Chapter 11
Gastrointestinal Stromal Tumours

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Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and represent ~0.2 % of all gastrointestinal neoplasms [1–3]. These tumours are comprised predominantly of spindle cells and result from activating mutations in the KIT (CD117) proto-oncogene or platelet-derived growth factor receptor alpha gene (PDGFRAα) [4, 5]. Immunohistochemical analysis has been instrumental in identifying markers characteristic of GIST, facilitating its differentiation from other mesenchymal neoplasms. Specifically, these markers include CD117 (95 %), DOG1 (96 %), protein kinase C theta (80 %), CD34 (60–70 %), and smooth muscle actin (30–40 %) [6]. Although they can arise in any location throughout the gastrointestinal tract, they are found primarily in the stomach (60 %) and small intestine (30 %) [7–9]. The cell of origin is the interstitial cell of Cajal [10].

Although the incidence and outcome of GISTs continue to evolve with improvements in detection, surgical technique, and the introduction of targeted molecular therapy, GISTs remain relatively rare tumours, with an estimated annual incidence in Western countries of 0.68–1.5 per 100,000 patients [12].

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Presentation[a] [11, 13]	Prognosis [11, 13] 5-year overall survival (OS)
• Localized (69 %)	64 %
• Metastatic (28 %)	30 %

[a]Due to incomplete epidemiological data on clinical staging, the combined incidence of localized and metastatic disease does not equal 100 %

The American Joint Committee on Cancer AJCC 7th edition is the current recommended staging system for GISTs. Prognostically, a positive regional lymph node (which occurs with an estimated incidence of 5 %) carries the same overall survival as M1 disease [13]. As such, the current AJCC guidelines place lymph node-positive disease as Stage IV.

Management

Primary Resectable GIST

Clinical scenario	Work-up	Management	Follow-up
Gastric tumours < 3 cm	• History and physical exam • Imaging: – CT abdomen and pelvis (gastric protocol) – Upper GI endoscopy (EGD) – Consider EUS and ultrasound-guided biopsy in selected cases (see indications below) • Multidisciplinary consultation	• Management remains controversial for incidental, asymptomatic submucosal gastric masses • In the absence of high-risk EUS features (irregular extra-luminal border, heterogeneous echo pattern, presence of cystic spaces and echogenic foci), close endoscopic and radiographic surveillance is reasonable [14] • Neoplasms that increase in size or become symptomatic should be resected (surgical resection with negative histological margins)	• History and physical exam every 3–6 months • CT abdomen/pelvis (gastric protocol) every 3–6 months for 1–5 years, then annually thereafter. If the mass remains stable over this re-evaluation period, the interval between serial cross-sectional imaging should be increased

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Clinical scenario	Work-up	Management	Follow-up
Localized, resectable tumours > 3 cm	• History and physical exam • Imaging: – CT chest/abdomen/pelvis – MRI scan (rectal neoplasms) – Endoscopy for gastric, duodenal, and rectal locations – Consider EUS and ultrasound-guided biopsy as appropriate • Consider endoscopic or percutaneous biopsy (see indications below) • Multidisciplinary consultation	• Surgical resection with negative histological margins [2, 15, 16] • Routine regional lymphadenectomy is ***NOT*** required • Adjuvant imatinib should be given to intermediate and high-risk patients following R0/R1 resection for 3 years [17–21]	• History and physical exam every 3–6 months • CT chest yearly for 5 years • CT abdomen/pelvis: – Every 3–6 months for 5 years [2, 14] – For low-risk tumours, every 6 months for 5 years [22] – Annually after 5 years

