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CLINICAL PRACTICE GUIDELINES

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

P. G. Casali[1], N. Abecassis[2], S. Bauer[3], R. Biagini[4], S. Bielack[5], S. Bonvalot[6], I. Boukovinas[7], J. V. M. G. Bovee[8], T. Brodowicz[9], J. M. Broto[10], A. Buonadonna[11], E. De Álava[10], A. P. Dei Tos[12], X. G. Del Muro[13], P. Dileo[14], M. Eriksson[15], A. Fedenko[16], V. Ferraresi[17], A. Ferrari[18], S. Ferrari[19], A. M. Frezza[1], S. Gasperoni[20], H. Gelderblom[21], T. Gil[22], G. Grignani[23], A. Gronchi[1], R. L. Haas[24], A. Hannu[25], B. Hassan[26], P. Hohenberger[27], R. Issels[28], H. Joensuu[29], R. L. Jones[30], I. Judson[31], P. Jutte[32], S. Kaal[33], B. Kasper[27], K. Kopeckova[34], D. A. Krákorová[35], A. Le Cesne[36], I. Lugowska[37], O. Merimsky[38], M. Montemurro[39], M. A. Pantaleo[40], R. Piana[41], P. Picci[19], S. Piperno-Neumann[6], A. L. Pousa[42], P. Reichardt[43], M. H. Robinson[44], P. Rutkowski[37], A. A. Safwat[45], P. Schöffski[46], S. Sleijfer[47], S. Stacchiotti[48], K. Sundby Hall[49], M. Unk[50], F. Van Coevorden[51], W. Van der Graaf[52], J. Whelan[53], E. Wardelmann[53], O. Zaikova[54] & J. Y. Blay[55], on behalf of the ESMO Guidelines Committee and EURACAN*

[1]Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; [2]Instituto Português de Oncologia de Lisboa Francisco Gentil, EPE, Lisbon, Portugal; [3]University Hospital Essen, Essen Germany; [4]Department of Oncological Orthopedics, Musculoskeletal Tissue Bank, IFO, Regina Elena National Cancer Institute, Rome, Italy; [5]Klinikum Stuttgart-Olgahospital, Stuttgart, Germany; [6]Institut Curie, Paris, France; [7]NORDER, Athens, Greece; [8]Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands; [9]Vienna General Hospital (AKH), Medizinische Universität Wien, Vienna, Austria; [10]Hospital Universitario Virgen del Rocío-CIBERONC, Sevilla, Spain; [11]Centro di Riferimento Oncologico di Aviano, Aviano; [12]Ospedale Regionale di Treviso 'S.Maria di Ca' Foncello', Treviso, Italy; [13]Integrated Unit ICO Hospitalet, HUB, Barcelona, Spain; [14]Sarcoma Unit, University College London Hospitals, London, UK; [15]Skane University Hospital-Lund, Lund, Sweden; [16]N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation; [17]Institute of Scientific Hospital Care (IRCCS), Regina Elena National Cancer Institute, Rome; [18]Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [19]Istituto Ortopedico Rizzoli, Bologna; [20]Azienda Ospedaliera Universitaria Careggi Firenze, Florence, Italy; [21]Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands; [22]Institut Jules Bordet, Brussels, Belgium; [23]Candiolo Cancer Institute, FPO IRCCS, Candiolo, Italy; [24]Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam and Department of Radiotherapy, Leiden University Medical Center, Leiden, The Netherlands; [25]Turku University Hospital (Turun Yliopistollinen Keskussairaala), Turku, Finland; [26]Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [27]Mannheim University Medical Center, Mannheim; [28]Department of Medicine III, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany; [29]Helsinki University Central Hospital (HUCH), Helsinki, Finland; [30]Royal Marsden Hospital, London; [31]The Institute of Cancer Research, London, UK; [32]University Medical Center Groningen, Groningen; [33]Radboud University Medical Center, Nijmegen, The Netherlands; [34]University Hospital Motol, Prague; [35]Masaryk Memorial Cancer Institute, Brno, Czech Republic; [36]Gustave Roussy Cancer Campus, Villejuif, France; [37]Maria Sklodowska Curie Institute, Oncology Centre, Warsaw, Poland; [38]Tel Aviv Sourasky Medical Center (Ichilov), Tel Aviv, Israel; [39]Medical Oncology, University Hospital of Lausanne, Lausanne, Switzerland; [40]Azienda Ospedaliera, Universitaria, Policlinico S. Orsola-Malpighi Università di Bologna, Bologna; [41]Azienda Ospedaliera, Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; [42]Fundació de Gestió Sanitària de l'Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [43]Helios Klinikum Berlin Buch, Berlin, Germany; [44]CRUK Department of Clinical Oncology, Weston Park Hospital NHS Trust, Sheffield, UK; [45]Aarhus University Hospital, Aarhus, Finland; [46]Leuven Cancer Institute, Leuven, Belgium; [47]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [48]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy; [49]Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway; [50]Institute of Oncology of Ljubljana, Ljubljana, Slovenia; [51]Netherlands Cancer Institute Antoni van Leeuwenhoek, Amsterdam, The Netherlands; [52]University College Hospital, London, UK; [53]Gerhard-Domagk-Institut für Pathologie, Universitätsklinikum Münster, Münster, Germany; [54]Ohio University Hospital, Norwegian Radium Hospital, Oslo, Norway; [55]Centre Leon Berard and UCBL1, Lyon, France

