GUIDELINES FOR THE MANAGEMENT OF GASTROINTESTINAL STROMAL TUMOURS (GIST)

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Key Recommendations

	Level of evidence & grading[1]
Management	
• The management of GISTs should be undertaken by a multidisciplinary team (MDT) with experience in this disease	C IV
Diagnosis	
• Pathological review of all cases should be made by a pathologist experienced in this tumour type	B III
• For resectable tumours, a definitive diagnosis is often made after surgery	C IV
• For patients with unresectable and/or metastatic tumours, a biopsy should be taken and a definitive diagnosis made before treatment	C IV
Imaging studies	
• Endoscopic ultrasonography (EUS), especially of the oesophagus, stomach, duodenum, and the anorectum, can confirm the diagnosis of small incidental GISTs <2 cm	B III
• For large tumours, computed tomography (CT) of chest, abdomen and pelvis is recommended to assess primary tumour extension and to stage for metastases	B III
• For ano-rectal tumours, magnetic resonance imaging (MRI) is useful in locoregional staging	B III
• PET-CT may be considered to aid assessment when radical surgery is required, particularly of the duodenum, rectum and oesophagus	C IV
• Contrast-enhanced CT scanning is the standard imaging modality for assessing response to tyrosine kinase therapies	B III
• PET-CT may be useful for monitoring response to therapy, emerging resistance and where there is diagnostic uncertainty on CT scans, but is not a substitute for contrast-enhanced CT scanning	B III
• PET-CT scans should be reviewed by an experienced sarcoma or gastrointestinal radiologist with knowledge of GISTs	C IV
• All imaging studies should be presented in a standardised and consistent format and reviewed and discussed by the MDT	C IV

Histopathology and immunohistochemistry

- Macroscopic examination of the resected tumour, with adequate sampling for histological examination and for immunohistochemistry, should be performed — C IV
- Biopsies should sample multiple sites and include some normal tissue — C IV
- Laparoscopic biopsies may be considered if a biopsy cannot be obtained by other means — C IV
- Control slides should include normal gastric body wall as a staining control and tumour to allow for direct comparison of staining — C IV
- The diagnosis of GIST is supported by positive CD117 staining as part of an adequately controlled immunohistochemical panel in a spindle cell tumour of the GI tract when morphologic and clinical features of the tumour are consistent with GIST — B III
- DOG1 is a useful marker of GIST and should be used in conjunction with CD117 and CD34 staining — B III

Prediction of tumour behaviour

- All GISTs have malignant potential, but the risk of this is minimal for very small tumours — B III
- The risk assessment criteria for prognosis proposed by Miettinen and Lasota (2006) should supersede those agreed by the National Institutes of Health Consensus workshop — B III
- All small bowel GISTs and all intermediate and high risk GISTs, regardless of location, should have mutational analysis — C IV
- Mutational analysis should include at least assessment of KIT exons 9 and 11, and PDGFRA exons 12 and 18 for mutations. If apparently wildtype, additional exons will need to be examined to rule out rare primary mutations — B III
- Mutational analysis should be performed at a recognised centre to ensure quality control — C IV

Treatment – Resectable disease

- Surgery is the principal treatment for GISTs and suitability for resection should be explored by an appropriate sub-specialist surgeon — B III
- Patients should be considered for inclusion in clinical trials of neoadjuvant and adjuvant therapy — C IV

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Preoperative assessment

• A chest, abdominal and pelvic CT should be included in the preoperative assessment	B III
• EUS may provide useful information prior to surgery on small <2 cm tumours	B III
• Endoscopy should not be used in isolation to assess small tumours (<2 cm) prior to surgery	C IV
• Percutaneous biopsies should not be used if the tumour is considered resectable	C IV
• If at assessment a tumour is deemed not resectable without unacceptable morbidity, treatment with imatinib is appropriate	B III
• The recommended starting dose of imatinib is 400 mg/day	A Ib

Principles of surgery

• A wide local resection with macroscopic and microscopic removal of the entire tumour is recommended (R0)	B III
• The surgeon should aim to preserve function, but not at the expense of an R0 resection	B III
• Extended lymphadenectomy is normally not required	B III
• Some small tumours may be resected laparoscopically	B III
• Where adjacent organs are involved, *en bloc* resection is recommended whenever possible – input from other specialist surgeons should be considered prior to embarking on such a resection	C IV
• Endoscopic resection is not recommended	B III

Treatment following resection

• Adjuvant therapy with imatinib may be considered in patients predicted to have a high risk of recurrence	A Ib
• The recommended starting dose of adjuvant imatinib is 400 mg/day	A Ia

Follow-up following resection

- All patients following resection should be discussed in a MDT — C IV
- All patients should be followed-up by clinicians linked to the MDT — C IV
- CT is the primary modality for detecting recurrence, but MRI can be considered for annual scans to reduce radiation dose — C IV
- After baseline clinical review, for patients with: — C IV
    - Very low risk tumours - no imaging
    - Low risk tumours - CT at 3 months following surgery then clinical follow-up
    - Intermediate risk tumours - CT at 3 months following surgery, the 6 monthly for 2 years, then annually to 5 years
    - High risk tumours - CT at 3 months following surgery, 3 monthly for 2 years, 6 monthly for 2 years, then annually
- Patients receiving adjuvant therapy with imatinib should have CT at 3 months after surgery, then 6 monthly for 2 years, then annually to 5 years (as per intermediate risk patients) — C IV
- Upon clinical suspicion of recurrence, patients should have a CT scan — B III

Treatment - Unresectable and/or metastatic disease

Prior to treatment

- Baseline assessment should include: — C IV
    - Full history and clinical examination
    - WHO performance status
    - Concomitant medication (see appendix)
    - Whether pregnant or breast feeding
    - Liver function tests
    - Full blood count
    - Weight
    - The patient should be staged fully by contrast-enhanced CT scanning

Treatment

• Conventional cytotoxic chemotherapy and radiotherapy are not recommended	B III
• There is no evidence of a benefit from debulking surgery, unless there is an immediate clinical need, such as to relieve bowel obstruction or stop bleeding	B III
• Imatinib should be used as first line treatment for unresectable and/or metastatic GISTs	B III
• The recommended starting dose of imatinib is 400 mg/day which can be escalated if necessary, to 800 mg/day (see below)	A Ia

Follow-up

• Patients should be seen fortnightly for the first month, at 3 months, then every 3 months thereafter depending on response and tolerability	C IV
• Liver function tests should be monitored at each visit	C IV
• Toxicities should be monitored at each visit	C IV
• CT scanning should be performed 3 monthly, at least initially, to assess response to therapy	C IV
• PET scanning should not be used routinely for long-term follow-up, but may be considered if there is an uncertainty of response on CT scanning	C IV
• Surgical resection may be considered if the tumour becomes operable	C IV
• Treatment should be continued until there is radiological and symptomatic progression	A I
• Choi criteria may be used to measure disease response as an alternative to conventional criteria, such as RECIST	B II
• An increase in tumour size does not always indicate disease progression or that treatment should be stopped	B II
• In patients with progressive disease, consider escalating dose of imatinib to 800 mg/day	B III
• Patients with confirmed exon 9 mutations may benefit from immediate dose escalation to imatinib 800 mg/day at initiation of treatment	B III
• Discontinuation of imatinib after disease progression, in the absence of any other therapeutic options, is not recommended because of the risk of generalised tumour flare on stopping imatinib	BII

Management after imatinib

• The MDT should discuss and decide the treatment approach on a case-by-case basis	C IV
• Surgery may have a role at any stage in management and should be considered in patients with localised disease progression (i.e. <3 sites)	B II
• Other interventional procedures may be beneficial such as stenting, radiofrequency ablation, embolisation, and local endoscopic treatment	C IV
• If patients show progression on imatinib after dose escalation, consider changing to sunitinib	A Ia
• The recommended starting dose of sunitinib is 50 mg/day for 4 weeks followed by 2 weeks rest (6 week intermittent cycle)	A Ia
• An alternative schedule of sunitinib given continuously at 37.5 mg/day may be considered for patients experiencing toxicity on the higher daily dose, or symptoms of tumour flare on the intermittent dosing schedule	B II
• Patients who progress on sunitinib should be considered for appropriate clinical trials	C IV
• For patients who progress on sunitinib for whom there is no appropriate clinical trial, imatinib may be reintroduced to provide symptomatic relief	B III

Special populations

• All patients should be advised to use contraception and women to avoid becoming pregnant whilst receiving imatinib/sunitinib treatment for GIST	B III
• Patients with compromised renal or hepatic function do not require modification of imatinib dose	B II

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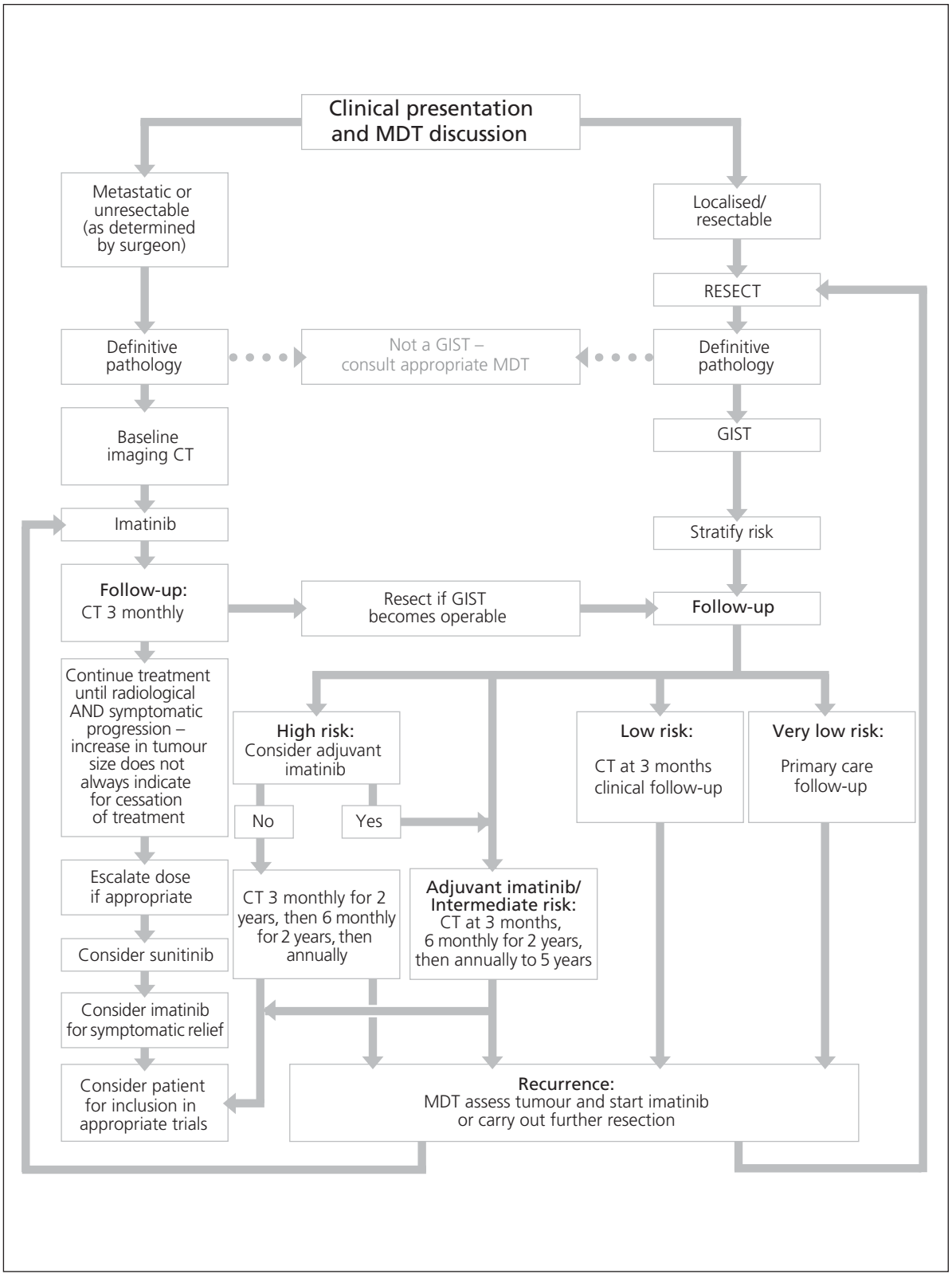
Algorithm of overall care



1.0 Introduction

1.1 Rationale and objective of guidelines

Over the past few years there have been significant advances in the management of gastrointestinal tumours (GISTs). The pathogenesis of GISTs is well established and it has been observed that the *KIT* gene is highly expressed and mutated in almost all tumours. The use of antibodies to CD117, the product of *c*-KIT, as part of an immunohistochemical panel and in combination with traditional histological and clinical examinations, means that it is possible to distinguish clearly GISTs from other gastrointestinal (GI) tract tumours. In addition, the tyrosine kinase inhibitor imatinib (Glivec®) represents a major breakthrough in the treatment of GISTs, as it has significant antitumour activity in these neoplasms, which are generally resistant to cytotoxic chemotherapy.

These guidelines have been updated based on advances made since their original publication in 2004. Their aim is to provide recommendations for the diagnosis and management of patients with GIST. These guidelines are not intended to be prescriptive, but aim to improve the quality of care for patients with GIST by helping to identify and inform the key decisions involved in their management. A multidisciplinary board of surgeons, oncologists, pathologists, radiologists and gastroenterologists produced these guidelines using the best available evidence.

1.2 Methods

An evidence-based review was undertaken using Medline and other databases in combination with manual searches of the most recent journals and reference lists in key articles. All evidence-based work was carried out according to standards published by the North of England Guidelines group and the NHS Centre for Reviews and Dissemination.[2]

2.0 Background

GISTs are tumours of mesenchymal origin that arise in the GI tract. GISTs are the most common mesenchymal malignancies of the GI tract.[3] These are rare representing approximately 0.1-3% of all GI.[3] Malignant GISTs are the most common mesenchymal malignancies of the GI tract.[3] Historically, these tumours were considered to be of smooth muscle origin and were generally regarded as leiomyomas or leiomyosarcomas. Electron microscopy and immunohistochemical studies indicated, however, that only a minority of stromal tumours had the typical features of smooth muscle, with some having a more neural appearance and others appearing undifferentiated.[4] 'Gastrointestinal stromal tumour' was subsequently introduced as being a more appropriate term for these neoplasms, with the variable histological features (smooth muscle, neural, or undifferentiated) considered to be of little clinical relevance. Gastrointestinal autonomic nerve tumour (GANT) was also introduced to describe sarcomas with ultrastructural evidence of autonomic nervous system differentiation;[5] these tumours are now recognised as a variant of GIST.[6]

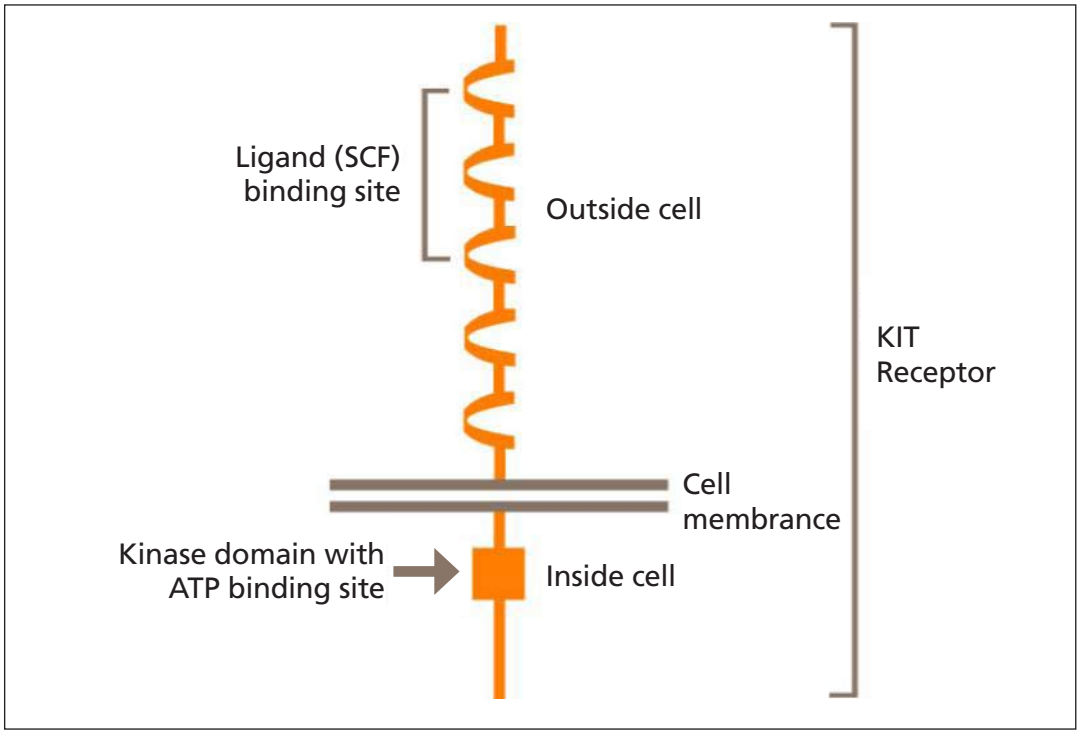
The discovery of CD34 expression in many GISTs[7,8] suggested that they were a specific entity, distinct from smooth muscle tumours. It was also observed that GISTs and the interstitial cells of Cajal (ICC), the pacemaker cells of the gut, expressed the receptor tyrosine kinase KIT[9,10] (CD117) and, more recently, DOG1.[11,12] This has led to the widely accepted classification of mesenchymal tumours of the GI tract into GISTs, true smooth muscle tumours, and, far less frequently, true Schwann cell tumours.