EGD esophagogastroduodenoscopy, *EUS* endoscopic ultrasound

Special Notes

- Biopsy of suspected, resectable GISTs is recommended if:
  - The diagnosis is not clear;
  - Preoperative treatment with imatinib is being considered; and/or
  - Enrollment into a clinical trial is planned.
- Biopsy of GISTs may cause tumour hemorrhage. There is a theoretical but unproven risk of tumour dissemination. Endoscopic ultrasound-guided biopsy is preferred over percutaneous sampling [14], if it can be done expeditiously and effectively.
- Response to imatinib is usually assessed using CT imaging, and is based on a combination of change in size, density, and vascularity [23, 24].
- Laparoscopic resection may be considered provided that oncologic principles and preservation of the tumour pseudocapsule are ensured. Expertise in advanced laparoscopic technique is required.
- Several validated tools utilizing tumour size, mitotic rate, and tumour location have been developed to predict the recurrence risk following surgical resection of primary GISTs [7, 25–28]. Currently, expert opinion holds that mutation status should be determined for all GISTs [29].
- Surgical considerations:
  - No role for regional lymphadenectomy
  - Goal is to achieve negative histological margins
  - *En bloc* resection should be used as needed
  - A laparoscopic approach may be considered in certain circumstances
  - Careful attention must be paid to the integrity of the tumour capsule (tumour rupture may result in disseminated disease)

Locally Advanced/Borderline Resectable/Functionally Unresectable GIST

Work-up	Management	Follow-up
• History and physical exam • Imaging: – CT chest/abdomen/pelvis – MRI scan (rectal neoplasms) – Consider endoscopy – Consider EUS as appropriate • Consider endoscopic or percutaneous biopsy (see indications below) • Consider FDG-PET CT scan and/or DCE-US for borderline resectable cases with early re-evaluation (2–4 weeks after initiation of targeted treatment) [14] • Multidisciplinary consultation	• Neoadjuvant imatinib at a starting dose of 400 mg/day • Early re-evaluation with cross-sectional imaging to assess tumour response to targeted therapy (within 3 months of initiating therapy) • **Responders:** – Imatinib should be continued until maximal tumour response is achieved [30]. However, if the goal of tumour downsizing is achieved (as in the case of borderline resectable disease), it may not be necessary to await maximal tumour response[a] – Surgical resection with negative histological margins following neoadjuvant imatinib is associated with a 12-month overall and progression-free survival of 95 % and 80 %, respectively [33] – *En bloc* resection of adjacent viscera may be considered in order to achieve negative histological margins [2, 15–34] – Routine regional lymphadenectomy is ***NOT*** required • **Non-responders:** – Consider escalating the dose of imatinib to 800 mg/day (as tolerated) or a change to sunitinib [14, 35]; this should also be considered for patients with Exon 9 mutations – Consider surgical resection with negative histological margins ± *en bloc* resection of adjacent viscera if the tumour remains resectable – In patients with tumour progression (following upfront targeted therapy) resulting in unresectable GIST, management is based on the algorithm described for unresectable/recurrent/metastatic disease (see below)	• Close radiographic surveillance every 3 months is necessary, as some patients may become unresectable [9, 10] • Imatinib should be resumed following surgery as soon as oral medications are tolerated, regardless of final surgical margins to minimize the risk of recurrence

FDG-PET 18F-fluorodeoxyglucose-positron emission tomography, *DCE-US* dynamic contrast-enhanced ultrasound

[a]Note: Several more recent studies, however, have demonstrated a negative impact of prolonged neoadjuvant therapy and thus some authors would suggest that neoadjuvant treatment should not exceed 10–12 months; it is thought that this may be related to the development of chemoresistance or the development of new mutations secondary to prolonged therapy [31, 32]

Special Notes

- Functionally unresectable disease is defined as:
  - Localized, non-metastatic GIST at initial presentation;
  - Upfront resection is associated with significant morbidity;
  - Upfront resection is associated with significant long-term functional impairment and/or loss of organ function (i.e. an abdominoperineal resection for a rectal GIST) [2]; and/or
  - Upfront surgery would not yield an R0 resection [22].
- Imatinib mesylate should be initiated at a dose of 400 mg/day [14, 36–38]. Neoadjuvant imatinib has been associated with higher rates of complete resection [31], improved organ preservation [39], and favourable OS and PFS [40] in several case series.
- In patients with advanced GISTs, approximately 90 % of patients respond to imatinib when their tumours have a *KIT* **exon 11** mutation; approximately 50 % of patients respond when their tumours harbor a *KIT* **exon 9** mutation, and the likelihood of response improves with the use of 800 mg/day rather than the standard 400 mg/day dose (based upon tolerance and side effect profile) [14].
- Most mutations in the PDGFRAα gene are associated with a response to imatinib, with the notable exception of D842V [14].
- In the absence of *KIT* and *PDGFRA*α mutations, advanced GISTs have a 0–45 % likelihood of responding to imatinib [14].
- Given the multidisciplinary management of patients with locally advanced/borderline resectable/functionally unresectable GIST, referral to a high-volume surgical oncology center is recommended.

