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 incidence of 1.5/100 000/year. This only covers the clinically relevant GISTs, since likely a much higher number of microscopic lesions could be found pathologically, if looked for.

diagnosis

When small oesophagogastric or duodenal nodules <2 cm in size are detected, endoscopic biopsy may be difficult, and laparoscopic/laparotomy excision may be the only way to get to a histological diagnosis. Many of these small nodules, if diagnosed as GIST, will be low risk, or entities whose clinical significance remains unclear. Therefore, the standard approach to these patients is endoscopic ultrasound assessment and then 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. 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 histologically proven small GIST, standard treatment is excision, unless major morbidity is expected. Alternatively, the decision can be shared with the patient to follow up the lesion, in the case of a low-risk GIST. 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. However, a follow-up policy may be an option, to be shared with the patient, in the case of small lesions.

On the other hand, the standard approach to nodules >2 cm in size is biopsy/excision, because, if GIST, they imply a higher risk. If there is an abdominal nodule not amenable to endoscopic assessment, laparoscopic/laparotomy excision is the standard approach. If there is a bigger mass, especially if surgery is likely to be a multivisceral resection, multiple core needle biopsies are the standard approach. They should be obtained preferably through endoscopic ultrasound guidance, or otherwise through an ultrasound/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 fibromatosis, germ cell tumours). The risk of peritoneal contamination is negligible if the procedure is properly carried out. Lesions at risk in this regard (e.g. cystic masses) should be biopsied only in specialized centres. 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 laparotomy for diagnostic purposes. The tumour sample should be fixed in formalin (Bouin fixation should be banned, since it prevents molecular analysis).

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry (CD117 and/or DOG1). A proportion of GISTs (in the 5% range) are CD117 negative. Mitotic count has prognostic value, and should be expressed as the number of mitoses per 50 high-power fields (HPF) (i.e. on a total area of 10 mm²). 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 predictive value for sensitivity to molecular targeted therapy and prognostic value, so that its inclusion in the diagnostic work-up of all GISTs is recommended. Centralization of mutational analysis in a laboratory enrolled in an external quality assurance programme 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 reference centres.

Collection of fresh frozen tissue and tumour imprints (touch preps) 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 risk of relapse is estimated on the basis of mitotic rate, tumour size, tumour site, surgical margins and whether tumour rupture occurred. Tumour size and mitotic count are considered by the 2002 Consensus risk classification. This was correlated with 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 favourable prognosis. In most of the population-based series, the ‘intermediate-risk’ category of the Consensus classification did not discriminate patients with an unfavourable prognosis.

A more recently proposed risk partitioning scheme incorporates primary tumour site in addition to the mitotic count and tumour size. In particular, it reflects the fact that gastric GISTs have a better prognosis than small bowel or rectal GISTs. The risk estimate for subgroups is based on a single retrospective analysis. However, this classification better distinguishes across different risk levels. A nomogram utilizing the same criteria has been developed on another series.

Tumour rupture, whether spontaneous or at the time of surgical resection, should be recorded, because it denotes a high risk, independent of any other prognostic factor.

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. MRI or contrast-enhanced ultrasound may be alternatives. For rectal GIST, 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 PET scan, or PET-CT/MRI, is useful mainly when early detection of tumour 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 centres for sarcomas and GIST, and/or within reference networks sharing multidisciplinary expertise.

limited disease

Standard treatment of localized GIST is complete surgical excision, without dissection of clinically negative lymph nodes [III, A]. If laparoscopic excision is planned, the technique needs to follow the principles of oncological surgery. A laparoscopic approach is clearly discouraged in patients who have large tumours. R0 excision is the goal.

If R0 surgery is not feasible, or it could be achieved through less mutilating surgery in the case of cytoreduction, imatinib pretreatment is recommended [IV, A]. This may also be the case if the surgeon believes that the surgical conduct would be 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 performed. Mutational analysis may help to exclude less sensitive mutational status (e.g. PDGFRA D842V mutations) from therapy with imatinib or to tailor design. PET scan, or PET CT/MRI, may be particularly useful to assess tumour response very rapidly, in terms of a few weeks, so that surgery is not delayed in the case of non-responding disease.

If a R1 excision has been made, re-excision may be a choice, provided the original site of lesion can be found, and major functional sequelae are not foreseen.

When R0 surgery implies major functional sequelae, and preoperative medical treatment has not helped or cannot be given, the decision can be shared with the patient to accept R1 margins. 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.

