NCCN Task Force Report: Update on the Management of Patients with Gastrointestinal Stromal Tumors

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Key Words

NCCN, gastrointestinal stromal tumor, GIST, gastric mass, stomach cancer, abdominal tumor, small bowel tumor, gastrointestinal tract, liver metastasis, tyrosine kinase inhibitors, TKIs, KIT, CD117, PDGFRA, wild-type GISTs, gene expression profiling, GEP, imatinib, sunitinib

Abstract

The standard of care for managing patients with gastrointestinal stromal tumors (GISTs) rapidly changed after the introduction of effective molecularly targeted therapies involving tyrosine kinase inhibitors (TKIs), such as imatinib mesylate and sunitinib malate. A better understanding of the molecular characteristics of GISTs have improved the diagnostic accuracy and led to the discovery of novel immunomarkers and new mechanisms of resistance to TKI therapy, which in turn have resulted in the development of novel treatment strategies. To address these issues, the NCCN organized a task force consisting of a multidisciplinary panel of experts in the fields of medical oncology, surgical oncology, molecular diagnostics, and pathology to discuss the recent advances, identify areas of future research, and recommend an optimal approach to care for patients with GIST at all stages of disease. The task force met for the first time in October 2003 and again in December 2006 and October 2009. This supplement describes the recent developments in the field of GIST as discussed at the October 2009 meeting. (*JNCCN* 2010;8[Suppl 2]:S1–S40)

Background

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Neoplastic GIST cells seem to arise from a common precursor cell, which gives rise to the interstitial cells of Cajal in the normal myenteric plexus.[1] GISTs can arise anywhere along the gastrointestinal tract but are most common in the stomach and small intestine, most commonly resulting from activating mutations in one of the receptor protein tyrosine kinases: KIT (CD117) or platelet-derived growth factor receptor alpha (PDGFRA).

The standard of care in the management of patients with GIST rapidly changed after the introduction of tyrosine kinase inhibitors (TKIs), such as imatinib mesylate and sunitinib malate. This supplement describes the recent developments in the field of GIST. Given the limitations of these data, the authors encourage enrollment of patients in clinical trials when possible.

Epidemiology

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 sarcomas are presumably 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, 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, with 54% men and 46% women.[3] Population-based studies from Iceland, the Netherlands, Spain, and Sweden reported annual incidence rates ranging from 6.5 to 14.5 cases per million, but these figures may also contain GISTs detected incidentally and at autopsy.[4–7] 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. The diagnosis of GIST has dramatically increased since 1992, and survival has greatly improved since 2002, when the FDA approved imatinib mesylate.[8] The increase in the number of GISTs diagnosed per year is likely from greater awareness and improved histopathologic detection, although the true incidence also may be increasing.[9]

Small GISTs (only a few millimeters in diameter) are common in the general adult population. These "mini-GISTs" are immunopositive for KIT and often contain an oncogenic mutation in the *KIT* or *PDGFRA* gene.[10] In a series of consecutive autopsies performed in Germany, small GISTs (1–10 mm) were grossly detectable in 22.5% of the autopsies in individuals older than 50 years.[10] These findings suggest that most small GISTs do not progress rapidly into large macroscopic tumors despite the presence of a *KIT* or *PDGFRA* mutation.

GIST has been reported in all age groups, including newborn infants. However, it is extremely rare in patients younger than 30 years. The median age at diagnosis ranges from 66 to 69 years in population-based series that include cases found at autopsy, which are diagnosed about a decade later than symptomatic GISTs.[4,7] In a study of 1765 gastric GISTs, the median age at diagnosis was 63 years.[11] In a series consisting of 906 jejunal and ileal GISTs, the mean age was 59 years.[12] In the latter 2 series, only 2.7% of gastric GISTs and 0.6% of small bowel GISTs were detected in patients younger than 21 years.

Thus, this supplement refers to the management of GIST in adult patients. Pediatric GIST and other GIST variants (familial GIST and neurofibromatosis-1 [NF-1]-associated GIST) that require specialized management are briefly discussed.

Clinical Presentation

In adult GISTs, the stomach (60%) and small intestine (30%) are the most common primary sites; duodenum (5%) and colorectum (< 5%) are the less common primary sites. Rectal GISTs are uncommon, and GISTs originating in the colon are rare. Only a small number of cases (< 1%) have been reported in the esophagus and appendix. On rare occasions GISTs develop outside the gastrointestinal tract in the mesentery, omentum, or retroperitoneum.[13,14] Extragastrointestinal (soft tissue) stromal tumors are histologically and immunophenotypically similar to their gastrointestinal counterpart but have an aggressive course similar to small intestinal than gastric stromal tumors.[15] Recurrence after resection is predominantly intra-abdominal, and the liver is the most common site of recurrence in patients with primary presentation and those with metastatic disease at presentation.[16] Lymph node metastases are extremely uncommon; spread to the lungs or other extra-abdominal locations are also extremely rare.

GISTs are associated with a broad range of presentations. Many are identified clinically because they cause symptoms and some are identified at autopsy. Small GISTs that are smaller than 2 cm usually do not produce any symptoms and are detected incidentally during abdominal exploration, endoscopy, or radiologic imaging.[17] In a recent population-based study, the median tumor size of GISTs that were detected based on symptoms, incidental findings, or during an autopsy were 8.9, 2.7, and 3.4 cm, respectively.[7]

In general, patients with a suspected GIST may present with various symptoms, including but not limited to early satiety, fatigue secondary to anemia, intraperitoneal hemorrhage, intraluminal gastrointestinal bleeding, or abdominal discomfort from pain or swelling. Some patients may present with an acute abdomen (as result of tumor rupture, gastrointestinal obstruction, or appendicitis-like pain), which requires immediate medical attention.

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 approximately 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 gastrointestinal 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 peritoneal surface. Rarely, a patient will have 2 separate GISTs at different locations in the gastrointestinal tract. In these cases, familial GIST should be considered, which is typically associated with interstitial cell of

Cajal hyperplasia within myenteric plexus.

Most GISTs show 1 of 3 histologic patterns: spindle cell type (70%; Figure 1), predominantly epithelioid cell type (20%; Figure 2), or a mixture of both spindle and epithelioid cells.[14] Epithelioid GISTs may have either a diffuse or nested architecture, whereas spindle cells GISTs are arranged in short fascicles or whorls. The stroma is usually scanty but may vary from hyalinized to myxoid; extensively myxoid GISTs are rare. Most spindle cell GISTs have a uniform cytology, with fibrillary eosinophilic cytoplasm and nuclei containing fine chromatin and inconspicuous nucleoli. Marked cytologic pleomorphism is rare and should raise the possibility of an alternative diagnosis. However, epithelioid GIST may often show evidence of bi- or multinucleation, and a more significant nuclear atypia, compared with the spindle cell counterpart. Unusual but striking features seen in a subset of cases are prominent paranuclear vacuoles (usually in gastric lesions), hyaline eosinophilic material known as *skeinoid fibers* (mainly in small bowel lesions), and extensive nuclear palisading.

The morphologic differential diagnosis of spindle cell GIST is broad and includes both benign and malignant lesions, such as smooth muscle tumors (leiomyoma, leiomyosarcoma), schwannoma, intra-abdominal desmoid-type fibromatosis, inflammatory myofibroblastic tumor, solitary fibrous tumor, and sarcomatoid carcinoma. The differential diagnosis for epithelioid GIST includes carcinoma, metastatic melanoma, clear cell sarcoma, epithelioid variants of leiomyosarcoma, and epithelioid hemangioendothelioma.

Obtaining adequate tumor tissue material for definitive diagnosis before surgical resection has been challenging. Because these tumors tend to be soft and friable, biopsy may cause tumor rupture and be associated with an increased risk for tumor dissemination. Furthermore, the diagnosis of GIST can be highly suspected based on endoscopic ultrasound (EUS) or esophagogastroduodenoscopy. Recent reports have suggested that definitive diagnosis of GIST requires tissue acquisition through EUS-guided fine-needle aspiration.[18] However, biopsy may not be necessary if the tumor is easily resectable and preoperative therapy is not required. Conversely, biopsy might be needed if preoperative therapy is being considered for unresectable or marginally resectable tumors.

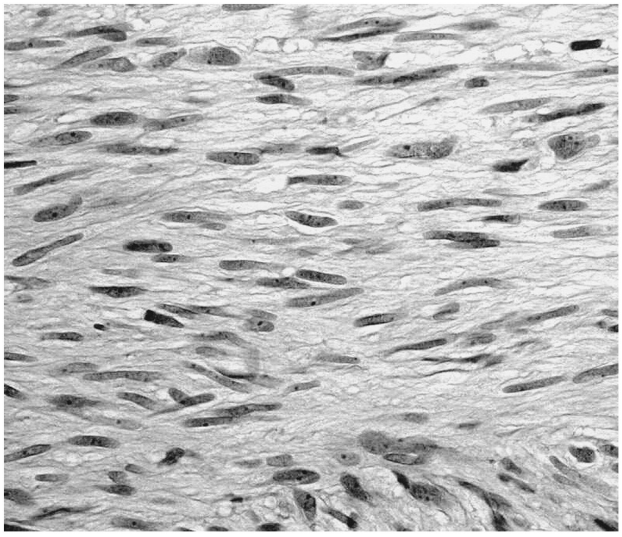

Figure 1 Spindle cell gastrointestinal stromal tumor (GIST). Typical morphology of a low-risk GIST comprised predominantly of spindle cells. This tumor was strongly KIT-positive and harbored a mutation in *KIT* exon 11 (H&E stain; original magnification, 400x).
Courtesy of Christopher L. Corless, MD,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

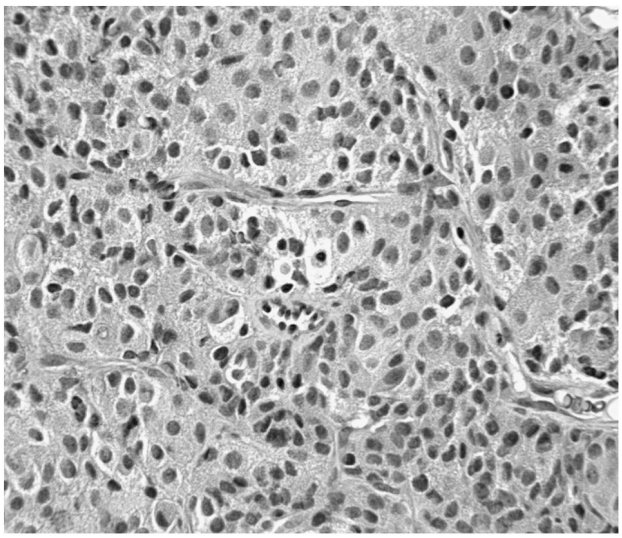

Figure 2 Intermediate-risk gastrointestinal stromal tumor (GIST) comprised predominantly of epithelioid cells. The tumor was KIT-positive and contained a mutation in *KIT* exon 9 (H&E stain; original magnification, 400x).
Courtesy of Christopher L. Corless, MD, PhD, Oregon Health & Science University.

The diagnosis of GIST has evolved over a short period. In patients with a remote history of an abdominal or pelvic tumor diagnosed as something different, such as a leiomyosarcoma or leiomyoblastoma, re-examination of the tumor using current morphologic, immunophenotypic, and genotypic

criteria might result in its reclassification as GIST.

Immunohistochemistry

GISTs have a characteristic immunohistochemical profile that is useful for confirming a suspected diagnosis.[19] Approximately 95% are positive for KIT (CD117). In general, KIT staining in GISTs is strongly and diffusely positive, but is not necessarily uniform across different regions of the tumor. Staining may appear in a cytoplasmic (most common), membranous, or a concentrated dot-like perinuclear pattern. Some cases show combinations of these patterns. Epithelioid GISTs tend to have a weaker and patchier staining pattern than spindle cell GISTs.

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 tittered. Overstaining for KIT has been a problem in some laboratories and has caused other mesenchymal tumors to be misdiagnosed 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] and although KIT-positivity is a major defining feature for GIST, KIT-positivity alone may not be sufficient for diagnosis. Non-GISTs that are positive for KIT include metastatic melanoma, angiosarcoma (50%), Ewing's sarcoma family of tumors (50%), childhood neuroblastoma (30%), extramedullary myeloid tumor, seminoma, and small cell lung carcinoma.[21] GIST can be confidently diagnosed if the morphology and immunophenotype are concordant; however, tumors with any unusual features should be sent to a referral institution with special expertise.

Other commonly expressed markers include CD34 antigen (70%), smooth muscle actin (SMA; 30%–40%), desmin (< 5%), and S100 protein (~5%).[19] The immunophenotype of GISTs varies depending on anatomic sites: CD34 is often positive in esophageal, gastric, and rectal lesions, whereas SMA is most often positive in small bowel tumors. S100 is more common in small intestinal GISTs than in gastric GISTs. CD34 and SMA staining can be either diffuse or focal. Staining for the other markers, when present, is usually patchy and weak. In an immunohistochemical analysis of 292 GISTs originating in the gastrointestinal tract, CD34 expression was variable (47% in small bowel and 96%–100% in the rectum and esophagus), whereas SMA expression was most frequent in small bowel GISTs (47%) and rare in GISTs of the rectum and esophagus (10%–13%). Desmin was seen only occasionally. S100 positivity was rare but was seen most frequently in small intestinal GISTs (15%).[22]

In contrast to GIST, leiomyoma and leiomyosarcoma are positive for SMA and desmin and negative for KIT and CD34. Malignant melanoma exhibits diffuse immunoreactivity for S100 protein, but can be focally positive for KIT. Schwannomas are strongly and diffusely immunoreactive for S100 protein and negative for KIT. Intra-abdominal desmoid-type fibromatosis may show weak, nonspecific staining for KIT, but express nuclear reactivity for beta-catenin. Sarcomatoid carcinoma tends to be pleomorphic, highly mitotically active, positive for cytokeratins, and negative for KIT and CD34.

KIT-Negative GISTs: Approximately 5% of GISTs are truly negative for detectable KIT expression, the so-called "KIT-negative GISTs."[23,24] Establishing the diagnosis of KIT-negative GIST remains a challenge and is best handled by a reference pathologist with expertise in this area. Precise diagnosis is of utmost importance because some KIT-negative tumors are known to be sensitive to imatinib. The location and morphology of the tumor and the results of immunohistochemical staining for KIT are essential to confirm diagnosis. In a proportion of KIT-negative GISTs, the genotypic analysis shows mutations in the *PDGFRA* gene rather than *KIT*.[25–27] Many of these *PDGFRA*-mutant GISTs have an epithelioid morphology (Figure 3). Immunostaining with PDGFRA has been shown in this particular setting to be helpful in discriminating between KIT-negative GISTs and other gastrointestinal mesenchymal lesions.[28–30]

BRAF mutations have also been reported in a small subset of intestinal high-risk GISTs (imatinib-naive or -resistant) lacking *KIT*/*PDGFRA* mutations.[31] This observation delineates a subgroup of patients who may benefit from selective *BRAF* inhibitors as an alternative to imatinib. These preliminary findings must be confirmed in a larger cohort.

Protein kinase C theta (PKCtheta) is a downstream effector in the KIT signaling pathway. It may play an important role in the diagnosis of KIT-negative GISTs, because it is expressed strongly in GISTs but not in leiomyosarcoma or other tumors that are

histopathologically similar to GIST.[32–34] It has also been suggested that PKCtheta is strongly activated in all GISTs, irrespective of their mutational status, and hence may serve as a novel therapeutic target.[32]

DOG1 is a calcium-dependent, receptor-activated chloride channel protein and seems to be expressed in GIST independent of mutation type.[35,36] Other KIT-positive tumors, such as melanoma, Ewing sarcoma, and extramedullary myeloid tumors, are consistently negative for DOG1. In a study of 1168 cases of GISTs, the overall sensitivity of DOG1 and KIT was nearly identical (94.4% and 94.7%, respectively) and a high concordance was seen between DOG1 and KIT immunohistochemistry (92.3% positivity for both).[37] Gastric spindle cell GISTs were nearly uniformly positive for both markers, whereas gastric epithelioid GISTs with *PDGFRA* mutations were slightly more sensitive for DOG1, and small intestinal GISTs were slightly more sensitive for KIT. Overall, approximately 2.6% of GISTs were negative for both DOG1 and KIT. DOG1 expression was not different between the *KIT*/*PDGFRA* mutant or wild-type GISTs, but a clear distinction was seen between *PDGFRA*- and *KIT*-mutant tumors. The *PDGFRA* mutant GISTs had a low KIT expression and high DOG1 expression, which can be used to diagnose KIT-negative tumors. Approximately 30% of KIT-negative cases could be confirmed with DOG1 immunohistochemistry. DOG1.1 immunostaining was positive in a small subset of synovial sarcomas (2.5%) and leiomyosarcomas (< 1%). DOG1.1 immunoreactivity was seen in fewer cases of carcinoma, melanoma, and seminoma than KIT.[38]

The experience with these novel immunomarkers is currently limited, and problems exist with the quality and availability of the commercial antibodies used to stain for them.

