Management of Gastrointestinal Stromal Tumors

Margaret von Mehren, MD

KEYWORDS

• GIST • KIT • PDGFRA • SDH-deficient GIST • Tyrosine kinase inhibitors
• Adjuvant therapy • Neoadjuvant therapy • Metastasectomy

KEY POINTS

- Gastrointestinal stromal tumors are malignant mesenchymal tumors of the intestinal tract that have varied behavior based on the molecular underpinnings of an individual tumor.
- Resection is the primary therapy for primary disease, with decisions on the type of surgery and need for neoadjuvant therapy influenced by tumor size, location, and molecular profile.
- Adjuvant therapy with imatinib therapy is indicated for tumors of high risk for recurrence.
- The role of resection in advanced disease is evolving but has been shown to be safe and seems to provide some benefit in progression-free survival in selected patients.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs), once known as gastrointestinal (GI) leiomyosarcomas, represent 1% of GI malignancies with an incidence of 0.32 per 100,000 in the United States.[1] They had the reputation for poor outcomes because of their lack of response to interventions other than surgery. The discovery of gain-of-function mutations involving the receptor tyrosine kinases (RTKs) *KIT* or platelet-derived growth factor alpha (*PDGFRA*)[2,3] significantly altered the biological understanding and management of this disease. Beginning in 2000, advances in the management of these tumors occurred with the availability of tyrosine kinase inhibitors (TKIs), including imatinib, sunitinib, and regorafenib. With the availability of systemic therapy has come increased understanding about the disease and those cases that require therapy and those that do not. This article reviews the role of surgery and systemic therapy based on a broad definition of risk, including risk of recurrence but also risk of lack of response. Decisions on how to treat an individual patient is based on the

Disclosure Statement: The author has served as a paid consultant in the past to Norvatis and Pfizer; The author do not currently have any relationships to disclose.
Department of Hematology/Oncology, Fox Chase Cancer Center, C-218, 333 Cottman Avenue, Philadelphia, PA 19111, USA
E-mail address: Margaret.vonmehren@fccc.edu

Surg Clin N Am 96 (2016) 1059–1075
http://dx.doi.org/10.1016/j.suc.2016.05.011 **surgical.theclinics.com**
0039-6109/16/$ – see front matter

stage of disease and pathologic characteristics, including the mutation status of the tumor, which has implications on prognosis.

MOLECULAR PATHOLOGIC CHARACTERISTICS OF GASTROINTESTINAL STROMAL TUMOR

GISTs, when viewed from the perspective of genetic changes, are relatively simple tumors. They have karyotypes with few genetic changes, particularly a subset of tumors that arise in the stomach.[4] Hirota and colleagues[5] were the first to identify that these tumors are driven by activating mutations in *KIT*. Since their discovery, it has become clear that most tumors contain mutations in *KIT* (85%) with an additional 5% to 10% having mutations in *PDGFRA*.[6] Mutations in *KIT* are found most commonly found in exon 11, followed by exons 9, 13, and 17, with rare reports of tumors in exon 14. *PDGFRA* mutations are found in exons 12 and 18, which are homologous with *KIT* exons 11 and 17. Rare cases of GIST, typically arising in the small bowel, have been associated with mutations in B-RAF or N-RAS.[6] GIST can be associated with neurofibromatosis in which, in addition to their *NF-1* mutation, the tumors can but do not always have typical *KIT* or *PDGFRA* mutations.[6,7]

More recently, gastric GIST without *KIT* or *PDGFRA* mutations, often arising in the stomach, have been recognized to contain defects in the Krebs cycle family of enzymes known as succinate dehydrogenase (SDH), either as a result of mutation or altered gene methylation. These tumors, formerly known as wild-type GIST, are now termed SDH-deficient GIST.[7,8]

PATHOLOGIC CHARACTERISTICS OF GASTROINTESTINAL STROMAL TUMOR

GISTs can develop anywhere along the GI tract. Although they can arise in any portion of the gut wall, most often they are found in the submucosa or muscularis propria. Typically, GISTs are well circumscribed with overlying mucosa intact but can be multinodular or ulcerated. Microscopically, tumors appear to have spindle cells, epithelioid cells, or a combination, with the epithelioid phenotype common in the stomach but not elsewhere.[9] Assessment of the number of mitoses per 50 high-power fields (HPF) is a critical component of pathologic assessment because it has implications for tumor prognosis.[10,11]

Immunohistochemistry

The most useful immunohistochemistry tests for GIST are CD117, DOG-1, and CD34. Ninety percent to 95% of GIST from all sites show strong cytoplasmic CD117 staining,[10,12] whereas CD34 stains up to 70% of spindle cell and epithelioid GISTs, especially colorectal and esophageal primaries. The DOG1 marker is particularly useful in tumors that histologically appear to be GIST but are negative for CD117.[13–15] A tumor that stains positive for desmin should be assessed closely because the most GISTs do not express this marker and the tumor likely represents another entity.

More recently, staining for succinate dehydrogenase B (SDHB) has been identified as useful in the assessment of gastric tumors.[7] Loss of SDHB staining is correlated with tumors that lack the common activating mutations in *KIT* or *PDGFRA*. These tumors contain mutations in the genes for the SDH family of proteins or alterations in methylation that result in deficiencies in SDHB production.[8,16] With loss of SDH, there is an accumulation of succinate that inhibits alpha-ketoglutarate-dependent dioxygenase enzymes and ultimately leads to a reduction of 5-hydroxymehtyl cytosine, which is required for DNA-demethylation.[17]