Gastrointestinal stromal tumors (GISTs) are rare, representing only 0.1% to 3% of all gastrointestinal (GI) malignancies, but they account for 80% of GI mesenchymal neoplasms. Mazur and Clark coined the descriptive term in 1983 to define intra-abdominal noncarcinomatous neoplasms that lacked the ultrastructural features of smooth muscle cells and immunohistochemical characteristics of nerve cells.

Illustration by James A. Cooper, MD
Until the late 1990s, there were no objective criteria to classify GISTs. They were frequently misclassified as leiomyomas, leiomyoblastomas, leiomyosarcomas, Schwannomas, or GI autonomic nerve tumors. Consequently, the interpretation of clinical results for GISTs published before 2000 is challenging.

**Receptor Tyrosine Kinase Mutations**

Since 1998, a series of major breakthroughs have drastically changed the management of primary and metastatic GIST in particular, and have served as a model for the targeted management of solid tumors in general. The first key development was the 1998 discovery of gain-of-function mutations in the c-kit proto-oncogene in GISTs. KIT encodes the transmembrane KIT receptor tyrosine kinase (TK), which is activated by binding its cytokine ligand, stem cell factor. Mutated KIT remains constitutively active even in the absence of ligand binding and results in both unregulated cell growth and malignant transformation.

More than 85% of GISTs have activating KIT mutations. Some GISTs that stain strongly for KIT by immunohistochemistry (KIT-positive) lack KIT mutations, whereas KIT-negative GISTs harbor KIT mutations. Another 3% to 5% of KIT-negative neoplasms have activating mutations in the platelet-derived growth factor receptor-α (PDGFRα) gene encoding a related receptor TK.

**Epidemiology**

**Age**

GIST has been documented in individuals of all ages, but is generally a malignancy of adults, with a median age at diagnosis of 60 years (range, 40-80). No consistent gender predilection has been noted. Occasionally, GISTs may be observed in children, often as a familial syndrome or as part of Carney’s triad (a rare constellation of gastric GIST, extra-adrenal paraganglioma, and pulmonary chondroma). Children more commonly present with multifocal gastric GISTs, harbor wild-type KIT/PDGFRA genes, and have a higher incidence of lymph node metastases.

**HEREDITARY GIST**

Most GISTs are sporadic. However, a growing number of kindreds with germline KIT mutations and at least one family carrying a PDGFRA mutation have been characterized with a predilection for developing multiple GISTs. Individuals with GISTs secondary to germline KIT mutations are usually younger than those with sporadic GISTs, but metastases are uncommon.

GISTs are found in approximately 7% of individuals with von Recklinghausen’s neurofibromatosis (NF1), most commonly in the small intestine. KIT and PDGFRα point mutations have been reported in 8% and 6% of GISTs, respectively, from patients with NF1. Conversely, NF1 gene mutations have not been identified in GISTs in non-NF1 individuals.

**INCIDENCE**

The true incidence of GIST remains uncertain. Epidemiologic data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program are difficult to interpret because many GISTs were previously misclassified as other GI mesenchymal neoplasms. The near doubling in the observed incidence of all GI mesenchymal tumors (more than 80% were GIST), from 0.17 per 100,000 in 1992 to 0.31 per 100,000 in 2002, in a contemporary SEER analysis is potentially the result of an increase in recognition, an increase in screening, and quite possibly a true increase in incidence of the tumor. The most recent National Comprehensive Cancer Network (NCCN) guidelines estimate an annual incidence of approximately 5,000 new cases in the United States. Population-based studies from Iceland and Sweden identified annual incidence rates of 11 and 14.5 cases per 1 million population, respectively.

**Clinical Presentation**

GISTs demonstrate a broad spectrum of clinical behavior. In a population-based study, 69% of tumors were symptomatic, 21% were discovered incidentally at surgery, and 10% were discovered at autopsy. Small GISTs (<2 cm) may remain asymptomatic, only detected incidentally on radiographic studies, endoscopy, or laparotomy. Approximately 50% to 70% of primary GISTs are identified in the stomach, 25% to 35% in small intestine, 5% to 10% in colon and rectum, 7% in mesentery or omentum, and less than 5% in the esophagus.

