

Gastrointestinal stromal tumour

Brian P Rubin, Michael C Heinrich, Christopher L Corless

Gastrointestinal stromal tumours are the most common mesenchymal neoplasm of the gastrointestinal tract and are highly resistant to conventional chemotherapy and radiotherapy. Such tumours usually have activating mutations in either KIT (75–80%) or PDGFRA (5–10%), two closely related receptor tyrosine kinases. These mutations lead to ligand-independent activation and signal transduction mediated by constitutively activated KIT or PDGFRA. Targeting these activated proteins with imatinib mesylate, a small-molecule kinase inhibitor, has proven useful in the treatment of recurrent or metastatic gastrointestinal stromal tumours and is now being tested as an adjuvant or neoadjuvant. However, resistance to imatinib is a growing problem and other targeted therapeutics such as sunitinib are available. The important interplay between the molecular genetics of gastrointestinal stromal tumour and responses to targeted therapeutics serves as a model for the study of targeted therapies in other solid tumours.

Gastrointestinal stromal tumours are the most common mesenchymal neoplasm of the gastrointestinal tract and are highly resistant to conventional chemotherapy. Over the past few years, scientists have begun to unravel the molecular abnormalities that underlie the pathogenesis of these tumours. These findings have led to substantial advances in the understanding of the biology of such tumours, increased accuracy in pathological diagnosis, and have provided a rationale for treatment with targeted therapies. This Seminar summarises the status of knowledge about gastrointestinal stromal tumours.

Clinical features

Gastrointestinal stromal tumours have no predilection for either sex, and although they occur over a wide age distribution, about 75% are diagnosed in patients older than 50 years (median 58 years).¹ These tumours can arise anywhere in the gastrointestinal tract, but their most frequent locations are the stomach (50%) and the small bowel (25%).^{1–10} About 10% of primary gastrointestinal tumours are in the colon and rectum.^{1,4,7,8} These tumours also develop within the mesentery, omentum, retroperitoneum, and pelvis in about 10% of cases.^{11,12}

Patients generally present with non-specific symptoms including early satiety, bloating, gastrointestinal bleeding, fatigue from anaemia, or obstruction. Small, clinically insignificant lesions may be found incidentally at endoscopy or at the time of surgery for other cancers such as gastric cancer.¹³ Since most gastrointestinal stromal tumours arise from the bowel wall, they can grow into the mucosa and cause ulceration or protrude towards the serosal side, in which case endoscopic ultrasound or CT-scanning might be necessary for visualisation.

Aggressive gastrointestinal stromal tumours have a defined pattern of metastasis to the liver or throughout the abdomen (usually as innumerable serosal-based nodules), or both.¹ Importantly, these tumours rarely metastasise to lymph nodes. Extra-abdominal spread is mainly to the lungs and bone but is unusual, except in the most advanced cases.¹⁴

Pathology

Gastrointestinal stromal tumours range in size from tiny tumours discovered incidentally, during tests for other diseases, measuring less than 10 mm to very large lesions measuring upwards of 350 mm (median 50 mm).¹³ Gastrointestinal stromal tumours share many features that can be identified by electron microscope and immunophenotyping with the interstitial cells of Cajal.^{15–19} The interstitial cells of Cajal are innervated cells associated with Auerbach's plexus that have autonomous pacemaker function and coordinate peristalsis throughout the gastrointestinal tract. A popular hypothesis is that gastrointestinal stromal tumours either arise from the interstitial cell of Cajal, or that they share a common stem cell. The tumours usually present as single nodules but they can consist of many nodules. They are usually fleshy and solid in consistency but can have central cystic degeneration.

Gastrointestinal stromal tumours tend to fall into three categories of morphology, epithelioid, spindle cell, or mixed.^{15,20,21} The tumours can have substantial histological variation, which necessitates a broad differential diagnosis and immunohistochemistry is often needed to verify diagnosis. The tumours can be positive for KIT (95%), CD34 (60–70%), ACAT2 (smooth muscle actin; 30–40%), S100 (5%), DES (desmin; 1–2%), and keratin (1–2%).^{15,20,21} KIT is the most specific and sensitive marker. However, about 5% of tumours are KIT-negative

Search strategy and selection criteria

We identified reports by searching PubMed (1984–2006) for the term “gastrointestinal stromal tumor”, with relevant subheadings “resistance”, “targeted therapies”, “imatinib”, “resection”, “surgery”, “radiology”, “oncology”, “pathology”, “therapy”, “sunitinib”, and “KIT”. We searched citation lists in selected papers to identify additional references. To limit the number of references, review articles, book chapters or the latest publications in a series of articles from the same laboratory were given preference. English language papers only were included.

Lancet 2007; 369: 1731–41

Department of Anatomic Pathology and Department of Molecular Genetics, Taussig Cancer Center and the Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA (B P Rubin MD); Department of Pathology (Prof C L Corless MD) and Department of Medicine and Department of Cell and Developmental Biology, Oregon Health & Science University Cancer Institute, Oregon Health & Science University, Portland, OR 97239, USA (Prof M C Heinrich MD); and Portland Veterans Affairs Medical Center, Portland, OR 97239, USA (Prof C L Corless MD, Prof M C Heinrich MD)

Correspondence to: Brian P Rubin MD, Departments of Anatomic Pathology and Molecular Genetics, Taussig Cancer Center and Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, OH 44195, USA
rubinb2@ccf.org

and a subset of these patients might benefit from KIT-targeted therapy.²⁰ Therefore, KIT-negative gastrointestinal stromal tumours should be reviewed by a reference pathologist for verification.

Prediction of prognosis of primary tumours has been studied intensively. Tumour size and mitotic activity were two principal factors in the risk stratification system originally proposed by Fletcher and colleagues,²⁰ a tenet of which was that almost all gastrointestinal stromal tumours have malignant potential. This idea has been supported by several retrospective reviews of tumours diagnosed before the availability of imatinib.^{10,14,22–24} Table 1 shows a revised version of the risk assessment scheme, which is based on several large series published by Miettinen and colleagues.²⁶ This scheme includes anatomic site as a factor, since small bowel stromal

tumours carry a higher risk of progression than gastric stromal tumours of similar size and mitotic activity.

Epidemiology

Population-based studies suggest that gastrointestinal stromal tumours are more common than was once thought, with as many as 4000–6000 new cases in the USA each year.^{20,22,27} The annual incidence is between 11 and 14.5 per million people, and prevalence is estimated to be 129 per million.^{22,23} Stratified by risk group according to Fletcher criteria,²² the prevalence is 22.2 per million for very low risk, 51.9 per million for low risk, 24.2 per million for intermediate risk, and 22.2 per million for high risk.²²

Risk factors and causative factors have not been identified, although neurofibromatosis type I confers an increased risk of developing gastrointestinal stromal tumours, as do two other tumour syndromes, Carney triad^{28–31} and familial gastrointestinal stromal tumour syndrome.^{32–39} Gastrointestinal stromal tumours do not seem to be associated with other malignancies.⁴⁰

Oncogenic kinase mutations

About 75–80% of gastrointestinal stromal tumours have *KIT* mutations.^{41–44} Most involve the juxtamembrane domain (exon 11) and consist of in-frame deletions or insertions, or missense mutations (or combinations thereof). Mutations also occur in the extracellular domains of *KIT* (exons 8 and 9), and in the kinase I and II domains (exons 13 and 17) (figure 1).

Of the 20–25% of gastrointestinal stromal tumours that have no *KIT* mutations, about a third (8%) have mutations in a homologous receptor tyrosine kinase, platelet-derived growth factor receptor, alpha polypeptide (*PDGFRA*).^{45,46} Sites of mutations in this kinase parallel those of *KIT* (figure 1). *KIT* and *PDGFRA* mutations are mutually exclusive. Altogether, about 85–90% of gastrointestinal stromal tumours have a mutation in one of these two kinase genes.

Binding of *KIT* ligand (stem cell factor) results in activation of two *KIT* receptors, activation of their respective kinase domains, and phosphorylation of several signalling substrates known to promote cell growth and survival.⁴⁷ The most common mutations affect the juxtamembrane region of *KIT* (exon 11), which structural studies have shown, normally inhibits *KIT* kinase activity in the absence of *KIT* ligand.⁴⁸ Disruption of this domain promotes spontaneous kinase activation (figure 2).^{49–51} Mutations in the kinase II domain, which are the most common type of mutation in *PDGFRA*, change the activation loop, which conformationally regulates the ATP-binding pocket. By these and probably other mechanisms, mutations of *KIT* and *PDGFRA* promote continuous oncogenic signalling in gastrointestinal stromal tumours.

