Chung IK, Lee SH, Lee TH, Park SH, Kim HS, et al. Endoscopic partial resection with the unroofing technique for reliable tissue diagnosis of upper GI subepithelial tumors originating from the muscularis propria on EUS (with video). Gastrointest Endosc. 2010;71(1):188–94.
17. Wallace MB, Hoffman BJ, Sahai AS, Inoue H, Van Velse A, Hawes RH. Imaging of esophageal tumors with a water-filled condom and a catheter US probe. Gastrointest Endosc. 2000;51(5):597–600.
18. Motoo Y, Okai T, Ohta H, Satomura Y, Watanabe H, Yamakawa O, et al. Endoscopic ultrasonography in the diagnosis of extraluminal compressions mimicking gastric submucosal tumors. Endoscopy. 1994;26(2):239–42.
19. Karaca C, Turner BG, Cizginer S, Forcione D, Brugge W. Accuracy of EUS in the evaluation of small gastric subepithelial lesions. Gastrointest Endosc. 2010;71(4):722–7.
20. Reddymasu SC, Oropeza-Vail M, Pakseresht K, Moloney B, Esfandyari T, Grisolano S, et al. Are endoscopic ultrasonography imaging characteristics reliable for the diagnosis of small upper gastrointestinal subepithelial lesions? J Clin Gastroenterol. 2012;46(1):42–5.
21. Gress F, Schmitt C, Savides T, Faigel DO, Catalano M, Wassef W, et al. Interobserver agreement for EUS in the evaluation and diagnosis of submucosal masses. Gastrointest Endosc. 2001;53(1):71–6.
22. Chen VK, Eloubeidi MA. Endoscopic ultrasound-guided fine-needle aspiration of intramural and extraintestinal mass lesions: diagnostic accuracy, complication assessment, and impact on management. Endoscopy. 2005;37(10):984–9.

23. Mekky MA, Yamao K, Sawaki A, Mizuno N, Hara K, Nafeh MA, et al. Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors. Gastrointest Endosc. 2010;71(6):913–9.
24. Sasaki Y, Niwa Y, Hirooka Y, Ohmiya N, Itoh A, Ando N, et al. The use of endoscopic ultrasound-guided fine-needle aspiration for investigation of submucosal and extrinsic masses of the colon and rectum. Endoscopy. 2005;37(2):154–60.
25. Sepe PS, Moparty B, Pitman MB, Saltzman JR, Brugge WR. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. Gastrointest Endosc. 2009;70(2):254–61.
26. Turhan N, Aydog G, Ozin Y, Cicek B, Kurt M, Oguz D. Endoscopic ultrasonography-guided fine-needle aspiration for diagnosing upper gastrointestinal submucosal lesions: a prospective study of 50 cases. Diagn Cytopathol. 2011;39(11):808–17.
27. Vander Noot MR, 3rd, Eloubeidi MA, Chen VK, Eltoum I, Jhala D, Jhala N, et al. Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer. 2004;102(3):157–63.
28. Ando N, Goto H, Niwa Y, Hirooka Y, Ohmiya N, Nagasaka T, et al. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. Gastrointest Endosc. 2002;55(1):37–43.
29. Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology. 1997;112(4):1087–95.
30. Akahoshi K, Sumida Y, Matsui N, Oya M, Akinaga R, Kubokawa M, et al. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. World J Gastroenterol. 2007;13(14):2077–82.
31. Watson RR, Binmoeller KF, Hamerski CM, Shergill AK, Shaw RE, Jaffee IM, et al. Yield and performance characteristics of endoscopic ultrasound-guided fine needle aspiration for diagnosing upper GI tract stromal tumors. Dig Dis Sci. 2011;56(6):1757–62.
32. Rong L, Kida M, Yamauchi H, Okuwaki K, Miyazawa S, Iwai T, et al. Factors affecting the diagnostic accuracy of endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) for upper gastrointestinal submucosal or extraluminal solid mass lesions. Dig Endosc. 2012;24(5):358–63.
33. Kida M, Araki M, Miyazawa S, Ikeda H, Takezawa M, Kikuchi H, et al. Comparison of diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration with 22- and 25-gauge needles in the same patients. J Interv Gastroenterol. 2011;1(3):102–7.
34. Saftoiu A, Vilmann P, Guldhammer Skov B, Georgescu CV. Endoscopic ultrasound (EUS)-guided Trucut biopsy adds significant information to EUS-guided fine-needle aspiration in selected patients: a prospective study. Scand J Gastroenterol. 2007;42(1):117–25.