Gene Expression Profiling

Gene expression profiling (GEP) studies have shown that primary nontreated GISTs are characterized by distinctive gene signatures that are homogenous and tightly clustered away from other subtypes of sarcomas.[39,40] Among the most prominent discriminatory genes, high expression of KIT, G-protein-coupled receptor 20, and PKCtheta were the most significant.[41] However, a transcriptional heterogeneity has been noted when comparing different clinical and molecular subsets of GISTs. Gastric and small bowel GISTs had strikingly different gene signatures,

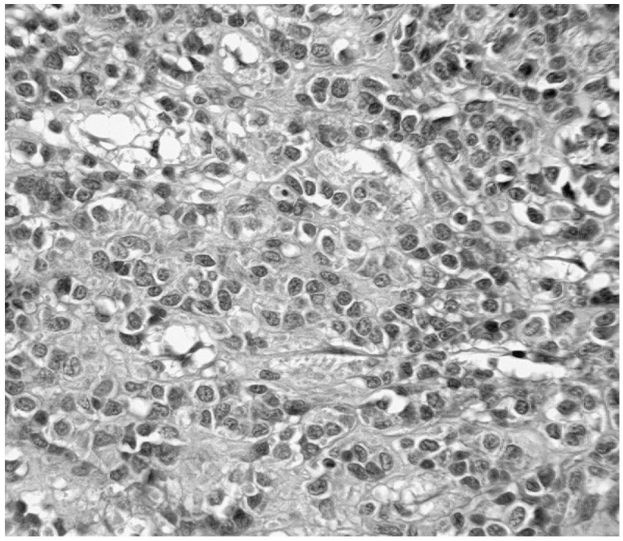

Figure 3 Platelet-derived growth factor receptor alpha (PDGFRA)–mutant gastrointestinal stromal tumor (GIST). This malignant, epithelioid GIST was *KIT*-negative and had a mutation in *PDGFRA* exon 18 (H&E stain; original magnification, 400x).
Courtesy of Christopher L. Corless, MD, PhD, Oregon Health & Science University.

whereas rectal GISTs had similar expression profiles as gastric GISTs.[40] Although GISTs with *PDGFRA* mutations clustered somewhat differently from those with *KIT* mutations, the distinction was not as highly significant as the anatomic location.[42] According to GEP, insulin-like growth factor 1 receptor (IGF1R) was consistently upregulated in pediatric wild-type GISTs.[43,44]

Compared with imatinib-naive GISTs, imatinib-responsive GISTs, which are electively surgically resected, showed down-regulation of genes involved in cell cycle control and up-regulation of genes involved in muscle differentiation and function.[45] These results suggest that chronic inhibition of KIT signaling with imatinib in responsive GISTs may induce immunophenotype changes, including weaker or negative KIT expression or transdifferentiation into a smooth muscle phenotype (positivity for SMA and desmin according to immunostaining) in 10% to 20% of tumors.[45] However, none of the pathologic or molecular factors analyzed in this study were able to predict the clinical outcome after surgical removal of stable or responsive disease. This study also showed that second-site KIT mutations are rare in imatinib-responsive GISTs compared with imatinib-resistant tumors.

Based on available data, GEP remains an investigational tool. It could be useful in predicting response to TKI therapy, identifying new molecular targets for tumor progression, and studying pathogenesis.

NCCN GIST Task Force Panel Recommendations for Diagnosing GIST

- Careful morphologic examination of adequate tumor tissue and immunohistochemical staining for KIT, corroborated with the gastrointestinal anatomic location of the lesion, are essential for confirming GIST diagnosis.
- The tumor size and mitotic index should be recorded for all GISTs and this information included in the final diagnosis of the pathology report. Pretreatment core needle biopsy samples are preferred over FNAs, because they may provide information regarding the mitotic rate.
- Fifty high power fields (HPFs) should be counted to get an accurate mitotic rate. If the mitotic index is based on counting fewer than 50 HPFs (i.e., in small biopsy tissue material), Ki-67 immunohistochemical analysis could further support the proliferation rate as determined by the mitotic index.
- DOG1 may be useful for cases that cannot be categorized as GIST based on KIT (CD117) immunostaining and mutation testing for KIT and PDGFRA. DOG1 and KIT could be used together in difficult cases exhibiting unexpected KIT negativity or positivity. The optimal management of patients with KIT/DOG1 double-negative tumors that have typical morphology of GIST remains uncertain and these patients should be referred to centers of expertise for potential clinical trials.
- The panel does not recommend DOG1 immunostaining for KIT-positive tumors.
- Although immunophenotypic changes have been shown in a subset of imatinib-responsive GISTs, these findings should not be used to guide therapy. In rare cases, deviations from the pre-imatinib immunoprofile (loss of KIT staining and expression of desmin) may cause diagnostic pitfalls for surgical pathologists and could suggest a change in the original diagnosis of GIST. When a pathologic response might lead to a change in treatment, the specimen should be sent out for re-review by an expert pathologist at another institution, and the patient possibly sent for a second opinion.
- GEP is not required for diagnosis or prognosis of adult GISTs; it may be helpful to distinguish between pediatric and wild-type GIST, but it is currently a research tool.

Prognostic Factors

The most important and widely used prognostic features of a primary tumor—their size and mitotic index—were the foundation for a consensus approach to risk stratification of GISTs published in 2002.[19] One of the tenets of this approach—that all GISTs have malignant potential—is supported by 3 large retrospective studies published by Miettinen et al.[11,12,46] at the Armed Forces Institute of Pathology (AFIP). 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 preimatinib era. The findings from these studies both validate and expand the 2002 consensus criteria for the risk stratification of GISTs.

Based on long-term follow-up of more than 1600 patients, Miettinen et al.[13] suggested guidelines for the risk stratification of primary GISTs based on mitotic index, size, and site (Table 1). According to these guidelines, gastric GISTs that are 2 cm or smaller with a mitotic index of 5 or less per 50 HPF can be regarded as essentially benign, but lesions larger than 2 cm with the same mitotic index have a risk for recurrence. Data are lacking on the prognosis of patients with GISTs smaller than 2 cm with a mitotic count of more than 5 per 50 HPF.

Miettinen and Lasota[13] also evaluated the prognosis of gastric and small intestinal GISTs in a large series. Findings confirmed the results of earlier, smaller studies indicating that anatomic location affects the risk for disease recurrence and progression; 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. Dematteo et al.[47] recently showed that in the absence of TKI therapy, recurrence in completely resected primary GIST can be independently predicted by mitotic rate, tumor size, and tumor location (patients with small intestinal GISTs have the greatest risk). Mitotic rate after imatinib treatment should not be used as a surrogate for prognostic implications, but may help establish response versus resistance.

Gold et al.[48] from Memorial Sloan-Kettering Cancer Center (MSKCC) developed a nomogram

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

Tumor Parameters		Risk for Progressive Disease*(%), Based on Site of Origin			
Mitotic Rate	Size	Stomach	Jejunum/Ileum	Duodenum	Rectum
≤ 5 per 50 HPF	≤ 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	> 2, ≤ 5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
	> 5, ≤ 10 cm	Low (3.6%)	Moderate (24%)	Insufficient data	Insufficient data
	> 10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
> 5 per 50 HPF	≤ 2 cm	None†	High†	Insufficient data	High (54%)
	> 2, ≤ 5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
	> 5, ≤ 10 cm	High (55%)	High (85%)	Insufficient data	Insufficient data
	> 10 cm	High (86%)	High (90%)	High (86%)	High (71%)

Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.
Abbreviations: GIST, gastrointestinal stromal tumor; HPF, high-power field.
*Defined as metastasis or tumor-related death.
†Denotes small numbers of cases.
Adapted from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Sem Diagn Pathol 2006;23:70–83.

(Figure 4) that uses tumor size, site, and mitotic index to predict relapse-free survival (RFS) after resection of localized primary GIST. The nomogram is based on 127 patients treated at the author's institution and was tested in patients from the Spanish Group for Research on Sarcomas (GEIS; 212 patients) and the Mayo clinic (148 patients). The nomogram achieved a concordance probability of 0.78 in the MSKCC data set and 0.76 and 0.80 in the GEIS and Mayo clinic cohorts, respectively. Nomogram predictions were well calibrated. Inclusion of tyrosine kinase mutation status in the nomogram did not improve its discriminatory ability, although this finding may be a result of the number of patients used in its development.

Concordance probabilities of the nomogram were better than those of the 2 National Institutes of Health staging systems (0.76 vs. 0.70 and 0.66 in the GEIS validation cohort; 0.80 vs. 0.74 and 0.78 in the Mayo cohort) and similar to those of the AFIP-Miettinen staging system (0.76 vs. 0.73 in the GEIS cohort; 0.80 vs. 0.76 in the Mayo cohort). Nomogram predictions of RFS seemed better calibrated than those made with the AFIP-Miettinen system. This nomogram accurately predicts RFS after resection of localized primary GIST, and may be useful for patient care, interpretation of trial results, and selection of patients for postoperative imatinib therapy.

Some studies have shown that Ki-67 index could be used to predict the malignant potential of GIST,[49,50] and in distinguishing between stable and progressive disease in patients treated with imatinib.

Significance of *KIT* and *PDGFRA* Mutation Status

KIT

Most *KIT* mutations occur in the juxtamembrane domain encoded by *KIT* exon 11 (allowing spontaneous [ligand-independent] receptor dimerization and kinase activation) and some are detected in the extracellular domain encoded by exon 9. KIT mutations have also been identified in the tyrosine kinase domain (exon 13 and 17), although they are rare.[51,52] *KIT* exon 11 mutations occur in different sites in the gastrointestinal tract, whereas *KIT* exon 9 mutations arise predominantly in the small intestine. *KIT* exon 9 mutations in the nongastric primary site seem to define a distinct subset of GISTs, associated with an unfavorable clinical course. *KIT* exon 17 mutations were more frequent in the small intestine than the stomach and may portend primary resistance to imatinib. *KIT* exon 13 mutations in imatinib-naïve patients are associated with durable responses to imatinib therapy.[53]

PDGFRA

Approximately 80% of the KIT-negative GISTs have *PDGFRA* mutations, and they are more common in the stomach and omentum. More than one third of GISTs with *PDGFRA* mutations may respond to imatinib, and mutational analysis be helpful in the management of these KIT-negative tumors.[27] Many of these *PDGFRA*-mutant GISTs have an epitheli-

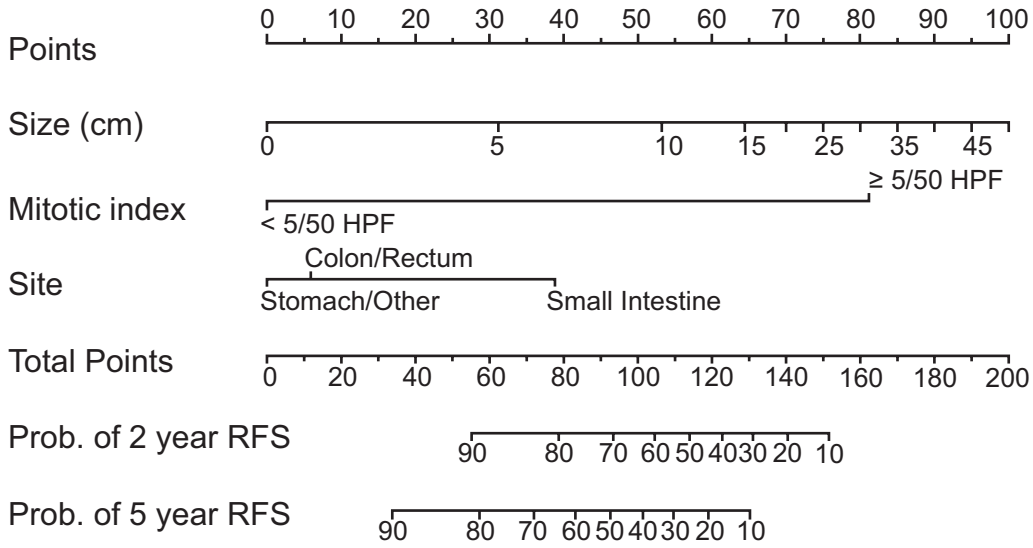

Figure 4 Nomogram for predicting probabilities of 2- and 5-year recurrence-free survival. Points are assigned for size, mitotic index, and site of origin by drawing a line upward from the corresponding values to the "Points" line. The sum of these 3 points, plotted on the "Total Points" line, corresponds to predictions of 2- and 5-year recurrence-free survival.
Abbreviations: HPF, high-power field; RFS, recurrence-free survival.
Data from Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 2009;10:1045–1052.

oid morphology (Figure 4) and express little or no KIT; however, these features are not unique to these tumors, and mutation status can be determined only through molecular analysis. Mutational analysis of *KIT* and *PDGFRA* genes is increasingly being used to establish the diagnosis of KIT-negative tumors. *PDGFRA* mutations are common in gastric GISTs and most affect exon 18 in the tyrosine kinase domain 2. Few mutations also occur in exon 12 (juxtamembrane domain) and 14 (tyrosine kinase domain 1), although mutations at these sites are rare.[51]

Wild-Type GIST

Approximately 10% to 15% of GISTs are negative for *KIT* and PDGFRA gene mutations; these tumors are often referred to as wild-type. Patients with wild-type GISTs are less responsive to imatinib-based therapies and have a poor prognosis.[23] Recent reports have suggested that IGF1R is highly expressed in adult and pediatric wild-type GISTs compared with *KIT* or *PDGFRA*-mutant GISTs, and that inhibition of IGF1R activity or down-regulation of expression led to cytotoxicity and induced apoptosis in both imatinib-sensitive and -resistant GIST cells.[54,55] Thus, aberrant expression of IGF1R may be associated with oncogenesis in a subset of GISTs that lack *KIT* or *PDGFRA* mutations.

Strong insulin-like growth factor 1 (IGF-1) expression significantly correlated with higher mitotic index and larger, higher-risk, metastatic, and relapsed GISTs.[56] Strong IGF-2 expression correlated with higher mitotic index and higher-risk GISTs. Increased IGF-1 and -2 expression also was associated with significant worsening of disease-free survival. In the subgroup of patients with resected high-risk GISTs, a better trend in disease-free survival was seen in those with GISTs with negative IGF-1 and -2 expression.

Thus, IGF1R could be used as a possible diagnostic marker in GISTs lacking *KIT* and *PDGFRA* mutations, but this remains investigational. A phase II study has been planned to evaluate the efficacy of an IGF1R inhibitor in adults and pediatric patients with advanced or unresectable wild-type GIST.

Prognostic Significance

The prognostic significance of *KIT* and *PDGFRA* mutations has been examined from the pre-imatinib era.[57,58] Some studies have shown that tumors harboring *KIT* exon 11 deletions are associated with a worse outcome than those with other *KIT* or *PDGFRA* mutant isoforms or no detectable mutation.[59] However, these earlier studies were confounded by the small number of patients and low rate of *KIT*

mutations detected. Other studies have suggested that *KIT* exon 11 mutations can be found in both malignant and benign tumors, the latter group being characterized as either mitotically inactive or incidental (< 1 cm) GISTs.[60,61]

KIT exon 11 mutations are heterogeneous and composed predominantly of in-frame deletions of variable number of amino acids, followed by substitutions and insertions. GISTs with internal tandem duplications in the 3′ end of KIT juxtamembrane domain define a clinicopathologically favorable subset of GISTs.[62] Other studies have shown that deletions affecting codons 557 to 558 are independent prognostic factors for RFS and for predicting the metastatic risk in patients with GISTs.[63] The consequence of these genetic abnormalities in KIT signaling requires further investigation.

