

## Review of Management of Gastrointestinal Stromal Tumour in Low-Resource Centres

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### Abstract

Gastrointestinal stromal tumours (GIST) account for 1% to 3% of gastrointestinal tract tumours and are the most common of the mesenchymal tumours. Carcinogenesis of GIST arises in the interstitial cells of Cajal (ICC) and in the myenteric plexus of the gastrointestinal tract due to a mutation of the kinase receptor (KIT, also known as CD117) and the platelet-derived growth factor A (PDGFA) gene leading to activation of the tyrosine kinase receptor. The exact incidence and prevalence of GIST is not known. Symptoms of GIST are non-specific; they present with GI bleeding due to ulceration (50%), abdominal pain (20% to 50%), dysphagia (oesophageal GIST) and GI obstruction (10% to 30%) (7,10). Signs include abdominal mass and fullness. A computerized tomographic (CT) scan is the preferred imaging to evaluate GIST. Diagnosis is confirmed by immunohistochemical (IHC) staining of a biopsy sample for medical treatment tyrosine kinase inhibitors (TKI). Surgical resection with negative microscopic margins is the gold standard treatment of GIST. TKI are required for tumour reduction to increase chances of resectability (neoadjuvant therapy) or to prevent recurrence and reduce the progression of advanced, resectable GIST.

**Keywords:** GIST; gastrointestinal stromal tumour; CD117; KIT; TKI

### Introduction

Gastrointestinal stromal tumours (GIST) account for 1% to 3% of gastrointestinal tract tumours and 5% to 6% of sarcomas, and are the most common subset of mesenchymal tumours (1–3). GIST have an annual incidence of 10-20 million people per year worldwide (4,5). GIST arise in the submucosa of the gastrointestinal (GI) tract but can also arise outside the GI tract, from the mesentery and greater omentum (extravisceral) (6–8). Carcinogenesis of GIST arises in the interstitial cells of Cajal (ICC) and in the myenteric plexus of the GI due to a mutation of the kinase receptor (KIT, also known as CD117) and the platelet-derived growth factor A (PDGFA) gene, leading to activation of the tyrosine kinase receptor (9,10). In histology, the 3 types of GIST include spindle cell type (70%), epithelioid type (20%) and mixed type (10%) (10,11).

GIST are usually asymptomatic and/or incidentally diagnosed during surgery or on imaging (12,13). Clinical presentation and management of GIST depend on size and location of the tumour and its clinical features (14). Although GIST can arise anywhere in the GI, 70% are gastric, 25% are small intestinal, 5% to 10% are in the colon and rectum, 5% are in the oesophagus and 10% are extravisceral (8).

GIST can appear at any age; median age is 60 years (7,13). Age is an important risk factor for GIST (7). The risk of GIST increases with an increase in mutations, which can be inherited and found in several members of one family (7). Since 95% of GIST are positive for CD117, diagnosis is based on a positive stain of KIT (CD117) on immunohistochemical (IHC) staining (15,16). Surgical resection with clear margins for resectable GIST and for GIST with resectable oligometastasis can be liver or peritoneal metastasis (12,17).



The aim of this paper is to discuss the management of GIST in a low-resource centre.

## History and evolution of GIST

Between 1930 and 1950, stromal tumours were considered to arise from smooth muscle, based on light microscopic features, and were classified as leiomyoma, leiomyosarcoma or leiomyoblastoma (18–20). In 1983, Muzur and Clark (21) introduced the term stromal tumour and were recognized for introducing the term with supporting evidence that these originated from the GI tract and were a distinct entity (22,23). In the mid-1990s, these tumours were discovered to be positive for CD34, a relatively specific marker for diagnosis (24). In 1998, KIT gene mutation was discovered by Hirota et al (25). PDGFA was discovered by Heinrich et al (26). The pro-growth signal that leads to development of GIST was identified by Agaram et al (27). In 2004, DOG, a calcium-dependence chloride channel protein anoctamin found in GIST regardless of the presence of CD117 and PDGFA, was discovered (28); 95% of GIST stain positive for CD117 and DOG (28).

