Gastrointestinal Oncology

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(Editors)

Gastrointestinal Oncology

A Practical Guide

Springer

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Preface

Gastrointestinal oncology practitioners aim to establish effective prevention and treatment strategies for patients with malignancies involving the GI tract, ultimately leading to a reduction in morbidity and mortality from GI cancers. GI tumours arise from a number of distinct anatomic sites and may or may not share underlying biologic similarities; however, they differ in their required radiotherapeutic or surgical approaches for limited, curable disease, as well as their chemosensitivity and treatment patterns in the advanced or metastatic settings. The best therapeutic approach to these cancers is usually multidisciplinary, involving medical, surgical, and radiation oncologists, with strong input from pathologists, gastroenterologists, and specialists in diagnostic imaging. Making major strides in future GI cancer control will certainly involve both expert clinicians and researchers, specializing in areas including new drug development, clinical trial design, biostatistics, experimental and molecular therapeutics, and molecular pathology.

This edition of *Gastrointestinal Oncology: A Practical Guide* features chapters devoted to each of the major GI anatomic sites, as well as sections on diagnostic imaging, interventional GI oncology, practical correlative science, and non-site specific tumours such as neuroendocrine cancers and gastrointestinal stromal tumours. The emphasis of this text is to furnish useful, evidence-based clinical advice, highlighting the multidisciplinary nature of GI oncology practice. This remains an incredibly exciting time in medicine. The knowledge leaps in molecular oncology in general and characterization and treatment of GI malignancies specifically have been prodigious. We hope you find the information in this text useful, guiding your everyday practice and stimulating thought regarding potential future advances.

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Gastrointestinal Stromal Tumors

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John R. Zalcberg, Desmond Yip, Christine Hemmings, Bruce Mann, and Charles D. Blanke

6.1 Epidemiology

6.1.1 Demographics

Gastrointestinal stromal tumors (GISTs) are the commonest mesenchymal tumors of the gastrointestinal tract. Although they most frequently arise in the stomach (around 60% of cases) and small intestine (30–35%), GISTs can occur anywhere in the tubular organs of the gastrointestinal tract, though they uncommonly arise from colorectum and appendix (5%) and esophagus (<1%) (Miettinen and Lasota 2006b). Extraintestinal examples (e.g., omental, mesenteric or retroperitoneal tumors) also occur, but metastasis from an intestinal primary should be considered in these cases; it is thought that true primary extra-intestinal disease represents less than 1% of all GISTs. Rare examples have been reported in the gallbladder (Mendoza-Marin et al. 2002; Park et al. 2004). The overall incidence of GISTs has been estimated at anywhere from 10 to 20 per million if small,

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incidentally discovered tumors are included. Sporadic GIST most commonly arises in the fifth and sixth decades, with a slight male preponderance, at least in terms of malignant tumors (Miettinen and Lasota 2006b). Recent autopsy series suggest around 20% of the general population harbor micro-GISTs, though only a small fraction will develop clinically significant tumors (Kawanowa et al. 2006).

While GISTs are relatively rare tumors, their incidence has apparently increased in recent times, in part because of better recognition due to the characteristic CD117 immunohistochemical staining for the c-KIT receptor that is expressed on the majority of GISTs. An additional reason for the apparent higher incidence is the increased attention and research interest due to the recognition of the key role of oncogenic KIT gain-of-function mutations first recognized and described by Hirota (1998), coupled with the availability of novel targeted therapies such as imatinib for the condition.

Finally, these tumors in the past have been misclassified as other soft tissue sarcomas such as leiomyosarcomas, leiomyomas or leimyoblastomas (Miettenen et al. 2002). For example a Dutch National Pathology Registry study found an incidence of 2.1 per million inhabitants in 1995 and one of 12.7 per million in 2003 (Goettsch et al. 2005). Similarly US SEER cancer registry data have documented an increase in cases from 2.8 per million population in 1992 to 6.9 per million in 2002. These changes are mainly due to reclassification of smooth muscle tumors as GIST, but there are also a noticeably increased number of cases of mesenchymal tumors diagnosed since 1992. Histopathological review of all cases of patients with potential GIST in western Sweden diagnosed between 1983 and 2000 determined an incidence of 14.5 per million (Nilsson et al. 2005). A similar Icelandic histopathological review of all gastrointestinal mesenchymal tumors diagnosed in the country between 1990 and 2003 has found an annual incidence of 11 per million population.

6.1.2 Special Types and Associations

6.1.2.1 Pediatric GIST

Fewer than 1% of GISTs occur in children, and these tumors have a strong predilection for the stomach. In contrast to sporadic GIST in adults, tumors arising in children show a striking female preponderance (around 75%), with a median age of 12; they are also more commonly multifocal and have a tendency to involve regional lymph nodes more frequently. The majority of tumors have an epithelioid phenotype. Despite the majority of tumors expressing CD117 immunohistochemically, only around 15% show KIT mutations (Janeway et al. 2007). Pediatric GISTs have been shown to have a distinct transcriptional signature, with overexpression of BAALC, PLAG1, IGF1R, FGF4, and NELL1 (Agaram et al. 2008a). Most are wild type in mutational profile and in vitro studies show that kinase inhibitors such as nilotinib, sunitinib, dasatinib, and sorafenib are more effective than imatinib. Association with Carney triad (see below) seems infrequent, despite demographic and histologic similarities (Miettinen et al. 2005a).

6.1.2.2 Familial GIST

Familial GIST is a rare autosomal dominant condition arising as a result of germline KIT or PDGFR mutations and is characterized by multiple tumors arising throughout the gastrointestinal tract, often in association with interstitial cell of Cajal (ICC) hyperplasia. These tumors tend not to arise until middle age, and their behavior varies from indolent to malignant. Other manifestations of KIT activation including mastocytosis and increased cutaneous pigmentation may be seen (Miettinen and Lasota 2006b).

6.1.2.3 Syndromic GIST

GIST cases are mostly sporadic but may also occur as part of a syndromic association such as Carney's triad where GIST can be associated with extra-adrenal paragangliomas and pulmonary chondromas, typically affecting young females (Carney 1999). In these cases, the tumors are typically gastric in location, epithelioid in morphology and arise in girls or young women. The majority of these tumors are indolent, with prolonged survival even after the development of liver metastases (Miettinen and Lasota 2006b; Miettinen et al. 2005a). There is also an autosomal dominant familial inherited association with paraganglioma alone affecting both males and females, which is thought to be a separate syndrome (Carney and Stratakis 2002). These pediatric and syndromic GISTs tend to be wild type and have a more indolent clinical course (Miettinen et al. 2005b).

GIST is relatively common in patients with neurofibromatosis, Type 1, accounting for around 5% of GIST cases (Miettinen et al. 2006). These tumors typically have a spindled morphology with few mitoses and lack CD117 expression but express CD34. They most often arise in the small intestine and are typically multiple and small (Miettinen and Lasota 2006a). They are often associated with diffuse ICC hyperplasia, and generally lack both KIT and PDGFR mutations (Miettinen and Lasota 2006b). Although they tend to be clinically indolent, in malignant examples primary imatinib resistance is common (Mussi et al. 2008b).

6.1.2.4 Other Associations

GIST may also occur in patients with other tumors, either synchronously or metachronously and indeed many GISTs are discovered incidentally during investigation of unrelated disease. The frequency of second tumors reportedly ranges from 4.5 to 33%, when Carney triad and neurofibromatosis are excluded. Gastric GISTs are the ones most often associated with other tumors, reflecting their overall high frequency. The commonest second malignancies in one series were gastrointestinal tract carcinoma (47%), hematologic malignancies (7%), and carcinoma of prostate (9%), breast (7%), kidney (6%), lung (5%) or female genital tract (5%). Others included carcinoid tumor (3%), sarcoma (3%), melanoma (2%)

and seminoma (2%). An association has been seen with myeloid leukemia (Miettinen et al. 2008). Collision tumors and metastases of carcinoma or sarcoma into GIST have also been reported (Agaimy et al. 2006).

6.2 Pathology

6.2.1 Gross Pathology

GISTs are believed to originate from ICC, or their stem-cell like precursors. ICC have both myoid and neural features and function as gut pacemakers, regulating GI motility. They are KIT-dependent cells located around the myenteric plexus and in the muscularis propria throughout the GI tract. ICC may differentiate into smooth muscle cells if KIT signaling is disrupted (Torihashi et al. 1999).

GISTs most often arise as intramural tumors, centered on muscularis propria. Tumor may erode overlying mucosa, classically producing a smooth nodule with central umbilication from which devastating hemorrhage may occur. GISTs vary widely in size, varying from less than 1 cm when discovered incidentally, to 30 cm or more (Hemmings, unpublished data). There is often relative constriction of tumor growth within muscularis propria, with bulging of larger tumors into submucosal and subserosal connective tissue, producing a "dumbbell" configuration. The cut surface of the tumor varies from myxoid to smooth, homogeneous, pale tumor with a soft fleshy texture, to firm and more fibrous, or more variegated with areas of hemorrhage and necrosis. Foci of calcification may produce a gritty texture on slicing.

6.2.2 Light Microscopy

6.2.2.1 Morphology

The commonest histologic pattern is that of a moderately cellular spindle-cell neoplasm, typically centered on muscularis propria but often extending into submucosa and/or subserosa (Fig. 6.1). The cells recapitulate the ICC's to varying degrees. Indeed, ICC hyperplasia may be identifiable in subjects with familial GIST. The degree of cellularity may vary considerably, as does the mitotic rate. Necrosis is an inconsistent finding but may be extensive.