Between 15% and 47% of GISTs are metastatic at diagnosis. Common sites of metastasis include liver, peritoneum, and omentum; lymph node metastases are rare. Unlike other sarcomas, lung and brain metastases are uncommon and appear only late in the disease course, if ever.
Diagnosis

**RADIOGRAPHIC STUDIES**

Contrast-enhanced computed tomography (CT) of the abdomen and pelvis is the most common imaging modality for both initial evaluation and surveillance for recurrence. Primary GISTs appear as well-circumscribed, often highly vascular masses associated with hollow viscera (Figure 1). Magnetic resonance imaging (MRI) may be of value in characterizing disease in the liver or around the rectum. [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) is a functional imaging technique that is sensitive in identifying metabolic activity within these tumors. It complements CT for detecting GISTs, characterizing ambiguous masses, monitoring response to therapy, and identifying emergence of drug-resistant clones, but is not specific enough for the diagnosis of the disease. Routine use of PET for surveillance after complete resection is not recommended.

**ENDOSCOPY, FINE-NEEDLE ASPIRATION, AND BIOPSY**

Endoscopic ultrasound (EUS) is not generally necessary to evaluate extent of disease. Because endoscopic biopsies and EUS-guided fine-needle aspiration (FNA) are not consistently diagnostic, diagnosis may be require additional cytologic morphology, immunohistochemistry, and reverse transcriptase-polymerase chain reaction analysis for KIT mutations from an EUS-FNA specimen.

A preoperative biopsy is not routinely necessary for a primary, resectable neoplasm suspicious for GIST. In fact, preoperative biopsy may rupture a suspected GIST and increase the risk for dissemination. However, if the differential diagnosis includes entities such as lymphoma, which would be treated differently, if neoadjuvant therapy is under consideration, or if there is metastatic disease, then biopsy is appropriate.

**Prognostic Factors**

Most experts now consider all GISTs to have malignant potential. Although tumors less than 1 cm likely have a low risk for recurrence, no tumors can be definitively called benign. Tumor size, mitotic index, and tumor site of origin are the 3 most widely accepted indices predictive of outcomes (Table 1). The mitotic index may be the most important single variable. Individuals with small-bowel GISTs carry a higher risk for progression than those with gastric tumors of comparable size and mitotic count.

Additional independent adverse prognostic factors observed in some but not all studies include high cellular proliferation index, aneuploidy, and telomerase expression. Univariate analysis suggests that KIT exon 9 mutations and KIT exon 11 deletions involving amino acid W557 and/or K558 have a higher risk for recurrence, whereas point mutations and insertions of KIT exon 11 may have a favorable prognosis. A macroscopically complete resection with or without microscopically negative margins (RO or R1 resection, respectively) is better than a macroscopically incomplete resection (R2 resection); there are no data to confirm that a microscopically positive margin (R1 resection) impacts survival.