However, GISTs with *KIT* exon 9 mutations (1530ins6) seem to be clinically more aggressive than tumors with *KIT* exon 11 mutations.[64] However, a recent study involving a large series of patients with small intestinal GISTs showed no significant difference in the outcome between *KIT* exon 9 or 11 mutants.[11,12] Gastric GISTs with exon 13 mutations are more aggressive than other gastric GISTs, whereas those with exon 17 mutations were not.[52] The behavior of small intestinal GISTs with exon 13 or 17 mutations did not differ from other small intestinal GISTs. In contrast, tumors with *PDGFRA* mutations are less aggressive than those with *KIT* mutations.[65,66]

Dematteo et al.[47] evaluated the relative impact of clinicopathologic factors on recurrence in a large series of patients who underwent surgical resection for primary localized GIST. Specific *KIT* mutations had prognostic significance according to univariate but not multivariate analysis. In particular, patients with *KIT* exon 11 point mutations or insertions had a favorable prognosis, whereas those with *KIT* exon 11 DEL557 or 8 and or *KIT* exon 9 mutations had a poor prognosis. *KIT* exon 11 with DEL557 or 8 in the stomach was associated with a worse prognosis, and a trend was also seen toward worse outcome in small intestine GISTs. No association between *PDGFRA* mutations and recurrence was noted in this study. Thus there is conflicting data on the role of kinase genotyping as part of routine prognostic assessment of a primary GIST; however, certain situations may warrant testing as outlined in Table 2.

Prediction of Response to Imatinib Therapy in Advanced or Metastatic Disease

The presence and status of *KIT* or *PDGFRA* mutations are predictive of response to imatinib therapy in advanced or metastatic GISTs. In randomized clinical trials, the presence of a *KIT* exon 11 mutation was associated with better response, progression-free survival (PFS), and overall survival (OS) rates than *KIT* exon 9 mutant GISTs or wild-type GISTs (Table 3).

In the U.S.-Finnish B2222 phase II trial, patients with *KIT* exon 11 mutations had better partial response, event-free survival, and OS rates than those with *KIT* exon 9 mutations or who had no detectable kinase mutations.[67] Partial response rates for patients with *KIT* exon 11 mutations, *KIT* exon 9 mutations, or no detectable kinase mutations were 83.5%, 48%, and no responses, respectively. Presence of *KIT* exon 11 mutations was the strongest prognostic factor, reducing the risk for death by more than 95%.

In the phase III EORTC-62005 trial, the presence of *KIT* exon 9 mutations was the strongest prognostic factor of risk for progression and death.[68] The risk for progression and death were also increased in patients with no detectable *KIT* or *PDGFRA* mutations. PFS (but not OS) for the exon 9 genotypes in this trial was significantly better in the high-dose imatinib arm (400 mg, twice daily) compared with the standard-dose arm (400 mg, daily), with a 61% reduction in relative risk ($P = .0013$).[69] In addition, the response rate after crossover from 400 mg of imatinib daily to 400 mg twice daily was much higher among patients with *KIT* exon 9 mutations (57%) than among those with *KIT* exon 11 mutations (7%).

The phase III SWOG S0033/CALGB 150105 trial also confirmed the findings from B2222 and EORTC-62005, namely that the *KIT* exon 11 genotype is associated with favorable outcome in patients with advanced GIST compared with *KIT* exon 9 genotype or wild-type GIST.[70] However, the PFS advantage in patients with *KIT* exon 9 mutations treated with high-dose imatinib observed in the EORTC study was not confirmed in the SWOG S0033/CALGB 150105 trial, although evidence showed improved response rates in these patients compared with those treated with 400 mg of imatinib (67% vs. 17%, respectively). The outcome of patients with exon 11 mutation was not influenced by drug dose

Table 2 NCCN GIST Task Force Recommendations for Mutational Analysis

Scenario	Recommendations
Primary disease	Mutational analysis is not routinely recommended at diagnosis because data are insufficient to support its use for improved risk stratification and prognostication of risk for relapse in individual patients. Mutation analysis might be prognostic but should not necessarily guide treatment recommendations. Mutational analysis may be useful in selecting patients for postoperative therapy after complete resection of primary GIST. Consider mutational analysis in selected cases: • To confirm the diagnosis of KIT-positive tumors with atypical morphology or clinical features, or KIT-negative GISTs, including those with *PDGFRA* mutations known to be sensitive to imatinib. • To differentiate GIST from desmoids tumors, weakly KIT-positive high-grade sarcomas, or other neoplasms. • To identify patients at higher risk for recurrence if considering postoperative imatinib therapy for patients with primary resected tumors.
Metastatic or advanced disease	Mutational analysis should be considered for metastatic or advanced disease. Three large randomized studies have shown that *KIT* exon 11 mutations are associated with higher response rates and longer progression-free survival than *KIT* exon 9 mutations. Mutational analysis may not be necessary for gastric GISTs because they rarely harbor exon 9 mutations. It can be considered for gastric GISTs that are unresponsive to imatinib, and for primary sites in which exon 9 mutations are more common (e.g., small bowel). Mutational analysis could have an impact on the dose of imatinib for small bowel GISTs because *KIT* exon 9 mutations are shown to respond better to higher-dose imatinib. Mutational analysis of disease progressive on imatinib is considered investigational, because these mutations are often heterogeneous and no other agents beyond imatinib and sunitinib are approved for metastatic GIST.

in either the EORTC-62005 or the SWOG S0033/CALGB 150105 trials.

Subsequently, data from the EORTC-62005 and SWOG S0033/CALGB 150105 trials were combined in a preplanned meta-analysis. This meta-analysis, which combined data on 1640 patients from these 2 trials, showed a benefit in PFS for patients with *KIT* exon 9 mutations treated with 800 mg of imatinib.[71]

Impact of Mutational Status on Response to Sunitinib

Heinrich et al.[72] recently reported that the clinical activity of sunitinib in imatinib-resistant GISTs is significantly influenced by both primary and secondary mutations in the *KIT* kinase domain (Table 4). Sunitinib induced responses in patients with the 3 most common genotypes: *KIT* exon 9, *KIT* exon 11, and wild-type GIST. Response rates were higher in patients with *KIT* exon 9 mutations than in those with *KIT* exon 11 mutations (58% vs. 34%, respectively). PFS and OS were significantly longer for patients with *KIT* exon 9 mutations or wild-type GIST than for those with *KIT* exon 11 mutations. No clinical benefit was seen for those with *PDGFRA* mutations (exon 12 and 18). Secondary *KIT* mutations in patients resistant to imatinib were clustered in exons 13 and 14 in the ATP binding pocket or in exon 17 in the KIT activation loop. In patients with secondary *KIT* mutations, longer PFS and OS was seen for those with exon 13 or 14 mutations than those with exon 17 or 18 mutations. Additional studies are needed to confirm these findings.

Conclusions

Current data suggest that mutational status has both prognostic significance and impact on response to TKI therapy. However, existing data are only preliminary and insufficient to mandate routine use of mutational analysis for risk stratification and prognostication of risk for relapse. Table 2 provides the NCCN GIST Task Force recommendations for mutational analysis.

Management of Adult Patients With GIST

Initial workup in patients with suspected GIST should include history and physical examination, appropriate imaging of abdomen and pelvis using

Table 3 Relationship Between *KIT* and *PDGFRA* Genotype and Response to Imatinib in Previously Published Clinical Trials

		U.S.-Finnish B2222 Phase II Trial (n = 127)[67]			EORTC-62005 Phase III Trial (n = 377)[69]			SWOGS0033/CALGB150105 Phase III Trial (n = 428)[70]		
Gene	Exon	Objective Response*	Stable Disease	Progressive Disease	Objective Response*	Stable Disease	Progressive Disease	Objective Response*	Stable Disease	Progressive Disease
KIT	9	48%	26%	17%	34%	46.5%	17%	37%	37.5%	9%
	11	83.5%	8%	5%	68%	25%	3%	63%	19%	6%
	13	100%	0	0	67%	33%	NR	40%	20%	20%
	17	50%	0	50%	67%	33%	NR	25%	50%	25%
PDGFRA	12	67%	0	33%	30%	30%	40%	100%	NR	NR
	18	0	0	67%	30%	30%	40%	25%	50%	25%
WT-GIST		0	33%	56%	23%	50%	19%	37%	28%	18%

Abbreviations: CALGB, Cancer and Leukemia Group B; GIST, gastrointestinal stromal tumor; NR, not reported; PDGFRA, platelet derived growth factor receptor alpha; RECIST, Response Evaluation Criteria for Solid Tumors; SWOG, Southwest Oncology Group; WT, wild-type (no mutation *KIT* or *PDGFRA*).
*Objective response: defined as a complete or partial response by RECIST criteria; excludes non-evaluable patients.

CT scan with contrast and/or MRI, endoscopy with or without EUS in selected cases of primary gastric or duodenal mass, EUS, liver function tests (LFTs), complete blood cell counts, and surgical assessment to determine tumor resectability and whether metastatic disease affects this decision.

Patients presenting with an acute abdomen require 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 or abdominal/pelvic CT), and determine stage.

In general, patients should be managed by a multidisciplinary team with expertise in sarcoma or tumors of the gastrointestinal tract. However, referral of patients with early stage or straightforward, uncomplicated metastatic disease to such specialists may not always be essential. All cases should be presented at a tumor board whenever possible. Any 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.

Medical Treatment of Patients With GIST

Determining whether any cytotoxic chemotherapy has meaningful clinical activity in patients with GIST is difficult based on studies published before 2000.[73] Review articles and series of patients with sarcoma treated with various chemotherapy regimens have compiled subsets of patients with advanced gastrointestinal leiomyosarcomas and then assumed that most, if not all, actually represented GIST. Response rates to standard chemotherapy regimens in these series have been poor (0%–27%). However, the true percentage of GISTs in those series is impossible to know.

Other trials, which also included patients with the specific diagnosis of GIST, have reported very low objective response rates (0%–5%).[74–76] In one open-label, randomized, multicenter trial evaluating the activity of imatinib in patients with advanced GIST, none of the patients treated previously with chemotherapy showed an objective response to any of the regimens.[77] Overall data strongly support the hypothesis that cytotoxic chemotherapy is generally not useful for managing GIST. There is universal agreement that chemotherapy should not be used in patients with GIST. The median survival for patients who are treated with cytotoxic chemotherapy is generally less than 2 years (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 KIT, the leukemia-specific BCR-ABL chimera, and PDGFRA. In laboratory studies, imatinib inhibited proliferation of leukemic cells expressing BCR-ABL, and both leukemia and GIST cells harboring activated KIT.[78–81]

Table 4 Response to Sunitinib by Primary and Secondary Tumor Genotype

Primary Mutation (n = 77)		Secondary Mutation (n = 65)	
Mutation	Clinical Benefit*	Mutation	Clinical Benefit*
		None	62%
KIT exon 9	58%	*KIT* exon 13	100%
		KIT exon 17	0
		None	10%
KIT exon 11	34%	*KIT* exon 13 or 14	59%
		KIT exon 17 or 18	10%
KIT exon 13	100%	*KIT* exon 17	100%
PDGFRA exon 12	0	*PDGFRA* exon 18	0
PDGFRA exon 18	0	None	0
No *KIT*/ *PDGFRA*	56%	None	50%

Abbreviations: PDGFRA, platelet-derived growth factor receptor alpha; RECIST, Response Evaluation Criteria for Solid Tumors.
*Defined as response or stable disease for 6 months or more according to RECIST.
Data from Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26:5352–5359.

GISTs are known to be associated with constitutive activation of the KIT receptor.[26] Most GISTs have *KIT* mutations, which lead to structural mutant isoforms of *KIT* that are uncontrollably active and contribute to oncogenic signaling,[60] and both mutant and nonmutant forms of *KIT* can be inhibited by imatinib. Therefore, the clinical development of imatinib for treating 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.[82] This single-patient experience rapidly expanded the global development of imatinib as therapy for patients with advanced GIST.

Based on experience using imatinib for patients with chronic myelogenous leukemia (CML), the doses considered safe were used in the B2222 trial.[77] This trial randomly assigned patients with metastatic or unresectable GIST to 2 daily doses of imatinib, either 400 or 600 mg. Imatinib induced a sustained objective response in more than half of the patients. The early results from this study were sufficiently positive and used to support the registration of imatinib as a safe and effective therapy in GIST. In February 2002, the FDA approved imatinib for treating patients with KIT-positive unresectable and/or metastatic GIST.[83] 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 yields complete responses in fewer than 5% of patients with GIST. Mature data showed that 68% of patients had an objective response and 15.6% of patients had durable stable disease for greater than one year.[84] Equivalent response rates were shown 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 dose levels.[77]

Dose Optimization: Just after the B2222 study began, the EORTC Soft Tissue and Bone Sarcoma Group began a formal phase I dose-ranging study of imatinib in patients with metastatic or unresectable GIST.[84] Although designed to include any histologic subtype of sarcoma, this study ultimately accrued 36 patients with GIST from a total of 40. 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). A therapeutic effect was noted at each dose level of imatinib. The maximum tolerated dose was judged to be 400 mg twice daily, because 500 mg twice daily led to unacceptably severe edema, malaise, and nausea and vomiting. Overall objective responses were seen in 69% of patients; this rate is remarkably consistent with the mature observations from the B2222 trial.[84] By 18 months follow-up, 66% of patients remained in the study and were progression-free. To expand on these observations, the EORTC Soft Tissue and Bone Sarcoma Group performed a phase II trial using imatinib at the maximum tolerated dose of 800 mg/d.[86] Again, the results were highly concordant with previous results showing a 71% objective response rate, with an additional 18% of patients showing prolonged stable disease. At 1-year follow-up, 73% of the patients remained progression-free.

What is the optimal dose of imatinib for patients with metastatic or unresectable GIST? Two separate

phase III trials (SWOG S0033/CALGB 150105[87] and EORTC 62005[88]) have assessed the efficacy of imatinib mesylate at 2 initial dose levels. Each one of these trials compared imatinib given at 2 different doses: 400 mg once or twice (800 mg) per day. Both studies showed equivalent response rates and OS for both dose levels. Higher dose of imatinib was associated with more side effects than the lower dose in both studies.

The EORTC 62005 trial randomly assigned 946 patients to receive imatinib at either 400 or 800 mg/d,[88] with time-to-disease progression (TTP) the primary end point. Results showed an earlier TTP for patients receiving 400 mg daily. At 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]). At a median follow-up of 760 days, 56% of patients randomized to imatinib once daily had experienced disease progression compared with 50% of those who were assigned to treatment twice daily (estimated hazard ratio, 0.82; $P = .026$). Imatinib was fairly well tolerated in both arms. More dose reductions and treatment interruptions were observed with higher-dose imatinib. Complete response, partial response, and stable disease were observed in 5%, 47%, and 32% of patients, respectively, with no difference among groups.[88]

Results of this study showed that a 400 mg/d dose of imatinib led to the same median OS as the 800 mg/d dose; thus, the suggested starting dose of imatinib is 400 mg/d. Imatinib could them be increased to 800 mg/d if patients showed signs of progression. However, recent studies suggest that patients with the *KIT* exon 9 mutations may benefit from the 800-mg dose of imatinib.[69]

The SWOG S0033/CALGB 150105 trial reported nearly identical response rates (40% and 42%, respectively), PFS (18 and 20 months), and OS (55 and 51 months) for the standard- and high-dose groups, respectively.[87] Median follow-up was 4.5 years. More grade 3, 4, and 5 toxicities were noted in the high-dose arm. After progression on standard-dose imatinib, 33% of patients who crossed over to high-dose imatinib experienced either an objective response or stable disease. This finding was consistent with the results from the EORTC study, in which 133 (55%) patients who progressed on low-dose imatinib crossed over to high-dose imatinib. Subsequently, 2% of patients experienced partial response and 27% stable disease.[89] However, the small advantage in PFS observed for high-dose imatinib in the EORTC 62005 trial was not corroborated by the SWOG S0033/CALGB 150105 trial. The reason for the discrepancy in PFS results is not completely understood.