3.0 Pathogenesis

The immunophenotype (CD117 positive) and ultra-structural features of GISTs suggest that they arise from a precursor of ICC.[10] This hypothesis is supported by a report that an embryonic form of smooth myosin in GISTs is similar to that found in ICC.[13] The principle function of the ICC is to serve as pacemaker cells controlling gut motility,[14] coordinating waves of peristalsis. Expression of the *KIT* proto-oncogene is considered essential for the development of the ICC and also for its slow wave activity.[15,16] In addition, KIT is functionally important and is widely expressed for example in germ cells, mast cells, some epithelial cells and in haematopoietic stem cells.[17,18]

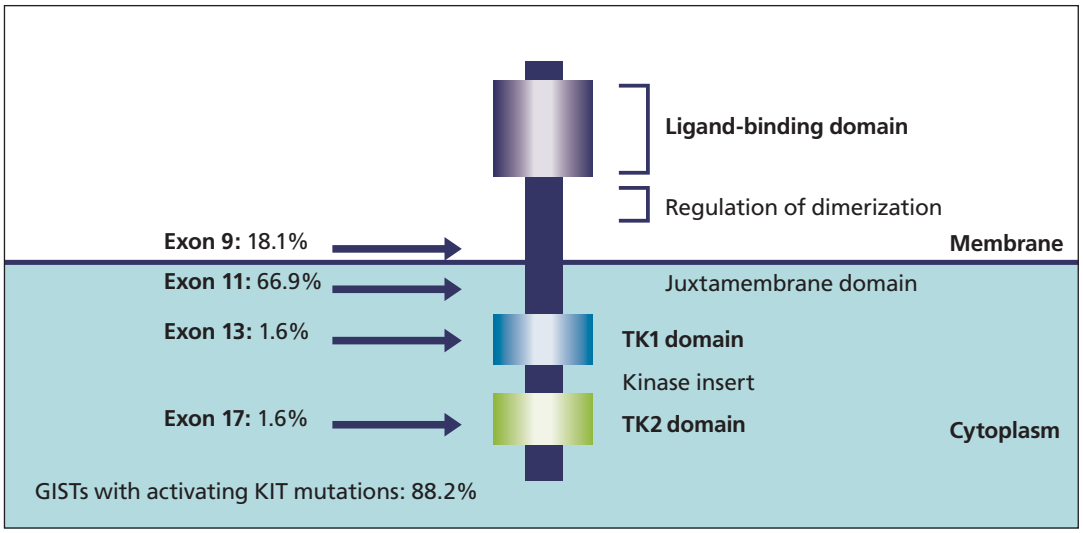
The product of the *KIT* proto-oncogene, KIT, is a member of the receptor tyrosine kinase family, closely related to the receptors for platelet-derived growth factor (PDGF), macrophage colony-stimulating factor (MCSF), and FMS-like receptor tyrosine kinase (FLT3) ligand.[19] Structurally, KIT possesses five immunoglobulin-like extracellular repeats, a transmembrane domain, a juxtamembrane domain, and a split kinase domain[20] (Figure 1). KIT is a transmembrane receptor for a growth factor known as stem cell factor (SCF) or mast cell growth factor.[21] Extracellular binding of SCF to the receptor results in dimerisation of adjacent KIT molecules with concomitant activation of the intracellular KIT kinase domain,[22] leading to activation of intracellular signalling cascades controlling cell proliferation, adhesion, and differentiation.

Figure 1: The structure of the KIT receptor tyrosine kinase



Activation of the KIT receptor tyrosine kinase is integral to the development of many GISTs. This activation involves a mutation within the c-*kit* gene.[23] Most GISTs (approximately 70%) harbour a mutation in exon 11, which encodes the juxtamembrane domain[24,25] (Figure 2). In about 15% of cases there is a mutation in exon 9 of *KIT*, which codes for the extracellular juxtamembrane domain, involved in dimerisation.[25,26] Less common (<10%) mutations occur in exons 13 and 17, which encode the first lobe of the split kinase domain and the phosphotransferase domain, respectively.[24] These mutations (including deletions and point mutations) result in gain of function.[20,23] Thus, KIT signalling is constitutively activated resulting in downstream phosphorylation in the signal transduction pathway, ultimately leading to increased cellular proliferation.[27]

Figure 2: KIT gain-of-function mutations in GISTs[25]



Abbreviations: GIST = gastrointestinal stromal tumour; TK = tyrosine kinase

In the wildtype state, the KIT juxtamembrane domain contains an amphipathic α-helix that suppresses KIT kinase activity in the absence of ligand binding.[28] There also appears to be differences in the precise downstream signalling events initiated by mutant KIT versus wild-type KIT.[29] Further studies are required to determine fully which oncogenic signalling pathways in GISTs are critical.

It is now clear that activating mutations in *KIT* are an early event and are even seen in very small lesions with very low malignant potential, e.g. those <1 cm in diameter with a low mitotic count.[30] Strong evidence that KIT mutational activation can serve as an initiating oncogenic event in GIST is also provided by the findings of germline-activating KIT mutations in individuals with familial GIST syndromes,[31,32,33] and the development of ICC hyperplasia and GISTs in mice transgenic for a KIT oncogene.[34]

Although *KIT* mutation is important, it is not sufficient by itself for malignant transformation in GISTs. In a minority of cases, GISTs result from mutational activation of the closely related tyrosine kinase PDGF receptor α (PDGFRA).[35,36] Evidence suggests that KIT and PDGFRA activation have similar biological ramifications,[35] which may be expected due to their structural similarities. KIT and PDGFRA gene mutations are mutually exclusive,[23,25,36] such that GISTs with activating mutations in *KIT* have normal PDGFRA, while GISTs lacking *KIT* mutations have either PDGFRA-activating mutations or no identified kinase mutations.[35] It is important to note that those GISTs that lack *KIT* mutations may still have high KIT kinase activity. Such GISTs may have *KIT* mutations that are not detected readily by conventional screening methods, or activation may be due to non-mutational mechanisms.[29]

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4.0 Cytogenetic Alterations

GISTs have a number of cytogenetic anomalies that may contribute to the development of malignant disease. Very low risk and low risk GISTs typically have noncomplex or even normal karyotypes, with deletion of chromosome 14 often being the only observable cytogenetic aberration[28,29] (see section 10.0 for explanation of risk assessment categories). In addition to loss of chromosome 14, intermediate-risk GISTs typically show deletions of chromosomes 1p, 9p, 11p, or 22q.[29] Malignant GISTs can often show extra aberrations including amplification of 8q and 17q.[28] A study by El-Rifai *et al.*[37] revealed that benign tumours had a mean of 2.6 cytogenetic abnormalities, malignant primary GISTs had a mean of 7.5 abnormalities, and metastatic GISTs had a mean of 9 abnormalities. There have been no noted chromosomal abnormalities at chromosome 4q,[22] the location of the *KIT proto*-oncogene,[38] consistent with preservation of functional (or activated) copies of *KIT* genes.

There is evidence that the p16 tumour suppressor gene might be altered in GIST, possibly due to deletion of 9p.[39] p16 inactivation could function in concert with KIT activation to promote cell proliferation in GISTs.[28] The consequences of other characteristic chromosomal abnormalities may include the enhancement of KIT signalling in GISTs. Monosomy of chromosomes 14 and 22 appears to occur as early events in tumourigenesis.[40,41]

5.0 Epidemiology

Numerous retrospective studies carried out using CD117 immunoreactivity as a diagnostic criterion have shown that GISTs are under-diagnosed. A reclassification of 102 tumours of relevant localisations diagnosed 48 (47%) GISTs compared to only 23 (22%) identified previously.[42] Another study suggested that 72% of cases now understood to be GISTs were classified previously as other tumours.[43,44] The morphological spectrum of GISTs is also wider than previously recognised. Based on these data, the annual incidence of GISTs is estimated to be around 15 per million,[45] which would equate to approximately 900 new cases per year in the UK.

This is in line with a more recent study, based on Swedish data, which concluded that the clinical aggressiveness, incidence and prevalence of GISTs have been historically underestimated.[46] In this study, the annual incidence of GIST was estimated at 14.5 per million per year with the prevalence of all GISTs risk groups estimated at 129 per million.[46] However, a population-based incidence study conducted in Iceland reported a slightly lower incidence of 1.1 per 100,000 per year.[47] In this study 11 of 22 non-gastric GISTs were classified as high risk compared to only 2 of 35 gastric GISTs. This indicates that non-gastric GISTs present a greater risk of malignant behaviour.[47]

6.0 Distribution

GISTs can occur anywhere in the GI tract from the oesophagus to the rectum.[48] Most arise in the stomach or small intestine, and less frequently in the oesophagus, mesentery, omentum, colon, or rectum (Table 1).[49] They are rare before the age of 40 years and very rare in children,[50] with a median age at diagnosis of 50-60 years.[51] Some data show a slight male predominance.[50,52,53] In a recent study of 1,765 cases of GISTs, 2.7% of tumours occurred before the age of 21 and 9.1% occurred before the age of 40.[53] In a study of GISTs of the jejunum and ileum, only 0.6% of tumours occurred before the age of 21 while 13.6% occurred before the age of 40.[54]

Table 1: Site of GISTs[49]

Site	n=200	Percentage
Stomach	78	39%
Small intestine	63	32%
Rectum	21	10%
Large intestine	11	5%
Other*	18	9%
Intestine unspecified	9	5%

** Other includes intraabdominal 9, mesentery 4, omentum 2, oesophagus 2, diaphragm 1*

Approximately 10-30% of GISTs are overtly malignant in behaviour.[50,51] The principal sites of metastasis are the liver and the peritoneal cavity.[49] Rarely, GISTs metastasise to other sites such as the lungs and bone.[55,56]

7.0 Clinical Features

The symptoms of GISTs are non-specific and depend on the size and location of the lesion.[57] Gastric GISTs, which range from a few millimetres to 15 cm in size, frequently present with GI bleeding, pain, and fatigue or malaise.[58] Small GISTs (2 cm or less) are usually asymptomatic and are detected during investigations or surgical procedures for unrelated disease. The vast majority of these are of low-risk of malignant behaviour.[59] In many cases the mucosa is normal. Incidental discovery accounts for approximately one third of cases.[60]

The most common symptom is GI bleeding which is present in approximately 50% of patients[61] (Table 2). In addition, systemic symptoms such as fever, night sweats, and weight loss are common in GIST and very rare in other sarcomas. Patients with larger tumours may experience abdominal discomfort or develop a palpable mass.[52] GISTs are often clinically silent until they reach a large size, bleed or rupture. Up to 25% of patients present with acute haemorrhage into the intestinal tract or peritoneal cavity from tumour rupture.[62] Symptomatic oesophageal GISTs typically present with dysphagia, while gastric and small intestinal GISTs often present with vague symptoms leading to their eventual detection by gastroscopy or radiology. Most duodenal GISTs occur in the second part of the duodenum where they push or infiltrate into the pancreas.[63] Colorectal GISTs may manifest with pain and GI obstruction, and lower intestinal bleeding. Rectal tumours are usually deep intramural tumours.[63]

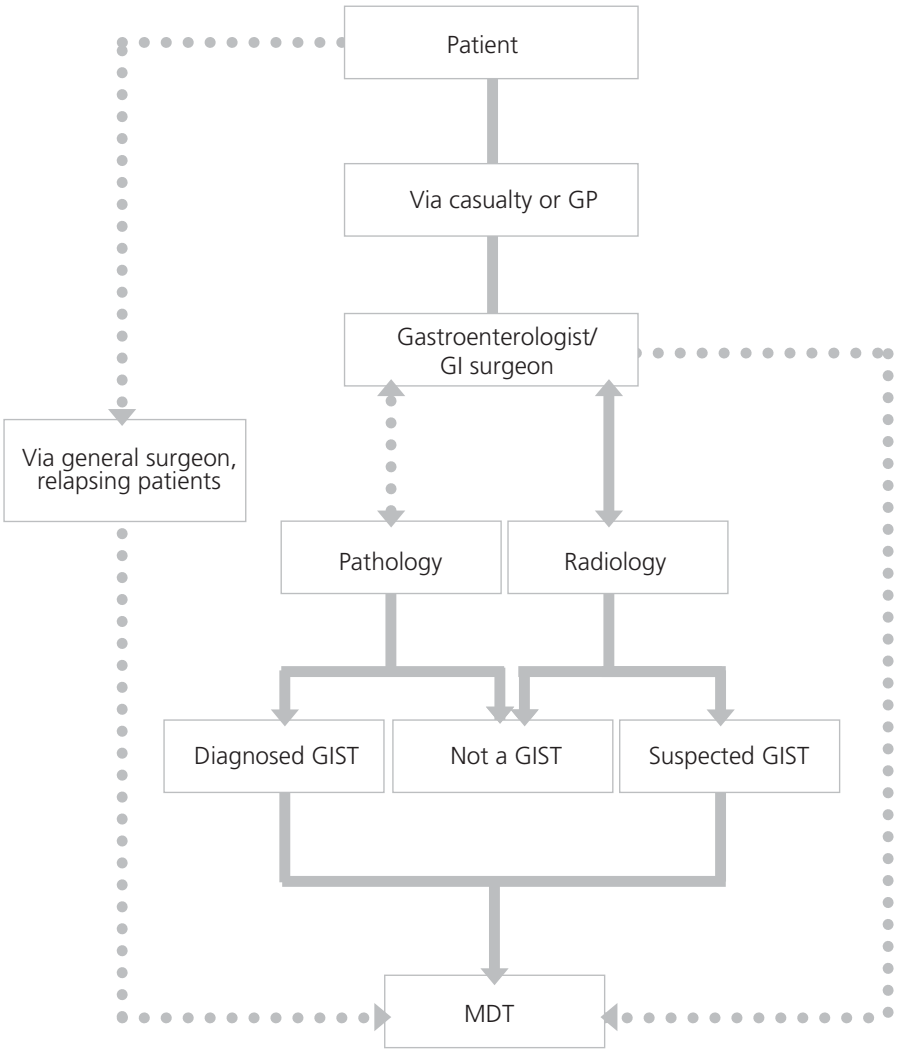
Table 2: Symptoms of GIST at diagnosis[57]

Symptoms	Incidence
Abdominal pain	20-50%
Gastrointestinal bleeding	50%
Gastrointestinal obstruction	10-30%
Asymptomatic	20%

8.0 Referral Pathway

It is the consensus view that the management of GISTs should be undertaken by a multidisciplinary team (MDT) with experience in this disease. At this time, all available clinical, surgical, radiological, histopathological, and immunohistochemical data should be utilised to formulate a treatment plan.

Figure 3: Referral pathway



9.0 Diagnosis

Key recommendations

- Pathological review of all cases should be made by a pathologist experienced in this tumour type
- For resectable tumours, a definitive diagnosis is often made after surgery
- For patients with unresectable and/or metastatic tumours, a biopsy should be taken and a definitive diagnosis made before treatment

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Imaging studies

- Endoscopic ultrasonography (EUS), especially of the oesophagus, stomach, duodenum, and the anorectum, can confirm the diagnosis of small incidental GISTs <2 cm
- For large tumours, computed tomography (CT) of chest, abdomen and pelvis is recommended to assess primary tumour extension and to stage for metastases
- For ano-rectal tumours, magnetic resonance imaging (MRI) is useful in locoregional staging
- PET-CT may be considered to aid assessment when radical surgery is required, particularly of the duodenum, rectum and oesophagus
- Contrast-enhanced CT scanning is the standard imaging modality for assessing response to tyrosine kinase therapies
- PET-CT may be useful for monitoring response to therapy, emerging resistance and where there is diagnostic uncertainty on CT scans, but is not a substitute for contrast-enhanced CT scanning
- PET-CT scans should be reviewed by an experienced sarcoma or gastrointestinal radiologist with knowledge of GISTs
- All imaging studies should be presented in a standardised and consistent format and reviewed and discussed by the MDT

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Histopathology and immunochemistry

- Macroscopic examination of the site of the resected tumour, with adequate sampling for histological examination and for immunohistochemistry, should be performed
- Biopsies should sample multiple sites and include some normal tissue
- Laparoscopic biopsies may be considered if a biopsy cannot be obtained by other means
- Control slides should include normal gastric body wall as a staining control and tumour to allow for direct comparison of staining
- The diagnosis of GIST is supported by positive CD117 staining as part of an adequately controlled immunohistochemical panel in a spindle cell tumour of the GI tract when morphologic and clinical features of the tumour are consistent with GIST
- DOG1 is a useful marker of GIST and should be used in conjunction with CD117 and CD34 staining

Appropriate management of GISTs requires accurate diagnosis and should involve a multidisciplinary approach. The majority of tumours are operable and diagnosis is usually confirmed by examination of the resected specimen. In these cases, initial diagnosis is based on imaging. GIST has been under-recognised and its malignant potential underestimated.[43] Pathological review of all cases by a pathologist experienced in this tumour type is recommended.

