Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO / European Sarcoma Network Working Group*

incidence

Gastrointestinal stromal tumors (GISTs) are rare tumors, with an estimated incidence of 1.5/100 000/year (unadjusted data) [1]. This only covers the clinically relevant GISTs, since likely a much higher number of microscopic lesions could be found pathologically, if looked for.

The median age is around 60–65 years, with a wide range. Occurrence in children is very rare, although pediatric GISTs represent a distinct subset, marked by female predominance, absence of KIT/platelet-derived growth factor alfa (PDGFRA) mutations, gastric multicentric location, and possible lymph node metastases [2].

Several syndromes are linked to GISTs:
(i) Carney triad syndrome: marked by gastric GISTs, paraganglioma, pulmonary chondromas, which may occur at different ages, making it difficult to rule out this condition in wild-type pediatric GISTs [3].
(ii) Type-1 neurofibromatosis: marked by generally wild-type GISTs, predominantly located at the small bowel and possibly multicentric [4].
(iii) Carney-Stratakis syndrome: marked by germ-line mutations of succinate dehydrogenase subunit B (SDHB), SDH subunit C (SDHC) and SDH subunit D (SDHD), leading to a dyad of GIST and paraganglioma [5, 6].

Families with germ-line autosomal dominant mutations of KIT or PDGFRA have been described, presenting with multiple GIST at an early age.

diagnosis

When small oesophago-gastric or duodenal nodules <2 cm in size are detected, endoscopic biopsy may be difficult and laparoscopic/laparotomic excision may be the only way to make a histological diagnosis. Many of these small nodules, if diagnosed as GISTs, will be low risk, or entities whose clinical significance remains unclear. Therefore, the standard approach to these patients is endoscopic ultrasound assessment and then annual follow-up, reserving excision for patients whose tumor increases in size or becomes symptomatic. Alternatively, the decision can be shared with the patient to make a histological assessment, also depending on age, life expectancy and comorbidities. If follow-up is the choice, an evidence-based optimal surveillance policy is lacking. A logical choice may be to have a short-term first control (e.g. at 3 months), and then, in case of no evidence of growth, a more relaxed follow-up schedule may be selected.

In a histologically proven small GIST, the standard treatment is excision, unless major morbidity is expected. Alternatively, in case of a low-risk GIST, the decision can be shared with the patient to follow-up the lesion. However, the standard approach to rectal (or recto-vaginal space) nodules is biopsy/excision after ultrasound assessment, regardless of the tumor size, because the risk of a GIST at this site is higher and the local implications for surgery are more critical. A follow-up policy may be an option, to be shared with the patient, in the case of small lesions and in specific clinical contexts.

The standard approach to nodules ≥2 cm in size is biopsy/excision because, if they are GISTs, they are associated with a higher risk. If there is an abdominal node not amenable to endoscopic assessment, laparoscopic/laparotomic excision is the standard approach. If there is a mass, especially if surgery is likely to be a multivisceral resection, multiple core needle biopsies are the standard approach. They should be obtained through endoscopic ultrasound guidance, or through an ultrasound/computed tomography (CT)-guided percutaneous approach. This may let the surgeon plan the best approach according to the histological diagnosis and may avoid surgery for diseases that do not merit it (e.g. lymphomas, mesenteric fibromatoses, germ cell tumors). The risk of peritoneal contamination is negligible if the procedure is properly carried out. Moreover, lesions at risk in this regard (e.g. cystic masses) should be biopsied only in specialized centers. Immediate laparoscopic/laparotomic excision is an alternative on an individualized basis, especially if surgery is limited. If a patient presents with obvious metastatic disease, then a biopsy of the metastatic focus is sufficient and the patient usually does not require a
Pathologically, the diagnosis of GIST relies on the morphology and the immunohistochemistry (CD117 and/or DOG1) [7, 8]. A proportion of GISTs (in the 5% range) are CD117-negative. The mitotic count has prognostic value and should be expressed as the number of mitoses on a total area of 5 mm², which conceptually is equivalent to 50 high-power fields. Mutational analysis for known mutations involving KIT and PDGFRA genes can confirm the diagnosis of GIST, if doubtful (particularly in CD117/DOG1-negative suspect GIST). Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy and prognostic value, so that its inclusion in the diagnostic work-up of all GISTs should be considered standard practice (with the possible exclusion of <2 cm non-rectal GISTs, which are very unlikely to be due for medical treatment). Centralization of mutational analysis in a laboratory (possibly enrolled in an external quality assurance program and with expertise in the disease) may be useful.

