Management of gastrointestinal stromal tumors: from diagnosis to treatment

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Abstract
Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of the digestive tract. Most gastrointestinal soft tissue neoplasms, previously classified as leiomyomas, schwannomas, leiomyoblastomas or leiomyosarcomas, are today classified as GIST on the basis of molecular and immunohistological features. They originate from gastrointestinal pacemaker cells and are characterised by over-expression of the tyrosine kinase receptor KIT. Overall 5-year survival after surgical resection of GIST is approximately 60%. However, these tumours span a wide clinical spectrum from benign to highly malignant. Prognostic factors have recently been identified for GIST and include tumour size, mitotic rate and other minor factors. At present, surgery is the standard treatment for primary resectable GIST. Benign GIST have an excellent prognosis after primary surgical treatment, with over 90% 5-year survival. While recurrent or malignant GIST, which are resistant to radiotherapy and chemotherapy, had until recently an extremely poor prognosis even after surgical resection, with median survival of 12 months. The development […]
Management of gastrointestinal stromal tumours: from diagnosis to treatment

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Summary

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of the digestive tract. Most gastrointestinal soft tissue neoplasms, previously classified as leiomyomas, schwannomas, leiomyoblastomas or leiomyosarcomas, are today classified as GIST on the basis of molecular and immunohistological features. They originate from gastrointestinal pacemaker cells and are characterised by over-expression of the tyrosine kinase receptor KIT. Overall 5-year survival after surgical resection of GIST is approximately 60%. However, these tumours span a wide clinical spectrum from benign to highly malignant. Prognostic factors have recently been identified for GIST and include tumour size, mitotic rate and other minor factors. At present, surgery is the standard treatment for primary resectable GIST. Benign GIST have an excellent prognosis after primary surgical treatment, with over 90% 5-year survival. While recurrent or malignant GIST, which are resistant to radiotherapy and chemotherapy, had until recently an extremely poor prognosis even after surgical resection, with median survival of 12 months. The development of a tyrosine kinase inhibitor has changed the management of unresectable malignant cases. This new tyrosine kinase inhibitor, imatinib mesylate, which inhibits the c-kit receptor, has proved highly effective against GIST and has improved survival in metastatic GIST. This paper reviews the literature and our experience of GIST, including: diagnosis, pathology, treatment and prognosis.

Key words: gastrointestinal stromal tumour (GIST); mesenchymal tumour; c-kit (CD117); tyrosine kinase inhibitor; imatinib mesylate (STI-571)

Introduction

Up to 20 years ago most mesenchymal tumours of the digestive tract were considered to be of smooth muscle or perineural origin. In 1983, Mazur and Clark [1] coined the term gastrointestinal stromal tumours (GIST) to indicate a distinctive subgroup of gastrointestinal mesenchymal tumours which could be classified neither as neurogenic- nor smooth muscle-derived. Kindblom et al. [2] proposed that these tumours may originate from the interstitial cell of Cajal, an intestinal pacemaker cell, and suggested the name gastrointestinal pacemaker cell tumour. This hypothesis is supported by the observation that GIST cells show ultrastructural features and express cell markers typical of the normal interstitial cell of Cajal [2]. Histological features of GIST may explain the past diagnostic confusion with other mesenchymal tumours. Today, on the basis of pathological features, most gastrointestinal mesenchymal tumours previously designated as smooth muscle tumours, such as leiomyomas, leiomyoblastomas and leiomyosarcomas, are GIST [3–5]. However, true gastrointestinal leiomyomas and schwannomas remain to be identified.

Although rare, GIST are the most common mesenchymal tumours of the gastrointestinal tract. GIST are of clinical relevance because in at least 10–30% of cases they are malignant [4, 6]. In the past, GIST chemo- and radio-resistance made treatment a challenging issue for physicians, while criteria for evaluation of the malignant potential of GIST were lacking. Currently, identification of reliable prognostic factors and the development of molecular-targeted anticancer strategies for GIST has given new hope to these patients [7–9].