9.1 Role of imaging studies

The type of imaging used initially will depend on the mode of presentation and local availability. If a small sub-mucosal mass is seen as an incidental finding at the time of endoscopy, then if available, endoscopic ultrasound (EUS) should be performed first. A significant proportion of these endoscopic findings will be due to extrinsic impression from normal adjacent structures e.g. gall bladder in the antrum, spleen in the proximal stomach. If this is the case, no further investigation is required. If EUS is not available computed tomography (CT) is an alternative investigation.
For larger palpable masses, or where the patients present with haemorrhage, abdominal pain or obstruction, CT is usually the initial investigation. CT is widely available (Figures 4 & 5) to assess both primary tumour extension and the presence of metastases.[64] Magnetic resonance imaging (MRI) may provide additional information. Positron emission tomography (PET) has also been introduced for the additional functional information it can provide; changes in FDG ([^{18}F]-2-fluoro-deoxy-D-glucose) uptake occur earlier than the gross morphological changes[66] (Figure 6).

Figure 4: CT of a patient with a GIST located at the oesophagogastric junction (courtesy of Mr Simon Toh)

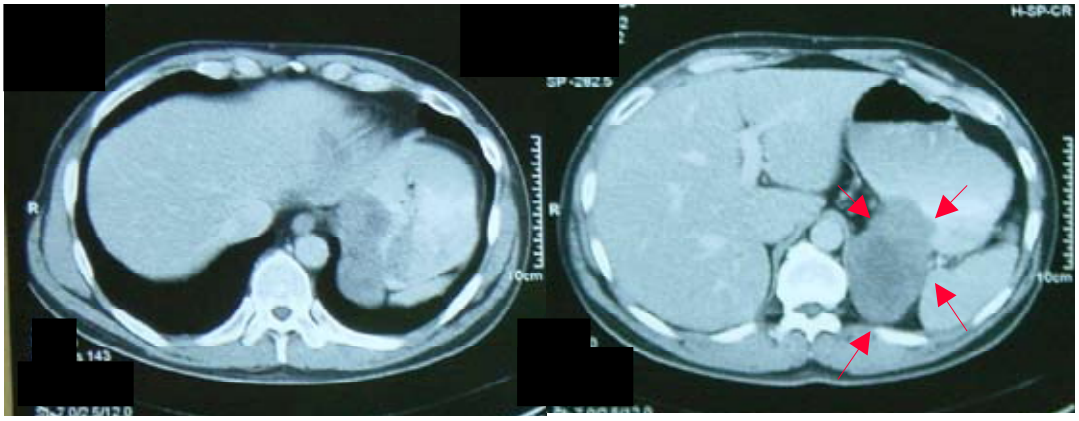


Figure 5: CT of patient with large abdominal mass with central necrosis (courtesy of Mr Simon Toh)

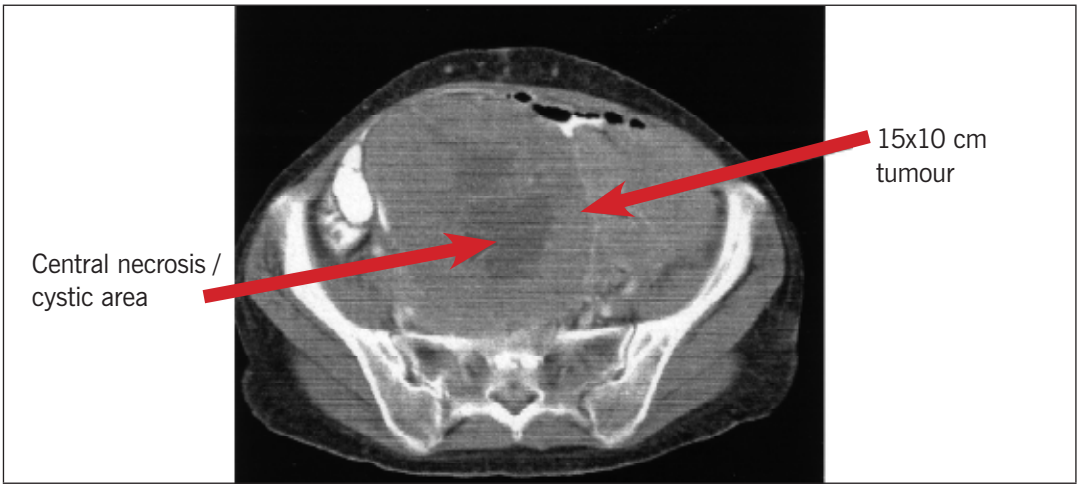
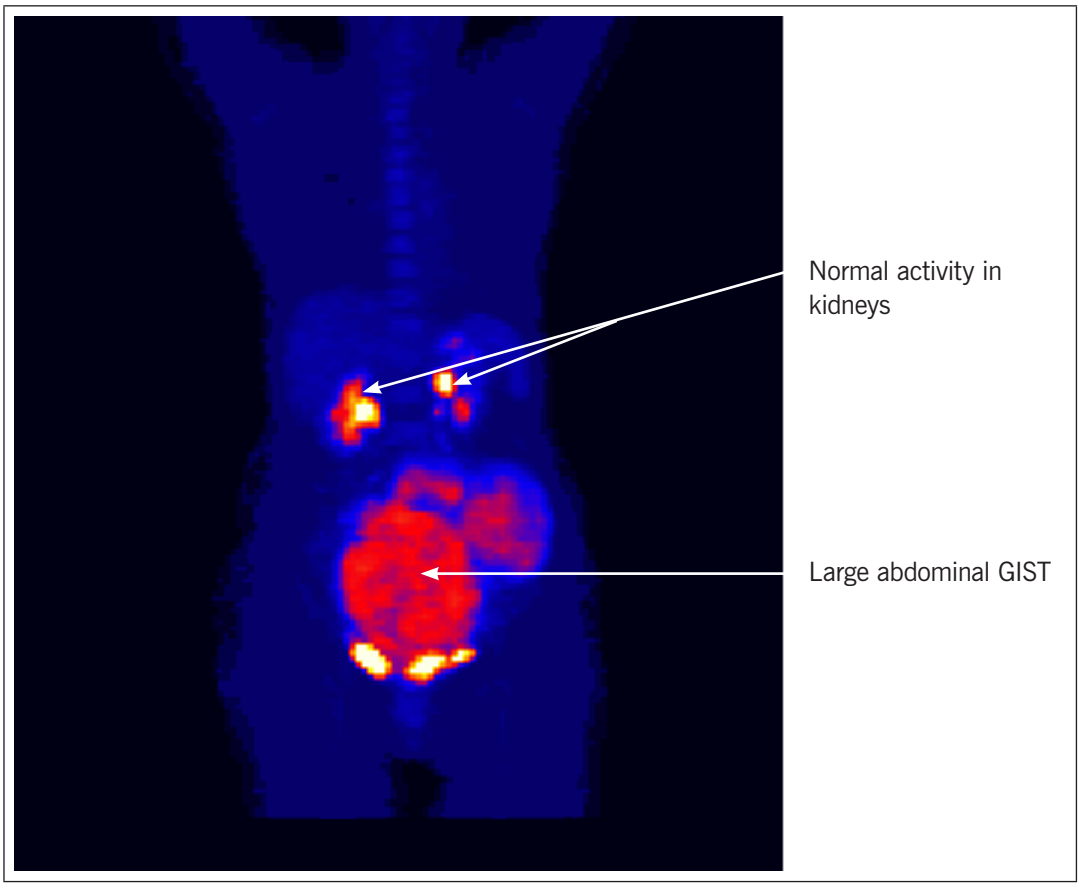


Figure 6: PET scan of patient with abdominal GIST



Please note that ^{18}FDG is taken up and expressed in healthy renal and cardiac tissue

9.1.1 Barium studies

Contrast studies using barium show the classic features of submucosal masses of the GI tract.[64] GISTs are often missed on conventional testing such as endoscopy and biopsy because of their intramural growth.

9.1.2 Ultrasonography

Trans-abdominal ultrasonography helps to characterise the internal echotexture of both primary and metastatic GIST;[64] this can define whether the lesion has undergone cystic necrosis either as a result of imatinib therapy or as part of the natural history of the disease. EUS is a valuable imaging technique for diagnosing small <2 cm incidental GISTs. The high frequencies used in EUS can delineate the gut wall layers and hence the layer of origin of a submucosal mass can be defined. GISTs are usually hypoechoic and lie within the muscularis propria. CT should be used for larger tumours (>5 cm), as the lower penetration of high frequency ultrasound may underestimate the extent of disease. EUS is most useful in the oesophagus, stomach, duodenum, and the anorectum.[64]

9.1.3 Computed Tomography

GIST imaging by CT typically shows an extraluminal mass, often with central necrosis, arising from the digestive tract wall.[60] Small tumours typically appear as sharply-margined, smooth-walled, homogeneous, soft tissue masses with moderate contrast enhancement.[64] Large tumours tend to have mucosal ulceration, central necrosis and cavitation, and heterogeneous enhancement[64] following IV contrast. As well as defining the presence and nature of a mass, if possible, the likely organ of origin should be defined. Multiplanar reconstruction can assist this, particularly with large masses. The authors prefer negative oral contrast (e.g. tap water) and intravenous contrast for the assessment of gastric GISTs in particular.

CT is also the most common technique used to assess hepatic metastases from GIST.[64] CT of chest, abdomen and pelvis is recommended for staging of GIST, with the exception of small incidental tumours. Unless emergency surgery is indicated, it is best performed pre-operatively to exclude distant metastases.

9.1.4 Magnetic Resonance Imaging

In general, MRI offers no additional information regarding the intra-lesional tissue characterisation of primary GISTs.[64] The appearances are variable and non-specific.[64] MRI provides better soft-tissue contrast resolution and direct multiplanar imaging, helping to localise the tumour and delineate the relationships of the tumour and adjacent organs.[64] This is particularly of benefit in anorectal disease.

9.1.5 Positron Emission Tomography

PET is not yet widely available; however, it can detect metabolic changes within the tumour in advance of visible changes on conventional imaging.[66] It may occasionally be used as part of a preoperative assessment, prior to planned resection of a large tumour, to exclude undetected distant metastases. It is also useful in advanced stage disease, but may not detect tumours <2 cm diameter.

The value of PET is two-fold. Most GISTs appear to take up ^{18}FDG avidly and thus PET represents a very sensitive staging tool, capable of demonstrating the presence of metastatic disease that is not visible on CT. Secondly, if the patient has metastatic disease, with a positive PET scan, and is going to receive treatment with imatinib, then PET will provide a rapid means of determining the responsiveness of the tumour to imatinib, showing response much earlier than response can be seen on CT.[65]

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9.1.6 Positron Emission Tomography – Computed Tomography (PET-CT)

PET-CT scanners combine the functions of standard PET scanners with those of CT scanners.[66] The result is a single scanner that can depict the metabolic or biochemical activity within the body precisely aligned with the anatomic imaging obtained from the CT scan. Although their use is increasing, these scanners are currently available at only a few centres

PET-CT scanners have been shown to display more metastases from GISTs than CT and PET alone.[67] Antoch *et al.* found that in 20 patients with GISTs, PET-CT demonstrated 282 lesions, whereas 249 were detected by CT alone and 135 by PET alone.[67] The authors also found improved accuracy in the characterisation of imatinib response when using PET-CT compared to CT or PET alone.[67]

PET-CT is a valuable new tool and should be considered to aid assessment when radical surgery is required, particularly of the duodenum, rectum and oesophagus. PET-CT scans also have an important role to play in monitoring response to therapy, emerging resistance and where there is diagnostic or treatment uncertainty. However, PET-CT scans are not without limitations. It should be noted that PET-CT is not a substitute for a proper contrast enhanced CT scan and that an experienced sarcoma or gastrointestinal radiologist with knowledge of GISTs should review any PET-CT scans. All imaging studies should be presented in a standardised and consistent format and reviewed and discussed by the MDT.

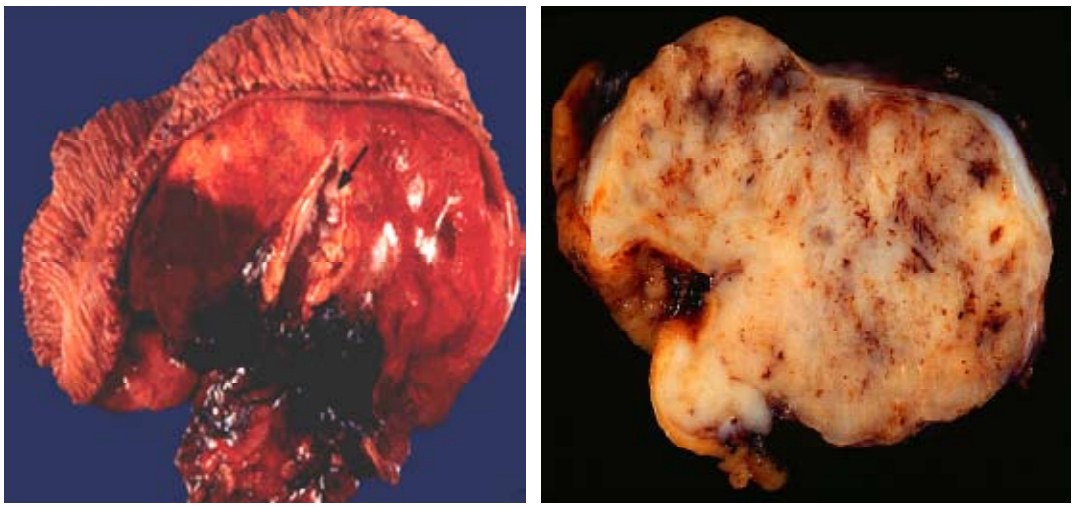
9.2 Histopathology and immunochemistry

In the majority of cases, a definitive diagnosis of GIST is made only after surgery. For inoperable or metastatic tumours biopsies should be taken, either by the percutaneous route or endoscopically, to allow definitive treatment. If possible, multiple biopsies should be taken to ensure good sampling. These biopsies should sample multiple areas, and should include some normal smooth muscle tissue. Laparoscopic biopsies may be considered if a biopsy cannot be done by other means. The resulting slides should be mounted with both normal tissue and tumour to allow for a direct comparison of staining. The pathologist's report should include (see section 14.1.4 for full details):

- Tumour site
- Mitotic index
- Tumour size
- Risk of recurrence

GISTs are usually well circumscribed but unencapsulated[3] (Figure 7). They often have a whorled fibroid-like or a softer more fleshy appearance on the cut surface. In general, GISTs occur in the submucosa, muscularis propria or serosa,[59] and grow in an endophytic or exophytic way perpendicular to the bowel lumen. Large tumours may have a 'dumbbell' appearance, with masses protruding both into the lumen and from the serosa of the bowel. Seeding of tumour deposits into the serosa or omentum is almost invariably a sign of malignancy.