An expert pathological second opinion is recommended in all cases when the original diagnosis is made outside a reference center.

Collection of fresh/frozen tissue is encouraged, because new molecular pathology assessments could be made at a later stage in the patient’s interest. Informed consent for tumor banking should be sought, enabling later analyses and research, as long as this is allowed by local and international guidelines.

stage classification and risk assessment

The TNM classification has several limitations and is therefore not recommended.

Prognostic factors are the mitotic rate, tumor size and tumor site (gastric GISTs have a better prognosis than small bowel or rectal GISTs). Surgical margins and tumor rupture are additional factors affecting prognosis. Therefore, tumor rupture, whether before or during surgery, should be recorded, because it represents a highly adverse prognostic factor.

A widely used risk classification is the Armed Forces Institute of Pathology, which incorporates the primary tumor site, mitotic count and tumor size, which are the three main prognostic factors in localized GISTs [9, 10]. The risk estimate for subgroups is based on limited data, but this classification better distinguishes across different risk levels in comparison with the 2002 National Institutes of Health (NIH) Consensus criteria. This was correlated with the prognosis in an epidemiological study, showing that the ‘high-risk’ category has a much worse prognosis than the others. ‘Very low-risk’ and ‘low-risk’ categories have a very favorable prognosis. In most of the population-based series, the ‘intermediate-risk’ category of the NIH Consensus classification did not discriminate patients with an unfavorable prognosis. A nomogram utilizing all the three criteria has been developed on another series [11]. When using these tools, it is important to appreciate that the mitotic index and tumor size are non-linear continuous variables, so that thresholds should be interpreted wisely (Table 1).

Tumor rupture is a highly unfavorable prognostic factor, so that its occurrence tends to offset the conventional prognostic factors.

Considering all this, novel prognostic heat and contour maps were generated through a pool of several series of GIST patients not treated with adjuvant therapy [12]. They incorporate the mitotic index and tumor size as continuous non-linear variables, while tumor rupture is considered in addition to tumor site. They have been validated against a reference series.

Mutational status has not been incorporated in any risk classification, so far, although some genotypes have a distinct natural history.

staging procedures

Staging procedures take into account the fact that most relapses affect the peritoneum and the liver. Contrast-enhanced

<table>
<thead>
<tr>
<th>Group</th>
<th>Tumor parameters</th>
<th>Mitotic rate</th>
<th>Gastric GISTs</th>
<th>Jejunal and ileal GISTs</th>
<th>Duodenal GISTs</th>
<th>Rectal GISTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤2 cm</td>
<td>≤5 per 50 HPFs</td>
<td>0 none</td>
<td>0 none</td>
<td>0 none</td>
<td>0 none</td>
</tr>
<tr>
<td>2</td>
<td>&gt;2 ≤5 cm</td>
<td>≤5 per 50 HPFs</td>
<td>1.9 very low</td>
<td>4.3 low</td>
<td>8.3% low</td>
<td>8.5% low</td>
</tr>
<tr>
<td>3a</td>
<td>&gt;5 ≤10 cm</td>
<td>≤5 per 50 HPFs</td>
<td>3.6 low</td>
<td>24 moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>&gt;10 cm</td>
<td>≤5 per 50 HPFs</td>
<td>12 moderate</td>
<td>52 high</td>
<td>34 high^b</td>
<td>57^ high^b</td>
</tr>
<tr>
<td>4</td>
<td>≤2 cm</td>
<td>&gt;5 per 50 HPFs</td>
<td>0^c</td>
<td>50^c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&gt;2 ≤5 cm</td>
<td>&gt;5 per 50 HPFs</td>
<td>16 moderate</td>
<td>73 high</td>
<td>50 high</td>
<td>52 high</td>
</tr>
<tr>
<td>6a</td>
<td>&gt;5 ≤10 cm</td>
<td>&gt;5 per 50 HPFs</td>
<td>55 high</td>
<td>85 high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6b</td>
<td>&gt;10 cm</td>
<td>&gt;5 per 50 HPFs</td>
<td>86 high</td>
<td>90 high</td>
<td>86 high^b</td>
<td>71 high^b</td>
</tr>
</tbody>
</table>

