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Guidelines

Gastrointestinal stromal tumours (GISTs): French Intergroup Clinical Practice Guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO)

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ABSTRACT

Background: This document is a summary of the French Intergroup guidelines regarding the management of gastrointestinal stromal tumours (GISTs) updated in December 2018.
Design: This collaborative work summarizes clinical practice recommendations (guidelines) on the management of GISTs. It is based on recent literature review, ESMO recommendations and expert opinions.
Results: The diagnosis of GIST is based on histological examination and immunohistochemistry with markers KIT and DOG-1. Each case must be discussed within a multidisciplinary team. Complete surgical resection tumour, avoiding peroperative perforation, is the potentially curative treatment of localized GISTs. The estimation of the recurrence risk is essential, or adjuvant treatment,and follow-up adaptation. Genotyping (*KIT* and *PDGFRA*) of all but very low-risk GISTs is recommended. The nature of mutation has a prognostic value and predictive influence on drug efficacy. Imatinib, a tyrosine-kinase inhibitor, is the standard adjuvant treatment after R0 resection of a GIST with a high risk of recurrence, and the first line therapy for advanced GISTs. Suninitib and regorafenib are respectively the second- and third-line standard treatments for advanced GISTs.
Conclusion: Guidelines for management of GISTs are continuously evolving and need to be regularly updated. This constant progress is made possible through clinical and translational research.

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1. Introduction

This guideline is a collaborative work under the auspices of most of the French medical societies involved in the management of gastrointestinal stromal tumours (GISTs). The primary aim was to develop recommendations using only methodologically established evidence-based guidelines or primary evidence, and to achieve an interdisciplinary consensus. A writing multidisciplinary committee (from 7 medical societies) comprising several experts from different specialties involved in the management of GISTs (surgeons, pathologists, medical oncologists and hepatogastroenterologists) was designated to review recent literature until September 2016 and to write a first document after interactive discussions. This initial document was reviewed and modified after further interactive discussions, writings by a review committee and the last version was finally validated by the steering committee of the participating National Societies. The present paper is a summary of the French intergroup guidelines published in March 2019 on the web site of the SNFGE society https://www.snfge.org/tncd. Levels of evidence were defined as follow: grade A, large meta-analysis or large randomized trial, grade B small randomized trials and grade C prospective non randomized study. Recommendations based on those levels of evidence were scored in 3 categories A, B and C with only expert opinion (agreement or not) when no scientific evidence was validated. All the statements in the present paper completely match the original full guidelines, with no additional data or comments. French recommendations for GIST management have taken into account the ESMO recommendations, and are based on randomized studies or expert agreements when lacking [1].

Gastrointestinal stromal tumours (GISTs) are mesenchymal tumours that develop mostly from the stomach and small intestine, more rarely the rectum, colon, oesophagus or mesentery. They are usually sporadic, incidence is about 15 cases/million inhabitants/year, median age at diagnosis 60 years, and sex ratio 1. They are derived from Cajal cells or one of their precursor, and their phenotype is usually KIT + (95%) and DOG-1 + (95%). They typically harbor activating mutations of the genes encoding tyrosine kinase receptors KIT or PDGFRA. GISTs represent a heterogeneous set in terms of molecular biology, clinical behavior and response to treatment. Oral tyrosine kinase inhibitors (TKI), originally imatinib, have revolutionized their management. National or international patient associations play a crucial role for diffusion of information and management of these rare tumours. Pediatric GISTs will not be addressed in this paper.

2. Pre-treatment assessment

2.1. Extension

Recommendations

- CT-scan (abdominopelvic and chest)

Options

- Endoscopic ultrasonography (EUS)
- Abdominal RMI (liver, peritoneum)
- Pelvic RMI (rectal GIST)
- TEP-Scan

2.2. Biopsies

Endoscopic biopsies are usually negative as the tumour growth from the *muscularis propria* [1,2]. A EUS-guided or transcutaneous biopsy may be discussed on individual basis, assessing the risk of bleeding or tumour spillage. When the diagnosis is suspected, it is mainly recommended in selected cases such as: doubtful diagnosis or resectability, mutilating surgery, or advanced disease. In localized GISTs, if feasible, EUS-guided biopsy should be preferred, even if preoperative biopsy did not show negative prognosis impact [3]. In advanced GISTs, the lesion the most accessible should be biopsied (eg transcutaneous liver biopsy for hepatic metastases). Biopsies of necrotic or kystic tumours must be performed in tertiary care centers. The biopsy sample has to be fixed by formalin 4 %. Collection of frozen tissue is encouraged [1].

