Gastrointestinal stromal tumors (GIST)

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GISTs are rare mesenchymatous tumors that develop in most cases in the stomach and small intestine, more rarely the rectum, colon, esophagus, or mesentery. They are defined by their expression of c-kit protein, a transmembrane receptor spontaneously activated after somatic mutation of the Kit gene.

Pretherapy workup

Assessment of extension

Abdominopelvic three-dimensional spiral CT with a thoracic passage

Options:
- Abdominal ultrasound
- Echoendoscopy (generally done at the diagnostic stage in small GISTs of the upper digestive tract or rectum)
- MRI (particularly in cases of rectal GIST)
- PET scan (scintigraphy with FDG-glucose) if there is doubt on metastatic lesion in TDM and/or MRI

Biopsies [1, 2]

Endoscopic biopsies are generally negative. There is no consensus on whether preoperative diagnosis using needle biopsy is necessary (echoendoscopic, percutaneous, or operative). There is a risk of hemorrhage and perhaps of peritoneal seeding when done percutaneously or by celioscope.

Recommendations outside of trials:

If the tumor seems resectable and the patient is operable, a preoperative needle biopsy is not recommended, but should be discussed in multi disciplinary consultation. It is recommended if the treatment choice is based on an uncertain histological diagnosis, particularly when first-line medical treatment is discussed:
- diagnostic doubt with another tumor requiring first-line chemotherapy, for example lymphoma, sarcoma, peripheral neuroectodermal tumor (PNET), seminoma, nonseminomatous germinal tumor, etc.
- location or extension raising the consideration of initial treatment with imatinib
- nonresectable, locally advanced, and/or metastatic lesion

Which approach should be used for needle biopsy?

If the lesion is not resectable because of local-regional invasion or distant metastases, the most easily accessible biopsy is performed: fine-needle liver biopsy with radiological guidance (ultrasound or CT) in cases of liver metastasis or biopsy of the primary tumor guided by echoendoscopy or radiology. Echoendoscopy-guided needle biopsy, when possible, can be preferred to the transperitoneal approach in nonmetastatic GISTs.

Familial syndromes

- Familial forms of multiple stomal tumors (exceptional)
- Carney’s triad (very rare): multiple gastric stromal tumors, pulmonary chondrome and extra-suprarenal paraganglioma.
- Type 1 neurofibromatosis.

In these cases, oncogenetic counseling is recommended after patient information and consent.

Operability workup

Oriented by antecedents, clinical examination, and anesthesia consultation

Histological analysis [1, 4]

GIST is diagnosed based on a standard histological test, read in consultation with an expert in delicate cases. Immunohistochemistry is necessary at diagnosis. The indispensable marker is KIT (CD117), with positive results in 95% of GISTs. KIT expression is not specific of GISTs, other digestive tract tumors can also be positive. Other markers are recommended to back up the diagnosis in case of negative results (CD34, desmin, h-caldesmon, protein S100).

To formally confirm KIT-negative GIST diagnosis, KIT and PDGFRA gene mutation should be sought. Outside of KIT-negative GISTs, the search for KIT and PDGFRA gene mutations using a molecular biology technique remains a research procedure in therapeutic projects or trials.
Other digestive tract or intra-abdominal, connective, melanocyte, or endocrine tumors can simulate a GIST. The most frequently confused with a GIST are smooth muscle tumors and fibromatoses.

**Monitoring**

**After resection of curative intent**

GISTs are tumors that probably all have a certain potential for malignancy [4]. For localized tumors, a histological prognosis classified based on the size of the tumor and the mitotic index was established during an earlier consensus meeting, even though it was not validated prospectively (Table below) [4]. The number of mitoses was evaluated on 50 fields at objective 40. Other topographic, histological, immunohistochemical, and molecular parameters are being evaluated.

<table>
<thead>
<tr>
<th>Risk of progression</th>
<th>Maximal diameter</th>
<th>Mitotic index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2 cm</td>
<td>&lt;5/50 HPF</td>
</tr>
<tr>
<td>Low risk</td>
<td>2–5 cm</td>
<td>&lt;5/50 HPF</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>&lt;5 cm</td>
<td>6–10/50 HPF</td>
</tr>
<tr>
<td></td>
<td>5–10 cm</td>
<td>&lt;5/50 HPF</td>
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<tr>
<td>High risk</td>
<td>&gt;5 cm</td>
<td>&gt;5/50 HPF</td>
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<tr>
<td></td>
<td>&gt;10 cm</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>&gt;10/50 HPF</td>
</tr>
</tbody>
</table>

HPF: high-power field

If approximately two-thirds of recurrences occur within 2 years, very late-onset recurrences are possible. There are no data in the literature that confirm that a precise monitoring protocol provides a benefit in terms of prognosis. The monitoring protocols proposed correspond to expert opinion, with optimal modalities still to be defined.