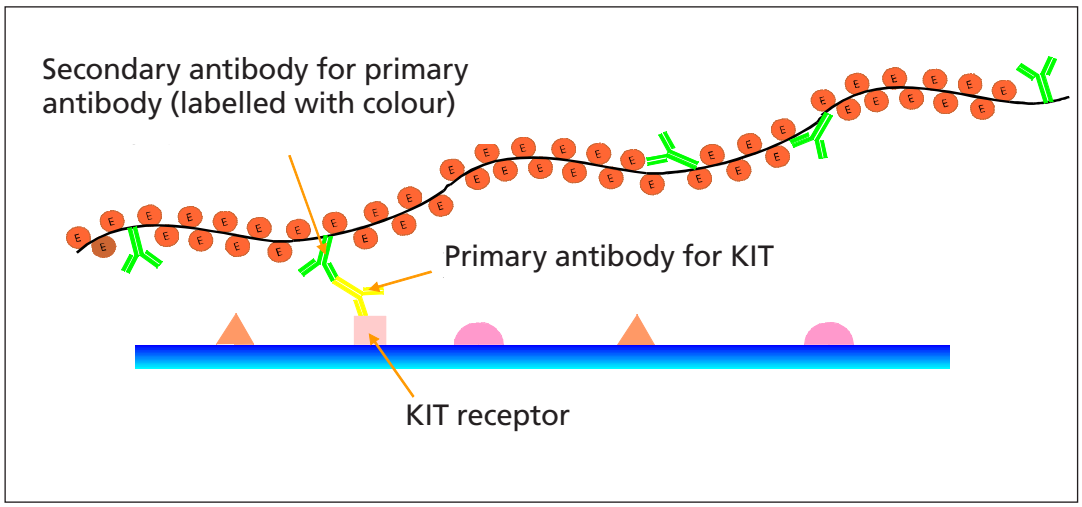
Figure 7: Macroscopic appearance of GISTs



Microscopically, most cases have a remarkably uniform appearances falling into one of three categories. Seventy per cent of GISTs are of spindle cell type, 20% of epithelioid type, and the remainder usually of mixed type.[48] GISTs of spindle cell type are composed typically of relatively uniform eosinophilic cells arranged in short fascicles or whorls, whereas GISTs of epithelioid type are composed of rounded cells with variably eosinophilic or clear cytoplasm.[48] Lesions of mixed cell type may exhibit an abrupt transition between spindle cell and epithelioid areas, or may have complex co-mingling of these cell types throughout, leading to an intermediate ovoid cytologic appearance. [48]

The increased diagnostic precision of GISTs over the last 15 years is due to increased awareness of their existence and the widespread use of CD117 (KIT) immunohistochemistry in the routine pathologic analysis of spindle and epithelioid neoplasms of the GI tract and associated anatomic regions[62] (Figure 8). Positive CD117 and/or DOG1 staining as part of an immunohistochemical panel in a spindle cell tumour of the GI tract confirms the diagnosis of GIST when morphologic and clinical features of the tumour are consistent with GIST. Staining is typically cytoplasmic, strong and diffuse, but often shows dot-like accentuation[63] in the Golgi. Scattered single cells positive for CD117 are likely to be mast cells,[63] which can be used as internal controls.

Figure 8: CD117 staining (courtesy of DAKO)



Recent studies have shown that the novel gene DOG1, which encodes for a chloride channel protein, is highly expressed in both *KIT* and *PDGFRA* mutant GISTs.[11,68] In one study of 139 assessable GISTs, 136 (97.8%) were DOG1 positive.[11] It was also found that other neoplasms such as desmoids fibromatosis and schwannoma were negative for DOG1. In the 438 non-GIST cases that were assessed only 4 were immunoreactive for DOG1.[11]

DOG1 staining has been found to be relatively simple to perform and produces clear results. As such, DOG1 represents a useful tool in the diagnosis of GISTs.[12,68] Immunostaining for DOG1 should be used in conjunction with CD117 staining, but should not be used as a replacement for it.

In addition to consistent positivity for CD117 and DOG1, approximately 60-70% of GISTs show immunopositivity for CD34, and 30-40% show immunopositivity for smooth-muscle actin (SMA) (Table 3, Section 9.3).[48] GISTs rarely express desmin, an intermediate filament protein typical of muscle, or S-100 protein, a neural (Schwann) cell marker. Other markers such as vimentin are also present in GISTs, but are either non-specific or too variable to be useful markers.[69] Recent studies have demonstrated that Ki-67 can be used as an indicator for malignant potential in GIST.[70]

Although CD117 is the primary immunohistochemical marker for GIST, importantly, approximately 4% of GISTs lack CD117 positivity.[71] These tumours have clinicopathological features of GIST but do not express KIT protein. In comparison to KIT positive GISTs, these KIT negative GISTs are more likely to have epithelioid cell morphology and contain PDGFRA oncogenic mutations.[71] It is important in these cases, where CD117 staining is negative, that other markers are investigated to confirm GIST diagnosis. This should include PDGRFA and could include protein kinase theta, which has been shown to be ubiquitous in GISTs.[72] It is important that the staining for these markers be performed in properly controlled centres with adequate quality assurance. In addition, if mutation analysis were positive either for KIT or PDGFRA, this would be regarded as proof of diagnosis of GIST; hence, mutational analysis should always be performed in cases of CD117 negative suspected GIST. Certain KIT or PDGFRA mutations in these patients may be sensitive to imatinib and patients may, therefore, still benefit from imatinib therapy.[71]

9.3 Differential diagnosis

It is important to differentiate between GISTs, which constitute approximately 80% of GI mesenchymal tumours, and the less common GI non-epithelial neoplasms, leiomyoma, leiomyosarcoma (10-15% of mesenchymal tumours), schwannomas (5%), and other malignant disorders.[3]

Nearly all GISTs display strong immunohistochemical staining for KIT,[73] and this can be utilised in their differential diagnosis and positive identification (Figure 9). Smooth muscle neoplasms, and neurogenic tumours (Schwannoma) do not show a positive expression of CD117[28,48] (Table 3). Other tumours such as metastatic melanomas, angiosarcomas, and seminomas in the retroperitoneal area may also be positive for CD117, but can be distinguished from GISTs by histological and clinical means.

Figure 9: GIST showing KIT immunohistochemical staining

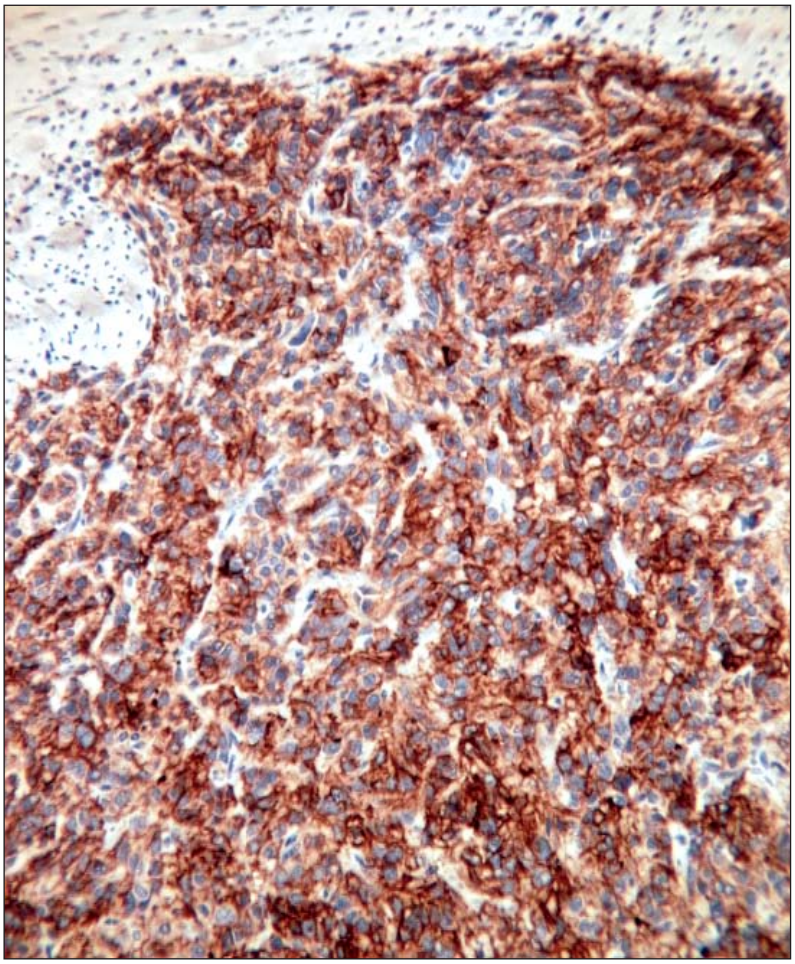


Table 3: *Immunohistochemical schema for the differential diagnosis of spindle cell tumours of the GI tract*[48,50]

	CD117 (cKIT)	CD34	SMA	Desmin	S-100
GIST	+ Around 95%	+ 60-70%	+ 30-40%	Very rare	+ 5%
Smooth muscle tumour	-	+ 10-15%	+	+	Rare
Schwannoma	-	+	-	-	+

It is recommended that CD117 immunostaining should be performed to facilitate the diagnosis of GIST for spindle cell or epithelioid tumours arising in the GI tract. Diagnosis however, should not be based purely on CD117 expression.

The diagnosis of CD117 negative GIST should only be made with extreme care, and only by those experienced in this area and aware of the potential pitfalls. If there is evidence of desmin or S-100 expression and the tumour is not associated with the gut wall then a diagnosis of a KIT negative GIST should not be made without supportive molecular findings or without DOG1 expression.

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10.0 Prediction of Tumour Behaviour

Key recommendations

- All GISTs have malignant potential, but the risk of this is minimal for very small tumours
- The assessment criteria for prognosis proposed by Miettinen and Lasota (2006) should supersede those agreed by the National Institutes of Health Consensus workshop
- All small bowel GISTs and all intermediate and high risk GISTs, regardless of location, should have mutational analysis
- Mutational analysis should include at least assessment of KIT exons 9 and 11, and PDGFRA exons 12 and 18 for mutations. If apparently wildtype, additional exons will need to be examined to rule out rare primary mutations
- Mutational analysis should be performed at a recognised centre to ensure quality control

10.1 Risk of relapse

All GISTs tumours have the potential for malignant behaviour and gross examination of the tumour size and estimation of the mitotic count are essential in assessing prognosis. A scheme for defining the risk of aggressive behaviour in GIST based on tumour size and mitotic count was originally proposed by the National Institutes of Health workshop in 2002.[48] However, these criteria were not particularly accurate in their estimation of risk, as they only used size and mitotic count per 50 high power fields (M/50HPF) to predict the likelihood of relapse and did not take site into account. Furthermore, they were based on consensus opinion rather than on actual clinical data. Miettinen and Lasota presented long-term follow-up data from a series of 1684 patients with resected GIST which has provided real estimates of risk of recurrence (Table 4a).[74] In an attempt to improve the assessment of GIST diagnosis, a new set of criteria have been proposed based on the Mittinen and Lasota dataset (Table 4b).[75] These criteria take into account tumour size, mitotic index and tumour site in order to predict the risk of relapse more accurately. In addition to the high risk group as defined by NIH classification, they also include in the classification of high risk non-gastric tumours measuring 2.0 – 5 cm with >5 M/50HPF, which are associated with a recurrence risk of ≥50%, and non-gastric GISTs measuring ≥5.0 – 10 cm with ≤5 M/50HPF which are associated with recurrence risk of >25%.

Table 4a: Risk of relapse (adapted from Miettinen and Lasota)[74]

Size cm	M/50HPF*	Gastric	Jejunal/Ileal	Duodenal	Rectal
≤2	≤5	Very Low (0%)	Very Low (0%)	Very Low (0%)	Very Low (0%)
>2≤5	≤5	Very Low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
>5≤10	≤5	Low (3.6%)	Moderate	-	-
>10	≤5	Moderate (12%)	High (52%)	High (34%)	High (57%)
≤2	>5	Very Low (0%)	High (50%)	-	High (54%)
>2≤5	>5	Moderate (16%)	High (73%)	High (50%)	High (52%)
>5≤10	>5	High (55%)	High (85%)	-	-
>10	>5	High (86%)	High (90%)	High (86%)	High (71%)

**Mitotic count per 50 high power fields*

Table 4b: Proposed modification of consensus classification (adapted from Joensuu)[75]

Risk category	Tumour size (cm)	Mitotic index (per 50 HPFs)	Primary tumour site
Very Low	<2.0	≤5	Any
Low	2.1-5.0	≤5	Any
Intermediate	2.1-5.0	>5	Gastric
	<5.0	6-10	Any
	5.1-10.0	≤5	Gastric
High	Any	Any	Tumour rupture
	>10	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1-5.0	>5	Non-gastric
	5.1-10.0	≤5	Non-gastric

It is recommended that these criteria for prognosis should supersede those originally put forward by the National Institutes of Health Consensus workshop. However, it should be noted that these criteria have yet to be validated on an independent data set.

10.2 Mutational analysis

Information regarding specific mutations can help to inform treatment decisions. Mutational analysis should include assessment of primary *KIT* exons 9, 11, 13 and 17 and *PDGFRA* exon 12 and 18 mutations. If no mutations are found at these common sites, other exons need to be examined before a tumour can be regarded as wildtype.

Mutational analysis should be performed at a recognised centre of excellence to ensure quality control. These centres include Ninewells Hospital Dundee, Bristol Royal Infirmary, University Hospital of Birmingham, The Institute of Cancer Research and the University of Manchester. It is recommended that all small bowel GISTs and all intermediate and high risk GISTs should have mutational analysis performed.

11.0 Treatment Recommendations

Key recommendations – Resectable disease

- Surgery is the principle treatment for GISTs and suitability for resection should be explored by an appropriate sub-specialist surgeon
- Patients should be considered for inclusion in clinical trials of neoadjuvant and adjuvant therapy

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Preoperative assessment

- A chest, abdominal and pelvic CT should be included in the preoperative assessment
- EUS may provide useful information prior to surgery on small <2 cm tumours
- Endoscopy should not be used in isolation to assess small tumours (<2 cm) prior to surgery
- Percutaneous biopsies should not be used if the tumour is considered resectable
- If at assessment a tumour is deemed not resectable without unacceptable morbidity, treatment with imatinib is appropriate
- The recommended starting dose of imatinib is 400 mg/day

Principles of surgery

- A wide local resection with macroscopic and microscopic removal of the entire tumour is recommended (R0)
- The surgeon should aim to preserve function, but not at the expense of an R0 resection
- Extended lymphadenectomy is normally not required
- Some small tumours may be resected laparoscopically
- Where adjacent organs are involved, *en bloc* resection is recommended whenever possible – input from other specialist surgeons should be considered prior to embarking on such a resection
- Endoscopic resection is not recommended

Treatment following resection

- Adjuvant therapy with imatinib may be considered in patients predicted to have a high risk of recurrence
- The recommended starting dose of adjuvant imatinib is 400 mg/day

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Follow-up following resection

- All patients following resection should be discussed in a MDT
- All patients should be followed-up by clinicians linked to MDT
- CT is the prime modality for detecting recurrence, but MRI can be considered for annual scans to reduce radiation dose
- After baseline clinical review, for patients with:
  - Very low risk tumours – no imaging
  - Low risk tumours – CT at 3 months following surgery, then clinical follow-up
  - Intermediate risk tumours – CT at 3 months following surgery, then 6 monthly for 2 years, then annually to 5 years
  - High risk tumours – CT at 3 months following surgery, 3 monthly for 2 years, then 6 monthly for 2 years, then annually
- Patients receiving adjuvant therapy with imatinib should have CT at 3 months after surgery, then 6 monthly for 2 years, then annually to 5 years (as per intermediate risk)
- Upon clinical suspicion of recurrence, patients should have a CT scan

Key recommendations – Unresectable and/or metastatic disease

Prior to treatment

- Baseline assessment should include:
  - Full history and clinical examination
  - WHO performance status
  - Concomitant medication (see appendix)
  - Whether pregnant or breast feeding
  - Liver function tests
  - Full blood count
  - Weight
  - The patient should be staged fully by contrast-enhanced CT scanning

Treatment

- Conventional cytotoxic chemotherapy and radiotherapy are not recommended
- There is no evidence of a benefit from debulking surgery, unless there is an immediate clinical need, such as to relieve bowel obstruction or stop bleeding
- Imatinib should be used as treatment for unresectable and/or metastatic GISTs
- The recommended starting dose of imatinib is 400 mg/day which can be escalated, if necessary, to 800 mg/day (see below)

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Follow-up

- Patients should be seen fortnightly for the first month, at 3 months, then every 3 months thereafter depending on response and tolerability
- Liver function tests should be monitored at each visit
- Toxicities should be monitored at each visit
- CT scanning should be performed 3 monthly, at least initially, to assess response to therapy
- PET should not be used routinely for long-term follow-up, but may be used if there is uncertainty of response on CT scanning
- Surgical resection may be considered if the tumour becomes operable
- Treatment should be continued until there is radiological and symptomatic progression
- Choi criteria may be used to measure disease response as an alternative to conventional criteria such as RECIST
- An increase in tumour size does not always indicate disease progression or that treatment should be stopped
- In patients with progressive disease, consider escalating therapy to imatinib 800 mg/day
- Patients with confirmed exon 9 mutations may benefit from immediate dose escalation to imatinib 800 mg/day at initiation of treatment
- Discontinuation of imatinib after disease progression, in the absence of any other therapeutic options, is not recommended because of the risk of generalised tumour flare on stopping imatinib

Management after imatinib

- The MDT should discuss and decide the treatment approach on a case-by-case basis
- Surgery may have a role at any stage in management and should be considered in patients with localised progression (i.e. <3 sites)
- Other interventional procedures may be beneficial such as stenting, radiofrequency ablation, embolisation, and local endoscopic treatment
- If patients show progression on imatinib after dose escalation, consider changing to sunitinib
- The recommended starting dose of sunitinib is 50 mg/day for 4 weeks followed by 2 weeks rest (6 week intermittent cycle)
- An alternative schedule of sunitinib given continuously at 37.5 mg/day may be considered for patients experiencing toxicity on the higher daily dose, or symptoms of tumout flare on the intermittent dosing schedule
- Patients who progress on sunitinib should be considered for appropriate clinical trials
- For patients who progress on sunitinib for whom there is no appropriate clinical trial, imatinib may be reintroduced to provide symptomatic relief

11.1 Resectable Disease

Surgical resection is the principal treatment for GISTs. Evaluation of the resectability of a GIST is determined by the surgeon and depends on the stage and the individual patient's fitness for surgery.