### Table 1. Risk Assessment for Primary Gastrointestinal Stromal Tumors

<table>
<thead>
<tr>
<th>Mitotic Rate</th>
<th>Tumor Size</th>
<th>Stomach</th>
<th>Duodenum</th>
<th>Jejunum/Ileum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50 hpf</td>
<td>≤2 cm</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2 to ≤5 cm</td>
<td>1.9/very low</td>
<td>8.3/low</td>
<td>4.3/low</td>
<td>8.5/low</td>
<td></td>
</tr>
<tr>
<td>&gt;5 to ≤10 cm</td>
<td>3.6/low</td>
<td>insuff. data</td>
<td>24/moderate</td>
<td>insuff. data</td>
<td></td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>12/moderate</td>
<td>34/high</td>
<td>52/high</td>
<td>57/high</td>
<td></td>
</tr>
<tr>
<td>&gt;5/50 hpf</td>
<td>≤2 cm</td>
<td>insuff. data</td>
<td>insuff. data</td>
<td>insuff. data</td>
<td></td>
</tr>
<tr>
<td>&gt;2 to ≤5 cm</td>
<td>16/moderate</td>
<td>50/high</td>
<td>73/high</td>
<td>52/high</td>
<td></td>
</tr>
<tr>
<td>&gt;5 to ≤10 cm</td>
<td>55/high</td>
<td>insuff. data</td>
<td>85/high</td>
<td>insuff. data</td>
<td></td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>86/high</td>
<td>86/high</td>
<td>90/high</td>
<td>71/high</td>
<td></td>
</tr>
</tbody>
</table>

hpf, high-power field; insuff., insufficient
Risk for recurrence based on data from the pre-imatinib era.
Surgical Therapy

Primary Disease

TECHNIQUE

The standard of care and only potentially curative therapy for patients with primary, resectable, localized GIST is surgery. The goal of the surgery should be a macroscopically complete resection with an intact pseudo-capsule and a negative microscopic margin (R0 resection). In general, primary GISTs do not invade surrounding organs despite CT appearance. Wedge or segmental resection of the involved stomach or bowel is typically all that is required. Rarely, a more extensive resection (total gastrectomy for a large proximal gastric GIST, pancreaticoduodenectomy for a peri-ampullary GIST, or abdominoperineal resection for a low rectal GIST) may be necessary. In a series of 140 patients with gastric GISTs, wedge resections were performed in 68%, partial gastrectomies in 28%, and total gastrectomies in only 4%.52 Lymphadenectomy is not required because lymph nodes are rarely involved.

All GISTs at least 2 cm in size should be resected when safely possible, as none of these are considered benign.45 Management of GISTs smaller than 2 cm is more debatable, as their natural history is unknown. Any symptomatic small GISTs (eg, hemorrhage from erosion through the mucosa) or GISTs that increase in size on serial follow-up should be resected.

Historically, small lesions (<1 cm) have been followed rather than resected. However, with the understanding that all GISTs have malignant potential, the rationale for observation is called into question. Such subcentimeter gastric GISTs are relatively common, found in 22.5% of autopsies in German individuals over the age of 50 and in 35% of Japanese patients undergoing gastrectomy for gastric cancer.53,54 Yet few of these neoplasms ever become clinically relevant, and thus management remains undefined. Further data are required to determine the natural history of these subcentimeter GISTs. Endoscopic resection of small gastric GISTs has been reported, but because of the inherent risks for positive margins (GISTs frequently involve the muscularis propria), its role remains controversial.55

GISTs 1 to 2 cm in size pose an even greater dilemma. Again, the natural history of such tumors is not known. The very low risk for recurrence in patients with GISTs less than 2 cm and a low mitotic index supports a more conservative, nonoperative approach. However, an accurate mitotic index cannot be determined on biopsy or FNA, and thus observation cannot be recommended based on size alone. Resection is preferred, particularly when laparoscopy is possible. The risks and benefits of surgery versus observation should be reviewed with the individual patient.

Given the higher risk for aggressive behavior in tumors originating in the small bowel and colon, any GIST in these locations should be resected irrespective of size.

Laparoscopic or laparoscopy-assisted resection of primary GISTs may be performed under appropriate circumstances using standard oncologic principles (Figure 2). Two studies confirmed the safety and feasibility of using a laparoscopic approach early on. Among 35 gastric GISTs resected laparoscopically, no local or distant recurrences were noted for tumors smaller than 4 cm with a median follow-up of 53 months.56 In another study of 50 gastric GISTs (1.0-8.5 cm) resected laparoscopically or using laparoscopy assistance, 92% of patients were disease-free with a mean follow-up of 3 years.57

The management of surgical margins is not as well defined for GISTs as it is for epithelial tumors such as adenocarcinoma. There are no data supporting the need for the same wide margins of resection typically

Figure 2. Endoscopic image of GIST along greater curvature of stomach (A) (arrow). Laparoscopic view of same tumor, with traction sutures placed proximally and distally (B). Stomach partially divided using stapling device (C).
recommended for adenocarcinomas. There also are no data indicating that patients who have an R1 resection require re-excision.