The importance of kinase mutations in these tumours is supported by many studies. *KIT* mutations are

	Size	Risk of progressive disease*			
		Gastric	Duodenum	Jejunum or ileum	Rectum
Mitotic index ≤5 per 50 hpf	≤2 cm	0%	0%	0%	0%
	2–5 cm	1.9%	4.3%	8.3%	8.5%
	5–10 cm	3.6%	24%
Mitotic index >5 per 50 hpf	>10 cm	10%	52%	34%	57%
	≤2 cm	54%
	2–5 cm	16%	73%	50%	52%
	5–10 cm	55%	85%
	>10 cm	86%	90%	86%	71%

*Defined as metastasis or tumour-related death. Data are from long-term follow-up of 1055 patients with gastric tumours, 629 with tumours of the small intestine, 144 with duodenal tumours and 111 rectal stromal tumours before availability of imatinib.^{10,24,25} Modified from reference 26 by permission of Elsevier. Data for oesophageal and extragastrointestinal stromal tumours are too few to include in table—mitotic index is likely to be the best indicator of aggressive behaviour. hpf=high-power field.

Table 1: Guidelines for risk assessment of primary gastrointestinal stromal tumours

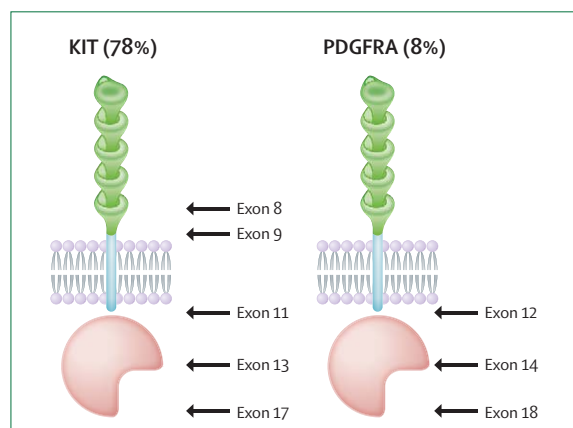


Figure 1: Location and frequency of *KIT* and *PDGFRA* mutations Identified in 1059 gastrointestinal stromal tumours sequenced consecutively in the laboratories of MCH and CLC. Overall mutation frequency=86%.

common in small (1 cm or smaller) gastrointestinal stromal tumours discovered incidentally, which suggests that the mutations occur very early.^{52,53} Extracts of gastrointestinal stromal tumours contain activated (phosphorylated) KIT or PDGFRA. Inhibition of KIT blocks growth of gastrointestinal stromal tumour cell lines.⁵⁴⁻⁵⁷ Similarly, introduction of *KIT* short hairpin RNA into these cell lines also inhibits their growth.⁵⁴ Expression of mutant KIT in transgenic knock-in mice results in KIT-positive tumours of spindle cells that morphologically resemble gastrointestinal stromal tumours.^{58,59} Finally, GIST tumours that become secondarily resistant to imatinib, a KIT inhibitor, after an initial response commonly acquire new mutations in KIT or PDGFRA that interfere with drug binding, which suggests continued dependence on signalling from these kinases.^{54,60-62}

Molecular classification

Subclassification of gastrointestinal stromal tumours according to their kinase mutation status has both biological and clinical implications (table 2). Whereas stromal tumours with mutations in *KIT* exon 9 arise almost exclusively in the small intestine and right colon, those with a *PDGFRA* D842V substitution (the most common *PDGFRA* mutation), are limited to the stomach and omentum. Additionally, stromal tumours with *KIT* exon 9 mutations are often high-risk or overtly malignant, suggesting an inherently aggressive biology.⁶⁵⁻⁶⁷ By contrast, tumours with *PDGFRA* mutations might be less aggressive than those with *KIT* mutations.⁶⁸ Gastrointestinal stromal tumours with juxtamembrane mutations of *KIT* or *PDGFRA*, and those without, occur at all locations in the gastrointestinal tract. The molecular subtypes of gastrointestinal stromal tumours differ greatly in their response to treatment with kinase inhibitors.

Familial

Several heritable mutations in exon 8, exon 11, exon 13 and exon 17 of *KIT* and in exon 12 of *PDGFRA* have been identified.^{32-37,69-74} Affected people develop many gastrointestinal stromal tumours of the stomach and small bowel as early as 18 years of age; diffuse hyperplasia of the interstitial cells of Cajal is often evident in the adjacent gut wall. Additional findings can include pigmented macules on the skin of the perineum, axilla, hands and face, and evidence of skin mastocytosis (urticaria pigmentosa).

Paediatric

Gastrointestinal stromal tumours are rare in paediatric patients and seem to fall into two subgroups: those with tumours that have a *KIT* or *PDGFRA* mutation, and those with tumours without mutations. The second group dominates; patients are almost exclusively females with one or more gastric stromal tumours by age 20 years.^{24,75}

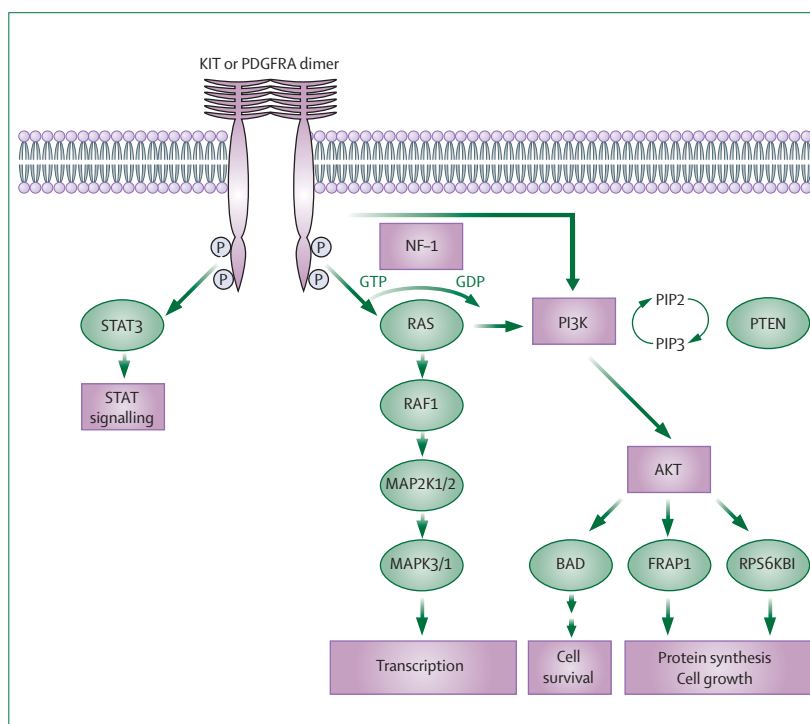


Figure 2: KIT and PDGFRA signaling in gastrointestinal stromal tumours

This diagram shows the predominant oncogenic pathways identified in gastrointestinal stromal tumours. Signaling through KIT or PDGFRA is initiated through a *KIT* or *PDGFRA* mutation resulting in constitutive activation of the KIT or PDGFRA signaling cascade, leading to inhibition of apoptosis and cell proliferation. Loss of function mutations in neurofibromin 1 are also associated with gastrointestinal stromal tumours and work independently of *KIT* or *PDGFRA* mutation. PI3K and STAT3 are thought to be the main targets of oncogenically activated KIT/PDGFRA. AKT=v-akt murine thymoma viral oncogene homolog. BAD=BCL2 antagonist of cell death. FRAP1=FK506 binding protein 12-rapamycin associated protein 1 (mTOR). GDP=guanosine diphosphate. GTP=guanosine triphosphate. MAP2K1=mitogen-activated protein kinase 1 (MEK1). MAP2K2=mitogen-activated protein kinase 2 (MEK2). NF1=neurofibromin 1. P=phosphate. PI3K=phosphoinositide-3-kinase. PIP2=phosphatidylinositol-4,5-bisphosphate. PIP3=phosphatidylinositol-3,4,5-triphosphate. PTEN=phosphatase and tensin homolog. NRAS=neuroblastoma RAS viral (v-ras) oncogene homolog. RAF1=v-RAF-1 murine leukaemia viral oncogene homolog. RPS6KBI=ribosomal protein S6 kinase, 70 kD, 1. STAT3=signal transducer and activator of transcription 3. STAT5=signal transducer and activator of transcription 5.

	Frequency	Familial examples	In vitro sensitivity to imatinib	Objective responses*†	Progressive disease*
<i>KIT</i> mutation	80%				
Exon 8	<1%	None	Yes
Exon 9	10%	None	Yes	34-40%	17%
Exon 11	67%	10 kindreds	Yes	65-67%	3%
Exon 13	1%	2 kindreds	Yes	Responses reported	..
Exon 17	1%	2 kindreds	Yes	Responses reported	..
<i>PDGFRA</i> mutation	5-8%				
Exon 12	1%	2 kindreds	Yes	Responses reported	..
Exon 14	<1%	None	Yes
Exon 18	5%	None	D842V is resistant, most others are sensitive	Responses reported	Yes (D842V)
Wild-type	12-15%	Yes	Yes	23-40%	19%

*Data combined from EORTC Australasian phase III trial and North American SWOG phase III trial.^{63,64} †Complete responses plus partial responses by RECIST criteria.

