Gastrointestinal Stromal Tumours (GIST)

Effective Date: February, 2016

The recommendations contained in this guideline are a consensus of the Alberta Provincial Sarcoma Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Gastrointestinal stromal tumours (GIST) are the most common stromal or mesenchymal neoplasms effecting the gastrointestinal (GI) tract, representing less than 1% of all GI tumours, and over 90% of sarcomas (1- 3). GISTs present primarily in the stomach and small intestine (60-70% and 30%, respectively), however, they may also occur in any portion of the alimentary tract, including the colon/ rectum and esophagus (4, 5).

The true incidence of GIST remains somewhat unclear, as early large scale studies did not use molecular characters to define diagnosis (6). Smaller studies have estimated the rate of GIST at 7-20 cases per million population years in the United States (6-8). A Swedish study estimates the frequency of GIST at approximately 14.5 cases per million population years (9), and an Icelandic study reports an incidence of 11 cases per million population years (10). A study conducted in Alberta found the incidence rate of GIST in Alberta is 0.91 per 10^5 person-years, reporting that advancing age was the only significant risk factor (11). The average age at diagnosis of GIST is 63 to 69 (6, 9, 10).

GUIDELINE QUESTIONS

- What is the role of pathology in the diagnosis and treatment of GIST?
- What imaging modalities are appropriate for the diagnosis and treatment monitoring of GIST?
- How should patients with newly diagnosed GIST be managed?
- How should patients with metastatic GIST be managed?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Sarcoma Tumour Team. Members of the Alberta Provincial Sarcoma Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Sarcoma Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

This guideline was originally developed in (February, 2016).

SEARCH STRATEGY

Multiple searches were performed using the PubMed database for articles published between January 1, 2010 and August 1, 2015: (Search 1)GIST [All Fields] AND "imaging"[All Fields] (Search2) Gist [All Fields] AND follow-up [All Fields] (Search 3) GIST [All Fields] AND Clinical Trial[ptyp] (Search 4) "neoadjuvant therapy"[MeSH Terms] OR ("neoadjuvant"[All Fields] AND "therapy"[All Fields]) OR "neoadjuvant therapy"[All Fields] OR "neoadjuvant"[All Fields]) AND ("imatinib"[Supplementary Concept] OR "imatinib"[All Fields]) AND gist[All Fields]) AND Clinical Trial[ptyp]

TARGET POPULATION

Patients who are at least 18 years of age, who have been diagnosed with (or there is suspicion of) a gastrointestinal stromal tumour.

RECOMMENDATIONS

General Summary

- Pathology should include the site and size of the tumour, the mitotic index, CD117 immunoreactivity, +/- DOG1 immunohistochemistry, margin status, site(s) of metastases, molecular genetic testing and a statement regarding the likely biological behavior using the NIH guidelines, when resection with the intent for cure has been carried out.
- CT is ideal for staging and assessing treatment response. Follow-up imaging should be performed every 3-6 months for five years following resection of intermediate and high risk GIST tumours. PET/MRI imaging may be useful if additional information is required to determine the optimal management strategy after CT imaging.
- Surgery remains the mainstay of therapy for resectable primary lesions. Neo-adjuvant imatinib is recommended for patients with borderline or unresectable tumours. Typically imaging with CT scan is sufficient, however, in some borderline unresectable GIST, PET scan may have utility in detecting imatinib response (particularly when molecular testing has not been performed).
- Adjuvant imatinib is appropriate for high-risk patients following surgery.
- Metastatic disease should be managed by an interdisciplinary team. Resection of the primary and where possible, metastatic disease should be considered, as this may impede the development of drug resistance. Imatinib should be initiated after the detection of metastatic disease, and continued until disease progression. In the event of intolerance, progression, or non-response, sunitinib should be initiated. In the event of treatment failure of both imatinib and sunitinib, regorafenib should be initiated.
- Wherever possible, enrolment of patients in clinical trials is strongly encouraged.