A subset of GIST has a more epithelioid morphology (Fig. 6.2), which may be seen exclusively or intermingled with areas of spindle cells. Some tumors, particularly those harboring PDGFR mutations, have abundant myxoid stroma (Fig. 6.3), which may appear chondroid and, on occasion, include true cartilaginous differentiation (Fig. 6.4). Metaplastic

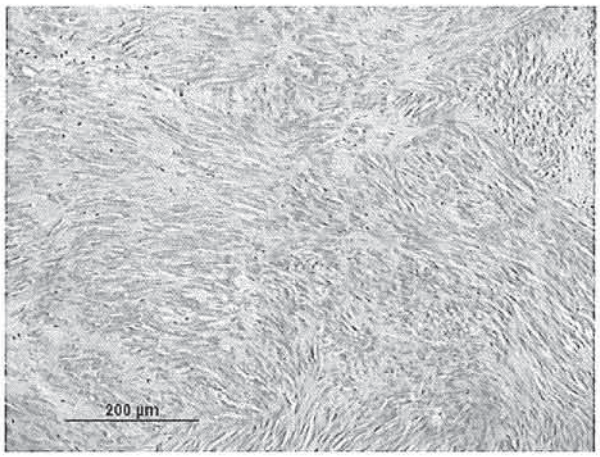

Fig. 6.1 Typical appearance of a spindle-cell GIST (H & E, original magnification ×200)

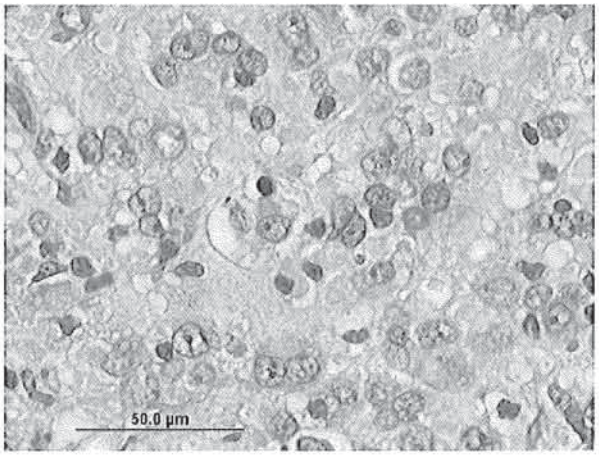

Fig. 6.2 Less commonly, the cells have a more epithelioid morphology (H & E, original magnification ×1,000)

osteoid or true ossification may also be seen (Fig. 6.5). Other less common findings include signet-ring, oncocytic or rhabdoid cells. Rhabdomyosarcomatous differentiation has been described following tyrosine kinase inhibitor therapy (Liegl et al. 2009).

6.2.2.2 Immunohistochemistry

CD117

Most GISTs (approximately 95%) express KIT protein, and a mainstay of diagnosis in GIST has been immunoperoxidase staining for CD117, a cell surface antigen on the extracellular domain of KIT (Croom and Perry 2003). CD117 staining is typically strong and diffuse in most GISTs, though some KIT negative tumors may still harbor *KIT* gene mutations, strongly

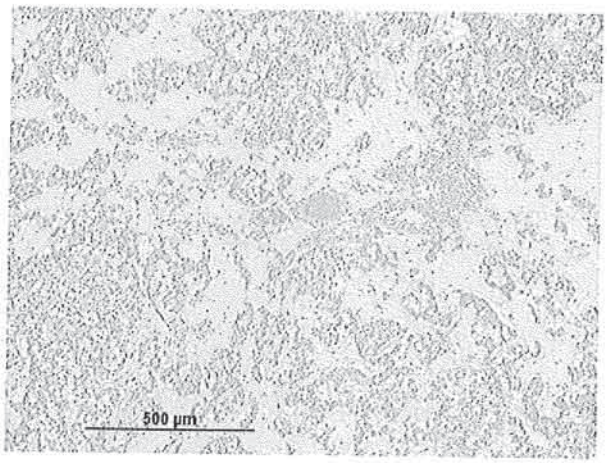

Fig. 6.3 Some tumors, particularly those harboring PDGFR mutations, exhibit abundant myxoid stroma (H & E, original magnification ×100)

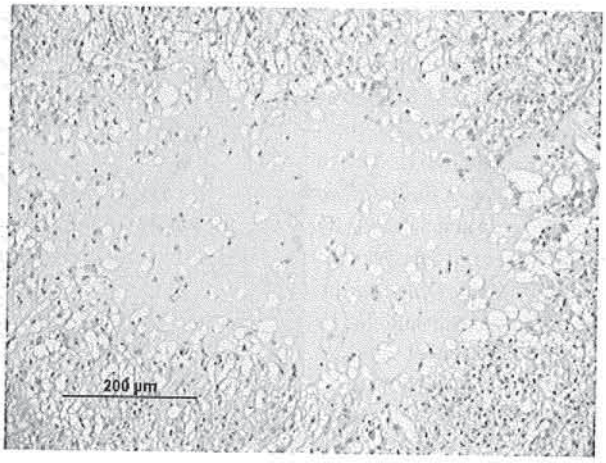

Fig. 6.4 The stroma may appear chondroid and, on occasion, show true cartilaginous differentiation (H & E, original magnification ×200)

suggesting that KIT is still involved in tumorigenesis. Many KIT-negative GISTs harbor PDGFR mutations. In some intestinal tumors the staining may be patchy, and a minority label as paranuclear dots only (Miettinen and Lasota 2006b).

Despite its relatively high sensitivity, CD117 staining should not be taken as definite evidence of GIST – a number of other tumors will show weak or focal positivity (particularly if antigen retrieval is employed; this should not be performed to reduce the risk of false positive staining). Particularly in unusual sites, other diagnoses such as solitary fibrous tumor (which is also typically positive for CD34) should be considered.

CD34

CD34 is a hemopoietic progenitor cell antigen which is also expressed in endothelial cells, some fibroblasts, and various mesenchymal neoplasms. Perhaps 70 (Miettinen and Lasota

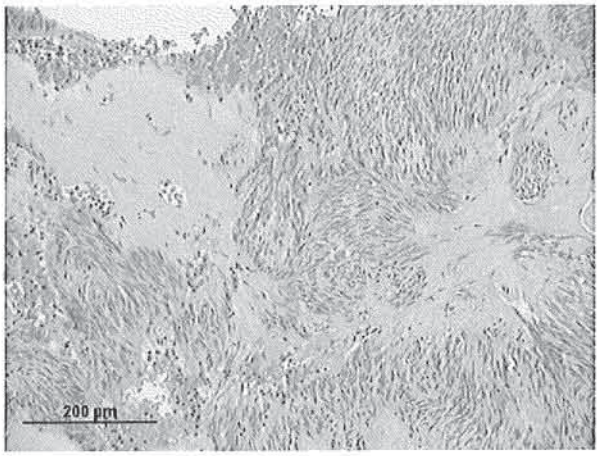

Fig. 6.5 Heterologous elements such as metaplastic osteoid or true ossification may also be seen (H & E, original magnification ×200)

2006b) to 85% (Miettinen and Lasota 2006a) of GIST express CD34, with almost universal positivity in tumors of the esophagus and rectum, whereas in the stomach epithelioid or sarcomatoid GIST may be negative.

PDGFR

It has been suggested that immunohistochemical staining for PDGFR has diagnostic value, particularly in KIT-negative GIST (Rossi et al. 2005), however the currently available antibodies appear to be unreliable on paraffin-embedded tissue (Miettinen and Lasota 2006a), and its use is not widespread. Furthermore, PDGFR may also be expressed in a subset of abdominal fibromatosis ("desmoid tumor") and is therefore not entirely specific (Rossi et al. 2005).

Protein Kinase C Theta

Protein kinase C (PKC) theta is a downstream effector in the KIT signaling pathway and has been suggested as an immunohistochemical marker as well as a potential further therapeutic target in GIST, often staining KIT-negative tumors as well (Lee et al. 2008). Positivity in GIST is reported to range from perhaps 85–100% of tumors (Miettinen and Lasota 2006b) however, a number of other mesenchymal tumors also react with the antibody (Lee et al. 2008), which is again said to be "difficult" in everyday laboratory applications and has not gained widespread use for routine diagnosis.

DOG-1

Gene expression profiling found that the gene *FLJ10261* Discovered On GIST-1 (DOG-1) was specifically expressed in GIST. Immunoreactivity was subsequently demonstrated in

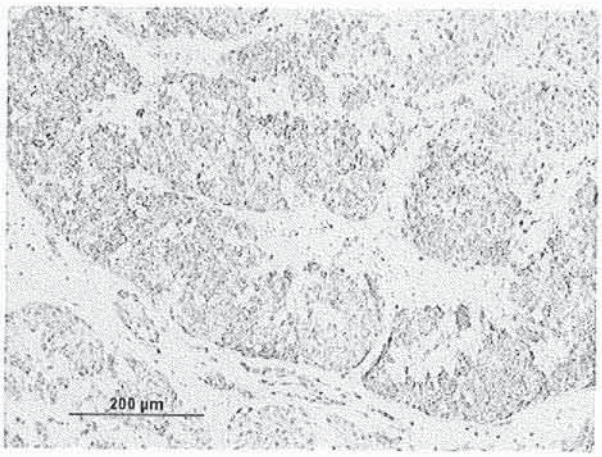

Fig. 6.6 Immunoperoxidase staining for DOG-1 is usually positive in GIST, including those that are negative for CD117. Mutational analysis of this case confirmed the presence of a PDGFR mutation, whereas kit was wild type (same case as Fig. 6.3). (DOG-1, original magnification ×200)

the vast majority of GIST, including in KIT-negative and PDGFR-mutant tumors. Very few non-GIST mesenchymal tumors have been shown to react with DOG-1 (West et al. 2004), which also appears to stain fewer cases of carcinoma, melanoma and seminoma than does CD117 (Espinosa et al. 2008). This antibody is now commercially available and provides a useful additional diagnostic tool in cases where CD117 staining is focal, weak or negative (Fig. 6.6).

