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NCCN Task Force Report: Optimal Management of Patients with Gastrointestinal Stromal Tumor (GIST)—Update of the NCCN Clinical Practice Guidelines

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After completion of this CME activity, participants should be able to:

- Illustrate the epidemiology of GIST and its typical presenting characteristics
- Identify characteristic pathologic features and appropriate immunohistochemical testing for diagnostic and prognostic purposes
- Define the role of multidisciplinary cooperation in selection and timing of therapeutic interventions
- Identify appropriate medical management
- Recognize surgical principles that apply to GIST management
- Define response criteria based on follow-up testing

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NCCN Task Force Report: Management of Patients with Gastrointestinal Stromal Tumor (GIST)—Update of the NCCN Clinical Practice Guidelines

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Key Words

NCCN Clinical Practice Guidelines, gastrointestinal stromal tumor, sarcoma, gastric mass, stomach cancer, abdominal tumor, small bowel tumor, gastrointestinal tract, liver metastasis, tyrosine kinase, KIT, CD117, imatinib, sunitinib, GIST

Abstract

The NCCN Soft Tissue Sarcoma Guidelines include a subsection about treatment recommendations for gastrointestinal stromal tumors (GISTs). The standard of practice rapidly changed after the introduction of effective molecularly targeted therapy (such as imatinib and sunitinib) for GIST. Because of these changes, NCCN organized a multidisciplinary panel composed of experts in the fields of medical oncology, molecular diagnostics, pathology, radiation oncology, and surgery to discuss the optimal approach for the care of patients with GIST at all stages of the disease. The GIST Task Force is composed of NCCN faculty and other key experts from the United States, Europe, and Australia. The Task Force met for the first time in October 2003 and again in December 2006 with the purpose of expanding on the existing NCCN guidelines for gastrointestinal sarcomas and identifying areas of future research to optimize our understanding and treatment of GIST. (*JNCCN* 2007;5[Suppl 2]:S1–S29)

Background

The National Comprehensive Cancer Network (NCCN), an alliance of 21 large academic cancer centers in the United States, has developed clinical practice guidelines to reflect existing data on cancer prevention, risk assessment, diagnosis, treatment, and

supportive care and to document care as practiced at its member institutions. The NCCN guidelines on soft tissue sarcoma include a subsection on treatment recommendations for gastrointestinal stromal tumors (GISTs). The standard of practice for GISTs rapidly changed after the introduction of effective molecularly targeted therapy (such as imatinib and sunitinib). Because of these changes, the NCCN organized a multidisciplinary panel composed of experts in medical oncology, molecular diagnostics, pathology, radiation oncology, and surgery to discuss the optimal approach to care for patients with GIST at all stages of the disease. The GIST Task Force is composed of NCCN faculty and other key experts from the United States, Europe, and Australia. The task force met for the first time in October 2003 and again in December 2006 for the purpose of expanding on the existing NCCN guidelines for gastrointestinal sarcomas and identifying areas of future research for GIST.

This monograph discusses current data about GIST. Given the limitations of these data, the authors encourage enrollment of patients in clinical trials when possible.

Epidemiology

GISTs are the most common mesenchymal tumor of the gastrointestinal tract; the neoplastic GIST cells

Management of GIST

appear to arise from a common precursor cell, which gives rise to the interstitial cells of Cajal in the normal myenteric plexus.¹ Older SEER (Surveillance, Epidemiology, and End Results) data from the National Cancer Institute in the mid-1990s indicated that sarcomas account for 2.2% of gastric cancers, 13.9% of small bowel cancers, and 0.1% of colorectal cancers; most of these gastrointestinal (GI) sarcomas are GISTs.² These percentages suggested that only 500 to 600 new cases of GIST would occur each year in the United States, but this significantly underestimated the true incidence of GIST, because many cases were not captured in the SEER registries for various reasons.

The age-adjusted yearly incidence rate of GIST was 6.8 per million in the SEER data from 1992 to 2000; 54% were men and 46% were women.³ Population-based studies from Iceland, the Netherlands, Spain, and Sweden reported GIST annual incidence rates ranging from 6.5 to 14.5 per million,⁴⁻⁷ but these figures may also contain GISTs detected incidentally and at autopsy. Assuming an annual incidence rate of 10 per million, approximately 3000 GISTs might be diagnosed in the United States per year. The incidence of GIST is not known for all populations; most data refer to Caucasian industrialized populations.

According to 2 studies, small GISTs (only a few millimeters in diameter) are common in the general adult population. In a series of consecutive autopsies performed in Germany, small GISTs (1 to 10 mm in size) were grossly detectable in 22.5% of the autopsies in individuals older than 50 years.⁸ Similarly, in a series of 100 whole stomachs resected from Japanese patients diagnosed with gastric cancer, 50 microscopic GISTs were found in 35 of the 100 stomachs.⁹ Such “mini-GISTs” are immunopositive for *KIT* and often contain an oncogenic mutation in the *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) gene.⁸ These findings suggest that most small GISTs do not progress rapidly into large macroscopic tumors despite the presence of a *KIT* or *PDGFRA* mutation.

The median age of adults at diagnosis of GIST ranges from 66 to 69 years in population-based series that include cases found at autopsy. These are diagnosed about one decade later than symptomatic GISTs.^{4,7} In a study of 1765 GISTs arising from the stomach, the median age at diagnosis was 63 years.¹⁰ In a series consisting of 906 jejunal and ileal GISTs, the mean age was 59 years.¹¹ In the latter 2 series, only

2.7% of gastric GISTs and only 0.6% of small bowel GISTs were detected in patients younger than 21 years. Thus, this monograph refers to GIST in adult patients; however, pediatric GIST is also briefly discussed (see page 7).

The diagnosis of GIST has dramatically increased since 1992, and survival has greatly improved since 2002, when imatinib mesylate was approved by the Food and Drug Administration (FDA) for GIST.¹² The increase in the number of GISTs diagnosed per year is likely due to greater awareness and improved histopathologic detection, although the true incidence may be increasing also.¹³

Presentation

GISTs can occur anywhere along the GI tract but are most common in the stomach (50%) and small bowel (25%).¹⁴ Colon (10%), omentum/mesentery (7%), and esophagus (5%) are less common primary sites.¹⁴ A few GISTs occur within the abdomen and retroperitoneum but show no clear anatomic association with the GI tract.¹⁵ Liver metastases and/or dissemination within the abdominal cavity are the usual clinical manifestations of malignancy.¹⁶ Lymph node metastases are extremely uncommon; its spread to the lungs or other extra-abdominal locations is also extremely rare.

Many GISTs are identified clinically because they cause symptoms; GISTs are also identified at autopsy. In general, patients with possible GIST present with 1) emergency presentation because of intra-abdominal hemorrhage, GI bleeding, perforation, or rarely bowel obstruction (i.e., acute abdomen); 2) large mass suspicious for GIST (abdominal swelling, upper GI bleeding) with or without symptoms (e.g., early satiety or fatigue due to anemia); 3) incidental findings at surgery or on radiographic imaging; or 4) incidental finding on endoscopy (lesions <2 cm). All GISTs 2 cm in size or greater should be resected. Although a 2-cm cutoff is somewhat arbitrary, recent data suggest that it is reasonable (see “Pathology and Differential Diagnosis,” opposite page).¹⁷ The management of incidentally encountered GISTs less than 2 cm in size remains controversial.

The initial workup in a patient with suspected GIST should include history and physical examination, appropriate imaging (i.e., abdominal and pelvic computed tomography [CT] with contrast and/or

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magnetic resonance imaging [MRI]; see “Imaging of GISTs,” page 19), endoscopy in selected cases of primary gastric mass, endoscopic ultrasound, liver function tests, complete blood counts, and surgical assessment (to decide if the tumor is resectable and to determine whether metastatic disease affects this decision). Preoperative biopsy may not be necessary if the tumor is easily resectable (see “Principles of Surgery,” page 14). Optimal pathology of a sufficient amount of tumor tissue is needed to diagnose GIST with certainty. Patients with an emergency presentation caused by acute abdomen need immediate surgery and are often not evaluated for GIST until after the pathology report is received. In these patients, it is important to confirm that the disease has been completely resected, assess for metastases (liver ultrasound), and determine stage.

In general, patients should be managed by a multidisciplinary team with expertise in sarcoma or tumors of the GI tract. However, referral of patients with early stage or straightforward, uncomplicated metastatic disease to such specialists may not always be essential. However, all cases should be presented at a tumor board whenever possible. Any GIST patient with complicated or unusual features or those patients with advanced refractory disease should be appropriately referred to a center with specialty expertise and experience in the management of GIST.

Pathology and Differential Diagnosis

GISTs range in size from incidental lesions a few millimeters in diameter to large masses of 35 cm or more; the median size at presentation is about 5 cm. The tumors are generally centered on the bowel wall but may form polypoid serosal- or mucosal-based masses. Ulceration of the mucosa is often associated with GI bleeding. Most GISTs present as a single, well-circumscribed nodule. The cut surface is fleshy and may show areas of cystic degeneration, necrosis, or hemorrhage. Occasionally, satellite nodules are within the adjacent muscularis propria or serosa. Rarely, a patient will have 2 separate GISTs at different locations in the GI tract. In such cases, familial GIST should be considered.

Most GISTs show 1 of 3 histologic patterns: predominantly spindle cells (the most common pattern; Figure 1), predominantly epithelioid cells (Figure 2), or a mixture of both spindle and epithelioid cells.

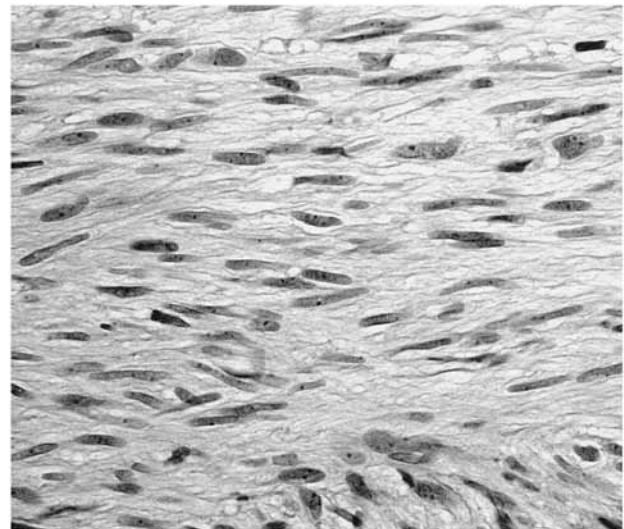


Figure 1 Spindle cell gastrointestinal stromal tumor (GIST). Typical morphology of a low-risk GIST comprised predominantly of spindle cells. This tumor was strongly KIT positive and harbored a mutation in *KIT* exon 11 (H&E stain; original magnification, 400×). Photomicrograph provided by Christopher L. Corless, MD, PhD (Oregon Health & Science University Cancer Institute).

Epithelioid GISTs may have either a diffuse or nested architecture, whereas spindle cell GISTs are arranged in short fascicles or whorls. The stroma is usually scanty but may vary from hyalinized to myxoid; purely myxoid GISTs are very rare. Most GISTs have a uniform cytology, with fibrillary eosinophilic cytoplasm

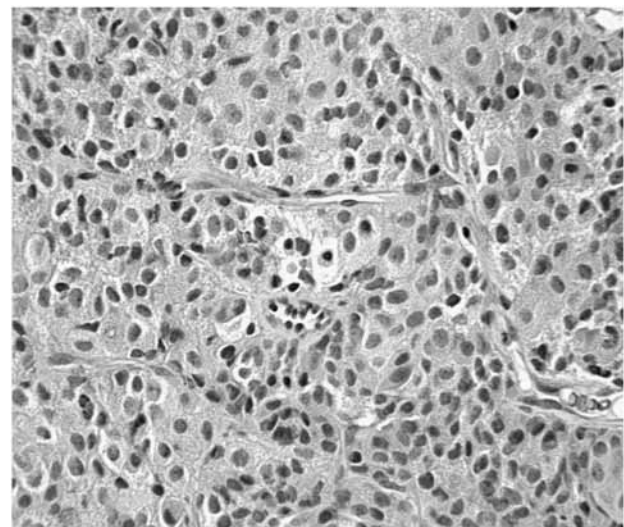


Figure 2 An example of an intermediate-risk gastrointestinal stromal tumor (GIST) comprised predominantly of epithelioid cells. The tumor was KIT positive and contained a mutation in *KIT* exon 9 (H&E stain; original magnification, 400×). Photomicrograph provided by Christopher L. Corless, MD, PhD (Oregon Health & Science University Cancer Institute).

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as well as nuclei containing fine chromatin and inconspicuous nucleoli. Marked cytologic pleomorphism is rare and should raise the possibility of an alternative diagnosis. Unusual but striking features seen in a few cases are prominent paranuclear vacuoles (usually in gastric lesions), hyaline eosinophilic cytoplasmic structures known as “skeinoid fibers” (mainly in small bowel lesions), and extensive nuclear palisading.

The morphologic differential diagnosis of spindle cell GIST is necessarily broad and includes leiomyosarcoma, leiomyoma, malignant melanoma, schwannoma, malignant peripheral nerve sheath tumor, fibromatosis (desmoid tumor), inflammatory myofibroblastic tumor, solitary fibrous tumor, and sarcomatoid carcinoma. The morphologic differential for epithelioid GIST includes neuroendocrine carcinoma, malignant melanoma, and epithelioid variants of leiomyosarcoma, malignant peripheral nerve sheath tumor, and angiosarcoma.

Immunohistochemistry

GISTs have a characteristic immunohistochemical profile that is useful for confirming a suspected diagnosis.¹⁸ About 95% are positive for KIT (CD117), 60% to 70% for CD34, 30% to 40% for smooth muscle actin, 5% for S-100 protein, 1% to 2% for desmin, and 1% to 2% for keratin. In general, KIT staining in GISTs is strongly and diffusely positive, but it is not necessarily uniform across different regions of the tumor. The staining may appear cytoplasmic (most common pattern), membranous, or concentrated in a dot-like perinuclear pattern; some cases show combinations of these patterns. CD34 and smooth muscle actin staining can be either diffuse or focal. Staining for the other markers, when present, is usually patchy and weak.