## Epidemiology of GIST

Though the exact incidence and prevalence of GIST is not known, it occurs at all ages, and 90% occur in those older than 40 years of age (4,29). The incidence in males and females is the same; however, a slight male predominance has been observed (28). Geographical location, race and occupation have no attributed risk to the development of GIST (4,29). Between 20% and 30% of GIST are malignant and can present with metastatic disease (4). Most GIST are sporadic, with familial cases reported at 1.4% to 4% (4,29). Familial GIST with autosomal dominance inheritance have been described (29). Familial GIST include neurofibromatosis, Carney-Stratakis syndrome and Carney triad. Carney et al (30) describe the Carney triad as composed of gastric GIST, extra-adrenal paraganglioma and pulmonary chondroma. However, a Carney triad needs to be distinguished from inherited GIST syndrome with paragangliomas, called Carney-Stratakis syndrome (29).

## Clinical features

Seventy percent of GIST are symptomatic, 20% asymptomatic and 10% discovered at autopsy (7,13). Though symptoms of GIST are non-specific, they present with GI bleeding due to ulceration (50%), abdominal pain (20% to 50%), dysphagia (oesophageal GIST) and GI obstruction (10% to 30%) (7,10). Signs include abdominal mass and fullness (10). Some GIST present with paraneoplastic symptoms of hypoglycaemia due to the effect of an insulin-like growth factor produced (10). GIST frequently metastasise to the liver (65%), the peritoneum through hematogenous metastasis (25%) and less frequently to the omentum, but rarely through lymphatic metastasis to regional lymph nodes and non-GI organs (31). Hematogenous metastasis to organs outside the abdomen occurs late in advanced disease (13). GIST tend to grow bigger and displace other organs without invading neighbouring organs (13). Caterino et al (32) reported GI bleeding and abdominal pain at 58% and 60%, respectively. Small GIST, up to 2cm, are usually asymptomatic, discovered incidentally during surgical interventions or surveillance for other conditions, until symptoms develop due to enlarging size (14).

Large GIST, of more than 5cm, present with obstruction or bleeding (2,33). Half of GIST are metastatic at presentation (7). Life-threatening haemorrhagic peritonitis may result from a ruptured GIST (4,7).

## Pathophysiology of GIST

GIST carcinogenesis arises from the muscularis propria smooth muscle pacemaker cells known as ICC. The role of ICC is to coordinate GI peristalsis due to mutation of the transmembrane protein, a tyrosine kinase receptor. This receptor's intracellular (juxtamembrane) domain stimulates cell proliferation and cell hyperfunction and inhibits apoptosis, a protooncogene called the KIT (CD117) gene (in 95% of patients) or the PDGFA (in 30% of patients lacking KIT gene mutation) (10,28,34,35). While DOG1 is present in 95% of GIST, even in the absence of KIT and PDGFA, its role in the diagnosis of GIST is still uncertain (28). Mutation of the KIT gene leads to uncontrolled and enhanced cell proliferation (13,28,29). Most mutations are deletion, duplication or point mutations that can be primary (original cell mutations) or secondary (because of mutations arising from treatment) (3,13,29). The most common mutations are in exon 11 (the most frequent malignant outcome), while rare mutations are in exon 9 and exon 13 (13).

Histological subtypes of GIST include 4 composed of an epithelioid pattern and another 4 composed of spindle cells (3,28,33). Histological subtypes include the following:

1. sclerosing epithelioid variant (polyhedral cells, collagenous stroma deposition, multinucleated and low mitotic rate),
2. dyscohesive epithelioid variant (polygonal cells, halo surrounded cells, mild nuclear pleomorphism),
3. hypercellular epithelioid variant (highly neoplastic with low mitotic rate),
4. sarcomatous epithelioid variant (high cellularity with high mitotic rate),
5. sclerosing spindle cell variant (hypocellularity, collagenous stroma and focal calcifications),
6. palisading vacuolated spindle variant (commonly gastric location, spindle- and schwannoma-like cells, prominent nuclear vacuolation with low mitotic rate),
7. hypercellular spindle variant (dense cell atypia with low mitotic rate), and
8. sarcomatous spindle variant (karyomegaly, nuclear hyperchromatism with high mitotic rate).

## Importance of imaging

The imaging of choice for diagnosing and evaluating the response to treatment and follow-up of primary and metastatic GIST is contrast-enhanced computer tomography (CECT) (13,28). Magnetic resonance imaging has a comparable yield, adds the advantage of lack of radiation and is accurate for diagnosis (2,10). A fluorodeoxyglucose positron emission tomography (FDG-PET) scan is used to obtain an initial diagnosis and for evaluating the presence of metastatic disease and response to treatment, but is not readily available in low-resource countries due to cost and non-availability in health facilities (13,33). A lack of metabolic response on an FDG-PET scan indicates primary resistance to treatment by tyrosine kinase inhibitors (TKI), while reoccurrence of metabolic activity indicates development of secondary resistance (33).