*Correspondence to ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

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Incidence and epidemiology

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, if investigated, a much higher number of lesions ≤ 1 cm in diameter (microGISTs) can be found at histopathological examination of stomach tissue in middle-aged and elderly individuals.

There is a slight prevalence in males. The median age is around 60–65 years, with a wide range. Occurrence in children is very rare. Paediatric GIST represents a clinically and molecularly distinct subset, marked by female predominance, absence of *KIT*/platelet-derived growth factor alpha (*PDGFRA*) mutations, frequent mutations or silencing of the four genes that encode the subunits of the succinate dehydrogenase (SDH) enzyme complex, gastric multicentric location and possible lymph node metastases [2].

Some syndromes are linked to GISTs:

- The Carney triad syndrome, marked by gastric GISTs, paragangliomas and pulmonary chondromas (these may occur at different ages) [3];
- Carney–Stratakis syndrome, marked by a dyad of GIST and paraganglioma [4, 5]; and
- Neurofibromatosis type 1(NF1), possibly leading to wild-type (WT), often multicentric GIST, predominantly located in the small bowel [6].

Families with germline autosomal dominant mutations of *KIT* are an extremely rare finding, presenting with multiple GISTs at an early age, possibly along with other associated features such as pigmented skin macules, urticaria pigmentosa and diffuse hyperplasia of the interstitial cells of Cajal in the gut wall.

Diagnosis and pathology/molecular biology

When small oesophagogastric 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 either low-risk or entities whose clinical significance remains unclear. Therefore, the standard approach to patients with oesophagogastric or duodenal nodules < 2 cm is endoscopic ultrasound assessment and then follow-up, reserving excision for patients whose tumour increases in size or becomes symptomatic [IV, C]. As an option, the patient can choose to undergo 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 approach 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 likely low-risk GIST on biopsy, the decision can be made with the patient to follow up the lesion. However, an exception is the standard approach to rectal nodules represented by biopsy or excision after endorectal ultrasound assessment and pelvic magnetic resonance imaging (MRI), regardless of the tumour size and mitotic rate. In fact, the progression risk of a clinically significant GIST at this site is higher, its prognosis is significantly worse compared with most gastric GISTs and the local implications for surgery are more critical. A follow-up policy may be an option, to be discussed with the patient, in the case of small lesions and whenever the surgical risk is particularly high (comorbidities, age, etc.).

The standard approach to tumours ≥2 cm in size is biopsy/excision, because they are associated with a higher risk of progression if confirmed as GIST [IV, C]. 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 avoid surgery for diseases which might not benefit (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 option on an individualised basis, especially if surgery is limited. If a patient presents with obvious metastatic disease, 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 formalin (Bouin fixative 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 (KIT) and/or DOG1 (see Table 1) [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 (HPF) area]. Mutational analysis for known mutations involving *KIT* and *PDGFRA* can confirm the diagnosis of GIST, if doubtful (particularly in rare CD117/DOG1-negative suspect GIST). Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy and to prognostic value. Its inclusion in the diagnostic work-up of all GISTs should be considered standard practice [II, A] (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. Centralised pathological diagnosis is more strongly recommended for *KIT/PDGFRA* WT GIST, to confirm the diagnosis of GIST with an expert pathologist at a reference centre. In *KIT/PDGFRA/BRAF* WT GIST, immunohistochemistry for SDHB is done to identify SDH-deficient GIST. In quadruple-negative GIST (*KIT/PDGFRA/BRAF/SDH*), an unrecognised underlying NF1 syndrome should be excluded [9]. The collection of fresh frozen tissue is encouraged, to allow new molecular pathology assessments to be made at a later stage. Informed consent for tumour storage (adhering to local and international guidelines) should be sought, enabling later analyses and research.