35. Storch I, Jorda M, Thurer R, Raez L, Rocha-Lima C, Vernon S, et al. Advantage of EUS Trucut biopsy combined with fine-needle aspiration without immediate on-site cytopathologic examination. Gastrointest Endosc. 2006;64(4):505–11.
36. Bain AJ, Owens DJ, Tang RS, Peterson MR, Savides TJ. Pancreatic rest resection using band ligation snare polypectomy. Dig Dis Sci. 2011;56(6):1884–8.
37. Huang WH, Feng CL, Lai HC, Yu CJ, Chou JW, Peng CY, et al. Endoscopic ligation and resection for the treatment of small EUS-suspected gastric GI stromal tumors. Gastrointest Endosc. 2010;71(6):1076–81.
38. Hwang JC, Kim JH, Shin SJ, Cheong JY, Lee KM, Yoo BM, et al. Endoscopic resection for the treatment of gastric subepithelial tumors originated from the muscularis propria layer. Hepatogastroenterology. 2009;56(94–95):1281–6.
39. Kawamoto K, Yamada Y, Furukawa N, Utsunomiya T, Haraguchi Y, Mizuguchi M, et al. Endoscopic submucosal tumorectomy for gastrointestinal submucosal tumors restricted to the submucosa: a new form of endoscopic minimal surgery. Gastrointest Endosc. 1997;46(4):311–7.
40. Lee IL, Lin PY, Tung SY, Shen CH, Wei KL, Wu CS. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. Endoscopy. 2006;38(10):1024–8.
41. Park YS, Park SW, Kim TI, Song SY, Choi EH, Chung JB, et al. Endoscopic enucleation of upper-GI submucosal tumors by using an insulated-tip electrosurgical knife. Gastrointest Endosc. 2004;59(3):409–15.
42. Kim HH, Park SJ, Lee SH, Park HU, Song CS, Park MI, et al. Efficacy of endoscopic submucosal resection with a ligation device for removing small rectal carcinoid tumor compared with endoscopic mucosal resection: analysis of 100 cases. Dig Endosc. 2012;24(3):159–63.
43. Lee SH, Park SJ, Kim HH, Ok KS, Kim JH, Jee SR, et al. Endoscopic resection for rectal carcinoid tumors: comparison of polypectomy and endoscopic submucosal resection with band ligation. Clin Endosc. 2012;45(1):89–94.
44. Sun S, Ge N, Wang C, Wang M, Lu Q. Endoscopic band ligation of small gastric stromal tumors and follow-up by endoscopic ultrasonography. Surg Endosc. 2007;21(4):574–8.
45. Sun S, Jin Y, Chang G, Wang C, Li X, Wang Z. Endoscopic band ligation without electrosurgery: a new technique for excision of small upper-GI leiomyoma. Gastrointest Endosc. 2004;60(2):218–22.
46. Sun S, Ge N, Wang S, Liu X, Lu Q. EUS-assisted band ligation of small duodenal stromal tumors and follow-up by EUS. Gastrointest Endosc. 2009;69(3 Pt 1):492–6.
47. Nilsson B, Bumming P, Meis-Kindblom JM, Oden A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib

mesylate era–a population-based study in western Sweden. Cancer. 2005;103(4):821–9.
48. Tryggvason G, Gislason HG, Magnusson MK, Jonasson JG. Gastrointestinal stromal tumors in Iceland, 1990–2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer. 2005;117(2):289–93.
49. Miettinen M, Lasota J. Gastrointestinal stromal tumors–definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch. 2001;438(1):1–12.
50. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005;29(1):52–68.
51. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol. 2006;30(4):477–89.
52. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. Am J Surg Pathol. 2000;24(2):211–22.
53. Chak A, Canto MI, Rosch T, Dittler HJ, Hawes RH, Tio TL, et al. Endosonographic differentiation of benign and malignant stromal cell tumors. Gastrointest Endosc. 1997;45(6):468–73.
54. Jeon SW, Park YD, Chung YJ, Cho CM, Tak WY, Kweon YO, et al. Gastrointestinal stromal tumors of the stomach: endosonographic differentiation in relation to histological risk. J Gastroenterol Hepatol. 2007;22(12):2069–75.
55. Sakamoto H, Kitano M, Matsui S, Kamata K, Komaki T, Imai H, et al. Estimation of malignant potential of GI stromal tumors by contrast-enhanced harmonic EUS (with videos). Gastrointest Endosc. 2011;73(2):227–37.