## Diagnosis of GIST

Initial evaluation should start with a thorough history and physical examination, followed by imaging to evaluate the primary tumour and presence of metastasis (10). Preoperative tissue diagnosis is not recommended in resectable tumours strongly suspected to be GIST, but tissue diagnosis may be required in advanced and unresectable GIST, requiring neoadjuvant therapy, or in metastatic GIST, requiring palliative adjuvant therapy with TKI (7,33). Tissue for histopathology can be obtained by endoscopic ultrasound, where available, or image-guided percutaneous biopsy (4,28,33). Pathological diagnosis is supported by tumour morphology and IHC staining of the tissue obtained either by en-bloc excision or fine-needle aspiration cytology (FNAC) (2,10). FNAC can be obtained by image guidance (ultrasound or endoscopic) (4,28,33). Diagnosis is confirmed by the presence of CD117 on IHC (7,13,28). GIST should be a differential diagnosis for any non-epithelial abdominal tumour (28,29).

## Management of GIST

The standard treatment of resectable GIST, which is considered curative, is wide surgical resection with microscopic negative surgical margins (R0) and is considered the gold standard treatment for 80% of GIST (4,6,7,28). Tumour adherence to neighbouring organs or invasion of adjacent organs, mitotic index and tumour size are important factors that guide treatment choice (7,28). Unresectable GIST, defined as GIST that is locally advanced, metastatic or too big to achieve a negative resection margin, is treated with neoadjuvant TKI or adjuvant TKI (7,15,28). According to the National Comprehensive Cancer Network (NCCN) guidelines, GIST smaller than 2cm should be managed conservatively, with follow-up by imaging and endoscopic ultrasound-guided (EUS) FNAC to assess the risk of malignancy (28,36). Any size GIST with high risk of malignancy should be treated by complete surgical resection (7,36). The risk of GIST is assessed by mitotic index (with mitoses more than 5 mitoses/50 high power field [HPF]) and an increase in tumour size; these are associated with a worse outcome (15,36).

High-risk GIST is defined by mitotic rate, tumour size, tumour perforation at surgery and primary organ of origin (6,7,29). According to Miettinen's criteria (6,7),

1. GIST smaller than 5cm and fewer than 5 mitoses/50 HPF are low-risk.
2. GIST larger than 5cm and more than 5 mitoses/50 HPF are high-risk;
3. gastric GIST up to 10cm and 5 mitoses/50 HPF are low-risk, while larger than 10cm and more than 5 mitoses/50 HPF are high-risk;
4. all intestinal GIST larger than 5cm and more than 5 mitoses/50 HPF are high-risk, while smaller than 5cm and fewer than 5 mitoses/50 HPF are low-risk.

## Medical management

Treatment with TKI is recommended in GIST that are resectable but with significant morbidity, borderline resectable (to shrink the tumour and increase negative resection margins), locally advanced (invasion of adjacent organs), metastatic or recurring (1,6,36). TKI can be used in neoadjuvant and adjuvant therapy. Gene sequencing of a biopsy or FNAC sample is required before treatment with medical therapy (neoadjuvant or adjuvant therapy)

to determine tumour response as mutation to PDGFA; 10% of other mutations show no response to TKI (7,12). However, there is no established criteria to measure tumour response (17).

The TKI available for medical treatment of GIST include imatinib for TKI mutation or avapritinib for PDGFA mutations (first line) and suratinab (second line, because it inhibits many KIT, PDGFA and vascular endothelial growth factor alpha tyrosine kinases), with no other regimen if these two TKI fail (13,28,36). Patients with undetectable KIT, PDGFA or known mutations resistant to TKI may not benefit from treatment with TKI (2).

## Neoadjuvant therapy

Neoadjuvant therapy is required to achieve negative resection margins and lowers surgical morbidity (by reducing extent of resection and lowering bleeding at surgery) (14,28). Neoadjuvant therapy is also indicated in organ-sparing or function -paring surgery such as esophagectomy for oesophageal GIST (28). NCCN guidelines recommend neoadjuvant therapy for those with resectable disease but with significant morbidity, borderline resectable disease, resectable recurrent or metastatic disease (36). Neoadjuvant therapy is recommended for 4 to 6 months, but such treatment should be decided on individual basis (36). Imaging is used to detect the response to neoadjuvant therapy (12,13,33). Stamatakis et al (4) report that reduced tumour size and vascularisation as a response to neoadjuvant therapy result in reduced chances of tumour rupture and peritoneal implantation. Some studies have reported unexpected, good responses in metastatic GIST to neoadjuvant therapy, with downsizing of GIST from unresectable to resectable (4,12).