Recommendations

If the diagnosis of GIST is suspected, a preoperative biopsy should be discussed in a multidisciplinary concertation meeting. It is recommended but not mandatory in localized GIST if resection is a simple procedure. It is mandatory as soon as the choice of the treatment relies on definite diagnosis:

- Differential diagnosis: lymphoma, fibromatosis, etc.
- Indication of a neodjuvant treatment with imatinib
- Non resectable or metastatic tumour
- Mutilating surgery

2.3. Syndromic GISTs [4,5]

Syndromic GISTs are rare conditions. For GISTs with no *KIT* nor *PDGFRA* mutation, immunohistochemestry for SDHB (succinate deshydrogenase subunit B) is recommended. GISTs harboring loss of expression of SDHB have a higher risk of lymphatic dissemination. Some features are described below.

- Type 1 neurofibromatosis: germinal mutation of *NF1* gene, GISTs are usually multiple, mainly in the small intestine. No *KIT* and *PDGFRA* mutation.
- SDH-deficient GISTs:
  - o Pediatric/young adult, no *KIT* and *PDGFRA* mutation, epithelioid type,
  - o Carney's triad: non heritable syndrome, girls and young women, variable association of gastric GISTs, paraganglioma and pulmonary chondroma
  - o Carney–Stratakis syndrome: germline mutation in any subunit of SDH, multiple gastric GISTs and paraganglioma
- Heritable *KIT* or *PDGFRA* mutations: young age, familial history, oesophageal motor disorders, pigmented skin macules, Cajal cell hyperplasia

A genetic counselling is indicated if an heritable disorder is suspected. Indications for genetic counselling and an algorithm of genetic analysis according to SDH-B immunohistochemistry are summarized in Appendix A.

2.4. GIST <2 cm in diameter

GISTs <1 cm in diameter are frequent in the proximal stomach, harboring mutations of *KIT/PDGFRA* [1]. Growing of such lesions is uncertain and malignant evolution of gastric GISTs <2 cm is uncommon [6]. Resection or follow-up are options for gastric GISTs <2 cm, considering the easiness of resection and patient's condition and opinion. No follow-up scheme is validated, but EUS monitoring at 6 months, 18 months and every 2 years is a reasonable option (expert opinion). Endoscopic resection should be an option in the future. For extra-gastric GISTs <2 cm, resection is recommended due to higher potential risk for evolution [1].

3. Pathology and molecular biology

Diagnosis of GIST is established by histological analysis and immunohistochemical staining (KIT positive 95%, DOG-1 positive

95%) [1,2]. Second pathological reading in an expert center is recommended. It limits misdiagnoses, and promotes mutational analysis, which is recommended except for very low risk GISTs [1].

The type of mutation influences both prognosis and treatment efficacy in adjuvant and advanced settings. Most GISTs harbor an activating mutation in KIT (75%), occurring mostly in exon 11 (65%) or exon 9 (10%). Nature of *KIT* alterations on exon 11 are variable (deletions, substitutions. . .). PDGFRA mutations occur in 10% of localized GISTs and 3% of metastatic GISTs, mainly in exon 18 (mutation D842V poorly sensitive to imatinib).

No KIT/PDGFRA mutation is found in 15% of GISTs. It is a heterogeneous group of tumours previously called wild-type GISTs. It includes sporadic GISTs and syndromic GISTs, some of which are driven by oncogenic mutations (SDH, RAS, NF1 . . .) or SDH loss of expression [7]. These GISTs express differences in terms of clinical behavior, molecular abnormalities, prognosis, and therapy sensitivity. Collection of frozen tissue is encouraged for a better knowledge of these subtypes.

4. Risk stratification and follow-up

4.1. After R0 resection

The estimation of the risk of recurrence is crucial to consider adjuvant treatment and adapt follow-up [1]. For localized GISTs, the risk of recurrence is currently evaluated according to the primary localization, the size and the mitotic index evaluated over 5 mm^2 (the most important parameter). Depending on these parameters, the risk of recurrence may be almost zero or exceed 70%. Tumour rupture in the abdominal cavity is another important parameter, as the risk of peritoneal recurrence is major in that case.

After initial NIH (National Institutes of Health) classification (based on expert consensus), many classifications (based on retrospective studies before imatinib) have been proposed to evaluate the risk of recurrence [8–10]. They have a roughly similar accuracy. However, the recurrence risk for gastric GIST with a low mitotic index is probably overestimated by the NIH classification. Usually the recurrence risk is arbitrarily evaluated as: high > 30 %, moderate 10–30%, low < 10%, very low risk 0–2%. AFIP and modified NIH classifications (Appendices B1 and B2) are the most used in France, while the TNM classification is little used. Some classifications, as prognostic contour maps, incorporate the mitotic index and size as continuous variables [11].

Recurrences after surgery are mainly hepatic and/or peritoneal. The mitotic index of the tumour influences the speed of recurrence. For patients at high risk of recurrence, they occur mainly within 3 years of completing adjuvant therapy. Most recurrences occur within 5 years of surgery or completion of adjuvant therapy. Later recurrences are possible but rare [1]. There is no data in the literature to validate a specific monitoring protocol. The proposed monitoring protocols therefore correspond to expert opinions. Abdominal MRI is an alternative to CT-scan, as exposure to ionizing radiation must be taken into account, especially since the patient is young and risk of recurrence is low [1].