**OUTCOMES**

Even after a macroscopically complete resection, disease may recur in as many as 50% of patients, with a median time to recurrence of 24 months. An RO or R1 resection is associated with 5-year overall survival (OS) rates of 34% to 63%, whereas R2 resection is associated with 5-year OS as low as 8.1,2,60-64

**Adjuvant Therapy for Primary Disease**

Another critical advancement in the management of GIST was identification of 2 effective, relatively well-tolerated, orally available, targeted tyrosine kinase inhibitors: imatinib mesylate and sunitinib malate. Imatinib, which was the first approved GIST-targeted agent, has a molecular mechanism of action that inhibits the activity of the KIT and platelet-derived growth factor receptor (PDGFR) tyrosine kinases. Sunitinib, a broad-spectrum receptor tyrosine kinase inhibitor, blocks the activity of multiple receptor tyrosine kinases. Both agents are approved for the treatment of GIST, and imatinib is approved as adjuvant therapy for high-risk localized GIST.

**Figure 3. (A) Recurrence-free survival and (B) overall survival Kaplan-Meier curves from the ACOSOG Z9001 Phase III trial of 1 year of adjuvant imatinib versus placebo after complete macroscopic resection of primary gastrointestinal stromal tumor.**

inhibitors (TKIs), imatinib mesylate (STI571, Gleevec, Novartis) and sunitinib malate (SU11248, Sutent, Pfizer, Inc.). These agents initially were developed for the management of patients with metastatic disease in whom standard systemic chemotherapy and radiation therapy were largely ineffective. The first effective agent identified was imatinib, which selectively inhibits several TKs, including KIT, PDGFRα, and ABL, among others. Its clinical potential was first demonstrated in a landmark case report of a Finnish patient with metastatic GIST who was treated with a daily dose of imatinib 400 mg and demonstrated a rapid and sustained partial response. Several clinical trials have subsequently confirmed that up to 80% of patients with metastatic GIST achieve a complete or partial response or demonstrated disease stability on imatinib.

Because recurrence rates are so high and survival rates so low after an R0/R1 resection, investigators have explored the role of adjuvant therapy with imatinib after resection of primary disease. These trials tested durations of adjuvant imatinib of 12 months (American College of Surgeons Oncology Group Z9000, ASOSOG Z9001, China Cooperative Group), 24 months (European Organization for the Research and Treatment of Cancer [EORTC] 62024), or 12 versus 36 months (Scandinavian Sarcoma Group [SSG] XVIII). For the sake of brevity, only data from the recently published ACOSOG Z9001 trial are discussed in detail. In this Phase III trial, patients with completely resected primary GISTs at least 3 cm in size were randomized to receive either postoperative placebo or imatinib for 1 year. This trial was halted early when a planned interim analysis of 644 evaluable patients confirmed that the 1-year recurrence-free survival (RFS) was significantly better in the imatinib arm (97% vs 83%; \( P = 0.0000014 \)). However, the slope of the Kaplan-Meier curves representing the 2 treatment arms were similar (Figure 3A). This suggested that adjuvant imatinib delayed recurrence, but did not result in a cure. Furthermore, there was no difference in OS between the 2 treatment arms (Figure 3B). Thus, the long-term impact of adjuvant imatinib currently is unknown. This issue will be explored further in EORTC 62024, which, like ACOSOG Z9001, compared placebo with 400 mg imatinib daily, but in contrast will examine OS as its primary end point. This study completed accrual in late 2008, but results are not yet available nor are they expected for quite some time. The SSG XVIII trial, which also completed accrual in late 2008, will in part address whether 3 years of imatinib results in improved RFS and OS compared with 1 year. However, the eligibility criteria for this trial also allowed enrollment of patients with tumor rupture or metastatic disease, so the data may not be directly applicable to the adjuvant setting. Thus, although adjuvant imatinib does seem to improve RFS, its long-term benefit in terms of OS and the optimal duration of treatment remain unknown. Perhaps most important is the question of whether administration of imatinib as an adjuvant agent following resection of primary disease is better than waiting until objective disease recurrence.