56. Shah P, Gao F, Edmundowicz SA, Azar RR, Early DS. Predicting malignant potential of gastrointestinal stromal tumors using endoscopic ultrasound. Dig Dis Sci. 2009;54(6):1265–9.
57. Palazzo L, Landi B, Cellier C, Cuillerier E, Roseau G, Barbier JP. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. Gut. 2000;46(1):88–92.
58. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002;33(5):459–65.
59. Laurini JA, Carter JE. Gastrointestinal stromal tumors: a review of the literature. Arch Pathol Lab Med. 2010;134(1):134–41.
60. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279(5350):577–80.
61. Kara T, Serinsoz E, Arpaci RB, Gubur O, Orekici G, Ata A, et al. Contribution of DOG1 expression to the diagnosis of gastrointestinal stromal tumors. Pathol Res Pract. 2013;209(7):413–7.
62. Liegl B, Hornick JL, Corless CL, Fletcher CD. Monoclonal antibody DOG1.1 shows higher sensitivity than KIT in the diagnosis of gastrointestinal stromal tumors, including unusual subtypes. Am J Surg Pathol. 2009;33(3):437–46.
63. Novelli M, Rossi S, Rodriguez-Justo M, Taniere P, Seddon B, Toffolatti L, et al. DOG1 and CD117 are the antibodies of choice in the diagnosis of gastrointestinal stromal tumours. Histopathology. 2010;57(2):259–70.
64. Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, et al. NCCN task force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw. 2010;8(Suppl 2):S1–41.
65. Mullady DK, Tan BR. A multidisciplinary approach to the diagnosis and treatment of gastrointestinal stromal tumor. J Clin Gastroenterol. 2013;47(7):578–85.
66. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009;20(Suppl 4):64–7.
67. Bruno M, Carucci P, Repici A, Pellicano R, Mezzabotta L, Goss M, et al. The natural history of gastrointestinal subepithelial tumors arising from muscularis propria: an endoscopic ultrasound survey. J Clin Gastroenterol. 2009;43(9):821–5.
68. Gill KR, Camellini L, Conigliaro R, Sassatelli R, Azzolini F, Messerotti A, et al. The natural history of upper gastrointestinal subepithelial tumors: a multicenter endoscopic ultrasound survey. J Clin Gastroenterol. 2009;43(8):723–6.
69. Kim MY, Jung HY, Choi KD, Song HJ, Lee JH, Kim do H, et al. Natural history of asymptomatic small gastric subepithelial tumors. J Clin Gastroenterol. 2011;45(4):330–6.
70. Lok KH, Lai L, Yiu HL, Szeto ML, Leung SK. Endosonographic surveillance of small gastrointestinal tumors originating from muscularis propria. J Gastrointestin Liver Dis. 2009;18(2):177–80.
71. Melzer E, Fidder H. The natural course of upper gastrointestinal submucosal tumors: an endoscopic ultrasound survey. Isr Med Assoc J. 2000;2(6):430–2.
72. Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. Nat Rev Gastroenterol Hepatol. 2009;6(6):363–71.
73. Zhang Y, Ye LP, Zhou XB, Mao XL, Zhu LH, He BL, et al. Safety and Efficacy of Endoscopic Excavation for Gastric Subepithelial Tumors Originating From the Muscularis Propria Layer: Results From a Large Study in China. J Clin Gastroenterol. 2013;47(8):689–94.
74. Zhang Y, Ye LP, Zhu LH, Zhou XB, Mao XL, Ding JX. Endoscopic muscularis excavation for subepithelial tumors of the esophagogastric junction originating from the muscularis propria layer. Dig Dis Sci. 2013;58(5):1335–40.

75. Seremetis MG, Lyons WS, deGuzman VC, Peabody JW, Jr. Leiomyomata of the esophagus. An analysis of 838 cases. Cancer. 1976;38(5):2166–77.
76. Fei BY, Yang JM, Zhao ZS. Differential clinical and pathological characteristics of esophageal stromal tumors and leiomyomata. Dis Esophagus. 2013;27(1):30–5.
77. Lee LS, Singhal S, Brinster CJ, Marshall B, Kochman ML, Kaiser LR, et al. Current management of esophageal leiomyoma. J Am Coll Surg. [Review]. 2004;198(1):136–46.
78. Kajiyama T, Sakai M, Torii A, Kishimoto H, Kin G, Uose S, et al. Endoscopic aspiration lumpectomy of esophageal leiomyomas derived from the muscularis mucosae. Am J Gastroenterol. 1995;90(3):417–22.