^aBased on previously published long-term follow-up studies on 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GISTs [12, 15, 18, 30].

^bGroups 3a and 3b or 6a and 6b are combined in duodenal and rectal GISTs because of the small number of cases.

^cDenotes the tumor categories with very small numbers of cases.

^dNo tumors of such category were included in the study. Note that small intestinal and other intestinal GISTs show a markedly worse prognosis in many mitotic rate and size categories than gastric GISTs.

GIST: Gastrointestinal stromal tumor; HPF: high-power field.
abdominal and pelvic CT scan is the investigation of choice for staging and follow-up. Magnetic resonance imaging (MRI) or contrast-enhanced ultrasound may be alternatives. For rectal GISTs, MRI provides better preoperative staging information. Chest CT scan or X-rays and routine laboratory testing complement the staging work-up of the asymptomatic patient. Evaluation of FDG uptake using an FDG-positron emission tomography (PET) scan, or FDG-PET–CT/MRI, is useful mainly when early detection of the tumor response to molecular targeted therapy is of special concern.

**treatment**

Multidisciplinary treatment planning is needed (involving pathologists, radiologists, surgeons and medical oncologists), such as that which is available in reference centers for sarcomas and GISTs, and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually.

**localized disease**

The standard treatment of localized GISTs is complete surgical excision, without the dissection of clinically negative lymph nodes [I, A]. If laparoscopic excision is planned, the technique needs to follow the principles of oncologic surgery [13] [I, A]. A laparoscopic approach is clearly discouraged in patients who have large tumors, because of the risk of tumor rupture, which is associated with a very high risk of relapse. R0 excision is the goal (excision margin without tumor cells).

When R0 surgery implies major functional sequelae, and preoperative medical treatment has not helped or cannot be given, the decision can be made and shared with the patient to accept R1 margins (excision margin containing tumor cells) [IV, B]. This is particularly true for low-risk lesions, in the lack of a formal demonstration that R1 surgery is associated with a worse overall survival (OS).

If R1 excision was carried out, re-excision may be an option, provided the original site of lesion can be found, and major functional sequelae are not foreseen.

The risk of relapse can be substantial, as defined by available risk classifications. Adjuvant treatment with imatinib for 3 years was associated with a relapse-free survival and OS advantage in a randomized trial in comparison with 1 year of therapy in high-risk patients [14]. Previously, a placebo-controlled trial demonstrated that imatinib doses for a planned duration of one year is able to prolong relapse-free survival in >3 cm localized GISTs with a macroscopically complete resection [15]. Therefore, adjuvant therapy with imatinib for 3 years is standard treatment of patients with a high risk of relapse [I, A]. Adjuvant therapy should not be considered when the risk is low. There is room for shared decision-making when the risk is intermediate [16].