Unresectable, Recurrent, or Metastatic

Work-up	Management	Follow-up (F/U)
• History and physical exam • Imaging: – CT chest/ abdomen/pelvis – MRI scan (rectal neoplasms) – Consider FDG-PET CT scan (may play a role in assessing tumour response to systemic therapy, pre-treatment scan required) – Consider endoscopy – Consider EUS (as appropriate) • Consider endoscopic or percutaneous biopsy (see indications below) • Multidisciplinary consultation	• Imatinib mesylate at a starting dose of 400 mg/day (a starting dose of 800 mg/day should be considered in patients with exon 9 mutations) [14, 22] – The imatinib dose should be escalated when there is evidence of tumour progression to 800 mg/day (as tolerated) [2, 14] – In patients with imatinib resistance (or drug intolerance), consider sunitinib as second-line treatment – In patients with resistance to both imatinib and sunitinib, consideration may be given to third-line tyrosine-kinase inhibitors such as sorafenib, dasatinib, nilotinib, and/or regorafenib [41]. Consider enrollment to available clinical trials as appropriate. • Close radiographic surveillance with CT scans every 3 months should be performed to assess tumour response [2, 14] • Surgery is largely reserved for symptom palliation and may be considered in the context of focally progressive disease refractory to systemic treatment or following a favourable response to systemic treatment[a] • Radiation therapy may be considered for symptomatic bone metastases [14] • Ablative therapies may be considered in localized, solid organ metastases [14] • Embolization may be effective in controlling hemorrhage	• History and physical exam every 3–6 months • CT chest—yearly for 5 years • CT abdomen/pelvis—the first CT scan following the initiation of imatinib should be at 3 months (or sooner based on clinical indication) [14], then every 3 months for 5 years [2, 14] • The interval between consecutive CT scans may be increased based on disease stability [22]

FDG-PET 18F-fluorodeoxyglucose-positron emission tomography

[a]Note: Attempted resection in patients with generalized, progressive disease on imatinib a associated with a 12-month overall and progression-free survival of 0 % [33]

Landmark Trials

Topic	Study	Methods	Results
c-KIT mutation	Hiroti et al. [4]	• Pathological DNA sequencing in GIST specimens	• Gain-of-function mutation in KIT identified in GISTs
Imatinib treatment	Van Oosterom et al. [42]	• Phase I clinical trial • *N* = 40 • Metastatic GIST	• Activity demonstrated with imatinib in GISTs with: – 32/36 (89 %) patients demonstrating inhibition of tumour growth – 19/36 (53 %) patients with partial response (>20 % tumour regression) – 24/27 (89 %) patients with symptomatic improvement
	Demetri et al. [43]	• Phase II Multicentre RCT • *N* = 147 • 400 mg/day imatinib vs. 600 mg/day	• Partial response (PR) to treatment was observed in 53.7 % of patients • Stable disease (SD) in 27.9 % • Early resistance with progressive disease (PD) in 13.6 % • No difference was observed between the two doses
	Heinrich et al. [44]	• Phase II RCT • *N* = 127 • Response to imatinib in metastatic GIST was correlated to exon mutation status within the KIT gene	• Patients with exon 11 and 9 mutations had 83.5 % and 47.8 % response rate, respectively • Patients without a detectable KIT or PDGFRAα mutation did not demonstrate a response to treatment
	Verweij et al. [45]	• Phase III RCT • *N* = 946 • 400 mg/day imatinib vs. 800 mg/day	• No difference in response or overall survival (OS) in the two groups • In short-term follow-up, there was an increase in PFS in the 800 mg/day group (54 % vs. 50 %) • Subgroup analysis showed improved PR in the exon 9 mutation patients with 800 mg/day
	Joensuu et al. [21]	• Phase III RCT • *N* = 400 • 12 vs. 36 months of adjuvant Imatinib (400 mg/day) in patients with high risk of recurrence	• With a median follow-up of 54 months, RFS was improved in the 36-month group relative to the 12-month group (5-year RFS 65.6 % vs. 47.9 %, respectively), as was OS (5-year OS of 92.0 % vs. 81.7 %, respectively)