Recommendations

- Clinical examination and abdominopelvic CT-scan or abdominal RMI
- Schedule to adapt on recurrence risk and clinical condition
- Chest CT-scan if high-risk and/or rectal GIST (at least annual)

Options (expert opinion) (Appendix C)

- High-risk patients (on adjuvant imatinib): every 3–6 months for 3 years
- High-risk patients (after adjuvant imatinib): every 3 months for 2 years, then every 6 months until 5 years, and annually for 5 more years
- Moderate-risk patients (without adjuvant imatinib): every 3–6 months for 3 years, then every 6 months until 5 years, and annually for 5 more years
- Low-risk patients: every 6–12 months for 5 years
- Very low-risk patients: no systematic follow-up

4.2. Genotyping

Mutational analysis is mandatory for optimal management of GISTs [1]. Genotype influences the recurrence risk and might impact the decisional process of adjuvant treatment. Tumours with *KIT* exon 9 alteration or *KIT* exon 11deletions experience more recurrence, whereas *PDGFRA* mutations or *KIT* exon 11 duplications are associated with a lower risk [1,12]. Moreover, genotype can be predictive of treatment sensitivity. Tumours with KIT exon 11 are the most sensitive to imatinib, those with PDGFRA Asp842Val are insensitive [1]. An expression signature of genes related to genome complexity has a strong prognostic value, and is tested in a randomized study for moderate-risk GISTs (GI-GIST trial).

4.3. Imaging during TKI therapy for advanced GISTs [1,2]

CT-scan is commonly used for response assessment (expert agreement). Tumours typically become hypodense and contrast capture as well as the tumour vascularity decrease in a few weeks. These changes are not always associated with a decrease in tumour size that is slower and more inconstant. Then, RECIST criteria are not perfectly adapted for the evaluation in imatinib-treated GISTs, and the measurement of tumour density is necessary. The decrease of the tumour vascularization, evaluated by dynamic scanner/RMI or echodoppler with injection of contrast medium, also reflects the effectiveness of the treatment (expert agreement). A review of imaging in a regional cancer center should be considered in doubtful cases. CT-scan criteria appropriate to GISTs have been proposed to define disease control: size reduction (one-dimensional measurement) >10% and/or decrease in density after injection (in Hounsfield units) at least 15% [2].

Abdominal MRI is an alternative to scanner. FDG-PET showed high sensitivity in detecting early tumour response. Doppler ultrasound with contrast injection also allows early evaluation of the response by evaluation of intratumoural infusion of hepatic metastases. They still are little used in current practice. Tumour progression in case of metastatic disease treated with imatinib may be localized (to 1 or 2 metastases, or appearance of a nodule in a necrotic mass), or be multifocal.

Recommendations

- Clinical examination, biology every month for 3 months then every 3 months
- Abdominopelvic CT-scan every 3 months or abdominal MRI (expert agreement).

Options

- Echo-Doppler with contrast medium (pre-therapeutic and then D7 or D28, then every 3 months) (expert opinion)
- FDG PET (pre-therapeutic and then D7 or D28, then every 3 months) not recommended in current practice (expert opinion).

5. Treatment

A clinical network for sarcomas (NETSARC: https://netsarc.sarcomabcb.org) has been accredited by INCa (French National Cancer Institute). It includes 28 expert centers in the management of sarcomas, including GISTs and desmoid tumours distributed throughout the country. This network highly recommends to submit GIST' files to specialized multidisciplinary meetings in these centers.

5.1. Surgery

5.1.1. Guidelines

An elaborate report from French Association of Surgery (AFC) on GIST therapy is available [13]. Complete R0 monobloc resection of GISTs without rupture is the gold standard [1,2]. Large GISTs are often fragile and to avoid perforation (associated with high-risk of sarcomatosis) is crucial. Limited macroscopic margins are considered to be sufficient, as long as the resection is R0. Enucleation is not recommended for gastric or rectal GISTs, because this procedure is associated with more local recurrences [13]. Lymph-node dissection is usually not indicated (lymph node metastases risk: 1%) except in pediatric GISTs. If resection is macroscopically incomplete (R2), or in case of resection of peritoneal nodules, the spontaneous prognosis is poor. Individual basis discussion is needed if resection is R1, as re-intervention is not always a simple procedure and prognosis of R1 resection not clearly established.

5.1.2. Localized primary tumours

Recommendations (according to localization)

- Gastric: wedge resection is the procedure of choice. If not feasible, a segmental resection is adequate. A laparoscopic approach is standard, but is discouraged for large tumours with a high risk of intraoperative rupture [13]. Total gastrectomy is rarely necessary (cardial location or extension). The endoscopic resection for small-sized GISTs (<2–3 cm) is not yet a standard in Europe.
- Intestinal: segmental resection
- Duodenal: wedge resection or duodenopancreatectomy according to the location and extension [14].
- Colorectal: segmental resection. A local transanal excision may be discussed for small-sized [1].
- Oesophageal: enucleation can be an alternative to oesophageal resection if technically possible [15].
- Neoadjuvant therapy by imatinib is not indicated for resectable tumours [1,2]. However, it might be discussed when it could simplify the surgery or allow a less injuring resection (e.g. sphincter preservation for rectal GIST [16].