Multidisciplinary treatment planning is needed, involving pathologists, radiologists, surgeons and, medical oncologists, as well as gastroenterologists, nuclear medicine specialists, etc., as applicable. Management should be carried out in reference centres for sarcomas and GISTs and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually.

Staging and risk assessment

The revised Union for International Cancer Control tumour, node and metastasis classification of malignant tumours (UICC

Table 1. Personalised medicine synopsis table

Biomarker	Method	Use	LoE	GoR
Mitotic index	Pathology	Disease classification Prognostic relevance Used for medical treatment decisions	IV	A
KIT/*PDGFRA*/*BRAF*	Sanger sequencing or NGS	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions Currently actionable/targetable	I	A
SDH	IHC	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions	III	A

GoR, grade of recommendation; IHC, immunohistochemistry; LoE, level of evidence; NGS, next generation sequencing; PDGFRA, platelet-derived growth factor receptor alpha; SDH, succinate dehydrogenase.

Table 2. Prognostic factors for GIST UICC TNM 8 (modified from [10])

Prognostic factors	Tumour related	Host related	Environment related
Essential	Anatomical site Histological type Size of tumour Depth of invasion Grade (well to poorly differentiated) M category Mitotic rate		
Additional	Presence of *KIT* mutation Mutational site in *KIT* or *PDGFRA* gene Surgical resection margins Presentation status (primary versus recurrence)	NF1 Age	Quality of surgery
New and promising	TP53 Ki-67 Tumour hypoxia		

GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type 1; PDGFRA, platelet-derived growth factor alpha; TNM, tumour, node, metastasis; TP53, tumour protein 53; UICC, Union for International Cancer Control.
Modified from [10] with permission from John Wiley & Sons, Inc.

TNM 8), incorporates the main prognostic factors in GIST (*see* Table 2) [10].

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, regardless of whether it took place before or during surgery. Mutational status has not been incorporated in any risk classification at present, although some genotypes have a distinct natural history and, above all, *KIT*/*PDGFRA* WT GISTs have peculiar clinical presentations and course. Localised GIST with *PDGFR D842V* mutation are generally associated with a good prognosis and resistance to imatinib.

Several risk classifications have been proposed. A widely used risk classification was proposed by the Armed Forces Institute of Pathology, which incorporates the primary mitotic count, tumour size and tumour site, i.e. the three main prognostic factors in localised GISTs [11, 12]. A nomogram utilising all three criteria has been developed on another series [13]. 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 [14]. They have been validated against a reference series.

Staging procedures consider 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 may be an alternative. For rectal GISTs, MRI provides better preoperative staging information. Chest CT scan 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.

Management of local/locoregional disease (see Figure 1)

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 [III, A] [15]. 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 is not effective, the decision can be made with the patient to accept possible R1 (microscopically positive) margins [IV, B]. This is even more acceptable for low-risk lesions, given the lack of any formal demonstration that R1 surgery is associated with a worse overall