In this review we report on the clinical aspects of GIST, from diagnosis to prognosis, and review the published literature as well as our experience. We also review the therapeutic options for GIST.
Clinical presentation

GIST, the most common mesenchymal tumours of the digestive tract, account for 0.1–3% of all gastrointestinal cancers. However, they represent up to 20% of small bowel malignancies [10]. The incidence of primary GIST is around 20/10^6 people/year [11]. GIST predominantly occurs in middle-aged and older persons (5th to 7th decade), with no significant difference in distribution between males and females [4, 12].

Most GIST arise in the stomach (approximately 60%) and small intestine (approx 30%), and infrequently from the duodenum, the colon and rectum or the mesentery. Oesophageal localisation is extremely rare [4, 13–15].

The symptoms, which depend on tumour size and location, are usually nonspecific [16]. Small GIST are usually asymptomatic and are detected either during investigations or surgical procedures for unrelated disease. Incidental discovery accounts for approximately one third of the cases. The commonest presentation of GIST is bleeding related to mucosal erosion (approximately 50%) [16], which may be either chronic, with anaemia, or acute, necessitating emergency treatment (approximately 40% of the cases presenting with haemorrhage) [17]. Some 20% of patients present abdominal discomfort, or even pain, which is generally associated with larger size GIST. In the small intestine bowel obstruction is also frequent. Bowel perforation is infrequent.

At first diagnosis some 10% of patients present with metastatic disease [13]. GIST usually, and primarily, metastasise to the liver. Peritoneal surface diffusion is less frequent, while lymph nodes and extra-abdominal sites are rarely involved.

Diagnosis

There are no recognised specific radiological examinations for GIST diagnosis. Barium contrast studies or endoscopy may provide useful data on localisation of GIST. As for the other intra-abdominal malignancies, computed tomography scan (CT scan) is the standard preoperative imaging technique [18]. CT scan may reliably localise GIST, as well as determining size and possibly revealing the presence of secondary localisations (i.e. hepatic metastases) [18]. GIST imaging by CT scan usually discloses an extraluminal mass originating from the digestive tract wall, with frequent central necrosis. Percutaneous needle biopsy carries the theoretical risk of peritoneal seeding and is indicated only for clearly unresectable disease or where treatment would be altered by pathological diagnosis. Demonstration of KIT positive cells may assist in diagnosing GIST on needle biopsy, although the positive predictive value of this approach needs to be defined [19]. Positron emission tomography with 18FDG is particularly useful for detection of secondary localisation of GIST, but hitherto has been chiefly used for patient follow-up [20, 21].

The diagnosis of GIST may be suggested during surgery by the presence of a well defined extraluminal mass, frequently polylobulate with a pseudocapsule. However, it always requires histological and immunohistochemical confirmation.

Pathology

On the basis of molecular and immunohisto logic features, most gastrointestinal soft tissue sarcomas previously designated as smooth muscle tumours, such as leiomyomas, schwannomas, leiomyoblastomas and leiomyosarcomas, are classified as GIST [5]. The histological and cytological features of GIST may explain the past diagnostic confusion with other mesenchymal tumours. However, true leiomyoma (especially in the oesophagus), leiomyosarcoma or neural cell tumours should still be classified as such and not as GIST [4]. In particular, the former is the most common mesenchymal tumour of the oesophagus and is characterised by a benign course [4].

It has become clear that the tumour cells comprising GIST are closely related to the interstitial cells of Cajal [22, 23]. These cells constitute a complex cellular network, the likely functions of which are gastrointestinal tract pacemaking and the regulation of intestinal motility [2, 5, 24]. The immunohistochemistry of the interstitial cells of Cajal is similar to that of GIST cells, being positive for KIT [2, 5, 24]. However, some GIST arise from the mesentery or omentum, which lacks interstitial cells of Cajal, suggesting an origin in multipotential mesenchymal stem cells of Cajal cell lineage [11, 25, 26].