**Recommendation outside of trials (expert agreement)**

- **Modalities:** Clinical examination and abdominopelvic spiral CT
- **Option:** Abdominal ultrasound

- **High-risk tumors:** Clinical examination and abdominopelvic spiral CT every 3 months for 2 years, then every 6 months to 5 years, then annually.
- **Intermediate-risk tumors:** Clinical examination and abdominopelvic spiral CT at 3 months, then every 6 months to 5 years, then annually.
- **Low-risk tumors:** Clinical examination and abdominopelvic spiral CT at 6 months, then annually to 5 years.
- **Very-low-risk tumors:** No systematic monitoring.

**Criteria for imaging evaluation and monitoring during imatinib treatment [1, 5, 6, 7]**

Tomodensitometry with contrast injection is currently the most commonly used imaging technique in evaluating tumor response. However, it has been shown that the WHO and RECIST tumor response criteria are not clearly adapted to evaluating tumor response in GISTs treated with imatinib. When there is a response, the mass becomes hypodense and the part taking up the contrast product as well as tumor vascularization diminish in a few weeks. These changes are not always associated with reduction in tumor size (which in certain cases can increase initially). Measuring tumor density in Hounsfield units is necessary. An increase in tumor size can reflect treatment efficacy; consequently an imaging review in a specialized oncology center should be planned before stopping this treatment.

FDG PET has shown high sensitivity in detecting early tumor response. PET is, however, costly and often unavailable.

As with PET, echo-Doppler with contrast injection may provide early detection of tumor response by evaluating intratumoral perfusion.

**Symptom improvement, tomodensitometry response (size and density), PET (SUVmax or visual assessment), and echo-Doppler (dB), are all predictive of tumor control with imatinib.**

**Recommendation outside of trial:**

- **Clinical examination, hemogram, and liver tests every month**
- **Abdominopelvic spiral CT with measurement of pretherapeutic density every 3 months**

**Options:**

- **Echo-Doppler with contrast injection (before therapy, then from D7 or D28, then every 3 months)**
- **FDG PET (before therapy, then from D7 or D28, then every 3 months)**

**Treatment**

**Surgical treatment [1, 5, 8]**

**Surgical principles**

- **Complete enbloc surgical resection** of the tumor (R0 resection) is the only treatment with curative potential for digestive tract stromal tumors.

**In cases of incomplete excision** (even if the prognosis associated with R1 resection remains the subject of discussion) or associated peritoneal metastatic nodule excision, the spontaneous prognosis is poor. There is no consensus on optimal resection margins.

- **A margin** of 1–2 cm is considered sufficient.

- **It is essential to avoid intraoperative perforation**, which can lead to peritoneal spread.

- **Lymph node removal** is not systematic, because lymph node metastases are rare and the risk of lymph node recurrence is limited.

**Nonmetastatic tumors**

**Localized tumors**

Surgery depends on the seat of the tumor.

**For a gastric tumor** with antrum or fundus seat, a wedge resection or segment resection is indicated, with a safety margin. Resection with celioscope is an option that remains to be validated if tumor breakage is not risked. It should be reserved for small tumors whose serous membrane has not been invaded. Tumors with a pericardial or pyloric antrum seat require noneemergency gastrectomy. With large tumors, total gastrectomy can be required because of anatomical restrictions.

**For small intestine tumors**, segment resection of the small intestine is indicated.

French Guidelines for Digestive cancers. Gastrointestinal stromal tumors (GIST)
For rectal and colon tumors, nonemergency resection is necessary.
For esophagus tumors, contrary to leiomyomas, GISTs cannot be excised by enucleation guided by thoracoscopy. Esophagectomy should be discussed.

Locally advanced tumors
Locally advanced tumors often correspond to tumors that are larger than 10 cm in diameter, which are extended to other adjacent organs in more than half the cases.
Wide excision, sometimes mutilating, is only acceptable if excision is complete. This aggressive attitude should be adapted to the organs involved and the patient's condition. The alternative of neoadjuvant treatment is being evaluated. It could limit the initial surgery and secondarily increase the chances of complete resection. However, the risk of sometimes fatal complications in terms of the primary tumor (hemorrhage, perforation, tumor rupture) with imatinib remain to be detailed.