6.2.2.3 Other Markers

Other markers which may be expressed in GISTs include the myoid markers smooth muscle actin (SMA) (20–35%) and heavy-caldesmon (80%), whereas desmin is only occasionally positive (<5%). Perhaps surprisingly, expression of S-100 protein is relatively unusual in GIST, being rare in the stomach but somewhat more common (perhaps 14%) in the small intestine. Most GISTs express nestin, but this is of limited value clinically as it is also expressed in gastrointestinal schwannoma, whereas GFAP is negative in GIST. Keratin positivity (generally focal) may be observed, particularly with antibodies reacting to keratin 18, whereas CK7 and CK20 are generally negative (Miettinen and Lasota 2006a).

6.2.3 Electron Microscopy

There are no diagnostic ultrastructural features specific to GISTs, and the appearances may vary somewhat according to anatomic location. Overall, gastric and omental tumors tend to have better developed myoid features than their intestinal counterparts. Cytoplasmic filaments and intercellular junctions are common, with filaments often forming paranuclear

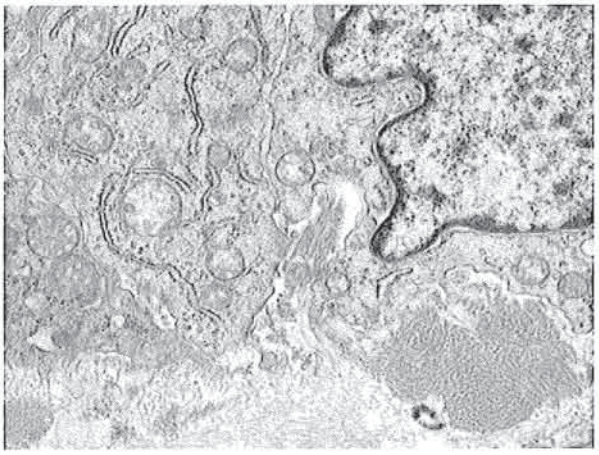

Fig. 6.7 Skeinoid fibers (bottom right, below the nucleus) are most often seen in small intestinal tumors (EM, original magnification ×20,000)

aggregates in epithelioid tumors. The cells tend to have surface filopodia and interdigitating cell processes, but these are often short in gastric and omental tumors whereas in the intestine they tend to be long and complex. External lamina is often poorly formed, and tends to be absent altogether in intestinal tumors. Pinocytotic vesicles are variable in frequency but tend to occur at all anatomic locations, whereas microtubules are more common in intestinal tumors but rare in the stomach or omentum. Skeinoid fibers occur in around one-third of small intestinal tumors, and appear to be largely confined to that location (Yantiss et al. 2002) see Fig. 6.7.

6.2.4 Molecular Biology and Mutational Analysis

6.2.4.1 KIT

The majority of GISTs (perhaps 85%) harbor mutations in the gene encoding the transmembrane receptor tyrosine kinase KIT. These mutations cause functional changes in KIT protein, usually leading to ligand-independent dimerization and constitutive activation of KIT signaling and thereby activation of downstream effectors. These processes commonly involve signal transduction via the transfer of ATP to tyrosine residues on substrate proteins, by tyrosine kinase enzymes. The end result is to stimulate cellular proliferation and impede apoptosis, thereby culminating in neoplasia. KIT mutations most often arise in the juxtamembrane position at exon 11 (around 67% of GISTs, arising at all anatomic sites), with exons 9 (extracellular domain, 10%, occurring in a higher percentage of intestinal GISTs), 13 (kinase 1 domain, 1%) and 17 (activation loop, 1%) being less commonly affected (Miettinen and Lasota 2006b).

6.2.4.2
PDGFR

Most GISTs lacking KIT mutations are wild type (~10%), or have PDGFRA mutations (5–7%). KIT and PDGFR are highly homologous receptor tyrosine kinases. Both genes are located at 4q12, suggesting a common ancestral gene (Miettinen and Lasota 2006b). PDGFR mutations most often occur in exons 12 (juxtamembrane, approximately 1% of GISTs) or 18 (activation loop, 6%), and are commoner in gastric tumors, often having a myxoid and epithelioid phenotype (see Fig. 6.5). Activation loop mutations at D842V (5%) are often associated with extraintestinal location (mesentery and omentum), and imatinib resistance. KIT and PDGFR mutations appear to be mutually exclusive (Miettinen and Lasota 2006b).

Thus molecular analysis for KIT and PDGFR mutations may be useful in establishing a diagnosis of GISTs in challenging cases, and should be performed at diagnosis in high-risk or metastatic GISTs, when it may serve to guide therapy (see below). Fully resected, low-risk GISTs need not be routinely tested.

6.2.4.3
IGF-1

IGF-1 and -2 bind to the IGF-1 receptor and lead to activation of MAPK and PI3K cascades. Braconi et al. (2008) found IGF-1R to be overexpressed in all 94 GISTs analyzed in a series. Strong IGF-1 expression correlated with higher mitotic index, larger size, and a higher risk of relapse and metastasis. IGF-1 and -2 expression both correlated with reduced disease-free survival, which was improved if both IGF-1 and -2 were negative. Immunohistochemistry, quantitative polymerase chain reaction (qPCR) and fluorescent in situ hybridization (FISH) of GISTs have demonstrated significant overexpression of IGF-1R and amplification of the *IGFR1* gene in wild type or pediatric GIST compared to mutant types (Godwin et al. 2008). Inhibition of IGF-1R activity using NVP-AEW541 has been shown to result in cytotoxicity and induce apoptosis in GIST cell lines, via AKT and MAPK signaling (Tarn et al. 2008) suggesting that IGF-1 drives pathogenesis in the subset of GISTs which do not have *KIT* or *PDGFR* mutations, and offers another potential therapeutic target.

6.2.4.4
BRaf V600E

A small subset of tumors studied by Agaram et al., (2008b) were found to harbor BRaf mutations at exon 15 (V600E). These tumors all arose in the small intestine and were classified as high risk and occurred in women aged 49–55 years, raising the possibility of a distinct subset of GISTs, providing an alternative mechanism of imatinib resistance and potentially offering another therapeutic target for some patients.

6.2.4.5 Other

As stated above, 20% of the population has micro-GISTs, with only a few becoming malignant. *KIT* gene mutation is known to be a very early event in tumor genesis, and it is felt additional alterations are necessary for progression to high-risk disease (e.g., loss of chromosomes 1p, 14q, 22q; telomerase reactivation, and microsatellite instability) (Kawanowa et al. 2006).

6.2.5 Behavior and Prognosis

6.2.5.1 Patterns of Metastasis

GISTs most often metastasize within the abdomen, either intraperitoneally or hematogenously to the liver. Metastasis to extra-abdominal sites is rare, but distant metastases can occur in unusual sites including brain (Hughes et al. 2004), testis (Doric et al. 2007) or soft tissues (Pasku et al. 2008).

6.2.5.2 Prediction of Behavior

Histology is an imperfect predictor of clinical behavior, which also varies according to primary site. Primary esophageal GISTs are rare, but most are malignant. Gastric tumors are commonest, with fundic tumors being more often malignant than those arising in the antrum. Small intestinal GISTs are more often malignant and although rare, primary colorectal GISTs frequently metastasize (around 50%) and often follow an aggressive clinical course. In comparison with gastric tumors, intestinal GIST tend to be larger at diagnosis, but even when controlling for size and mitotic count, intestinal tumors tend to be more aggressive, also reflected in differing gene expression profiles. Be that as it may, the two best-documented early criteria for assessment of biologic potential were size and mitotic count. NIH-consensus risk-group stratification criteria for risk of GIST recurrence following resection were published in 2002 (Fletcher et al. 2002) but these did not reflect the importance of location in predicting behavior or of the negative impact of tumor rupture (Joensuu 2008). More recently, the Armed Forces Institute of Pathology (AFIP) (Miettinen and Lasota 2006a) attempted to refine the criteria in terms of location as well as size and mitotic count, although data for rare sites such as esophagus and rectum are still limited. Gastric GISTs <10 cm and with five mitotic figures (mf) per 50 high-power fields (hpf) have a low risk for metastases, whereas those with >5 mf/50 hpf are at high risk. In contrast, intestinal GISTs >5 cm have at least a moderate risk of metastasis, and those with >5 mf/50 hpf are at high risk. Intestinal GISTs <5 cm or <5 mf/50 hpf are relatively at low risk. See Table 6.1.