Grossly, GIST vary greatly in size, ranging from 1 cm to more than 20 cm. They not infrequently exhibit areas of necrosis, cystic degeneration or focal haemorrhage. The tumours are well circumscribed and pseudo-encapsulated. They arise in the digestive tract wall, generally with extraluminal development, and not infrequently cause ulceration of the overlying mucosa. They are composed of either spindle-shaped cells (70%) or
epithelioid cells, while mixed cell populations have rarely been encountered (Figure 1) [4].

In contrast to leiomyomas and leiomyosarcomas, GIST are typically immunoreactive for KIT (CD117). They are immunohistochemically positive for KIT, with a reported frequency of 90 to 100% depending on the method used [4], while positivity for CD34, the haematopoietic progenitor cell antigen, is reported in 70–80% of GIST [4]. GIST are frequently vimentin positive. They may be focally positive for smooth muscle actin (30%) and keratin (<10%) but are negative usually for desmin and protein S100. It should be noted that some other tumour types (e.g. melanoma, mastocytoma) may also be CD117 positive, but the differential diagnosis may depend on histological and immunohistochemical differences. In summary, histological (i.e. cellular type and organisation) and immunohistochemical (i.e. KIT, CD34) findings are the defining features of GIST.

**Molecular biology of GIST**

KIT, which is a growth factor transmembrane receptor, is the product of the proto-oncogene c-kit (chromosome 4). As a member of the tyrosine kinase receptor, KIT is closely related to the receptors for platelet-derived growth factor (PDGF) and other receptors of this family [27, 28]. KIT is expressed by haematopoietic progenitor cells, mast cells, germ cells and interstitial cells of Cajal. Activation of the KIT receptor by its ligand, known as stem-cell factor, leads to cascades involved in oncogenesis, including proliferation, adhesion, apoptosis and differentiation [27, 28]. While activation of wild-type c-kit is required for interstitial Cajal cell development [29], gain of function mutations of c-kit occurs in up to 90% of GIST [3, 5, 11, 15], the most frequent being mutations of exon 11 (70% of GIST) and 9 [3, 27, 28, 30, 31]. These mutations lead to constitutional activation of the receptor, which in normal circumstances takes place upon binding of the ligand. The activating mutation perpetuates the KIT signal and the downstream transduction pathway, ultimately leading to activation of cellular proliferation [30, 32, 33]. Inherited germline mutations of exon 11 or 13 produce an autosomal dominant susceptibility to the formation of GIST [34, 35].

Affected individuals develop diffuse hyperplasia of the interstitial cells of Cajal and are subject to the occurrence of multiple GIST during adulthood [34]. Thus mutations in KIT seem to play a gatekeeper role in transformation of the interstitial cells of Cajal into a GIST [27, 29, 35]. However, apparently KIT mutation alone does not cause malignant transformation of GIST. This is consistent with data on the prognosis of patients with sporadic or familial GIST. The proportion of GIST with KIT mutation attains 90%, and comparison of the prognosis of GIST with or without KIT mutation has thus far shown no strong correlation [35–37]. Factors causing the transformation of benign to malignant GIST have still to be identified, but degeneration from benign to malignant GIST is apparently associated with chromosomal deletion and/or acquisition of mutations in various oncogenes [27].

However, some GIST, which are not KIT positive (approximately 5% of GIST), do not present mutation of the c-kit proto-oncogene [28], although some of them harbour mutation of the PDGFRA receptor, another tyrosine kinase receptor, and this could be related to oncogenesis in these cases [28, 35, 38].
Prognostic factors

GIST display different degrees of aggressiveness. Indeed, study of site-specific and combined series of GIST have shown that these tumours have a spectrum spanning from small, benign nodules to overtly malignant tumours at all sites of occurrence [13]. Predicting the potential biological behaviour of these tumours remains difficult, and the literature contains many conflicting reports on this issue [9, 39–41]. Since A. P. Stout et al. [42] pointed out that the number of mitoses is a prognostic factor for stromal tumours, many criteria have been correlated with prognosis or survival, including: localisation [43], tumour size (<5 cm in diameter) [14, 43–47], mitotic activity (>5 mitoses/high-power fields) [3, 43, 44, 46, 48], tumour necrosis [44, 48–50], staining for proliferating cells (MiB1 >10%) [3, 51–53], invasive character [41, 48, 53, 54], presence of symptoms [48], histological type [55], immunohistochemical profile [53], presence of metastases or lymph node invasion [14, 40], and others. The role of GIST localisation is debated, some authors having found that prognosis is significantly influenced by localisation and others not. However, except the presence of metastases, none of these factors taken independently is predictive for the malignant potential of GIST [6, 36, 39, 55, 56]. It is of importance that the presence of multiple synchronous GIST does not appear to affect outcome [57, 58].