Pathology(12)

1. All cases should be reviewed by a pathologist with expertise in sarcomas.
2. *Gross and histologic evaluation*: The pathology report should include the location and maximum dimension of the tumour, along with margin status. The closest margin and adjacent tissue, along with one tissue block per cm of the tumour should be examined microscopically. The morphologic subtype (spindle, epithelioid or mixed), mitotic rate (evaluated over a 5 mm^2 area, which may be represented by 20-50 HPF depending on the field diameter), presence/extent of necrosis and tumor focality should be reported. Risk assessment should be performed based on tumor site, tumor size and mitotic rate (13). In the neoadjuvant treatment setting, an approximation of the treatment effects based on percentage of viable tumor in the resected tumor should be noted.
3. *Ancillary immunohistochemical analysis*: Immunohistochemical (IHC) analysis should be performed to confirm the diagnosis of GIST and rule out potential morphologic mimics. The confirmatory IHC panel should include CD117 (KIT) and ideally DOG1 (ANO1) as well if available. The addition of DOG1 increases the diagnostic sensitivity for GIST and a combined positivity for CD117 and DOG1 is highly specific for GIST. IHC marker such as CD34 is less specific. In the setting where the clinical, radiologic and histologic findings are compatible with a diagnosis of GIST, immunopositivity for CD117 and/or DOG1 would confirm the diagnosis of GIST. It is important to note that about 10% of GIST can show a CD117-positive/DOG1-negative or DOG1-positive/CD117-negative IHC profiles. However, a number of other tumor types (i.e. melanoma, germ cell tumor and various sarcoma types) can also be positive for CD117 and it is important to exclude histologic mimics of GIST with additional IHC markers (S100, HMB45, desmin, caldesmon, smooth muscle actin, beta-catenin), particularly if the clinical/radiologic features are unusual. *KIT/PDGFRA* mutation analysis should be performed if there is uncertainty in the diagnosis and

this includes the settings where a suspected GIST is negative for both CD117 and DOG1 and/or if the suspected GIST exhibits unusual histologic features (sarcomatous).
4. *Ancillary genetic analysis*: In cases where there is uncertainty regarding the diagnosis of GIST after histologic and IHC evaluation (including cases in which clinical and histologic findings are compatible with GIST but the tumor is negative for CD117), mutational analysis for *KIT* (exon 8, 9, 11, 13 and 17) and *PDGFRA* (exon 12, 14 and 18) should be performed for diagnostic confirmation. It is important to note that *KIT* mutations may be present in melanomas and several other tumor types as well. In addition to diagnostic utility, the exact *KIT/PDGFRA* mutation type along with exon 9 mutation can provide clinically important prognostic and predictive information for the management of GIST patients. While mutation typing should ideally be performed on all patients with GIST, it is acceptable at the present to perform mutation analysis on diagnostically challenging cases and on cases with clinical indication (i.e. requested by the patient's oncologist/surgeon).
5. *KIT/PDGFRA-wild type GIST:* Approximately 5-10 percent of GISTs lack demonstrable *KIT* and *PDGFRA* mutations (referred to as wild-type GIST). About half of these wild-type GISTs (which encompass the majority of pediatric GIST) are deficient for succinate dehydrogenase (SDH) subunits – SDHA, SDHB, SDHC and SDHD. The mutation underlying SDH-deficiency may be germline in nature with syndromic implications (Carney-Stratakis syndrome with gastric GIST and paraganglioma). Furthermore, SDH-deficient GIST shows poor response overall to imatinib. Referral to centers that perform SDH IHC and/or mutation analysis should be considered in these settings.