Table 6.1 Risk stratification of primary GIST by mitotic index, size and site (based on Miettinen and Lasota 2006a)

Mitoses per 50 high-power fields	Size	Gastric	Duodenal	Distal small bowel	Colorectal
<5/50	<2 cm	None	None	None	None
	2–5 cm	Very low	Low	Low	Low
	5–10 cm	Low	Moderate	ID	ID
	>10	Moderate	High	High	High
>5/50	<2 cm	None[a]	High[a]	ID	High
	2–5 cm	Moderate	High	High	High
	5–10 cm	High	High	ID	ID
	>10	High	High	High	High

ID insufficient data
[a]Small numbers

Furthermore, gastric GISTs may be subclassified histologically, which improves estimation of biologic potential. Sclerosing spindle cell GISTs are usually small, mitotically inactive and relatively paucicellular tumors with abundant collagenous matrix which may calcify. The prognosis of this subtype is excellent. Palisading spindle cell tumors reminiscent of schwannoma typically have a low mitotic rate but may attain larger size, despite which the prognosis is generally favorable. Hypercellular spindle cell GISTs without nuclear palisading tend to have more frequent mitoses (often >5 mf/50 hpf), and carry a moderate risk of metastasis. Sarcomatoid spindle cell GIST have diffuse atypia and increased mitoses (often >20 mf/50 hpf), and a greater tendency to metastasize. In the epithelioid group, sclerosing tumors with a somewhat syncytial appearance tend to have few mitoses and a low risk of metastasis. Dyshesive tumors with clearly defined cell borders are intermediate in behavior, whereas hypercellular and sarcomatoid tumors are more aggressive (Miettinen and Lasota 2006a).

Other morphologic factors which may have adverse prognostic significance include the presence of multiple peritoneal nodules and fat infiltration (regardless of primary site), coagulative necrosis and/or ulceration, mucosal invasion (Miettinen and Lasota 2006a), serosal involvement (Goh et al. 2008), the presence of metastases at diagnosis, and tumor rupture (Joensuu 2008, Takahashi et al. 2007). On the other hand, nuclear palisading is statistically favorable in both gastric and intestinal GISTs (Miettinen and Lasota 2006a). Immunohistochemically, loss of p16 expression is common (perhaps 50% of cases), does not correlate with age, sex, histologic subtype, or the presence of necrosis, but appears to be an independent predictor of poor prognosis (Schneider-Stock et al. 2005).

Although metastases may resemble the primary tumor histologically, they are often genetically heterogeneous, harboring a variety of secondary mutations not seen in the primary (Wardelmann et al. 2006). Response to targeted therapy may therefore vary between different tumor deposits (Cameron et al. 2009).

6.3 Diagnosis and Staging

6.3.1 Clinical Presentation

GISTs have a predilection for adults older than 50 years, with a peak at around 60 years. They arise slightly more commonly in men (Miettinen et al. 2005c). GISTs may have a variety of presentations. They may be incidentally detected at gastroscopy, abdominal imaging or laparotomy for unrelated conditions (Miettinen et al. 2005c). The most common presentation is with bleeding, which may manifest as iron deficiency anemia due to chronic blood loss, or as an acute gastrointestinal hemorrhage from the primary causing hematemesis or melena. Rarely rupture of the primary or a metastasis into the peritoneal cavity may produce hemoperitoneum. Obstructive symptoms may occur depending on the location of the primary. For example dysphagia may occur with esophageal GISTs and altered bowel habits in rectal primaries. Advanced disease may present with ascites and a palpable mass. Patients may have considerable disease bulk at initial diagnosis, though this occurs less commonly in modern series. The most common sites of spread are into the liver and the peritoneum. Lung, cutaneous, intracerebral, and bony involvement occur less commonly.

6.3.2 Investigations

Incidental submucosal lesions may be encountered during endoscopy and a biopsy using forceps may be difficult to conduct. Endoscopic ultrasound (EUS) may be used to detect the component of the gastric wall from where the lesion is arising and also to determine echogenicity, which may allow lipomas to be distinguished (these are intensely hyperechoic and arise from the submucosa). Lesions may be observed if small and non-suspicious. If lesions are symptomatic or intramural and hypoechoic, then these are suspicious for malignancy and should be referred for resection (Hwang et al. 2006).

Small bowel GISTs may be more difficult to detect. An abnormality may be found on a barium follow-through examination. Active bleeding sites in the small bowel may be localized by mesenteric angiography however video wireless capsule endoscopy is a more accurate way of diagnosing intraluminal small bowel lesions than conventional imaging modalities (Mazzarolo and Brady 2007).

If lesions are deemed to be easily resectable, preoperative percutaneous biopsy may not be advisable due to the risk of tumor rupture or dissemination (The NCCN Clinical Practice Guidelines in Oncology 2008). A tissue diagnosis is always required however, before instituting neoadjuvant therapy or placing a patient onto a clinical trial.

If GIST is suspected or confirmed, computed tomography (CT) with contrast of the chest, abdomen and pelvis is important in staging the patient to determine the local extent

of disease as well as presence of metastases, with respect to planning further management. MRI imaging of the pelvis for rectal GISTs can give more anatomical information than CT scanning. Functional imaging with fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning is a very useful modality for initial staging as well as monitoring of treatment response to therapy and is complementary to CT imaging.

6.4 Clinical Management

Similarly to other gastrointestinal malignancies, the management of GISTs is multidisciplinary, involving a number of different specialties.

6.4.1 Surgical Management

The technical aspects of the surgery for GIST follow general surgical oncological principles with nuances specific to this tumor type. This means, surgeons with site-specific or disease-specific expertise should be involved with elective surgical treatment. When GISTs present with acute bleeding, perforation, or obstruction and require emergency laparotomy by a general surgeon, pathological material should be available to guide further management.

6.4.1.1 Resectable Primary GIST

Resection without definitive biopsy material is appropriate when the diagnosis of GIST is likely, except as discussed above. Endoscopic biopsy is often unable to definitively diagnose GIST, as a common result is normal overlying mucosa. EUS-guided fine-needle aspiration is usually inadequate to provide a definitive diagnosis (American Gastroenterological Association Institute 2006; Pidhorecky et al. 2000). Transperitoneal core biopsy in a patient with apparently resectable disease risks tumor rupture and seeding (Demetri et al. 2007; Gold and Dematteo 2006; Pidhorecky et al. 2000). A difficulty is when radiological imaging has GIST as one of a number of differential diagnoses, with lymphoma being another. These cases must be decided on an individual basis.

All GISTs are considered potentially malignant, and resection should be considered even for small intramural lesion (≤2 cm) (Blackstein et al. 2006; Blay et al. 2005; Corless et al. 2002). Most treatment guidelines mandate removal of lesions 2 cm in size of larger (Demetri et al. 2007).The decision to observe or remove will depend on the features of the tumor and also its location and the age and fitness of the patient. Small tumors that are not resected should be monitored with periodic EUS or computerized tomography (CT).

The objective of GIST surgery is to remove the primary tumor with negative microscopic margins. This may require *en bloc* resection of adjacent organs and structures such as the spleen, tail of pancreas, diaphragmatic crus, etc. for gastric GISTs. Tumor handling

should be minimized since tumor rupture is associated with poor outcome (Blackstein et al. 2006; Eisenberg and Judson 2004; Gold and Dematteo 2006; Pidhorecky et al. 2000). Open surgery has been standard, but, there is little evidence for avoiding laparoscopic resection of lesions (Everett and Gutman 2008).The principals of laparoscopic surgery are similar to those of open surgery-macroscopic tumor resection, minimal tumor handling, and protection from port-site implantation by the use of a specimen retrieval bag.

As lymphatic spread is rare and nodal metastasis indicates advanced disease, lymphadenectomy is not part of standard surgery for GIST (Blackstein et al. 2006; Eisenberg and Judson 2004; Gold and Dematteo 2006). Clinically or radiologically involved nodes should be resected when feasible as part of the primary operation, but if there is nodal involvement, systemic disease is likely and preoperative systemic therapy would be appropriate. Postoperatively, patients with intermediate- or high-risk primary GIST should be considered for adjuvant imatinib therapy or for entry into an adjuvant trial (see Adjuvant imatinib therapy).

6.4.1.2
Borderline Resectable Disease

Though highly likely to be GIST on imaging (or proven on biopsy) a disease of borderline resectability definitely requires referral to a surgeon with interest and experience in the field and consideration in an appropriate multidisciplinary setting. Options include attempted resection (which may include biopsy for confirmation if unresectable) or non-operative biopsy and subsequent imatinib treatment.

The role of preoperative imatinib is not clearly defined; however, in many patients the disease becomes resectable after response to imatinib. Situations where neoadjuvant therapy might be considered include: potentially resectable GIST where surgery would cause functional impairment (e.g., rectal GIST requiring abdominoperitoneal resection) or loss of organ function (e.g., total gastrectomy), or where a tumor is large and truly locally advanced (Blay et al. 2005).Close monitoring for possible tumor progression on treatment is necessary, though it would be unusual to worsen on short-term therapy. The surgical and medical oncologists should decide the optimal timing of the surgery. As 75% of responding patients achieved their maximal response by 23 weeks in clinical trials, the optimal time to operative after neoadjuvant treatment is at about 6 months (Blanke et al. 2008a). Surgery after treatment with imatinib follows similar principles as primary surgery. The tumor is usually quite soft, which may increase the risk of rupture; however, the vascularity may be reduced, which may facilitate surgery. Imatinib should be continued in patients who have had tumor resection following response to imatinib, and the patient may resume taking drug as soon as oral intake is feasible (Blay et al. 2005).