In the EORTC 62005 study, tumor genotype had major prognostic significance for PFS and OS. Patients whose tumors encoded a *KIT* exon 9 mutation were found to have a significantly superior PFS ($P = .0013$) when treated with high-dose imatinib.[69] In the SWOG S0033 study, patients whose tumor harbored a *KIT* exon 9 mutation had superior response rates when treated with 800 mg of imatinib but no difference in survival when compared with those treated with 400 mg/d.[70]

The results of the meta-analysis of 1640 patients from both trials showed that treatment with high-dose imatinib (400 mg, twice daily) results in a small but significant PFS advantage compared with standard-dose imatinib (400 mg/d). Because of the crossover design, it is not surprising that no OS advantage was seen, in that the patients randomized to 400 mg/d crossed over to 800 mg at progression.[71] Statistically significant evidence shows that the relative benefit of high-dose imatinib depends on the mutation type, and that starting imatinib at a daily dose of 800 mg will prolong median PFS in patients with *KIT* exon 9 mutations. However, no evidence shows that this will improve survival.

Potential Drug Interactions With Imatinib Mesylate: Imatinib is extensively metabolized by the cytochrome P450 (CYP) enzyme system. CYP3A4 in the liver is the main enzyme responsible for imatinib metabolism, and drugs that potentially interact with CYP3A4 will alter the plasma level of imatinib.

CYP3A4 inhibitors such as ketoconazole, itraconazole, grapefruit juice, or pomegranate juice increase plasma levels of imatinib. In these cases, dose adjustment of imatinib may be necessary if drug-associated toxicities occur because of transiently high imatinib levels and another medication that does not affect CYP3A4 levels cannot be substituted.

CYP3A4 inducers decrease the plasma concentration of imatinib. Rifampin increased the oral clearance of imatinib 3.8-fold and reduced the plasma concentration by 70%. 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, phenytoin, or St. John's wort.

Imatinib is a competitive inhibitor of CYP3A4 and thus has the potential to increase the concentration of drugs such as warfarin and midazolam, as well as other drugs that are metabolized by CYP450 isoenzymes. Dose adjustment of medications may be necessary. If substitution is not possible, particular caution is recommended when administering imatinib with CYP3A4 substrates.

Imatinib Plasma Levels: Free plasma levels of imatinib have been shown to correlate with the frequency of severe adverse events.[90,91] The occurrence of side effects was more frequent at higher imatinib exposure levels. However, considerable interpatient variability was seen: plasma imatinib area under the curve (AUC) levels were widely distributed in patients who had no significant side effects than those who did. Higher free imatinib AUC also predicted a higher probability of therapeutic response when taking into account tumor KIT genotype, with the strongest association in patients with exon 9 mutations or wild-type KIT.

The correlation of imatinib trough plasma levels with clinical outcome was evaluated in a subgroup of patients (n = 73) from the B2222 study, for whom pharmacokinetic data were available at day 1 and at steady-state, day 29.[92] Patients were grouped into quartiles according to imatinib trough concentration. Although the imatinib plasma trough concentration showed a high interpatient variability, clinical outcomes were evaluated by steady-state imatinib plasma trough level quartile. The median TTP was 11.3 months for patients in the lowest imatinib exposure quartile (Q1, < 1100 ng/mL) compared with more than 30 months for Q2 to Q4 (P = .0029). Overall objective benefit rate (complete response plus partial response plus stable disease) was also inferior in Q1 patients. Among patients whose GIST had a *KIT* exon 11 mutation (n = 39), the overall objective benefit rate was 67% for those in Q1 versus 100% for all others (P = .001). These findings suggest that a minimal plasma threshold may be necessary to achieve and maintain clinical response. Patients with *KIT* exon 11 mutations exhibited improved clinical outcomes with imatinib trough levels greater than 1100 ng/mL. Too few patients had *KIT* exon 9 mutations to draw any conclusions.

Conclusions

- Retrospective data suggest that imatinib trough plasma levels correlate with PFS in patients with metastatic GIST.
- Currently, whether patient management based on imatinib trough levels improves patient outcome is unknown, and no data suggest that the drug levels impact management of patients who experience resistance.
- Therefore, the task force panel does not recommend routine imatinib plasma level testing except in the setting of a clinical trial. Monitoring imatinib plasma levels may be useful in determining patient adherence to therapy, after introduction of new drugs that interact with imatinib, and in patients who develop unusually excessive toxicity to standard-dose imatinib.
- Optimal level of drug exposure, which varies depending on the characteristics of the patient and genotype, has not been confirmed in prospective studies. SARC-019 (www.sarctrials.org) is a randomized phase III study designed to evaluate whether dose escalation of imatinib improves PFS in patients with metastatic GIST with low imatinib plasma trough levels (< 1100 ng/mL).

Management of Toxicities Caused by Imatinib Mesylate: Fluid retention, diarrhea, nausea, fatigue, muscle cramps, abdominal pain, and rash are the most common nonhematologic toxicities reported in clinical trials.[93] The side-effect profile may improve with prolonged therapy. Dyspepsia and gastrointestinal side effects can be mitigated by taking the drug with food, which does not seem to decrease absorption. Dyspepsia can also 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 (e.g., lung toxicity, LFT abnormalities, low blood counts, gastrointestinal bleeding) have rarely been reported and often improve after imatinib is withheld. LFT abnormalities are seen in fewer than 5% of patients. Recent reports suggest that concomitant administration of steroids and imatinib in patients with LFT abnormalities may allow patients to receive therapy.[94] If life-threatening side effects occur with imatinib that cannot be managed with maximum supportive treatment, sunitinib should be considered.

Patients with large bulky tumors may have a 5% risk for tumor hemorrhage not associated with thrombocytopenia. These patients should be moni-

tored 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 temporary withholding of imatinib until hemoglobin has stabilized, or transfusion if patients are symptomatic. Surgical intervention should be considered if bleeding does not resolve. Emergency surgery may also be required in patients who have other complications (bowel obstruction, abscess). Patients on long-term imatinib may develop anemia that may be multifactorial (iron deficiency, chronic disease, B_{12} deficiency, folate deficiency, suppression of hematopoiesis by the TKI).

Leukopenia is rare and imatinib has rarely been associated with neutropenic fever. In patients with an absolute neutrophil count less than 1000 cells/mm^3, withholding imatinib leads to recovery within several days. Reinitiation of imatinib without dose reduction is recommended, often without recurrence of the leukopenia. If a patient continues to experience significant leukopenia, imatinib dose should be decreased and/or granulocyte growth factors could be considered. Rare cases of myelodysplastic syndrome and acute myeloid leukemias have been observed.[95] Rarely, severe myelosuppression may occur sporadically, even in patients who were previously stable with chronic dosing; continued monitoring is medically necessary.

Fluid retention is a common symptom in most patients. Edema can be associated with the development of pleural effusions and ascites, and 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. Dose reduction is not necessary as long as other supportive measures can control the edema.

Patients who develop a 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, calcium supplements, electrolyte replacement beverages, tonic water, and possibly using muscle relaxants. Rarely patients with muscle cramping also have hypophosphatemia and hyperphosphaturia. These are seen in patients with both GIST and CML and seem to resolve on discontinuation of imatinib. The ultimate effect of imatinib on bone metabolism is unclear, because no apparent increase in fracture risk occurs while on the medication; however, monitoring of serum calcium, phosphate, and vitamin D levels may be useful.[96,97]

A recent report described congestive heart failure (CHF) as a potential side effect of imatinib.[98] However, clinical trial data have not documented a significant incidence of severe cardiac dysfunction. In a retrospective analysis of 219 consecutive patients treated with imatinib, grade 3 or 4 cardiotoxic adverse events (mostly edema or effusions) occurred in 8.2% of patients, were manageable with medical therapy, and infrequently required dose reduction or discontinuation of imatinib.[99] Arrhythmias, acute coronary syndromes, or heart failure were uncommon, occurring in fewer than 1% of treated patients. The authors concluded that imatinib is an uncommon cause of cardiotoxicity, and that the cardiovascular adverse events are manageable when recognized and treated. The authors of this study therefore recommend these patients be treated for risk factors of cardiovascular disease according to American Heart Association guidelines for prevention and treatment of heart failure. 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.

Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib. Thyroid stimulating hormone (TSH) levels should be closely monitored in these patients.

TKI therapy–associated depression has been reported in 6 patients with metastatic GIST and 1 patient in the postoperative setting.[100] Although symptoms improved with dose reduction or interruption, response to antidepression medications was not consistent. Further studies are needed to evaluate the incidence and risk factors of depression in patients treated with imatinib. Patients should undergo routine screening for depressive symptoms and suicidal ideations.

Imatinib Mesylate Resistance: Imatinib benefits most patients with advanced GIST; however, some patients are resistant to the drug. Imatinib

fails in some patients almost immediately after initiation (primary resistance). Other patients initially show response or disease stabilization but later develop progressive disease while on medication (secondary resistance).

Primary resistance is defined as evidence of clinical progression developing during the first 6 months of imatinib therapy and is most commonly seen in patients with *KIT* exon 9, *PDGFRA* exon 18, or wild-type GIST.[101] Secondary resistance appears to be related to the acquisition of new kinase mutations.[102] Patients taking imatinib for more than 6 months with an initial response who then experience progression are categorized as having secondary resistance.

Several series have supported a link between newly acquired kinase mutations and late resistance to imatinib.[103–106] The newly acquired kinase mutations are always located in exons encoding tyrosine kinase domain (exon 13, 14, and 17). The acquired mutations were not random, and in vitro studies confirmed that they conferred resistance to imatinib through either directly altering the ATP binding pocket (V654A and T6701 mutations) or interfering with access to this pocket through conformational changes in the activation loop of the kinase domain (D820Y and N822K mutations). 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 of the target receptor, but this seems to be uncommon.

B2222 is the largest trial assessing molecular correlates of both types of imatinib resistance in advanced GIST.[106] Of 147 patients who entered the original trial, 92 had documented imatinib resistance; 43 of these patients consented to an assessment of tumor samples obtained before or during the first week of therapy compared with samples taken at clinical resistance. The cytoplasmic domains of *KIT* and *PDGFRA* were screened for mutations, and activation of KIT and PDGFRA and downstream signaling pathways, including mammalian target of rapamycin (mTOR), AKT, and MAPK, were evaluated.

Based on in vitro studies, the mutant isoforms of KIT commonly identified in primary GISTs are fully sensitive to imatinib.[78–80] In contrast, the most common GIST-associated mutation in *PDGFRA (D842V)* confers complete resistance to imatinib. 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 reactivation of upstream and downstream effectors.

Primary resistance was most commonly seen in patients with *KIT* exon 9 or *PDGFRA* exon 18 (D842V) mutations, or with wild-type for both genes. Secondary resistance was primarily seen in patients who had primary 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 mutation (usually in *KIT*, but at least once in *PDGFRA*). The molecular mechanisms conferring the primary resistance in GISTs with *KIT* exon 9 mutations are not well understood. The authors speculated that some *KIT* exon 9 mutant GISTs have an alternative mechanism of KIT activation not requiring enzymatic triggering.[106] 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.

Recent reports have shown that secondary mutations are expressed exclusively in tumor nodules undergoing progression as a consequence of clonal evolution,[107] and the mutations are substantially heterogeneous among patients with clinically progressing GISTs.[108] KIT resistance mutations were not found in wild-type GISTs or *KIT*-mutant GISTs with unusual morphology, with or without the loss of KIT expression.[108] Newly acquired mutations in the same patient may differ within a particular tumor nodule and metastatic site (so-called "polyclonal resistance"). GISTs with secondary exon 14 mutations (T670I) were more aggressive, with earlier metastasis and shorter PFS, whereas slow-progressing tumors might acquire secondary mutations in exon 13 or 17 after prolonged treatment with imatinib.[107]

Drug-induced upregulation of ATP-binding cassette (ABC) proteins (ABCG2 and ABCB1) has been described as a novel mechanism of acquired

pharmacokinetic drug resistance.[109,110] Drug-induced overexpression was much more pronounced for ABCG2 than for ABCB1.[110] Because imatinib has also been shown to be a substrate for these drug transporters, overexpression of ABCG2 and ABCB1 might decrease the intracellular concentration of imatinib. This novel mechanism of resistance has important implications for using imatinib at different dose levels to improve clinical outcome. However, whether imatinib exposure will enhance expression of ABC transporters must be confirmed in clinical studies.

Imatinib resistance can be managed by increasing the dose to 800 mg/d; however, the median TTP is approximately 11 weeks. Alternatively, patients can be switched directly to sunitinib from low-dose imatinib (400 mg/d). Currently, which management scheme will yield the best outcomes is unclear; some imatinib-resistant disease will not respond to sunitinib.

Sunitinib Malate

Sunitinib malate is a receptor 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-related tyrosine kinase 3, colony-stimulating factor (CSF)-1R, and RET. Thus, sunitinib possesses potential antiangiogenic activity in addition to antitumor action related to receptor tyrosine kinase inhibition TKI. Preclinically, sunitinib inhibits some KIT mutant isoforms that are resistant to imatinib.

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 a placebo in a double-blind phase III study involving patients with advanced GIST who were intolerant or refractory to imatinib (n = 312). Patients were randomized (2:1) to either sunitinib (50 mg/d on an intermittent dosing schedule of 4 weeks on treatment, followed by 2 weeks off) or placebo.[111] The trial was unblinded early, when a planned interim analysis showed that its primary end point—TTP based on 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 at 26 weeks and OS were better for patients treated with sunitinib. Interestingly, these results were obtained despite a low objective response rate with sunitinib (7% partial response).

These results suggest that, as with imatinib, the achievement of stable disease on sunitinib suffices to extend survival. The phase III trial reported treatment-related serious adverse events in 20% of patients, including fatigue, diarrhea, hand–foot syndrome (HFS), hypertension, and myelosuppression. Data from this study and others suggest that patients treated with sunitinib may develop hypothyroidism, which should be closely monitored in those taking it long-term. Sunitinib also showed acceptable and predictable safety with long-term treatment. In January 2006, the FDA approved second-line use of sunitinib in patients with advanced GIST. The recent long-term analysis of this study confirmed the long-term OS benefit provided by sunitinib compared with placebo in patients with imatinib-resistant or -intolerant GIST.[112]

Continuous Daily Dosing of Sunitinib: The safety and efficacy of sunitinib on a continuous daily dosing schedule was evaluated in an open-label, multicenter, randomized phase II study in patients with advanced GIST after imatinib failure.[113] Patients were randomized (1:1) to receive continuous daily sunitinib (37.5 mg/d) in either the morning or the evening for 28 days (1 cycle). The primary end point was the clinical benefit rate defined as the percentage of patients with complete responses, partial responses, or stable disease for 24 weeks or more based on RECIST.

The overall clinical benefit rate was 53% (13% experienced partial responses and 40% stable disease). Median PFS and OS were 34 and 107 weeks, respectively. The most commonly reported treatment-related adverse events (diarrhea, fatigue, and nausea) were consistent with those known to be associated with sunitinib intermittent dosing. Treatment-related hypertension was experienced by 28% of patients and was successfully managed with or without antihypertensive medication. Treatment-related hypothyroidism was reported in 12% of patients (vs. 13% in long-term analysis of the phase III study with intermittent dosing) and was manageable with thyroid hormone replacement therapy. Both of these adverse events have also been associated with the long-term use of sunitinib on intermittent dosing. The results of this study suggest that continuous daily dosing appears to be an effective alternative dosing strategy with acceptable safety for patients with imatinib-resistant or -intolerant GIST.

Potential Drug Interactions With Sunitinib Malate: Sunitinib is also metabolized by CYP3A4. Therefore, drugs that potentially interact with CYP3A4 alter the plasma level of sunitinib.