79. Hu B, Mou Y, Yi H, Wang Y, Luo R, Zhang Q, et al. Endoscopic enucleation of large esophageal leiomyomas. Gastrointest Endosc. 2011;74(4):928–31.
80. Sugimoto K, Sato K, Maekawa H, Sakurada M, Orita H, Ito T, et al. Unroofing technique for endoscopic resection of a large colonic lipoma. Case Rep Gastroenterol. 2012;6(2):557–62.
81. Kim CY, Bandres D, Tio TL, Benjamin SB, Al-Kawas FH. Endoscopic removal of large colonic lipomas. Gastrointest Endosc. 2002;55(7):929–31.
82. Aydin HN, Bertin P, Singh K, Arregui M. Safe techniques for endoscopic resection of gastrointestinal lipomas. Surg Laparosc Endosc Percutan Tech. 2011;21(4):218–22.
83. Kaltenbach T, Milkes D, Friedland S, Soetikno R. Safe endoscopic treatment of large colonic lipomas using endoscopic looping technique. Dig Liver Dis. 2008;40(12):958–61.
84. Soares JB, Goncalves R, Rolanda C. Endoscopic resection of a large colonic lipoma by unroofing technique. Endoscopy. 2011;43(Suppl 2 UCTN):E407.
85. Geraci G, Pisello F, Arnone E, Sciuto A, Modica G, Sciume C. Endoscopic resection of a large colonic lipoma: case report and review of literature. Case Rep Gastroenterol. 2010;4(1):6–11.
86. Arnold R. Endocrine tumours of the gastrointestinal tract. Introduction: definition, historical aspects, classification, staging, prognosis and therapeutic options. Best Pract Res Clin Gastroenterol. 2005;19(4):491–505.
87. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012;61(1):6–32.
88. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934–59.
89. Nakamura S, Iida M, Yao T, Fujishima M. Endoscopic features of gastric carcinoids. Gastrointest Endosc. 1991;37(5):535–8.
90. Oberg K, Akerstrom G, Rindi G, Jelic S. Neuroendocrine gastroenteropancreatic tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v223–7.
91. Modlin IM, Latich I, Kidd M, Zikusoka M, Eick G. Therapeutic options for gastrointestinal carcinoids. Clin Gastroenterol Hepatol. 2006;4(5):526–47.
92. Kulke MH, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas. 2010;39(6):735–52.
93. Lawrence B, Kidd M, Svejda B, Modlin I. A clinical perspective on gastric neuroendocrine neoplasia. Curr Gastroenterol Rep. 2011;13(1):101–9.
94. Murray SE, Sippel RS, Lloyd R, Chen H. Surveillance of small rectal carcinoid tumors in the absence of metastatic disease. Ann Surg Oncol. 2012;19(11):3486–90.
95. Choi CW, Kang DH, Kim HW, Park SB, Jo WS, Song GA, et al. Comparison of endoscopic resection therapies for rectal carcinoid tumor: endoscopic submucosal dissection versus endoscopic mucosal resection using band ligation. J Clin Gastroenterol. 2013;47(5):432–6.
96. Rimal D, Thapa SR, Munasinghe N, Chitre VV. Symptomatic gastric heterotopic pancreas: clinical presentation and review of the literature. Int J Surg. 2008;6(6):e52–4.
97. Park SH, Kim GH, Park do Y, Shin NR, Cheong JH, Moon JY, et al. Endosonographic findings of gastric ectopic pancreas: a single center experience. J Gastroenterol Hepatol. 2011;26(9):1441–6.
98. Matsushita M, Hajiro K, Okazaki K, Takakuwa H. Gastric aberrant pancreas: EUS analysis in comparison with the histology. Gastrointest Endosc. 1999;49(4 Pt 1):493–7.
99. Khashab MA, Cummings OW, DeWitt JM. Ligation-assisted endoscopic mucosal resection of gastric heterotopic pancreas. World J Gastroenterol. 2009;15(22):2805–8.
100. Voskuil JH, van Dijk MM, Wagenaar SS, van Vliet AC, Timmer R, van Hees PA. Occurrence of esophageal granular cell tumors in The Netherlands between 1988 and 1994. Dig Dis Sci. 2001;46(8):1610–4.
101. Humphris JL, Jones DB. Subepithelial mass lesions in the upper gastrointestinal tract. J Gastroenterol Hepatol. 2008;23(4):556–66.