6.4.1.3
Surgery for Recurrence

Before effective systemic therapy evolved, resection of recurrent disease in the liver and/or peritoneal cavity was the only potential treatment and was routinely considered. While apparent complete resection was sometimes possible, the disease inevitably recurred, and

so the role of surgery in metastatic GIST is uncertain. Resection may be considered in patients with disease responding to imatinib in whom the disease is apparently completely resectable, and in otherwise stable oligo- or multi-focal disease where one tumor mass is growing (clonal escape) and resection is feasible (Demetri et al. 2007; Eisenberg 2006). One report details a progression-free survival rate of 33% at 1 year with such an approach (Raut et al. 2006).The true impact of this approach on disease outcome is the subject of at least two ongoing or proposed clinical trials. Surgery in patients with evidence of generalized progression is associated with poor outcomes and is not recommended.

Occasionally surgery may be useful for palliation of a particular lesion that is bleeding or obstructing. Such surgery is often difficult and potentially morbid, and should only be undertaken after consideration of other options, such as hepatic embolization.

6.4.2 Medical Management

6.4.2.1 Chemotherapy

Historically conventional chemotherapy treatments have not been very successful in the treatment of GISTs. Cytotoxic agents active in soft tissue sarcomas have formerly been employed. A Mayo Clinic study compared patients with leiomyosarcomas with those with GIST treated with a schedule of dacarbazine, mitomycin, doxorubicin and cisplatin plus GM-CSF support. There was a one response seen in 21 patients with GISTs while a 67% (12/18) response rate was seen in leiomyosarcomas. Reviews of the MD Anderson Cancer Center experience of treatment of gastrointestinal leiomyosarcomas (most of which would be GISTs) found a response rate of 3.3% using doxorubicin containing regiments in 120 patients treated between 1948 and 1989 (Plager et al. 1991) and of 13.3% in 30 patients treated with ifosfamide between 1985 and 1989 (Patel et al. 1991). A more recent phase II trial by the same group found no responses to temozolamide in a group of 18 patents with GIST (Trent et al. 2003).

6.4.2.2 Imatinib mesylate (Glivec, Gleevec, (STI571) Novartis)

Imatinib mesylate is an oral phenylaminopyrimidine tyrosine kinase inhibitor that inhibits the PDGFR receptor, KIT kinase, BCR-ABL and ABL kinases. Developed for its activity against the PDGFR receptor, it was also found to be effective against chronic myeloid leukemia. In vitro experiments found the drug to be a potent inhibitor of KIT and also of a GIST cell line (Tuveson et al. 2001). Imatinib selectively inhibits the tyrosine kinase activity associated with KIT, which forms the rationale for its use in GIST (Croom and Perry 2003). The proof of principle came with the treatment of a Finnish woman in 2000 with rapidly progressive advanced GIST refractory to chemotherapy (Joensuu et al. 2001). After a month of starting treatment there was a 52% reduction in tumor diameters in the

liver on MRI imaging and loss of FDG uptake on PET scanning. Fine needle biopsy of the liver metastases showed decreased density of tumor cells as well as development of myxoid degeneration.

This single case study led to the commencement of two early phase studies. The EORTC conducted a phase I study of imatinib with doses ranging from 300 to 1,000 mg/day in soft tissue sarcoma patients (van Oosterom et al. 2001). Thirty six patients with GIST were enrolled and dose limiting toxicity was seen at a dose of 500 mg bd with doses at 400 mg bd and below being more manageable in terms of side effects and less need for dose reduction. Most patients were seen to have major and rapid improvements in symptoms and performance status. Twenty-five patients had an objective response to treatment, with 19 of these being partial remissions.

The US–Finland B2222 study conducted at the same time randomized 147 patients to receive either 400 or 600 mg/day of imatinib (Demetri et al. 2002). A partial response was seen in 53.7% of these patients with 27.9% having stable disease in the initial publication. PET imaging was again found to be a sensitive and rapid indicator of response or resistance to imatinib. An update of this study with a median of 63 months follow-up (and 71 months maximum follow-up) has found an overall response rate of 68% with two cases of complete remission seen (Blanke et al. 2008a). The median time to progression was 24 months. This gives an estimated 5-year survival of 57% with no differences in either overall response, time to progression, response duration or overall survival between the two doses. Twenty eight percent of the cohorts were still taking imatinib at the last follow-up, suggesting that long-term survival, even with advanced disease, is possible.

The North American Sarcoma Intergroup S0033 phase III trial randomized 746 patients to two dose levels (400 vs. 800 mg) of imatinib (Blanke et al. 2008b). Crossover to the higher dose level was allowed on disease progression. At a median follow-up of 4.5 years, no difference was seen in the overall response rate in either arm of 45%. The median progression-free survivals were 18 and 20 months, respectively, and median overall survivals 55 and 51 months, respectively; neither of which were statistically different. A third of the patients on the standard arm who crossed over to the higher dose achieved an objective response or stabilization of their disease. Serious adverse events and possible treatment related deaths were higher on the 800-mg arm.

The EORTC, Italian Sarcoma Group (ISG) and Australasian Gastrointestinal Trials Group (AGITG) conducted a parallel randomized study which enrolled 946 patients with advanced GIST to 400 vs. 400-mg bd of imatinib (Verweij et al. 2004). After approximately 25-months median follow-up, 56% of patients in the 400 mg arm were found to have disease progression compared to 50% in the higher dose arm ($P=0.026$). However, at the 40-month median follow-up, there was no statistical difference in the progression-free survivals of each arm (Casali et al. 2005). No differences were seen in the response rates in either arm and in total for the group there was a 5% complete remission rate, 47% partial remission and 32% stable disease. As expected there were a higher number of dose reductions (60 vs. 16%) and dose interruptions (64 vs. 40%) in the higher dose arm due to toxicity compared to the lower dose arm. Patients on this study were also allowed to cross over to the higher dose on progression if they were on the standard dose to start with. Fifty-four percent of the patients who met protocol criteria for crossover (113/241) went over to the higher dose and only 17% required a subsequent dose reduction (Zalcberg et al. 2005).

The partial response rate with dose escalation was 2 and 27% with stable disease. Eighteen percent were progression-free at 12 months following crossover.

The licensed starting dose of imatinib for metastatic GIST is 400–600 mg/day. The EORTC-ISG-AGITG and the North American Intergroup S0033 trials both compared two dose levels of imatinib (400 vs. 800 mg/day). The studies were designed so that data could be combined in a preplanned meta-analysis, the MetaGIST project (Van Glabbeke et al. 2007). With a median follow-up of 45 months no difference in overall survival was seen in the arms but there was a small improvement in progression-free survival with the high dose arm (HR 0.89, $P=0.04$). Multivariate analyses were carried out to determine whether there were any factors that influenced survival and to find subgroups that benefitted from the higher dose. Adverse prognostic factors were found to be male sex, poor performance status, bowel origin, low baseline hemoglobin and high baseline neutrophil counts. Exon mutational analysis was available from 47% of the cohort. This confirmed that exon 11 mutations had a better PFS and overall survival (26 and 60 months) than either exon 9 (13 and 31 months), wild type (16 and 43 months) and other mutations (16 vs. 34 months). The only factor that showed a benefit to high dose imatinib in improved PFS was exon 9 mutation status (HR 0.58, $P=0.017$) but this did not translate into improved overall survival (numbers were small, however). This would support a strategy of using an imatinib starting dose of 800 mg/day (Casali et al. 2008). Where licensing restrictions prevent this, patients with the mutation may be able to start on 600 mg/day or alternatively they need closer monitoring for evidence of lack of disease control on the 400 mg dose so that dose escalation can be implemented on progression.

Tumors with exon 11 mutations are often aggressive but tend to respond to imatinib because the mutation results in a conformational change in KIT which allows a better "fit" of the imatinib molecule into the ATP-binding pocket in the intracellular domain of the KIT molecule. Tumors with exon 11 *duplication* may be associated with better survival. Exon 9 mutations are more often seen in intestinal tumors rather than gastric, and are associated with aggressive behavior. Higher dose imatinib is indicated in these tumors (Debiec-Rychter et al. 2006).

Many patients who initially respond to imatinib ultimately develop progressive disease. This secondary imatinib resistance often arises after around 2 years of therapy in primary exon 11 mutations (Heinrich et al. 2008) and is usually associated with secondary KIT or PDGFR mutations. Several distinctive secondary point mutations have been identified, generally affecting the same allele as the primary mutation (Antonescu et al. 2005). Furthermore, after mutated receptors are switched off, heterologous wild-type tyrosine kinase receptors may become an important means of maintaining signaling activation in imatinib-exposed GIST (Negri et al. 2009).

6.4.2.3 Toxicity of Imatinib

The toxicities of imatinib mesylate are generally manageable (Harrison and Goldstein 2006). In many clinical trials gastrointestinal hemorrhage either into the gut or into the abdominal cavity has been observed in a small number of patients. This may be a result of

direct mucosal disruption or of tumor response. The latter tends to affect patients with high tumor bulk and emergency surgical intervention may be indicated. In the US–Finland trial hemorrhage occurred in 5.4% of patients (Demetri et al. 2002). The S0033 trial reported significant bleeding in 5% of the low dose arm and 11% of the higher dose with four patients in the higher dose dying from the hemorrhage (Blanke et al. 2008b).

