

Diagnosis and Treatment of Rectal Gastrointestinal Stromal Tumors

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CASE SUMMARY: A 69-year-old man presented with a rectal mass that was noted on physical examination. Flexible sigmoidoscopy confirmed the presence of a well-defined mass 3 cm from the anal verge (Fig. 1). Magnetic resonance imaging of the pelvis identified a 5.8-cm heterogeneous mass with intersphincteric extension. Positron emission tomography-computed tomography revealed no evidence of distant metastatic disease. Endoscopic ultrasound (EUS) with fine-needle aspiration revealed a noncircumferential submucosal hypoechoic mass (Fig. 2) with pathology significant for spindle cells staining positive for CD117, consistent with a GI stromal tumor (GIST). The patient received 5 months of neoadjuvant imatinib with great response (Fig. 3) and subsequently underwent transanal endoscopic microsurgical resection. He continues on adjuvant imatinib and is currently without signs of recurrence at 18 months postprocedure; he is undergoing restaging CT chest/abdomen/pelvis and surveillance flexible sigmoidoscopy every 6 months.

CLINICAL QUESTIONS

- What is the preoperative workup of a rectal GIST?
- When should preoperative chemotherapy be given?
- What are the surgical management options?



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BACKGROUND

Gastrointestinal stromal tumors make up only 1% of primary GI cancers and only 0.1% of tumors arising in the rectum. They are frequently defined as KIT-(CD117) or PDGFRA-positive mesenchymal spindle cell tumors. KIT is a tyrosine kinase receptor and an important target in therapy. Gastrointestinal stromal tumors most commonly occur in the stomach and small intestine, with up to 5% of GISTs occurring in the rectum. Elderly men in their 70s appear to be at highest risk, with blacks at approximately twice the risk of whites.¹

PRESENTATION AND DIAGNOSIS

Patients may present with nonspecific symptoms, including abdominal pain, GI bleeding, anemia, or weight loss. Rectal GISTs are frequently found incidentally, either on cross-sectional imaging, screening colonoscopy, or clinical examination. Low-lying GISTs may be felt as a smooth, firm mass on physical examination.

Computed tomography scan with oral and intravenous contrast is often the initial imaging modality of choice, both for detection and staging, for patients with suspected rectal GIST. Gastrointestinal stromal tumors usually appear as large, well-circumscribed, eccentric masses that enhance with intravenous contrast. Larger (>10 cm), heterogeneous tumors with areas of ulceration or necrosis are associated with higher rates of malignancy in nonrectal GISTs. Magnetic resonance imaging is beneficial in cases where CT cannot adequately identify the tumor organ of origin, or assists in delineating surrounding pelvic structures. Endoscopic ultrasound is useful to further characterize the lesion. Most GISTs originate from the muscularis propria and occasionally from the muscularis mucosa, which can be distinguished on EUS as a hypoechoic lesion with well-defined margins. In general, rectal GISTs can be diagnosed based on their clinical and radiographic appearance; however, if uncertainty exists or there is concern for metastasis, then EUS-guided biopsy is preferred.² Malignant GISTs have a high risk for metastasis, commonly intraperitoneally or to the liver, whereas

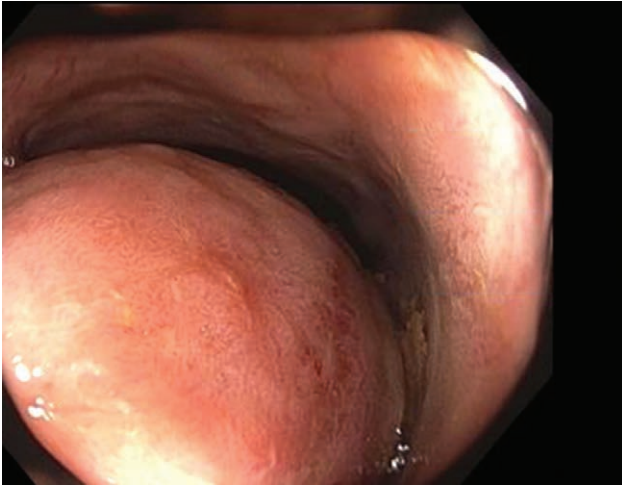


FIGURE 1. Flexible sigmoidoscopy of rectal GIST. GIST = GI stromal tumor.