5.1.3. Locally advanced primary tumours

No randomized study is avalaible. Initial surgery is not recommended if R0 resection is not feasible. Bleeding or tumour rupture risks must also be evaluated. Neoadjuvant therapy by imatinib for cytoreduction might be considered. Maximal tumour response is usually reached after 6-12 months, and surgery can be performed in most cases [1]. This approach should be reserved to expert centers.

5.1.4. Metastatic tumours

First-line imatinib is the standard of care. Initial surgery is not recommended, but may be discussed secondarily.

Options

Primary tumour resection may be discussed if bleeding or rupture risks are considered as important. These risks for upfront imatinib therapy are limited [17–19]. Secondary resection of large nodules which has become necrotic with imatinib are preferable to emergency surgery for rupture (expert opinion) [1].

Complete resection of residual disease in patients responding to imatinib is an option [1,2,20]. Its impact on overall survival remains unknown, as 2 randomized trials were closed before completion [21]. Surgery (and/or radiofrequency) may also be considered for focal progression, but are not recommended for diffuse progression [1]. For all procedures, imatinib can be stopped the day before surgery, and must be reintroduced as soon as possible.

5.2. Chemotherapy, radiotherapy

Systemic chemotherapies are not effective in advanced GISTs. Data for radiotherapy are limited. It has been used occasionally for painful or bleeding tumours, or bone metastases. A short series (phase 2, 25 patients) suggests it may sometimes be useful to control abdominal or hepatic lesions evolving on TKIs [22].

5.3. Imatinib

Imatinib is the standard first-line therapy for advanced GISTs, and adjuvant therapy for high-risk GISTs.

5.3.1. Metastatic/locally advanced settings

The standard dose is 400 mg/d. The mutation type impacts the prognosis [1,2]. GISTs harboring *KIT* exon 11 mutation are the most sensitive. GISTs with *KIT* exon 9 mutations or no KIT/PDGFRA mutation experience less favorable PFS (progression-free survival) and OS (overall survival). A higher dosage (800 mg/d) is recommended for *KIT* exon 9 mutated GISTs, as a meta-analysis demonstrated a longer PFS (19 vs 6 months; $p = 0.017$) [1]. The OS was not significantly increased (35 vs 28 months; $p = 0.15$), but the population was limited and cross-over authorized [23]. GISTs with *PDGFRA* exon 18 D842 V mutations are usually resistant to imatinib [24].

Imatinib therapy is recommended until progression or intolerance. The BFR14 study randomized patients between continuation and interruption of imatinib after 1, 3 and 5 years in non-progressive metastatic patients. It has established that the standard of care is continuation of imatinib until disease progression. Even if most patients remained sensitive to imatinib after progression in the interruption arm, the PFS and depth of response were lower after reintroduction of imatinib in these patients [1].

Most patients experience side-effects, usually of mild intensity [1,2]. Oedema, fatigue and digestive disorders are the most frequent. Tolerance is dose-dependent. Compliance has to be regularly evaluated. Effective management of side-effect is the key factor for compliance to all ITKs. Dosage adaptations must be made in accordance to good clinical practice recommendations. They can be modulated according to plasmatic dosage of imatinib, as inter-individual variations are important [25].

Resistance to imatinib may be primary (before 6 months, 5–10%) or mostly secondary. In such cases, the compliance and drug-interactions must be evaluated. A plasmatic dosage of imatinib is also recommended (expert opinion) [26]. Inclusion in clinical trials should be prioritized at every stages. Progression on imatinib may be focal or multifocal. If resistance to imatinib is proven, ITK therapy must not be stopped for a long period (flare-up risk). A local therapy (surgery, radiofrequency ...) may be discussed for isolated or oligometastatic progression, associated with imatinib continuation (at the same or at an increased dosage according to tolerance, *KIT* exon 9 mutation or not and plasmatic dosage if available). Higher dosage of imatinib (800 mg/d, particularly for patients with low plasmatic imatinib level or *KIT* exon 9 mutation treated at 400 mg/d) or second-line sunitinib should be discussed for multifocal progression [1].

Imatinib rechallenge is a common practice in patients resistant to all available TKIs and not suitable for a clinical trial [1] as documented by a phase III study showing a benefit on median PFS (1.8 vs

0.9 months without therapy) and a disease control rate at 12 weeks of 32%.