The risk of relapse can be substantial, as defined by risk classifications (see Table 1). Given the efficacy of imatinib in the disease, adjuvant treatment with the drug has been studied.
Optimal duration of treatment in these cases is unknown. Patients should be considered for imatinib therapy. The occult peritoneal disease can be assumed. This puts the patient has been spillage of tumour cells in the peritoneal cavity, so that longer follow-up is needed to draw definitive conclusions with regard to: the absolute relapse rate after a substantial time interval; the length of the delay in relapse; the time to secondary resistance to imatinib in subsequently relapsing patients. At this time, there is no global consensus in the medical community on adjuvant imatinib as standard treatment for GIST patients with localized disease. Having been approved by regulatory bodies such as EMA and FDA, adjuvant imatinib can be proposed as an option for those patients with a substantial risk of relapse, for shared decision-making [II, B]. In addition to the risk assessment, mutational analysis may guide the selection of those patients who are more likely to benefit from the treatment. If the decision is made to use imatinib as an adjuvant, the currently available trial data support its use for 1 year. The results are awaited of a trial that compared 1 and 3 years of treatment duration.

In the case of tumour rupture at the time of surgery, there has been spillage of tumour cells in the peritoneal cavity, so that 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.

**Extensive Disease**

In locally advanced inoperable patients and metastatic patients, imatinib is standard treatment [III, A]. This applies also to metastatic patients who have been completely relieved of all lesions surgically. The standard dose of imatinib is 400 mg daily [I, A]. Data have been provided that patients with exon 9 KIT mutations fare better in terms of progression-free survival on a higher dose level, i.e. 800 mg daily, which is therefore standard treatment in this subgroup [III, A]. Treatment should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumour progression in virtually all cases, even when lesions have been previously surgically excised [I, B].

When treatment is started, the patient should be alerted about the importance of compliance with therapy, as well as of interactions with co-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 in the case of excessive, persistent toxicity.

Close monitoring of tumour response should be continued throughout treatment, since the risk of secondary progression persists over time.

Retrospective data suggest that suboptimal plasma levels of imatinib are associated with a worse outcome. Further studies are needed.

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 still to be demonstrated whether this is due to surgery or to patient selection. Therefore, surgery of metastatic responding patients is under investigation, and enrollment of patients in ongoing clinical studies is encouraged. Outside these trials, the surgical option should be individualized after sharing decision-making with the patient.

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, it may be a palliative option in the individual patient with a limited progression. Non-surgical procedures (local treatment, such as ablations, etc.) may be selected.

The standard approach in the case of tumour progression on 400 mg is to increase the imatinib dose to 800 mg daily [III, B], with the possible exception of insensitive mutations. Dose escalation may be useful in the case of a KIT exon 9 mutated GIST, possibly in the case of changes in drug pharmacokinetics over time, or perhaps in the case of some molecular 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 progression or intolerance on imatinib, second-line standard treatment is sunitinib [II, B]. The drug was shown to be effective in terms of progression-free survival using a ‘4 weeks on–2 weeks off’ regimen. Data have been provided that a continuously dosed daily oral regimen with a lower daily dose 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.

After failing on sunitinib, the patient with metastatic GIST should be considered for participation in a clinical trial of new therapies or new combinations.

There is anecdotal evidence that patients who have already progressed on imatinib may occasionally have a 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, of course 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 may be an option. On the other hand, combinations of anti-tyrosine kinase agents should be discouraged outside of clinical studies, because of the potential for considerable toxicity.

**Response evaluation**

Antitumour activity translates into tumour shrinkage in the majority of patients, but some patients may show only changes in tumour density on CT scan, or these changes may precede a delayed tumour shrinkage. These changes in tumour radiological appearance should be considered as tumour response. In particular, even some increase in tumour size may be indicative of tumour response if tumour density on CT scan is decreased. Even the ‘appearance’ of new lesions may depend on their being more evident when becoming less dense. Therefore, both tumour size and tumour density on CT scan, or consistent changes on MRI or contrast-enhanced ultrasound, should be considered as criteria for tumour response. FDG–PET scan has proved to be highly sensitive in early assessment of tumour response, and may be useful in...
doubtful cases, or when early prediction of response is highly useful (e.g. preoperative cytoreductive treatments). The absence of tumour progression after months of treatment equally amounts to tumour response. On the other hand, tumour progression may not be accompanied by changes in tumour size. In fact, some increase in tumour density within tumour lesions may be indicative of tumour progression. A typical progression pattern is the ‘nodule within the nodule’, 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 peritoneum or in the liver. The mitotic rate likely affects the speed at which relapses take place. Risk assessment based on mitotic count, tumour size and tumour site may help in choosing the routine follow-up policy. High-risk patients generally relapse within 2–3 years, while low-risk patients may relapse later, although much less likely. That said, routine follow-up schedules differ across institutions. As an example, in some institutions intermediate–high-risk patients undergo a routine follow-up with CT scan every 3–4 months for 3 years, then every 6 months until 5 years, and yearly afterwards; for low-risk tumours, follow-up is carried out with CT scan every 6 months for 5 years. Very low-risk GIST probably do not deserve routine follow-up, although one must be aware that the risk is not nil.

**note**

These Clinical Practice Guidelines have been developed following a consensus process based on a consensus event organized by ESMO in Lugano in November 2009. 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 EU-funded network of excellence CONTICANET (CONnective Tissue CAncers NETwork) and EUROBONET (EUROpean BOne NETwork) also financially supported the consensus process.

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**literature**

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