Mutational analysis is critical to making a clinical decision about adjuvant therapy. In fact, there is consensus that PDGFRA D842V-mutated GISTs should not be treated with any adjuvant therapy, given the lack of sensitivity of this genotype both in vitro and in vivo [IV, A]. Given the data supporting the use of a higher dose of imatinib (800 mg daily) in the case of an exon 9 KIT mutation in advanced GIST, many clinicians prefer to use this dose even in the adjuvant setting for this genotype [17–19]. Regulatory problems may limit this practice, which is not backed by any controlled trial in the adjuvant setting. There is no consensus about whether wild-type GISTs should be treated with adjuvant therapy. This reflects their lower sensitivity to imatinib, as well as their peculiar natural history, which is often more indolent, especially in the case of syndromic GIST. Subgroup analyses of the available randomized trials are too limited to provide sufficient evidence on this. European and international cooperation is vital to determine best practices in the exceedingly rare pediatric GIST.

In case of tumor rupture at the time of surgery, there is spillage of tumor cells into the peritoneal cavity, and therefore, occult peritoneal disease can be assumed. This puts the patient at a very high risk of peritoneal relapse. Therefore, these patients should be considered for imatinib therapy. The optimal duration of treatment in these cases is unknown, given the uncertainty as to whether they should be viewed as virtually metastatic.

If R0 surgery is not feasible, or it could be achieved through less mutilating/function sparing surgery in the case of cytoreduction (this includes total gastrectomy and all other major procedures), imatinib pre-treatment is recommended [20, 21] [IV, A]. This may also be the case if the surgeon believes that the surgical conduct is safer after cytoreduction (e.g. the risk of bleeding and tumor rupture is decreased). Following maximal tumor response, generally after 6–12 months, surgery is performed. Mutational analysis is crucial because it helps to exclude less sensitive or resistant genotypes (e.g. PDGFRA D842V mutations) from therapy with imatinib and allows the use of the appropriate dose for KIT exon 9 mutations. Early tumor response assessment is mandatory, so that surgery is not delayed in the case of non-responding disease. Particularly in the lack of a mutational analysis, functional imaging makes it possible to assess the tumor response very rapidly, within a few weeks. There are limited data to guide the physician on when to stop imatinib before surgery; however, it can be safely stopped 2–3 days before surgery and it can be resumed promptly when the patient recovers from surgery.

**metastatic disease**

In locally advanced inoperable patients and metastatic patients, imatinib is the standard treatment [22–26] [III, A]. This applies also to metastatic patients who have been completely relieved of all lesions surgically, though surgery as a primary approach to metastatic GIST is not recommended. The standard dose of imatinib is 400 mg daily [I, A]. However, data have shown that patients with KIT exon 9 mutations fare better in terms of progression-free survival (PFS) on a higher dose level, i.e. 800 mg daily, which is therefore the standard treatment in this subgroup [27] [III, A].

Treatment should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumor progression in almost all cases, even when lesions have been previously surgically excised [28] [II, B].
When treatment is started, the patient should be alerted to the importance of compliance with therapy, as well as of interactions with concomitant medications and foods, and proper handling of side effects. Dose intensity should be maintained by proper management of side effects, and a correct policy of dose reductions and interruptions should be applied in the case of excessive, persistent toxicity.

Close monitoring of the tumor response should be carried out in the early phases of treatment. Follow-up should be continued throughout the treatment, since the risk of secondary progression persists over time. However, in the case of tumor response, monitoring may be relaxed with time (e.g. from 3 to 6 months), especially after 5 years of persisting response, because there are preliminary data that suggest a decrease in the risk of relapse.

Retrospective data suggest that suboptimal plasma levels of imatinib are associated with a worse outcome [29]. Further studies would be needed to confirm this prospectively. Aside from its potential use to tailor the imatinib dose, plasma level assessment may be useful in the case of: (i) patients receiving concomitant medications that put them at risk of major interactions; (ii) unexpected observed toxicities; (iii) progression on 400 mg, to rationally lead the physician to increase the dose to 800 mg daily.