11.1.1 Pre-operative Assessment

A chest, abdominal and pelvic CT should be included in the preoperative assessment for all patients. If the tumour is located in the right or left upper quadrant then the patient should have an endocrine assessment to exclude a large functioning adrenal tumour. Male patients (under the age of 40 years) presenting with large centrally placed retroperitoneal tumours should have α-fetoprotein and β-HCG levels measured to exclude non seminomatous germ cell tumour. In cases of small (<2 cm) tumours, endoscopy should not be used in isolation for the purposes of assessment. In these situations, EUS may provide useful information prior to surgery.

Percutaneous- (US or CT) or laparoscopically-guided biopsies should not be used in resectable disease due to the risk of tumour rupture or seeding, unless it may result in a change of treatment.[59] Laparoscopy may be considered to stage for peritoneal and distant spread of disease; however, laparoscopic biopsy of the primary tumour in potentially operable disease should be avoided. Deep sub-mucosal endoscopic biopsies can be used, but the clinician should be aware that it is generally not recommended because of the risk of haemorrhage and diagnostic failure.

If at assessment a tumour is deemed not resectable without unacceptable morbidity, treatment with imatinib is appropriate. The recommended starting dose of imatinib is 400 mg/day, which can be escalated, if necessary, to 800 mg/day.[76]

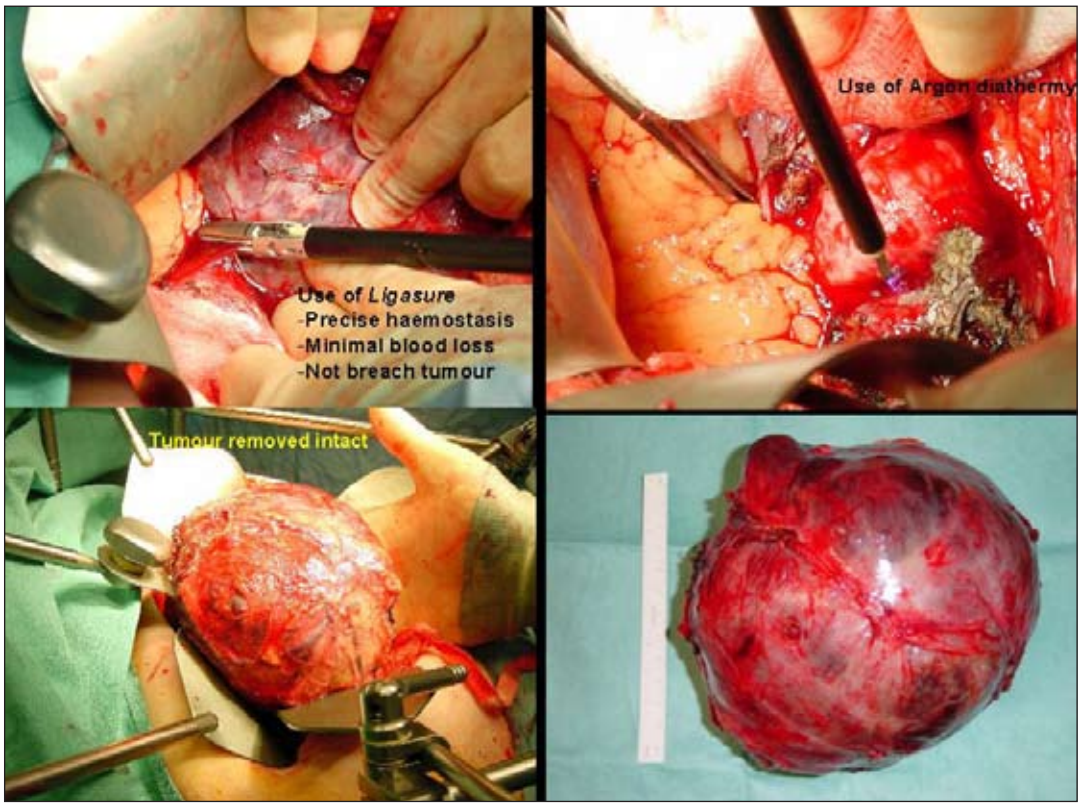
Studies are ongoing to determine the role of imatinib as preoperative therapy.[77]

11.1.2 Principles of surgery

Surgery should be performed by a surgeon who is fully trained and experienced in radical cancer surgery in the relevant area of the body from where the tumour appears to arise. The primary goal of surgery is complete resection of the disease with avoidance of tumour rupture. All tumours should be considered by a MDT for possible resection. Care is necessary as GISTs are often soft and fragile,[57] and tumour rupture may seed potential implants in the peritoneal cavity and liver.[78]

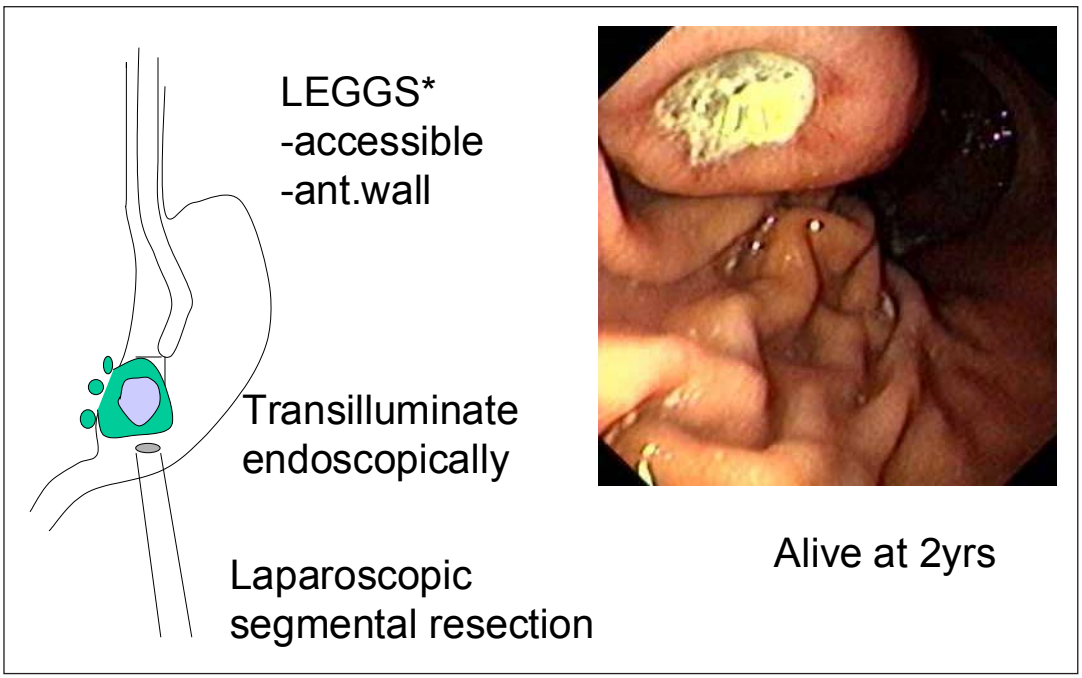
A wide local resection with macroscopic removal of the entire tumour to achieve microscopic clearance (R0 resection) is recommended[57,59] (Figure 10). An adequate cancer margin is considered to be 2 cm, but this is not always possible. The surgeon should aim to preserve function, but not at the expense of an R0 resection. In cases where adjacent organs are involved, *en bloc* resection is recommended whenever possible.[59] If the surgeon is not familiar with resecting a particular organ(s) then he/she should either refer to a surgeon with soft tissue/ sarcoma experience or involve other relevant surgical teams in the operation (i.e. urologists if the tumour is adherent to a kidney etc.).

Figure 10: Macroscopic removal of an intact large abdominal mass (courtesy of Mr Simon Toh)



As GISTs rarely metastasise to lymph nodes, extended lymphadenectomy is seldom warranted.[62] However, if doubt exists about the likely diagnosis, then a nodal clearance should be performed. In general, however, there is no evidence to suggest that procedures more extensive than removal of all gross tumour prolong survival or delay recurrence.[59] A laparoscopic approach may be feasible for smaller tumours (<5 cm) (Figure 11). Endoscopic resection is inappropriate for small GISTs.

Figure 11: Laparoscopic resection of a GIST arising in the stomach



**LEGGS = laparoscopic endoscopically-guided gastric surgery. Technique modified by S. Toh after Walsh et al.[79] (courtesy of Mr Simon Toh)*

Occasionally patients present with tumours causing small or large bowel obstructions and bleeding, and in these cases the primary aim of surgery is to save the patient's life. Upon recuperation, further resection of any remaining tumour may be necessary. The opinion of a surgeon with an interest in dealing with soft tissue tumours of the abdomen should be sought if the disease is confined to the abdomen and operability is still uncertain.

11.1.3 Small incidental tumours

The management of small, <2 cm, asymptomatic tumours (very low risk) is controversial due to the limited evidence base. It is suggested that these tumours if not removed should have a repeat assessment with EUS or CT after approximately 6 months. A further assessment after another 12 months should also be considered. Indefinite follow-up may be advised. All asymptomatic suspected GISTs of >2 cm in diameter should be resected if possible.

11.1.4 Adjuvant therapy

There is preliminary evidence that imatinib may play an important role as adjuvant therapy following GIST resection. The early results suggest that imatinib increases recurrence-free survival and may be an effective treatment to prevent recurrence following primary surgery.

A recent paper by DeMatteo et al reports the findings of the phase III trial Z9001.[80] The aim of this study was to assess the effectiveness of imatinib as adjuvant therapy in patients who had undergone a complete resection of primary GIST. In total, 708 patients who underwent complete gross resection of a primary GIST measuring at least 3 cm and expressing KIT were randomised in a double-blind fashion to 1 year of imatinib at 400 mg/day or placebo.[80] Upon recurrence, treatment was unblinded and patients were permitted to cross over to imatinib if they were on placebo or increase the dose to 800 mg/day if they were already receiving the drug. The primary endpoint was recurrence-free survival. Accrual was stopped early because the trial crossed the interim analysis efficacy boundary for recurrence-free survival.[80] Patients assigned to the imatinib arm had a 1 year recurrence-free survival of 98%, while those assigned to the placebo arm had a 1 year recurrence free survival of 83% (95% CI 96-100 vs. 95% CI 78-88; hazard ratio 0.35 (0.22-0.53); one-sided P<0.0001).[80] It was concluded that imatinib increases recurrence-free survival when administered following the complete resection of primary GIST.[80]

Although the long term effects of adjuvant therapy with imatinib have yet to be thoroughly assessed, particularly in terms of the potential development of resistance on adjuvant treatment, optimal imatinib dose, optimal duration of imatinib, and whether a significant overall survival benefit is gained, the results from the above study do indicate a benefit of imatinib in terms of recurrence-free survival when given after primary surgery. Issues still to be clarified are the optimal duration of treatment, the choice of patients who should be considered for adjuvant therapy, i.e. at what level of risk of recurrence is this appropriate, the dose of imatinib to be used for patients with *KIT* exon 9 mutant disease and whether it is appropriate at all to consider giving adjuvant imatinib to patients with no detectable mutations (wildtype). The primary endpoint of the EORTC study 62024 of adjuvant imatinib, which with 900 patients randomised to 2 years of imatinib or observation alone is the only study powered to detect a survival difference, will be time to secondary resistance. If time to treatment failure on imatinib for those patients who received adjuvant treatment and subsequently progressed is similar to that of patients with advanced disease receiving imatinib as primary therapy then it is likely that a survival advantage will ultimately be demonstrated. If time to secondary resistance is shorter, there may be no survival advantage. The adjuvant study SSGXVIII conducted by the Scandinavian Sarcoma Group in collaboration with German centres, which closed in 2008, randomised patients with very high risk disease to one versus three years of adjuvant imatinib. This study will provide valuable information on the optimal duration of therapy.[81]

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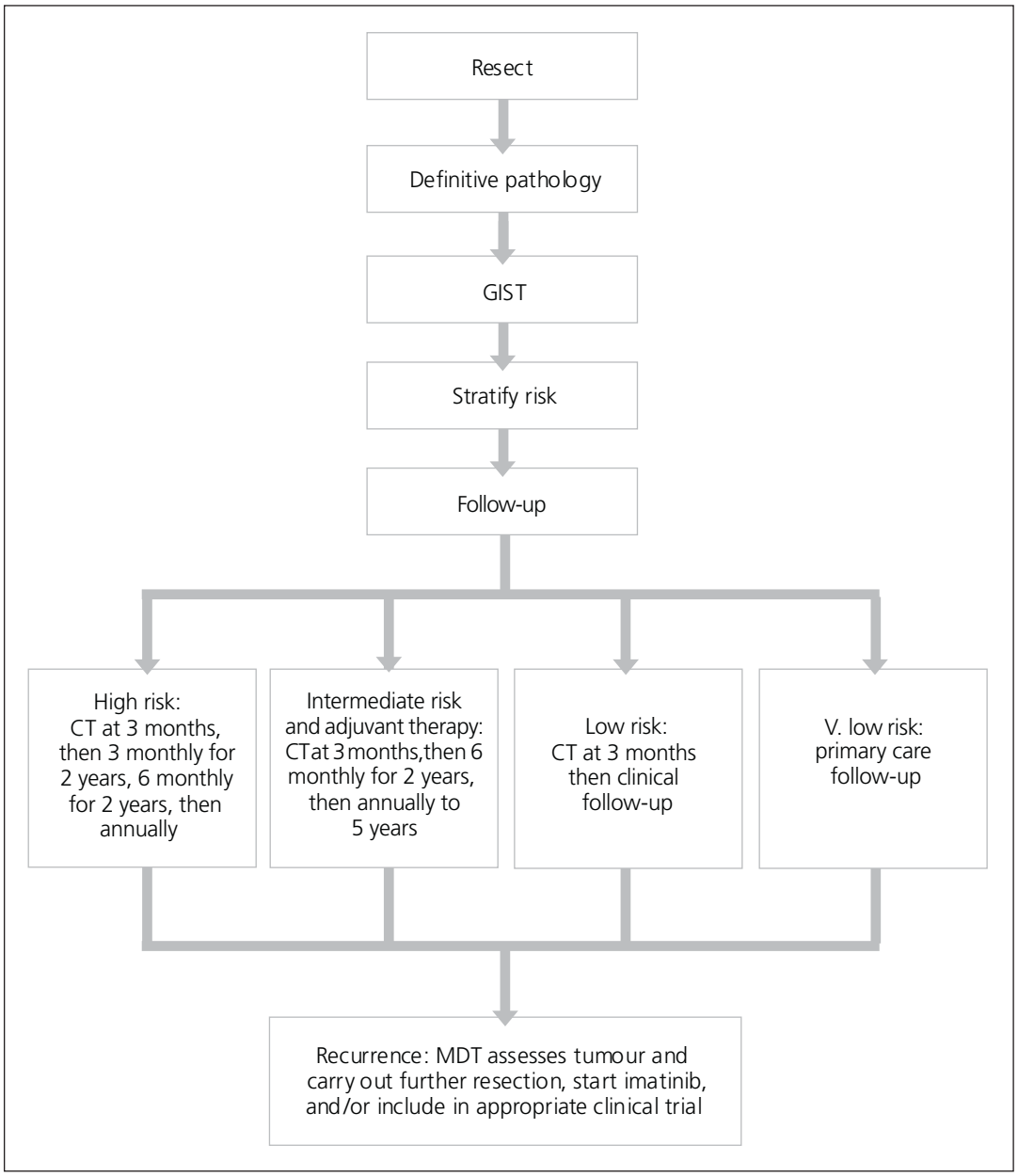
11.1.5 Follow-Up

It is recommended that all patients should be followed up centrally by a MDT. Observation is the current standard of care after complete resection of a primary tumour.[62] The frequency of surveillance should be dependent on risk as judged by a consensus of the treating MDT. It is suggested that after clinical assessment, very low risk tumours require no scans. Low risk tumours should have a single CT at baseline (3 months after surgery) then clinical assessment only with no further scans unless indicated. Intermediate risk tumours should have a CT at baseline, then every 6 months for 2 years, then annually to 5 years. High risk tumours should have a CT at baseline, then further scans every 3 months for 2 years, then 6 monthly for 2 years, and from this point on they should be scanned annually. Patients receiving adjuvant therapy with imatinib should have a CT scan at 3 months after surgery (baseline), then every 6 months for 2 years, then annually to 5 years (as per the intermediate risk group). Although CT is the primary modality for detecting recurrence, MRI can be considered for annual scans to reduce radiation dose associated with surveillance scanning. Upon suspicion of recurrence, patients should have a full assessment including contrast-enhanced CT scanning. Regardless of risk, clinic review should be indefinite, as these tumours may recur several years after apparently curative resection.