other sites such as lymph nodes, lungs, or bone are rare.³ Positron emission tomography-computed tomography is useful in detecting metastases as well as evaluating tumor response to targeted molecular therapy.⁴

MANAGEMENT

All GISTs are considered to have malignant potential, and, for that reason, all rectal GISTs should be considered for resection. National Comprehensive Cancer Network guidelines recommend that even smaller lesions (<2 cm) with high-risk features, such as irregular borders, heterogeneity, and ulceration, be resected.⁵ A number of risk-stratification tools have been developed, and 2017 American Joint Committee on Cancer recommendations on staging of rectal GISTs include both tumor size (≤ 2 cm, 2–5 cm, 5–10 cm, and >10 cm) and mitotic rate (≤ 5 mitoses or >5 mitoses per 50 high-power field) to help determine rates of disease progression.⁶

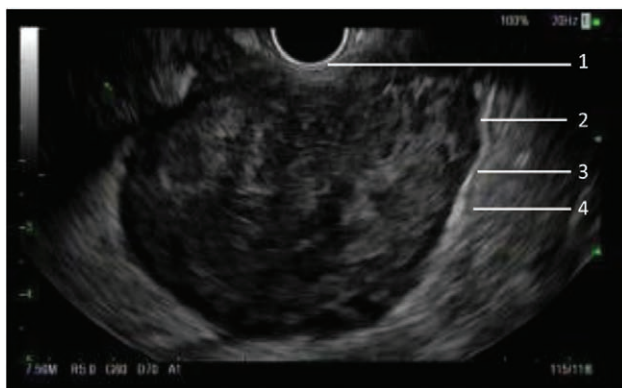


FIGURE 2. Endoscopic ultrasound of rectal GIST. 1, Mucosa; 2, Submucosa; 3, Muscularis propria; 4, Adventitia with mesorectum. GIST = GI stromal tumor.

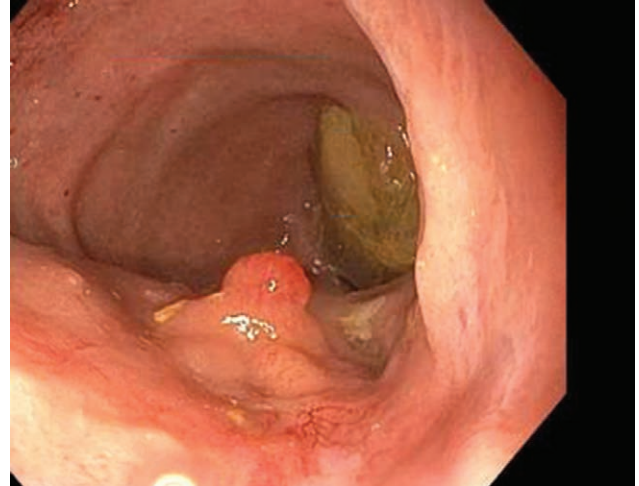


FIGURE 3. Flexible sigmoidoscopy of rectal GIST after neoadjuvant imatinib. GIST = GI stromal tumor.

Given their rarity and complexity in management, a tumor board evaluation should be considered for all cases of rectal GIST. Rectal GISTs provide a unique challenge compared with other locations within the GI tract, not only because of their worse prognosis and high local recurrence rate, but also because of the anatomical constraints of the pelvis. Because of this, imatinib, a tyrosine kinase inhibitor has proven beneficial in management. Neoadjuvant imatinib should be considered in all cases where a reduction in tumor size would substantially reduce the morbidity of the operation (eg, large tumor size, borderline resectability, local organ invasion, or allow sphincter salvage). Imatinib should also be considered in those with intermediate- or high-risk tumor status. Neoadjuvant imatinib has been associated with improved surgical margins, and perioperative imatinib has been shown to improve disease-free and overall survival.^{7–9}

Transabdominal, transanal, and endoscopic resections of rectal GISTs have all been described. The goal of all resections is to achieve grossly and microscopically negative margins. In addition, care should be taken to avoid tumor rupture. Lymphatic metastasis is rare for GISTs, and therefore mesorectal excisions, including abdominoperineal resection, are generally not required unless there is extensive local invasion. Choice of surgical approach should be tailored to each patient, location and size of the tumor, extent of local invasion, ability for sphincter salvage, and risk of malignancy. In certain patients, such as those with a small, low-risk GISTs at high risk of surgical morbidity, resection may be deferred for imatinib therapy and close surveillance instead.