The most easily applicable and recognised pathological criteria for prediction of recurrence risk are tumour size and mitotic rate, and over the last decade prognostic scales combining these two criteria have been evaluated [39, 45, 55, 56]. Recently, via a consensus approach supported by the National Institute of Health, these criteria have been combined in a new scale to define the risk of aggressive-behaviour GIST (Table 1) [6]. This scale is easy to apply for pathological classification. According to this scale the the prognosis of very low risk GIST is excellent, while high risk tumours are associated with a high rate of recurrence and decreased survival. However, the prognosis of low and intermediate risk GIST is in-between and not well defined. Thus the reliability and clinical usefulness of this prognostic scale is questionable, since it is not suited to specifically identifying high-risk patients who may benefit from more aggressive treatments. We have recently proposed a new scaling system for GIST based on their malignant potential [58]. In accordance with the recent studies of Yan et al. [54], it is not only based on tumour size and mitotic rate but refers to other criteria with the aim of improving the classification of intermediate risk cases. The scale is composed of five minor criteria (i.e. tumour size >5 cm, mitotic rate >5/50 HPF, MiB1 >10%, presence of necrosis and invasive components to mucosa or serosa), and two major criteria (presence of either lymph node invasion or metastases (Table 2). GIST harbouring either four of the five minor criteria, or one major criterion, are considered to have high malignant potential, while others are considered of low malignant potential (benign). This scaling system significantly correlates with overall and event-free survival and makes it possible to detect all GIST at risk of recurrence, which would benefit from more aggressive treatment. With this scale, the 5-year survival of low malignant potential GIST is 95% and of high malignant potential GIST less than 20%. However, the scales of both Fletcher et al. and ourselves need to be validated in large prospective GIST cohorts in terms of positive and negative predictive value for risk of recurrence and reliability, on the basis of patient survival.

### Table 1

Proposed approach for assessing risk of aggressive behavior of GIST (adapted from Fletcher et al. [6]).

<table>
<thead>
<tr>
<th>Tumour size*</th>
<th>Mitotic count**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2 cm &lt;5/50 HPF</td>
</tr>
<tr>
<td>Low risk</td>
<td>2–5 cm &lt;5/50 HPF</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>&lt;5 cm 6–10/50 HPF</td>
</tr>
<tr>
<td></td>
<td>5–10 cm &lt;5/50 HPF</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;5 cm &gt;5/50 HPF</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm any mitotic rate</td>
</tr>
<tr>
<td></td>
<td>any size &gt;10/50 HPF</td>
</tr>
</tbody>
</table>

* Size represents the single largest dimension.  
** Ideally, mitotic count should be standardised according to surface area examined (based on size of high-power fields, HPF). Despite inevitable subjectivity in recognition of mitoses and variability in the area of HPF, mitotic counts still prove useful.

### Table 2

Proposed classification of GIST according to malignant potential (adapted from Bucher et al. [58]).