## Adjuvant therapy

TKI is recommended in those with GIST that are high-risk, resectable with tumour rupture, unresectable, recurrent, or metastatic (2,29,36,37). Imatinib has been recommended as adjuvant treatment after surgical resection because it has the benefit of reducing recurrence after surgery (36,37). Imatinib can also be used in palliative treatment of GIST (36,37). Resected GIST without adjuvant treatment with TKI have an overall survival (OS) of 35% at 5 years (29). Adjuvant therapy is continued for 3 years to reduce tumour recurrence (29,36). Beham et al (29) report a 5-year OS of 54% in those with advanced GIST, with 19 months median survival, and 12 months in those with recurrent disease. Stamatakis et al (4) report 50% response to imatinib in a prospective trial; 50% to 75% had stable disease, while 2-year survival after imatinib was 70%.

## Surgical treatment

Currently, surgical resection is the gold standard and aims at achieving a negative resection margin (en-bloc resection of local disease including involved adjacent organs) without tumour rupture (6,7,36). Surgical resection of primary localised disease offers a 5-year OS of 48% to 70% (7). Beham et al (29) report that complete resection is associated with a 5-year OS of 42%, and 19% if resection is incomplete. Formal lymph node dissection is not advised by current guidelines (13,36). Lymph node metastasis is not common in GIST, and most studies have reported negative lymph nodes after dissection (14,36). However, Madhavan et al (14) report occurrence of a positive lymph node after total



gastrectomy with distal pancreatectomy and splenectomy for a fundal GIST in a patient who received neoadjuvant therapy. This patient did not have recurrent disease after 12 months of adjuvant therapy and after 24 months follow-up (14). Palliative surgery may be done for control of symptoms or complications (bleeding or compression of adjacent organs) (4,36).

Surgical resection with microscopic negative margins can be achieved by open surgery (especially for large GIST) or minimally invasive surgery (laparoscopic or robotic) (7,29). Low-resource centres tend to perform open surgery due to the cost of laparoscopic or robotic surgery (7,13,29).

## Prognosis

All GIST are considered malignant until proven otherwise, even though tumour mitotic index and tumour size are the most important prognostic factors (4,13). Coe et al (38) investigated mortality in GIST smaller than 2cm and found mortality rates of 34% in regionally advanced GIST, 34.4% in metastatic GIST and 5.5% in localised GIST. GIST cannot be considered benign simply on account of small size (36,38). Bischof et al (1) report a 3-year OS after surgery for locally advanced at 87%, while recurrent or metastatic disease had an OS of 80%.

## Outcome

Complete resection without tumour rupture avoids peritoneal seeding, intra-abdominal tumour recurrence and tumour recurrence in a surgical scar, while liver metastasis is hematogenously spread (7,12,13). Complete resection with negative margins has a 5-years OS of 60% (12). Complete resected GIST has a liver recurrence of 65%, peritoneal recurrence of 50% and both liver and perineal recurrence of 20% (4). Though microscopic negative resection margins have a 5-year OS of 48% to 65%, OS is determined by tumour size and mitotic index and not by negative resection margins (4). High-risk GIST should receive neoadjuvant or adjuvant therapy with imatinib to improve outcome. Lim (33) reports that in a study with 170 patients who underwent complete resection with microscopic negative margins and adjuvant therapy with imatinib, median survival was 7.3 years to 8.7 years.

## Follow-up

The outcome of GIST is unpredictable, and therefore long follow-up is required (4,36,37). Follow-up should be done with history and physical exam every 3 to 4 months for 2 years, then every 6 months for 2 years, and yearly afterwards (36,37). NCCN guidelines recommend follow-up with imaging (CT/CT-PET) every 3 to 6 months for 3 to 5 years, and then yearly thereafter (36). Blood tests can be done yearly (36,37).

## Conclusion

GIST are rare, non-epithelial GIT tumours that arise from ICC with an unpredictable clinical course and high chances of malignancy. The preferred imaging for GIST is CECT scan. Preoperative diagnosis is not required for resectable GIST, except where neoadjuvant therapy for borderline resectable or resected high-risk GIST, or if the tumour is unresectable and requires adjuvant therapy. Tumour size and mitotic index are the most important prognostic factors in the management of GIST.

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