Concurrent administration of sunitinib with CYP3A4 inhibitors, such as ketoconazole, resulted in a 51% increase in the combined AUC of sunitinib and its active metabolite. Co-administration of sunitinib with strong CYP3A4 inhibitors should be avoided. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. If sunitinib must be co-administered with a strong CYP3A4 inhibitor, a dose reduction to a minimum of 37.5 mg/d should be considered. Grapefruit may also increase sunitinib concentrations.

Concurrent administration of sunitinib with CYP3A4 inducers, such as rifampin, resulted in a 46% reduction in the combined AUC of sunitinib and its active metabolite. Co-administration of sunitinib with CYP3A4 inducers should be avoided because it may result in subtherapeutic sunitinib levels. If sunitinib must be coadministered with a CYP3A4 inducer, the dose should be increased to a maximum of 87.5 mg with careful monitoring for toxicity.

Management of Toxicities Caused by Sunitinib Malate: Sunitinib-related toxicities can often 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.

Sunitinib should be discontinued if it causes profound neutropenia (absolute neutrophil count ≤ 1000 cells/mm^3). Recurrent episodes of neutropenia require dose reductions to 37.5 or 25 mg/d, depending on the frequency. Anemia, if acute, should be managed with interruption of sunitinib and evaluation for a source of bleeding; sunitinib can be resumed at the initial dose. Patients may experience gastrointestinal symptoms, such as nausea, vomiting, or diarrhea. However, in the randomized phase III trial, the incidence of nausea, vomiting, and abdominal pain were equivalent for patients taking 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. Some patients also note skin and hair discoloration, which are self-limited and resolve during the rest period or after drug cessation. Some patients also notice a change in urine color. Other side effects noted in initial trials include profound increases in amylase and lipase levels, although these effects are asymptomatic and therefore no therapy is indicated.

Hypertension is a common side effect reported in clinical trials, because sunitinib targets VEGFR.[114] The risk varies with the tumor type; results of a recent meta-analysis showed higher risk (25.9%) in patients with renal cell carcinoma (RCC) than in those with non-RCC (19.6%).[115] The relative risks for developing hypertension were 8.2% and 1.42% in patients with RCC and GIST, respectively. Patients should monitor their blood pressure closely, and those who experience an increase should be treated with antihypertensives.[116] The task force panel does not recommend a particular antihypertensive agent because controlled studies addressing the subject are lacking. Treatment with antihypertensive drugs should be individualized.

A retrospective analysis reviewed all cardiovascular events (including left ventricular dysfunction and blood pressure) in 75 patients with imatinib-resistant, metastatic GISTs who had been enrolled in a phase I/II trial investigating the efficacy of sunitinib.[117] Among these, 8 (11%) experienced a cardiovascular event, CHF was recorded in 6 (8%), 10 of 36 (28%) treated with the approved dose had absolute reductions in the left ventricular ejection fraction (LVEF) of at least 10%, and 7 of 36 (19%) had LVEF reductions of 15% or more. Sunitinib induced increases in mean systolic and diastolic blood pressure, and 35 (47%) individuals developed hypertension (> 150/100 mmHg). CHF and left ventricular dysfunction generally responded to withholding of sunitinib and institution of medical management.

Patients with a history of coronary artery disease or cardiac risk factors should be closely monitored for signs and symptoms of possible CHF, hypertension, and LVEF reduction. Patients presenting with significant fluid retention should be evaluated carefully and those with CHF should discontinue suni-

tinib. Sunitinib should be used with caution in patients with a history of QT interval prolongation and management similar be to that for any other drug that might induce a QT prolongation. Echocardiogram at baseline and periodically thereafter should be considered for patients who are at high risk for a depressed ejection fraction. Electrolyte levels (calcium, magnesium, potassium) should be monitored and abnormalities corrected to within normal limits with supplements.[118] Sunitinib should be withheld if QTc is greater than 500 ms or if QTc increases 60 ms from baseline. Concomitant treatment with strong CYP3A4 inhibitors should be used with caution and dose reduction should be considered.

Recent reports also highlighted the development of hypothyroidism in patients receiving sunitinib.[119] In a prospective, observational cohort study, abnormal serum TSH concentrations were documented in 62% of patients and risk for hypothyroidism increased with duration of therapy.[120] Routine monitoring (every 3–6 months) of TSH is indicated. If hypothyroidism is suggested, patients should undergo thyroid hormone replacement therapy.

Sunitinib is associated with a significant risk for developing HFS.[121] Early detection and proper management are vital during treatment. HFS can be prevented with routine application of emollient lotions. If significant, interruption of therapy is indicated; if severe, dose reduction should be considered. Further understanding of its pathogenesis might lead to early prevention and optimal drug dosing.

Sunitinib Malate Resistance: Sunitinib is an inhibitor of multiple receptor tyrosine kinases, including KIT, PDGFR, and VEGFR. It is very sensitive to ATP-binding pocket mutation (V654A) and the gatekeeper mutation T670I that confers resistance to imatinib. However, certain imatinib-resistant mutations including D816H/V are also resistant to sunitinib. Gajiwala et al.[122] suggested that sunitinib resistance exhibited by D816H and D816V proteins could be caused by a shift in equilibrium toward the active kinase conformation and an accelerated autophosphorylation of these mutants, and that the conversion from the drug-favorable unactivated kinase conformation to the drug-insensitive active form in the presence of physiologic ATP concentrations results in loss of inhibition. Guo et al. reported that sunitinib-resistant tumor samples from patients who developed resistance after at least 1 year of radiographic response showed increased cellularity, high mitotic activity, and strong expression of KIT according to immunohistochemistry. Secondary mutations identified were restricted to the KIT activation loop (D820Y, D820E, N822K), as opposed to those observed in imatinib-resistant tumors. In vitro screening studies showed that these mutations were sensitive to dasatinib and nilotinib.

However, comprehensive molecular studies investigating the mechanisms of resistance are limited because of the low number of patients who are surgical candidates after failure of 2 TKI therapies. Nevertheless, the findings highlight new mechanisms of resistance to second-generation TKIs and provide a rationale for developing alternating therapeutic options for patients resistant to sunitinib therapy.

Investigational Agents

Options are limited for patients progressing on imatinib and sunitinib. Kao et al.[124] recently reported that the addition of sunitinib to image-guided radiotherapy is tolerable in patients with oligometastasis, without potentiating toxicity. An ongoing multiinstitutional phase II trial is evaluating the combination of sunitinib and radiation therapy (50 Gy). Second-generation TKIs, such as sorafenib, dasatinib, and nilotinib, have shown activity in patients with imatinib- and sunitinib-resistant GIST.

Sorafenib inhibits KIT, VEGFR, PDGFRβ, and other kinases, and is approved for the treatment of RCC and hepatocellular carcinoma. Preliminary results of a multicenter phase II study from the University of Chicago Phase II Consortium showed that sorafenib induced partial response in 13% of patients and 58% experienced stable disease when used as third-line therapy in patients with unresectable, KITpositive GIST who experienced progression on imatinib and sunitinib.[125] Median PFS and OS were 5.3 and 13.0 months, respectively. Estimated 1-year OS was 62%. In another retrospective analysis, sorafenib displayed significant clinical activity as a fourth-line therapy in patients with GIST refractory to imatinib, sunitinib, and nilotinib.[126] Partial response and stable disease were seen in 21% and 42% of patients, respectively. Median PFS and OS were 5.0 and 8.1 months, respectively. A phase III randomized study from Cancer and Leukemia Group B will reportedly examine sorafenib versus imatinib in patients resistant to imatinib and sunitinib, and participation in this study is recommended.

Dasatinib inhibits BCR-ABL, SRC family kinases, KIT, EPHA2, and PDGFRβ and is approved for the treatment of adults with chronic-, accelerated-, or blast-phase CML resistant or intolerant to imatinib. Dasatinib is active against imatinib-resistant activation loop mutants (D816) and also efficiently inhibits the *PDGFRA* D842V isoform, compared with sorafenib and nilotinib.[127,128] In a phase I dose-escalation study, 3 of 19 patients with refractory GIST had stable disease, which lasted for more than 3 months in 1 patients.[129] Sarcoma Alliance for Research through Collaboration (SARC) is completing a phase II multi-arm study of dasatinib in imatinib- and sunitinib-refractory GIST.

Nilotinib inhibits BCR-ABL, PDGFR, KIT, CSF-1R, and DDR and is approved for the treatment of chronic- and accelerated-phase CML in patients resistant or intolerant to prior therapy, including imatinib. A phase I dose-escalation study showed that nilotinib (400 mg, twice a day), alone or in combination with imatinib (400 mg, once daily), was well tolerated and active in patients with imatinib-resistant GIST,[130] with 38 patients experiencing stable disease and 2 partial response. Median PFS was 134 days for the entire group. In a retrospective analysis, nilotinib resulted in 10% response and 37% disease control rates in patients for whom prior treatment with imatinib and sunitinib failed.[131] Median PFS and OS were 12 and 34 weeks, respectively. The efficacy and safety of nilotinib as third-line therapy for GIST are being studied in an ongoing phase III trial.

Although the efficacy of second-generation TKIs must be confirmed in large prospective clinical trials, preliminary data show that sorafenib and nilotinib resulted in improved performance status and/or symptoms in patients pretreated with imatinib and sunitinib. Other targeted therapies, such as mTOR and heat shock protein 90 (HSP90) inhibitors, have been evaluated in clinical trials, including a phase III study of HSP90 inhibitor IPI-504, but results have not achieved the level of activity to recommend it as a treatment option for patients who are no longer experiencing benefit from imatinib or sunitinib.

Management of Metastatic or Unresectable Disease

Based on available data from the randomized phase III studies and meta-analysis, the task force panel agreed that the appropriate initial dose of imatinib is 400 mg/d for patients with metastatic or unresectable disease. Some members of the task force recommend 800 mg/d for patients with documented exon 9 mutations. This is a category 2B recommendation.

Dose escalation (600–800 mg, as tolerated) may be appropriate if disease progression occurs at 400 mg/d, after careful review of appropriate imaging studies to document progressive disease. Patients with unresectable disease progressing on higher-dose imatinib should be managed as described in the next section. Resection should only be considered in patients with localized progression.

Management of Progressive Disease

The task force recommends that patients experiencing progression be referred to a center specializing in GIST. Dose escalation (600–800 mg, as tolerated) is one option for patients experiencing progression on standard-dose imatinib. However, a dose increase is not likely to help many patients who experience progression within 2 months after initiation of imatinib. Before dose escalation, all clinical and radiologic data, including lesion density on CT, should be taken into account. PET may indicate imatinib activity after 2 to 4 weeks of therapy when rapid readout of activity is necessary. Progression may be determined by CT or MRI with clinical interpretation; PET may be used to clarify whether CT or MRI is ambiguous.

For patients with limited progression, options include continuing imatinib at the same dose or increasing the dose as tolerated; 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 (0–2), options include dose escalation of imatinib (600–800 mg, as tolerated), switching to sunitinib, or enrollment in clinical trials.

The task force panel recommends that patient compliance to imatinib therapy at standard dose should be assessed before altering the dose of imatinib or switching to sunitinib. If the patient is no longer experiencing clinical benefit from imatinib or sunitinib, based on the limited data available from the preliminary studies, the task force panel believed that sorafenib, nilotinib, or dasatinib could be considered. 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 no longer receiving clinical benefit from cur-

rent TKI therapy should be evaluated for entry onto a clinical trial testing other novel approaches to controlling GIST.

Continuation of TKI Therapy and Best Supportive Care: The prospective multicenter randomized phase III study (BFR14) showed that in patients with advanced disease who had stable or responsive disease on imatinib, discontinuation of therapy after 1 or 3 years resulted in significant decreases in PFS.[132] Response was re-induced in 93% of patients after imatinib reintroduction. In the setting of active disease progression on TKI therapy, discontinuing therapy may lead to accelerated tumor growth by withdrawing control of sensitive clones of the disease (even if limited disease sites have been shown to exhibit resistance to therapy and hence to progress more rapidly). Therefore, in the absence of a clinical trial testing a different hypothesis, the task force panel strongly feels that continuing TKI therapy should be an essential component of best supportive care for patients with progressive disease.

Recent data reported by Fumagalli et al.[133] support rechallenging patients with imatinib after standard and investigational therapeutic options fail; 17 patients with advanced GIST resistant to second- or third-line therapy were rechallenged with imatinib. All but 5 patients were treated at 800 mg/d. Interestingly, 2 patients experienced a partial response and 5 stable disease. Median treatment duration was 105 days and the therapy was tolerated. In summary, rechallenge with imatinib is feasible and can result in disease activity.

The panel recommends that patients with limited progression of GIST no longer experiencing benefit from current TKI therapy should be given another trial of previously tolerated and effective therapy for as long as they can tolerate. Finally, the decision to discontinue therapy depends on various factors, such as the rate of progression, tolerability of therapy, patient preference, goals of care, quality of life, and risk/benefit assessment.

Issues of Patient Adherence to TKI Therapy: Factors affecting adherence to a prescribed regimen include depression, asymptomatic disease, medication side effects, infrequent follow-up, complexity of treatment, and cost of medication.[134] Treatment interruptions and nonadherence might lead to undesirable clinical outcomes. The results of the Adherence Assessment with Glivec: Indicators and Outcomes (ADAGIO) study showed that patients with suboptimal response had significantly higher mean percentages of imatinib not taken (23.2%) than did those with optimal response (7.3%), and that nonadherence was associated with poorer response to imatinib.[135]

The prescribed daily dosing of TKI therapy must be maintained to achieve optimal clinical outcome. However, short interruptions for 1 to 2 weeks, when medically necessary, have not been shown to impact negatively on the control of disease or other outcomes. No apparent difference was seen in sunitinib activity between the intermittent and continuous daily dosing schedules.[113] In the imatinib discontinuation study, interruption of imatinib did not promote resistance.[136] Older people, patients who are taking multiple medications (polypharmacy), and those with asymptomatic disease, especially those on postoperative imatinib, are at a higher risk for noncompliance.

Identifying patients who could be at risk, emphasizing the value of therapy and the effect of adherence, discussing physical or financial barriers to them taking the drug, adequate and appropriate management of side effects, and scheduling appropriate follow-ups to review side effects and barriers are some strategies that could be used by health care providers to improve patient adherence to therapy.

TKI therapy is standard care for patients with GIST. However, the optimal duration of treatment is not known. The task force panel strongly recommends that patients continue taking TKI therapy as long as they are experiencing clinical benefit (response or stable disease).

Principles of Surgery for GIST and the Need for Multidisciplinary Management

Primary Disease

Surgery remains the mainstay of therapy for patients with primary GIST with no evidence of metastasis, and should be initial therapy if the tumor is technically resectable and associated with acceptable risk for morbidity.

Because it is an uncommon disease, GIST may not be considered in the differential diagnosis of a patient with a 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 it may not be necessary and is associated with slight

risks. GISTs may be soft and fragile, and biopsy may cause hemorrhage and increase the risk for 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.

GISTs should be handled with care to avoid tumor rupture. If the pseudocapsule is torn, bleeding and tumor rupture may ensue. 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; the rectovaginal or -vesical location; and the liver, to identify metastasis.

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, requiring an en bloc resection of adjacent tissue. 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.[137]

The value of negative microscopic margins 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). No evidence shows that patients who have undergone complete resection of all macroscopic disease but have microscopically positive margins require re-excision. The multidisciplinary care team should carefully consider the possible risks and benefits of re-excision, watchful waiting, or postoperative imatinib. If the marginal area can be identified on re-exploration, then a wider resection can be considered if technically feasible without significant morbidity.

Some patients 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 these patients may be spared radical resection even after experiencing a partial response to preoperative imatinib.

