Management of Gastrointestinal Stromal Tumors

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KEYWORDS

• Gastrointestinal stromal tumor • GIST • Gastric mass • Abdominal tumor
• Tyrosine kinase inhibitor • TKIs • Imatinib • Sunitinib

KEY POINTS

- Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract, most commonly arising in the stomach.
- The introduction of effective molecularly targeted tyrosine kinase inhibitors (TKIs) significantly improved the prognosis of patients with GIST.
- Surgery is indicated for primary resectable GIST. Recurrence is common; patients at intermediate or high risk of recurrence should receive imatinib postoperatively.
- The standard of care for unresectable or recurrent disease is TKI therapy with first-line imatinib, second-line sunitinib, and third-line regorafenib.
- Cytoreductive surgery may be considered in recurrent GIST in carefully selected patients on TKI therapy, following a multidisciplinary approach.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare neoplasms, accounting for 0.1% to 3% of all gastrointestinal malignancies.[1,2] The most common mesenchymal tumors of the gastrointestinal tract, GISTs have an annual incidence of 10 to 15 per million people and as many as 5000 to 6000 new cases in the United States each year.[2–6] GISTs can arise anywhere along the gastrointestinal tract, but develop most commonly in the stomach and small intestine as a result of activating mutations in *KIT* (*CD117*) or *PDGFRA*, genes encoding receptor protein tyrosine kinases.[3] Over

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the past 2 decades, remarkable advances have been made in the understanding of GISTs. The identification of key signaling transduction pathways and the development of molecularly targeted therapies has dramatically changed management of GISTs and improved patient prognosis.

EPIDEMIOLOGY

The median age at diagnosis is 60 years with no gender, racial, or ethnic predilection.[2,3,7,8] Although GISTs can be secondary to germline *KIT* or *PDGFRA* mutations[9,10] or as part of familial syndromes (including von Recklinghausen neurofibromatosis [NF1]),[11] Carney triad,[12] or Carney-Stratakis syndrome[13]), most are sporadic.

CLINICAL PRESENTATION

GISTs most commonly arise in the stomach (50%–60%) and small bowel (20%–35%); less common primary sites include colon, rectum, duodenum, and esophagus.[2,3,6] Most present as a single, well-circumscribed nodule with a median size of approximately 5 cm at presentation. GISTs are generally centered on the bowel wall but may form polypoid serosal-based or mucosal-based masses. Mucosal ulceration is often associated with gastrointestinal bleeding.[3]

Two-thirds of GISTs present with symptoms related to the gastrointestinal tract, including those caused by mass effect exerted by tumor within the abdominal cavity (vague abdominal discomfort, dysphagia, early satiety, palpable mass, bowel obstruction, intestinal perforation) and bleeding (anemia, gastrointestinal bleeding).[2,4,6] The remainder are discovered incidentally, during surgery for other conditions or at autopsy.[8]

Approximately 15% to 47% of patients present with overt metastatic disease; common sites of metastasis include liver, peritoneum, and omentum.[4,6,14] Lymph node metastases are rare, usually occurring only in pediatric forms of the disease. Unlike other sarcomas, lung and bone metastases are rare and occur late in the disease course, if at all.

DIAGNOSIS

Radiographic Studies

The initial imaging study for a suspected or confirmed GIST is contrast-enhanced computed tomography (CT) of the abdomen and pelvis to characterize an abdominal mass and assess for the presence of metastasis at the initial staging work-up. Primary GISTs are typically well-circumscribed masses within the walls of hollow viscera. MRI may help characterize metastatic liver or primary perirectal disease. PET has no defined role in the evaluation of primary disease.[2,3]

Preoperative Biopsy and Endoscopy

A preoperative biopsy is not routinely necessary for a primary, resectable neoplasm suspicious for GIST if it is easily resectable and preoperative therapy is not required. Biopsy may be needed if preoperative therapy is being considered to downstage the scope of surgery (eg, from laparotomy to laparoscopy) (**Fig. 1**), for unresectable or marginally resectable tumors, or if the differential diagnosis includes entities (eg, lymphoma) that would be treated differently.[2,3] For suspected GISTs arising in the esophagus, duodenum, or rectum, where surgical management may drastically differ based on diagnosis, pretreatment diagnosis is recommended.