Minor criteria  
- Tumour size ≥5 cm
- Mitotic index ≥5 mitoses/50 hpf
- Presence of necrosis
- Infiltration of adjacent structures (i.e. mucosa or serosa)
- MiB1 index ≥10%

Major criteria  
- Presence of lymph node invasion
- Presence of GIST metastases

**Low malignant potential GIST:** GIST with fewer than 4 minor criteria

**High malignant potential GIST:** GIST with 4 or 5 minor criteria or 1 major criterion

Management of gastrointestinal stromal tumours  148
Surgical treatment

The treatment of choice for GIST is surgical resection. All GIST should be approached with the intention of performing complete en bloc removal (R0 resection) of the tumour and surrounding tissue [14, 47, 59–62]. It has been shown that completeness of resection correlates with survival after primary resection of GIST [14, 59, 63–65]. This is true of localised disease, but for metastatic disease the role of synchronous hepatic metastasis resection has not been defined in the imatinib mesylate era (Figure 2). However, synchronous liver metastasis resection is advocated when applicable, since a complete and long term response to imatinib mesylate has not thus far been demonstrated. In some cases with primarily non-resectable metastases complementary resection should be done, if possible after response to imatinib mesylate treatment (Figure 2). The rate of resectable GIST, reported in the literature ranges from 50 to 90% [12, 14, 44, 60, 61]. These discrepancies are partly attributable to the type of patient cohort studied. Series concerning GIST with primary presentation in non-specialised centres report a resectability rate higher than those evaluating GIST referred to specialised centres, where the cases collected are chiefly advanced tumours. In our experience GIST resectability is some 90%. However, resection of the primary lesion, even incomplete, is indicated for the palliation of symptoms associated with mass effect and especially the risk of bleeding [14, 66].

Several reviews have reported that small GIST (2 cm or less) can be treated adequately by wedge (gastric) or segmental (bowel) resection [61]. Larger GIST may require more extensive en bloc resection including adjacent structures or organs if involved [61].

GIST, even with high malignant potential, metastasise to lymph nodes with insufficient frequency to warrant lymph node dissection [3, 14, 58, 59, 61, 67]. Similarly to other sarcomas, lymph node invasion is generally encountered after development of blood-borne metastases and appears to be a late event in the natural history of malignant GIST [68, 69].

Surgical resection in patients with a primary GIST is associated with a 5-year survival rate of 48–70% [12, 14, 43, 44, 48, 59, 61, 69]. However, prognosis of low risk (low malignant potential) GIST after complete resection is excellent [40, 58], while high risk (high malignant potential) GIST have a high rate of recurrence (Figure 2) [6, 14, 40, 58]. There is no indication for chemotherapy and radiation therapy after surgical resection of GIST, as these tumours are notoriously unresponsive to such treatment [12, 14, 37, 67].

![Treatment algorithm for patient with primary presentation of GIST.](image-url)
Molecularly targeted treatment

Several protein kinases are deregulated or overexpressed in human cancers due to gene mutations, and are therefore targets for selective pharmacological inhibitors. Imatinib mesylate (formerly referred to as STI571, and now manufactured as Glivec in Europe) is a powerful and relatively selective inhibitor of all ABL tyrosine kinases, including: c-kit, c-ABL, bcr-ABL and platelet-derived growth factor receptor (PDGFRA) [70, 71]. The efficacy of imatinib mesylate as a tyrosine kinase inhibitor and its pharmacokinetics in humans have been assessed in studies of patients with chronic myeloid leukaemia (CML) [72]. In CML, a chromosomal rearrangement in haematopoietic stem cells causes the formation of a fusion protein, BCR-ABL, in which the tyrosine kinase component is constitutively active, a ligand-independent activation similar to the role of KIT in GIST cells [73]. In 1996 Druker et al. [74] reported that imatinib specifically inhibited or killed proliferating myeloid cells containing BCR-ABL. Imatinib mesylate at therapeutic drug levels inhibits the receptors KIT and PDGFRA by reversible binding [71, 75]. It has been shown that the vast majority of KIT mutants as well as wild-type KIT are sensitive to imatinib mesylate. Moreover, activation of ligand-stimulated native PDGFRA and PDGFRA mutant are potently inhibited by imatinib mesylate [71, 75, 76].

The response rate of recurrent or metastatic GIST to imatinib mesylate treatment is some 60–70% [7, 9, 15, 37, 77]. Long term results of patient survival on imatinib mesylate treatment are not available, but while patient median survival was
less than 12 months before the imatinib mesylate era, large series have shown that after 2 years the median of survival was not attained in patients under treatment [7, 15]. Some cases experience stable disease (15%) under treatment, while some patients do not respond at all to treatment and show disease progression after introduction of imatinib mesylate [7, 15]. For these cases an increase in drug dosage may be indicated and, if this is not sufficient, an investigational protocol of complementary treatment could be tried (Figure 2).