Survival after surgery alone for GIST is favorable when compared with other intra-abdominal sarcomas. At MSKCC, 200 patients with likely GIST were treated between 1983 and 1997 and followed up prospectively.[16] Although these patients were not confirmed to have *KIT* or *PDGFRA* mutation or expression, most 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. Other investigators have reported similar survival results after resection of primary GIST.[138–140]

All GISTs 2 cm or larger should be resected. Although a 2-cm cutoff is somewhat arbitrary, recent data suggest that it is reasonable.[13] However, the management of incidentally encountered GISTs smaller than 2 cm remains controversial. The natural history of these small tumors, including growth rate and metastatic potential, remains unknown. A recent study by Kawanowa et al.[141] showed that the incidence of subclinical GISTs is higher than expected. In this study, 100 whole stomachs resected from patients with gastric cancer were sectioned at 5-mm intervals, and 50 tumors identified (35 in the stomach), all positive for KIT or CD34. All tumors were smaller than 5 mm and of a spindle cell type, and 90% were located in the proximal stomach. Agaimy et al.[142] recently reported that incidental microscopic GISTs are uncommon in intestinal resections, contrasting with their gastroesophageal coun-

terparts. The remarkable variation in incidence of microscopic GISTs at different gastrointestinal sites suggests that these GISTs originate from heterogeneous subsets of interstitial cells of Cajal with varying potentials for neoplastic transformation.

Small or microscopic GISTs may accompany clinically overt GISTs or be found incidentally in resection specimens for gastroesophageal malignancies. Even the smallest lesion has been shown to harbor *KIT* mutations. They are often biologically indolent, and most lesions seem to remain small and/or show evidence of involution. However, some may be the precursors of clinically significant GISTs.[143] Endoscopic resection of small GISTs has been reported, but because of its inherent risks for positive margins, tumor spillage, and potential perforation, its role remains controversial.[144] Although these small GISTs may be followed up endoscopically until they grow or become symptomatic, the frequency of follow-up remains uncertain.

Results of a recent retrospective analysis showed that only a few small tumors (3 of 23; 13.0%) without high-risk EUS features (large size, irregular extraluminal border, heterogeneous echo pattern, presence of cystic spaces, and echogenic foci) progressed during long-term follow-up with EUS.[145] In this series, patients with progressive tumors underwent surgical excision. Whether EUS surveillance for small tumors is useful remains unclear. The poor compliance of patients in undergoing regular EUS surveillance is another important limitation to this approach.

Sun et al.[146] recently reported that endoscopic band ligation with systematic follow-up by EUS is an effective and safe treatment for small GISTs. The study included 29 patients with small gastric GISTs. Follow-up with EUS ranged from 36 to 51 months. Only one recurrence was observed 4 months postoperatively. This approach does not allow for tumor sampling, which is a limitation given the prognostic importance of the number of mitoses. Currently, any endoscopic approach should be considered investigational and would be best performed in a clinical trial.

Data are currently insufficient to guide the management of very small GISTs (< 2 cm) discovered incidentally on endoscopy, and the usefulness of regular EUS surveillance remains unestablished. Complete surgical resection is the mainstay of treatment in symptomatic patients. For a subset of patients with very small gastric GISTs (< 2 cm) with no high-risk EUS features, endoscopic surveillance at 6- to 12-month intervals may be considered (Figure 5).[18]

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.[147] A prospective, randomized trial remains to be performed. However, literature reports based on small series of patients and retrospective analyses have shown that laparoscopic or laparoscopic-assisted resections are not only possible but are also associated with low recurrence rates, short hospital stay, and low morbidity.[148–152]

Novitsky et al.[148] performed 50 laparoscopic resections of gastric GISTs (mean tumor size, 4.4 cm; range, 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.[149] removed 35 gastric GISTs measuring 2 to 5 cm through laparoscopic wedge resections. No local or distant disease recurrences were noted for tumors smaller than 4 cm. These data confirm that laparoscopic or laparoscopic-assisted resections can be performed safely in experienced hands.

Nakamori et al.[150] recently reported that in patients who underwent initial laparoscopic resection for gastric GISTs (2–5 cm), the pathologic phenotype, especially tumor mitosis, directly correlated with survival even if the resected tumor size was relatively small.

Nishimura et al.[151] reviewed 67 consecutive patients who underwent laparoscopic or traditional open resection of gastric GISTs. No difference was seen in operating time and blood loss. For tumors larger than 5 cm, laparoscopic manipulation became technically challenging, although no recurrence was noted in this subgroup. Overall recurrence rate was comparable between the groups.

Laparoscopic resection is a reasonably safe and feasible procedure for patients with low-risk smaller gastric GISTs. Gastric GISTs 5 cm or smaller may be removed through laparoscopic wedge resection. GISTs larger than 5 cm may be resected using a laparoscopic or laparoscopic-assisted technique with a hand port, depending on the location and shape

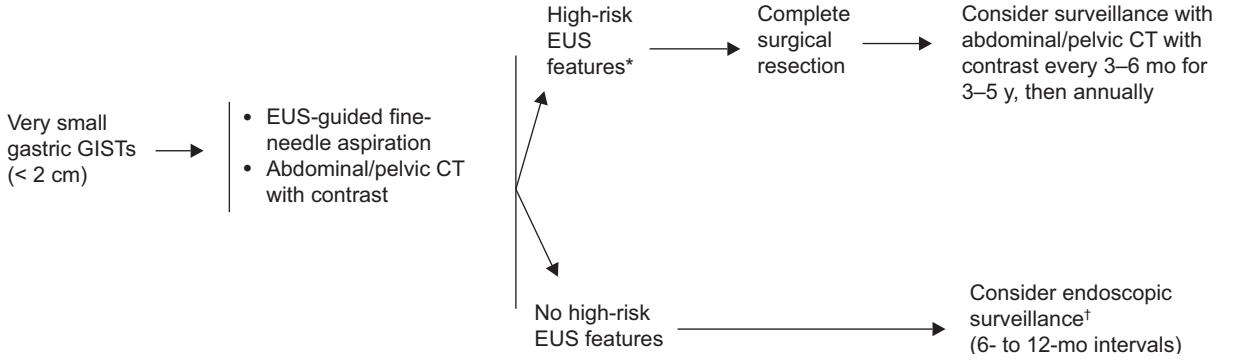

Figure 5 Approach for the management of very small gastric gastrointestinal stromal tumors (GISTs).*
*Possible high-risk endoscopic ultrasound (EUS) features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity.
†EUS should only be considered after a thorough discussion with the patient regarding the risks and benefits.
Adapted from Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. Nat Rev Gastroenterol Hepatol 2009;6:363–371. The panel included this approach as a category 2B recommendation.

of the tumor. 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 for port site recurrence. No lymphadenectomy is needed and, whenever feasible, care should be taken to preserve the vagus nerves. Laparoscopic surgery could be feasible in other anatomic sites, such as smaller rectal GISTs. However, data on laparoscopic resection of GISTs at other sites are limited.

Preoperative Imatinib: The role of preoperative imatinib for treating primary localized GIST is a matter of surgical and medical discretion. In many patients with very large localized GISTs, the disease can reasonably be considered unresectable without risk for unacceptable morbidity or functional deficit. Therefore, using imatinib as the first-line therapy to downstage the tumor is possible. Preoperative imatinib is recommended for both large tumors and poorly positioned small GISTs that are considered marginally resectable on technical grounds. Patients with primary localized GIST whose tumors are deemed unresectable should also start imatinib. Two randomized phase II trials have evaluated the safety and efficacy of imatinib as preoperative therapy for primary GIST.[153,154]

The RTOG 0132/ACRIN 6665 was the first prospective nonrandomized trial to evaluate the efficacy of preoperative imatinib in patients with potentially resectable primary disease (n = 30) or potentially resectable recurrent or metastatic disease (n = 22). Both groups received 600 mg/d.[153] Response rates following 8 weeks of preoperative imatinib according to RECIST were 7% partial and 83% stable disease. The corresponding response rates in patients with recurrent or metastatic disease were 4.5% and 91%, respectively. In the latter group, disease progression was observed in 4.5% of patients. The estimated OS rates were 93% for patients with primary GIST and 91% for those with recurrent or metastatic GIST, and the 2-year PFS rates were 83% and 77%, respectively. Postoperative imatinib was continued for 2 years. Complications of surgery and imatinib toxicity were minimal.

A trial conducted at M. D. Anderson Cancer Center (MDACC), randomized 19 patients undergoing surgical resection to receive 3, 5, or 7 days of preoperative imatinib (600 mg/d).[154] All patients received postoperative imatinib for 2 years. When perioperative adverse events were compared with those in an imatinib-naïve historical control, results showed that imatinib did not affect surgical morbidity. The response rate assessed with 18-fluorouracil (FDG)-PET and dynamic CT was 69% and 71%, respectively. Median disease-free survival of patients treated with surgery and imatinib was 46 months. Tumor size was a predictor of recurrence after postoperative imatinib.

Although the results of these 2 trials showed the safety of preoperative imatinib in patients undergoing surgical resection, survival benefit of preoperative imatinib could not be determined because all patients received imatinib postoperatively for 2 years. The duration of preoperative therapy and pa-

tient selection criteria must be defined.

Currently, the decision to use preoperative therapy for patients with resectable primary or locally advanced GIST should be made on an individual basis. In unresectable or locally advanced GISTs, preoperative imatinib could be useful to improve resectability and reduce surgical morbidity. If surgical morbidity would be improved by cytoreducing the size of the tumor, then preoperative imatinib should be considered. Because the optimal duration of preoperative therapy remains unknown, imatinib may be continued until maximal response is noted in patients. Maximal response is defined as no further improvement between 2 successive CT scans, which can take as long as 6 to 12 months.[155] However, it is not always necessary to wait for a maximal response to perform surgery. Each new cross-sectional imaging should prompt multidisciplinary reappraisal of the surgery timing or continuation of preoperative imatinib. If progression is confirmed with CT scan, surgery is recommended after discontinuing imatinib. The medical oncologist and surgeon must collaborate to determine the appropriateness of surgery after major response or stable disease.

Preoperative imatinib is also an option to facilitate organ-preserving surgery, function-preserving surgery, and surgery with low morbidity for tumors in the gastroesophageal junction and rectum. Data from a large series of patients suggesting the benefits of preoperative imatinib for these tumors are lacking. However, several case reports have shown that use of preoperative imatinib enables organ-sparing surgery and improves surgical outcomes in patients with rectal GISTs. In a study of 36 patients with advanced GISTs (esophagus/gastroesophageal junction [n = 5], stomach [n = 17], duodenum [n = 2], small bowel [n = 3], or rectum [n = 9]), preoperative imatinib (400 mg/d for 6 months) resulted in substantial tumor shrinkage, thereby facilitating radical but conservative organ-preserving surgery in most patients.[156] Dose was adjusted to 800 mg for patients with exon 9 mutations. Complete tumor removal was possible in 28 patients without surgical mortality, and a less extensive procedure could be performed in 21 patients. Exploratory surgery showed 6 patients to be unresectable, and 5 were found to be resectable after preoperative imatinib.

Because rectal and gastroesophageal junction GISTs may respond to preoperative imatinib, sphincter-sparing surgery (rectal GISTs) and esophagus-sparing surgery (gastroesophageal junction GISTs) should be considered after preoperative imatinib. Because limited data offer specific recommendations, the NCCN task force panel suggests that these types of patients should be referred to centers with expertise in the management of GISTs.

Postoperative Imatinib: Standard care for primary resectable localized GIST is surgery followed by postoperative radiologic surveillance for recurrence. However, because many patients develop recurrence after resection, imatinib is being studied in the postoperative setting to determine whether it reduces recurrence.

The American College of Surgeons Oncology Group (ACOSOG) Z9000 first conducted a single-arm, multicenter, phase II Intergroup trial to evaluate the efficacy of postoperative imatinib in 106 evaluable patients with primary GIST at high risk for recurrence based on clinicopathologic factors. Patients were treated with 1 year of imatinib at 400 mg/d.[157] Results showed that postoperative imatinib prolonged RFS after complete resection and was also associated with improved OS compared with historical controls.

In a phase III, double-blind randomized trial (Z9001) of postoperative imatinib after resection of primary localized GISTs, ACOSOG randomized patients to imatinib 400 mg/d (n = 359) or placebo (n = 354) for 1 year. Patients in the placebo group were eligible to crossover to imatinib if they experienced recurrence. Interim analysis showed that the use of postoperative imatinib after resection of primary GIST improved RFS.[158]

In a recent analysis of 713 patients from 230 sites with a median follow-up of 19.7 months,[159] 67% of patients completed 1 year of postoperative imatinib. Imatinib significantly improved RFS at 1 year compared with placebo (98% vs. 83%), but no difference was seen in OS. Although the trial was not designed to assess patient subsets, subset analysis showed that patients taking imatinib had longer RFS than those in the placebo group for each size category (3–6 cm, 6–10 cm, and ≥ 10 cm). The RFS did not statistically favor the imatinib arm in patients with moderate- (6–10 cm; 98% vs. 76% for placebo; $P = .05$) and high-risk tumors (≥ 10 cm; 77% vs. 41% for placebo; $P \leq .0001$). However, the trial results currently are not conclusive regarding the appropriate duration of

treatment and the effect of imatinib resistance and genetic mutations on the outcome of postoperative imatinib. Long-term follow-up is ongoing.

Based on the results of ACOSOG Z9001, in December 2008 the FDA approved imatinib for postoperative treatment of adult patients after resection of KIT-positive GIST. Optimum duration of postoperative treatment has not yet been determined. Postoperative imatinib after complete resection for primary GIST is recommended for at least 12 months in intermediate- to high-risk patients. Higher-risk patients may require longer treatment. ACOSOG Z9001 startified risk only based on tumor size.

A prospective, open-label, multicenter trial from the China Gastrointestinal Cooperative Group and a single-center study from China also evaluated postoperative imatinib after complete resection for patients with an intermediate or high risk for recurrence.[160,161] The long-term impact of postoperative imatinib is currently unknown. Two major trials in Europe are assessing the impact of duration of postoperative imatinib on RFS: 1) the Scandinavian/German SSG XVIII/AIO trial, which is a randomized, open-label trial of 1 versus 3 years of postoperative imatinib at 400 mg/d after resection of high-risk primary or metastatic GIST (http://clinicaltrials.gov/ct2/show/NCT00116935), and 2) EORTC 62024, which is a randomized, open-label study of 2 years of postoperative imatinib at 400 mg/d versus no treatment after resection of intermediate or high-risk GIST (http://clinicaltrials.gov/ct2/show/NCT00103168).

Recurrent or Metastatic Disease

For recurrent or metastatic GIST, standard treatment is now imatinib. Data before the era of imatinib showed that the median time to recurrence after resection of primary GIST was approximately 2 years.[16,138] Notably, in the MDACC series, only 10% of 132 patients were disease-free after a median follow-up of 68 months.[138] 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, widespread intraperitoneal recurrence may not be detectable with radiologic imaging. Historically, outcome was poor for patients with metastatic GIST treated with surgery alone. The median survival of 94 patients who presented with metastatic disease at MSKCC was 19 months, and only 28 (30%) could undergo complete surgical resection.[16]

Because the median time to recurrence on imatinib is less than 2 years, surgery has been added to medical management of selected patients with metastatic GIST to delay or prevent recurrence. However, the true benefit of this strategy has not been proven in a randomized clinical trial. Hypothetically, patients whose disease is rendered resectable on medical treatment may experience longer PFS with gross tumor resection before secondary resistance develops. Even in the setting of partial response or stable disease on TKI therapy, residual tumors typically harbor viable cells, and complete pathologic responses are rare (< 5%).[162–164] 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 restarted when the patient is able to begin oral intake. However, sunitinib is stopped 5 to 7 days before surgery and usually restarted 2 weeks after surgery.

Several studies have evaluated the impact of cytoreductive surgery on survival in patients with advanced GIST after treatment with imatinib. The first large study to report survival rates in patients who underwent resection of advanced GIST after medical therapy found that outcomes of surgery and survival rates correlated with response to TKI therapy.[165]

Three clinical categories of disease response to TKI therapy were defined. Stable disease was defined as disease that was radiographically stable or responding to TKI therapy and for which all sites of progression could be resected. Limited (localized) disease progression was defined as progression on TKI therapy at one or a few 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 for which TKI therapy and complete resection was not possible.