In contrast to GIST, leiomyoma and leiomyosarcoma are positive for desmin and negative for KIT. Malignant melanoma exhibits diffuse immunoreactivity for S-100 protein but can be focally positive for KIT. Schwannomas are strongly and diffusely immunoreactive for S-100 protein and negative for KIT. Malignant peripheral nerve sheath tumors and desmoid fibromatosis are negative for KIT. Sarcomatoid carcinoma tends to be pleomorphic, highly mitotically active, positive for cytokeratins, and negative for KIT and CD34. Non-GISTs that are positive for KIT include some sarcomas (especially angiosarcoma, Ewing’s sarcoma), extramedullary myeloid tumor, seminoma, and small cell lung carcinoma.

noma.¹⁹ A diagnosis of GIST can be assigned with confidence if the morphology and immunophenotype are concordant; however, tumors with any unusual features should be sent to a referral institution with special expertise.

Because KIT is expressed in nearly all GISTs and KIT positivity was a requirement in early trials of imatinib, this marker has been emphasized in the biomedical literature and is often used for diagnosis. However, caveats exist to the use of this marker. First, the CD117/KIT antibody must be properly titered. Overstaining for KIT has been a problem in some laboratories and has led to the misdiagnosis of other mesenchymal tumors as GIST. Second, the intensity of KIT staining in GISTs is somewhat variable. Third, staining intensity does not predict the likelihood of a response to treatment with imatinib.²⁰ Finally, about 5% of GISTs are truly negative for detectable KIT expression—so-called “KIT-negative GISTs.”^{21,22}

Establishing the diagnosis of KIT-negative GIST remains a challenge and is best handled by a reference pathologist with expertise in this area. Factors that weigh into this diagnosis are the location and morphology of the tumor, the results of other immunohistochemical stains and, increasingly, the use of mutational analysis of the kinase genes *KIT* and *PDGFRA* (see “Significance of Kinase Mutation Status,” opposite page). New immunomarkers that have been explored in the diagnosis of KIT-negative GISTs include protein kinase C theta (PKCtheta), *PDGFRA*, and *DOG-1*.^{23–25} However, experience with these markers is currently limited, and there are problems with the quality and availability of the commercial antibodies used to stain for them.

The diagnosis of GIST has evolved over a relatively short period of time. In patients with a remote history of an abdominal or pelvic tumor diagnosed as a leiomyosarcoma, leiomyoblastoma, or neurofibrosarcoma, re-examination of the tumor using current morphologic, immunophenotypic, and genotypic criteria might result in its classification as a GIST.

Prognostic Features

Based on published series of GISTs, the 2 most important prognostic features of a primary tumor are its size and mitotic index. These 2 features were the foundation for a consensus approach to risk stratification of GISTs published in 2002.¹⁸ One of the tenets of this approach is that all GISTs have malignant potential. This concept is supported by 3 large

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retrospective studies recently published by Miettinen et al.^{10,11,26} at the Armed Forces Institute of Pathology. Together, these studies represent the largest published series of GISTs classified by current criteria for which long-term clinical follow-up is available from the pre-imatinib era. The findings from these studies serve both to validate and expand the 2002 consensus criteria for the risk stratification of GISTs, as detailed in Table 1. In addition, Miettinen and Lasota.¹⁷ confirmed the results of earlier, smaller studies indicating that anatomic location affects the risk of disease recurrence and progression. Thus, small intestinal GISTs are more aggressive than gastric GISTs of equal size, and this should be factored into the risk assessment of a primary tumor. Based on the summary in Table 1, GISTs that are 2 cm or less in size can be regarded as essentially benign, but lesions larger than 2 cm have a risk of recurrence.

Significance of Kinase Mutation Status

Approximately 80% of GISTs have an oncogenic mutation in the KIT tyrosine kinase.^{27,28} Most of these mutations affect the juxtamembrane domain encoded by KIT exon 11, allowing spontaneous (ligand-independent) receptor dimerization and kinase activation. However, mutations also occur in exons 9, 13, and 17, and these may support constitutive KIT signaling through other mechanisms. A subset (5%–7%) of GISTs has an activating mutation in the KIT-homologous tyrosine kinase PDGFRA.^{29,30} Many of these

PDGFRA-mutant GISTs have an epithelioid morphology (Figure 3) and express little or no KIT; however, such features are not unique to these tumors, and mutation status can be determined only through molecular analysis. About 10% to 15% of GISTs are negative for KIT and PDGFRA gene mutations; these tumors are often referred to as *wild-type* GISTs.

The prognostic significance of mutations in the KIT and PDGFRA genes has been examined in GISTs from the pre-imatinib era, and tumors with a KIT exon 11 mutation are associated with a worse outcome than tumors with other KIT or PDGFRA mutant isoforms or with no detectable mutation.^{31–34} Conversely, KIT exon 11 mutations have been found in mitotically inactive GISTs 1 cm or less in size, suggesting that oncogenic KIT activity contributes to early tumor growth.^{8,35} GISTs with a KIT exon 9 mutation arise predominantly in the small intestine and colon and appear to be clinically more aggressive than tumors with KIT exon 11 mutations.^{36,37} In contrast, tumors with PDGFRA mutations are less aggressive than those with KIT mutations.^{38,39} However, insufficient data are available to support incorporation of kinase genotype into the routine prognostic assessment of a primary GIST.

Based on in vitro studies, the mutant isoforms of KIT that are commonly identified in primary GISTs are fully sensitive to the kinase inhibitor imatinib.^{40–42} In contrast, the most common GIST-associated mutation in PDGFRA confers complete resistance to this

Table 1 Risk Stratification of Primary GIST by Mitotic Index, Size, and Site*

Tumor Parameters		Risk of Progressive Disease* (%)			
Mitotic Index	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
≤ 5 per 50 hpf	≤ 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
≤ 5 per 50 hpf	> 2 ≤ 5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
≤ 5 per 50 hpf	> 5 ≤ 10 cm	Low (3.6%)	Moderate (24%)	(Insuff. data)	(Insuff. data)
≤ 5 per 50 hpf	> 10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
> 5 per 50 hpf	≤ 2 cm	None†	High†	(Insuff. data)	High (54%)
> 5 per 50 hpf	> 2 ≤ 5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
> 5 per 50 hpf	> 5 ≤ 10 cm	High (55%)	High (85%)	(Insuff. data)	(Insuff. data)
> 5 per 50 hpf	> 10 cm	High (86%)	High (90%)	High (86%)	High (71%)

Abbreviations: GIST, gastrointestinal stromal tumor; hpf, high power field; Insuff, insufficient.

Adapted from Miettinen and Lasota, 2006. Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs. (Miettinen et al. 2001, 2005, and 2006).

*Defined as metastasis or tumor-related death.

†Denotes small numbers of cases.

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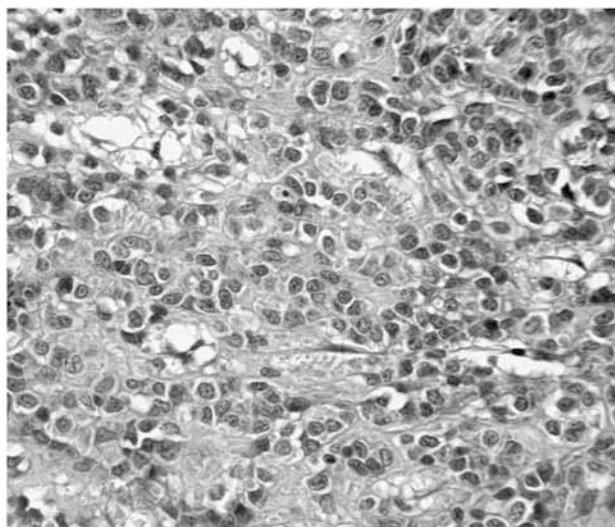


Figure 3 PDGFRA-mutant gastrointestinal stromal tumor (GIST): This malignant, epithelioid GIST was KIT negative and had a mutation in platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 (H&E stain; original magnification, 400×). Photomicrograph provided by Christopher L. Corless, MD, PhD (Oregon Health & Science University Cancer Institute).

drug.^{29,30} The *in vitro* activity of sunitinib malate against primary KIT and PDGFRA mutations found in GISTs essentially parallels that of imatinib, but this drug also has activity against some forms of KIT with secondary imatinib-resistance mutations.⁴³

Kinase genotype has predictive significance with regard to response to imatinib therapy. The presence of a *KIT* exon 11 mutation was the single best pre-

dictor of a favorable response to imatinib in the U.S.-Finnish B2222 phase II trial, the EORTC (European Organisation for Research and Treatment of Cancer)-Australasian GI Trials Group phase III trial (EORTC-ISG-AGITG trial), and the North American SWOG (Southwest Oncology Group) S0033 phase III trial (Table 2).

Correspondingly, patients with exon 11-mutant GIST have superior progression-free survival (PFS) and overall survival as compared with those with exon 9-mutant or wild-type tumor.^{44,45} The exon 11 advantage was not influenced by drug dose in either the EORTC-Australasian or the SWOG S0033 phase III trials. In contrast, PFS (but not overall survival) for the exon 9 genotypes in the EORTC-Australasian trial was statistically significantly better in the high-dose arm (400 mg imatinib twice daily) compared with the standard dose arm (400 mg daily). In addition, the response rate after crossover from 400 mg daily to 400 mg twice daily imatinib was much higher among patients with exon 9-mutant GIST (57%) than among patients with exon 11-mutant tumors (7%).⁴⁵ The apparent difference in dose sensitivity for exon 9-mutant tumors was not confirmed in an interim analysis of the SWOG S0033 trial, but there was a strong supporting trend. The final data set for this trial and a meta-analysis of both phase III trials will become available later in 2007.

Table 2 Relationship Between Kinase Genotype, Response, and Outcome on Imatinib Mesylate Therapy by Study			
	B2222 Phase II (n = 127)	EORTC-Australasian Phase III (n = 363)	North America SWOG S0033 Phase III (n = 324)
Objective response*			
<i>KIT</i> exon 11	83%†	70%†	67%†
<i>KIT</i> exon 9	48%	35%	40%
No mutation	0%	25%	39%
Progressive disease			
<i>KIT</i> exon 11	4.7%	3.2%	NR
<i>KIT</i> exon 9	17.4%	17.2%	NR
No mutation	55.6%	19.2%	NR

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; NR, not reported; RECIST, Response Evaluation Criteria in Solid Tumors; SWOG, Southwest Oncology Group.

Data are from Heinrich et al.,⁴⁴ Debiec-Rychter et al.,⁴⁵ and Heinrich et al.⁷⁹

*Defined as complete or partial response by RECIST criteria; excludes nonevaluable patients.

†Statistically significant difference versus *KIT* exon 9 and no mutation groups.

Currently, the task force strongly encourages that mutational analysis be performed if imatinib therapy is begun for unresectable or metastatic disease. Mutational analysis can be considered for patients with primary disease, particularly those with high-risk tumors. The kinase genotype can be determined from any available paraffin-embedded tumor sample: primary, recurrent, or metastatic.

Pediatric GISTs

GIST in patients younger than 30 years is extremely rare. However, GIST has been reported in all age groups, including newborn infants. Substantial evidence exists that “pediatric GIST” represents a biologically different disease from adult GIST; therefore, treatment useful for adult patients may not apply to pediatric patients. Based on published series, GIST in patients younger than 15 years is characterized by female gender, primary location in the stomach, and predominantly epithelioid or mixed epithelioid/spindle cell morphology. Lymph node metastases seem to be more frequent compared with adult GIST cases.

Although CD117 staining is uniformly positive, mutation analysis shows no detectable mutation in *KIT* or *PDGFRA* in most patients younger than 15 years; thus, the disease is considered wild type.^{46,47} However, wild-type disease in pediatric patients may differ from that in adult patients. Obtaining detailed pathologic information on patients with pediatric GIST is important. The predominant clinical symptom in children is anemia caused by insidious GI bleeding, with patients consequently developing weakness and syncope.

Local recurrence in the gastric stump is more frequent in pediatric GIST, probably based on an initially multifocal occurrence, leading to subsequent growth of unresected small nodules.² Therefore, frequent endoscopic follow-up is important. As in adults, metastases occur predominantly in the liver and peritoneum; however, nodal metastases can also occur. The clinical course is characterized by slow-growing disease, leading to longer survival even with metastatic disease. This finding supports a different biologic behavior of pediatric GIST.

Whether imatinib has comparable activity in children with GIST needs to be established by a larger series. Given that most pediatric cases are wild type, a lesser responsiveness (e.g., stable disease) would be expected, as supported by single case studies and un-

published data. Sunitinib has been reported to show activity in a small series of imatinib-refractory pediatric patients.⁴⁸ Both pediatric and adult GISTs, with respective typical behavior, are seen in young adults. The task force recommends that patients with pediatric GIST be referred to specialty centers.

Medical Treatment of GISTs

Determining whether any cytotoxic chemotherapy has meaningful clinical activity in patients with GIST is difficult using studies published before 2000.⁴⁹ Review articles and series of sarcoma patients treated with various regimens have compiled subsets of patients with advanced GI leiomyosarcomas and then assumed that most, if not all, of those GI sarcomas actually represented GIST. Response rates to standard chemotherapy regimens in these series have been poor (range, 0%–27%). However, the true percentage of GISTs in those series is impossible to know. Overall data strongly support the hypothesis that conventional cytotoxic chemotherapy is generally not useful in the management of GIST. In a large study of patients with metastatic GIST (defined by the most up-to-date and rigorous criteria), the response rate to any cytotoxic chemotherapy regimen was 0%.⁵⁰ Other trials, which also included patients with the specific diagnosis of GIST, have reported very low objective response rates (0%–5%).^{51,52} There is universal agreement that standard chemotherapy should not be used in patients with GIST as primary therapy. The median survival for patients with GIST who are treated with standard cytotoxic chemotherapy is generally less than 2 years (range, 14–18 months).