Imaging

6. Computed tomography (CT) scans are typically sufficient for imaging most GISTs; however, there may occasionally be a role for combination positron emission tomography (PET)/CT where results could affect management decisions. Magnetic resonance imaging (MRI) may also be considered.
7. Small tumours found incidentally by endoscopy should be evaluated using CT or endoscopic ultrasound (US). Typically, unenhanced CT is sufficient to detect most lesions, and intratumoural hemorrhage. Triphasic imaging is required after imatinib treatment to avoid misinterpretation of hepatic lesions which may not represent new or progressive disease.
8. MRI is generally preferred for preoperative staging of rectal GISTs, whereas CT is preferred for evaluating tumour response after treatment with imatinib, though PET/CT may be required in some instances where CT alone provides unclear results. CT/PET may be useful for detecting primary resistance of borderline resectable GISTs allowing timely resection before progression, particularly in GISTs which have not been assessed with molecular tests. When evaluating treatment response, PET is only useful if a baseline PET is available for comparison
9. Treatment response should be evaluated by a radiologist with experience evaluating GIST treatment response. CT is typically sufficient to assess treatment response (though PET/CT may be valuable in some instances where CT provides unclear results).
10. Tumour shrinkage alone may be an unreliable indicator of early response to treatment. Decreased tumour density and changes in morphology on CT (or in some cases MRI) may be valuable. Cystic degeneration on CT during therapy may be misidentified as the development of new lesions. A growing nodule within a stable mass on contrast-enhanced CT may be an early indicator of disease progression.
11. When patients are on treatment, follow-up with CT every 3-6 months is recommended.
12. Follow-up CT imaging is recommended every 3-6 months for a minimum of five years post-resection for intermediate- and high-risk patients. For low-risk tumours the usefulness of a routine follow-up is not known; if selected this is carried out with abdominal CT scan or MRI every 6-12 months for 5 years. Very low risk GIST's probably do not deserve routine follow-up although one must be aware that the risk is not zero (14).

TREATMENT WITH CURATIVE INTENT

Table 1. Risk Stratification for GIST

	Very Low Risk	Low Risk	Intermediate Risk	High Risk
Modified NIH consensus classification (used in the SSGXVIII/AIO study) (15)	**Any location:** <2 cm and ≤5 mitotic index	**Any location:** 2.1–5 cm and ≤5 mitotic index	**Gastric:** 5.1–10 cm and ≤5 mitotic index; ≤5 cm and 6–10 mitotic index	**Any location:** tumor rupture; >5 cm and >5 mitotic index; >10 cm; >10 mitotic index **Non-gastric:** ≤5 cm and >5 mitotic index; 5.1–10 cm and ≤5 mitotic index **Tumor rupture**

Note: The Alberta imatinib funding model is based on these criteria although other risk stratification strategies (16-18) are commonly used (See Appendix A, Table 2).

Treatment: Surgery

13. Straight-forward, resectable primary lesions suspected to be GIST do not require biopsy, and generally, precutanous biopsy is not recommended as it may lead to tumour hemorrhage and/or tumour seeding. Core biopsy can be considered when the diagnosis remains unclear despite imaging, or when biopsy has the potential to change treatment decision. Tissue biopsy is required if neo-adjuvant imatinib is required to facilitate resection (endoscopic preferred). Fine-needle aspiration cytology is not likely to be of great value in establishing a diagnosis of GIST
14. Surgery remains the mainstay of therapy for resectable primary GIST, provided there is no evidence of metastases. Resection may be appropriate before a pathological diagnosis is obtained. The goal of surgery is complete resection of visible and microscopic disease. Small (<2cm) GISTs which are stable in size may be observed (especially gastric GISTs). Extreme care is required when handling GISTs to avoid tumour rupture or spillage. En bloc resection is advised for GISTs that are adherent to nearby structures. Negative microscopic margins are associated with a decreased risk of peritoneal recurrence.
15. Laparoscopic resection of GISTs is reasonable when risk of tumour rupture is low.
16. Lymphadenectomy is not required when the diagnosis of GIST has been established.
17. Neo-adjuvant imatinib should be considered for “functionally unresectable” GIST, where surgery would result in significant morbidity or loss of organ function, for the purpose of downsizing the tumour and preserving organ function. Tumours near gastroesophageal junction, duodenal GISTs requiring pancreaticoduodenectomy or low rectal GISTs requiring abdomino-perineal resection may be suitable for neo-adjuvant imatinib. If neo-adjuvant imatinib is deemed appropriate, initiation should be prompt, and ideally surgery should be performed within 12 months later at a tertiary-care center. CT scans should be used to assess tumour shrinkage in three month intervals, and maximal shrinkage is defined as no further shrinkage on two consecutive CT scans. The surgeon should participate in the management of care to assess the risk of hemorrhage with neo-adjuvant treatment (19).
18. Imatinib is recommended for borderline unresectable GIST. A potentially small window of opportunity exists before the GIST becomes unresectable in the case of primary resistance necessitating PET scans before initiating imatinib and then within 6 weeks after initiation of imatinib is recommended.