A macroscopically complete resection was performed 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 OS rates were 95%, 86%, and 0%, respectively ($P < .0001$). Therefore, patients

with stable disease who underwent surgery showed substantial rates of PFS and OS. 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.[155,166–171] However, no definitive data prove whether surgical resection in addition to TKI therapy improves clinical outcome in patients with resectable metastatic GIST, although 3 prospective phase III trials are planned or underway to assess whether resection changes outcome. The EORTC is conducting a prospective randomized trial to evaluate if surgery will improve PFS in patients whose metastatic GIST is responding to a minimum of 6 months of imatinib therapy (http://clinicaltrials.gov/ct2/show/NCT00956072). A similar trial of surgery in imatinib-stable metastatic GIST is being planned in the United States, and a third trial in China is evaluating the role of surgery in patients treated with 4 months of imatinib and randomized to surgery versus no surgery irrespective of response to imatinib.

Therefore, the indications for considering cytoreductive surgery in recurrent or metastatic GIST are 1) disease that is stable or responsive to TKI therapy when complete gross resection is possible; 2) isolated clones progressing on TKI therapy after initial response (indicative of secondary drug resistance), while other sites of disease remain stable (limited disease progression); or 3) emergencies, including hemorrhage, perforation, obstruction, or abscess. Surgery should also be considered for patients with impending emergencies, such as those with significant cystic degeneration at potential risk for perforation.

The impact of surgery in patients with imatinib-resistant disease on sunitinib is not known. Recent data from one relatively large study show that cytoreductive surgery on sunitinib in heavily pretreated patients is feasible, and that carefully selected patients may experience durable control of previously progressive disease than that expected for sunitinib treatment alone.[172] However, incomplete resections were frequent (although often planned in advance) and complication rates were high. Response to sunitinib at surgery did not correlate with resectability or PFS or OS. Preoperative factors predictive of better surgical outcome, other than age, could not be identified. Palliative and therapeutic benefits of cytoreductive surgery should be weighed against symptoms and alternative treatment options.

At laparotomy for metastatic GIST after TKI therapy in patients deemed to be suitable candidates, 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 for numerous other nodules to be identified 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.

Radiofrequency ablation (RFA), hepatic artery embolization, and liver transplantation are other alternative options for treating liver metastases.[173] RFA or cryoablation in conjunction with liver resection may be required to completely treat or eradicate liver parenchymal disease. Percutaneous ablation of liver lesions smaller than 5 cm may also be considered. Hepatic artery embolization should be considered for bulkier disease and progressive liver disease in imatinib-resistant patients who are not suitable for sunitinib as a second-line therapy.[174–176] RFA is usually reserved for unresectable tumors. Pawlik et al.[177] reported that treatment with RFA either alone or in combination with surgery and lack of adjuvant chemotherapy predicted shorter disease-free survival; however, this study reviewed hepatic metastases from various sarcomas, including GIST, and reported a subset analysis of the patients with GIST.[177] In another small series, combined liver transplantation plus imatinib for unresectable metastases of GIST showed promising results.[178] Based on the initial diagnosis, 3 patients underwent liver transplantation, and histologic reevaluation then changed the diagnosis to GIST. Subsequent treatment with imatinib resulted in the control of recurrence, and survival times were 92, 48, and 46 months for the 3 patients. However, the NCCN task force currently cannot recommend transplantation based on only 3 reported and a handful of anecdotal cases.

An unresolved issue is how long to keep patients on imatinib/sunitinib therapy before sur-

gery if the tumors are still responding. Data from the EORTC-62005 trial indicated that the median time to development of secondary resistance to imatinib was approximately 2 years.[84] Thus, surgery (if planned) should be performed 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.[166] reported that the first 5 patients in their series who underwent cytoreductive surgery after imatinib for advanced disease did not resume imatinib; among them, 4 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 among multiple disciplines. Thus, patients must be managed with combined pathology, medical oncology, surgical oncology, and imaging expertise in both initial evaluation and management and in continued follow-up. Reducing recurrence, optimizing timing of surgery and organ preservation, prolonging survival, increasing the number of resectable cases through pharmacologic debulking, and possibly enhancing response to imatinib through surgical cytoreduction are all potential benefits of multidisciplinary management.

Imaging of GISTs

Imaging is performed to assess tumors (including diagnosis, initial staging, restaging), monitor response to therapy, and perform follow-up surveillance of possible recurrence. CT scan and MRI are very effective at delineating extent of disease. FDG-PET is very effective at identifying extent and activity of GIST.

CT

Initial Evaluation: CT (or occasionally MRI) is the initial imaging modality when evaluating abdominal mass or nonspecific abdominal symptoms. Contrast-enhanced CT is the preferred imaging modality to characterize and evaluate the extent of an abdominal mass, and assess the presence or absence of metastasis at the initial staging workup for biopsy-proven GIST. At presentation, the mass is typically exophytic, and the origin may be difficult to identify when the mass is very large. Despite the large size of some GISTs, clinical evidence of gastrointestinal obstruction is uncommon. When a small tumor is found incidentally during endoscopy, the extraluminal extent of disease should be evaluated using CT. Metastasis may occur through locoregional infiltration or 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, bone, or lymph nodes.

Baseline CT should be performed 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 the 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 that of the surrounding hepatic parenchyma. Well-performed multiphasic (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" and "pseudo new" lesions on follow-up CT (Figure 6). Unenhanced CT images are also useful in detecting intratumoral hemorrhage, which can mask a decrease in tumor density or enhancement in responding tumors.

Response Assessment: Traditional tumor response criteria such as RECIST are based on unidimensional tumor size and do not take into account changes in tumor metabolism, tumor density, and decrease in the number of intratumoral vessels. All of these changes indicate response to TKI therapy in patients with GIST. Hence, response assessment according to RECIST are known to be insensitive in evaluating response to TKI therapy.[179] Le Cense et al.[180] recently reported that RECIST can be used for screening studies and practical decision-making if it is only used to assess progressive disease. If no disease progression is seen after 6 months of imatinib, RECIST has no prognostic value for further outcome.

Decreased density on contrast-enhanced CT indicates response to therapy and correlates with tumor necrosis or cystic or myxoid degeneration. Holdsworth et al.[181] showed that no reduction in the CT bi-dimensional tumor measurements at 1 month

after imatinib therapy is an effective indicator of prolonged treatment success in patients with advanced GISTs. However, further studies are needed to validate the use of new anatomic metrics criteria in patients undergoing TKI therapy.

The CT response criteria proposed by Choi et al.[182,183] use both tumor density and size to assess the response of GIST to TKI therapy (Table 5). These criteria correlate much better with PET in predicting response to imatinib than do RECIST and have been validated in one center in patients with GIST who had not previously undergone TKI therapy (i.e., naïve patients). However, these criteria have not yet been universally accepted, and ease of use outside specialized centers is unknown.

Typically, 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 7). When a GIST responds to imatinib, it generally becomes homogenous and hypodense. The tumor vessels and solid enhancing nodules disappear (Figure 8). These changes can be seen within 1 to 2 months in most GISTs with a good response to imatinib, and have been shown to have a prognostic value and represent a favorable effect of therapy on the disease, even in the absence of anatomic shrinkage of the tumor bulk. Recognizing the pattern of tumor response on CT is particularly important in the early stage. For patients with marginally resectable GISTs, knowledge of these early changes might be beneficial in surgical decision-making.

In the early stages of imatinib therapy, 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 9). 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. After tumors become hypodense, lesion size may decrease slowly and eventually stabilize.

Stable disease according to CT criteria (i.e., no tumor growth) has been shown to be predictive of time-to-treatment failure, and patient outcomes seem to better correlate with clinical and radiologic responses

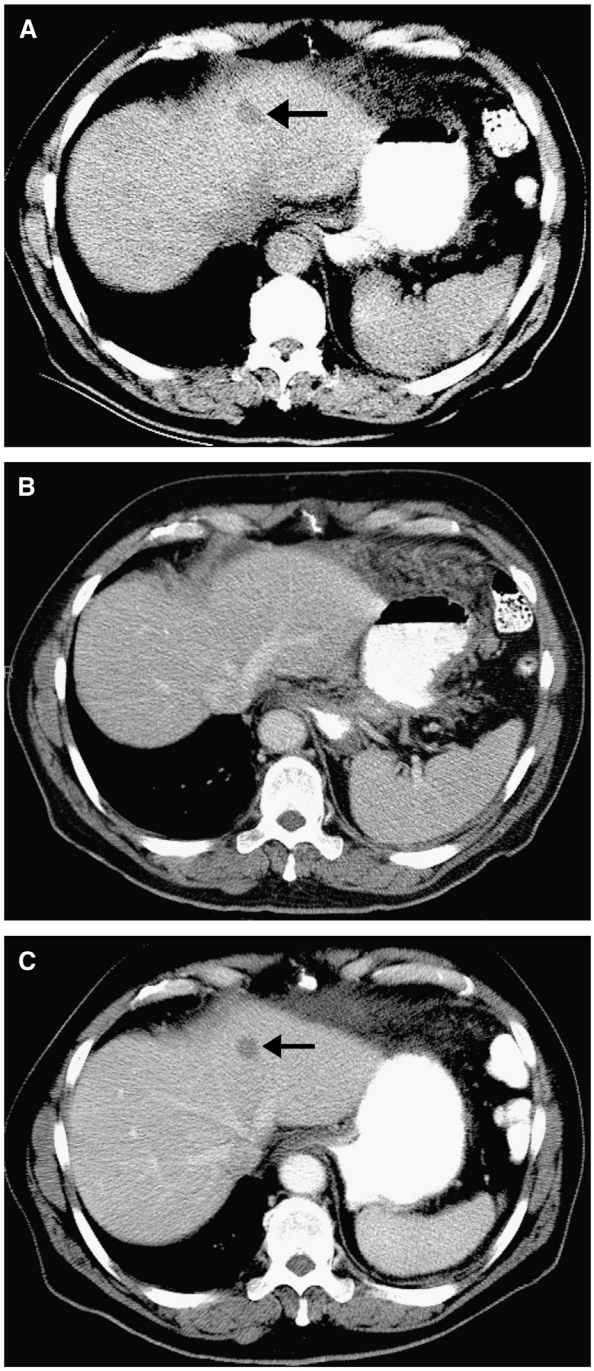

Figure 6 A spurious "new" lesion on follow-up CT in a 41-year-old man with primary gastrointestinal stromal tumor in the small bowel who received imatinib treatment. (A, B) On pretreatment CT, a metastatic lesion (arrow) in the liver could only be detected on an unenhanced image (A) but not on the enhanced 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. Courtesy of Haesun Choi, MD, The University of Texas M. D. Anderson Cancer Center.

Table 5 Modified CT Response Evaluation Criteria

Response	Definition
Complete response	Disappearance of all lesions No new lesions
Partial response	A decrease in size* of ≥ 10% or a decrease in tumor density (HU) ≥ 15% on CT No new lesions No obvious progression of nonmeasurable disease
Stable disease	Does not meet the criteria for complete response, partial response, or progressive disease No symptomatic deterioration attributed to tumor progression
Progressive disease	An increase in tumor size of ≥ 10% and does not meet criteria of partial response by tumor density (HU) on CT New lesions New intratumoral nodules or increase in the size of the existing intratumoral nodules

Abbreviations: HU, Hounsfield unit; RECIST, Response Evaluation Criteria in Solid Tumors.
*The sum of longest diameters of target lesions as defined in RECIST.
From Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol 2007;25:1753–1759; with permission.

to imatinib than PET-CT. CT plays an important role in showing tumor stability and 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.

Progression often presents as a new, small intratumoral nodule without change in overall tumor size or general configuration of the treated lesion (Figure 10), or as an increase in size of existing intratumoral tumor nodules.[184] When progression occurs, imaging frequency should be increased. Each treated lesion should be carefully analyzed for new intratumoral changes.

CT 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.

Follow-Up: In patients who have undergone surgical resection of 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, less-frequent follow-up is appropriate. In patients with advanced disease, CT is an excellent imaging modality to monitor disease during the course of treatment and surveillance. FDG-PET can be considered when CT findings are inconclusive or inconsistent with clinical findings.

PET

PET scans help differentiate active tumor from necrotic or inactive scar tissue, malignant from benign tissue, and recurrent tumor from nondescript benign changes.[185] Tumors have an increased demand for glucose, and 18-fluorodeoxyglucose (^{18}FDG) uptake in tumors is proportional to the glycolytic metabolic rate of viable tumor cells. Metabolic changes within the tumor can be measured using the standardized uptake value (SUV) or maximum SUV (SUV_{max}).The magnitude of the decrease in SUV relative to the baseline SUV is used to determine whether the therapy is effective, and these changes have been shown to predict time to treatment failure.[186]

The EORTC developed metabolic response criteria for tumors evaluated with PET that provide definitions for complete metabolic response, partial metabolic response, stable metabolic disease, or disease metabolic progression.[187] These criteria have been shown to have prognostic value for TTP and OS in various cancers. However, because a 95% correlation exists between the information from regular contrast-enhanced CT and PET-CT scans, administration of FDG involves exposure to extra radiation, and intravenous contrast CT has a superior definition than the noncontrast scans performed with PET, CT scans with intravenous contrast are the preferred routine imaging modality for patients with GIST undergoing TKI therapy.[182]

PET can be useful to assess complex metastatic disease in patients who are being considered for surgery or those on TKIs after failure of imatinib, in whom mixed responses are common. Even in this clinical setting, no clear evidence shows that PET provides significant information that cannot be obtained using intrave-

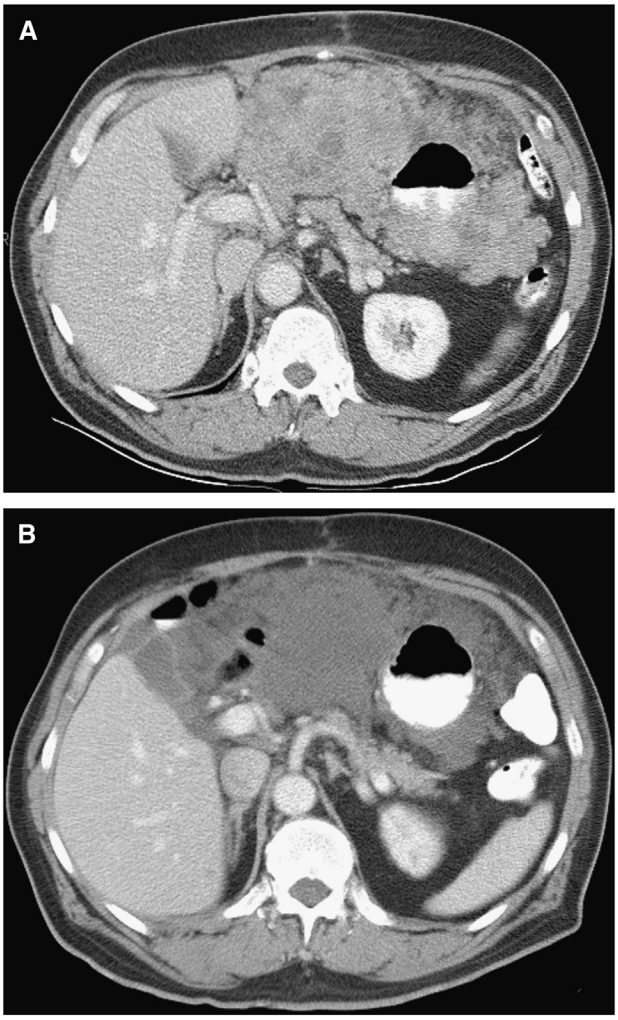

Figure 7 Typical appearance of gastrointestinal stromal tumor (GIST) in a 70-year-old man with an unresectable GIST of the stomach. (A) A pretreatment CT image showed a very large hyperdense mass completely surrounding the stomach. Endoscopic biopsy was negative for malignancy. (B) The mass became hypodense and homogenous on CT obtained 8 weeks after imatinib treatment.
Courtesy of Haesun Choi, MD, The University of Texas M. D. Anderson Cancer Center.

