# Combined Therapy of Gastrointestinal Stromal Tumors

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**KEYWORDS**

• Gastrointestinal stromal tumor • Neoadjuvant therapy • Adjuvant therapy • Imatinib • Surgery

**KEY POINTS**

- Preoperative (neoadjuvant) therapy in locally advanced GIST may facilitate resection with microscopically clear margins, decrease the risk of perioperative tumor spill, and decrease extent and morbidity of the surgical procedure.
- Existing evidence-based clinical practice guidelines suggest adjuvant imatinib for at least 36 months for patients with high-risk GIST (tumor >5 cm in size with high mitotic rate [>5 mitoses/50 high-power fields] or tumor rupture or a risk of recurrence that is >50%).
- Surgical removal of residual disease during imatinib treatment may allow for complete remission (in approximately 20%) in selected patients with GIST after response to therapy, probably prolonging durable remission.
- The time of the implementation of surgical treatment warrants further studies; mutilating surgery in metastatic GIST should be avoided, as systemic therapy is the mainstay of treatment in this setting and surgery is only adjunctive to tyrosine kinase inhibitors therapy.

## INTRODUCTION: GASTROINTESTINAL STROMAL TUMORS GENERAL OVERVIEW

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract. Morphologically and clinically they are a heterogeneous group of tumors, with a biological behavior that is difficult to predict, ranging from clinically benign to malignant. Radical surgery is the treatment of choice in primary resectable GIST. Nevertheless, approximately 40% to 50% of patients will develop recurrent or metastatic disease after curative resection.[1–4] Understanding

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the molecular mechanisms of their pathogenesis demonstrated that most GISTs are associated with activating, constitutive, mutually exclusive mutations of 2 genes: *KIT* and *PDGFRA* (platelet-derived growth factor receptor-$\alpha$). These are the early oncogenic events during GIST development and result in overexpression and activation of oncoproteins KIT and PDGFR.[2,5–8] A significant subset of GIST is still diagnosed at a locally advanced, unresectable and/or disseminated stage of disease. Metastases preferably occur in the peritoneal cavity and/or the liver.[3,5] Conventional cytotoxic chemotherapy treatment is ineffective in advanced cases of GIST. Radiotherapy is also of limited value in the management of GIST, mainly because these tumors are often located in close proximity with dose-limiting vital organs.[3,5] However, advances in the understanding of molecular mechanisms of GIST pathogenesis have recently resulted in the development of a treatment modality that has become a model of targeted therapy in oncology. Imatinib mesylate is a tyrosine kinase inhibitor of KIT, BRC/ABL fusion protein, FMS (receptor for colony stimulating factor 1), Abl-related gene, and PDGFR-alpha and PDGFR-beta. It has revolutionized the treatment of advanced GIST and was the first effective nonsurgical treatment in inoperable and/or metastatic cases.[1,2,5–8] Current survival in advanced GIST is strikingly superior to historical clinical data, with a reported median overall survival (OS) of 5 to 6 years[4,9] and median progression-free survival (PFS) ranging from 2 to 3 years.[10–13] In case of progression during imatinib treatment (which is mainly related to occurrence of new secondary *KIT*/*PDGFRA* mutations) there are currently several therapeutic strategies, such as escalation of the dose of imatinib to 800 mg daily, surgical removal of focally progressive lesions, and therapy with registered second-line drug sunitinib malate and third-line drug regorafenib (both are multitargeted tyrosine kinase inhibitors with anti-angiogenic properties).[14–18] Recently, imatinib has been registered for adjuvant therapy in patients after resection of primary GIST with high risk of recurrence based on the results of 2 randomized trials (ACOSOG Z9001 and Scandinavian Sarcoma Group XVIII = SSGXVIII/AIO).[19,20] Currently in selected cases of locally advanced GISTs, a strategy of neoadjuvant imatinib therapy has become a common approach.

In this review article we have focused on the evolving role of combined therapy with surgery and tyrosine kinase inhibitors in GIST management.

## RISK ASSESSMENT OF PRIMARY GASTROINTESTINAL STROMAL TUMORS

The treatment of choice in primary, resectable, localized GISTs is radical surgery with negative margins, but virtually all GISTs are associated with a risk of recurrence, and approximately 40% of patients with potentially curative resections will ultimately develop recurrent or metastatic disease.[2–4] The identification of the risk factors for recurrence after primary surgery is crucial for reliable prognosis, follow-up schedule, and the selection of patients who may potentially benefit from the adjuvant therapy, aiming for a decrease in disease recurrences. The main criteria of aggressive behavior of GISTs are based on the presence of invasion of adjacent structures and/or the presence of metastases (overtly malignant cases), as well as on primary tumor site, size, and mitotic index.[21] Several risk-stratification systems have been proposed in the recent years. In 2001, a Consensus Conference held at the National Institutes of Health (NIH) provided the first evidence-based definition and a practical scheme for the risk assessment in the clinical course of this disease. The risk categorization was based on evaluation of the tumor size and mitotic rate (evaluated per 50 high-powered fields [HPF] or $mm^2$) as the most reliable prognostic factors.[22–24] Additional analysis in patients with primary tumor after complete macroscopic resection