Imatinib Mesylate

Imatinib mesylate is a selective, potent, small molecule inhibitor of a family of structurally related tyrosine kinase signaling enzymes, including 1) *KIT*; 2) the *ABL* family of tyrosine kinases, including the leukemia-specific *BCR-ABL* chimera; and 3) *PDGFR*. In laboratory studies, imatinib inhibited proliferation of leukemic cells expressing *BCR-ABL* as well as both leukemia and GIST cells that harbored activated *KIT*.^{40–42,53}

It is known that 1) GISTs are associated with constitutive activation of the *KIT* receptor;⁵⁴ 2) most GISTs have *KIT* mutations, which lead to structural mutant isoforms of *KIT* that are uncontrollably active and contribute to oncogenic signaling;⁵⁵ and 3) both

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mutant and non-mutant forms of KIT can be inhibited by exposure to imatinib. Therefore, the clinical development of imatinib for treatment of GIST had a very solid scientific justification. A single-patient pilot study confirmed the activity of imatinib in a patient with heavily pretreated bulky advanced-stage metastatic GIST.⁵⁶ This single-patient experience generated a rapid expansion in the global development of imatinib as therapy for patients with advanced GIST.

Based on experience using imatinib for patients with chronic myelogenous leukemia, the doses considered to be safe were used in the multicenter United States–Finland trial.^{50,57} This trial randomly assigned patients with advanced GIST (metastatic or unresectable) between 2 daily oral doses of imatinib: either 400 or 600 mg. The early results from this study were sufficiently positive and were used to support the registration of imatinib as a safe and effective therapy in GIST; the initial results showed an overall response rate of 38%.⁵⁸ However, it became clear that a therapeutic effect could take several months (median, 3 months) to evolve. The rate of objective responses increased with further treatment and longer follow-up; however, imatinib rarely (fewer than 5% of cases) yields complete responses in patients with GIST.⁵⁹ Although imaging can suggest complete response, residual lesions may still be present.⁶⁰ Mature data made clear that 66% of patients showed an objective confirmed partial response, whereas another 17% of patients showed durable stable disease (> 6 months); 85% were alive at 76 weeks. Equivalent response rates were demonstrated in the 2 treatment arms, but the study did not have sufficient statistical power to assess whether small but clinically meaningful differences occurred between these different dose levels.⁵⁰

Were the chronic myelogenous leukemia doses the correct doses for patients with GIST? Just after the United States–Finland study began, the Sarcoma Group of the EORTC began a formal phase I dose-ranging study of imatinib in patients with advanced (metastatic or unresectable) GIST. Although designed to include any histologic subtype of sarcoma, this inter-cohort dose-escalation study ultimately accrued 36 GIST patients of a total of 40.⁶¹ In this trial, imatinib was given at dose levels of 400 mg once daily and then 600, 800, or 1000 mg daily (given as 300, 400, or 500 mg twice daily). The maximum tolerated dose of imatinib in this study was judged to be 400 mg twice

daily, because 500 mg twice daily led to unacceptably severe edema, malaise, and nausea and vomiting.⁶¹

In the EORTC-ISG-AGITG trial, 946 patients were randomly assigned to receive imatinib at either 400 or 800 mg/d.⁵⁹ Results showed that a daily dose of 400 mg of imatinib was sufficient; thus, the suggested starting dose of imatinib is 400 mg/day. Longer PFS was noted in GIST patients receiving imatinib at 800 mg/d; however, more dose reductions and treatment interruptions occurred in these patients. Thus, most patients could receive an initial dose of imatinib at 400 mg/d. Patients could then increase to 800 mg/d of imatinib if they showed signs of progression. However, recent studies suggest that patients with the KIT exon 9 mutation may benefit from the 800-mg dose of imatinib.⁴⁵

A therapeutic effect was noted in patients with GIST at each dose level of imatinib. Overall objective responses were seen in 69% of patients with GIST; this rate is remarkably consistent with the mature observations from the United States–Finland trial. By 18 months of follow-up study, 66% of patients remained in the study and free of disease progression. Progression can be assessed using CT (see “Imaging of GISTs,” page 19). To expand on these observations, the EORTC Sarcoma Group performed a phase II trial in patients with GIST using imatinib at the maximum tolerated dose of 800 mg per day.⁶² Again, the results were highly concordant with previous results showing a 71% objective response rate, with an additional 18% of patients demonstrating prolonged stable disease; 73% of the patients remained free of progression with 1 year of follow-up.

What optimal dose of imatinib should be used to begin dosing for patients with advanced metastatic or unresectable GIST? Two separate phase III trials have been conducted using imatinib: 1) by the North American Sarcoma Intergroup, consisting of U.S. cooperative oncology groups (SWOG, CALGB [Cancer and Leukemia Group B], ECOG [Eastern Cooperative Oncology Group]) and the National Cancer Institute of Canada (NCIC) Sarcoma Group; and 2) by the EORTC Sarcoma Group aligned with AGITG and the Italian Sarcoma Group (ISG).

Each one of these large phase III trials in patients with advanced GIST compared imatinib given orally at 2 different doses: 400 or 800 mg daily (given as split doses of 400 mg twice a day) in patients with metastatic or unresectable GIST. Both studies showed that

the higher dose of imatinib was associated with more side effects than the lower dose. Both studies also showed equivalent response rates and overall survival for both dose levels.^{62,63} The North American trial (Intergroup S0033) reported nearly identical response rates (49% vs. 48%, respectively), PFS at 12 months (71% vs. 70%), and 1-year overall survival (86% vs. 85%). The European and Australasian trial similarly showed no response advantage between doses (50% for 400 mg/d vs. 51% for 800 mg/d). The North American trial documented 25% versus 38% grade 3 toxicities and 7% versus 11% grade 4 toxicities in the low-dose versus high-dose arms, respectively.

The European and Australasian trial had time-to-disease progression as their primary endpoint. This study documented an earlier time-to-progression for patients receiving 400 mg daily. With a median follow-up of 17 months, the extrapolated difference at median PFS favored the higher dose in a slight though statistically significant way (8% better [hazard ratio, 0.78]). This small advantage in PFS was not corroborated by the North American study. The PFS advantage initially seen for the whole group is no longer statistically significant with longer follow-up, but a striking difference is observed for the *KIT* exon 9 mutant tumor group.⁴⁵

The reason for the discrepancy in PFS results is not completely understood. An analysis of Intergroup S0033 found more frequent dose delays and dose reductions in the 800 versus 400 mg daily groups.⁶⁴

In addition, a recent analysis by the EORTC-led trial suggests that GIST tumors with exon 9 mutations may have an improved disease-free survival if treated at 800 mg daily compared with 400 mg daily.⁴⁵ Analysis of the U.S. Intergroup trial may confirm this finding. Response assessment may prove challenging in GIST, and there is a chance that disease judged to be progressing may have actually responded to therapy. At this time, our ability to interpret these dose-ranging data is limited, and we await additional analyses from these important studies.

For a patient with metastatic or unresectable GIST, the task force agreed that the appropriate initial dose of imatinib is 400 mg daily. This dose is recommended because current data do not consistently show major differences in overall survival based on dose and because patients receiving 400 mg twice a day have an increased risk of unacceptably severe toxicity. Some members of the task force recommend 800

mg daily for patients with documented exon 9 mutations; this is a category 2B recommendation. Whether dosing at 800 mg is appropriate for patients with exon 9 mutations may be resolved when a meta-analysis of the EORTC-Australasian and the SWOG S0033 phase III trials is published later in 2007.

Dose escalation may be appropriate for patients started on imatinib at 400 mg daily who, after careful review of appropriate imaging studies, are judged to have disease progression. A dose increase is not likely to help many patients who progress within 2 months after initiation of imatinib. The United States–Finland trial escalated the dose in patients from 400 to 600 mg daily, whereas the phase III randomized trials increased the dose to 400 mg twice a day. Some patients (30%–40%) may benefit (median PFS, 11 weeks) from an increase in imatinib dosing to 800 mg/d; however, long-term follow-up for patients receiving a dose escalation is not available at this time.

In addition, clinicians must be sure that patients have progressed if the dose is increased, given the possibility that an increase in tumor size alone may not represent progression. For patients with limited progression, options include continuing imatinib at the same dose, increasing the dose of imatinib as tolerated, or switching from imatinib to sunitinib. However, imatinib compliance should be assessed before altering the dose or switching to sunitinib. Patients with limited progression should not be switched to sunitinib if most of the disease is still controlled by imatinib. For patients with generalized progression and reasonable performance status (PS 0–2), either the imatinib dose can be increased as tolerated or the patient can be switched to sunitinib.

The therapeutic effect should be monitored using positron emission tomography (PET) or CT. Patients should remain on imatinib or sunitinib as long as possible; however, if the patient is no longer receiving clinical benefit from imatinib or sunitinib, then the drugs should be discontinued and best supportive care used. The task force recommends that patients with progression be referred to a center specializing in GIST.

Patients with unresectable disease that is progressing on higher-dose imatinib (resection should only be considered in patients with localized progression) are candidates for therapy with sunitinib (see “Sunitinib Malate,” page 13) or a clinical trial.

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When patients have experienced progression on imatinib and sunitinib and are not candidates for a clinical trial, the task force believes that discontinuing therapy targeting KIT/PDGFR α may lead to accelerated tumor growth by withdrawing control of sensitive clones of the disease (even if limited sites of disease have been shown to exhibit resistance to therapy and hence to progress more rapidly). Therefore, absent a clinical trial testing a different hypothesis, the task force recommended that patients with limited progression of GIST should continue imatinib or sunitinib at a dose they can tolerate. However, these patients should continue to be closely monitored, because resistant clones may become problematic and other sites of resistance may emerge. The task force recommends that patients with resistance to imatinib and sunitinib be evaluated for entry onto a clinical trial testing novel approaches to controlling GIST.

Surgery is now recommended in addition to tyrosine kinase inhibitors for selected patients with metastatic GIST (see “Principles of Surgery,” page 14).

Management of Toxicities Caused by Imatinib Mesylate:

The most common side effects reported in GIST patients receiving imatinib mesylate are fluid retention, diarrhea, nausea, fatigue, muscle cramps, abdominal pain, and rash.^{50,58,61,63} The side-effect profile may improve with prolonged therapy.⁶² Minimal data have been published on the management of side effects in patients with GIST. Dyspepsia and GI side effects can be mitigated by taking the drug with food, which does not appear to decrease absorption. Dyspepsia also can be managed symptomatically with antacids or proton pump inhibitors. Loose stools and diarrhea are managed with loperamide hydrochloride or atropine sulfate/diphenoxylate hydrochloride. Serious side effects (such as lung toxicity, liver function test abnormalities, low blood counts, GI bleeding) have occasionally been reported. If life-threatening side effects occur with imatinib that cannot be managed by maximum supportive treatment, then sunitinib should be considered. Liver function test abnormalities are seen in fewer than 5% of patients. These results often improve after the agent is withheld. Recent reports have suggested that concomitant administration of steroids and imatinib in patients with liver function test abnormalities may allow patients to receive therapy.⁶⁵

Patients with large bulky tumors who are receiving imatinib may have a 5% risk of tumor hemorrhage not associated with thrombocytopenia.^{50,58} Patients with such large, high-risk tumors should be monitored very closely for evidence of a decline in hemoglobin in the first 4 to 8 weeks of imatinib. Asymptomatic bleeding can be monitored closely while imatinib is continued. However, acute large decreases in hemoglobin of greater than 2 g/dL may require temporarily withholding imatinib doses until hemoglobin has stabilized, transfusing if patients are symptomatic, and considering surgical intervention if bleeding does not resolve. Emergency surgery may also be required in patients receiving imatinib who have other complications (bowel obstruction, abscess). Patients on long-term imatinib may develop anemia.

Leukopenia is quite rare in GIST patients treated with imatinib, and the drug only rarely has been associated with neutropenic fever in this patient population. Patients may safely continue on imatinib unless the absolute neutrophil count is less than 1000 cells/mm³; withholding the drug leads to recovery, usually within several days. Re-initiation of drug without dose reduction is recommended, often without recurrence of the leukopenia. If a patient continues to experience significant leukopenia, the imatinib dose should be decreased. Rarely, severe myelosuppression may occur sporadically, even in patients who were previously stable with chronic dosing; continued monitoring is medically necessary.⁶⁶

Fluid retention is a common symptom that may be most notable to patients. Edema can be associated with the development of pleural effusions and ascites as well as some increase in creatinine levels. Patients with more than a 5-lb increase in weight during 1 week should be counseled to decrease salt in their diets; clinicians should consider the addition of furosemide, with judicious dosing to avoid intravascular volume depletion. Decreasing the dose of imatinib is not necessary for edema management as long as other supportive measures can control the edema.

Patients who develop rash often find that it resolves with time. Symptomatic management with topical or oral diphenhydramine hydrochloride is helpful. Muscle cramping may be mitigated by increasing oral fluid intake on a regular basis and possibly by using quinine sulfate. Some patients with muscle cramping also have hypophosphatemia and hyperphosphaturia. These are seen in patients with both GIST and chronic

myelogenous leukemia who take imatinib⁶⁷ and appear to resolve on discontinuation of the drug.⁶⁸ The ultimate effect of imatinib on bone metabolism is unclear, because no apparent increase in fracture risk occurs on imatinib; however, monitoring of serum phosphate and vitamin D levels may be useful for these patients.

A recent report described congestive heart failure as a potential side effect of imatinib.⁶⁹ However, clinical trial data have not documented a significant incidence of severe cardiac dysfunction. The collective experience of the task force members suggests that cardiac dysfunction is a rare event. However, patients on imatinib who present with significant fluid retention should be evaluated carefully.