5.3.2. Adjuvant setting

Three phase III randomized trials have tested adjuvant imatinib 400 mg/d for 1, 2 or 3 years. Designs of these 3 studies were different. All three demonstrated an improvement of RFS (recurrence-free survival) in comparison to placebo or follow up. Moreover, the study randomizing 3 vs 1 year of adjuvant imatinib for high-risk GISTs showed also an OS improvement.

The first US study compared imatinib therapy for 1 year versus placebo in R0 resected GISTs of more than 3 cm in diameter [27]. One-year RFS was of 97.7% in the imatinib group versus 82.3% in the placebo group ($p < 0.0001$), but OS was similar. Secondary analyses showed that: (1) very low and low-risk GISTs did not benefit from therapy; (2) RFS benefit was observed for *KIT* exon 11 mutation but not exon 9 mutation or *WT* GISTs (in particular neurofibromatosis) [28]; (3) *PDGFRA* mutations were at lower recurrence risk, and no benefit of adjuvant imatinib was observed for *PDGFRA* exon 18 D842V mutation.

The Scandinavian Sarcoma Group XVIII/AIO study compared imatinib 3 years versus 1 year in high-risk (NIH classification) or perforated GISTs [29]. With a median follow-up of 54 months, RFS was 66% in the 3-year group versus 48% in the 1-year group ($p < 0.0001$), and OS was 92% vs 82 % ($p = 0{,}02$). Longer RFS and higher OS at 5 years (93% vs 87; $p = 0.03$) in the 3 year- group persisted in actualized results with a median follow-up of 90 months [30]. A subgroup analysis confirmed that the benefit of adjuvant therapy was greater in *KIT* exon 11 mutated GISTs.

The EORTC study compared imatinib for 2 years versus follow-up in high or moderate risk resected GISTs [31]. The primary end point was imatinib failure–free survival (IFFS). Estimated 5-year IFFS was 87% in the imatinib arm versus 84% in the control arm ($p = 0.21$, and 5-year OS 100% versus 99%. This study confirmed that adjuvant imatinib has an impact on RFS, but also suggest a more suspensive than curative effect.

A non-randomized phase 2 trial (PERSIST-5) evaluated RFS for patients with moderate or high risk GISTs treated by adjuvant imatinib for 5 years [32]. About half of the patients completed 5 years of imatinib therapy. Estimated 5-year RFS was 90% and OS was 95%. No patient with imatinib-sensitive mutations had disease recurrence during therapy. Two randomized trials are ongoing in patients with high-risk GISTs, comparing imatinib 3 years vs 5or 6 years.

To sum up, adjuvant therapy is recommended for 3 years in high-risk GISTs. Genotyping is essential as it might impact the decisional process of adjuvant treatment [1]. Patients harboring *KIT* exon 11 mutation experience the greatest benefit, while patients with *PDGFRA* exon 18 D842V mutation (20% of gastric GISTs) no benefit. Impact of adjuvant therapy in case of *KIT* exon 9 mutations or no *KIT*/*PDGFRA* mutation remains poorly known. Several experts suggest in case of *KIT* exon 9 mutations a higher dose of imatinib as adjuvant therapy (800 mg/d), but this opinion is not shared by the French panel. A longer duration of treatment may be more efficient, and is currently tested in randomized trials. In case of rupture (very-high risk), ideal duration is not clearly defined and is at least 3 years (expert opinion). Patient's condition and opinion, and the tumour genotype, are important for the decision of adjuvant therapy in moderate-risk GISTs. Three-year imatinib treatment is an option, but moderate-risk GISTs showed similar outcome to low-risk GISTs in the EORTC adjuvant trial [31].

5.3.3. Neoadjuvant setting

No randomized phase III trial is available. The goals of neoadjuvant imatinib is either organ preservation or facilitate R0 resection. Imatinib is used at standard dosage for 6 to 12 months (option: 800 mg/d in case of *KIT* exon 9 mutation). Complete resection is possible in about 80 % of patients when treatment lasts more than 6 months. Surgery is performed when maximal response is attained (2 consecutive CT-scans not showing further regression) or if the surgeon deems a radical and/or organ-sparing resection possible [17].

5.4. Second-line therapy: sunitinib

Sunitinib is an oral multitarget TKI, with activity notably against KIT, PDGFRA, VEGFR. Its efficacy has been demonstrated in a multicenter phase III study in 312 patients with advanced GISTs with resistance or intolerance to imatinib [33,34]. TKIs after the first-line are more likely to stabilize the disease than induce radiological responses. The standard dosage is 50 mg/d 4 weeks out of 6. Continuous treatment at 37.5 mg/d had a similar efficacy in a phase II study in GISTs [35]. Compliance with treatment is essential, and schedule should be personalized (dosage, intermittent or continuous regimen) according to the tolerance. The early and effective management of side-effects is essential. Due to important inter-individual variations, plasmatic dosages of sunitinib may be an aid. Drug interactions (especially with proton pump inhibitors) should be considered.

