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

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incidence

Gastrointestinal stromal tumours (GISTs) are rare tumours, with an estimated unadjusted incidence of around 1/100 000/year [1]. This only covers clinically relevant GISTs, since it is likely that 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 paediatric GIST represents a distinct subset, marked by female predominance, absence of *KIT*/platelet-derived growth factor alpha (PDGFRA) mutations, gastric multicentric location, and possible lymph node metastases [2].

Some syndromes are linked to GISTs:

- the Carney triad syndrome in succinate dehydrogenase subunit B (SDHB)-deficient GIST, marked by gastric GISTs, paraganglioma, and pulmonary chondromas (these may occur at different ages) [3].
- Carney-Stratakis syndrome, marked by germ-line mutations of SDH subunits A, B, C, and D, leading to a dyad of GIST and paraganglioma [4, 5].
- neurofibromatosis type 1, marked by wild-type, often multicentric GIST, predominantly located to the small bowel [6].

Families with germ-line autosomal dominant mutations of *KIT* are a rare finding, presenting with multiple GISTs 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 tumour 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 co-morbidities. 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 the case of no evidence of growth, a more relaxed follow-up schedule may be selected.

In a histologically proven small GIST, standard treatment is excision, unless major morbidity is expected. Alternatively, in the 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 tumour 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 GIST, they are associated with a higher risk. If there is an abdominal nodule 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 allow the surgeon to plan the best approach according to the histological diagnosis and may avoid surgery for diseases that do not merit it (e.g. lymphomas, mesenteric fibromatosis, and germ cell tumours). 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 specialised centres. Immediate laparoscopic/laparotomic excision is an alternative on an individualised 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 laparotomy for diagnostic purposes. The tumour sample should be fixed in 4% buffered

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formalin (Bouin fixation should not be used, since it prevents molecular analysis).

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry, the latter being positive for CD117 and/or DOG1 [7, 8]. A proportion of GISTs (in the range of 5%) are CD117-negative. The mitotic count has a prognostic value and should be expressed as the number of mitoses on a total area of 5 mm^2 (which replaces the former 50 high-power field area). 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 ever to be candidates for medical treatment). Centralisation of mutational analysis in a laboratory enrolled in an external quality assurance programme and with expertise in the disease may be useful. In *KIT*/PDGFRA wild type (WT) GIST, immunohistochemistry for SDHB is done. The diagnosis should be made or confirmed by an expert pathologist at a reference centre. The 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 tumour 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 its use is therefore not recommended.

Prognostic factors are the mitotic rate, tumour size and tumour site (gastric GISTs have a better prognosis than small bowel or rectal GISTs). Tumour rupture is an additional adverse prognostic factor and should be recorded, whether it took place before or during surgery. Mutational status has not been incorporated in any risk classification at the moment, although some genotypes have a distinct natural history, and, above all, *KIT*/PDGFRA WT GISTs have peculiar clinical presentations and course.

Several risk classifications have been proposed. A widely used risk classification was proposed by the Armed Forces Institute of Pathology, which incorporates the primary tumour site, mitotic count, and tumour size, i.e. the three main prognostic factors in localised GISTs [9, 10]. A nomogram utilising all three criteria has been developed on another series [11]. When using these tools, it is important to appreciate that the mitotic index and tumour size are non-linear continuous variables, so that thresholds are interpreted wisely. Prognostic contour maps were generated through a pool of series of GIST patients not treated with adjuvant therapy, which incorporate the mitotic index and tumour size as continuous non-linear variables, while tumour rupture is considered in addition to tumour site [12]. They have been validated against a reference series.

staging procedures

Staging procedures take into account the fact that most relapses affect the peritoneum and the liver. Contrast-enhanced abdominal and pelvic CT scan is the investigation of choice for staging and follow-up. Magnetic resonance imaging (MRI) may be an alternative. 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. The evaluation of fluorodeoxyglucose (FDG) uptake using an FDG-positron emission tomography (PET) scan, or FDG-PET–CT/MRI, is useful mainly when early detection of the tumour response to molecular-targeted therapy is of special interest.