Complete excision of residual metastatic disease has been shown to be related to a good prognosis, provided the patient is responding to imatinib, but it is left to be demonstrated whether this is due to surgery or to patient selection [30–32]. Randomized trials did not prove feasible; thus, at the present time, the surgical option should be individualized after sharing the decision with the patient in cases of uncertainty [III, C].

Surgical excision of progressing disease has not been rewarding in published series, but surgery of limited progression, such as the ‘nodule within a mass’, has been associated with a progression-free interval in the same range as for second-line treatment with sunitinib. Therefore, this may be a palliative option in the individual patient with a limited progression, while continuing imatinib [V, C]. Non-surgical procedures (local treatment, such as ablations, etc.) may be selected.

The standard approach in the case of tumor progression on 400 mg is to increase the imatinib dose to 800 mg daily [23–26] [III, B], with the possible exception of insensitive mutations (if treated with the lower dose). Dose escalation is particularly useful in case of a KIT exon 9 mutated GIST (if a higher dose was not selected from the beginning), possibly in case of changes in drug pharmacokinetics over time, or perhaps in case of some molecular secondary alterations [27]. False progression on imaging should be ruled out, due to the response patterns (see below). Also patient non-compliance should be ruled out as a possible cause of tumor progression, as well as drug interactions with concomitant medications.

In case of progression or rare intolerance on imatinib (after attempts to manage side effects also through expert advice), standard second-line treatment is sunitinib [33] [I, B]. The drug was proved effective in terms of PFS following a ‘4 weeks on–2 weeks off’ regimen. Data have been provided that a continuously dosed daily oral regimen with a lower daily dose (37.5 mg) may be effective and well tolerated, although no formal comparison has been performed within a randomized clinical trial. This schedule can therefore be considered an option on an individualized basis [34] [III, B].

After failing on sunitinib, a prospective placebo-controlled randomized trial proved that regorafenib is able to prolong the PFS [35]. When commercially available, this therapy is recommended for the third-line targeted therapy of patients failing to respond to imatinib and sunitinib [I, B].

Patients with a metastatic GIST should be considered for participation in clinical trials on new therapies or combinations.

There is anecdotal evidence that patients who have already progressed on imatinib may occasionally benefit when rechallenged with the same drug. Likewise, maintaining treatment with an anti-tyrosine kinase agent, even in the case of progressive disease, may slow down progression as opposed to stopping it (if no other option is available at the time). Therefore, rechallenge or continuation treatment with an anti-tyrosine kinase agent to which the patient has already been exposed is an option in patients with progression [V, B]. On the other hand, the use of combinations of anti-tyrosine kinase agents outside of clinical studies should be discouraged, because of the potential for considerable toxicity.

**response evaluation**

Antitumor activity translates into tumor shrinkage in the majority of patients, but some patients may show only changes in tumor density on CT scan, or these changes may precede delayed tumor shrinkage. These changes in tumor radiological appearance should be considered as the tumor response. In particular, even some increase in the tumor size may be indicative of the tumor response if the tumor density on CT scan is decreased [36, 37]. Even the ‘appearance’ of new lesions may be due to their being more evident when becoming less dense. Therefore, both tumor size and tumor density on CT scan, or consistent changes on MRI or contrast-enhanced ultrasound, should be considered as criteria for tumor response. An FDG-PET scan has proved to be highly sensitive in early assessment of tumor response and may be useful in doubtful cases, or when early prediction of the response is highly useful (e.g. preoperative cytoreductive treatments). A small proportion of GISTs have no FDG uptake, however. The absence of tumor progression after months of treatment equally amounts to a tumor response. On the other hand, tumor progression may not be accompanied by changes in the tumor size. In fact, some increase in the tumor density within tumor lesions may be indicative of tumor progression. A typical progression pattern is the ‘nodule within the mass’, by which a portion of a responding lesion becomes hyperdense.