Optimal imatinib dosage in the metastatic setting appears to be related to the mutational status of the primary tumor. Although the adjuvant trials to date employed an imatinib dose of 400 mg daily, it is known that patients with advanced GIST whose tumors contain KIT exon 9 mutations have improved survival if treated with 800 mg daily. It is not known whether imatinib dosing in the adjuvant setting should be adjusted based on GIST mutational status, an issue further complicated by the fact that mutational status is not routinely determined.

Figure 4. Computed tomography image of large locally advanced gastric gastrointestinal stromal tumor (A) before and (B) after 9 months of neoadjuvant imatinib therapy. Note not only the change in size of the mass, but also the change in density.
Neoadjuvant Therapy for Primary Disease

The Radiation Therapy Oncology Group (RTOG) 0312 trial is the only reported multicenter study thus far to evaluate the use of imatinib as a neoadjuvant agent. In this Phase II trial, patients with resectable primary or recurrent GIST were treated with imatinib 600 mg per day for 8 to 12 weeks before surgery. Patients who did not progress were eligible for surgery followed by 2 years of adjuvant imatinib.78 Of patients with primary GIST, 90% demonstrated an objective response before surgery, and 92% underwent R0/R1 resections. The 2-year RFS was 83%, which compares favorably with the 2-year RFS of 73% reported from the Phase II ACOSOG Z9000 trial, which treated patients with 1 year of adjuvant imatinib (and no neoadjuvant imatinib) after resection of solitary GISTs at least 10 cm in size, ruptured/hemorrhaging GISTs, or multifocal GISTs (<5). Although it is impossible to compare the results of RTOG 0132 and ACOSOG Z9000, the data raise 2 questions: Does neoadjuvant imatinib improve progression-free survival (PFS)? Is 2 or more years of adjuvant imatinib better than just 1 year?

RTOG 0132 confirmed the safety of neoadjuvant imatinib, but only treated patients with a relatively short course of preoperative therapy. Data from trials of advanced GIST have demonstrated that maximal radiographic response to imatinib generally required 6 to 9 months of treatment.1,2,64 Consequently, the optimal preoperative imatinib regimen may be upward of 6 months or more as continued radiographic response is observed (Figure 4).

Advanced Disease

The majority of patients experience tumor recurrence despite successful resection of their primary tumor. At the time of recurrence, 66% have liver disease and 50% have peritoneal disease.79,80 Imatinib (400 mg/d) is the first-line therapy for advanced (unresectable primary or metastatic) GIST. In patients who develop progressive disease on 400 mg, dose escalation is effective.81-84 If disease progresses on higher doses of imatinib, or if such doses are not tolerated, then second-line sunitinib is started. When sunitinib resistance develops, protocol-based therapies should be considered.

Surgery for metastatic disease or disease rendered resectable following neoadjuvant chemotherapy is a relatively common practice for some solid tumors, such as those from ovarian, testicular, and colonic primary sites. With the advent of imatinib and sunitinib therapy, the philosophy on the role of surgery in the management of advanced GIST is changing. Three observations support the consideration of a similar strategy of aggressive cytoreductive surgery in patients with metastatic GIST on TKI therapy. First, the majority of patients experience durable periods of partial response or stable disease on imatinib, lasting months to years. Second, pathologic complete responses are rare, noted in less than 5% of patients.83,84 Third, response to imatinib is not maintained indefinitely; the median time to progression due to the development of secondary resistance to imatinib is 18 to 24 months.71,72 When drug resistance develops, disease progression may be either