Potential Drug and Food Interactions With Imatinib Mesylate: Potential drug interactions with imatinib are largely those that affect the cytochrome P450 isoenzyme 3A4 (CYP450 3A4). Various drugs may induce or inhibit CYP450 3A4 and thus have the potential to alter the plasma level of imatinib (Table 3).⁷⁰⁻⁷⁴ Such patients may need a change in imatinib dose if drug-associated toxicities occur because of transiently high imatinib levels and it is not possible to substitute another medication that does not affect CYP450 3A4 levels. For example, the dose of imatinib should be increased at least 50% (and clinical response should be carefully monitored) in patients receiving imatinib along with a potent CYP3A4 inducer such as rifampin or phenytoin. Similarly, imatinib may inhibit CYP450 isoenzymes and has the potential to increase the concentration of drugs listed in Table 3 as well as other drugs known to undergo metabolism by this CYP450 isoenzyme. Grapefruit juice (200–250 mL) inhibits CYP450 levels and thus increases levels of imatinib; pomegranate juice also inhibits CYP3A.⁷⁵

Imatinib Mesylate Resistance Imatinib therapy benefits most patients with advanced GIST; however, some patients are resistant to the drug. The drug fails in some patients almost immediately after initiation. Other patients initially show disease response or stabilization but later develop progressive disease while on medication. Researchers have long speculated that different mechanisms are responsible for resistance in these different scenarios. This may have implications in how patients are treated after disease progression on imatinib, based on the quality of the original response and when the drug failed.

Patients who never show a true tumor response (or even prolonged stable disease) during the first 6 months of imatinib are defined as having primary resistance to the drug.⁷⁶ Patients who show a partial remission (or no significant tumor growth for 6 months) and then experience progression are categorized as having secondary resistance. The largest trial to date assessing molecular correlates of both types of imatinib resistance in advanced GIST was a correlative study of the United States–Finland B2222 trial, recently reported on with 52 months of follow-up.^{18,77-79} Of 147 patients who entered the original trial, 92 had documented imatinib resistance. Of the latter, 43 patients consented to an assessment of tumor samples obtained before or during the first week of therapy compared with samples taken at the time of clinical resistance. The cytoplasmic domains of *KIT* and *PDGFRA* were screened for mutations, and activation of *KIT* and *PDGFR* was evaluated as well as downstream signaling pathways including mTOR, AKT, and MAPK.

In general, *KIT* phosphorylation was present in pretreatment specimens, but it became nearly undetectable during the first several days of successful therapy. Major decreases in the activated forms of downstream effectors also were noted. Specimens from patients with primary resistance showed phosphorylated *KIT* and activation of downstream pathways, both before and during therapy. Patients with secondary resistance showed re-activation of both upstream and downstream effectors. Primary resistance was most commonly seen in patients with mutations in *KIT* exon 9, in *PDGFRA* exon 18 (D842V), or with wild-type for both genes. Secondary resistance was primarily seen in patients who had pretreatment mutations in *KIT* exon 11.

Patients with primary resistance almost always showed the same mutations before and after imatinib, without development of a new mutation. Samples taken after progression in patients with secondary resistance, however, commonly had one or more new kinase mutations (usually in *KIT*, but at least once in *PDGFRA*). The molecular mechanisms conferring the primary resistance are not yet well understood. The authors speculated that mutant GISTs with primary resistance have an alternative mechanism of *KIT* activation not requiring enzymatic triggering.^{77,79} Secondary resistance appears to be related to the new mutations. The acquired mutations were not random,

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Table 3 Potential Drug Interactions with Imatinib Mesylate*		
Drug	Brand Name	Interaction
Acetaminophen	Tylenol	Imatinib can cause LFT abnormalities. Liver failure and death occurred in one patient taking large doses of both acetaminophen and imatinib. The use of acetaminophen should be limited in patients taking imatinib. For most patients, this means taking 1300 mg acetaminophen per day or less. Acetaminophen levels increase when it is coadministered with imatinib, because imatinib inhibits acetaminophen glucuronidation.
Aprepitant	Emend	Aprepitant inhibits CYP450 3A4, increasing the imatinib plasma concentration.
Carbamazepine	Tegretol	Carbamazepine induces CYP450 3A4 and decreases the plasma concentration of imatinib. Increase in imatinib dose is usually necessary.
Clarithromycin	Biaxin	Clarithromycin inhibits CYP450 3A4, increasing the imatinib plasma concentration.
Cyclosporine	Sandimmune	Imatinib inhibits CYP450 3A4, increasing the cyclosporine plasma concentration; this is a concern given the narrow therapeutic window of cyclosporine.
Dexamethasone	Decadron	Dexamethasone induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
Dihydropyridine calcium channel blockers (e.g., amlodipine, nitrendipine, and nifedipine)	Procardia and others	Imatinib may increase plasma levels of dihydropyridine Ca++ channel blockers
Erythromycin		Erythromycin inhibits CYP450 3A4, increasing the imatinib plasma concentration
Hypericum perforatum	St. John's wort	St. John's wort induces CYP450 1A2 and may decrease the imatinib plasma concentration. Increase in imatinib dose may be necessary in patients receiving St. John's wort.
Itraconazole	Sporanox	Itraconazole inhibits CYP450 3A4, increasing the imatinib plasma concentration.
Ketoconazole	Nizoral	Ketoconazole inhibits CYP450 3A4, increasing the imatinib plasma concentration.
Levothyroxine	Synthroid	Hypothyroid patients receiving imatinib need increased levothyroxine doses. A 2-fold increase in levothyroxine substitution therapy is recommended before initiation of imatinib treatment.
Phenobarbital		Phenobarbital induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
Phenytoin	Dilantin	Phenytoin induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
Pimozide	Orap	Imatinib inhibits CYP450 3A4, increasing pimozide plasma concentration. This is a concern given the narrow therapeutic window of pimozide.
Rifabutin	Mycobutin	Rifabutin induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
Rifampin	Rifadin, Rimactane	Rifampin induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.
Rifapentine	Priftin	Rifapentine induces CYP450 3A4, decreasing the imatinib plasma concentration. Increase in imatinib dose is usually necessary.

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Table 3 Continued

Simvastatin	Zocor	Imatinib inhibits CYP450 3A4, increasing the simvastatin plasma concentration. A dose adjustment of simvastatin may be necessary.
Triazolobenzodiazepines (e.g., alprazolam)	Xanax	Imatinib may increase drug levels of alprazolam.
Warfarin	Coumadin	Warfarin is metabolized by the CYP450 isoenzymes CYP 2C9 and CYP 3A4. Use of warfarin with imatinib could cause an increase in the availability of warfarin. Patients requiring anticoagulation should be given heparin or low-molecular-weight heparin instead of warfarin.

Abbreviations: CYP450, cytochrome P450; LFT, liver function test.

*The U.S. brand name for imatinib is Gleevec; Glivec is the international brand name.

and in vitro studies confirmed that they conferred resistance to imatinib either by directly altering the ATP/drug binding pocket or by interfering with access to this pocket through conformational changes in the activation loop of the kinase domain. Interestingly, the primary mutations, still present in patients with secondary resistance, remained sensitive to imatinib. Another potential mechanism for secondary imatinib resistance is genomic amplification but this appears to be rather uncommon.^{77,79,80}

Support for a link between new, acquired kinase mutations and late resistance to imatinib has come from several additional series.^{14,15,80–82} If most GISTs with secondary imatinib resistance remain dependent on KIT or PDGFRA signaling, then this has important implications for salvage therapies now in clinical development.

Imatinib resistance can be managed by increasing the dose of imatinib to 800 mg/day; however, the median time to progression is about 11 weeks. An alternative method of managing imatinib resistance is to switch patients directly to sunitinib from low-dose imatinib (400 mg/day).⁸³ Currently, it is not clear which management scheme will yield the best outcomes; some imatinib-resistant disease will not respond to sunitinib.⁴³

Sunitinib Malate

Sunitinib malate (SU011248, Sutent) is an oral TKI that is less specific than imatinib mesylate. In addition to inhibiting KIT and PDGFR, sunitinib acts on vascular endothelial growth factor receptors (VEGFR₁₋₃), Fms-like tyrosine kinase-3, colony-stimulating factor 1, and RET. Thus, sunitinib possesses potential antiangiogenic activity in addition to antitumor action related to receptor tyrosine kinase inhibition.

Preclinically, sunitinib inhibits some KIT mutant isoforms that are resistant to imatinib.⁴³

After a phase I/II trial established reasonable safety and promising efficacy (using a 4-week on, 2-week off schedule), sunitinib was tested against placebo in a double-blind phase III study involving patients with advanced GIST.⁸³ Imatinib-intolerant or -refractory patients ($n = 312$) were randomly assigned in a 2:1 fashion either to sunitinib (50 mg daily for 4 weeks, followed by a 2-week break [discontinuous dosing schedule]) or to placebo. The trial was unblinded early, when a planned interim analysis showed its primary endpoint—time-to-tumor progression using RECIST (Response Evaluation Criteria in Solid Tumors) criteria—was more than 4 times longer in those receiving sunitinib (27.3 vs. 6.4 weeks for placebo; $P < .0001$). PFS, percent progression-free at 26 weeks, and overall survival were all better for sunitinib-treated patients. Interestingly, these results were obtained despite a low objective response rate with sunitinib (7%).

This result suggests that, as with imatinib, the achievement of stable disease on sunitinib suffices to extend survival. On the phase III trial, treatment-related serious adverse events were reported in 20% of patients. These adverse events included but were not limited to fatigue, diarrhea, palmar-plantar erythrodysesthesia (hand-foot) syndrome, hypertension, and myelosuppression. This study, as well as other data, suggested that patients treated with sunitinib may develop hypothyroidism, which should be closely watched for in patients given this drug long term. In January 2006, the FDA approved second-line use of sunitinib in patients with advanced GIST. Its potential role in first-line treatment, the pediatric population, or in combination with other active agents

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remains to be determined, and other dosing schedules (e.g., daily continuous administration) are being explored.

To date, no other drugs have been approved for treatment of GIST. Various promising agents are in early or late phase testing, some aiming at similar pathways (e.g., sorafenib, AMG706, or nilotinib [AMN107]; which are more potent KIT and PDGFRA inhibitors) and some inhibiting novel targets (e.g., bevacizumab, which binds to VEGF, and IPI-504, which antagonizes heat shock protein 90).

Potential Drug Interactions With Sunitinib Malate:

Potential drug interactions with sunitinib include those that affect CYP450. Various drugs may induce or inhibit CYP450 3A4, and thus have the potential to alter the plasma level of sunitinib (Table 4). In patients receiving sunitinib, selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Sunitinib dose modification is recommended in patients who must receive concomitant CYP3A4 inhibitors or inducers. A dose reduction for sunitinib to a minimum of 37.5 mg daily should be considered if sunitinib must be co-administered with a strong CYP3A4 inhibitor (such as ketoconazole). Conversely, a dose increase for sunitinib to a maximum of 87.5 mg daily should be considered if sunitinib must be co-administered with a CYP3A4 inducer (such as dexamethasone). Grapefruit may also increase sunitinib concentrations (<http://www.fda.gov/cder/foi/label/2006/0219681bl.pdf>; accessed May 25, 2007).

Management of Toxicities Caused by Sunitinib Malate:

Sunitinib-related toxicities often can be managed with dose interruptions or reductions; however, sometimes sunitinib must be discontinued. Imatinib can be reintroduced if appropriate. In a phase I trial, the dose-limiting toxicities were fatigue, nausea, and vomiting. Other common toxicities include hematologic toxicities (anemia, neutropenia), diarrhea, abdominal pain, mucositis, anorexia, and skin discoloration. Less frequent toxicities include bleeding, fever, hypertension, and hand-foot syndrome.

Sunitinib should be discontinued if it causes profound neutropenia (absolute neutrophil count of 1000 cells/mm³ or less). Recurrent episodes of neutropenia require dose reductions to 37.5 or 25 mg daily, depending on the frequency. Anemia, if acute, should be managed with interruption of sunitinib and evaluation for a source of bleeding; the agent can be re-

sumed at the initial dose. Patients may experience GI symptoms, such as nausea, vomiting, or diarrhea; therapy should be continued with appropriate supportive measures. If supportive measures do not improve symptoms, a decrease in dose can be considered. However, in the randomized phase III trial, the incidence of nausea, vomiting, and abdominal pain were equivalent for patients receiving sunitinib or placebo; therefore, these symptoms may be related to the tumor. In addition, patients may develop mucositis, which causes a burning sensation while eating acidic or highly spiced foods. Most patients can be treated with supportive measures and avoidance of irritating foods, but severe cases may warrant a dose reduction. In addition, some patients note skin and hair discoloration, which are self-limited and resolve during the rest period or after cessation of the drug. Some patients also notice a change in urine color. Other side effects noted in initial trials include profound increases in amylase and lipase levels; however, no therapy is indicated because these increased levels are asymptomatic.

Because sunitinib targets VEGFR, some patients experience an increase in blood pressure and should be treated with antihypertensives. Patients may experience hand-foot syndrome. Clinicians can try to prevent hand-foot syndrome with routine application of emollient lotions. If significant hand-foot syndrome occurs, interruption of therapy is indicated; if it is severe, a dose reduction is needed before therapy is continued.

Recent reports have also highlighted the development of hypothyroidism in patients receiving sunitinib,⁸⁴ and routine monitoring of thyroid stimulating hormone levels is indicated. If hypothyroidism is suggested, patients should receive thyroid replacement therapy. Patients presenting with significant fluid retention should be evaluated carefully; those with congestive heart failure should discontinue sunitinib.