Hematological toxicities are common and usually mild not requiring any treatment. It is dose related and on the clinical trials where a higher dose is used significant anemia, neutropenia and thrombocytopenia is observed which may require treatment interruption and dose reductions.

The most commonly described nonhematological side effects are gastrointestinal, especially nausea and vomiting. These may respond to splitting the dose or taking the tablets with food and water or at night. Diarrhea may occur and respond to anti-diarrheal agents.

An erythematous and pruritic maculopapular rash can occur which responds to treatment interruption and dose reduction as well as topical steroids and antihistamines. Superficial edema of the legs as well as in the periorbital region is common and usually does not required specific treatment. Severe cases may require use of diuretics.

Liver function abnormalities can occur uncommonly and may be managed again by dose interruption and reduction; rarely systemic steroids are needed.

Investigators from the EORTC-ISG-AGITG study have analyzed the relationship of toxicities to imatinib and pretreatment factors to see which are prognostic ones (Van Glabbeke et al. 2006). Anemia was found to correlate with dose and baseline hemoglobin, while neutropenia was found to correlate with baseline neutrophil count and hemoglobin level but was not dose dependent. Nonhematological toxicities were also dose related. High toxicity rates were found in female sex (edema, nausea and diarrhea), older age (edema, rash, fatigue), poor performance status (fatigue and nausea), prior cytotoxic treatment (fatigue), small lesions (rash) and identified gastrointestinal origin tumor (diarrhea). A predictive spreadsheet calculator incorporating this model has been validated on a separate dataset and is available from www.eortc.be/tools/imatinibtoxicity.

6.4.2.4 Dosing of Imatinib Mesylate

The pharmacokinetics of imatinib may vary between individuals due to factors such as body weight, loss of absorptive surface of the small bowel due to resection, cytochrome P_{450} 3A4 polymorphisms, P glycoprotein polymorphisms, OCT1 efflux pump activity, albuminemia and alpha1 acid glycoprotein binding (Gurney et al. 2007; White et al. 2006; Widmer et al. 2006). Over time serum levels in individual patients may also vary due to drug interactions (especially those that interact with cytochrome P_{450} 3A4) and medication non-compliance. It has been found that there is a trend towards increased imatinib clearance with long-term exposure (Judson et al. 2005). Low plasma imatinib trough levels have been found to correlate with a lower overall response rate and time to progression in a subset of patients treated on the B2222 study where pharmacokinetic monitoring was carried out (von Mehren et al. 2008). Maintaining imatinib trough levels above 1110 ng/mL may help to optimize dosing of the drug for therapeutic effect (Demetri et al. 2008).

Excessively high plasma levels may provide an explanation for treatment toxicities and support implementation of dose reduction without an expected loss of efficacy.

6.4.2.5
Duration of Imatinib Therapy

Imatinib may produce striking responses in metastatic GISTs, with marked tumor shrinkage and loss of functional tracer uptake on PET imaging. However, serial biopsies of responding lesions have shown that despite the development of myxoid degeneration there continued to be viable tumor cells present (Joensuu et al. 2001). The French Sarcoma Group BFR14 study attempted to assess the effect of treatment interruption of patients on imatinib vs. continuation (Blay et al. 2007). This trial enrolled 182 patients with advanced GIST and 58 of the 98 patients who had received a year of imatinib and were stable or responding were randomized to treatment interruption or discontinuation. At the date of analysis 8 of 26 patients in the continuation arm had progressed while 26 of 32 patients had progressed on the interruption arm. There were no differences observed in the quality of life, overall survival or the rate of resistance to reintroduction of imatinib. The trial has continued with another randomization of 50 patients (excluding patients who were interrupted at 1 year) who were still responding at 3 years (Adenis et al. 2008). Again it was found that there was a high rate of progression with 1 year PFS in the interruption arm being 23.7 vs. 87.7% for continuation. Another randomization is ongoing at the 5-year mark (Duffaud et al. 2009). All progressing patients were salvaged on reintroduction of imatinib and no impact on overall survival was seen. No difference so far has been seen in the time to development of secondary resistance on either arms of the study, and reintroduction of imatinib leads to reinduction of response in 93% of subjects (Duffaud et al. 2009). This study thus indicates that discontinuation of imatinib is associated with a high relapse rate and that maintenance treatment is recommended.

6.4.2.6
Management of Progression on Imatinib

Isolated areas of tumor progression indicating the development of resistant clones may be treated by surgery or ablative procedures such as radiofrequency ablation whilst continuing imatinib to maintain control of sensitive clones. This is aimed at eliminating the drug resistant clones and may be associated with prolonging progression-free survival (Raut et al. 2006). See above Sect. 6.4.1.3.

Generalized or multifocal progression should be first treated by dose escalation of imatinib to 400 mg bd if patients are already on the 400 mg/day dose. This may establish tumor control in about a third of patients (Verweij et al. 2004). Dose escalation is associated with increased side effects, but the rate of dose reduction required within 6 months with dose escalation from 400 to 800 mg/day is less if patients are initially started on the higher dose (17 vs. 50%) (Zalcberg et al. 2005). The median duration of benefit in dose escalation is estimated at 11.6 weeks (Zalcberg et al. 2005).

If dose escalation is ineffective then use of the multi-kinase inhibitor sunitinib should be implemented outside of a clinical trial setting (see below). Continuation of imatinib until alternative therapy is started is recommended to prevent a flare response of the imatinib sensitive clones on withdrawal of the medication which may cause rapid clinical deterioration.

6.4.2.7 Sunitinib (Sutent (SU11248) Pfizer)

Sunitinib is an oral multikinase inhibitor which blocks a number of targets including KIT, PDGFR, VEGFR, RET and CSF-1R. In a randomized phase III registration study, 312 advanced GIST patients with imatinib resistance or intolerance received either sunitinib or placebo in a 2:1 allocation in a 4-weeks on and 2-week off schedule of 50 mg/day (Demetri et al. 2006). Crossover of the placebo arm was allowed on tumor progression. The trial was unblinded early when planned interim analysis revealed a prolongation in time to progression with sunitinib. Median time to progression was 27.3 vs. 6.4 weeks with placebo. An overall response rate of 7% was seen with sunitinib and 0% with placebo. Stable disease lasting at least 22 weeks was seen in 17%. Despite the crossover overall survival was better in the upfront sunitinib group (HR 0.49, $P=0.007$). As a result sunitinib is licensed for second line therapy of advanced GIST in the 4 week on and 2 week off schedule.

Continuous daily dosing of sunitinib at 37.5 mg/day either in the evening or in the morning has been shown be safe and efficacious in a phase II study in patients with imatinib resistant or intolerant GIST (George et al. 2009). There were no other new toxicities seen and response rates as well as toxicity were similar to those reported in the 4 weeks on 2 weeks off schedule. Constant serum levels were maintained with no accumulation over time. Twenty-three percent of patients still required dose reductions to 25 mg daily.

Sunitinib is associated with side effects of nausea, fatigue, diarrhea, mucositis, hand-foot syndrome, and skin discoloration. The drug may also cause hematological toxicity in terms of anemia and neutropenia. These side effects were generally mild and manageable by dose delay or reduction. Hypertension may occur due to its anti-VEGF effect, and initiation or titration of an antihypertensive may be required. Hypothyroidism is well recognized as a complication of sunitinib therapy. In a series of 42 patients with advanced GIST treated with the drug, 62% exhibited TSH abnormalities with 38% becoming hypothyroid (Desai et al. 2006). Some patients were noted to have a transient fall in the TSH level before developing hypothyroidism and two patients were found to have absent thyroid tissue on neck ultrasound, suggesting that the mechanism for this is the induction of a destructive thyroiditis. It is thus important to measure monitor thyroid functioning and initiate thyroid replacement therapy if necessary.

The effect of primary and secondary kinase genotypes in sunitinib response has been studied in a series of 97 patients with imatinib refractory GIST (Heinrich et al. 2008). The clinical benefit of sunitinib observed on patients with primary exon 9 or wild type mutations were higher than those with exon 11 mutations (58 vs. 56% vs. 34%). Similarly the

overall response was higher in exon 9 than exon 11 (37 vs. 5%, $P=0.02$). Longer median progression-free survivals were seen with exon 9 (19.4 months, $P=0.005$) and wild type (19.0 months, $P=0.0356$) compared to exon 11 (5.1 months). This translated into higher median overall survivals of exon 9 (26.9 months, $P=0.012$) and wild type GISTs (30.5 months, $P=0.0132$) compared to exon 11 (12.3 months). Secondary kinase mutations were seen more commonly in the primary exon 11 patients compared to exon 9 (73 vs. 19%) and no secondary mutations were observed in wild type GISTs on imatinib. Patients with acquired exon 13 or 14 mutations which encode the receptor ATP binding pocket had a median progression-free survival of 7.8 months compared to exon 17 or 18 which encode the activating loop (2.3 months, $P=0.0157$) correlating with higher clinical benefit (61 vs. 15%, $P=0.011$) with sunitinib. This is supported by in vitro autophosphorylation studies indicating that exon 13 and 14 mutations were sensitive to sunitinib while secondary exon 17 and 18 mutations were resistant.