Table 2: Molecular classification of gastrointestinal stromal tumours

Carney triad

The association of gastric stromal tumours, paraganglioma, and pulmonary chondroma, known as Carney triad, is a rare tumour syndrome occurring primarily in girls and young women.⁷⁶ Gastrointestinal stromal tumours associated with the Carney triad do not have *KIT* or *PDGFRA* mutations (Heinrich and Corless, unpublished).^{24,75}

Type I neurofibromatosis

Gastrointestinal stromal tumours (mostly in the small intestine) arise in a subset of patients with neurofibromatosis type I. A Swedish study of 70 patients with neurofibromatosis type I showed gastrointestinal stromal tumours in about 7% of patients.³¹ The tumours are frequently multifocal and strongly *KIT*-positive by immunohistochemistry, yet they are generally negative for *KIT* mutations.^{29,30,77-79}

Molecular progression

Cytogenetic analyses of gastrointestinal stromal tumours support a general model for chromosomal changes that are associated with malignant progression: from *KIT* or *PDGFRA* mutation to 14q deletion, 22q deletion, 1p deletion, 8p gain, 11p deletion, 9p deletion, and 17q gain.⁸⁰ About two-thirds of such analyses show either monosomy,¹⁴ or partial loss of 14q, and at least two tumour suppressor loci have been suggested to reside on this chromosome.^{45,80-84} Similarly, loss of the long arm of chromosome 22 is seen in about half of tumours.^{45,81,82,84} Losses on chromosomes 1p, 9p, and 11p are clearly associated with malignant progression.^{45,81,82-86} A key gene on chromosome 9p is *CDKN2A* (*p16INK4A*), which encodes an important cell cycle regulator and is commonly inactivated in malignant stromal tumours of the gastrointestinal tract.⁸⁷ Gains on chromosomes 8q and 17q have been associated with metastatic behaviour.^{82,88,89} A subset of tumours (about 15%) is either hemizygous or homozygous for the primary *KIT* or *PDGFRA* mutation, suggesting selective pressure against expression of the wild-type kinase in these tumours.⁶⁵

Activated signalling pathways

Analyses of tumour extracts have shown that tumours with *KIT* mutations have strong *KIT* phosphorylation and show evidence for activation of downstream signalling pathways including MAPK3/1, AKT, RPS6KB1 (p70 S6 kinase), STAT1 and STAT3 (figure 2).^{80,90} Similar pathways of signal transduction activation are seen in tumours with *PDGFRA* mutations.⁴⁵ By contrast, the MAP2K4 (stress-activated protein kinase) and STAT5 pathways are not activated in gastrointestinal stromal tumours. Specific inhibitors of *KIT*, MAP2K1 (MEK1), MAP2K2 (MEK2), PI3 kinase, or FRAP1 (mTOR), have shown that activation of the PI3 kinase and FRAP1 pathway, but not the MAP kinase pathway, is important in *KIT*-mediated oncogenic signalling in gastrointestinal

stromal tumours.⁹⁰ This finding accords with a continuing trial of a FRAP1 inhibitor for the treatment of imatinib-resistant gastrointestinal stromal tumours. Tumours with mutations of *KIT* exon 9 show substantially less AKT phosphorylation than tumours with mutations of exon 11, providing further evidence for biological differences between subtypes of tumour.⁹⁰

Experiments have shown that mutant isoforms of *KIT* are unstable and need interaction with a heat shock protein (HSP90) to avoid rapid degradation.⁹¹ IPI-504 (Infinity Pharmaceuticals, Cambridge, MA, USA), an HSP90 inhibitor is in phase I trials. Furthermore, preliminary evidence suggests that imatinib inhibits the interaction of oncogenic *KIT* and HSP90 in a gastrointestinal stromal tumour cell line, suggesting that imatinib could work synergistically with an HSP90 inhibitor.⁵⁵

Radiological assessment

Gastrointestinal stromal tumours are often discovered incidentally by CT or endoscopy. Endoscopic ultrasound is very accurate in locating lesions on the wall of the gastrointestinal tract.⁹² CT and 18F-fluoro-deoxyglucose PET are both useful for preoperative staging of such tumours.⁹³ Although CT shows greater anatomic detail, PET can reveal small metastases and establish baseline metabolic activity, which can later aid assessment of therapy effectiveness. Scans providing both PET and CT images are gaining popularity.⁹⁴ MRI does not offer any advantages in imaging gastrointestinal stromal tumours, except in the anorectal region where greater anatomic detail can be necessary to plan appropriate surgery.

One of the main issues arising from clinical trials is how to monitor clinical response. Standard (RECIST) criteria for evaluation of response of these tumours, which needs a 30% reduction in tumour size to be termed a partial response, is clearly not appropriate because a decrease in size does not necessarily correspond with therapeutic response. Indeed, lesions can remain stable in size after therapy because of the replacement of tumour by fibrous tissue, or they might seem larger because of decreased tumour density from intratumoural oedema or haemorrhage.^{95,96} Generally, tumours that respond become hypocellular with myxoid stroma and variable amounts of necrosis.⁹⁷⁻⁹⁹ Quantitative decreases in standard uptake value between pretreatment and post-treatment PET scans can predict long-term clinical response.¹⁰⁰ Predictive criteria for assessment of CT scans have also been validated.⁹⁷ Lesions that respond can lose density on CT images over time. The Canadian Advisory Committee on Gastrointestinal Stromal Tumours recommended that follow-up CT imaging be done every 3–6 months for a minimum of 5 years after resection in patients without residual disease.¹⁰¹ Triphasic CT (assessing arterial, venous, and portal phases of circulation) is recommended for liver lesions arising after imatinib treatment.

Management of localised disease

Preoperative biopsy is not recommended for lesions that are highly suspected of being gastrointestinal stromal tumours.¹⁰¹ For lesions of indeterminate type, endoscopy techniques including fine needle aspiration or biopsy, are the methods of choice for accessible lesions; open biopsy is recommended for lesions that are not accessible by endoscopy.¹⁰² Percutaneous biopsy is not recommended because of the risk of tumour rupture and peritoneal spread.

The main treatment for localised gastrointestinal stromal tumours is surgical resection. The goal of surgery is complete gross resection with preservation of an intact pseudocapsule. These tumours should be handled carefully to avoid tumour rupture, which confers a very high risk of intra-abdominal dissemination. In a large retrospective series, patients whose complete resection was complicated by tumour rupture had significantly shortened survival compared with patients who had complete resections without tumour rupture.^{103,104} Generally, segmental tumour resection is recommended with the goal of obtaining negative microscopic margins. However, simple enucleation of the tumour should be avoided. In skilled hands, laparoscopic surgery can be used to resect small to intermediate sized tumours, especially from the stomach. This approach decreases morbidity and shortens hospital stay and has local recurrence rates similar to open procedures.^{105–109} As discussed above, the prognosis following complete surgical resection is strongly affected by both tumour size and mitotic activity.¹³ Since gastrointestinal stromal tumours metastasise to lymph nodes only rarely, routine lymphadenectomy is not recommended.

Management of advanced disease

Metastasis typically presents with tumours isolated in the peritoneal cavity or the liver, or both. Historically, the median survival of patients with advanced gastrointestinal stromal tumours was 18–24 months.^{1,103,104,110,111} Some patients present with metastatic gastrointestinal stromal tumours that are technically resectable with acceptable morbidity. However, almost all patients undergoing resection for advanced disease have subsequent recurrence, irrespective of the quality of the procedure.^{1,103,104,111} Before the introduction of imatinib, treatment options were extremely limited for patients with unresectable or metastatic gastrointestinal stromal tumours. These tumours respond poorly to conventional cytotoxic chemotherapy agents and radiation therapy.