It has been shown that the type of KIT mutation influences response to treatment with imatinib mesylate. Patients whose tumours express exon 11 mutant KIT protein have a significantly better response rate to imatinib therapy (83.5%) than patients whose tumours express either exon 9 mutant KIT (47.8%) or contain no detectable mutation of KIT or PDGFRA (0%) [28]. This was, however, associated with longer overall survival. Not all GIST without mutation of the KIT receptor are resistant to imatinib mesylate. Sensitivity and response to therapy in these cases may be explained by the presence of PDGFRA mutations [28, 78].

The duration of treatment with imatinib mesylate is a matter of debate, no clear data having emerged regarding the need to continue therapy indefinitely [8]. However, KIT-positive Ki67-negative cells (non-proliferating cells), probably representing non-cycling or dormant GIST cells, may be encountered several months after starting imatinib mesylate even in a responding patient, and development of secondary resistance to treatment may supervene [79]. The current recommendation is to continue the treatment indefinitely while trials are under way to assess the evolution of patients after imatinib mesylate withdrawal [15].

For patient follow-up during imatinib mesylate treatment, positron emission tomography (PET scan) with 18FDG is the method of choice [20]. PET scan is a highly sensitive tool for monitoring of response to treatment, while CT scan is unable to detect response for 3–6 months after treatment initiation (Figure 3). Moreover, it has been shown that GIST response assessed by PET scan eight days after the start of imatinib mesylate treatment correlates with prognosis and survival at one year in patients with non-resectable GIST [20, 21].

With regard to the pharmacokinetics of imatinib mesylate, it is well absorbed after oral administration with a half-life in the circulation of approx. 16 hours, a period compatible with administration once daily. While it has been associated with only a few minor side effects [15, 80, 81], gastrointestinal or intra-abdominal haemorrhage have been reported in patients with large GIST after initiation of imatinib mesylate treatment; this may be related to the rapid anti-cancer effect on the tumours, with disruption of tumour-related vasculature [15].

### Prognosis

In the literature patient survival after primary surgical resection of GIST ranges from 48% to 80% at 5 years [12, 14, 15, 59]. However, these data concern the era before imatinib mesylate and GIST prognosis has drastically changed since its introduction. Moreover, overall GIST prognosis is of little value, as low risk and high risk GIST do not have the same natural history after surgical resection. For low malignant potential (low risk) GIST, the 5-year survival rate (approximately 95%) is similar to the normal population [58], while for high malignant potential (high risk) GIST the 5-year survival rate ranged from 0% to 30% before the introduction of imatinib mesylate [58]. No long-term survival data are available for malignant GIST in the imatinib mesylate era, but current experience show major improvement at 1 year, to 90% versus <50% before the imatinib mesylate era [15, 20, 21]. Recurrences are extremely rare for low malignant potential GIST, while in our experience, which is in agreement with the literature, more than 80% of high malignant potential GIST will recur [40]. Patient follow-up after curative surgical resection of GIST should be tailored to the malignant potential of their tumour [40, 58, 63, 65]. While follow-up on a yearly basis appears to suffice for low malignant potential GIST, closed control is required for high malignant potential GIST as up to 50% of recurrences occur during the first year post resection [65]. For patient follow-up PET scan is currently the most reliable investigation; abdominal CT scan is valuable for detection of recurrence [14, 20, 21, 58].

### Discussion

In this paper we have reviewed current knowledge of gastrointestinal stromal tumour (GIST) management. Surgical resection is the treatment of choice for these tumours. GIST studies have shown that after surgical resection these tumours span a wide
is reason to believe that imatinib may be even more effective when given earlier in the management of GIST, for example as adjuvant therapy for high malignant potential GIST. This approach is under investigation [77, 84].

References


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