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Topic	Study	Methods	Results
Sunitinib treatment	Demetri et al. [35]	• Phase III RCT • *N*=312 (imatinib resistant) • Sunitinib vs. placebo	• Progression-free survival (PFS) was 24.1 weeks for sunitinib versus 6 weeks in the placebo arm
Regorafenib treatment	George et al. [46]	• Phase II Multicentre Trial • *N*=34 • Results of regorafenib treatment in patients with advanced GISTs after failure of at least imatinib and sunitinib	• Partial response to treatment was observed in 11.8 % of patients • Stable disease was observed in 64.7 % of patients for ≥16 weeks • Median PFS was 10 months
	Demetri et al. [41]	• Phase III Multicentre RCT • *N*=199 • Best supportive care+regorafenib (160 mg/day) vs. best supportive care+placebo in patients with metastatic or unresectable GIST with failure of at least imatinib and sunitinib	• Improved progression-free survival (PFS) in regorafenib group (4.8 vs. 0.9 months) • No apparent overall survival benefit (may be explained by crossover design)
Surgery	DeMatteo et al. [15]	• Retrospective review • *N*=200 • Results of surgical resection in localized and metastatic disease (pre-imatinib era)	• Initial presentation: – Localized disease (46 %) – Metastatic disease (47 %) – Isolated recurrence (7 %) • 5-year survival following complete resection (R0/R1): 54 % • Survival was largely predicted by tumour size
	Dematteo et al. [17]	• Phase III Multicentre RCT • *N*=713 • Adjuvant imatinib for 1 year after R0/R1 resection (tumours moderate to high risk, >3 cm)	• Improved recurrence-free survival (RFS) for adjuvant imatinib compared to resection alone (98 % vs. 83 % at 1 year) • No statistically significant difference in OS
	Mussi et al. [30]	• Retrospective review • *N*=80 • Surgery for metastatic GIST after best clinical response vs. after focal progression	• 2-year PFS in the best clinical response group (64.4 % vs. 9.7 %) • 5-year DSS was 82.9 % vs. 67.6 % in favour of the best clinical response group

OS overall survival, *RFS* recurrence-free survival, *PFS* progression-free survival, *DSS* disease-specific survival, *PR* partial response

Referring to Medical Oncology

- All patients with histologically confirmed GISTs, other than those with very low to low-risk features, should be referred to medical oncology to (1) evaluate the risk of tumour recurrence; and (2) to establish the role of targeted therapy with a tyrosine-kinase inhibitor. If any doubt exists regarding patient risk stratification, referral to medical oncology is warranted.

Referring to Radiation Oncology

- Patients with symptomatic bone metastases not responsive to targeted therapy should be referred to radiation oncology for consideration of palliative therapy.

Referring to Multidisciplinary Cancer Conference

- All patients with a diagnosis of GIST should be discussed to confirm pathologic diagnosis, determine the indications for mutational analysis, and evaluate the indications for adjuvant or neoadjuvant targeted therapy.
- Patients started on neoadjuvant-targeted therapy or who experience limited progression after responding to targeted therapy should be discussed again at Multidisciplinary Cancer Conference (MCC) to re-evaluate the sequencing of multimodality treatment.

Toronto Pearls

- The multidisciplinary management of GISTs is the cornerstone of evidence-based treatment.
- Neoadjuvant imatinib is ***NOT*** associated with prohibitive risk of bleeding. In fact, surgical experience is that GISTs become less vascular and less friable, and therefore less prone to intraoperative rupture.
- Mutational analysis is part of a complete assessment of GIST.

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