**follow-up**

There are no published data to indicate the optimal routine follow-up policy of surgically treated patients with localized disease. Relapses most often occur to the liver and/or peritoneum (other sites of metastases, including bone lesions, are rare). The mitotic rate likely affects the speed at which relapses take place. Risk assessment based on the mitotic count, tumor size and tumor site may be useful in choosing
the routine follow-up policy. High-risk patients generally have a relapse within 1–2 years from the end of adjuvant therapy. Low-risk patients may have a relapse later, although this is much less likely. That said, routine follow-up schedules differ across institutions.

The optimal follow-up schedules are not known. As an example, in some institutions high-risk patients undergo a routine follow-up with CT scan or MRI every 3–6 months for 3 years during adjuvant therapy (with tighter clinical follow-up due to the need to manage the side effects of adjuvant therapy), unless contraindicated, then on cessation of adjuvant therapy every 3 months for 2 years, then every 6 months until 5 years from stopping adjuvant therapy and annually for an additional 5 years.

For low-risk tumors, the usefulness of a routine follow-up is not known; if selected, this is carried out with a CT scan or MRI every 6–12 months for 5 years.

Very low-risk GISTs probably do not deserve routine follow-up, although one must be aware that the risk is not nil. X-ray exposure is a factor to take into account, with abdominal MRI being an option as an alternative option to a CT scan.

note

These Clinical Practice Guidelines have been developed following a consensus process based on a consensus event organized by ESMO in Milan, Italy in January 2012 and refined afterwards. This involved experts from the community of the European sarcoma research groups, sarcoma Networks of excellence and ESMO Faculty. Their names are indicated hereafter. The text reflects an overall consensus among them, although each of them may not necessarily find it consistent with his/her own views. The panel worked on the text of ESMO Guidelines of previous years, whose authorship should also be credited.

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acknowledgements

We deeply thank Barbara Dore, Estelle Lecointe and Roger Wilson (SPAEN), who were observers as patient representatives.

conflict of interest

Prof. Blay has reported: consultancy/honoraria: Novartis, Roche, GlaxoSmithKline, PharmaMar; research funding: PharmaMar. Dr. Boukovinas has reported: royalty fees from Novartis. Dr. Casali has reported: consultancy/honoraria: Bayer, GlaxoSmithKline, Janssen Cilag, Merck Sharp & Dohme, Novartis, Pfizer, PharmaMar, and Sanofi-Aventis. Prof. De Alava has reported: research funding from PharmaMar. Dr. Dei Tos has reported: consultancy for Novartis, Pfizer, and GlaxoSmithKline; research grant from Novartis. Dr. Eriksson has reported: honoraria from Novartis, Swedish Orphan Biovitrum, GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer. Dr. Fedenko has reported: speakers’ bureau for Roche, Jansen, Lilly. Dr. Ferrari has reported: research funding: Amgen, MolMed, PharmaMar, Infinity; consultancy: Takeda and Merck. Dr. Gelderblom has reported: research funding from Pfizer, Novartis, PharmaMar, Eisai, GlaxoSmithKline, and Infinity. Mr. Grimer has reported: speakers’ bureau for Takeda. Dr. Gronchi has reported: honoraria and advisory board compensation from Novartis Pharma; honoraria and travel coverage from PharmaMar; honoraria from Pfizer. Prof. Hassan has reported: investigator-initiated, early phase trials with Takeda and Astellas; conference chair for Takeda satellite symposia; scientific board of Sarcoma UK; grants with Cancer Research UK and EU FP7. Prof. Hohenberger has reported: research funding: Novartis, GlaxoSmithKline, PharmaMar; Advisory Boards for Novartis, PharmaMar, GlaxoSmithKline, and Pfizer. Prof. Joensuu has reported: research support from Novartis. Prof. Jurgens has reported: institutional research grants: Roche, Pfizer, and Takeda. Prof. Kager has reported: advisory board for Takeda.
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Other authors have reported no potential conflicts of interest.

references