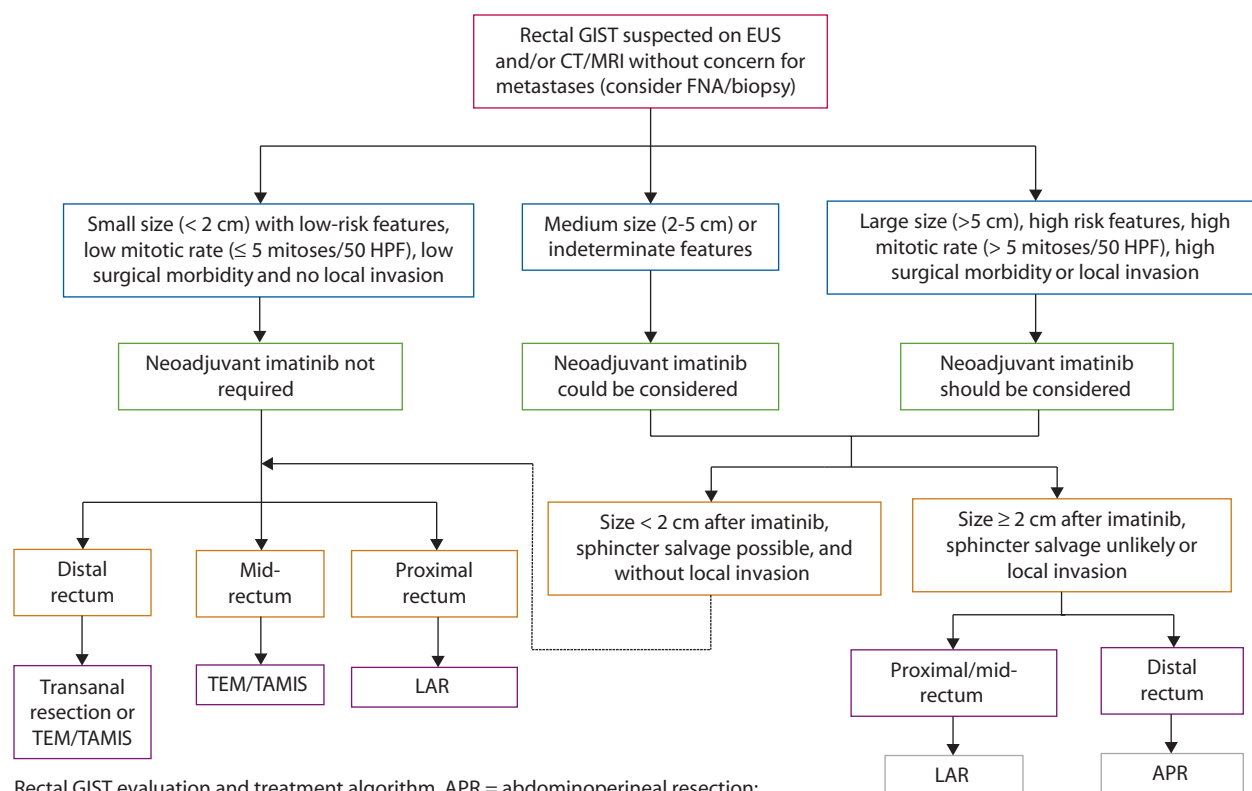
Small GISTs with limited bowel circumference extension located in the distal rectum may be candidates for transanal resection. In this case, full-thickness excision of the rectal wall should be performed to completely excise the lesion. The defect can be closed primarily with

care taken not to narrow the bowel lumen. Transanal endoscopic microsurgery or transanal minimally invasive surgery may also be pursued in the case of similar GISTs within the distal to mid rectum. Proximal rectal GISTs often require a transabdominal approach such as a low anterior resection. Larger and lower-lying tumors with local invasion or close proximity to the anal sphincters frequently demand an abdominoperineal resection to achieve oncologic resection.¹⁰