---

**Table 2. Resection and Survival Rates for Cytoreductive Surgery For Advanced GIST After TKI Therapy**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>RTKI Therapy</th>
<th>PR/SD on RTKI, %</th>
<th>PD on RTKI, %</th>
<th>R0/R1, %</th>
<th>1-Yr PFS, %</th>
<th>1-Yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raut85</td>
<td>69</td>
<td>IM/SU</td>
<td>33</td>
<td>Limited, 47 Generalized, 20</td>
<td>83</td>
<td>PR/SD, 80 Limited PD, 33 Generalized PD, 0</td>
<td></td>
</tr>
<tr>
<td>Rutkowski89</td>
<td>24</td>
<td>IM</td>
<td>75</td>
<td>25</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bonvalot87</td>
<td>22</td>
<td>IM</td>
<td>95</td>
<td>5</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andtbacka86</td>
<td>46</td>
<td>IM</td>
<td>45</td>
<td>55</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeMatteo78</td>
<td>40</td>
<td>IM/SU</td>
<td>50</td>
<td>Limited, 33 Generalized, 17</td>
<td>80</td>
<td>PR/SD, 70 Limited PD, 48 Generalized PD, 14</td>
<td></td>
</tr>
<tr>
<td>Gronchi88</td>
<td>38</td>
<td>IM</td>
<td>71</td>
<td>Limited, 21 Generalized, 8</td>
<td>82</td>
<td>PR/SD, 96 Limited PD, 0</td>
<td></td>
</tr>
</tbody>
</table>

IM, imatinib mesylate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RO, macroscopically complete resection with negative microscopic margins; R1, macroscopically complete resection with positive microscopic margins; RTKI, receptor tyrosine kinase inhibitor; SD, stable disease; SU, sunitinib malate

Reprinted from Raut CP, Bertagnolli MM. Controversies in the surgical management of GIST in the era of imatinib. Oncology. 2009;23(1):69, 74-76, with permission from CMPMedica LLC.
GIST treated with TKI therapy (Table 2). The goal of salvage cytoreductive surgery in patients with advanced documented the first PFS and OS rates following extensive surgery may prolong the time until second-line sunitinib therapy is necessary. If imatinib treatment does not cure the patient, but instead suppresses metastatic cells present at the time of resection for a finite period of time, then additional surgery may prolong the time until second-line sunitinib therapy is necessary.

Several single-institution retrospective studies have documented the first PFS and OS rates following extensive cytoreductive surgery in patients with advanced GIST treated with TKI therapy (Table 2). The goal of such operations is to perform an R0 or R1 resection when safely possible. However, the disease frequently may be too extensive to be removed completely, in which case progressing lesions are preferentially removed. Following surgery, these patients remain on imatinib indefinitely, as failure to resume imatinib results in rapid disease recurrence.

In the experience at Brigham and Women’s Hospital/Dana-Farber Cancer Institute (BWH/DFCI), liver resections were required in approximately 40% of patients, and more than 60% included peritoneectomy and/or omentectomy. More than 60% underwent multivisceral resections. Radiofrequency ablation may be considered for liver disease. Complication rates ranged from 40% to 60%, although the majority were minor. Perioperative deaths were rare, usually occurring in the setting of emergency procedures.

In the BWH/DFCI series, the best results were generally seen in patients whose disease was still responsive to TKI therapy at the time of surgery. The ability to remove all macroscopic disease was greatest in patients demonstrating ongoing response to TKI therapy. After surgery, there was no evidence of any residual disease in 78%, 25%, and 7% of patients with responsive disease, limited progression, and generalized progression, respectively. On the other hand, bulky residual disease remained after surgery in 4%, 16%, and 43% of patients with responsive disease, limited progression, and generalized progression, respectively.