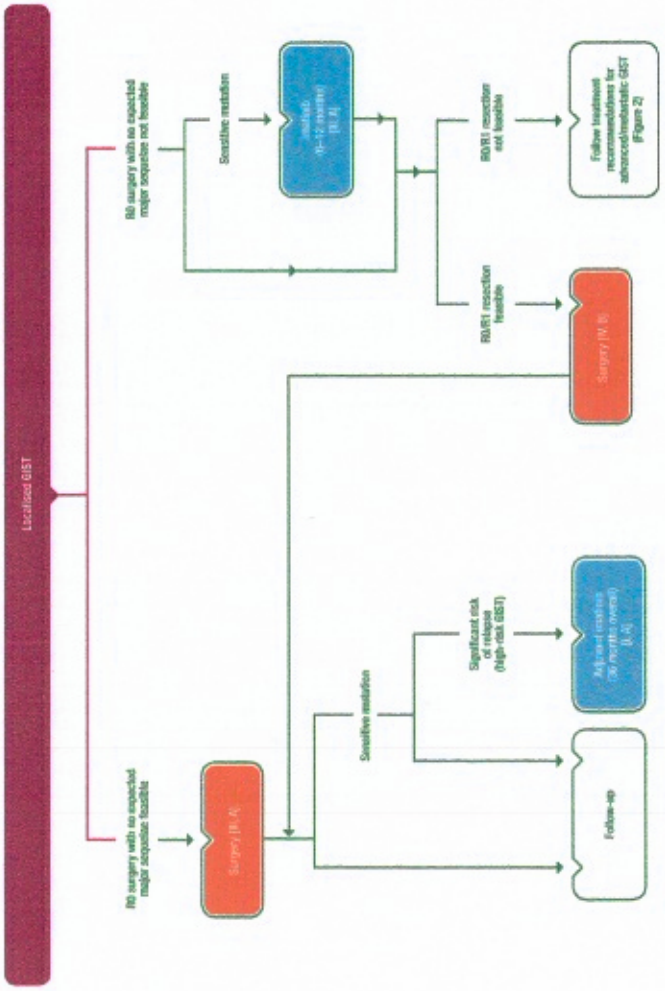

Figure 1. Management of local/locoregional GIST.
GIST, gastrointestinal stromal tumour; R0, no residual tumour; R1, microscopic residual tumour.

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 (RFS) and OS advantage in comparison with 1 year of therapy in high-risk patients in a randomised trial [16]. Previously, a placebo-controlled trial demonstrated that imatinib dosed for a planned duration of 1 year can prolong RFS in localised GISTs having a diameter ≥ 3 cm with a macroscopically complete resection [17]. Therefore, adjuvant therapy with imatinib for 3 years is the standard treatment for patients with a significant risk of relapse [I, A]. A shared decision-making process is needed when the risk is intermediate [18]. Randomised clinical studies are ongoing to test longer durations of adjuvant therapy in GISTs.

The benefit associated of adjuvant imatinib may vary according to the type of *KIT/PDGFRA* mutation, being greater in patients with *KIT* exon 11 deletion mutations [19, 20]. Mutational analysis is critical to make a clinical decision about adjuvant therapy. There is a 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, D]. 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, some expert clinicians prefer to use this dose even in the adjuvant setting for this genotype [II, B] [21–23]. Regulatory constraints may limit this practice, which is currently not supported in the adjuvant setting by controlled trials.

With regard to so called *KIT/PDGFRA/BRAF* WT GIST, there is a consensus on avoiding adjuvant treatment in NF1-related and SDH expression-negative GISTs [IV, D]. This reflects their lack of sensitivity to imatinib and other approved tyrosine kinase inhibitors (TKIs) in the advanced setting, as well as their peculiar natural history, which is often more indolent. Subgroup analyses of available randomised trials are, however, 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 is spillage of tumour cells into the peritoneal cavity; therefore, occult peritoneal disease can be assumed to exist. This puts the patient at a very high risk of peritoneal relapse [24]. Therefore, these patients should be considered for imatinib therapy [IV, A]. The optimal duration of treatment in these cases is unknown, given the uncertainty whether these cells should be considered as metastatic.

If R0 surgery is not feasible, or it could be achieved through less mutilating/function-sparing surgery in the case of volumetric reduction (this includes total gastrectomy and all other major procedures), pre-treatment with imatinib is standard [III, A] [25, 26]. This may also be the case if the surgeon believes that the surgical resection is safer after cytoreduction (e.g. the risk of bleeding and tumour rupture is decreased). A shortcoming may be the lack of reliable mitotic counting for accurate risk stratification for adjuvant postoperative therapy. A biopsy with histological and mutational analyses is recommended to confirm the histological diagnosis, to exclude resistant genotypes to therapy with imatinib (e.g. *PDGFRA D842V* mutations) and to propose the 800 mg imatinib dose for less sensitive *KIT* exon 9 mutations. Following maximal tumour response, generally after 6–12 months, surgery is carried out. Early tumour response assessment is required to avoid delaying surgery 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 absence of mutational analysis. There are limited data to guide the physician on when to stop imatinib treatment before surgery; however, it can be safely stopped a few days or even one day before surgery and can be resumed promptly when the patient recovers from surgery.