5.5. Third-line therapy: regorafenib

Regorafenib is an oral multitarget TKI, approved in third-line. Its efficacy has been demonstrated in a multicenter, placebo-controlled phase III study in patients with advanced GISTs resistant or intolerant to imatinib and sunitinib [36]. The recommended dose is 160 mg/d 3 weeks out of 4. As for other TKIs, prevention, early and effective management of side-effects are essential for compliance and efficacy.

5.6. Other drugs

Promising new molecules are evaluated for resistant advanced GISTs in clinical trials. They are mainly multitarget TKIs with efficacy on so-called secondary *KIT* mutations (exon 13–14/17–18) (eg ponatinib, avapritinib, ipretinib ...). Some have potential efficacy on *PDGFRA* D842V mutation (avapritinib, crenolanib). VEGFR2 inhibitors (eg vandetanib, cabozantinib) and immunotherapy (pembrolizumab) are also undergoing evaluation.

Some TKIs showed some efficacy in phase II studies but were not further developed in advanced GISTs, eg sorafenib, pazopanib. Clinical trials of masitinib have been suspended. Nilotinib showed interesting activity, but development was stopped as no superiority over imatinib was observed in a phase III first-line study.

6. Therapeutic indications

All therapeutic decisions must be discussed during a multidisciplinary discussion group. An advice opinion from a regional referral center for the treatment of sarcomas and connective tumours (NETSARC network, https://netsarc.sarcomabcb.org) is recommended to favor inclusion in clinical trials, and should be systematic for atypical or difficult cases. Many recommendations for GIST management reflect expert opinions. Algorithms schematizing the main therapeutic indications appear in the appendices (Appendices C and D).

6.1. Resectable localized GIST, curative surgery (R0)

Recommendations

- Curative surgery (R0) (*recommendation level: grade A*).

- High-risk patients: imatinib 400 mg/d for 3 years (*recommendation level: grade A*) except for patients with PDGFRA D842 V or NF1 mutations (observation only)

Options

- Intermediate-risk patients: imatinib for 3 years or simple follow-up to discuss with the patient.
- Perforation of GIST: no expert agreement on imatinib duration (at least 3 years)
- Specific cases: small-sized GIST
  - o Gastric/<2 cm: follow-up or surgical resection. Follow-up: EUS at 6 and 18 months, then every 2 years
  - o Gastric/>2 cm, or extragastric (any size): surgical resection

Clinical trials

- ImadGIST: efficiency of imatinib treatment maintenance or interruption after 3 years of adjuvant treatment in patients with GIST (NCT02260505)
- GI-GIST: efficacy of imatinib in patients with intermediate-risk gastrointestinal stromal tumour with a high-risk genomic grade index (NCT02576080)

6.2. Resectable localized GIST, R1 or R2 resection

Options (expert opinions)

- Reoperation should be discussed as an individual procedure, especially after R2 surgery, according to the global prognosis. The importance of surgery and evaluation of risks have to be evaluated. In case of very high-risk tumour (perforation, serosa invaded) the prognosis is more related to metastatic recurrence.
- In case of R2 resection and with reoperation not possible, imatinib and subsequent surgery reevaluation (long term imatinib if not possible)
- R1 resection: imatinib for 3 years for high/intermediate risk tumours

6.3. Inherited resectable GISTs

- Type 1 neurofibromatosis: GISTs usually multiple, mainly in the small intestine. Adjuvant imatinib not indicated [1].
- Carney–Stratakis syndrome or SDHB loss of expression (epithelioid gastric GISTs, age < 30): lymph-node metastases are reported, a lymph-node dissection should be discussed.
- Heritable KIT exon 13 mutation: long-term imatinib may be proposed in case of symptomatic, or fastly growing, or >3 cm GISTs [5].

6.4. Doubtful resectable GIST or maiming-risk surgery (eg oesophagus/rectum)

Options

- Discussion of neoadjuvant imatinib therapy
- Secondary resection in a specialized center after 6–12 months of treatment
- Adjuvant imatinib (3 years in total)

Clinical trials

- Not available

6.5. Non resectable localized GIST

Recommendations

- Imatinib 400 mg/d (*recommendation level: grade A*).
- Secondary resection in a specialized center after 6–12 months of treatment to discuss

Options

- Imatinib 800 mg/d if KIT exon9 mutation

Clinical trials

- Not available

6.6. Metastatic GIST

Recommendations

- Imatinib 400 mg/d (*recommendation level: grade A*).
- Surgery of primitive tumour in selected cases (high complication risks and limited operation)
- Imatinib 800 mg/d if KIT exon9 mutation

Options (expert opinion)

- Disease control by imatinib and R0 resection possible: surgery and/or radiofrequency plus imatinib continuation.
- Resection of high-risk of rupture necrotic metastases
- Specific case 1. Initial resection of a limited metastatic extension with the primitive tumour: adjuvant imatinib for at least 3 years, except in case of *PDGFRA* D842V mutation
- Specific case 2. *WT* GIST slowly evolving: resection or destruction of metastases
- Plasmatic dosage of imatinib

Clinical trials

- ALT GIST: a randomised trial of imatinib alternating with regorafenib compared to imatinib alone for the first line treatment of advanced gastrointestinal stromal tumour (NCT02365441)

6.7. Progression on imatinib 400 mg/d

Recommendations

- Adress patient to a tertiary care center
- No sudden stop of imatinib
- Check radiological progression
- Check compliance
- Check drug interactions
- Increase imatinib dose to 800 mg/d (especially if treatment underdosed or KIT exon 9 mutation) or change for sunitinib (50 mg/d, 4/6 weeks) (*recommendation level: grade A*).