Another critical finding in 3 of the series was that the highest rates of PFS and OS were observed when cytoreductive surgery occurred while the patients were still responding to TKI therapy. PFS rates for patients with ongoing response to TKI therapy (ie, partial response or stable disease at the time of surgery) were 70% to 96% at 1 year after surgery and 72% at 4 years from initiation of imatinib therapy (Figure 5). In contrast, the 1-year PFS for patients with generalized progression ranged from 0% to 14%. OS rates approached 100% at 1 year after surgery in patients responding to TKI therapy and only 0% to 60% at 1 year in the setting of generalized progression. Although patients with limited progression had lower rates of PFS than those with responsive disease, the rates of OS were not consistently different; the benefits of surgery in this population remain uncertain.

Based on these data from limited single-institution series, the patients who seemed to derive the most benefit from cytoreductive surgery were those still responding to TKI therapy at the time of surgery (partial response or stable disease). These patients should be considered for surgery on an individual basis. Patients with generalized progression do not appear to derive any benefit from surgery and are best treated with nonsurgical therapies, except for palliative or emergency purposes. Most importantly, although cytoreductive surgery is feasible, there is still no evidence that outcomes are superior or even equal to those for patients who continue on TKI therapy without surgery. This can be answered in a randomized clinical trial; such trials are under development in the United States and already have opened in Europe and China.

**Surveillance**

The postoperative follow-up for patients who have successfully undergone surgical resection of a primary GIST recommended by the NCCN consensus panel includes history and physical examination every 3 to 6 months, imaging every 6 to 12 months, and additional laboratory studies as indicated.
months during the first 5 years and abdomen/pelvis CT scans with IV contrast every 3 to 6 months during the first 3 to 5 years, then annually thereafter.\(^\text{13}\)

**Conclusion**

Prior to the development of imatinib, the principal treatment modality for GIST was surgery. Recurrence was common, and survival in the setting of recurrent or metastatic disease was poor. With the advent of therapy with TKIs—first imatinib, and then sunitinib—patient outcomes have improved considerably. Ongoing studies will establish the role of TKIs as adjuvant and neoadjuvant agents. The type and dose of TKI administered soon may be guided by mutational analysis. Future studies will focus on the integration of surgery with targeted therapy and the development of new agents for drug-resistant GIST.

Because of its relatively low toxicity and significant efficacy in treatment of GIST, TKI therapy has altered dramatically the natural history of this disease. Early studies have demonstrated the feasibility and safety of neoadjuvant imatinib for primary GIST and dramatic improvement in RFS with adjuvant imatinib after complete macroscopic resection of primary GIST. They have not adequately addressed the optimal length and dose of adjuvant and neoadjuvant imatinib therapy, defined the subset of candidates most likely to benefit from such therapy, or determined the long-term impact on OS. Studies also suggest that cytoreductive surgery should be considered in a certain subset of patients with advanced disease, but Phase III trial data are necessary to determine if surgery adds any benefit in terms of PFS/RFS and OS over continuing imatinib therapy alone.

**References**


Figure 2 will appear in a chapter by Dr. Raut in the Atlas of Minimally Invasive Surgical Techniques, edited by Ashley SW and Vernon AH, to be published by Elsevier in 2010.

**AUTHOR DISCLOSURES**—Dr. Raut discloses that he serves on the advisory board of Novartis.
Join us in Washington, DC as SAGES & CAGS host the 12th World Congress of Endoscopic Surgery

April 14 - 17, 2010
Gaylord National Resort and Convention Center
Landover, MD
(just outside Washington, DC)

Registration & Program Information will be available Summer, 2009

PROGRAM CHAIRS:
Daniel Herron, MD
(SAGES Co-Chair)
Barry Salky, MD
(SAGES Chair)
Christopher Schlachta, MD
(CAGS Chair)

Hosted by SAGES & CAGS
Society of American Gastrointestinal and Endoscopic Surgeons and Canadian Association of General Surgeons