treatment

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

localised disease

The standard treatment of localised GISTs is complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes [III, A]. If laparoscopic excision is planned, the technique needs to follow the principles of oncological surgery [13] [III, A]. A laparoscopic approach is clearly discouraged in patients who have large tumours, because of the risk of tumour rupture, which is associated with a very high risk of relapse. R0 excision is the goal (i.e. an excision whose margins are clear of tumour cells). When R0 surgery implies major functional sequelae, and preoperative medical treatment has not helped or cannot be exploited, the decision can be shared with the patient to accept possible R1 (microscopically positive) margins (i.e. excision margins containing tumour cells) [IV, B]. This is all the more acceptable for low-risk lesions, given the lack of any formal demonstration that R1 surgery is associated with a worse overall survival (OS).

If R1 excision was already 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 randomised trial in comparison with 1 year of therapy in high-risk patients [14]. Previously, a placebo-controlled trial demonstrated that imatinib dosed for a planned duration of 1 year is able to prolong relapse-free survival in localised GISTs having a diameter of 3 cm or more with a macroscopically complete resection [15]. Therefore, adjuvant therapy with imatinib for 3 years is the standard treatment of patients with a significant 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 consensus on avoiding adjuvant treatment in neurofibromatosis 1-related GISTs, which are insensitive to imatinib in the advanced setting. On the other hand, a consensus is lacking among experts about whether wild-type SDH-negative 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, but subgroup analyses of available randomised trials are too limited to provide sufficient evidence. European and International cooperation would be vital to determine best practices in the exceedingly rare paediatric GIST.

In case of tumour rupture at the time of surgery, there has been spillage of tumour cells into the peritoneal cavity, and therefore occult peritoneal disease can be assumed to exist. This puts the patient at a very high risk of peritoneal relapse [20]. 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), pre-treatment with imatinib is standard [21, 22] [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 tumour rupture is decreased). Following maximal tumour response, generally after 6–12 months, surgery is carried out. 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 proper dosing for *KIT* exon 9 mutations. Early tumour response assessment is mandatory, so that surgery is not delayed in the case of non-responding disease. Functional imaging makes it possible to assess the tumour response very rapidly, within a few weeks, particularly in the lack of a mutational analysis. There are limited data to guide the physician on when to stop imatinib before surgery; however, it can be safely stopped a few days or even 1 day before surgery and it can be resumed promptly when the patient recovers from surgery.

metastatic disease

In locally advanced inoperable and metastatic patients, imatinib is standard treatment [23–26] [III, A], even if the patient previously received the drug as adjuvant therapy without relapsing during it. 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 tumour progression, 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 of the best ways to handle 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. Retrospective data suggest that suboptimal plasma levels of imatinib are associated with a worse outcome, although a correlation with the outcome has not been established prospectively [29]. Aside from its potential use to tailor the imatinib dose, assessment of plasma level may be useful in the case of: (i) patients receiving concomitant medications that put them at a risk of major interactions or patients with previous surgical resections able to decrease plasma levels; (ii) unexpected observed toxicities; and (iii) progression on 400 mg, to rationally lead the physician to increase the dose to 800 mg daily.

Close monitoring of the tumour 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. 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 has never been demonstrated prospectively whether this is due to surgery or to patient selection [30–32]. Randomised trials did not prove feasible, with the exception of a small positive trial, in which all patients had peritoneal disease [33]. Thus, at the present time, the surgical option should be individualised after sharing the decision with the patient in the case 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 limited progression, while continuing imatinib [V, C]. Non-surgical procedures (local treatment, such as ablations, etc.) may be selected. In the case of tumour progression on 400 mg, an option may be 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 the case of a *KIT* exon 9 mutated GIST (if a higher dose was not selected from the beginning), possibly in the case of changes in drug pharmacokinetics over time, or perhaps in the case of some molecular secondary alterations. 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 tumour progression, as well as drug interactions with concomitant medications.