Principles of Surgery for GIST and the Need for Multidisciplinary Management

Primary Disease

Surgery remains the mainstay of therapy for patients with primary GIST who do not have evidence of metastasis and should be the initial therapy if the tumor is technically resectable with acceptable risk of

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Table 4 Potential Drug Interactions with Sunitinib Malate*

Drug†	Brand Name	Interaction
Aprepitant	Emend	Aprepitant inhibits CYP450 3A4 and may increase the sunitinib plasma concentration. A dose reduction for sunitinib to a minimum of 37.5 mg daily should be considered if sunitinib must be co-administered with a strong CYP3A4 inhibitor.
Carbamazepine	Tegretol	Carbamazepine induces CYP450 3A4 and may decrease the plasma concentration of sunitinib. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended.
Clarithromycin	Biaxin	Clarithromycin inhibits CYP450 3A4 and may increase the sunitinib plasma concentration.
Dexamethasone	Decadron	Dexamethasone induces CYP450 3A4 and may decrease the sunitinib plasma concentration. A dose increase for sunitinib to a maximum of 87.5 mg daily should be considered if sunitinib must be co-administered with a CYP3A4 inducer.
Erythromycin		Erythromycin inhibits CYP450 3A4 and may increase the sunitinib plasma concentration.
Hypericum perforatum; St. John's wort		St. John's wort induces CYP450 3A4 and may decrease the sunitinib plasma concentration unpredictably. Patients receiving sunitinib should not take St. John's wort concomitantly.
Itraconazole	Sporanox	Itraconazole inhibits CYP450 3A4 and may increase the sunitinib plasma concentration.
Ketoconazole	Nizoral	Ketoconazole inhibits CYP450 3A4, increasing the sunitinib plasma concentration. A dose reduction for sunitinib to a minimum of 37.5 mg daily should be considered if sunitinib must be co-administered with a strong CYP3A4 inhibitor.
Phenobarbital		Phenobarbital induces CYP450 3A4 and may decrease the sunitinib plasma concentration.
Phenytoin	Dilantin	Phenytoin induces CYP450 3A4 and may decrease the sunitinib plasma concentration.
Rifabutin	Mycobutin	Rifabutin induces CYP450 3A4 and may decrease the sunitinib plasma concentration.
Rifampin	Rifadin, Rimactane	Rifampin induces CYP450 3A4 and may decrease the sunitinib plasma concentration.
Rifapentine	Priftin	Rifapentine induces CYP450 3A4 and may decrease the sunitinib plasma concentration.

Abbreviation: CYP450, cytochrome P450.

*In patients receiving sunitinib, selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Sunitinib dose modification is recommended in patients who must receive concomitant CYP3A4 inhibitors or inducers. A dose reduction for sunitinib to a minimum of 37.5 mg daily should be considered if sunitinib must be coadministered with a strong CYP3A4 inhibitor. A dose increase for sunitinib to a maximum of 87.5 mg daily should be considered if sunitinib must be co-administered with a CYP3A4 inducer. According to the package insert, in vitro studies indicate that sunitinib does not induce or inhibit major cytochrome enzymes.

†Other drugs that inhibit CYP450 and, therefore, should be used with caution in conjunction with sunitinib include voriconazole, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin.

morbidity. For both large tumors and poorly positioned small GISTs that are considered marginally resectable on technical grounds, neoadjuvant imatinib is recommended. Patients with primary localized GIST whose tumors are deemed unresectable should also start imatinib.

Because it is an uncommon disease, GIST may not be considered in the differential diagnosis of a patient with localized abdominal mass. Thus, a pathologic diagnosis of GIST may not be known before or even during surgery. Preoperative biopsy of a resectable mass is commonly performed but may not be necessary

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and is associated with slight risks. GISTs may be soft and fragile, and biopsy may cause hemorrhage and increase the risk of tumor dissemination. Many pathologists cannot make a definitive diagnosis using a fine-needle aspirate. Furthermore, a core needle biopsy may be inconclusive if a necrotic or hemorrhagic portion of the tumor is sampled. Thus, postoperative pathology assessment is essential to confirm the diagnosis after removal of any suspected GIST.

Several principles are noteworthy regarding the surgical treatment of GIST. The goal is complete gross resection with an intact pseudocapsule and negative microscopic margins. At laparotomy, the abdomen should be explored thoroughly with careful inspection of the peritoneal surfaces, particularly the lesser sac in gastric GIST and the recto-vaginal or -vesical excavation as well as the liver, to identify metastasis. GISTs should be handled with care to avoid tumor rupture. If the pseudocapsule is torn, bleeding and tumor rupture may ensue.

Primary GISTs often emanate from the stomach or intestine and, like other sarcomas, tend to displace adjacent structures. Consequently, despite an ominous appearance on cross-sectional imaging, primary GISTs can often be lifted away from surrounding organs. Some may become densely adherent to nearby structures. In this setting, an en bloc resection of adjacent tissue is required. Segmental resection of the stomach or intestine should be performed, with the goal of achieving negative microscopic margins. Anatomic gastric resection, formal lymph node dissection, and wider resection of uninvolved tissue show no apparent benefit. Lymphadenectomy is usually unnecessary because lymph node metastases are rare with GIST and sarcomas in general.⁸⁵

The value of negative microscopic margins on the resected organ is uncertain with large (> 10 cm) GISTs, which may shed cells from anywhere along their surface directly into the peritoneum.¹⁶ The management of a positive microscopic margin on final pathologic analysis is not well defined and depends on whether the surgeon believes the finding accurately reflects the final surgical procedure (because resection specimens may retract and yield challenges in interpretation for even the most expert pathologist). There is no evidence that patients with complete resection of all macroscopic disease, but who have microscopically positive margins, need to undergo re-excision. Such patients should be carefully evaluated by the multi-

disciplinary care team to consider possible risks and benefits of re-excision, watchful waiting, or adjuvant treatment with imatinib. If the marginal area in question can be identified on re-exploration, then a wider resection can be done if technically feasible without significant morbidity.

All GISTs 2 cm in size or greater should be resected. However, the management of incidentally encountered small GISTs less than 2 cm in size remains controversial. The natural history of such small tumors, including growth rate and metastatic potential, remains unknown. A recent study by Kawanowa et al.⁹ demonstrated that the incidence of subclinical GIST is higher than expected. In this study, 100 whole stomachs resected from patients with gastric cancer were sectioned at 5-mm intervals. A total of 50 tumors were identified in 35 stomachs, all positive for KIT or CD34. All tumors were less than 5 mm in size and were of a spindle cell type, and 90% were located in the proximal stomach. At present, there are insufficient data to guide the management of subcentimeter GISTs discovered incidentally on endoscopy. Endoscopic resection of small GISTs has been reported, but with its inherent risks of positive margins and tumor spillage, its role remains controversial.⁸⁶ Although these small GISTs may be followed endoscopically until they grow or become symptomatic, the frequency of follow-up remains uncertain.

The role for laparoscopy in the resection of GISTs continues to expand. The same principles of complete macroscopic resection and avoidance of tumor rupture observed during laparotomy apply to laparoscopy.⁸⁷ A prospective, randomized controlled trial remains to be done. However, 2 studies demonstrated that not only are laparoscopic or laparoscopic-assisted resections possible, but they are also associated with low recurrence rates. Novitsky et al.⁸⁸ performed 50 laparoscopic resections of gastric GISTs (mean tumor size 4.4 cm, 1.0–8.5 cm), all with negative resection margins (2–45 mm). At a mean follow-up of 36 months, 46 (92%) patients were disease free. Of the remaining 4 patients, 2 died of metastatic disease, 1 with metastases died of an unrelated event, and 1 was alive with recurrent disease. No local or port site recurrences were identified.

Otani et al.⁸⁹ removed 35 gastric GISTs measuring 2 to 5 cm in size through laparoscopic wedge resections. No local or distant disease recurrences were noted for tumors less than 4 cm in size. These data

confirm that laparoscopic or laparoscopic-assisted resections can be performed safely in experienced hands. Generally, gastric GISTs 5 cm in size or less may be removed by a laparoscopic wedge resection. Those GISTs greater than 5 cm in size may benefit from a laparoscopic-assisted technique with a hand port. Data on laparoscopic resection of GISTs at other sites (including small bowel) are limited. As with other laparoscopic resections for cancer, standard surgical principles should be applied, and the tumor should be removed in a protective plastic bag to minimize the risk of port site recurrence.

Some patients with GIST may require extensive surgery for a poorly situated tumor. The operative risks and anticipated postoperative recovery must be weighed against the oncologic benefit of tumor resection. For instance, a tumor located near the gastroesophageal junction may require a proximal or total gastrectomy. Pancreaticoduodenectomy may be necessary to remove a duodenal GIST. Occasionally, an abdominoperineal resection is needed for a low rectal GIST. In these situations, preoperative multidisciplinary review is critical, because such patients may be spared radical resection after even a partial response to neoadjuvant imatinib (see following discussion).

Survival after surgery alone for GIST is favorable when compared with other intra-abdominal sarcomas. Patients ($n = 200$) with likely GIST were treated at Memorial Sloan-Kettering Cancer Center between 1983 and 1997 and were followed up prospectively.¹⁶ Although these patients were not confirmed to have *KIT* or *PDGFRA* mutation or expression, most of the tumors were almost certainly GIST based on histopathology characteristics and clinical course. Of 93 patients who presented with a primary tumor without metastasis, 80 (86%) were able to undergo complete resection of all gross disease. In this subset of 80 patients, the 5-year disease-specific survival rate was 54% with a median of 66 months. Similar survival results after resection of primary GIST have been reported by others.⁹⁰⁻⁹²

Neoadjuvant Imatinib

The role of imatinib mesylate in the preoperative “neoadjuvant” setting for primary localized GIST is a matter of surgical and medical discretion. The National Cancer Institute–sponsored clinical trial conducted by the Radiation Therapy Oncology Group (RTOG) tested the use of imatinib before surgical resection of GIST (RTOG 0132; <http://www.RTOG.org>. Accessed

May 25, 2007); the study has completed accrual and results are pending. However, for many patients with very large GISTs, the disease can reasonably be considered “unresectable” without risk of unacceptable morbidity or functional deficit. Therefore, using imatinib as the first-line anticancer therapy is possible. Patients can be treated with imatinib until the optimal time for surgery (when the GIST becomes resectable and the chance of morbidity is acceptable), which can take as long as 6 to 12 months.⁹³ Maximal response is defined as no further improvement between 2 successive CT scans. However, it is not always necessary to wait for a maximal response to perform surgery. Each new cross-sectional imaging should prompt multidisciplinary re-appraisal of the surgery timing.

Adjuvant Imatinib

For primary localized GIST that is resectable, the standard of care is surgery followed by postoperative radiologic surveillance for recurrence. However, because many patients with primary GIST develop recurrence after resection, imatinib is being studied in the postoperative adjuvant setting to determine whether it reduces recurrence. Four major trials testing adjuvant imatinib are underway. The American College of Surgeons Oncology Group (ACOSOG) Z9000 is a phase II intergroup trial that accrued 106 evaluable patients with primary GIST at high risk of recurrence based on clinicopathologic factors. Patients were treated with 1 year of imatinib at 400 mg/day. The treatment was tolerated well, with no grade 4 or 5 toxicities, and 83% of patients completed the prescribed therapy.⁹⁴ The final analysis will be performed in fall 2008. ACOSOG Z9001 is an intergroup phase III double-blind, randomized trial of adjuvant imatinib (400 mg/day vs. placebo) after resection of primary GISTs measuring at least 3 cm in size. The target accrual of 803 patients is expected to be reached by June 2007. The Scandinavian/German SSG XVIII/AIO trial is a randomized, open-label trial of 1 versus 3 years of imatinib at 400 mg/day after resection of high-risk primary or metastatic GIST; accrual of 280 patients is about to be completed. An increase in sample size is currently under discussion.

EORTC 62024 is a randomized, open-label study of 2 years of adjuvant imatinib at 400 mg/day versus no treatment after resection of intermediate or high-risk GIST. More than 400 patients are already accrued, with the target accrual of 780 patients expected to be

reached by the end of 2007. Although no data support the adjuvant use of imatinib in primary completely resected GIST, some physicians administer adjuvant imatinib for high-risk patients outside of a clinical trial.

Recurrent or Metastatic Disease

For recurrent or metastatic GIST, the standard of care is now treatment with imatinib. Data before the era of imatinib showed that the median time to recurrence after the resection of primary GIST was about 2 years.^{16,95} Notably, in the University of Texas M. D. Anderson Cancer series, only 10% of 132 patients were free of disease after a median follow-up of 68 months.⁹⁵ The site of first recurrence in GIST is typically within the abdomen and involves the peritoneum, liver, or both. A true local recurrence (which is limited to the site of the prior surgery) is unusual, and typically there is widespread intraperitoneal recurrence that may not be detectable by radiologic imaging. Historically, when patients with metastatic GIST were treated with surgery alone, their outcome was poor. The median survival of 94 patients who presented with metastatic disease at Memorial Sloan-Kettering Cancer Center was 19 months, and only 28 (30%) of them could undergo complete surgical resection.¹⁶

Because the median time to recurrence on imatinib is 2 years, surgery has been added to medical therapy for selected patients with metastatic GIST in an effort to delay or prevent recurrence. However, the true benefit of the addition of surgery to TKI therapy in metastatic GIST has not yet been proven in a randomized clinical trial. Hypothetically, patients whose disease is rendered resectable on medical treatment may achieve longer PFS by gross tumor resection before secondary resistance develops. Even in the setting of partial response or stable disease on TKIs, the residual tumors typically harbor viable cells; complete pathologic responses are rare (<5%).⁹⁶⁻⁹⁸ This observation supports surgery for advanced disease that is responding to TKI therapy and is completely resectable if no access to a clinical trial testing this approach is available. Imatinib can be given to patients until surgery and can be restarted when the patient can start oral intake. However, sunitinib is stopped 5 to 7 days before surgery and usually restarted 2 weeks after surgery.

The first large study to report survival rates after resection of advanced GIST after medical therapy

came from Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center and detailed the results of surgery in patients with advanced GIST on TKI therapy.⁹⁹ Outcomes of surgery and survival rates correlated with response to TKIs. Three clinical categories of disease response to TKIs were defined. Stable disease was defined as disease that was radiographically stable or responding to drug therapy and for which all sites of disease progression could be resected. Limited (localized) disease progression was defined as progression on drug therapy at one or a few (but not all) sites of disease. In these patients, all sites of progressing disease could be resected and other sites of stable disease were resected if the associated morbidity was relatively low. Generalized disease progression was defined as disease progressing in multiple sites in patients on drug therapy and in whom complete resection of all progressing disease sites was not possible.