6.4.3 Assessing Response to Therapy

CT scan imaging may be used to monitor response to therapy. Scans should be performed with oral contrast (to outline bowel) and in triple phase (to detect hypervascular liver metastases). Conventional measurement of response to treatment in solid tumors is with the use of the response evaluation criteria in solid tumors (RECIST) criteria (Therasse et al. 2000). This relies on measuring change in maximal tumor diameters. However, a number of factors in GIST serve to make RECIST a less than ideal methodology for response measurement. Increase in tumor size may occur due to intratumoral hemorrhage or cystic changes developing due to myxoid degeneration in lesions as a result of treatment response. Localized intratumoral progression may occur with resistant clones causing a new 'nodule within a mass' to develop without increasing the size of the preexisting lesion (Shankar et al. 2005). Choi et al. (2007) have proposed a new set of CT scan criteria to measure response in GIST which incorporates changes in tumor density (quantified by change in Hounsfield units) and smaller changes in tumor sizes. This has been found to correlate well with functional response measured with PET scans. These criteria have been validated in a independent dataset (Benjamin et al. 2007).

FDG-PET is useful in detecting early response to biological therapy if the tumors are FDG avid to begin with. A marked reduction in metabolic activity may be seen within days of initiation of therapy much earlier than can be detected on CT imaging (Stroobants et al. 2003). Changes in tumor density can cause apparently new lesions to appear on CT imaging on response to therapy and PET may determine these are hypofunctioning and not due to tumor progression. Conversely this modality is useful in detecting tumor relapse or progression. See Fig. 6.8.

Dynamic contrast-enhanced Doppler ultrasound (DCE-US) is currently being developed as a functional imaging method of monitoring response of GIST to therapy. It involves the measurement of uptake of ultrasound microbubble contrast agents by tumor (Lamuraglia et al. 2006). This may become a less expensive method and more widely used functional imaging modality once validated.

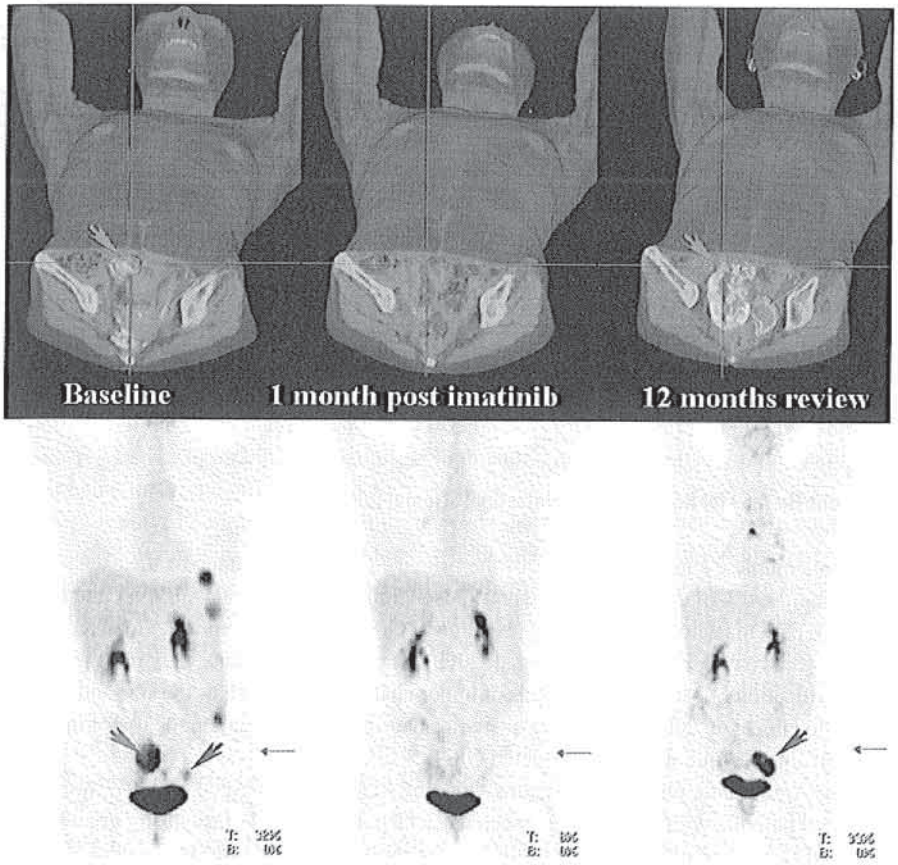

Fig. 6.8 FDG-PET/CT imaging of patient with metastatic GIST shows a baseline study with several metabolically-active peritoneal deposits. Highlighted are two pelvic lesions in the pelvis as visualized on volume-rendered PET/CT above and coronal PET images below. There is a larger and more intense abnormality at baseline (red arrow) and smaller, less intense lesion (blue arrow). One month following imatinib there was a complete metabolic response in all lesions. By 12 months there had been significant CT regression of most lesions except the left pelvic lesion. PET demonstrated recrudescent activity in the small right pelvic lesion as well as intense uptake in the previously low-grade left pelvic lesion. These images emphasize the heterogeneity that can exist in biology at baseline evaluation and a variable response to therapy, suggesting clonal mutational variations

6.4.4 Radiotherapy

There is paucity of data in the literature regarding the utility of radiotherapy in GIST. The location of GISTs and their pattern of spread usually make it difficult to deliver adequate doses of radiotherapy without causing toxicity to surrounding organs.

There are some isolated reports of its use as adjuvant therapy after resection. In a prospective series of 50 patients from Toronto ten patients with small intestinal GIST were

given adjuvant radiotherapy (Crosby et al. 2001). All the patients who received radiation subsequently relapsed with three of the cases being within the radiotherapy field and six outside the field. In the remaining patient it was not possible to determine where the recurrence was relative to the field. There is a case report of a rectal GIST patient with probable microscopic positive margins who remained disease free on 2-year follow-up after receiving radical radiotherapy (50.5 Gy) to the tumor bed (Pollock et al. 2001). A more recent series of 39 patients with primary or recurrent rectal or pararectal space, GISTs identified 6 patients who received radiotherapy. One patient achieved stabilization of disease after imatinib failure and out of five where post operative radiotherapy was received, only one developed a further recurrence (Mussi et al. 2008a).

The consideration of use of palliative radiotherapy in symptomatic areas such as bony or cutaneous metastases would be reasonable, but data as to effectiveness are lacking.

6.4.5 Adjuvant Therapy for Resected Gastrointestinal Stromal Tumor

Despite complete surgical resection of the primary GISTs, recurrence or metastases may occur in 40–90% of cases (Eisenberg and Judson 2004). The five-year survival rate from a series of patients who achieved gross resection of GIST from the Memorial Sloan Kettering Cancer Centre was 54% (DeMatteo et al. 2000). The risk of recurrence may be determined by stratification of patients on the basis of tumor characteristics such as the size and mitotic rate (Fletcher et al. 2002). A number of studies have been conducted on the use of imatinib in adjuvant systemic therapy of resected GISTs.

The American College of Surgeons Oncology Group (ACOSOG) Z9001 study randomized patients with completely resected c-KIT positive GISTs measuring greater than or equal to 3 cm to placebo or imatinib 400 mg daily for 1 year (DeMatteo et al. 2007a). On relapse patients were allowed to crossover to the drug if on placebo or double the dose of imatinib if already on it. The trial was stopped early when interim analysis showed a significant advantage in reduction in relapse with the imatinib. One-year relapse free survival with imatinib vs. placebo was 97 vs. 83% and 2 year relapse free survival 90 vs. 71%. After unblinding, the placebo arm patients were allowed to go onto imatinib for a year. The patients had been stratified on the basis of tumor size only (with no consideration of mitotic rate) and the group that obtained the most benefit was the >10 cm group; however, patients with GISTs of all sizes statistically obtained improved results. No difference in overall survival has yet been seen. This may be due to the short period of follow-up or possibly that imatinib may be successfully reserved for salvage of relapsed disease.

An earlier adjuvant study performed by the ACOSOG was the phase II Z9000 trial of imatinib 400 mg/day for 1 year in c-KIT positive patients with high risk resected GIST (DeMatteo et al. 2008). High risk was defined as tumors ≥10 cm, ruptured or multifocal. At 3 years median follow-up relapse free survival at 1, 2, and 3 years have been reported as 94, 73, and 61% respectively. Overall survivals for the same time periods are 99, 97, and 97%.

Nilsson has reported a small pilot series of 23 patients with high-risk resected GIST patients who were also treated for 1 year with imatinib (Nilsson et al. 2007). With a mean

follow-up of 40 months only 1 (4%) of the patients has relapsed. This was compared to a matched historical control group of 48 patients derived from a population based series (Nilsson et al. 2005) where 32 patients (67%) relapsed. Mutational analysis was performed and interestingly the relapse in the pilot study was in a wild type pediatric GIST case. Another small multicentre single armed study has been reported early results from China where 57 patients with high risk GIST were enrolled to receive imatinib for at least 12 months (Zhan and China Gastrointestinal Cooperative, 2007). With about 75% of patients completing 12 months of treatment only two relapses have been seen.

There are two other large phase III trials of adjuvant imatinib in resected GIST which have completed enrollment but are yet to report results. The first is the EORTC 62024 trial which randomized 750 patients with resected intermediate and high risk GIST to either observation or 2 years of imatinib 400 mg daily. The primary endpoint of this study was overall survival but this was subsequently amended to time to secondary resistance. Another trial the Scandinavian Sarcoma Group SSGXVIII trial enrolled 400 patients and compares 12 vs. 36 months of imatinib in high and very risk patients with the main endpoint being recurrence free survival.