Imatinib is a small molecule tyrosine kinase inhibitor with activity against ABL, BCR-ABL, KIT, PDGFRA, PDGFRB, ARG and possibly CSF1R (figures 3 and 4).¹¹² Its structure mimics ATP and it binds competitively to the ATP binding sites of the target kinases. Two important findings suggested that imatinib might be effective against gastrointestinal stromal tumours. The first was that imatinib could inhibit the kinase activity of both wild-type

and mutant KIT.¹¹³ The second was that it inhibited the growth of a gastrointestinal stromal tumour cell line containing a *KIT* gene mutation.⁵⁷ After a patient with widespread gastrointestinal stromal tumours responded well to imatinib in a compassionate use protocol (figure 5) multi-institutional phase I and phase II studies to treat metastatic unresectable gastrointestinal stromal tumours with imatinib were initiated.¹³ The results of these studies are summarised in table 3.^{114,118}

Two randomised, phase III trials to compare the efficacy of 400 mg of imatinib given either once or twice a day were done in Europe and Australasia, and North America (table 3).^{63,116} The trial designs were intentionally similar except that the primary endpoints differed (progression free survival in the European Organisation for Research and Treatment of Cancer (EORTC) trial⁶³ in Australasia and overall survival in the US National Cancer Institute (NCI) trial¹¹⁶). Notably, the results are very similar. Both doses of imatinib gave equivalent objective response rates

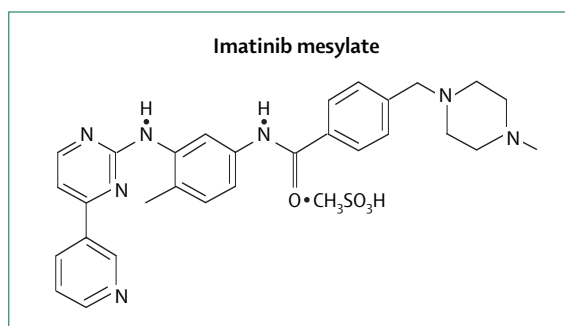


Figure 3: Chemical structure of imatinib mesylate

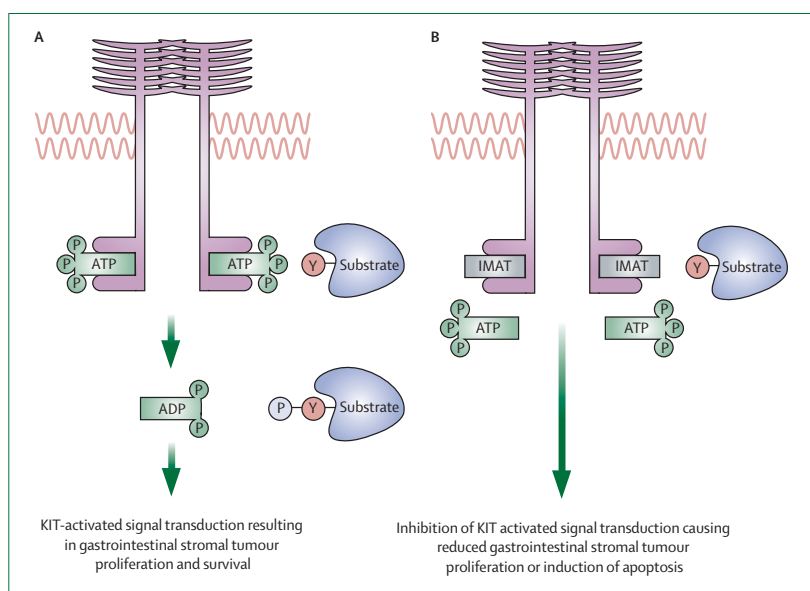


Figure 4: Mechanism of action of imatinib mesylate

(A) Normally, ATP binds to the active site of KIT or PDGFRA where it donates a phosphate to either KIT or PDGFRA, resulting in autoactivation, or to substrate molecules, resulting in activation of signal transduction. (B) Imatinib is a competitive inhibitor, binding to the same site as ATP, thus preventing phosphorylation of downstream substrates and resulting in inhibition of KIT or PDGFRA signalling.

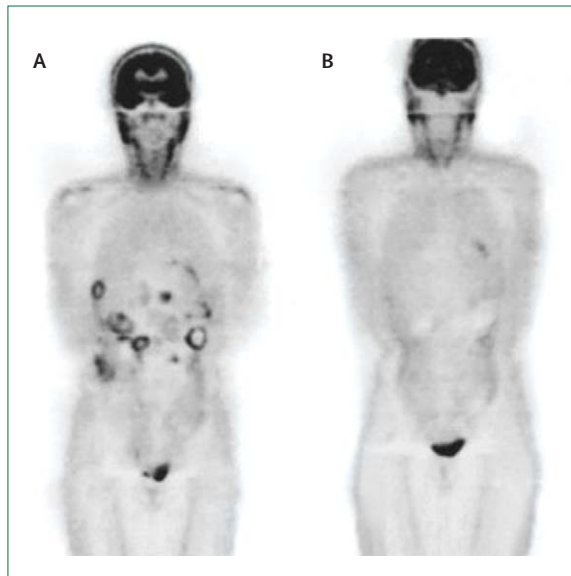


Figure 5: PET studies with ^{18}F -fluorodeoxyglucose in a patient with gastrointestinal stromal tumour with intra-abdominal dissemination. The study shown in (A) was done before imatinib therapy. Note the increased PET signal in the right renal pelvis, indicative of hydronephrosis. After 4 weeks of therapy with imatinib (B), metabolic activity, as shown by loss of PET signal, was lost in the tumour nodules and the right kidney. Reproduced from reference 98 with permission of The Massachusetts Medical Society.

For more on risk calculation see www.eortc.be/tools/imatinibtoxicity

in both trials (figure 6). However, the 400 mg twice daily dose had significantly longer progression-free survival in the EORTC trial (hazard risk 0.82; 95% CI 0.69–0.98, $p=0.026$). More dose reductions (16% vs 60%) were seen in the twice-daily dose arm in the EORTC trial. The difference in progression-free survival between the two treatments might largely be due to the reported benefit in patients with *KIT* exon 9 mutations treated with the 400 mg twice-daily regimen.¹¹⁹ No significant difference has been seen in overall survival between the two treatment arms in either trial. A meta-analysis of the two trials, including the mutational-clinical correlation data is planned for 2007 by the Meta-GIST consortium, including study coordinators from US NCI and EORTC GIST, and statisticians from SWOG and EORTC.

Imatinib reliably achieves disease control in 70–85% of patients with advanced gastrointestinal stromal tumours and the median progression-free survival is in the range of 20–24 months. Importantly, the estimated median overall survival time with imatinib therapy exceeds 36 months in all large clinical studies.^{41,63,116} By contrast, front-line doxorubicin-based chemotherapy is associated with a median survival of only 9 months.^{1,103,116,120} In all of the above studies, imatinib at doses of 400–800 mg/day proved to be efficacious, well tolerated, and safe. The toxicity profile of imatinib is generally better than that of traditional chemotherapy. A study that reviewed common toxicities noted that 13% of patients had grade 3 or higher anaemia and 7% had neutropenia of that severity. About a third of patients had grade 2 or higher oedema, or fatigue, about a fifth had nausea or diarrhoea, and a sixth had skin rash of similar severity.¹²¹ Toxicity was generally dose-related and risk factors included increasing age and female gender, possibly related to decreased imatinib clearance in these patient groups.¹²¹ A risk calculator is available for assessing individual patient's risk of imatinib toxicity.¹²¹ Imatinib has been approved in the USA and the EU for the treatment of unresectable and metastatic gastrointestinal stromal tumours.

Objective clinical response to imatinib correlates with the tumour genotype, with best response rates in tumours with *KIT* exon 11 mutations (table 3, figure 7).^{41,122} Patients with gastrointestinal stromal tumours that expressed a *KIT* exon 11 mutant isoform also had longest median time to treatment failure and overall survival. By contrast, tumours with no *KIT* mutation or with the *PDGFRA* D842V mutation were less likely to have favourable or durable responses to imatinib.^{41,122} Patients whose tumours have *KIT* exon 9 mutations might benefit from the use of higher imatinib doses.^{119,123} These results highlight the heterogeneity of this tumour type and the clinical value of the molecular classification of gastrointestinal stromal tumours.⁶⁵

In a phase II trial in France, patients who responded well to imatinib for 12 months were randomised to either stopping the drug or continuing therapy. By 3 months, disease progression was significantly more common in those who stopped treatment, and the trial was stopped.¹²⁴ Patients who stop taking imatinib before switching to new therapies can have rapid tumour growth, increased clinical symptoms and a tumour flare seen by ^{18}F -fluorodeoxyglucose PET.¹⁰² For these reasons, patients who show a response to, or are stable with, imatinib should remain on treatment indefinitely, unless drug tolerance becomes an issue.

Management of imatinib-resistant tumours

Although imatinib has greatly improved the quality of life and survival of patients with advanced gastrointestinal stromal tumours, most patients are not cured.^{41,63,116} Imatinib resistance can be divided into two categories. Patients who do not achieve stable disease or who

	Phase	Patients enrolled	Dose	Objective response*	Tumour control†
EORTC ¹¹⁴	I	36	400–800 mg	63%	90%
EORTC ¹¹⁵	II	27	400 mg twice a day	71%	89%
EORTC-AustralAsian ¹¹⁶	III	473	400 mg once a day	50%	82%
EORTC-AustralAsian ⁶³	III	473	400 mg twice a day	54%	86%
US-Finnish ¹¹⁷	II	73	400 mg once a day	66%	83%
US-Finnish ¹¹⁷	II	74	600 mg once a day	66%	83%
US-Canadian ⁶⁴	III	345	400 mg once a day	48%	75%
US-Canadian ⁶⁴	III	349	400 mg twice a day	48%	74%

*Complete responses plus partial responses. †Complete response plus partial response plus stable disease.