In the case of confirmed progression or rare intolerance on imatinib (after attempts to manage side-effects also through expert advice, also exploiting dose reductions and possibly plasma level assessment), standard second-line treatment is another tyrosine kinase inhibitor, sunitinib [34] [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) is effective and well tolerated, although no formal comparison has been carried out within a randomised clinical trial. This schedule can therefore be considered an alternative on an individualised basis [35] [III, B].

After confirmed progression on sunitinib, a prospective placebo-controlled randomised trial proved that regorafenib, at the dose of 160 mg daily for 3 every 4 weeks, is able to significantly prolong PFS [36]. This therapy, as it becomes routinely available, is therefore standard for the third-line targeted therapy of patients progressing on or 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 controlled evidence that patients who have already progressed on imatinib may benefit when re-challenged with the same drug [37]. Likewise, there is evidence that 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, re-challenge 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

Response evaluation is complex, and early progression, in particular, should be confirmed by an experienced team. Anti-tumour activity translates into tumour shrinkage in the majority of patients, but some patients may show changes only in tumour density on CT scan, or these changes may precede delayed tumour shrinkage. These changes in tumour radiological appearance should be considered as the tumour response. Even increase in the tumour size, in particular, may be indicative of the tumour response if the tumour density on CT scan is decreased [38]. Even the 'appearance' of new lesions may be due to their being more evident when becoming less dense. Therefore, both tumour size and tumour density on CT scan, or consistent changes in MRI or contrast-enhanced ultrasound, should be considered as criteria for tumour response. An FDG-PET scan has proved to be highly sensitive in early assessment of tumour response and may be useful in cases where there is doubt, or when early prediction of the response is particularly useful (e.g. pre-operative cytoreductive treatments). A small proportion of GISTs have no FDG uptake, however. The absence of tumour progression at 6 months [39] after months of treatment also amounts to a tumour response. On the other hand, tumour progression may not be accompanied by changes in the tumour size. In fact, some increase in the tumour density within tumour lesions may be indicative of tumour progression. A typical progression pattern is the 'nodule within the mass', by which a portion of a responding lesion becomes hyperdense [40].

follow-up

There are no published data to indicate the optimal routine follow-up policy of surgically treated patients with localised disease. Relapses most often occur to the liver and/or peritoneum (other sites of metastases, including bone lesions and other sites, may be less rare along the course of metastatic disease treated with several lines of therapy). The mitotic rate likely affects the speed at which relapses take place. Risk assessment based on the mitotic count, tumour size and tumour site may be useful in choosing the routine follow-up policy. High-risk patients generally have a relapse within 1–3 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 an abdominal CT scan or MRI every 3–6 months for 3 years during adjuvant therapy (with a 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 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 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, especially in low-risk GIST, with abdominal MRI being an option as an alternative.

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for a bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, and experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [41].

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 1. Statements without grading were considered justified standard clinical practice by the panel members.

consensus panel ESMO Guidelines 2014

These Clinical Practice Guidelines have been developed following a consensus process based on a consensus event organised by ESMO in Milan, Italy, in December 2013 and refined by July 2014. This involved experts from the community of the European sarcoma research groups 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.

- Paolo G. Casali, Italy (*Moderator*)
- Jean-Yves Blay, France (*Moderator*)
- Alexia Bertuzzi, Ireland
- Stefan Bielack, Germany
- Bodil Bjerkehagen, Norway
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- Ioannis Boukovinas, Greece
- Paolo Bruzzi, Italy
- Angelo Paolo Dei Tos, Italy
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- Mikael Eriksson, Sweden
- Alexander Fedenko, Russian Federation
- Andrea Ferrari, Italy
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- Hans Gelderblom, Belgium
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conflict of interest

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