Follow-up and surveillance after resection of rectal GIST is not well established. Low-grade malignant tu-

mors often take 10 to 15 years to recur and/or develop metastases.¹¹ Without imatinib, the local recurrence rate of rectal GIST is high; however, recent data suggest that the recurrence rate may be low in patients who receive perioperative imatinib.⁹ Further research is warranted, and surveillance with both restaging CT scans and interval flexible sigmoidoscopies should be individualized to the patient. Risk calculators, such as the modified National Institutes of Health consensus criteria, offer clinicians a tool to determine which patients are at higher risk of recurrence and should be considered for adjuvant imatinib.¹²

EVALUATION AND TREATMENT ALGORITHM



Rectal GIST evaluation and treatment algorithm. APR = abdominoperineal resection; EUS = endoscopic ultrasound; FNA = fine-needle aspiration; GIST = GI stromal tumor; HPF = high-power field; LAR = low anterior resection; TAMIS = transanal minimally invasive surgery; TEM = transanal endoscopic microsurgery.

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Expert Commentary on the Diagnosis and Treatment of Rectal GI Tumors

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Drs Kane and Friel have written an excellent overview of the diagnosis and treatment of rectal GI tumors (GISTs). Before discussing management, I think it is critical to understand the differences between GISTs and other tumors of mesenchymal origin. Before its molecular characterization, GISTs were grouped with other morphologically similar lesions, such as leiomyoma, leiomyosarcoma, and leiomyoblastoma. The understanding of GIST biology and clinical behavior changed with the following 2 findings: identification of the c-Kit (proto-oncogene encoding for tyrosine kinase receptor) pathway and the interstitial cells of Cajal, which are part of the autonomic nervous system of the intestine and give rise to GISTs. These findings helped pave the way for the not-so-new kid on the block.

Rectal GISTs are rare, slow-growing tumors, which are often asymptomatic. Locally advanced lesions may be palpable on rectal examination or present with large-bowel obstruction, rectal bleeding, perforation, and pain. The majority of referrals to my clinic are for rectal GISTs, which have been found incidentally on screening colonoscopy. These have a typical appearance of a submucosal mass. I typically avoid endoscopically resecting these lesions as

GISTs, and other similar submucosal lesions may involve deeper layers of the bowel wall, risking incomplete resection and possibly even perforation. Unless there is surface erosion, I avoid biopsy of these lesions endoscopically, because the biopsy forceps rarely sample the deeper tissue levels necessary for diagnosis. Often, excision, if feasible, will serve both diagnostic and therapeutic purposes. I would pursue biopsy, preferably with endoscopic-guided fine needle aspiration, for large and locally advanced lesions to allow for diagnostic confirmation before neoadjuvant treatment.

As referenced by the authors, rectal GISTs have a malignant potential. Staging CT is standard of care given the risk for hematogenous spread. In addition, I like to personally perform an endorectal ultrasound and a rigid proctoscopy for local staging and more accurate assessment of location, size, and distance from the sphincter complex. This assessment is critical in surgical planning, especially if considering transanal approaches, such as transanal endoscopic microsurgery or transanal minimally invasive surgery. I find rectal protocol MRI helpful as an adjunct, specifically for larger lesions, in identifying the involvement of adjacent structures and distance of the lesion from the sphincter complex.

All rectal GISTs (>2 cm) are presented at the multidisciplinary tumor board at our institution, and these patients are typically followed concurrently by a medical oncologist. Surgical resection offers the best chance for cure. I usually perform a local excision for small (<2 cm), low-risk lesions with at least a 1-cm margin, assuming the sphincter complex is uninvolved. For high-risk lesions (≥2 cm, deep invasion, involvement of sphincter complex, or high mitotic rate), I prefer down-staging with imatinib preoperatively to improve resectability and sphincter preservation. These lesions often contain a pseudocapsule, so

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