Table 3: Clinical studies of imatinib for advanced unresectable gastrointestinal stromal tumour

progress within 6 months of an initial clinical response have primary resistance. Tumours with a *KIT* exon 9 mutation or no detectable kinase mutation (wild-type tumours) are over-represented in this group.^{41,122,123} Patients who develop one or more sites of disease progression after more than 6 months clinical response are classified as having secondary resistance. In patients with secondary resistance, new, acquired kinase mutations are commonly seen in *KIT* (or *PDGFRA*) that interfere with imatinib activity.^{54,60–62,125,126} Protein modelling reveals that most of these mutations involve imatinib contact sites or change the accessibility of the ATP-binding pocket to the drug.^{46,54,56,127} In all likelihood, the emergence of these secondary mutations is due to a population of tumour cells for which imatinib is cytostatic rather than cytotoxic. As with other cancers, medical cure of gastrointestinal stromal tumours might need eradication of the transformed stem cells that give rise to the tumour.

Resistant lesions are commonly seen on imaging studies as a new nodule within a larger, pre-existing tumour mass.¹²⁸ In many cases, only one or a few such nodules are detectable (seen as higher density tissue on CT); most of the tumour remains under the control of imatinib.^{128,129} In this circumstance, dose escalation of imatinib could slow the growth of these resistant lesions.¹³⁰ However, when dose escalation fails, patients should be assessed for possible surgical resection or radiofrequency ablation of resistant tumours, or both, or undergo hepatic artery chemoembolisation of liver lesions.¹³¹

Another approach to the treatment of imatinib-resistant stromal tumours, especially those with multifocal disease, is the use of alternative kinase inhibitors that can inhibit conformations of *KIT* or *PDGFRA* kinase that are associated with secondary mutations. Sunitinib (Sutent, Pfizer, New York, NY, USA) was approved by the US Food and Drug Administration on Jan 26, 2006, for the treatment of advanced gastrointestinal stromal tumours in patients who fail (or are intolerant of) imatinib therapy. In addition to targeting *KIT*, sunitinib also has antiangiogenic effects by inhibition of vascular endothelial growth factor receptor. In a double-blind, phase III trial of this drug, the median time to progression with sunitinib was 6·3 months versus 1·5 months with placebo.¹¹⁰ With a target dose of 50 mg/day, taken for 4 weeks then 2 weeks off treatment, the main side-effects were diarrhoea, skin discolouration, mucositis, fatigue, hypertension and bleeding. Analysis of a phase I/II trial revealed that patients with tumours with *KIT* exon 9 mutations, or wild-type gastrointestinal stromal tumours, had better and more durable responses to sunitinib than those with *KIT* exon 11 mutations.¹³² Thus, the effectiveness of this drug for salvage treatment could be affected by the underlying biology of gastrointestinal stromal tumours.

Other drugs being tested for the treatment of imatinib-resistant gastrointestinal stromal tumours include the kinase inhibitors dasatinib, nilotinib,

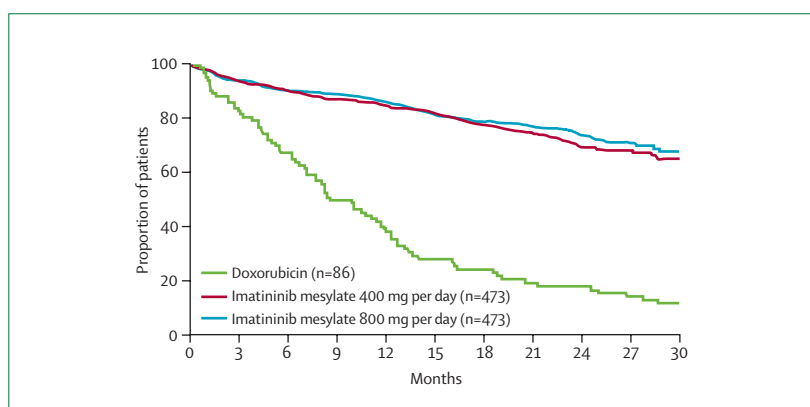


Figure 6: Overall survival for study population of EORTC 62005

The study data are compared with historical gastrointestinal stromal tumour controls from the EORTC database. Reproduced from reference 116 with permission of Elsevier.

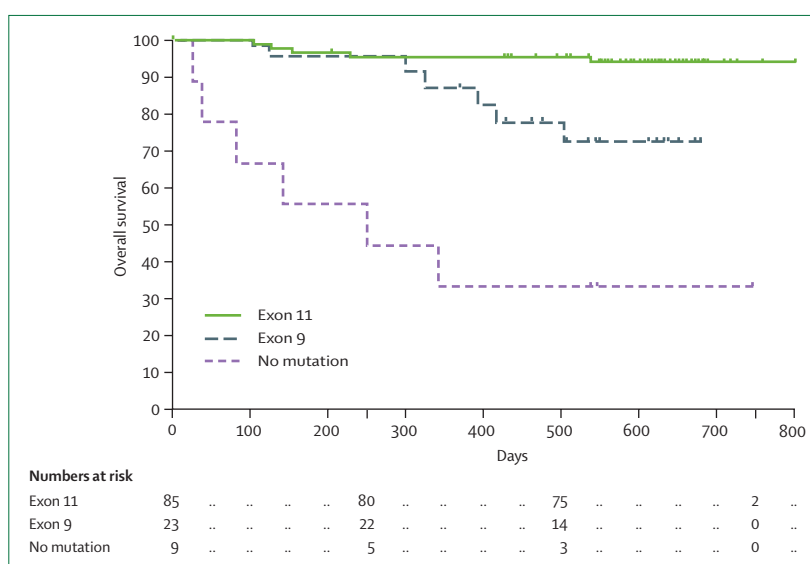


Figure 7: Overall survival stratified by *KIT* mutation in patients from EORTC phase III study

Kaplan-Meier estimate of overall survival for patients with *KIT* exon 11 mutation, *KIT* exon 9 mutation, or no mutation of *KIT* or *PDGFRA*. Reproduced from reference 119 with permission of Elsevier.

AMG-706 (Amgen, Thousand Oaks, CA, USA), the FRAP1 inhibitor everolimus, and the HSP90 inhibitor IPI-504.

Future directions

Adjuvant imatinib therapy will probably be effective—since the development of imatinib resistance seems to be due to the emergence or expansion of individual clones, the risk of developing these resistant clones might be reduced by using imatinib for minimum residual disease. Several trials are investigating the role of adjuvant therapy in the management of patients with completely resected gastrointestinal stromal tumours with intermediate or high risk of recurrence (table 3).^{120,133,134} At present, the use of adjuvant imatinib is investigational and physicians are encouraged to enrol eligible patients into clinical studies.

Another subject of active investigation is the use of neoadjuvant imatinib to downsize primary or metastatic disease before surgery. Many reports have been published of this approach to convert an unresectable mass to one that is surgically approachable, or to reduce the morbidity of a procedure (eg avoiding an abdominal-perineal resection).¹⁰¹ The use of neoadjuvant imatinib, with or without adjuvant imatinib, to reduce or eradicate micrometastatic disease is also being assessed.^{135,136}

Sunitinib is as an active agent for the treatment of imatinib-resistant gastrointestinal stromal tumours and other kinase inhibitors will probably have activity as third-line therapy. These agents might also be appropriate for testing against imatinib-naïve gastrointestinal stromal tumours. The theoretical advantages of some of these agents compared with imatinib monotherapy include: greater potency against wild-type KIT kinase; greater potency against imatinib-resistant mutations; or more effective inhibition of tumour-associated angiogenesis. However, whether such agents are as active and well tolerated as first-line imatinib therapy remains to be established. In addition to the development of more potent KIT/PDGFR inhibitors, combination of a kinase inhibitor with an agent that targets a critical downstream pathway (eg, PI3K/AKT) or an alternative biological mechanism such as antiangiogenesis could improve long-term results by delaying onset of drug resistance.

In summary, the treatment and prognosis of patients with gastrointestinal stromal tumours has been substantially changed by the discovery of oncogenic kinase mutations in the vast majority of these tumours and the introduction of specific molecular therapies that inhibit this molecular defect. However, gastrointestinal stromal tumours include several different molecular subtypes that vary in their response to kinase inhibitors. This variety is analogous to the situation with breast cancer in which the response to endocrine therapy or trastuzumab can be estimated by molecular assessment of oestrogen receptor and HER2 expression, respectively.^{137,138} We believe that these diseases serve as a new framework, in which appropriate molecular classification of tumours is essential for optimisation of cancer treatment and clinical outcomes.

Conflict of interest statement

BPR is a member of the Novartis Speakers Bureau, is a consultant to Pfizer, and receives research support from Novartis Pharmaceuticals. CLC is a consultant to Novartis Pharmaceuticals and Pfizer and is a member of the Novartis Speakers Bureau. MCH is a consultant to Novartis Pharmaceuticals and Pfizer, and is a member of the Novartis Speakers Bureau, and has received research support from Novartis Pharmaceuticals and Pfizer. MCH has an equity interest in Molecular MD.

Acknowledgments

MCH was supported in part by a VA Merit Review Grant. BPR, CLC, and MCH receive grant support from The Life Raft Group.