Options

- Resection or transparietal destruction of metastatis in focal progression, and increase of imatinib dose
- Sunitinib 37,5 mg/d
- Imatinib plasmatic dosage

Clinical trials

- NAVIGATOR: study of BLU-285 (avapritinib) in patients with GIST (NCT02508532)
- INTRIGUE: phase III. ipretinib versus sunitinib in second line (NCT03673501)
- CABOGIST: phase II. cabozantinib in GIST (NCT02216578)
- CRENOGIST: phase III. crenolanib versus best supportive care for D842V mutant GISTs (NCT02847429)

6.8. *Progression after imatinib/sunitinib*

Recommendations

- Regorafenib 160 mg/d, 3/4 weeks (*recommendation level: grade A*).
- Information, prevention, and adaptation of therapy to tolerance. Compliance checking

Options

- No

Clinical trials

- VOYAGER: phase III. study of avapritinib vs regorafenib in patients with locally advanced unresectable or metastatic GIST (NCT03465722)

6.9. *Treatment after 3rd line*

Recommendations

- No standard
- Inclusion in a clinical trial

Options

- Patients not suitable for a clinical trial: reintroduction of imatinib, or another TKI previously tested in phase II in GISTs (no marketing authorization, under physician responsibility, patient information and consent needed).

Clinical trials

- INVICTUS: phase 3 study of DCC-2618 (ipretinib) vs placebo in advanced GIST patients who have been treated with prior anticancer therapies (NCT03353753) (study completed)

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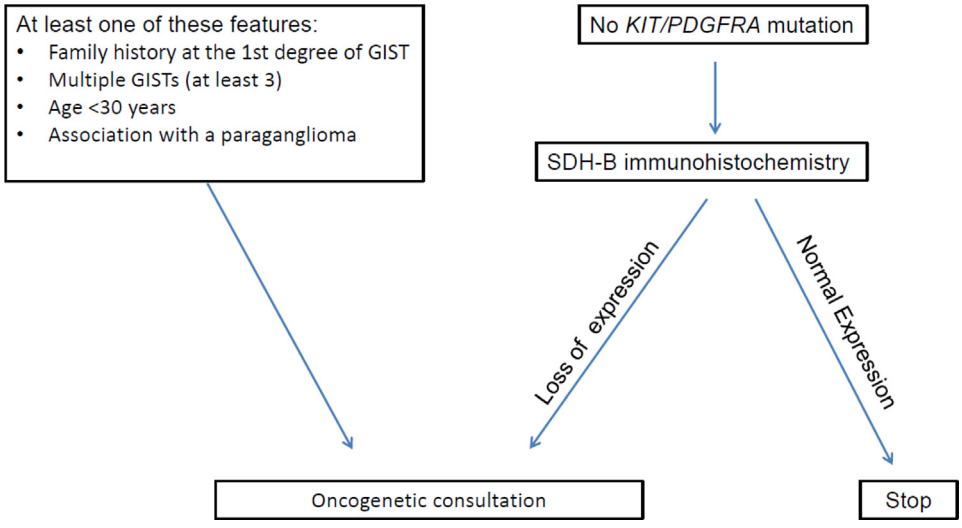
Appendix A. Indications of oncogenetic consultation and constitutional genetic analysis algorithm according to SDH immunohistochemistry



Appendix B1. Estimation of the risk of disease-related recurrence or death in localized GISTs resected in groups defined by size, mitotic index, and tumour site (AFIP: Armed Forces Institute of Pathology). (according to Miettinen and Lasota [9])