Management of advanced/metastatic disease (see Figure 2)

Imatinib is the standard treatment for locally advanced inoperable and metastatic disease [I, A] [27–30], as well as for patients previously treated with adjuvant imatinib who did not relapse while receiving it. Imatinib is also the standard treatment for patients with metastatic disease who have had all lesions removed surgically, although surgery is not recommended as a primary approach in the metastatic setting. The standard dose of imatinib is 400 mg daily [I, A]. However, data have shown that patients with tumours harbouring the *KIT* exon 9 mutation have significantly better progression-free survival (PFS) on a higher dose level, i.e. 800 mg daily, which is therefore held as standard treatment in this subgroup [III, B] [31]. Patients with a *PDGFRA D842V* mutation are generally insensitive to imatinib [32] and other TKIs and are, therefore, candidates for clinical studies on new agents targeting this mutation. It is doubtful whether patients with so-called WT SDH-deficient GIST benefit from available TKIs, though there are reports of activity of sunitinib [33].

In the metastatic setting, treatment with imatinib should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumour progression, even when lesions have been previously surgically excised [I, A] [34]. When treatment is started, the patient should be alerted to the importance of compliance with therapy, as well as interactions with concomitant medications and foods, and 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 never been established prospectively [35]. 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 associated with 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 [36–39]. Randomised trials did not

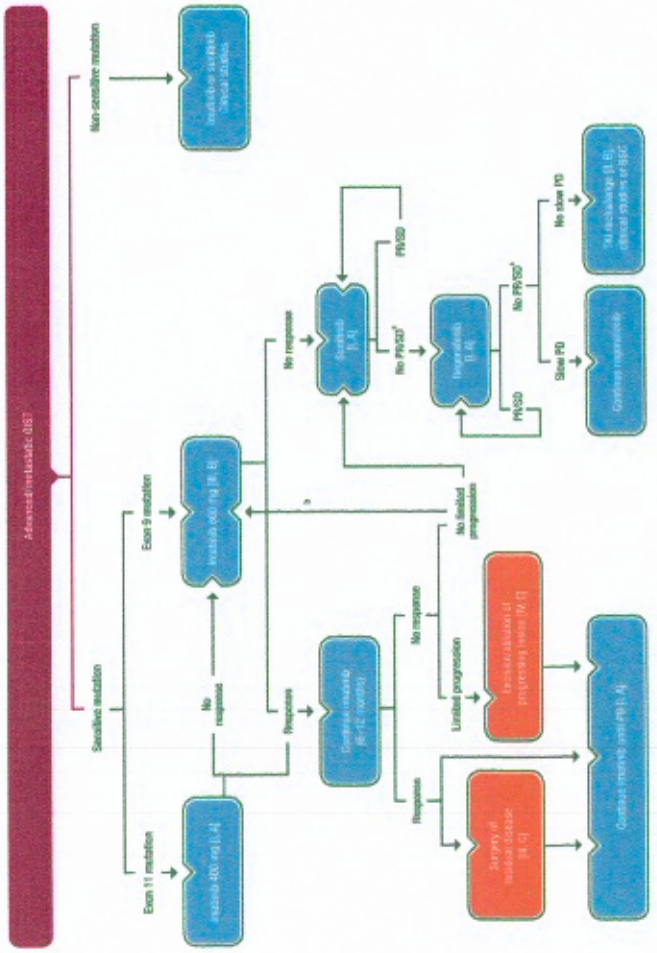

Figure 2. Management of advanced/metastatic GIST.
[a]Surgery of limited progression may be considered.
[b]If previously treated with 400 mg imatinib.
BSC, best supportive care; GIST, gastrointestinal stromal tumour; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