References

- DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000; **231**: 51–58.
- Brainard JA, Goldblum JR. Stromal tumors of the jejunum and ileum: a clinicopathologic study of 39 cases. *Am J Surg Pathol* 1997; **21**: 407–16.
- Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. *Am J Surg Pathol* 2000; **24**: 211–22.
- Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Gastrointestinal stromal tumors and leiomyosarcomas in the colon: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases. *Am J Surg Pathol* 2000; **24**: 1339–52.
- Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol* 2005; **29**: 52–68.
- Tworek JA, Appelman HD, Singleton TP, Greenson JK. Stromal tumors of the jejunum and ileum. *Mod Pathol* 1997; **10**: 200–09.
- Tworek JA, Goldblum JR, Weiss SW, Greenson JK, Appelman HD. Stromal tumors of the anorectum: a clinicopathologic study of 22 cases. *Am J Surg Pathol* 1999; **23**: 946–54.
- Tworek JA, Goldblum JR, Weiss SW, Greenson JK, Appelman HD. Stromal tumors of the abdominal colon: a clinicopathologic study of 20 cases. *Am J Surg Pathol* 1999; **23**: 937–45.
- Miettinen M, Kopczynski J, Makhlof HR, et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. *Am J Surg Pathol* 2003; **27**: 625–41.
- Miettinen M, Makhlof H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. *Am J Surg Pathol* 2006; **30**: 477–89.
- Reith JD, Goldblum JR, Lyles RH, Weiss SW. Extragastric stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. *Mod Pathol* 2000; **13**: 577–85.
- Miettinen M, Monihan JM, Sarlomo-Rikala M, et al. Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. *Am J Surg Pathol* 1999; **23**: 1109–18.
- Demetri GD, Benjamin R, Blanke CD, et al. NCCN task force report: optimal management of patient with gastrointestinal stromal tumor (GIST)—expansion and update of NCCN clinical practice guidelines. *J Natl Comp Cancer Network* 2004; **2** (suppl 1): S1–S26.
- Miettinen M, Furlong M, Sarlomo-Rikala M, Burke A, Sobin LH, Lasota J. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. *Am J Surg Pathol* 2001; **25**: 1121–33.
- Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol* 1998; **152**: 1259–69.
- Kluppel M, Huizinga JD, Malysz J, Bernstein A. Developmental origin and Kit-dependent development of the interstitial cells of cajal in the mammalian small intestine. *Dev Dyn* 1998; **211**: 60–71.
- Ramon y Cajal S. Sur les ganglions et plexus nerveux de l'intestin. *Comp Rend Soc Biol Paris* 1893; **45**: 217–23.
- Sanders KM. A case for interstitial cells of Cajal as pacemakers and mediators of neurotransmission in the gastrointestinal tract. *Gastroenterology* 1996; **111**: 492–515.
- Thunberg L. Interstitial cells of Cajal: intestinal pacemaker cells? *Adv Anat Embryol Cell Biol* 1982; **71**: 1–130.
- Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol* 2002; **33**: 459–65.
- Sarlomo-Rikala M, Kovatich AJ, Barusevicius A, Miettinen M. CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. *Mod Pathol* 1998; **11**: 728–34.
- Nilsson B, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. *Cancer* 2005; **103**: 821–29.

- 23 Tryggvason G, Gislason HG, Magnusson MK, Jonasson JG. Gastrointestinal stromal tumors in Iceland, 1990–2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. *Int J Cancer* 2005; **117**: 289–93.
- 24 Miettinen M, Lasota J, Sobin LH. Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. *Am J Surg Pathol* 2005; **29**: 1373–81.
- 25 Miettinen M, Lasota J. Gastrointestinal stromal tumors—definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch* 2001; **438**: 1–12.
- 26 Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006; **23**: 70–83.
- 27 Blanke C, Eisenberg BL, Heinrich M. Epidemiology of GIST. *Am J Gastroenterol* 2005; **100**: 2366.
- 28 Min KW, Balaton AJ. Small intestinal stromal tumors with skeinoid fibers in neurofibromatosis: report of four cases with ultrastructural study of skeinoid fibers from paraffin blocks. *Ultrastruct Pathol* 1993; **17**: 307–14.
- 29 Takazawa Y, Sakurai S, Sakuma Y, et al. Gastrointestinal stromal tumors of neurofibromatosis type I (von Recklinghausen's disease). *Am J Surg Pathol* 2005; **29**: 755–63.
- 30 Yantiss RK, Rosenberg AE, Sarran L, Besmer P, Antonescu CR. Multiple gastrointestinal stromal tumors in type I neurofibromatosis: a pathologic and molecular study. *Mod Pathol* 2005; **18**: 475–84.
- 31 Zoller ME, Rembeck B, Oden A, Samuelsson M, Angervall L. Malignant and benign tumors in patients with neurofibromatosis type I in a defined Swedish population. *Cancer* 1997; **79**: 2125–31.
- 32 Beghini A, Tibiletti MG, Roversi G, et al. Germline mutation in the juxtamembrane domain of the kit gene in a family with gastrointestinal stromal tumors and urticaria pigmentosa. *Cancer* 2001; **92**: 657–62.
- 33 Chompret A, Kannengiesser C, Barrois M, et al. PDGFRA germline mutation in a family with multiple cases of gastrointestinal stromal tumor. *Gastroenterology* 2004; **126**: 318–21.
- 34 Hirota S, Okazaki T, Kitamura Y, O'Brien P, Kapusta L, Dardick I. Cause of familial and multiple gastrointestinal autonomic nerve tumors with hyperplasia of interstitial cells of Cajal is germline mutation of the c-kit gene. *Am J Surg Pathol* 2000; **24**: 326–27.
- 35 Isozaki K, Terris B, Belghiti J, Schifflmann S, Hirota S, Vanderwinden JM. Germline-activating mutation in the kinase domain of KIT gene in familial gastrointestinal stromal tumors. *Am J Pathol* 2000; **157**: 1581–85.
- 36 Li FP, Fletcher JA, Heinrich MC, et al. Familial gastrointestinal stromal tumor syndrome: phenotypic and molecular features in a kindred. *J Clin Oncol* 2005; **23**: 2735–43.
- 37 Maeyama H, Hidaka E, Ota H, et al. Familial gastrointestinal stromal tumor with hyperpigmentation: association with a germline mutation of the c-kit gene. *Gastroenterology* 2001; **120**: 210–15.
- 38 Nishida T, Hirota S, Taniguchi M, et al. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. *Nat Genet* 1998; **19**: 323–24.
- 39 O'Brien P, Kapusta L, Dardick I, Axler J, Gnidec A. Multiple familial gastrointestinal autonomic nerve tumors and small intestinal neuronal dysplasia. *Am J Surg Pathol* 1999; **23**: 198–204.
- 40 Agaimy A, Wunsh PH. Gastrointestinal stromal tumours in patients with other-type cancer: a mere coincidence or an etiological association? A study of 97 GIST cases. *Gastroenterology* 2005; **43**: 1025–30.
- 41 Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* 2003; **21**: 4342–49.
- 42 Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; **279**: 577–80.
- 43 Rubin BP, Singer S, Tso C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res* 2001; **61**: 8118–21.
- 44 Wardelmann E, Losen I, Hans V, et al. Deletion of Trp-557 and Lys-558 in the juxtamembrane domain of the c-kit protooncogene is associated with metastatic behavior of gastrointestinal stromal tumors. *Int J Cancer* 2003; **106**: 887–95.
- 45 Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003; **299**: 708–10.
- 46 Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. *Gastroenterology* 2003; **125**: 660–67.
- 47 Blume-Jensen P, Claesson-Welsh L, Siegbahn A, Zsebo KM, Westermark B, Heldin CH. Activation of the human c-kit product by ligand-induced dimerization mediates circular actin reorganization and chemotaxis. *Embo J* 1991; **10**: 4121–28.
- 48 Mol CD, Dougan DR, Schneider TR, et al. Structural basis for the autoinhibition and STI-571 inhibition of c-Kit tyrosine kinase. *J Biol Chem* 2004; **279**: 31655–63.
- 49 Chan PM, Ilangumaran S, La Rose J, Chakrabarty A, Rottapel R. Autoinhibition of the kit receptor tyrosine kinase by the cytosolic juxtamembrane region. *Mol Cell Biol* 2003; **23**: 3067–78.
- 50 Kitayama H, Kanakura Y, Furitsu T, et al. Constitutively activating mutations of c-kit receptor tyrosine kinase confer factor-independent growth and tumorigenicity of factor-dependent hematopoietic cell lines. *Blood* 1995; **85**: 790–98.
- 51 Ma Y, Cunningham M, Wang X, Ghosh I, Regan L, Longley B. Inhibition of spontaneous receptor phosphorylation by residues in putative alpha-helix in the KIT intracellular juxtamembrane region. *J Biol Chem* 1999; **274**: 13399–402.
- 52 Corless CL, McGreevey L, Haley A, Town A, Heinrich MC. KIT mutations are common in incidental gastrointestinal stromal tumors one centimeter or less in size. *Am J Pathol* 2002; **160**: 1567–72.
- 53 Agaimy A, Wunsch PH, Hofstaedter F, et al. Minute Gastric Sclerosing Stromal Tumors (GIST Tumorlets) Are Common in Adults and Frequently Show c-KIT Mutations. *Am J Surg Pathol* 2007; **31**: 113–120.
- 54 Heinrich MC, Corless CL, Blanke CD, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. *J Clin Oncol* 2006; **24**: 4764–74.
- 55 Nakatani H, Kobayashi M, Jin T, et al. STI571 (Glivec) inhibits the interaction between c-KIT and heat shock protein 90 of the gastrointestinal stromal tumor cell line, GIST-T1. *Cancer Sci* 2005; **96**: 116–19.
- 56 Tarn C, Skorobogatko YV, Taguchi T, Eisenberg B, von Mehren M, Godwin AK. Therapeutic effect of imatinib in gastrointestinal stromal tumors: AKT signaling dependent and independent mechanisms. *Cancer Res* 2006; **66**: 5477–86.
- 57 Tuveson DA, Willis NA, Jacks T, et al. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. *Oncogene* 2001; **20**: 5054–58.
- 58 Rubin BP, Antonescu CR, Scott-Browne JP, et al. A knock-in mouse model of gastrointestinal stromal tumor harboring kit K641E. *Cancer Res* 2005; **65**: 6631–39.
- 59 Sommer G, Agosti V, Ehlers I, et al. E. Gastrointestinal stromal tumors in a mouse model by targeted mutations of the Kit receptor tyrosine kinase. *Proc Natl Acad Sci USA* 2003; **100**: 6706–11.
- 60 Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res* 2005; **11**: 4182–90.
- 61 Chen LL, Trent JC, Wu EF, et al. A missense mutation in KIT kinase domain 1 correlates with imatinib resistance in gastrointestinal stromal tumors. *Cancer Res* 2004; **64**: 5913–19.
- 62 Debiec-Rychter M, Cools J, Dumez H, et al. Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. *Gastroenterology* 2005; **128**: 270–79.
- 63 Benjamin RS, Rankin C, Fletcher C, et al. for the Sarcoma Intergroup. Phase III dose-randomized study of imatinib mesylate (STI571) for GIST: Intergroup S0033 early results. *Proc Am Soc Clin Oncol* 2003; **22**: 814.
- 64 Rankin C, von Mehren M, Blanke C, et al. Collaborating Investigators of the North American Sarcoma Intergroup. Dose effect of imatinib (IM) in patients (pts) with metastatic GIST - Phase III Sarcoma Group Study S0033. *Proc Am Soc Clin Oncol* 2004; **23**: 815.
- 65 Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004; **22**: 3813–25.