A macroscopically complete resection was achieved in 78%, 25%, and 7% of patients with stable disease, limited disease progression, and generalized disease progression, respectively ($P < .0001$). The 12-month PFS rates for patients with stable disease, limited disease progression, and generalized disease progression were 80%, 33%, and 0%, respectively ($P < .0001$). The 12-month overall survival rates were 95%, 86%, and 0%, respectively ($P < .0001$). Thus, patients with stable disease who underwent surgery showed substantial rates of PFS and overall survival. In patients with limited disease progression preoperatively, cytoreductive surgery did not prevent disease recurrence (reflecting the evolution of more aggressive tumor biology). In patients with generalized disease progression, surgery offered no survival benefit, with median PFS of 2.9 months and median time to death of 5.6 months.

Data from the other studies are remarkably consistent.^{60,93,100-103} More follow-up is necessary to determine the long-term survival of the patients in these retrospective series. A randomized trial of surgery in imatinib-stable metastatic GIST is being opened in Europe and one is being planned in the United States.

Thus, the indications for surgery in recurrent or metastatic GIST are 1) disease that is stable or shrinking on TKI therapy when complete gross resection is possible (stable disease); 2) isolated clones progressing on TKI therapy after initial response (indicative of secondary drug resistance), while other sites of dis-

ease remain stable (limited disease progression); or 3) emergencies including hemorrhage, perforation, obstruction, or abscess. In contrast, patients with widespread or diffuse disease progression on imatinib (generalized disease progression) should have their imatinib dose increased as tolerated, should be treated with a second-line agent like sunitinib, or should be enrolled in clinical trials.

At laparotomy for metastatic GIST that has been treated with TKIs, multivisceral resections (including liver resections) are often necessary because of the extent of disease. For intraperitoneal metastases, the tumors tend to be more adherent to the surrounding tissue, thereby precluding the less-extensive resections seen in primary resectable disease. Unfortunately, CT often underestimates the extent of peritoneal disease, and it is not uncommon to identify numerous other nodules at laparotomy. Omentectomy or peritoneal stripping and liver resection are frequently necessary. Liver metastases are commonly distributed in both lobes, often precluding standard hepatectomies for complete resection. To fully treat or eradicate liver parenchymal disease, radiofrequency ablation or cryoablation in conjunction with liver resection may be required.^{60,102} Percutaneous ablation of liver lesions less than 5 cm in size may also be considered. For bulkier disease, hepatic artery embolization should be considered.^{104,105}

An unresolved issue is how long to keep patients on imatinib/sunitinib therapy before surgery if the tumors are still responding to therapy. Data from the EORTC trial indicated that the median time to development of secondary resistance was about 2 years.⁵⁹ Thus, surgery (if planned) should be done before 2 years, and most experts would recommend discussing surgery after 6 to 12 months of disease stability or response.

Retrospective studies also support continuation of drug therapy after surgery. Rutkowski et al.⁶⁰ reported that in their series, the first 5 patients who underwent cytoreductive surgery after imatinib for advanced disease did not resume imatinib; among them, 4 patients developed recurrent disease. Reintroduction of imatinib in all 4 patients resulted in partial radiographic responses.

Multidisciplinary Management

The optimal management of GIST requires a combined effort between multiple disciplines. Thus, patients with GIST need to be managed with combined

pathology, medical oncology, surgical oncology, and imaging expertise in both initial evaluation and management as well as in continued follow-up. Reducing recurrent disease, optimizing timing of surgery and organ preservation, prolonging survival, increasing the number of resectable cases by pharmacologic debulking, and possibly enhancing response to imatinib by surgical cytoreduction are all potential benefits of multidisciplinary management.

Imaging of GISTs

Computed Tomography

Initial Evaluation: CT (or occasionally, MRI) is the initial imaging modality when evaluating an abdominal mass or nonspecific abdominal symptoms. Contrast-enhanced CT is the imaging modality of choice to characterize an abdominal mass, as well as to evaluate its extent and the presence or absence of metastasis at the initial staging workup for biopsy-proven GIST. FDG (¹⁸fluoro-deoxy-glucose)-PET/CT can also be useful in GIST staging. Typically, a GIST is a solid hyperdense-enhancing mass on CT. However, large GISTs (> 10 cm) are often more complex because of necrotic, hemorrhagic, or degenerating components (Figure 4). At presentation, the mass is typically exophytic, and the origin may be difficult to identify when the mass is very large (Figure 4). Despite the large size of some GISTs, clinical evidence of GI obstruction by GIST is uncommon. When a small tumor is found incidentally during endoscopy, the extraluminal extent of disease should be evaluated using CT. Metastasis from GIST may occur by locoregional infiltration or by a hematogenous route of spread, most often to the liver, omentum, and peritoneal cavity. Metastases can also be found in the soft tissues (such as the abdominal wall) and rarely in the lungs and pleura. Metastases to the bone or lymph nodes are very rare.

Follow-Up: In patients who have undergone surgical resection of the GISTs, CT is performed for surveillance of metastatic or recurrent disease, and abdominal/pelvic CT scans should be obtained every 3 to 6 months. For very low-risk GISTs (Table 1), less frequent follow-up is appropriate. In patients with advanced disease, CT is an excellent imaging modality to monitor the disease, particularly if ¹⁸FDG-PET/CT is not available.

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CT is also used to monitor systemic therapy. CT (with or without PET) is recommended within 3 months of initiating TKI therapy in patients with definitively unresectable or metastatic disease, and imaging before 3 months may be appropriate in some patients. When a GIST responds to imatinib, it generally becomes homogenous and hypoattenuating (hypodense; Figure 4), and the tumor vessels and solid enhancing nodules disappear (Figure 5). These changes can be seen within 1 to 2 months in most GISTs with a “good response” to imatinib. Such early changes on CT images have been shown to have a prognostic

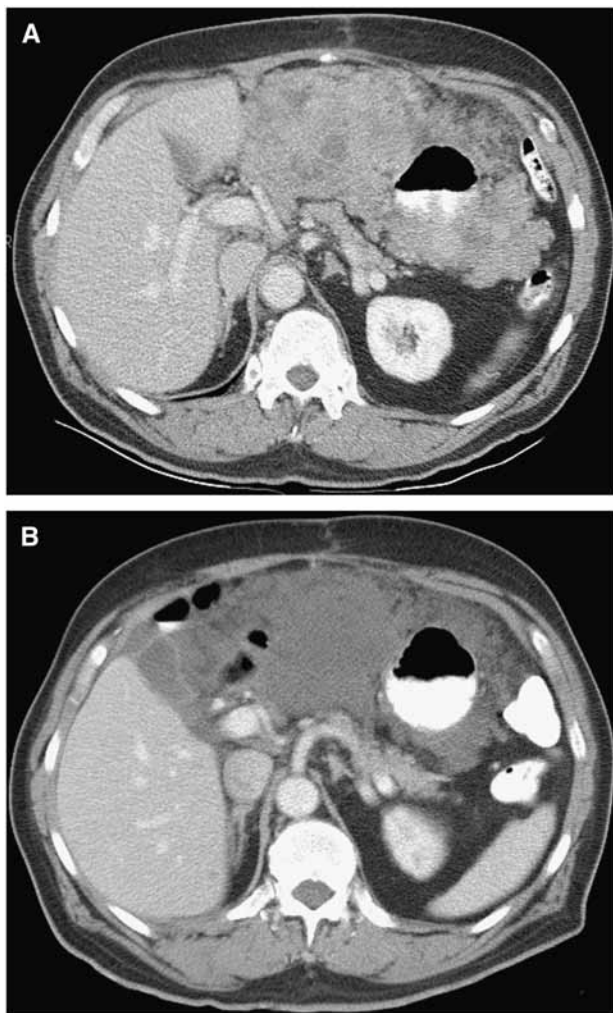


Figure 4 Typical appearance of gastrointestinal stromal tumor (GIST) in a 70-year-old man with an unresectable GIST of the stomach. (A) A pretreatment computed tomography (CT) image showed a very large hyperdense mass completely surrounding the stomach. Endoscopic biopsy was negative for malignancy. (B) The mass became hypodense and homogenous on CT obtained 8 weeks after imatinib treatment. Photomicrographs were provided by Haesun Choi, MD (The University of Texas M. D. Anderson Cancer Center).

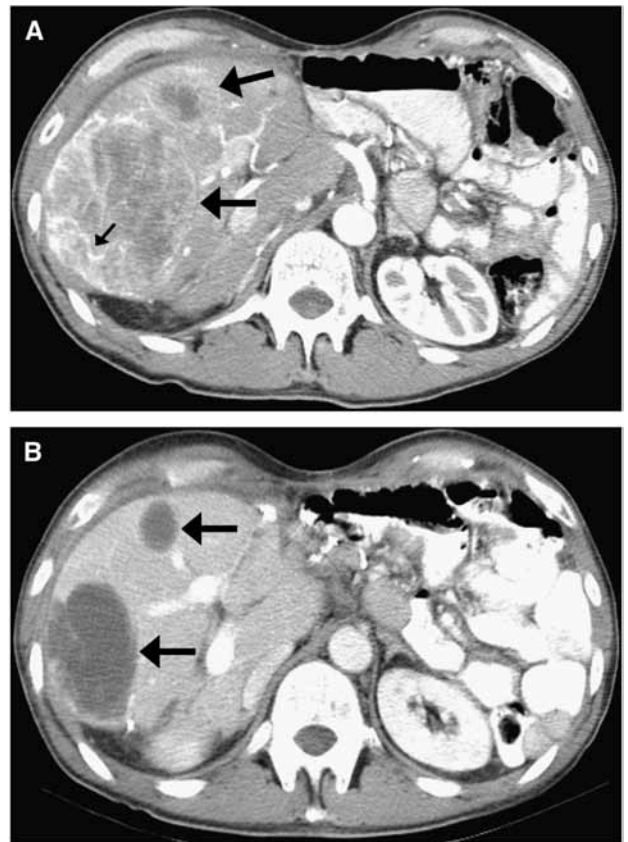


Figure 5 “Good response” to imatinib treatment in a 50-year-old man with metastatic gastrointestinal stromal tumor (GIST) of the stomach. (A) A late arterial-phase image of pretreatment computed tomography (CT) demonstrated multiple hypervascular metastases in the liver (large arrows). Notice small tumor vessels within the mass (small arrow). (B) On CT obtained 8 weeks after treatment, the masses became hypodense (arrows), and the tumor vessels and enhancing nodules are no longer seen. Photomicrographs provided by Haesun Choi, MD (The University of Texas M. D. Anderson Cancer Center).

value¹⁰⁶ and represent a favorable effect of therapy on the disease, even in the absence of anatomic shrinkage of the tumor bulk.

Response assessment according to RECIST (traditional tumor response criteria based on tumor size change) is known to be insensitive in evaluating response to TKI.¹⁰⁷ The outside dimensions of a tumor mass may not accurately reflect tumor activity; however, the degree of enhancement is indicative of tumor behavior. Decreased density on contrast-enhanced CT of responding GISTs indicates response to therapy and correlates with tumor necrosis or with cystic or myxoid degeneration.

The CT response criteria proposed by Choi et al.^{106–108} use both tumor density and size to assess the response of GIST to TKI therapy. Choi et al.’s CT response evaluation criteria are described in Table 5.

Table 5 Modified Computed Tomography Response Evaluation Criteria (Choi et al.'s Criteria)*

Response	Definition
Complete response	<ol style="list-style-type: none"> 1. Disappearance of all lesions 2. No new lesions
Partial response	<ol style="list-style-type: none"> 1. A decrease in size[†] of 10% or more OR a decrease in tumor density (HU) of 15% or more on CT 2. No new lesions 3. No obvious progression of nonmeasurable disease
Stable disease	<ol style="list-style-type: none"> 1. Does not meet criteria for complete response, partial response, or progression 2. No symptomatic deterioration attributed to tumor progression
Progression of disease	<ol style="list-style-type: none"> 1. An increase in tumor size[†] of 10% or more AND does not meet criteria of partial response by tumor density (HU) on CT 2. New lesions 3. New intratumoral nodules or increase in the size of existing intratumoral tumor nodules

Abbreviations: CT, computed tomography; HU, Hounsfield unit.

Data are from: Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.

*These criteria are for assessing response to therapy in patients with solid tumors.

[†]Size: the sum of the longest diameters of target lesions as defined in RECIST.

These criteria correlate much better with PET in predicting response to imatinib than do RECIST criteria.^{107,108} Choi et al.'s CT criteria have been validated in one center in patients with GIST who had not previously received TKI therapy (i.e., “naïve” patients).^{107,109} However, these criteria have not yet been universally accepted, and ease of use outside specialized centers is unknown.

Lack of tumor growth on CT 1 month after imatinib in “naïve” GIST patients also may have a predictive value similar to Choi et al.'s CT criteria or to the metabolic response seen on FDG-PET at that time.¹¹⁰ However, further studies are needed to vali-

date the use of new anatomic metrics criteria in patients receiving TKIs. FDG-PET scans (see “PET” page 23) also may be used for staging, restaging, and monitoring the therapeutic response to TKIs. FDG-PET scans may be used to clarify ambiguous findings seen on CT or MRI. Progression may be determined or confirmed by MRI or ¹⁸FDG-PET.

For patients with “marginally resectable” GISTs, knowledge of these early changes might be beneficial in surgical decision-making. In the early stages of imatinib, the decreases in tumor size may not parallel changes in tumor density, and patients may have substantial symptomatic improvement even in the absence of tumor shrinkage (Figure 6). In some cases, tumor size can even increase, mostly because of the development of intratumoral hemorrhage or myxoid degeneration. Tumor implants in the peritoneal cavity usually disappear quickly, whereas changes in size of metastatic tumors in the liver may take longer to see. A maximum response in tumor size in any location may not be achieved until 6 to 12 months or more of imatinib. Recognizing the pattern of tumor response on CT images is particularly important in these tumors, particularly in the early stage. TKI therapy should continue as long as the patient shows clinical benefit in disease control or prolongation of survival.