Metastatic tumors
Metastases are for the most part intra-abdominal, peritoneal, and hepatic. Imatinib is now the reference treatment for these patients. Primary tumor excision is indicated when clinical signs show serious disease (occlusion, hemorrhage) and is desirable (depending on the patient's condition and the scope of the surgery) before treatment so as to avoid onset of local complication. The advantage of residual metastasis excision or destruction by radiofrequency has not been clearly established and should be discussed on a case by case basis.

Chemotherapy, radiotherapy. [5, 9]

Treatment of advanced forms or metastases
The efficacy of systemic chemotherapy in stromal tumors is very low, with a response rate of 0%-10%. Radiotherapy has only been used punctually to treat symptoms in cases of fixed tumors, responsible for pain or hemorrhage. The limited data available suggest that radiotherapy is not very effective for palliative treatment. Radiotherapy to treat symptoms can be indicated in rare cases.

Adjuvant treatment
Adjuvant radiotherapy has only been used in small series of patients who had poor prognostic factors (local invasion, invaded margins, tumor rupture), without any advantage demonstrated. Nothing has come out in favor of adjuvant chemotheraphy other than those used in general studies on sarcomas.

Imatinib (Glivec®) [1, 5, 9, 10-14]
The efficacy of imatinib (a tyrosine-kinase inhibitory drug, including KIT and PDGFRA) in locally advanced or metastatic stromal tumors is now well established. However, its benefit in adjuvant or neoadjuvant treatment before surgery is being evaluated. Optimal administration modalities have not been definitively established, and practices may evolve rapidly (optimal dose, treatment duration, etc.). The recommended dose is currently one 400-mg tablet per day taken during a meal. It is recommended that the treatment continue until progression (see above), intolerance, or patient refusal. The dose should not be lowered if there is no major toxicity.
Side effects occur in the majority of patients, but are most often moderately intense and regress during treatment [51, 55]. Imatinib tolerance is dose-dependent. The three most frequent side effects are edema, asthenia, and digestive problems. Treatment compliance should be monitored by the physician.

Treatment resistance can be primary (in the first 6 months) (<10%) or secondary. In the latter case, partial resistance (progression in a limited number of metastatic lesions) can be distinguished from multifocal resistance, which occur with a similar frequency. It should be known that stopping imatinib may be associated with a tumor flare-up even in patients in progression. If the patient cannot be included in a clinical trial with a new drug, continuing imatinib and even increasing doses is often proposed. An opinion from a regional oncology pole (Measure 30 of the Cancer plan) is recommended.

Recommendations
All therapeutic decisions concerning a GIST should be made in multidisciplinary consultation. An opinion from a regional oncology pole is recommended in any atypical case or case requiring delicate management, or any case that may be included in a therapeutic trial.

1- Resectable nonmetastatic GIST, resection R0
Trials
EORTC 62024 adjuvant trial: surgery followed by imatinib 2 years versus surgery alone (high risk or intermediate risk)
Recommendation without trial
Surgery alone

2- Resectable nonmetastatic GIST, resection R1 or R2
Trials
EORTC 62024 adjuvant trial: surgery followed by imatinib 2 years versus surgery alone (R1 high risk or intermediate risk)
BFR14 trial (for R2): if response or stability after 3 years of imatinib, cessation versus continuing imatinib
Recommendations without trial
• Discuss reoperation
• If impossible, discuss treatment with imatinib.

3- GIST of uncertain resectability or mutilating surgery (esophagus or rectum)
Trial
BFR14 trial if tumor could not be resected: if response or stability after 3 years of imatinib, cessation versus continuation of imatinib
Recommendations without trial
• Discuss neoadjuvant treatment with imatinib 400 mg/day
• Secondary surgical resection to be discussed at the maximum of objective response after 6–12 months of imatinib in a specialized center

4- Nonresectable, nonmetastatic GIST
Trial
Trial (for R2): if response or stability after 3 years of imatinib, cessation versus continuation of imatinib
Recommendations without trial
• Treatment with imatinib 400 mg/day
• Secondary surgical resection to be discussed at the maximum of objective response after 6–12 months of imatinib in a specialized center

5- Metastatic GIST

Trials
BFR14 trial: if response or stability after 3 years of imatinib, cessation versus continuation of imatinib
AB1010 phase II trial: first-line (trial with few centers)
FNCLCC-FFCD trial project: resection versus no resection of metastases

Recommendations without trial
• Primary tumor excision should be discussed if there is a risk of complication
• Treatment with imatinib 400 mg/day

6- Progression with imatinib

Recommendations
Opinion from regional multidisciplinary consultation (increasing doses of imatinib, sumatinib, second line trials...)

REFERENCES