- 66 Lasota J, Jasinski M, Sarlomo-Rikala M, Miettinen M. Mutations in exon 11 of c-Kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. *Am J Pathol* 1999; **154**: 53–60.
- 67 Sakurai S, Oguni S, Hironaka M, Fukayama M, Morinaga S, Saito K. Mutations in c-kit gene exons 9 and 13 in gastrointestinal stromal tumors among Japanese. *Jpn J Cancer Res* 2001; **92**: 494–98.
- 68 Lasota J, Dansonka-Mieszkowska A, Sobin LH, Miettinen M. A great majority of GISTs with *PDGFRA* mutations represent gastric tumors of low or no malignant potential. *Lab Invest* 2004; **84**: 874–83.
- 69 Carballo M, Roig I, Aguilar F, et al. Novel c-*KIT* germline mutation in a family with gastrointestinal stromal tumors and cutaneous hyperpigmentation. *Am J Med Genet A* 2005; **132**: 361–64.
- 70 Hartmann K, Wardelmann E, Ma Y, et al. Novel germline mutation of KIT associated with familial gastrointestinal stromal tumors and mastocytosis. *Gastroenterology* 2005; **129**: 1042–46.
- 71 Hirota S, Nishida T, Isozaki K, et al. Familial gastrointestinal stromal tumors associated with dysphagia and novel type germline mutation of KIT gene. *Gastroenterology* 2002; **122**: 1493–99.
- 72 Kim HJ, Lim SJ, Park K, Yuh YJ, Jang SJ, Choi J. Multiple gastrointestinal stromal tumors with a germline c-*kit* mutation. *Pathol Int* 2005; **55**: 655–59.
- 73 Lasota J, Miettinen M. A new familial GIST identified. *Am J Surg Pathol* 2006; **30**: 1342.
- 74 O'Riain C, Corless CL, Heinrich MC, et al. Gastrointestinal stromal tumors: insights from a new familial GIST kindred with unusual genetic and pathologic features. *Am J Surg Pathol* 2005; **29**: 1680–83.
- 75 Prakash S, Sarran L, Socci N, et al. Gastrointestinal stromal tumors in children and young adults: a clinicopathologic, molecular, and genomic study of 15 cases and review of the literature. *J Pediatr Hematol Oncol* 2005; **27**: 179–87.
- 76 Carney JA. Gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney Triad): natural history, adenocortical component, and possible familial occurrence. *Mayo Clin Proc* 1999; **74**: 543–52.
- 77 Andersson J, Sihto H, Meis-Kindblom JM, Joensuu H, Nupponen N, Kindblom LG. NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. *Am J Surg Pathol* 2005; **29**: 1170–76.
- 78 Kinoshita K, Hirota S, Isozaki K, et al. Absence of c-*kit* gene mutations in gastrointestinal stromal tumours from neurofibromatosis type 1 patients. *J Pathol* 2004; **202**: 80–85.
- 79 Miettinen M, Fetsch JF, Sobin LH, Lasota J. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. *Am J Surg Pathol* 2006; **30**: 90–96.
- 80 Heinrich MC, Rubin BP, Longley BJ, Fletcher JA. Biology and genetic aspects of gastrointestinal stromal tumors: KIT activation and cytogenetic alterations. *Hum Pathol* 2002; **33**: 484–95.
- 81 Bergmann F, Gunawan B, Hermanns B, Hoer J, Schumpelick V, Fuzesi L. Cytogenetic and morphologic characteristics of gastrointestinal stromal tumors. Recurrent rearrangement of chromosome 1 and losses of chromosomes 14 and 22 as common anomalies. *Verh Dtsch Ges Pathol* 1998; **82**: 275–78.
- 82 Debiec-Rychter M, Lasota J, Sarlomo-Rikala M, Kordek R, Miettinen M. Chromosomal aberrations in malignant gastrointestinal stromal tumors: correlation with c-*KIT* gene mutation. *Cancer Genet Cytogenet* 2001; **128**: 24–30.
- 83 Fukasawa T, Chong JM, Sakurai S, et al. Allelic loss of 14q and 22q, *NF2* mutation, and genetic instability occur independently of c-*kit* mutation in gastrointestinal stromal tumor. *Jpn J Cancer Res* 2000; **91**: 1241–49.
- 84 Kim NG, Kim JJ, Ahn JY, et al. Putative chromosomal deletions on 9p, 9q and 22q occur preferentially in malignant gastrointestinal stromal tumors. *Int J Cancer* 2000; **85**: 633–38.
- 85 el-Rifai W, Sarlomo-Rikala M, Miettinen M, Knuutila S, Andersson LC. DNA copy number losses in chromosome 14: an early change in gastrointestinal stromal tumors. *Cancer Res* 1996; **56**: 3230–33.
- 86 O'Leary T, Ernst S, Przygodzki R, Emory T, Sobin L. Loss of heterozygosity at 1p36 predicts poor prognosis in gastrointestinal stromal/smooth muscle tumors. *Lab Invest* 1999; **79**: 1461–67.
- 87 Schneider-Stock R, Boltze C, Lasota J, et al. High prognostic value of p16INK4 alterations in gastrointestinal stromal tumors. *J Clin Oncol* 2003; **21**: 1688–97.
- 88 El-Rifai W, Sarlomo-Rikala M, Andersson LC, Knuutila S, Miettinen M. DNA sequence copy number changes in gastrointestinal stromal tumors: tumor progression and prognostic significance. *Cancer Res* 2000; **60**: 3899–903.
- 89 El-Rifai W, Sarlomo-Rikala M, Andersson LC, Miettinen M, Knuutila S. High-resolution deletion mapping of chromosome 14 in stromal tumors of the gastrointestinal tract suggests two distinct tumor suppressor loci. *Genes Chromosomes Cancer* 2000; **27**: 387–91.
- 90 Duensing A, Medeiros F, McConarty B, et al. Mechanisms of oncogenic KIT signal transduction in primary gastrointestinal stromal tumors (GISTs). *Oncogene* 2004; **23**: 3999–4006.
- 91 Bauer S, Yu LK, Demetri GD, Fletcher JA. Heat shock protein 90 inhibition in imatinib-resistant gastrointestinal stromal tumor. *Cancer Res* 2006; **66**: 9153–61.
- 92 Nickl NJ. Gastrointestinal stromal tumors: new progress, new questions. *Curr Opin Gastroenterol* 2004; **20**: 482–87.
- 93 Gayed I, Vu T, Iyer R, et al. The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. *J Nucl Med* 2004; **45**: 17–21.
- 94 Rosenbaum SJ, Stergar H, Antoch G, Veit P, Bockisch A, Kuhl H. Staging and follow-up of gastrointestinal tumors with PET/CT. *Abdom Imaging* 2006; **31**: 25–35.
- 95 Benjamin RS, Blanke CD, Blay JY, Bonvalot S, Eisenberg B. Management of gastrointestinal stromal tumors in the imatinib era: selected case studies. *Oncologist* 2006; **11**: 9–20.
- 96 Choi H, Charnsangavej C, de Castro Faria S, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. *AJR Am J Roentgenol* 2004; **183**: 1619–28.
- 97 Abdulkader I, Cameselle-Teijeiro J, Forteza J. Pathological changes related to Imatinib treatment in a patient with a metastatic gastrointestinal stromal tumour. *Histopathology* 2005; **46**: 470–72.
- 98 Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; **344**: 1052–56.
- 99 Loughrey MB, Beshay V, Dobrovic A, Zalberg J, Waring PM. Pathological response of gastrointestinal stromal tumour to imatinib treatment correlates with tumour KIT mutational status in individual tumour clones. *Histopathology* 2006; **49**: 99–100.
- 100 Van den Abbeele AD, Badawi RD. Use of positron emission tomography in oncology and its potential role to assess response to imatinib mesylate therapy in gastrointestinal stromal tumors (GISTs). *Eur J Cancer* 2002; **38** (suppl 5): S60–65.
- 101 Blackstein ME, Blay JY, Corless C, et al. Gastrointestinal stromal tumours: consensus statement on diagnosis and treatment. *Can J Gastroenterol* 2006; **20**: 157–63.
- 102 von Mehren M, Watson JC. Gastrointestinal stromal tumors. *Hematol Oncol Clin North Am* 2005; **19**: 547–64.
- 103 Ng EH, Pollock RE, Munsell MF, Atkinson EN, Romsdahl MM. Prognostic factors influencing survival in gastrointestinal leiomyosarcomas. Implications for surgical management and staging. *Ann Surg* 1992; **215**: 68–77.
- 104 Ng EH, Pollock RE, Romsdahl MM. Prognostic implications of patterns of failure for gastrointestinal leiomyosarcomas. *Cancer* 1992; **69**: 1334–41.
- 105 Bedard EL, Mamazza J, Schlachta CM, Poulin EC. Laparoscopic resection of gastrointestinal stromal tumors: not all tumors are created equal. *Surg Endosc* 2006; **20**: 500–03.
- 106 Granger SR, Rollins MD, Mulvihill SJ, Glasgow RE. Lessons learned from laparoscopic treatment of gastric and gastroesophageal junction stromal cell tumors. *Surg Endosc* 2006; **20**: 1299–304.
- 107 Guerin E, Willemse E, Lefebvre JC, et al. Stromal tumour of the rectum: laparoscopic approach of a rare localization of GIST. *Acta Chir Belg* 2006; **106**: 605–07.
- 108 Nguyen SQ, Divino CM, Wang JL, Dikman SH. Laparoscopic management of gastrointestinal stromal tumors. *Surg Endosc* 2006; **20**: 713–16.
- 109 Novitsky YW, Kercher KW, Sing RF, Heniford BT. Long-term outcomes of laparoscopic resection of gastric gastrointestinal stromal tumors. *Ann Surg* 2006; **243**: 738–47.