After tumors become hypodense, lesion size may decrease slowly and eventually stabilize. Stable disease by CT criteria (i.e., no tumor growth) has been shown to be predictive of time-to-treatment failure.¹¹¹ CT plays an important role in showing tumor stability and in identifying any true tumor progression that might signal the clonal emergence of resistance to imatinib. Tumor recurrence after surgical resection can be a metastasis or can occur at the site of primary disease. After successful treatment of metastatic disease, progression often presents as a new, small intratumoral nodule (without change in overall tumor size or in general configuration of the treated lesion; Figure 7) or as an increase in the size of existing intratumoral tumor nodules.¹¹²

When progression occurs, imaging frequency should be increased. Each treated lesion should be carefully analyzed for new intratumoral changes. When the CT findings are inconclusive or inconsistent with clinical findings, ¹⁸FDG-PET should be performed.

Although CT is essential at initial presentation and for surveillance, the baseline CT should be per-

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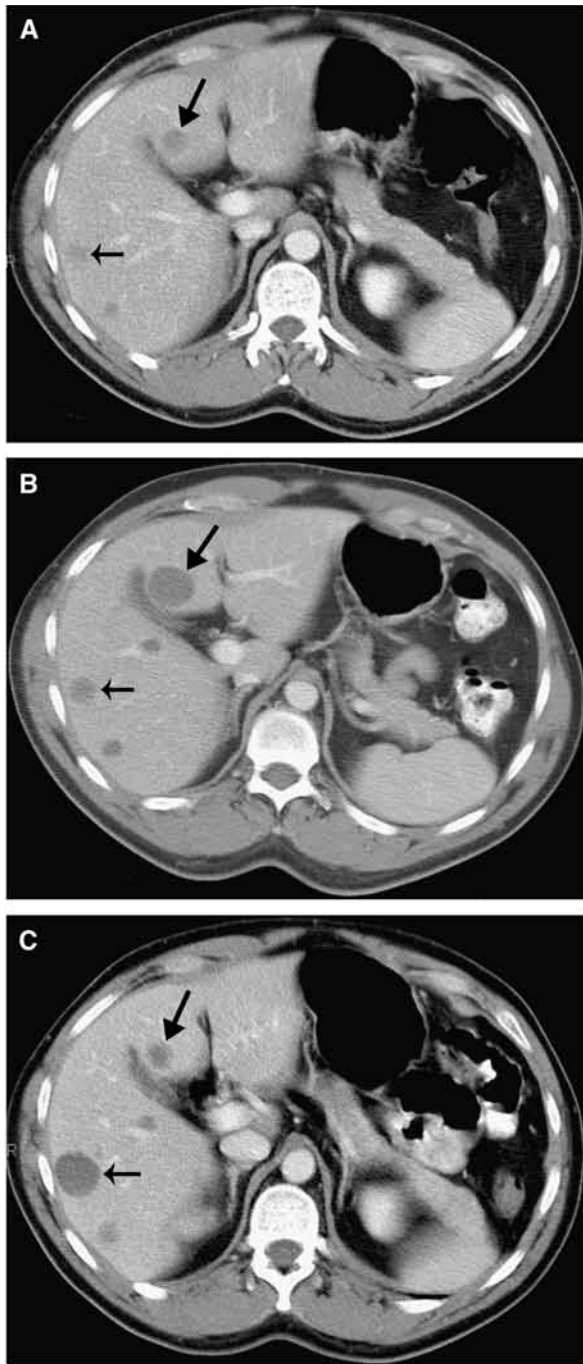


Figure 6 Increasing tumor size and spurious “progression” of disease in a 41-year-old man with a primary gastrointestinal stromal tumor (GIST) of the small bowel who had a “good response” to imatinib treatment. (A) A portal-venous phase image of pretreatment computed tomography (CT) showed multiple, small hyperdense metastases in the liver (arrows). (B) At 8 weeks after treatment, the lesions became homogenous and hypodense (indicating “good response”) but increased in size significantly (arrows). (C) At 16 weeks after treatment, the lesion in the medial segment of the left lobe decreased significantly (large arrow). Notice the lesion in the right lobe (small arrow) had continuously increased but remained hypodense. This lesion became smaller on the follow-up CTs (not shown). Photomicrographs provided by Haesun Choi, MD (The University of Texas M. D. Anderson Cancer Center).

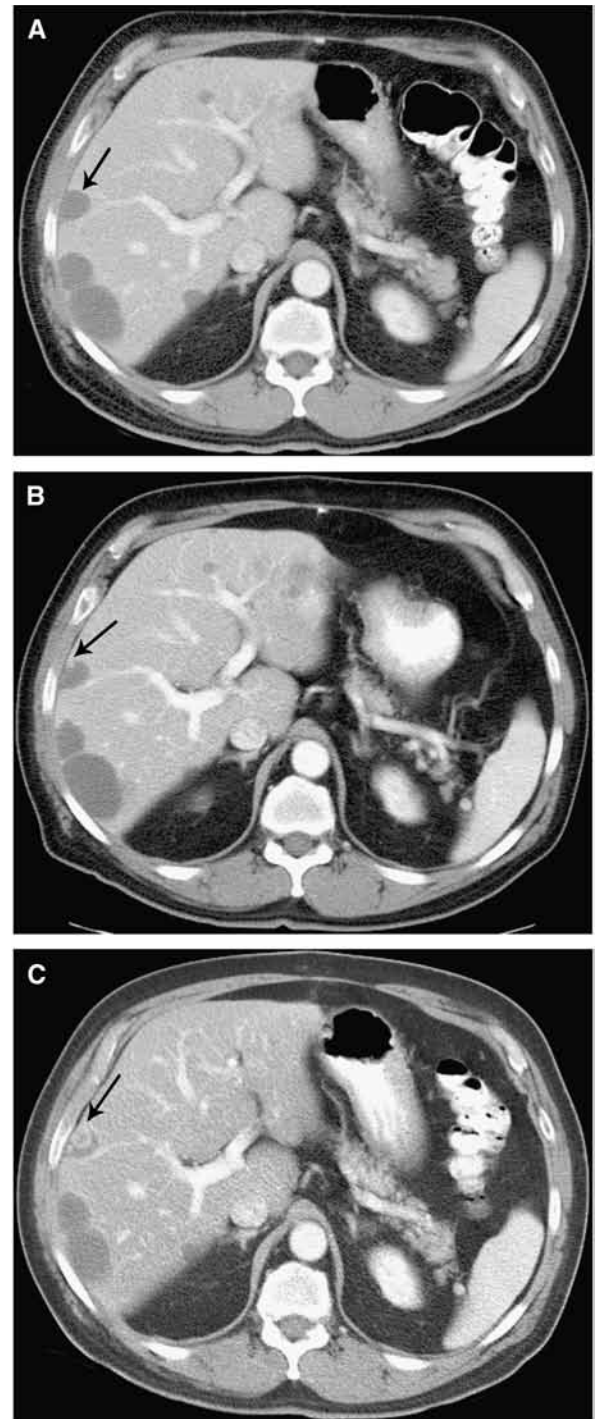


Figure 7 Intratumoral recurrence after imatinib in a 72-year-old man with a primary gastrointestinal stromal tumor (GIST) in the duodenum. (A) An enhanced computed tomography (CT) image obtained 12 months after treatment demonstrated multiple, treated hypodense metastasis in both lobes of the liver (arrow). (B, C) On follow-up CTs, a continuously increasing intratumoral nodule (arrow) was noted at 17 months (B) and 22 months (C) after treatment. Photomicrograph provided by Haesun Choi, MD (The University of Texas M. D. Anderson Cancer Center).

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formed with oral contrast administration to define bowel margins. More importantly, use of intravenous contrast is essential to observe the degree and pattern of enhancement and to observe tumor vessels. The portal-venous-phase images of enhanced CT (“routine” CT at most radiology practices) may mask the hypervascular hepatic metastases from GIST, because the enhancement of the tumors becomes similar to the enhancement of the surrounding hepatic parenchyma. Well-performed multiphase (e.g., biphasic or triphasic) imaging techniques would be necessary to recognize these hypervascular hepatic metastases. However, if unenhanced and enhanced CT images are carefully compared, this assessment may avoid “missing” lesions and “pseudo new” lesions on follow-up CT (Figure 8). Unenhanced CT images are also useful in detecting intratumoral hemorrhage, which can mask a decrease in tumor “density” or enhancement in responding tumors.

PET

In patients with GIST, imaging is done to assess tumors (including diagnosis, initial staging, restaging), monitor response to therapy, and perform follow-up surveillance of possible recurrence. Imaging studies can include anatomic imaging with CT (as discussed) and functional imaging with ^{18}F FDG-PET. Both CT and ^{18}F FDG-PET can identify an abnormal mass; however, ^{18}F FDG-PET helps to differentiate active tumor from necrotic or inactive scar tissue, malignant from benign tissue, and recurrent tumor from nondescript benign changes.¹¹³ Tumors have an increased demand for glucose, and ^{18}F FDG uptake in tumors is proportional to the glycolytic metabolic rate of viable tumor cells. As such, FDG-PET provides significant value to the standard CT images, because changes in the metabolic activity of tumors often precede anatomic changes on CT. FDG-PET also allows for quantitative evaluation of the metabolic activity within a tumor using a semi-quantitative measurement like the standardized uptake value (SUV) or maximum SUV (SUVmax) to evaluate response to therapy. It also allows for true quantitation and pharmacokinetic compartmental analysis of the tumor metabolism and of the metabolic changes occurring within the tumor after a therapeutic intervention. Responses by FDG-PET are often expressed as changes in SUV or SUVmax as an absolute value or as percent change relative to the baseline scan. The magnitude of the decrease in SUV relative to the baseline SUV is used to determine

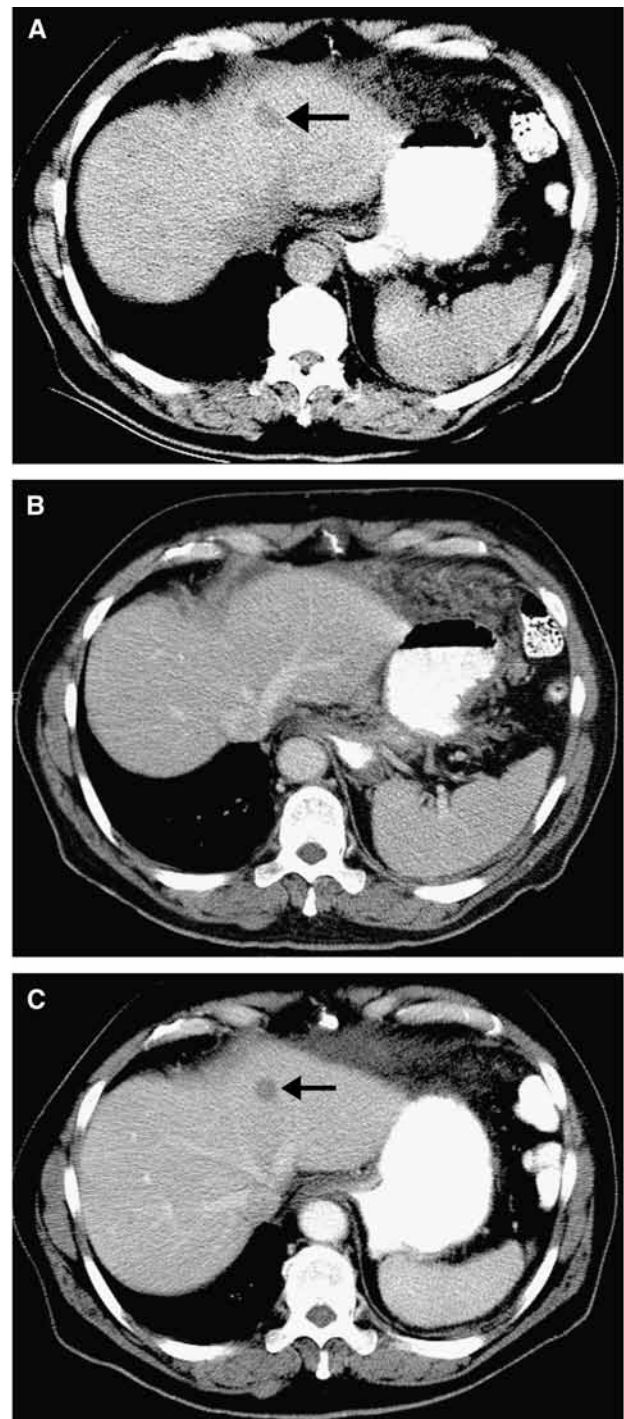


Figure 8 A spurious “new” lesion on follow-up computed tomography (CT) in a 41-year-old man with primary gastrointestinal stromal tumor in the small bowel who received imatinib treatment. (A, B) On pre-treatment CT, a metastatic lesion (arrow) in the liver could only be detected on an unenhanced image (A) but not on the enhanced portal-venous phase image (B), because the lesion was enhanced to the same degree as the surrounding parenchyma. (C) A portal-venous phase image of CT obtained 8 weeks after treatment showed that the lesion (arrow) became clearly visible, which should not be misinterpreted as a new lesion. Photomicrographs provided by Haesun Choi, MD (The University of Texas M. D. Anderson Cancer Center).

whether the therapy is effective. The EORTC has developed metabolic response criteria for tumors evaluated with FDG that provide definitions for complete metabolic response, partial metabolic response, stable metabolic disease, or disease metabolic progression.¹¹⁴ These criteria have been shown to be of prognostic value for time-to-progression and overall survival in a variety of cancers.