Figure 12: Follow-up algorithm



11.2 Unresectable and/or metastatic disease

Prior to the introduction of imatinib, patients with advanced GISTs faced severe morbidity and short life expectancy. Relapse rates range from 5% for complete resections up to 90% in locally advanced disease.[82]

Since there is no clear evidence of a benefit from initial debulking surgery,[83] it is not recommended unless there is an immediate clinical need, such as to remove an obstruction or to stop bleeding. However, the question of whether there is benefit in removing macroscopic disease in patients who have responded to imatinib is now the subject of a prospective randomised trial (EORTC 62063) being conducted by the EORTC.

The management of unresectable peritoneal and hepatic metastases from GISTs has been a challenging problem since historically, malignant GIST has been highly refractory to conventional cytotoxic therapy.[84]

11.2.1 Chemotherapy and radiotherapy

GISTs are resistant to conventional cytotoxic chemotherapy.[84] Evaluation of various single-agent and multiple chemotherapy regimens have yielded low objective response rates.[85]

The use of radiation has been limited because the dose of radiation required to control GISTs is likely to exceed the tolerance of surrounding tissues, given that most recurrences are diffuse, occurring in the liver or as peritoneal soft tissue masses.[85] Consequently, radiation therapy is not considered to be a viable radical treatment option, although it could be considered at low doses for palliation in carefully selected cases.

11.2.2 Rationale for the development of imatinib

A programme of rational drug design of tyrosine kinases inhibitors led to the discovery of a small molecule selective inhibitor that was termed STI571 (imatinib, Glivec®). This binds to and selectively inhibits the activity of – c-Abl, ARG, PDGFR, and the KIT tyrosine kinases.[86,87,88]

In vitro tests demonstrated inhibition of KIT signalling.[87] Initial trials were carried out in patients with chronic myeloid leukaemia, in which ABL is activated by translocation resulting in the fusion protein BCR-ABL. Very promising activity was observed, even in patients with very advanced disease. Studies in GIST followed soon afterwards and demonstrated substantial activity in this disease too,[89,90,91] subsequently confirmed in large international trials.[92,93]

Imatinib, a derivative of 2-phenylaminopyrimidine, is a competitive antagonist of ATP binding which blocks the ability of KIT to transfer phosphate groups from ATP to tyrosine residues on substrate proteins (Figures 13 & 14). This, in turn, interrupts KIT-mediated signal transduction. The inhibitory activity of imatinib on KIT in particular and on other tyrosine kinases in general is highly selective, and has relatively little effect on kinases that function in normal cell growth and proliferation;[84] this has important implications for the safety profile of the drug.

Figure 13: Molecular structure of imatinib

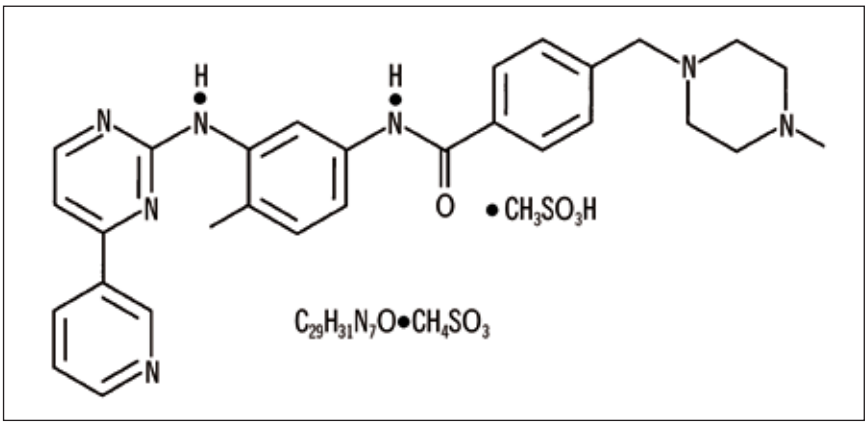
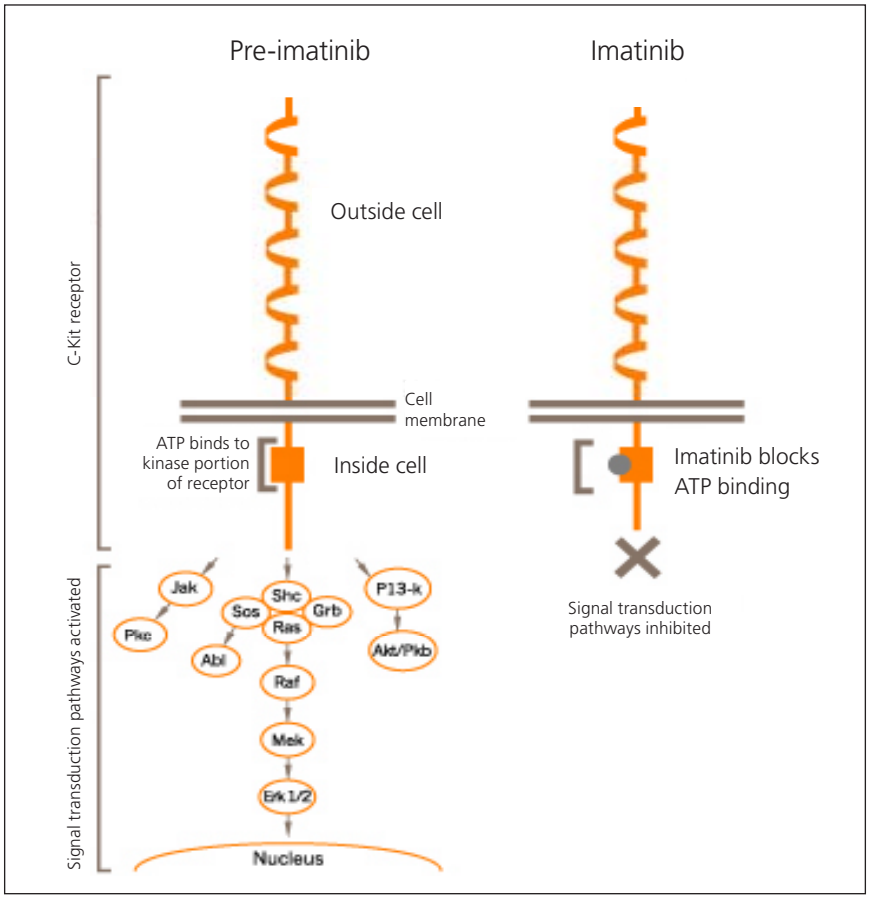


Figure 14: Visualisation of the action of imatinib at the KIT receptor



11.2.3 Effectiveness of imatinib in advanced GIST

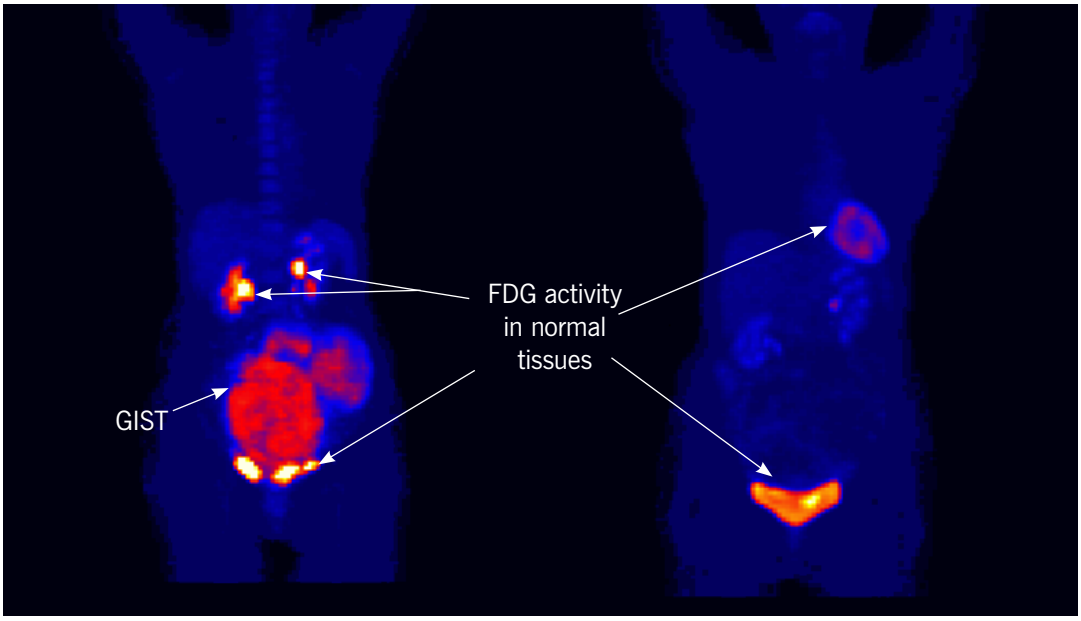
Imatinib was licensed on the basis of an open label, randomised, multicentre registration trial.[89] One hundred and forty-seven pre-treated patients (98% prior surgery, 51% prior chemotherapy, and 15% prior radiation therapy) were randomised to receive imatinib 400 mg or 600 mg orally taken once daily. The primary aim was to evaluate the objective response rate of GISTs to imatinib, and the secondary aim was to assess the safety, tolerability, pharmacokinetics, time to treatment failure, and survival. Tumour response was evaluated by CT or MRI. All complete (CR) or partial responses (PR) were confirmed 4–12 weeks later by a second assessment.[18] FDG-PET scanning was performed to assess possible changes in the metabolic profile of the tumours and in order to compare this imaging technique with standard CT imaging.

An analysis of data collected for up to 34 months showed that 84% of patients derived clinical benefit from imatinib therapy, maintaining CR (1%) or PR (67%) or stable disease (SD; 16%).[89] Imatinib was well tolerated with a low incidence of severe side effects. The 600 mg dose was not significantly more toxic than the 400 mg dose.[89] Following the initiation of imatinib therapy, 80% of the patients (20/25) demonstrated a metabolic response based on evaluation of the PET images. A metabolic response could be observed as early as 24 hours following the administration of a single dose of imatinib.[89] Median time to onset of a CR or PR was 13 weeks.[89]

The long-term results of this study were reported by Blanke *et al*.[94] Response rates, median progression-free survival and median overall survival were essentially identical in both treatment arms and the median survival was 57 months for all patients.[94] In total 46 patients were still taking imatinib at 5 years, and 41 patients were still being treated at the time of data cut off.[94] Nearly 50% of patients with advanced GIST treated with imatinib survived for more than 5 years regardless of 400 or 600 mg/day starting dose.[94]

Concurrent with the randomised phase II study in the US, the EORTC performed a dose escalation study over the range of 400 to 1000 mg daily. This established 800 mg daily as the maximum tolerated dose[90] and a phase II expansion was then performed at 800 mg in patients with GIST and other sarcomas.[95] Phase III trials were then performed both in Europe and Australasia (EORTC 62005 study) [92] and in North America (S0033 Intergroup study).[93] These studies both compared imatinib at doses of 400 mg and 800 mg. Apart from confirming the efficacy of imatinib in a larger patient population, a progression-free survival for the 800 mg dose was reported in the larger EORTC study.[92] It was subsequently demonstrated that this benefit was effectively confined to those patients with *KIT* exon 9 mutations.[26] Although a trend for improved response and progression-free survival was seen in the North American study this was not significant.[93] However, a meta-analysis of the combined dataset of 1640 patients has proven that patients with *KIT* exon 9 mutations have a better outcome if treated at 800 mg daily.[96] Both the phase III trials reported that a proportion of patients progressing on imatinib 400 mg daily, who were allowed to cross-over to 800 mg daily, experienced response or disease stabilisation. In the EORTC study, approximately 30% of patients were still on treatment at 12 months after cross-over.[97] Similar results were reported by Blanke *et al.* (2008).[93] All the phase I-III studies are summarised in table 5.

Figure 15: Imatinib response at one month measured by FDG-PET



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It has been shown that the type of c-*kit* mutation influences response to imatinib therapy.[25] The PR rate in patients whose tumours express exon 11 mutant KIT protein was significantly better (83.5%) than in patients with tumours containing exon 9 *KIT* mutation (47.8%; P=0.0006), or no detectable mutation of KIT or PDGFRA (0%; P<0.0001) [See section 11.2.4 regarding dose escalation for patients with exon 9 mutations].[25] These results have now been confirmed in the larger datasets of the European and Australian, and North American, phase III studies.[26,93]

The Eastern Cooperative Oncology Group (ECOG) performance status has a scale of 0 (fully active) to 5 (dead) to indicate how the disease affects patients' daily living abilities.[98] In the registration study,[89] the proportion of patients with normal functional status (ECOG performance status of 0) had increased by 50%: from 42% at study entry to 64% after four months treatment (144 patients still receiving treatment). Furthermore, the number of patients with substantially impaired functional status (ECOG performance status of 2/3) had decreased from 19% at study entry to 5% during the same time period.[89]

Table 5: Overview of imatinib clinical studies in GISTs

No. of sites / location	Phase and design	Imatinib dosing schedule / duration	No. patients	Median age (yr)(range)	Response rate	Overall survival
EORTC, 62001, European sites[91]	I	Dose ranging 400-1000 mg	40 (35 with GIST)	53 (29-69)	PR = 54%	Median not reported
EORTC, 62001, European sites[95]	II	800 mg od	27 GIST (24 other sarcomas)	53	CR = 4% PR = 67% SD = 18 %	Median not reported
Novartis registration trial (CSTI571-B2222)[89] 4 (USA, Finland)[94]	II R, O, M	• 400 mg od • 600 mg od 63 months median follow-up (71 months maximum)	147	54 (18–83)	Overall: CR = 1% PR = 67% SD = 16%	Overall: Median survival was 57 months for all patients
EORTC, ISG and AGITG centres, 62005, Netherlands, Italy, Australia, France, Germany, Belgium, UK[92,99]	III R,O,M	Comparison between 400 mg and 800 mg od 17 months median follow-up	946	59 (18–91)	400 mg od: CR = 6% PR = 45% SD = 33%	Overall: Median survival has not been reached at 17 months at publication
57 Intergroup S0033 centres (USA, Canada)[93]	III R,O,M	Comparison between 400 mg and 800 mg od 4.5 years median follow-up	746	61 (17-94)	400 mg od: CR = 5% PR = 40% SD = 25%	400 mg od: Median survival was 55 months
					800 mg od: CR = 3% PR = 42% SD = 22%	800 mg od: Median survival was 51 months

EORTC: European Organisation for Research and Treatment of Cancer
R = randomised; O = open-label; M = multicentre;
od = once daily
CR = complete response; PR = partial response; SD = stable disease

In summary, imatinib is an effective treatment for unresectable and/or metastatic GISTs that affects the natural history (time to progression) of the disease. In addition, imatinib increases survival in patients with metastatic and/or unresectable GISTs, in comparison with historical treatment.

11.2.4 Treatment

The target group of patients for imatinib treatment are those with CD117-positive tumours which are classified as metastatic and/or unresectable. However, it should be noted that some KIT negative GISTs have imatinib sensitive *KIT* or *PDGFRA* mutations and therefore may still benefit from imatinib therapy.[71] The aim of treatment with imatinib is to provide disease control/stabilisation and to extend time to progression in this tumour.

The recommended starting dose of imatinib is 400 mg/day, which can be escalated, if necessary, to 800 mg/day.[92, 93] This is usually taken with a meal or large glass of water to minimise gastrointestinal irritation. Evidence suggests that interrupted administration of imatinib does not prevent the development of resistance.[100] Furthermore, it has been demonstrated by Blay *et al.* that interruption of treatment results in rapid disease progression in most patients with advanced GISTs.[100] In a prospective, randomised, multicentre phase III study of patients with advanced GIST who had responded to one year's treatment with imatinib, 26 patients were treated with imatinib continuously and 32 patients received interrupted imatinib therapy. In total, 26 (81%) of the patients who had received interrupted therapy experienced documented progression, compared to only 8 patients (31%) in the continuous treatment group ($P<0.0001$).[100] It was also found that there was no difference in the development of imatinib resistance between the two arms.[100] It is therefore recommended that interruption therapy should not be routine practice and should only be considered if a patient experiences significant toxicity.

