Current management of gastrointestinal stromal tumors: Surgery, current biomarkers, mutations, and therapy

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In the past decade, the addition of molecular diagnosis of mutations and use of tyrosine kinase inhibitors (TKIs), either as neoadjuvant/adjuvant therapy with surgery or as primary therapy in nonresectable gastrointestinal stromal tumors (GIST), has improved patient outcomes markedly. Additional therapeutics also are on the horizon. The goal of this review is to identify the current incidence, diagnostic modalities, and trends in personalizing the medical and operative management for patients with GIST. Medline, PubMed, and Google scholar were queried for recently published literature regarding new molecular mechanisms, targeted therapies, and clinical trials investigating the treatment of GIST. The objective of this review is to highlight the biomarkers under development, newly discovered mutations, and newer therapies targeting specific mutational phenotypes which are continually improving the outlook for patients with this disease. (Surgery 2015;158:1149-64.)

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Gastrointestinal stromal tumors (GISTs) arise from the interstitial cells of Cajal (ICC) or a common cellular precursor, both of which express type III tyrosine kinase receptors. Mutations in the tyrosine kinase receptor c-KIT (CD117) or related tyrosine kinase receptors contribute to loss of growth control and tumor formation in GISTs. GISTs belong to a spectrum of nonepithelial, mesenchymal tumors, which range from small indolent tumors to large malignant sarcomas. GIST is the most common of the abdominal soft-tissue sarcomas.[1]

In the era before the availability of imatinib, complete operative excision provided the only possibility for long-term survival and cure from GIST. Still, recurrence was almost inevitable, and the median survival for patients with unresectable or metastatic GIST was 10–20 months[2]; however, the development and use of the tyrosine kinase inhibitor (TKI) imatinib served as an inflection point in treating GIST. Since then, several additional small-molecule tyrosine kinase inhibitors have been developed to target the tyrosine kinases that are mutationally activated in GIST, and other inhibitors are being tested. Collectively, these treatment options are continuing to increase the quality of life and lengthen the survival of patients with GIST.

Our previous review of GIST[3] illustrated its epidemiology, pathogenesis, and medical and operative management. The goals of this review are to provide an updated examination of current approaches in the diagnosis and risk stratification of GIST, as well as the evolving treatment options for managing patients with differing GIST subtypes. Herein, we aim to highlight specifically the molecular pathology and genomics of these tumors, which have resulted in a more effective

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and precise multidisciplinary approach to the treatment of these patients.

INCIDENCE AND PATHOLOGIC CLASSIFICATION

In the United States, the annual incidence of GIST is estimated between 3.2 and 7 per million.[4,5] A greater incidence of 15–20 per million has been reported in Europe,[6] Korea, and Hong Kong.[7] Because incidence data are derived from large population-based tumor registries that do not capture benign tumors, it is frequently hypothesized that the true incidence of GIST may be greater.[2,8,9]

The incidence of GIST, defined as the diagnosis of new cases, exponentially increased after 1998.[10-14] This was attributable to the discovery that c-KIT and platelet-derived growth factor receptor alpha (PDGFRA) were reliable biomarkers for these tumors. Review of the Surveillance Epidemiology and End Results (SEER) data revealed a step-wise increase in the proportion of mesenchymal tumors that were labeled as GIST.[3,15] In 1999, 24% of all mesenchymal tumors were classified as GIST. In contrast, in 2002, a majority (82%) of gastrointestinal (GI) mesenchymal tumors were classified as GIST; this increased to 90% in 2011.[15] In their re-review of 1,765 cases of gastric smooth-muscle tumors from 1976 to 1996, the Armed Forces Institute of Pathology[16] reclassified 94% of tumors previously diagnosed as gastric smooth muscle neoplasms as GIST. Therefore, the true incidence of GIST gradually has been better estimated by routine use of c-KIT and other molecular markers. This increase in incidence therefore marks the increased accuracy with which these tumors are now detected.

GISTs are found most commonly in the stomach (50–60%), followed by the small intestine (30–35%), colon and rectum (5%), esophagus (<1%), and rarely, in locations outside the GI tract (mesentery, omentum, and retroperitoneum; <5%).[5,7] The median age at diagnosis is 63 years; less than 1% of the patients are younger than 20 years of age. Familial syndromes such as the Carney triad,[5,17] familial GIST syndrome,[5,9] or neurofibromatosis type 1[5] when associated with GIST, result in the appearance of these tumors in the first 2 decades life.

Although mesenchymal tumors are rare, the number of mesenchymal tumor types with well-defined molecular characteristics has expanded rapidly. Traditionally, these were divided into the GISTs, leiomyomas (either benign leiomyoblastomas or malignant leiomyosarcomas), and schwannomas.[6] The classification of mesenchymal tumors that involve the tubular GI tract and surrounding soft tissues now also includes GIST, inflammatory fibroid polyps, desmoid tumors, synovial sarcomas, inflammatory myofibroblastic tumor, and clear cell sarcoma[18]; However, GISTs are still the most common mesenchymal neoplasm affecting the GI tract.

Since Mazur and Clark first described GIST as a separate entity from GI smooth-muscle and nerve-sheath tumors in 1983,[16,19] our present understanding of these tumors has been augmented considerably by the discovery of c-KIT gain-of-function mutations.[20] GISTs are presently identified as c-KIT mutation-driven mesenchymal tumors of the GI tract.

The historic misdiagnosis of GIST: Smooth-muscle neoplasm. As has been discussed in our previous review of this topic, GISTs previously were misclassified as GI smooth-muscle tumors[3]; however, GIST tumors have ultrastructural similarities to the GI tract's pacemaker cells—the ICC—and the 2 also have very similar immunophenotypes, which include both *KIT* and CD34 expression. Collectively, this led to the well-accepted hypothesis that GIST arises either from the ICC or a common precursor cell, yet to be identified.[6,20-22] Accurate molecular identification of GISTs was made in 1998—after the discovery that 80% of GISTs contain a gain-of-function mutation in the proto-oncogene *c-KIT* (CD 117).[20] In a landmark study in 2003, Heinrich et al[23] further identified the role of *PDGFRA* in the pathogenesis of GISTs that were negative for *c-KIT* expression. With these advances, we have come to understand GISTs as predominantly *c-KIT*- or *PDGFRA*-associated mesenchymal tumors.

SEER DATA, AND CURRENT OUTCOMES

An update of our previous survival analysis using the SEER dataset[3] revealed that both the diagnostic accuracy and prognosis for patients with GIST have improved. Analysis of 21 years of SEER data (using SEER statistical software) reveals progressive improvements in both the 12-month and 5-year survival rates (12 months: 1990–1998 = 81.5%, 1999–2005 = 86.4%, 2006–2011 = 89.7%; 5 years: 1990–1998 = 48%, 1999–2005 = 63.1%, 2006–2011 = 69%), $P < .05$.[15] This notable improvement in survival has been attributed, in part, to elimination of the misclassification of these as mesenchymal tumors, improvements in our understanding of GIST's pathogenesis, and the development of targeted approaches to systemic molecular therapy.

Before the introduction of imatinib, patients with GIST had a median survival of 10–20 months.