As mentioned previously, CT is usually the initial imaging modality, but FDG-PET is more sensitive than CT,¹¹⁵ even though it does not substitute for CT. Most imaging centers that provide PET services are now equipped with hybrid systems combining a PET scanner and a CT scanner as one imaging system with one gantry (PET/CT). This combined system allows matching and fusing of any abnormal FDG activity to an anatomic (CT) finding. Conversely, combined PET/CT can show that an anatomic abnormality may not correlate to an abnormal metabolic activity and, therefore, most likely represents response to treatment despite the presence of a residual mass on CT. This is important for GIST patients treated with TKI, because residual tumor masses may persist for months or years on CT in these patients despite response to imatinib. The CT portion of the FDG-PET/CT study can be done with or without oral and intravenous contrast. If performed without contrast, an additional diagnostic CT with contrast may be needed if clinically warranted. As previously discussed, CT can show morphologic and density changes within GIST tumors, which represent a positive response to TKI. However, FDG-PET can show metabolic changes within these tumors without ambiguity earlier than the morphologic or density changes seen on CT; as early as 24 hours after the first dose of imatinib.¹¹⁶

If a clinician considers using FDG-PET to monitor therapy, a baseline FDG-PET should be obtained before any TKI administration (Figure 9); additional PET images can be obtained after therapy. These PET scans are then used to determine the magnitude of metabolic changes occurring after therapy relative to baseline. These changes can be assessed quantitatively based on the absolute value of SUVmax or the percent change in SUVmax relative to baseline and have been shown to predict time to treatment failure.^{110,117,118} If a baseline scan was not obtained, PET scanning after imatinib is still useful because many PET scans show a complete metabolic response after imatinib.

Although most patients can be adequately imaged with CT for treatment planning, FDG-PET may be valuable in certain settings. Use of ¹⁸F-FDG-PET in the management of GIST includes 1) staging and detecting metastases that may otherwise not be apparent; 2) detecting an otherwise unknown primary site; 3) monitoring response to TKI therapy; 4) detecting primary resistance to TKI as well as secondary resistance to TKI in follow-up; and 5) resolving ambiguities from CT (e.g., when the CT findings are inconclusive or inconsistent with clinical findings). For example, PET is useful when a small increase or decrease in tumor size is seen on CT, but it is not clear whether the lesion is progressing or responding. FDG-PET is also useful for patients with marginally resectable GIST or GIST that is resectable with risk of significant morbidity. If urgent information is needed to assess response and to consider surgical intervention, a second PET can be done early (1–2 weeks after starting TKI). However, PET is not necessary for very low-risk tumors (<2 cm) or for resectable biopsy-proven primary GIST (unless surgery might be associated with excessive morbidity or if neoadjuvant therapy is being considered).

In patients with GIST who are receiving neoadjuvant therapy, FDG-PET can be used to assess response to therapy.⁵⁰ A good response to imatinib is observed on FDG-PET as a marked decrease in ¹⁸F-FDG uptake in the tumors (Figure 9). Response can be seen as early as 24 hours after a single dose of imatinib. The ability of FDG-PET to detect an early response is valuable, because major changes in tumor volume that are detected by CT tend to occur much later after initiation of imatinib (median time to CT response measured by tumor shrinkage is about 3–4 months, whereas FDG-PET imaging can detect response within hours to days). Identifying patients who are not responding to imatinib may be important, so they can receive optimal treatment, especially for primary disease for which aggressive surgical resection may be the alternative to imatinib continuation.

For a patient with a large mass who is judged to have a high risk of metastasis, a baseline FDG-PET scan is recommended to assess the presence or absence of disseminated disease. In these patients, small lesions can occasionally be difficult to detect within bowel folds, in the pelvis, or in the omentum. If a patient has a marginally resectable GIST for which immediate surgery might cause a large risk of poten-

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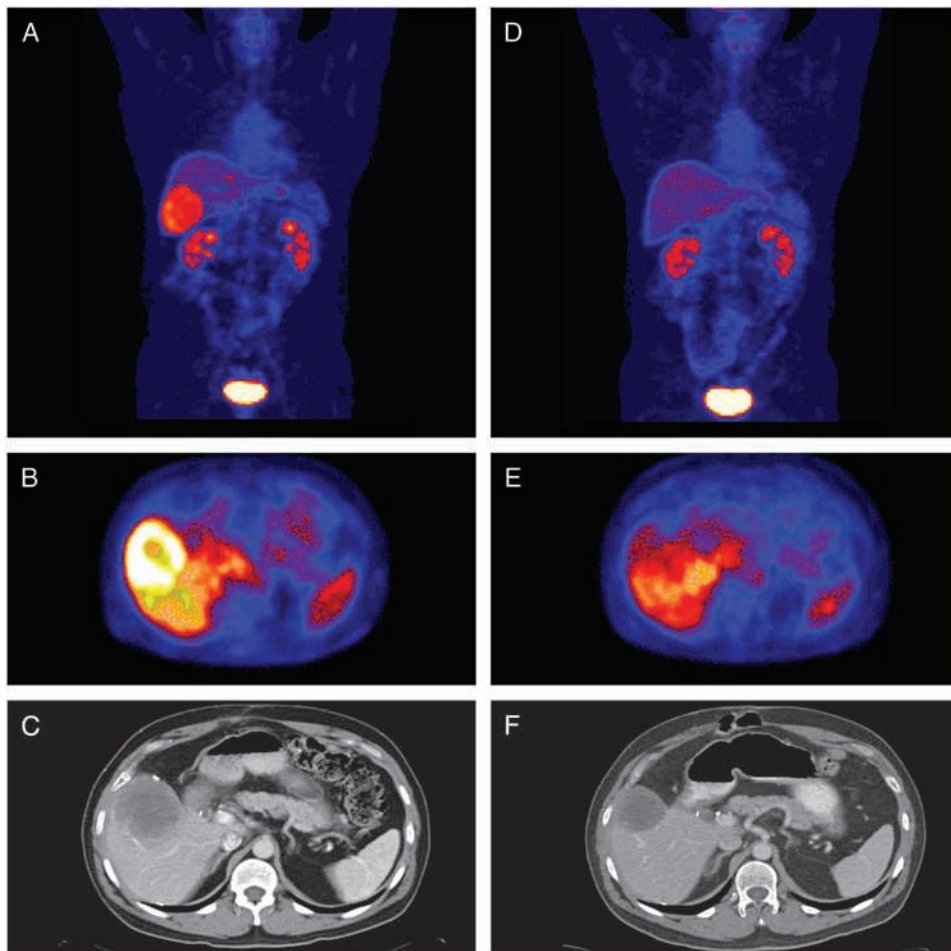


Figure 9 “Good response” to imatinib in gastrointestinal stromal tumor (GIST) can be observed earlier when using ^{18}F fluorodeoxyglucose positron emission tomography (^{18}F FDG-PET) than with computed tomography (CT). (A, B, and C) Baseline images before imatinib therapy: the ^{18}F FDG-PET whole body image (A) and PET axial slice (B) (which is through the liver metastasis) show intense uptake of ^{18}F FDG at the site of a prominent liver metastasis from recurrent GIST. The correlating axial CT image (C) also shows a prominent liver metastasis from recurrent GIST. (D and E) After 4 weeks of imatinib therapy, the metastasis no longer demonstrates abnormal uptake on the ^{18}F FDG-PET scan. (F) After 3 months of therapy, the CT image still shows a residual hypodense (hypodense) mass, which has somewhat decreased in size. Photomicrographs provided by Annick D. Van den Abbeele, MD, and George D. Demetri, MD (Dana-Farber/Brigham and Women’s Cancer Center).

tial morbidity, a FDG-PET scan may prove useful if there is a narrow window for moving to surgical resection if imatinib was ineffective. Thus, clinicians should strongly consider FDG-PET when they need to rapidly monitor therapeutic response to inform surgical decision-making.

In addition, FDG-PET can resolve ambiguities from CT. For example, CT might suggest tumor growth but actually represent bleeding into a tumor or other tumor swelling from myxoid degeneration, not true tumor progression. In this context, FDG-PET will show no increase in metabolic activity within the tumor mass, confirming that the increase in tumor size does not represent progression. Conversely, a positive FDG-PET in the context of an enlarging mass on CT

(i.e., a scan that shows increased metabolic activity within a growing mass) would confirm tumor progression. FDG-PET may be critical for patients with ambiguous CT findings. Progression does not necessarily mean that therapy should be changed if most of the tumor is responding.

Re-emergence of glycolytic activity as shown by FDG-PET in the follow-up of patients on imatinib is consistent with secondary resistance to the drug or with lack of compliance to the drug regimen. When imatinib was stopped in patients with GIST that had become refractory to the drug, a marked rebound of glycolytic activity was observed within the tumor, which is termed a “flare” phenomenon.¹¹⁹ This flare phenomenon suggested that portions of

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the tumor were still responding to imatinib, while other parts had developed a new clonal evolution resistant. This observation of the flare phenomenon also suggested that 1) viable tumor cells may still be present within the tumor despite clinical and radiologic responses to imatinib; 2) imatinib needs to be considered as long-term therapy; 3) compliance with the therapeutic regimen is critical, because this flare phenomenon can be seen within days after drug termination; 4) resection of the residual tumor mass could be considered even after successful response to TKI; and, 5) a therapeutic approach involving a combination of TKIs might need to be considered to address clonal differentiation in a tumor that is still partially responding to the first line of TKI therapy.

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Post-test

Please circle the correct answer on the enclosed answer sheet.

1. Gastrointestinal stromal tumors (GISTs) have a characteristic immunohistochemical profile that is useful in confirming a suspected diagnosis; about 95% of GISTs are positive for KIT (CD117).
 - a. True
 - b. False
2. Imatinib mesylate is a small molecule inhibitor of a family of structurally related tyrosine kinase signaling enzymes; imatinib often yields complete responses in patients with GISTs.
 - a. True
 - b. False
3. Which of the following statements is/are TRUE about sunitinib malate?
 - a. Objective response rates are very high (> 70%) with sunitinib.
 - b. Sunitinib has been approved by the U.S. Food and Drug Administration as first-line therapy for patients with GISTs.
 - c. Profound neutropenia never occurs with sunitinib.
 - d. Hypothyroidism can occur in patients receiving sunitinib.
 - e. All of the above
 - f. None of the above
4. Which of the following statements is/are TRUE about imatinib mesylate?
 - a. It is generally not necessary to decrease the dose of imatinib to manage edema as long as other supportive measures can control it.
 - b. Dyspepsia and gastrointestinal side effects can be decreased by taking the drug with food, which does not appear to decrease absorption.
 - c. Patients with large bulky GISTs who are receiving imatinib have a risk of tumor hemorrhage.
 - d. Drinking grapefruit juice (200-250 mL) will increase levels of imatinib.
 - e. All of the above
 - f. None of the above
5. For patients with advanced or metastatic GISTs who are receiving imatinib mesylate therapy, the median time to progression is:
 - a. 1 year
 - b. 2 years
 - c. 4 years
 - d. 6 years
 - e. 8 years
 - f. 10 years
6. Computed tomography often underestimates the extent of peritoneal disease in patients with GISTs, and it is not uncommon to identify many other nodules at laparotomy.
 - a. True
 - b. False
7. Metastasis from GIST occurs:
 - a. Most often to the liver, omentum, and peritoneal cavity
 - b. In the soft tissues (such as abdominal wall)
 - c. Rarely in pleura
 - d. Very rarely to lung, bone, or lymph nodes
 - e. All of the above
 - f. None of the above
8. Adverse events with sunitinib malate include:
 - a. Neutropenia
 - b. Mucositis
 - c. Hand-foot syndrome
 - d. Hypertension
 - e. All of the above
 - f. None of the above
9. When a GIST responds to treatment with imatinib mesylate, the tumor generally becomes homogenous and hypoattenuating on computed tomography, and the tumor vessels and solid enhancing nodules disappear.
 - a. True
 - b. False
10. Aside from GIST, tumors that may be KIT-positive by immunohistochemistry include which of the following?
 - a. Angiosarcoma
 - b. Ewing sarcoma
 - c. Extramedullary myeloid tumor
 - d. Small cell lung carcinoma
 - e. All of the above
 - f. None of the above

Post-Test Answer Sheet

Please circle one answer per question. A score of at least 70% on the post-test is required.

- | | |
|----------------|-----------------|
| 1. a b | 6. a b |
| 2. a b | 7. a b c d e f |
| 3. a b c d e f | 8. a b c d e f |
| 4. a b c d e f | 9. a b |
| 5. a b c d e f | 10. a b c d e f |

<p>Please evaluate the achievement of the learning objectives using a scale of 1 to 5. (1 = Not met; 3 = Partially met; 5 = Completely met)</p>	<p>Please indicate the extent to which you agree or disagree with the following statements: (1 = Strongly disagree; 3 = Not sure; 5 = Strongly agree)</p>
<p>Illustrate the epidemiology of GIST and its typical presenting characteristics.</p>	<p>The material was presented in a fair and balanced manner.</p>
<p>1 2 3 4 5</p> <p>Identify characteristic pathologic features and appropriate immunohistochemical testing for diagnostic and prognostic purposes.</p>	<p>1 2 3 4 5</p> <p>The information presented in this monograph was pertinent to my educational needs.</p>
<p>1 2 3 4 5</p> <p>Define the role of multidisciplinary cooperation in selection and timing of therapeutic interventions.</p>	<p>1 2 3 4 5</p> <p>The information presented was scientifically rigorous and up-to-date.</p>
<p>1 2 3 4 5</p> <p>Identify appropriate medical management.</p>	<p>1 2 3 4 5</p> <p>The information presented in this monograph has motivated me to modify my practice.</p>
<p>1 2 3 4 5</p> <p>Recognize surgical principles that apply to GIST management.</p>	<p>1 2 3 4 5</p> <p>I would recommend this monograph to my colleagues.</p>
<p>1 2 3 4 5</p> <p>Define response criteria based on follow-up testing.</p>	

**NCCN Task Force Report: Optimal
Management of Patients with Gastrointestinal
Stromal Tumor (GIST)—*Update of the
NCCN Clinical Practice Guidelines***

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