Treatment: Medical Oncology, Adjuvant Therapy

20. Assessment of risk of recurrence using NIH consensuses (modified or un-modified) criteria or Miettinen-Lasota/Armed Forces Institute of Pathology (M-L/AFIP) criteria is required (Table 1).
21. Adjuvant imatinib (400 mg/d, for at least 3 years) is indicated for patients at high risk of recurrence (Tumour diameter >10cm, Tumour mitosis count >10/50 HPF or size >5cm and >5/50 HPFs) or ruptured tumour (spontaneous or during surgery) as this leads to DFS and OS benefits.
22. Intermediate risk patients may derive benefit from imatinib therapy; however, at this time there is insufficient evidence to recommend imatinib treatment for this patient population. Currently, imatinib therapy is not funded for low-/intermediate- risk GIST patients in Alberta (18, 20, 21, 22).
23. In high risk GIST, 3 years of adjuvant imatinib is superior to 1 year of imatinib as it results in longer relapse-free and overall survival (, 23). .

Treatment: Medical Oncology, Neo-Adjuvant Therapy

24. Neo-adjuvant imatinib may be considered for patients who require tumour debulking, shrinking of the tumour to reduce surgery-associated morbidity, to facilitate surgery for unresectable tumours, or to reduce the perioperative risks associated with surgery (24-26).
25. A multidisciplinary team should oversee the treatment of patients who are candidates for neo-adjuvant imatinib (with representation from surgery and medical oncology) (24).
26. In the neo-adjuvant setting, imatinib should be given at a dose of 400-800 mg/d at the discretion of the medical oncologist, CT scans should be used to assess tumour shrinkage in three month intervals, and maximal shrinkage is defined as no further shrinkage on two consecutive CT scans (at which point the patient should proceed to surgery, if possible), within 12 months of therapy is typical if the tumour is responsive to therapy, disease progression on imatinib in this setting is associated with poor outcomes.
27. Ideally, imatinib should be discontinued 5 days prior to surgery.
28. Imatinib should be resumed post-surgery (at the discretion of the medical oncologist) based on risk of relapse/progression.

METASTATIC/ RECURRENT DISEASE

Medical Oncology/ Surgery General Considerations

1. Recurrent disease should be managed as metastatic disease.
2. Imatinib is the recommended first-line therapy.
3. If the primary and/or metastatic disease can be resected, then treatment should include some combination of imatinib and resection of the primary tumour and metastases. Although not curative, resection can prolong the time to tumour progression and imatinib-resistance. Imatinib can be administered before and after surgery at the discretion of the treating surgeon/ medical oncologist (27). These options should be discussed in the context of interdisciplinary rounds.
4. Patients with unresectable or widespread metastatic disease should have a core biopsy.
5. Stable residual disease should be treated with maintenance imatinib therapy. At the discretion of the surgeon/ medical oncologist, there may be benefit to removing the primary tumour to prevent the development of imatinib-resistance.
6. Limited progressive disease (radiologic evidence of limited progression in the context of otherwise stable disease) should be managed with surgery if possible to minimize the development of imatinib resistance. The benefits and potential morbidities associated with repeat resection should be discussed with the patient. Local control options (surgery, radiofrequency ablation, sterotactic body radiation therapy) may be considered as a potential alternative to surgery.

7. Hepatic artery embolization maybe considered for large resistant hepatic metastases, and may be particularly useful in the emergency management of intratumoural hemorrhage.
8. Surgery is usually not appropriate for multifocal progressive disease, as there is a high risk of post-operative mortality and significant morbidity. Surgery may be considered if the patient is symptomatic.