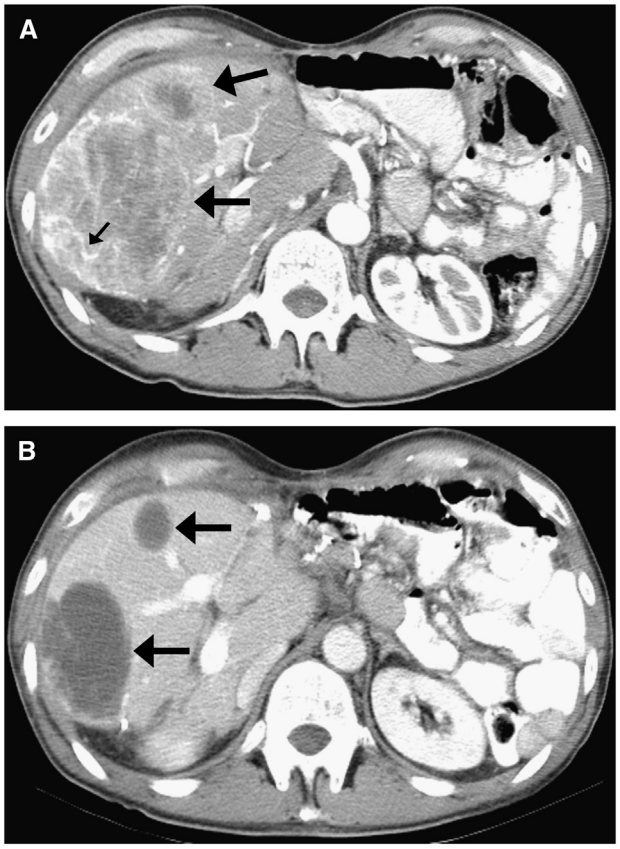

Figure 8 Good response to imatinib treatment in a 50-year-old man with metastatic gastrointestinal stromal tumor of the stomach. (A) A late arterial-phase image of pretreatment CT showed multiple hypervascular metastases in the liver (large arrows). Notice small tumor vessels within the mass (small arrow).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

nous contrast-enhanced CT. PET may be of benefit in patients with an allergy to intravenous contrast, particularly for peritoneal disease; MRI with or without contrast usually yields excellent anatomic definition of liver metastases.

Reemergence of glycolytic activity as shown with PET in the follow-up of patients on imatinib is consistent with secondary resistance to the drug or lack of compliance to the drug regimen, and is recognized on intravenous contrast scan as either new disease or growth of "tumor(s) within a tumor." If a clinician considers using PET to monitor response to therapy, a baseline PET scan should be obtained before TKI therapy is administered.

A marked increase in the glycolic activity within the tumor, known as the *flare phenomenon*, was observed when imatinib was stopped in patients with GIST that had become refractory to the drug, suggesting that portions of the tumor were still responding to imatinib, whereas other parts had developed a new clonal evolution resistant.[188] This observation parallels the clinical observation of rapid increase in symptoms on discontinuation of TKIs in patients with metastatic GISTs, and indicates that TKI therapy should be administered life-long, even in the setting of progressive disease, to try and slow the growth of clones that con-

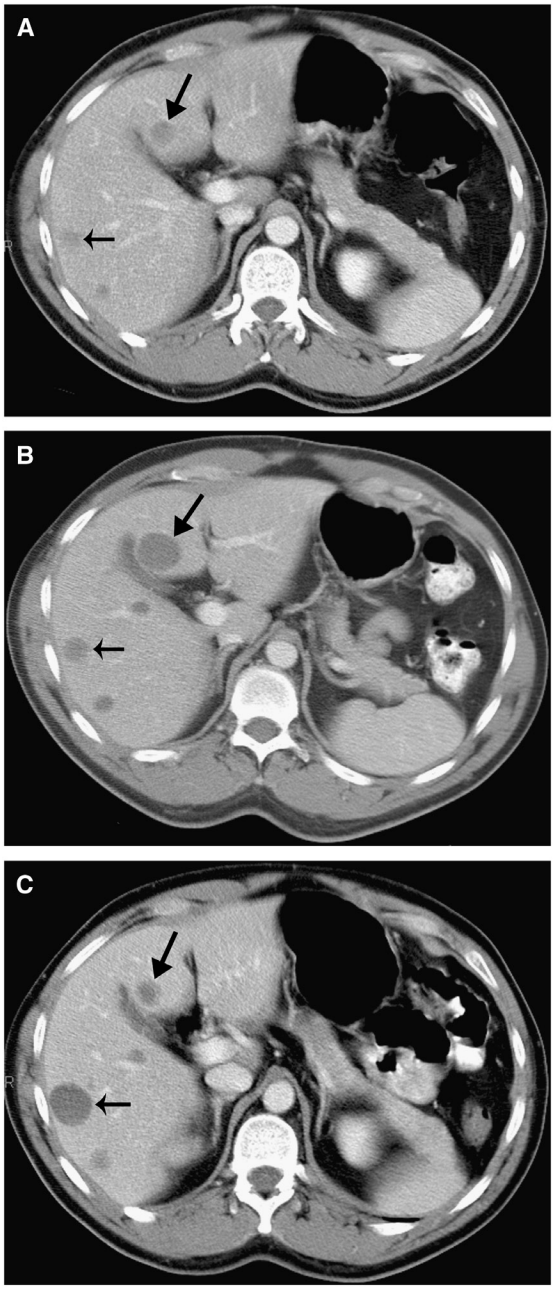

Figure 9 Increasing tumor size and spurious progression of disease in a 41-year-old man with a primary gastrointestinal stromal tumor of the small bowel who experienced a good response to imatinib treatment. (A) A portal-venous phase image of pretreatment CT showed multiple, small hyperdense metastases 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 follow-up CTs (not shown).
Courtesy of Haesun Choi, MD, The University of Texas M. D. Anderson Cancer Center.

tinue to respond to TKIs.

Prior et al.[189] assessed the tumor metabolism with PET before and after the first 4 weeks of sunitinib therapy (4 weeks of 50 mg/d, 2 weeks off). Median PFS rates were 29, 16, and 4 weeks for metabolic partial response, metabolically stable, and progressive disease, respectively. Multivariate analysis showed shorter PFS in patients who had higher residual SUVs, primary resistance to imatinib, or nongastric GIST, regardless of the mutational status. However, the preliminary findings from this study must be confirmed in larger prospective studies.

CT scans with intravenous contrast yield excellent results for monitoring patients during therapy and surveillance, and are the preferred routine imaging modality for patients with GIST on TKI therapy.

Pediatric GISTs

Pediatric GISTs are fundamentally different clinicopathologic entities and constitute approximately 1% to 2% of all GISTs. They typically lack *KIT*/*PDGFRA* mutations. Pediatric GISTs occur predominantly in girls, and patients present with multiple nodules in the stomach. The tumors often have epithelioid morphology and strongly express CD117. Although CD117 staining is uniformly positive, mutation analysis shows no detectable *KIT* or *PDGFRA* mutations in most patients younger than 18 years.[190,191] Pediatric GISTs in women are typically wild-type GIST, but mutation-positive tumors have been reported in boys.

Pediatric GISTs also have a distinct genomic profile, characterized by the overexpression of *BAALC*, *PLAG1*, *IGF1R*, *FGF4*, and *NELL1*.[44] GEP studies have shown increased expression of IGFR1 in a significant number of pediatric GISTs and, to lesser extent, adult wild-type GISTs.[44] Most pediatric wild-type GISTs progress to malignancy without acquiring large-scale chromosomal aberrations, whereas in adult GISTs characteristic cytogenetic changes occur during progression to malignancy.[192] KIT activation levels in pediatric wild-type GISTs are comparable with those in KIT-mutant GISTs. Therefore, therapies that inhibit KIT activation, or crucial KIT signaling intermediates, should be further explored in pediatric wild-type GISTs.

Pediatric GISTs have an indolent clinical course despite a high rate of recurrence, and are associated with longer survival even in patients with metastatic

disease. Local recurrence in the gastric stump is more frequent in pediatric GISTs than those in adults, probably based on their characteristic multifocal presentation.[2] Therefore, frequent endoscopic follow-up is recommended. As in adults, metastases occur predominantly in the liver and peritoneum. Locoregional lymph node metastases may occur in small subsets of patients, and thus lymph node sampling may be indicated in selected cases. The predominant clinical symptom in children is anemia caused by insidious gastrointestinal bleeding, with patients consequently developing weakness and syncope.

Surgery has a significant role in the management of pediatric GISTs, with patients undergoing multiple resections. Data are limited on the benefit of TKI therapy. Given that most pediatric cases are wild-type, response rates to imatinib may be lower than those seen in adult GIST patients, as supported by single case studies and unpublished data. Sunitinib has shown substantial antitumor activity and acceptable tolerability in a small series of imatinib-refractory pediatric patients.[193] TTP was longer on sunitinib than on prior imatinib treatment in some patients. Whether imatinib and sunitinib have comparable activity in children with GIST must be established in a larger series. However, a prospective trial limited to children is not feasible.

NCCN GIST Task Force Recommendations

- Because wild-type GISTs in pediatric patients differ from those in adults, treatment algorithms used for adult patients may not apply to pediatric patients. Furthermore, pathologic criteria that reliably predict the risk for malignancy (size, mitotic activity) in adult GISTs do not apply to pediatric GISTs.
- Obtaining detailed pathologic information on patients with pediatric GIST is important. Mutational analysis is required for pediatric GISTs, especially in young adults.
- The task force recommends that patients with pediatric GIST be referred to specialty centers or treated in the context of clinical trials. The National Institutes of Health organized a consortium for pediatric and wild-type GIST research (http://www.pediatricgist.cancer.gov/CPGR). Pediatric patients with wild-type GISTs who have advanced or unresectable disease can consider enrolment in a clinical trial.

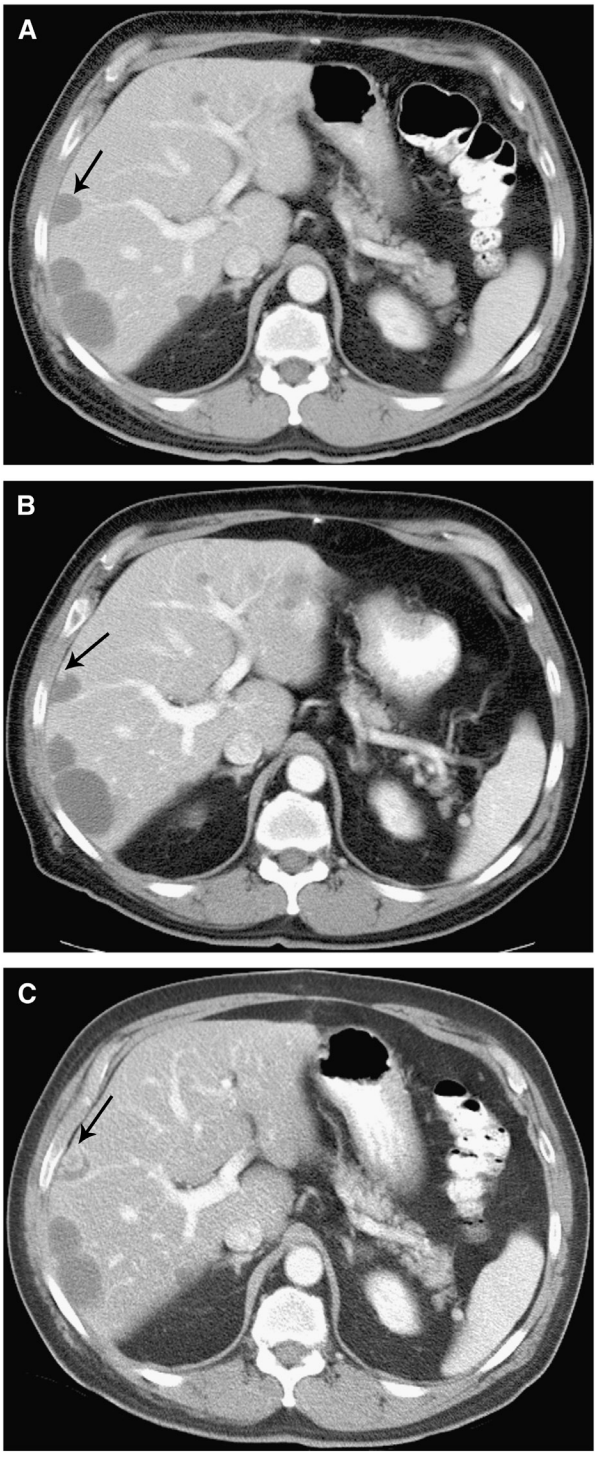

Figure 10 Intratumoral recurrence after imatinib in a 72-year-old man with a primary gastrointestinal stromal tumor in the duodenum. (A) An enhanced CT image obtained 12 months after treatment showed multiple, treated, hypodense metastasis in both lobes of the liver (arrow). (B, C) On follow-up CTs, a continuously increasing intratumoral nodule (arrow) was noted at 17 months (B) and 22 months (C) after treatment.
Courtesy of Haesun Choi, MD, The University of Texas M. D. Anderson Cancer Center.

Carney's Triad

Carney's triad includes gastric GIST and 1 or 2 other rare tumors: paraganglioma and pulmonary chondroma.[194] It affects fewer than 100 patients worldwide. Carney's triad is noninherited, shares similar features with pediatric GIST, and lacks a defined mechanism of KIT activation. It occurs more commonly in women and is characterized by multifocal disease within the stomach, which often requires multiple gastric operations/total gastrectomies. Patients follow a relatively prolonged clinical course, even in the presence of lymph node or liver metastases. Its significant overlap with GIST occurring in children suggests that pediatric GIST may represent a forme fruste of Carney's triad.

Syndromic GISTs

Familial GISTs

Familial GISTs are characterized by inherited germline mutations in either *KIT* or *PDGFRA*. They have additional associated clinical findings, such as cutaneous hyperpigmentation and gastrointestinal symptoms, including irritable bowel syndrome, dysphagia, and diverticular disease.[195,196] The median age of onset is approximately 47 years and 90% of these patients with germline mutations are at a risk for being diagnosed with GIST by 70 years of age. Familial GISTs are typically multifocal, have a low mitotic rate, are more common in the small bowel than other anatomic sites, and have clinical characteristics that do not differ based on mutation type.[197]

Familial GISTs seem to have favorable histologic features and the diagnosis does not seem to lead to shortened survival. Familial GISTs could be treated similar to nonhereditary GIST. No data show the role of surgery or imatinib in preventing the development of GIST.

The NCCN GIST Task Force Panel recommends that patients with an inherited disposition be tested in clinical human genetics departments.

Carney-Stratakis Syndrome

Carney-Stratakis syndrome involves 2 of the 3 conditions required for Carney's triad: GIST and paraganglioma.[194] It is associated with loss of function mutations within succinate dehydrogenase (SDH) genes.[198,199] *SDHB* is most commonly mutated, resulting in loss of its protein expression. The stomach is the most common primary site. Metachronous disease is common.

Neurofibromatosis Type 1–Associated GIST

GIST is one of several malignancies that can be seen in the setting of NF-1, with gliomas and neurofibromas more common. NF-1–related GISTs strongly express KIT according to immunohistochemistry, but are usually wild-type for both *KIT* and *PDGFRA*. The common abnormality is the somatic inactivating NF-1 mutations of the wild-type allele. However, in 11% of tumors, mutations in either *KIT* or *PDGFRA* have been identified.[200,201] Age at presentation is similar to that for adult sporadic GIST. Small bowel is the most common primary site. Imatinib has limited efficacy: median survival was 21 months.

The task force recommends that patients with Carney's triad and syndromic GISTs be referred to specialty centers or treated in the context of clinical trials.

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Individual Disclosures for the NCCN Task Force: Update on the Management of Patients with Gastrointestinal Stromal Tumors Panel Members					
Panel Member	**Clinical Research Support**	**Advisory Boards, Speakers Bureau, Expert Witness, or Consultant**	**Patent, Equity, or Royalty**	**Other**	**Date Completed**
George D. Demetri, MD	ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Daiichi- Sankyo Co.; Johnson & Johnson; Novartis Pharmaceuticals Corporation; Infinity Pharmaceuticals; and Pfizer Inc.	Amgen Inc.; ARIAD Pharmaceuticals, Inc.; Bayer Healthcare; Genentech, Inc.; Johnson & Johnson; Novartis Pharmaceuticals Corporation; Alnylam; EMD-Serono; Idera; Pfizer Inc.; Infinity Pharmaceuticals; Kolltan Pharmaceuticals; N-of-One; PamGene; Plexxikon; and ZioPharm	None	None	2/26/10
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