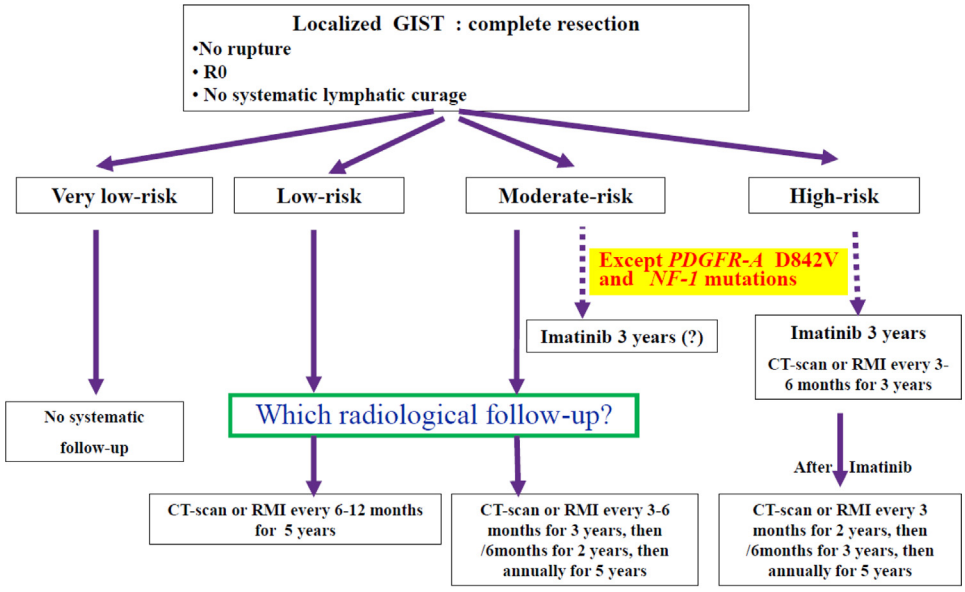
Tumour maximal diameter (cm)	Mitotic Index**	Gastric GIST	Jejunoilea GIST	Duodenal GIST	Rectal GIST
≤2	≤5	0	0	0	0
>2–5	≤5	1,9 % (very low)	4,3 % (low)	8,3 % (low)	8,5 % (low)
>5–10	≤5	3,6 % (low)	24 % (moderate)	–*	–*
>10	≤5	12 % (moderate)	52 % (high)	34 % (high)	57 % (high)
≤2	>5	0	50 % (high)	–*	54 % (high)
>2–5	>5	16 % (moderate)	73 % (high)	50 % (high)	52 % (high)
>5–10	>5	55 % (high)	85 % (élevé)	–*	–*
>10	>5	86 % (high)	90 % (high)	86% (high)	71 % (high)

*Insufficient number of patients for estimation.
**Mitotic count is determined by Miettinen on a 5 mm^2 surface, not on 50 HPF (5 mm^2 correspond to 20–25 HPF on modern microscopes).

Appendix B2. Estimation of the risk of recurrence for localized GIST resected in the modified NIH classification. It aims to better split moderate and high risk GISTs, and incorporates the pejorative nature of perforation [10]

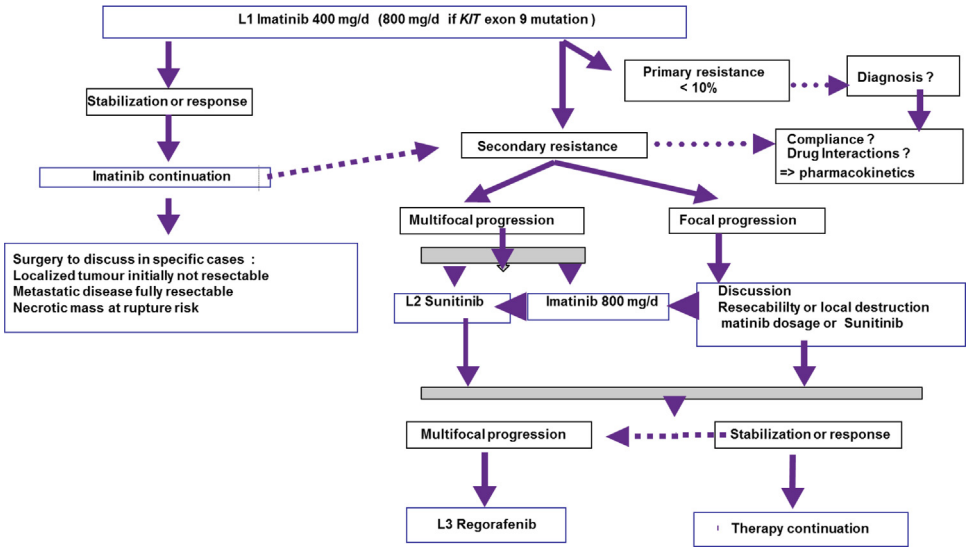
Recurrence risk	Diameter	Mitotic index	Localization
Very low	≤2 cm	≤5	Any
Low	>2–5 cm	≤5	Any
Moderate	≤5 cm	6 10	Gastric
	>5–10 cm	≤5	Gastric
High	Any	Any	Tumour perforation
	>10 cm	Any	Any
	Any	>10	Any
	>5 cm	>5	Any
	≤5 cm	>5	Extra-gastric
	>5–10 cm	≤5	Extra-gastric

Appendix C. Localized GISTs: management and monitoring algorithm



Radiologic procedures : Abdominopelvic CT-scan or RMI ; High-risk or rectal GIST : chest CT-scan at least 1/year

Appendix D. Metastatic or locally advanced GISTs: management algorithm



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