In summary, 12 months of imatinib mesylate does seem to reduce early recurrences. Longer follow-up will be required along with the results of ongoing randomized studies to determine whether this is sustained and whether this may translate into an overall survival benefit. The appropriate duration of adjuvant therapy will also be partly answered by these studies.

6.4.6 Neoadjuvant Therapy for Locally Advanced GISTs

The use of neoadjuvant systemic biological therapy for locally advanced GISTs may be justified if the aim is to render initially inoperable tumors resectable by shrinkage (so-called conversion therapy) or if it allows preservation of organ function by allowing a less radical operation by shrinkage of the disease. A number of retrospective series have described this approach. A Polish series (Rutkowski et al. 2006) analyzed surgical resection of 32 out of 141 patients with inoperable or metastatic GIST who were treated with imatinib. Surgery was carried out either for residual disease after response (24 patients, 17%) or for salvage (eight patients) after progression on imatinib. In those patients who achieved complete remission after resection of downstaged tumor and did not continue imatinib the early relapse rate was high. Subsequent patients were continued on imatinib post surgery and more durable remissions were achieved. Despite the continuation of imatinib the results of salvage surgery was not good with five patients relapsing. A French paper (Bonvalot et al. 2006) reported surgery in 22 (12%) out of 180 advanced GIST patients treated with imatinib. Of these five patients, emergency operations were due to tumor rupture. The rest were planned resections either for the primaries or metastases. The observed progression-free survivals for downstaged tumors were however similar to that of nonoperated patients. An Italian series (Fiore et al. 2009) of 15 patients found that all patients responded to imatinib and underwent surgery with a 77% 3-year progression-free survival from commencement of imatinib. The recently published RTOG 0132 phase II

trial examined the use of preoperative imatinib 600 mg daily in 63 patients potentially resectable GIST (Eisenberg et al. 2009). These were a mix of primary GIST and recurrent GIST. An additional 24 months of adjuvant imatinib was given post operatively. Operative complications and toxicity of therapy were found to be minimal. Likewise a Memorial Sloan Kettering Cancer Centre series described 40 patients who received tyrosine kinase therapy before proceeding to resection after a median of 15 months (DeMatteo et al. 2007b). All but one patient initially had disease stabilization or partial response. In the 20 patients who were responding at the time of resection, the 2-year progression-free survival and overall survival were 61 and 100%, respectively. Of the 13 patients who had surgery for focal progression the median time to progression was 12 months and the 2-year overall survival 36%. Multifocal disease progression was associated with poor outcomes with surgery in seven patients. The median time to progression was 3 months with 1-year survival of 36%. This would suggest that surgery in the context of multifocal progression is not indicated.

The German APOLLO study is a phase II study to examine the benefit of neoadjuvant imatinib in locally advanced GIST. The primary endpoints are radiological and histological response, and secondary endpoints are achievement of R0 resection and organ preservation. The EORTC is conducting a randomized trial of surgery or no surgery in patients with locally advanced GIST who are downstaged to potential resectability.

6.4.7 Other Agents in Development

6.4.7.1 Nilotinib (AMN107, Tasigna, Novartis)

Nilotinib is a second generation tyrosine kinase inhibitor with activity against KIT, PDFR and BCR-ABL. It achieves 7–10 times the intracellular concentration as imatinib. In vitro studies show some activity in imatinib resistant cell lines and also some synergy with imatinib. A phase I dose escalation study was conducted in 53 patients with imatinib refractory GIST (Von Mehren et al. 2007). Eighteen patients received nilotinib alone and 35 received it in combination with imatinib. The maximal tolerated dose (MTD) was established as being nilotinib 400 mg bd with imatinib 400 mg daily. In the monotherapy cohort of 18 patients 1 partial remission and 13 stable disease were seen (tumor control rate of 78%) with median duration of disease control being 158 days. In the MTD cohort of 16 patients 1 partial remission and 9 patients had stable disease (tumor control rate 62%) with median duration of control being 259 days (Blay et al. 2008). A retrospective analysis has been conducted for 42 patients with imatinib and sunitinib resistant GIST enrolled onto a multicountry European compassionate access program of nilotinib at a dose of 400 mg bd. Four partial remissions and 15 stable disease response were seen giving a clinical benefit of 45%. Toxicity led to cessation of the medication in 12%. The median overall survival was 211 days. A phase III study of third line nilotinib vs. best supportive care has been completed and results are awaited. A frontline phase III study of imatinib vs. nilotinib has also been initiated.

6.4.7.2
Sorafenib (BAY 43 1006, Nexavar, Bayer)

Sorafenib is an oral multikinase inhibitor that inhibits KIT, VEGFR, PDGFR and Raf kinases. In vitro inhibition of imatinib resistance GIST cell lines have been observed (Guo et al. 2007). Preliminary results of a phase II trial of sorafenib in patients with imatinib resistant and both imatinib and sunitinib resistant advanced GIST patients have shown activity of the drug (Wiebe et al. 2008). Three out of 24 patients have had a partial remission and 14 stable disease with disease control rate 71%. Median progression-free survival was 5.3 months and median survival 13 months. A European series has reported preliminary data on 24 GIST patients treated with sorafenib in the fourth line setting following failure of imatinib, sunitinib and nilotinib) (Gelderblom et al. 2009). Twenty percent have achieved partial remission and 50% stable disease. Half the patients had a clinical benefit in terms of improvement in performance status or symptoms.

6.4.7.3
Retaspimycin Hydrochloride (IPI-504, Infinity Pharmaceuticals)

Retaspimycin is a water soluble heat shock protein 90 (HSP90) inhibitor. HSP90 is a protein chaperone that is responsible for the folding, stability and localization of mutated "client" proteins such as c-KIT and PDGFR. In vitro experiments have shown that HSP90 inhibition has inhibitory effects on imatinib sensitive and imatinib resistant GIST cell line KIT oncoproteins (Bauer et al. 2006). A phase I study has determined a dosing schedule of 400 mg twice weekly for 2 weeks out of three (Wagner et al. 2008). Forty-five patients with GIST were treated and 32 assessable for response. At 6 weeks the partial remission rate was 3% and stable disease 67% (70% disease control rate). The median progression-free survival was 12 weeks. Commonly seen side effects were fatigue, headache, nausea, diarrhea, myalgia and first-degree heart block. A phase III double blind, placebo controlled study of retaspimycin (RING trial) in refractory GIST commenced enrolment of patients who have previously been treated with at least imatinib and sunitinib. This study was halted in April 2009 when early review of data found a higher than expected mortality in the study arm.

6.4.7.4
Everolimus (RAD001, Afinitor, Novartis)

Everolimus is an oral mammalian target of rapamycin (mTOR) inhibitor. It has been found that in imatinib resistance that downstream kinase signaling pathways which include the AKT/mTOR and MAP kinase pathways remain activated (Fletcher et al. 2003). Synergism has been found between imatinib and everolimus in GIST cell lines leading to the conduct of a phase I/II trial of this combination in imatinib resistant GIST (van Oosterom et al. 2005). This established a safe tolerable dose of imatinib 600 mg and everolimus 2.5 mg daily. In the phase I part of this study 31 patients were treated in dif-

ferent everolimus dose cohorts. Stable disease was observed in eight patients and two experienced partial remissions. The phase II part of the study enrolled patients in two strata; those following one line of prior therapy, and those who were second line failures (Dumez et al. 2008). Four-month progression-free survival was 17.4% in 23 evaluable out of 28 patients in the first stratum while it was 37.1% in the 35 of 47 evaluable patients in the second cohort. Common side effects included mild fatigue, diarrhea, vomiting, nausea, anemia, headache and rash.

6.4.7.5
Motesanib Diphosphate (AMG706, Amgen)

Motesanib is an oral small molecule multi-kinase inhibitor targeting c-KIT, PDGFR and VEGFR1–3. Two phase II clinical trials have been performed with this agent in advanced imatinib refractory GIST patients. The first multinational study enrolled 139 patients of whom 120 were eligible on the basis of confirmed prestudy disease progression (Benjamin et al. 2006). The response rate on RECIST criteria was 3% with 46% of patients having stable disease as the best response. Durable stable disease of more than 22 weeks was seen in 24%. Median progression-free survival was 16 weeks and median overall survival was 14.8 months. FDG PET imaging was performed at 8 weeks and in the 89 patients who had baseline and week 8 scans the response was 30%. Choi criteria was also used to evaluate responses at week 8 and of the 96 patients evaluable for efficacy the response rate was 33% on the basis of reduced tumor density and/or tumor size. The second study was conducted in Japan and reported on the initial 35 patients who had received more than one dose of motesanib (Yamada et al. 2008). There was one partial response and seven patients had stable disease for more than 24 weeks. Median progression-free survival was 113 days.

6.5
Conclusion

Great progress has been made in the understanding of the biological basis behind the pathogenesis of GISTs in the last 10 years. This understanding has translated directly into clinical breakthroughs in the management of this rare disease, which in the past had no effective therapies except surgery. These developments in targeted biological therapies have come at a rapid rate and made an enormous difference in the survival and quality of life of patients with advanced disease. The management of GIST is necessarily multidisciplinary and involves coordinated care of patients spanning gastroenterologists, surgeons, pathologists, scientists, radiologists, nuclear physicians and medical oncologists. Further advances in the understanding of the tumor biology will lead to progression of new agents from the laboratory to the clinic, thereby providing further therapeutic options for patients in the future.

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