- 110 Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; **368**: 1329–38.
- 111 Shiu MH, Farr GH, Papachristou DN, Hajdu SI. Myosarcomas of the stomach: natural history, prognostic factors and management. *Cancer* 1982; **49**: 177–87.
- 112 Buchdunger E, Cioffi CL, Law N, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. *J Pharmacol Exp Ther* 2000; **295**: 139–45.
- 113 Heinrich MC, Blanke CD, Druker BJ, Corless CL. Inhibition of KIT tyrosine kinase activity: a novel molecular approach to the treatment of KIT-positive malignancies. *J Clin Oncol* 2002; **20**: 1692–703.
- 114 van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001; **358**: 1421–3.
- 115 Verweij J, van Oosterom A, Blay JY, et al. Imatinib mesylate (STI-571 Glivec, Gleevec) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target. Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study. *Eur J Cancer* 2003; **39**: 2006–11.
- 116 Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004; **364**: 1127–34.
- 117 von Mehren M, Blanke C, Joensuu H, et al. High incidence or durable responses induced by imatinib mesylate (Gleevec) in patients with unresectable and metastatic gastrointestinal stromal tumors (GISTs). *Proc Am Soc Clin Oncol* 2002; **21**: 403a.
- 118 Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; **347**: 472–80.
- 119 Debiec-Rychter M, Sciot R, Le Cesne A, et al. *KIT* mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer* 2006; **42**: 1093–103.
- 120 Dematteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. *Hum Pathol* 2002; **33**: 466–77.
- 121 Van Glabbeke M, Verweij J, Casali PG, et al. Predicting toxicities for patients with advanced gastrointestinal stromal tumours treated with imatinib: a study of the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastro-Intestinal Trials Group (EORTC-ISG-AGITG). *Eur J Cancer* 2006; **42**: 2277–85.
- 122 Debiec-Rychter M, Dumez H, Judson I, et al. Use of c-*KIT*/*PDGFRA* mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2004; **40**: 689–95.
- 123 Heinrich MS, Corless C, Hollis D, Demetri GD, Bertagnoli M, Fletcher JA. Correlation of target kinase genotype with clinical activity of imatinib mesylate in patients with metastatic GI stromal tumors expressing KIT. *Proc Am Soc Clin Oncol* 2005; **24**: 3s.
- 124 Blay J-Y BP, Perol D, Ray-Coquard I, et al. Continuous vs intermittent imatinib treatment in advanced GIST after one year: a prospective randomized phase III trial of the French Sarcoma Group. *Proc Am Soc Clin Oncol* 2004; **23**: 815.
- 125 Fletcher JA, Corless C, Dimitrijevic S, et al. for the GIST Working Group Mechanisms of resistance to imatinib mesylate (IM) in advanced gastrointestinal stromal tumor (GIST). *Proc Am Soc Clin Oncol* 2003; **22**: 815.
- 126 Tamborini E, Bonadiman L, Greco A, et al. A new mutation in the KIT ATP pocket causes acquired resistance to imatinib in a gastrointestinal stromal tumor patient. *Gastroenterology* 2004; **127**: 294–99.
- 127 Tamborini E, Priol S, Negri T, et al. Functional analyses and molecular modeling of two c-*Kit* mutations responsible for imatinib secondary resistance in GIST patients. *Oncogene* 2006; **25**: 6140–46.
- 128 Shankar S, van Sonnenberg E, Desai J, Dipiro PJ, Van Den Abbeele A, Demetri GD. Gastrointestinal stromal tumor: new nodule-within-a-mass pattern of recurrence after partial response to imatinib mesylate. *Radiology* 2005; **235**: 892–98.
- 129 Desai J, Shankar S, Heinrich M, et al. Clonal evolution of resistance to imatinib. *Proc Am Soc Clin Oncol* 2004; **22**: 197.
- 130 Zalcberg JR, Verweij J, Casali PG, et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. *Eur J Cancer* 2005; **41**: 1751–57.
- 131 Kobayashi K, Gupta S, Trent JC, et al. Hepatic artery chemoembolization for 110 gastrointestinal stromal tumors: response, survival, and prognostic factors. *Cancer* 2006; **107**: 2833–41.
- 132 Maki R, Fletcher JA, Heinrich M, et al. Results from a continuation trial of SU11248 in patient (pts) with imatinib (IM)-resistant gastrointestinal stromal tumor (GIST). *Proc Am Soc Clin Oncol* 2005; **24**: (Abst 9011).
- 133 <https://www.acosog.org/studies/closed.jsp>. 2005.
- 134 <https://www.acosog.org/studies/synopses/Z9001.Synopsis.pdf>. 2005.
- 135 <https://www.rtog.org>. 2005.
- 136 Trent JC, Benjamin RS. New developments in gastrointestinal stromal tumor. *Curr Opin Oncol* 2006; **18** (4): 386–95.
- 137 Hutchins LF, Green SJ, Ravdin PM, et al. Randomized, controlled trial of cyclophosphamide, methotrexate, and fluorouracil versus cyclophosphamide, doxorubicin, and fluorouracil with and without tamoxifen for high-risk, node-negative breast cancer: treatment results of Intergroup Protocol INT-0102. *J Clin Oncol* 2005; **23**: 8313–21.
- 138 Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; **353**: 1673–84.