102. Xu GQ, Chen HT, Xu CF, Teng XD. Esophageal granular cell tumors: report of 9 cases and a literature review. World J Gastroenterol. 2012;18(47):7118–21.
103. Orlowska J, Pachlewski J, Gugulski A, Butruk E. A conservative approach to granular cell tumors of the esophagus: four case reports and literature review. Am J Gastroenterol. 1993;88(2):311–5.
104. Zhong N, Katzka DA, Smyrk TC, Wang KK, Topazian M. Endoscopic diagnosis and resection of esophageal granular cell tumors. Dis Esophagus. 2011;24(8):538–43.
105. Palazzo L, Landi B, Cellier C, Roseau G, Chaussade S, Couturier D, et al. Endosonographic features of esophageal granular cell tumors. Endoscopy. 1997;29(9):850–3.
106. Wehrmann T, Martchenko K, Nakamura M, Riphaus A, Stergiou N. Endoscopic resection of

submucosal esophageal tumors: a prospective case series. Endoscopy. 2004;36(9):802–7.
107. Zheng J, Jing H. Adenocarcinoma arising from a gastric duplication cyst. Surg Oncol. 2012;21(2):e97–101.
108. Fazel A, Moezardalan K, Varadarajulu S, Draganov P, Eloubeidi MA. The utility and the safety of EUS-guided FNA in the evaluation of duplication cysts. Gastrointest Endosc. 2005;62(4):575–80.
109. Van Dam J Rice TW Sivak MV Jr. Endoscopic ultrasonography and endoscopically guided needle aspiration for the diagnosis of upper gastrointestinal tract foregut cysts. Am J Gastroenterol. 1992;87(6):762–5.
110. Bhutani MS, Hoffman BJ, Reed C. Endosonographic diagnosis of an esophageal duplication cyst. Endoscopy. 1996;28(4):396–7.
111. Geller A, Wang KK, DiMagno EP. Diagnosis of foregut duplication cysts by endoscopic ultrasonography. Gastroenterology. 1995;109(3):838–42.
112. Napolitano V, Pezzullo AM, Zeppa P, Schettino P, D'Armiento M, Palazzo A, et al. Foregut duplication of the stomach diagnosed by endoscopic ultrasound guided fine-needle aspiration cytology: case report and literature review. World J Surg Oncol. 2013;11:33.
113. Joyce AM, Zhang PJ, Kochman ML. Complete endoscopic resection of an esophageal duplication cyst (with video). Gastrointest Endosc. 2006;64(2):288–9.
114. Will U, Meyer F, Bosseckert H. Successful endoscopic treatment of an esophageal duplication cyst. Scand J Gastroenterol. 2005;40(8):995–9.
115. Ferrari AP, Jr., Van Dam J, Carr-Locke DL. Endoscopic needle aspiration of a gastric duplication cyst. Endoscopy. 1995;27(3):270–2.
116. Antaki F, Tringali A, Deprez P, Kwan V, Costamagna G, Le Moine O, et al. A case series of symptomatic intraluminal duodenal duplication cysts: presentation, endoscopic therapy, and long-term outcome (with video). Gastrointest Endosc. 2008;67(1):163–8.
117. Carmack SW, Genta RM, Schuler CM, Saboorian MH. The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients. Am J Gastroenterol. 2009;104(6):1524–32.
118. Daum O, Hatlova J, Mandys V, Grossmann P, Mukensnabl P, Benes Z, et al. Comparison of morphological, immunohistochemical, and molecular genetic features of inflammatory fibroid polyps (Vanek's tumors). Virchows Arch. 2010;456(5):491–7.
119. Liu TC, Lin MT, Montgomery EA, Singhi AD. Inflammatory fibroid polyps of the gastrointestinal tract: spectrum of clinical, morphologic, and immunohistochemistry features. Am J Surg Pathol. 2013;37(4):586–92.
120. Matsushita M, Hajiro K, Okazaki K, Takakuwa H. Endoscopic features of gastric inflammatory fibroid polyps. Am J Gastroenterol. 1996;91(8):1595–8.
121. Matsushita M, Hajiro K, Okazaki K, Takakuwa H. Gastric inflammatory fibroid polyps: endoscopic ultrasonographic analysis in comparison with the histology. Gastrointest Endosc. 1997;46(1):53–7.
122. Carmack SW, Genta RM, Graham DY, Lauwers GY. Management of gastric polyps: a pathology-based guide for gastroenterologists. Nat Rev Gastroenterol Hepatol. 2009;6(6):331–41.
123. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008;39(10):1411–9.