Treatment: Medical Oncology

10. Imatinib should be initiated promptly following the diagnosis of metastatic GIST.
11. Imatinib should be given initially at a dose of 400 mg/day. If the tumour responds poorly, consider raising the dose to 800 mg/day (28, 29). Poor response at 400 mg/day is more frequent amongst patients with exon 9 mutation (30). PDGFRA D842V mutation is associated with imatinib and sunitinib resistance, however, there is some evidence that regorafenib may be effective(31).
12. All patients with advanced GIST should receive imatinib until there is progression or intolerance.
13. In the event of progression or intolerance on imatinib, consider sunitinib (50mg/day for the first 28 days of a 42-day cycle) as it has been shown to significantly prolong OS (32, 33).
14. In patients with unresectable GIST (or metastatic GIST) who experience treatment failure on imatinib and sunitinib, regorafenib (160 mg/day for the first 21 days of each 28-day cycle) should be considered as it has been shown to increase DFS (no statistical difference in OS, possibly due to patient cross-over)(34).

GLOSSARY OF ABBREVIATIONS

Acronym	Description
CT	Computed tomography
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
IHC	Immunohistochemical
MRI	Magnetic resonance imaging
PET	Positron emission tomography
US	Ultrasound

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControlAlberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Sarcoma Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControlAlberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Sarcoma Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES

1. Rubin BP, FLetcher JA, Fletcher CD. Molecular Insights into the Histogenesis and Pathogenesis of Gastrointestinal Stromal Tumors. Int J Surg Pathol. 2008 8(1): 5
2. Miettinen M, Kopczynski J, Makhlouf HR, et al. Gastrointestinal stromal tumors, intramural leimyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetics study of 167 cases. Am J Surg Pathol. 2003. 27: 625-641
3. Vij M, Agrawal V Kumar A, et al. 2012. Gastrointestinal stromal tumors: a clinicopathological and immunohistochemical study of 121 cases. Indian J Gastroenterol. 2010 29: 231-236
4. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumours. Ann Chir Gynaecol 1998. 87: 278-281
5. Hasegawa T, Matsuno Y, Shimoda T, et al. Gastrointestinal stromal tumor: consistent CD117 immunostaining for diagnosis, and prognostic classification based on tumor size and MIB-1 grade. Hum Pathol 2002. 33: 669-676
6. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol. 2005 100(1): 162
7. Fletcher CD, Berman JJ, Corless C. et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002 33(5): 459
8. Ma GL, Murphy JD, Martinez ME, et al. Epidemiology of Gastrointestinal Stromal Tumors in the Era of Histology Codes: Results of a Population-Based Study. Cancer Epidemiol Biomarkers Prev pii: cebp.1002.2014
9.Nilsson B, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. Cancer. 2005 103(4):821
10. Tryggvason G, Gislason HG, Magnusson MK, et al. Gastrointestinal stromal tumors in Iceland, 1990-2003: the Icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer. 2005 117(2): 289
11. Yan BM, Kaplan GG, Urbanski S. et al. Epidemiology of Gastrointestinal Stromal Tumors in a Defined Canadian Health Region: A Population-Based Study. Int J Surg Pathol 16(3): 241-250
12. Ruben BP, Blanke CD, Demetri GD, et al. 2010. Protocol for the Examination of Specimens from patients with GAstrointestinal Stromal Tumor (GIST). Based on AJCC/UICC TNM, yth edition. Accessed August 24, 2015 http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2010/gist_net_10.pdf
13. Miettinen M, Lasota J, et al. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006; 130(10): 1466-78
14. ESMO/ European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25(sup 3): iii21-iii26
15. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012; 307(12): 1265-1272
16. NCCN. Soft Tissue Sarcoma Version I.2015. Accessed August 25, 2015 http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
17. ESMO/ European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25(sup 3): iii21-iii26
18. Agaimy A. Gastrointestinal stromal tumors (GIST) from risk stratification systems to the new TNM proposal: more questions than answers? A review emphasizing the need for a standardized GIST reporting. Int J Clin Exp Pathol 2010; 3(5): 461-71
19. Wang D, Zhang Q, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stomal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. Ann Surg Oncol 19(4): 1074-80
20. Casali P, Le Cesne A, Velasco AP, et al. Imatinib failure-free survival (IFS) in patients with localized gastrointestinal stromal tumors (GIST) treated with adjuvant imatinib (IM): the EORTC/AGITG/FSG/GEIS/ISG randomized controlled phase III trial (abstract). J Clin Oncol 2013; (supple; abstr 10500)
21. DeMatteo RP, Ballman KV, Antonescu CR, et al. Placebo-Controlled Randomized Trial of Adjuvant Imatinib Mesylate Following the Resection of Localized, Primary Gastrointestinal Stromal Tumor (GIST). Lancet 2009; 373(9669): 1097-1104
22. Casali PG, Le Cesne A, Velasco AP, et al. Research and Treatment of Cancer Soft Tissue and Bone SArcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group,

UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas. J Clin Oncol 2015; 33(36): 4276-4283
23. Joensuu H, Eriksson M, Hall SK. Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial. J Clin Oncol 2016; 34(3): 244-50
24.Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol 2009; 99(1): 42-7
25. Andtbacka RH, Ng CS, Scaife CL, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. Ann Surg Oncol 2007; 14(1): 14-24
26. Raut CP, Posner M, Desai J, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol 24(15): 2325-31
27. Du CY, Zhou Y, Song C, et al. Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal sumours responding to imatinib: a prospective randomised trial in China. Eur J Cancer 2014; 50(10: 1772-8
28. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008; 26: 626-632
29. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004; 364: 1127-34
30. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006; 42: 1093-103
31. Kollar A, Maruzzo M, Messiou C, et al. 2014. Regorafenib treatment for advanced, refractory gastrointestinal stromal tumor: a report of the UK managed access program. Clin Sarcoma Res 4: 17
32. Casali PH, Garrett CR, Blackstein ME, et al. Updated results from a phase III trial of sunitinib in GIST patients (pts) for whom imatinib (IM) therapy has failed due to resistance or intolerance [abstract 9513] Proc Am Soc Clin Oncol 2006; 24
33. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006; 368: 1329-38
34. Demetri GD, Reichardt P, Kang YK, et al. 2013. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381(9863): 295-302

APPENDIX A

Table 2. Commonly used risk stratification criteria for GIST

	Very Low Risk	Low Risk	Intermediate Risk	High Risk
NIH consensus criteria (15)	<2 cm and <5 mitotic index	2–5 cm and <5 mitotic index	5−10 cm and <5 mitotic index; <5 cm and 6–10 mitotic index	>5 cm and >5 mitotic index; >10 cm; >10 mitotic index
AFIP classification system (criteria used in NCCN and ESMO guidelines) (16, 17)	**Gastric:**≤2 cm and any mitotic index; ≤5 cm and ≤5 mitotic index **Non-gastric:** ≤2 cm and ≤5 mitotic index	**Gastric:** >5 cm and ≤10 cm, and ≤5 mitotic index **Non-gastric:** >2 cm and ≤5 cm, and ≤5 mitotic index	**Gastric:**>10 cm and ≤5 mitotic index; >2 cm and ≤5 cm, and >5 mitotic index **Jejunal or ileal:** >5 cm and ≤10 cm, and ≤5 mitotic index	**Gastric:** >5 cm and >5 mitotic index **Duodenal or rectal:** >5 cm **Non-gastric:**>10 cm; >5 mitotic index
Modified NIH consensus classification (used in the SSGXVIII/AIO study) (18)	**Any location:** <2 cm and ≤5 mitotic index	**Any location:** 2.1–5 cm and ≤5 mitotic index	**Gastric:** 5.1–10 cm and ≤5 mitotic index; ≤5 cm and 6–10 mitotic index	**Any location:** tumor rupture; >5 cm and >5 mitotic index; >10 cm; >10 mitotic index **Non-gastric:** ≤5 cm and >5 mitotic index; 5.1–10 cm and ≤5 mitotic index **Tumor rupture**