Although the starting dose of imatinib should be 400 mg/day, dose escalation to 800 mg/day may be appropriate in some patients. Blanke *et al.* reported on the randomised Intergroup S0033 study, in which patients received either 400 mg/day or 800 mg/day of imatinib.[93] While there was no significant difference in response rates or overall survival, it was found that 33% of patients who were crossed over to the high dose regimen, after disease progression on the standard dose, achieved either an objective response or stable disease.[93] Similar findings were reported in the European-Australasian study 62005.[97] The authors concluded that therapy should be initiated at 400 mg/day and then escalation could be considered on progression of disease.[93] Patients with exon 9 mutations have been identified as most likely to benefit from high dose imatinib therapy.[26,96] It is recommended that patients with confirmed exon 9 mutations may benefit from immediate dose escalation to imatinib at 800 mg/day at initiation of treatment.

11.2.5 Toxicities

Toxicities of imatinib include nausea and vomiting, diarrhoea, myalgia, skin rash, hepatic and occasional neutropenia (Table 6). Although frequent, these toxicities rarely require withdrawal of imatinib.

Table 6: Very common (>1/10) adverse reactions

Blood and lymphatic system disorders	Neutropenia, thrombocytopenia, anaemia
Nervous system disorders	Headache
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain
Skin and subcutaneous tissue disorders	Periorbital oedema, dermatitis / eczema / rash
Musculoskeletal, connective tissue and bone disorders	Muscle spasm and cramps, musculoskeletal pain including arthralgia
General disorders and administration site conditions	Fluid retention and oedema, fatigue

Gastrointestinal bleeding/intratumoural bleed, may be life-threatening and require surgical intervention or embolisation.

Oedema is most commonly periorbital, but may occasionally result in pleural effusion, ascites, or generalised oedema. Diuretic therapy should be initiated or the dose of diuretics increased as soon as possible. In patients with severe fluid retention, imatinib should be discontinued; the oedema controlled with diuretics. Imatinib can then be restarted, possibly at a reduced dose, while maintaining or increasing diuretic therapy.

For grade 3 elevations of transaminases therapy should be interrupted (although this is rare and may be much more common with CML where it could be related to the leukaemic process). When the transanimases fall to grade 1 or less, imatinib is reintroduced at a reduced dose. If the liver toxicity does not recur within 6-12 weeks, re-escalation to the initial dose can be performed while closely monitoring the liver function blood tests (LFTs). If grade 3 toxicity recurs, a more thorough hepatic evaluation is indicated, and imatinib may be continued at the lower, tolerated dose (some patients derive benefit from doses as low as 100 mg daily). Grade 2 LFT abnormalities (2.5-5 times the upper limit of normal) do not require automatic drug discontinuation, but must be monitored.

Skin rash is mostly mild, self-limiting and easily manageable with antihistamines or topical steroids, whereas a short course of oral steroids can be used to treat more severe cases. Most settle rapidly with temporary discontinuation of the drug. Most do not recur with reintroduction of the drug. In some patients, severe rashes develop with desquamative components, including a report of Stevens-Johnson syndrome. In such cases, immediate discontinuation of therapy and systemic steroids (e.g. prednisolone 1 mg/kg/day) are indicated.

11.2.6 Medical management

Imatinib has demonstrated activity and should be offered when appropriate to patients with unresectable and/or metastatic GISTs. As with other anticancer agents, the incidence of side effects correlates with declining performance status and earlier treatment is likely to be both better tolerated and more effective.

11.2.7 Prior to medical treatment

In order to monitor treatment, measurable or assessable disease should be documented. Patients should be made aware of their prognosis, the duration of treatment and the likely side effects of therapy. Baseline assessment of patients should include:

- Full history and clinical examination
- World Health Organization (WHO) performance status
- Concomitant medication (see appendix)
- Patient should not be pregnant or breast-feeding (patient should be counselled with regard to becoming pregnant)
- Liver function tests (caution required with deranged LFTs, but no level of bilirubin/transaminases has been defined as an absolute contraindication or indication for dose adjustment at start of therapy)
- Full blood count
- Weight
- The patient should be staged fully by CT

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11.2.8 Follow-up

Imatinib has been shown to be highly effective, but resistance and disease progression have been observed.[92,93,97,100] Patients should have a CT scan every 3 months and LFTs should be monitored at each visit. Symptomatic improvement of patients is a positive sign, but 4 weeks is too soon to make assessment of response (may see some noticeable symptomatic change after 12 weeks).

It is important to note that response by conventional criteria such as RECIST may not occur, or may only happen after many months of treatment. The difficulties of response evaluation has been addressed by Choi.[101,102] RECIST are based on unidimensional tumour size and do not take into account decreases in tumour density and decreases in intratumoural vessels which are seen in responding GISTs. Choi proposes a new set of objective criteria based upon tumour density and tumour size [see Section 14.4 for details].[101,102] It is therefore recommended that the Choi criteria be used in place of conventional RECIST criteria when evaluating response in GIST.

Although CT and ^{18}FDG-PET have comparable sensitivity and positive predictive values in staging malignant recurrent GISTs, ^{18}FDG-PET is superior in predicting early response to imatinib therapy.[103] If PET is available, it is important that a high-quality system is used to ensure that small lesions or subtle differences are not missed.[99] PET should not be routinely used for long-term follow-up, but should be considered if there is a suspicion of resistance to imatinib that is not clearly demonstrated with CT scanning or in situations where an early assessment of response is indicated.

Surgery may be considered in patients thought initially to be inoperable, but where imatinib has led to a reduction in disease bulk such that an R0 resection may be achieved. For example, it has been reported that a patient who presented with a 35 cm tumour and multiple liver metastases who was treated with imatinib had eradication of their liver metastases and shrinkage of the primary tumour to the point of resectability.[104] Similarly, a more recent study by Bauer *et al.* reports on a series of 90 patients with metastatic GIST in whom treatment with imatinib enabled 12 patients with mostly recurrent and extensive disease to be considered for resection of residual disease.[105] In 11 of the 12 patients, complete resection could be achieved. However, it should be noted that the role of surgery in advanced disease following treatment is as yet unproven; there is no evidence at present that such surgery results in longer survival. Indeed, a number of retrospective case series' of surgery following medical therapy for GIST have shown that, while the best survival is observed in patients who are responding to imatinib, survival is poorer in patients who have surgery for limited disease progression, and very poor for those who have surgery for generalised disease progression.[106,107,108] Thus surgery in the latter situation is not recommended. Surgery for other patients should be considered on an individual patient basis. Furthermore, the EORTC Soft Tissue and Bone Sarcoma Group opened a study (EORTC 62063) in 2008 which aims to clarify the role of surgery in patients with metastatic GIST responding to imatinib, randomising between surgery and observation.[109]

On disease progression on imatinib 400 mg/day, dose escalation of imatinib to 800 mg/day should be considered.[93,97] Progressive disease should be confirmed radiologically and discussed by the MDT, as tumour liquefaction (cystic degeneration) can occur which may give the appearance of progressive disease although the tumour is in reality responding.[101] Furthermore, progressing patients can experience worsening symptoms (tumour 'flare' phenomenon) if imatinib is withdrawn.[66] This suggests that even in patients who have begun to progress on imatinib, there may exist tumour cell populations for which imatinib remains effective.[66]

11.2.9 Management after imatinib

The MDT should discuss and decide the treatment approach for progressing and recurrent disease on a case-by-case basis. Surgery may have a role at any stage in the management of GISTs, and should be considered in patients with localised progression (i.e. <3 sites) although at present the role of surgery in this situation remains unproven (see section 11.2.8).

Peritoneal recurrence may be either near the site of the primary tumour or at a distant location and usually is not found to invade the underlying organs or involve the lymph nodes.[62] Peritoneal recurrences of GIST can often be removed with limited resection.[62] It should be noted, however, that the extent of peritoneal disease is often under-represented by cross-sectional imaging and the discovery of countless sub-centimetre nodules at laparotomy is not unusual.[62]

The liver is a common site of recurrence, with most liver metastases being unresectable due to diffuse intrahepatic disease or inoperable due to extrahepatic disease.[62] The opinion of a liver surgeon should be sought if resection of hepatic recurrence is considered an option.

In recent years, a new therapy for GIST has become available, sunitinib (Sutent®), which is indicated for the treatment of unresectable and/or metastatic GISTs after failure of imatinib treatment due to resistance or intolerance.[110] Demetri *et al.* conducted a randomised, double-blind, placebo-controlled, multicentre, international trial to assess the efficacy and tolerability of sunitinib.[111] In total, 207 patients, who were resistant or intolerant to imatinib, initially received sunitinib (50 mg starting dose in 6 week cycles; 4 weeks on and 2 weeks off treatment) and 105 received placebo. However, the trial was unblinded early when interim analysis showed a significantly longer time to tumour progression (the primary endpoint) with sunitinib than placebo.[111] Median time to progression was 27.3 weeks in patients receiving sunitinib and 6.4 weeks in those receiving placebo (hazard ratio 0.33; $P<0.0001$).[111] Therapy with sunitinib was reasonably well-tolerated, with the most common adverse events being fatigue, diarrhoea, skin discolouration, and nausea. Of potential clinical significance, the second most common non-haematological, Grade 3 adverse event associated with sunitinib was hand-foot syndrome, affecting 4% of treated patients in the study.[111] It was concluded by the authors that, compared to placebo, sunitinib conferred significant clinical benefit in terms of disease control and superior survival in patients with advanced GISTs after failure and discontinuation of imatinib.[111]
It is therefore recommended that if patients show progression on imatinib, after escalation to 800 mg/day, that they should be started on sunitinib at 50 mg/day for 4 weeks, followed by a 2 week rest period to comprise a 6 week treatment cycle. Lower doses of sunitinib may be given continuously (e.g. 37.5 mg/day) for patients who are unable to tolerate sunitinib at 50 mg/day.[110,112]

If patients show progression of disease on sunitinib, reintroduction of imatinib therapy may be considered to provide symptomatic relief. Patients should also be considered for appropriate clinical trials.

A potentially beneficial intervention for locally progressive disease is radiofrequency ablation (RFA).[113] RFA appears to be an effective means of treating small to moderate sized liver metastases, but there is no current evidence to support its routine use in hepatic metastases from GIST.

12.0 Special Populations

Key recommendations

- All patients should be advised to use contraception and women to avoid becoming pregnant whist receiving imatinib/sunitinib treatment for GIST
- Patients with compromised renal or hepatic function do not require modification of imatinib dose

12.1 Pregnant women

Although GISTs usually occur in older patients, some may be of child bearing age and wish to have children. It is important to thoroughly discuss the issues surrounding imatinib and pregnancy in order for the patient to make an informed choice. In a recent paper by Pye *et al.*, the effect of imatinib on pregnancy outcome was explored.[114] Out of 125 women with various malignancies whose pregnancy outcome data were available, there were a total of 12 infants with abnormalities, 3 of which showed similar complex malformations. It was concluded that while most pregnancies exposed to imatinib are likely to have a successful outcome, there remains a risk that exposure may result in serious fetal malformations.[114]

There are currently no studies of sunitinib use in pregnant women; however, studies have been carried out in animal models. In a study by Patyna *et al*., pregnant rats and rabbits received sunitinib at 0-30 mg/kg/day.[115] Fetal malformations included thoracic and lumber vertebral alterations in rats and cleft lip/palate in rabbits.[115] The study concluded that sunitinib treatment is associated with embryo-fetal developmental toxicity in rats and rabbits.[115]

Overall, it is recommended that patients be advised to practice contraception and avoid pregnancy while receiving treatment for GIST.[76,110]

12.2 Patients with compromised renal or hepatic function

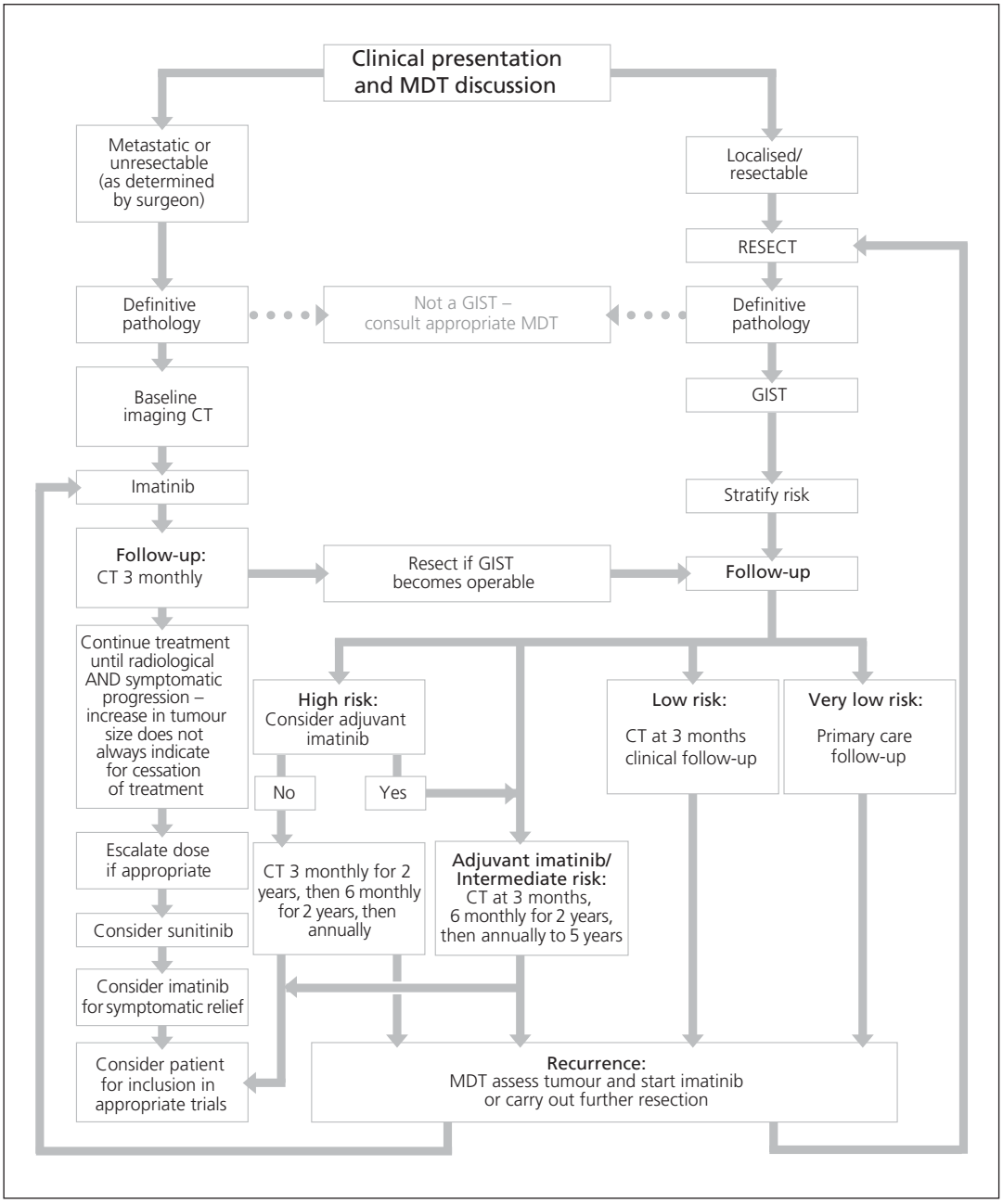
Imatinib has been shown to be well tolerated in patients with renal dysfunction or hepatic dysfunction. In a recent study by Gibbons *et al.*, 60 adult patients with advanced solid tumours and varying renal function (normal [creatinine clearance, CrCL, $\geq$60 mL/min], mild dysfunction [CrCL 40-59 mL/min], moderate dysfunction [CrCL 20-39 mL/min], or severe dysfunction [CrCL <20 mL/min]) were given daily doses of imatinib at 100 to 800 mg.[116] This study found that imatinib was well tolerated in patients with mild or moderate renal dysfunction at doses up to 800 mg and 600 mg, respectively.[116] However, there were too few patients with severe dysfunction to draw any meaningful conclusions for that group.[116]

A study of imatinib in 89 patients with advanced malignancies and varying degrees of liver dysfunction was conducted by Ramanathan *et al*.[117] The patients were stratified into 4 groups according to serum total bilirubin and AST (normal, mild liver dysfunction, moderate liver dysfunction and severe liver dysfunction) and were treated with escalating doses of imatinib. The maximum tolerated dose for patients receiving imatinib with mild liver dysfunction was found to be 500 mg/day.[117] The maximum tolerated dose for moderate liver dysfunction and for severe liver dysfunction were not determined.

Based on these two studies, it is recommended that the standard dose of imatinib does not require modification in patients with renal or hepatic dysfunction. However, more research is needed to determine the effects of imatinib at higher than the standard 400 mg/day dose in patients with severe renal or hepatic dysfunction.

Sunitinib has been found to be tolerated in patients with mild to moderate hepatic dysfunction; however, no studies have been carried out in patients with severe hepatic dysfunction.[110]
No clinical studies with sunitinib have been performed in patients with impaired renal function.[110]

13.0 Algorithm of Overall Care



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14.0 Appendices

14.1 Guidelines for pathological dissection and reporting of biopsy and resection specimens with gastrointestinal stromal tumours

14.1.1 Specimen reception

Ideally all large GIST resection specimens, irrespective of anatomic site, should be received fresh (unfixed) in the laboratory. However, in practice many specimens will be received fixed or partly fixed. In many cases the GIST will be discovered following surgery for other gastrointestinal malignancy or intra-abdominal mass. This protocol should be adhered to as closely as possible in such specimens.

14.1.2 Resection specimen handling

The specimen is examined externally and inked circumferentially to define margin status.

The specimen is then opened in the manner appropriate for the anatomic location.

If the specimen is received fresh, a small sample of tumour tissue should be removed with a clean scalpel blasé, placed in a screw top plastic tube and stored no warmer than minus 70°C for future molecular analysis. A small portion of normal tissue, e.g. stomach or bowel wall, should be similarly obtained and frozen. These matched tumour-normal pairs (labelled with the surgical pathology number) are held in the local tumour bank facility until submitted for molecular biology analysis. If the specimen is received fixed, no tissue is frozen.

The specimen is then pinned out, if suitable or required, and fixed in the manner most appropriate for the anatomic location. If the tumour mass is very large, fixation will be facilitated by serial sectioning.

14.1.3 Specimen dissection and taking tissue blocks for histopathology

After fixation, the specimen is dissected according to the protocol appropriate for the anatomic site of origin. The tumour mass is measured in three dimensions. Evidence of extension into mucosa, ulceration and depth of invasion are all noted. The distances to all surgical and circumferential resection margins are recorded.

On transverse slicing, areas of softening (necrosis), haemorrhage or gelatinous (myxoid) change are noted.

Tissue blocks are taken from the surgical and circumferential resection margins. Blocks from the tumour mass are taken to ensure that all grossly different patterns are sampled at a rate of one block per cm of greatest diameter of tumour.

Blocks to demonstrate mucosal infiltration, depth of invasion and possible vessel invasion, if suspected grossly, are taken. Lymph nodes are dissected and blocked in the standard fashion.

14.1.4 Histopathological reporting

Morphological description and immunohistochemistry

The histopathological report should include:

Microscopic description

Tumour type	Spindle / Epithelioid / Mixed
Necrosis	Yes / No
Haemorrhage	Yes / No
Other histological patterns	Myxoid / Nested / Other
Invasion of structures	Mucosa / Muscularis / Other organ
Mitotic rate	Number / 50 high power fields
Margin status	Positive / Negative
Lympho-vascular invasion	Yes / No
Lymph node status	……
Other features / pathology	……
Risk of recurrence	……

Immunohistochemistry

Immunohistochemistry must be performed on every case. A block of well fixed tumour without necrosis or haemorrhage is selected. The following panel of epitopes is suggested:

KIT (CD 117)	Almost 100% positive *
DOG1	97%
CD 34	Positive 50 – 60%
Desmin	Negative **
Smooth Muscle Actin	Variably positive
S100	Variably positive, < 5%
Vimentin	Positive 100%
Cytokeratin	Negative

* A small number of KIT negative GISTs have been reported. The diagnosis of GIST in the context of negative KIT staining may require mutational analysis of the C-KIT and PDGF genes (see Appendix A)

** Only a few scattered cells may be positive. Diffuse strong positivity is not in keeping with GIST.

A variety of antibodies to these epitopes are available commercially. However not all laboratories will have access to all of them, in particular to CD117. Referral of a tissue block and H&E slide to another centre is then recommended. It must be remembered that other tumours may express CD117.

Particular caution must be employed when using polyclonal antibodies to KIT with antigen retrieval, as false positives may occur. It is helpful to perform the immunohistochemical test with and without antigen retrieval and with appropriate controls.

Monoclonal antibodies (with strict adherence to the manufacturers' protocols) may have advantages in reducing false positives.

14.2 Response Evaluation Criteria in Solid Tumors (RECIST)[118]

RECIST is a set of guidelines that define when cancer patients improve ("respond"), stay the same ("stable"), or worsen ("progression") during treatments (Table 7). These criteria were developed under the auspices of the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group.

Table 7: Overall responses for all possible combinations of tumour responses in target and nontarget lesions with or without the appearance of new lesions[118]

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response
PR = partial response
PD = progressive disease
SD = stable disease
NE = inevaluable

14.3 Choi Response Criteria[102]

The response criteria proposed by Choi *et al.* supersede RECIST by taking into account tumour density as well as tumour size.

Response	Definition
CR	Disappearance of all lesions No new lesions
PR	A decrease in size* of ≥ 10% or a decrease in tumour density (HU) ≥ 15% on CT No new lesions No obvious progression of nonmeasurable disease
SD	Does not meet criteria for CR, PR, or PD No symptomatic deterioration attributed to tumour progression
PD	An increase in tumour size of ≥ 10% and does not meet criteria of PR by tumour density (HU) on CT New lesions New intratumoural nodules or increase in size of the existing tumoural nodules

CR = Complete response
PR = Partial response
HU = Hounsfield unit
CT = Computed tomography
SD = Stable disease
PD = Progression of disease

**The sum of the longest diameters of target lesions as defined in RECIST*

14.4 Interaction of imatinib with other drugs[76]

- Warfarin, paracetamol, fluconazole, dexamethasone, erythromycin, and antiepileptics are relative contra-indications to imatinib
- CYP3A4/5 inducers (e.g. carbamazepine, dexamethasone, phenytoin, phenobarbital, progesterone, rifampicin, and St John's Wort) will reduce imatinib levels
- Drugs that inhibit CYP3A4/5 enzyme activity might result in increased plasma levels of imatinib (e.g. cimetidine, erythromycin, fluoxetine, ketoconazole, ritonavir, itraconazole, and verapamil). Patients should be cautioned against excessive intake of grapefruit juice as it is also an inhibitor of CYP3A4/5
- Drugs metabolised by other cytochrome enzymes can also cause interactions when given concomitantly with imatinib (e.g. simvastatin, cyclosporine A)

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14.5 Interaction of sunitinib with other drugs[110]

- Concomitant administration of sunitinib with the CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib plasma concentrations
- Concomitant administration of sunitinib with CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital and St John's Wort) may decrease sunitinib plasma concentrations
- Haemorrhage has been observed rarely in patients treated with sunitinib; patients receiving treatment with anti-coagulants should be monitored by complete blood counts, coagulation factors and physical examination

14.6 Key to levels of evidence and grading of recommendations[1]

The interpretation of evidence and grading of recommendations used in these guidelines originates from the US Agency for Health Care Policy and Research and is summarised below in the following table.

Statements of Evidence	
Ia	Evidence obtained from meta-analysis of randomised trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed, non-experimental, descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorites

Grades of Recommendation	
A	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of the recommendation. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates the absence of directly applicable clinical studies of good quality. (Evidence level IV)

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16.0 Abbreviated Prescribing Information

▼GLIVEC® (imatinib) 100mg and 400mg Tablets

Presentation: 100mg Tablets: Very dark yellow to brownish-orange film-coated tablet, round with "NVR" on one side and "SA" and score on the other side. 400mg Tablets: Very dark yellow to brownish-orange, ovaloid, biconvex film-coated tablet with bevelled edges, debossed with "NVR" on one side and "SL" on the other side.

Indications:

CML: For the treatment of adults and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. For the treatment of adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alfa therapy or in accelerated phase or blast crisis.

Ph+ALL: For the treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy and adult patients with relapsed or refractory Ph+ ALL as monotherapy.

GIST: For the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).

For the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.

DFSP: For the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

MDS/MPD: For the treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.

HES/CEL: For the treatment of adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

Dosage: Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate. Prescribed dose administered orally, with a meal and a large glass of water.

CML: Adults: The recommended dosage of Glivec is 400mg/day for patients in chronic phase CML and 600mg/day for patients in accelerated phase or blast crisis. Dose increases from 400mg to 600mg or 800mg in patients with chronic phase disease, or from 600mg to a maximum of 800mg (given as 400mg twice daily) in patients with accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia. Doses of 400mg or 600mg should be administered once daily whereas a daily dose of 800mg should be administered as 400mg twice a day, in the morning, and in the evening.

Children: Dosing is recommended on the basis of body surface area (mg/m^2). Doses of 340mg/m^2 daily is recommended for children with chronic phase CML and advanced phase CML (not to exceed the total dose of 800mg). There is no experience with the treatment of children below 2 years of age.

Dose increases from 340mg/m^2 daily to 570mg/m^2 daily (not to exceed the total dose of 800mg) may be considered in children in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia.

Ph+ ALL: The recommended dose of Glivec is 600mg/day for patients with Ph+ ALL. On the basis of the existing data, Glivec has been shown to be effective and safe when administered at 600mg/day in combination with chemotherapy in the induction phase, the consolidation and maintenance phases of chemotherapy (see section 5.1 of the SmPC) for adult patients with newly diagnosed Ph+ ALL. For adult patients with relapsed or refractory Ph+ALL Glivec monotherapy at 600mg/day is safe, effective and can be given until disease progression occurs.

GIST: The recommended dosage of Glivec is 400mg/day for patients with unresectable and/or metastatic malignant GIST. Limited data exist on the effect of dose increases from 400mg to 600mg or 800mg in patients progressing at the lower dose. Treatment should be continued until disease progression. The recommended dose of Glivec is 400 mg/day for the adjuvant treatment of adult patients following resection of GIST. Optimal treatment duration is not yet established. Length of treatment in the clinical trial supporting this indication was 12 months.

DFSP: The recommended dose of Glivec is 800mg/day for patients with DFSP.

MDS/MPD: The recommended dose of Glivec is 400mg/day for patients with MDS/MPD. Treatment duration: In the only clinical trial performed up to now, treatment with Glivec was continued until disease progression (see section 5.1 of the SmPC). At the time of analysis, the treatment duration was a median of 47 months (24 days - 60 months).

HES/CEL: The recommended dose of Glivec is 100mg/day for patients with HES/CEL. Dose increase from 100mg to 400mg may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. Paediatric use: There is no experience in children with CML below 2 years of age (see section 5.1 of the SmPC). There is limited experience in children with Ph+ ALL. There is no experience in children or adolescents with GIST.

Dose adjustments for adverse reactions: *Non-haematological adverse reactions*: In severe cases withhold treatment until the event has resolved. Elevations of bilirubin >3 x institutional upper limit of normal (IULN) or if liver transaminases >5 x IULN, withhold treatment until bilirubin levels have returned to <1.5 x IULN and transaminase levels to <2.5 x IULN. Treatment may then be continued at a reduced daily dose. *Haematological adverse reactions*: Severe neutropenia and thrombocytopenia; reduce dose or interrupt treatment. (See full prescribing information).

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Precautions: Patients with impaired renal function should be given the minimum starting dose. Although very limited information is available, patients with severe renal dysfunction or on dialysis should also start on the same dose of 400mg. Caution is recommended in these patients. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored. Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored regularly in patients receiving Glivec. Caution is recommended in thyroidectomy patients receiving levothyroxine during treatment with Glivec; closely monitor TSH levels. Use with caution and monitor in patients with a history of cardiac disease or risk factors for cardiac failure. Evaluation by a cardiology specialist, performance of an echocardiogram and determination of serum troponin should be considered in patients with HES/CEL and MDS/MPD associated with high eosinophil levels before imatinib is administered. Interactions are possible with other medications affecting or affected by the cytochrome P450 isoenzyme CYP3A4. Concomitant use with strong CYP3A4 inducers should be avoided. Caution is advised when imatinib is administered with CYP2D6 substrates that have a narrow therapeutic index such as metoprolol. Patients requiring anticoagulation should receive low-molecular weight or standard heparin rather than warfarin. Caution with concomitant paracetamol. Use of Glivec in combination with chemotherapy requires special precaution. Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib. When imatinib is combined with high dose chemotherapy regimens in Ph+ ALL patients, an

increase in serious hepatic reactions has been detected. Hepatic function should be carefully monitored in circumstances where imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction.

Side-effects. *Very Common:* Neutropenia, thrombocytopenia, anaemia, headache, nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, fluid retention and oedema, periorbital oedemas, dermatitis, eczema, rash, muscle spasm and cramps, musculoskeletal pain including myalgia, arthralgia, bone pain, fatigue, weight increase. *Common:* Anorexia, febrile neutropenia, dizziness, taste disturbance, paraesthesia, insomnia, conjunctivitis, lacrimation increased, vision blurred, epistaxis, dyspnoea, abdominal distension, flatulence, constipation, gastritis, gastro-oesophageal reflux, weight decrease, increased hepatic enzymes, pancytopenia, hypoaesthesia, facial oedema, eyelid oedema, conjunctival haemorrhage, dry eye, photosensitivity reaction, flushing, cough, dry mouth, pruritus, erythema, dry skin, alopecia, night sweats, joint swelling, pyrexia, weakness, rigors, chills, haemorrhage, anasarca. *Uncommon:* Sepsis, pneumonia, herpes simplex, herpes zoster, upper respiratory tract infection, influenza, Raynaud's syndrome, gastroenteritis, bone marrow depression, dehydration, hyperuricaemia, hypokalaemia, appetite increase or decrease, gout, hypophosphataemia, hypercalcaemia, hyperglycaemia, hyponatraemia, depression, anxiety, libido decreased, palpitations, cerebral haemorrhage, syncope, peripheral neuropathy, somnolence, migraine, memory impairment, nasopharyngitis, sinusitis, cellulitis, eye irritation, eye pain, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema, orbital oedema, pulmonary oedema, tachycardia, haematoma, hypertension, hypotension, cardiac failure congestive, peripheral coldness, pleural effusion, pharyngolaryngeal pain, gastrointestinal haemorrhage, pharynigitis, stomatitis, melaena, ascites, gastric ulcer, mouth ulceration, oesophagitis, haematemesis, dysphagia, pancreatitis, eructation, jaundice, hepatitis, hyperbilirubinaemia, petechiae, contusion, sweating increased, chest pain, urticaria, onychoclasis, purpura, hypotrichosis, cheilitis, skin hyperpigmentation, skin hypopigmentation, psoriasis, exfoliative dermatitis, rash pustular, ecchymosis, increased tendency to bruise, folliculitis, bullous eruptions, sciatica, joint and muscle stiffness, renal pain, renal failure acute, urinary tract infection, urinary frequency increased, haematuria, gynaecomastia, breast enlargement, scrotal oedema, menorrhagia, nipple pain, sexual dysfunction, erectile dysfunction, menstruation irregular, malaise, blood alkaline phosphatase increase, blood creatinine increase, blood creatinine phosphokinase increased, blood lactate dehydrogenase increased, thrombocythaemia, lymphopenia, eosinophilia, lymphadenopathy, restless leg syndrome, tremor. *Rare*: Hyperkalaemia, confusion, increased intracranial pressure, convulsions, papilloedema, glaucoma, pericardial effusion, pulmonary fibrosis, colitis, ileus, hepatic failure, hepatic necrosis, vesicular rash, Stevens-Johnson syndrome, acute febrile neutrophilic dermatosis (Sweet's syndrome), Blood amylase increased, muscular weakness, arthritis, hypomagnesaemia, fungal infections, haemolytic anaemias, optic neuritis, cataract, arrhythmia, atrial fibrilliation, cardiac arrest, myocardial infarction, angina pectoris, pleuritic pain, pulmonary hypertension, pulmonary haemorrhage, inflammatory bowel disease, nail discolouration, angioneurotic oedema, erythema multiforme, leucocytoclastic vasculitis, acute generalised exanthematous pustulosis (AGEP), rhabdomyolysis/myopathy, Haemorrhagic corpus luteum/ haemorrhagic ovarian cyst,. *Not Known:* Anaphylactic shock, tumour haemorrhage, tumour necrosis, pericarditis, cardiac tamponade, cerebral oedema, vitreous haemorrhage, acute respiratory failure, interstitial lung disease, ileus/intestinal obstruction, gastrointestinal perforation, diverticulitis, avascular necrosis, hip necrosis, thrombosis, embolism, lichenoid keratosis, lichnen planus, toxic epidermal necrolysis. Refer to the SPC for a full list of all side effects.

Legal Category POM

Packs

GLIVEC 100mg Tablets 60 pack **MA Number** EU/1/01/198/008
Basic NHS price £802.04

GLIVEC 400mg Tablets 30 pack **MA Number** EU/1/01/198/010
Basic NHS price £1604.08

GLIVEC® is a registered Trade Mark

Full prescribing information is available on request from Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR. Telephone (01276) 692255. Fax number (01276) 692508.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk

Adverse events should also be reported to Novartis on (01276) 698370

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