prove feasible (stopped early because of slow accrual), except for a small positive trial in which all patients had peritoneal disease [40]. Thus, the surgical option should be individualised after making the decision with the patient in the case of uncertainty [III, C]. Surgical excision of progressing disease has not been beneficial in published retrospective series, but surgery of limited progression, such as the 'nodule within a mass', has been associated with a PFS in the same range as for second-line treatment with sunitinib. Therefore, this may be a palliative option for an individual patient with limited progression, while continuing imatinib [IV, C]. Non-surgical procedures (e.g. local treatment, such as ablations or palliative radiotherapy) 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 [III, B], with the exception of insensitive mutations (if treated with the lower dose) [27–30]. 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 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 through expert advice, exploiting dose reductions and possibly plasma level assessment), standard second-line treatment is another TKI, sunitinib [I, A] [41]. The drug was proved effective in terms of PFS following a '4 weeks on/2 weeks off' regimen. Data have shown that a continuously dosed daily oral regimen with a lower daily dose (37.5 mg) is effective and well tolerated, although no formal comparisen has been carried out within a randomised clinical trial [42]. This schedule could therefore be considered an option on an individualised basis [III, C].

After confirmed progression on sunitinib, a prospective placebo-controlled randomised trial proved that regorafenib, at the dose of 160 mg daily for 3 out of every 4 weeks, can significantly prolong PFS. This therapy, as it becomes routinely available, is therefore standard third-line therapy for patients progressing on or failing to respond to imatinib and sunitinib [I, A] [43].

Patients with a metastatic GIST should be considered for participation in clinical trials of 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 [44]. Likewise, there is evidence that continuing a treatment with a TKI, 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), at least in a proportion of patients with a slow progression. Therefore, re-challenge or continuation of treatment beyond progression with imatinib to which the patient has already been exposed is an option [II, B]. On the other hand, the use of combinations of TKIs outside of clinical studies should be discouraged, because of the potential for considerable toxicity. Several TKIs have been tested in uncontrolled phase II trials in imatinib-resistant patients, with observations of activity in only a fraction of total patients.

Response evaluation

Response evaluation is complex, and early progression, in particular, should be confirmed by an experienced team. Antitumour activity translates into tumour shrinkage in most 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 an increase in the tumour size may be indicative of the tumour response if the tumour density on CT scan is decreased [45]. The 'appearance' of new lesions could also be due to the easier detection of less dense tumours. 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 proven 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. preoperative cytoreductive treatments) [46]. However, a small proportion of GISTs have no FDG uptake. The absence of tumour progression after 6 months of treatment is also considered as tumour response [47]. 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 [48].

Follow-up

There are no published data to indicate the optimal routine follow-up policy of surgically treated patients with localised disease. Relapses occur more often 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. 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 may be carried out with abdominal CT scan or MRI, e.g. every 6–12 months for 5 years.

Very low-risk GISTs probably do not require routine follow-up, although the risk is not zero. X-ray exposure is a factor to consider, especially in low-risk GIST, with abdominal MRI being an alternative [49].

Methodology

These Clinical Practice Guidelines have been produced by ESMO in partnership with EURACAN, the European Reference Network for rare adult solid cancers. These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). They are conceived to provide the standard approach to diagnosis, treatment and survivorship on sarcomas and GISTs. Recommended interventions are intended to correspond to the 'standard' approaches, according to current consensus among the European multidisciplinary sarcoma community of experts. These are represented by the members of the ESMO Sarcoma Faculty and experts appointed by all institutions belonging to the Sarcoma domain of EURACAN. Experimental interventions considered to be beneficial are labelled as 'investigational'. Other non-standard approaches may be proposed to the single patient as 'options' for a shared patient-physician decision in conditions of uncertainty, as long as some supporting evidence (though not conclusive) is available. Algorithms accompany the text, covering the main typical presentations of disease, and are meant to guide the user throughout the text. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 3. Levels of evidence and grades of recommendation have been applied using the system shown in Table 4. Statements without grading were considered justified standard clinical practice by the experts.

Disclosure

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Table 3. Summary of recommendations

Diagnosis and pathology/molecular biology
- Endoscopic ultrasound assessment and then follow-up is the standard approach for patients with oesophagogastric or duodenal nodules < 2 cm [IV, C]
- Biopsy/excision is the standard approach to tumours ≥ 2 cm in size [IV, C]
- Mutational analysis inclusion in the diagnostic work-up of all GISTs should be considered standard practice [II, A] (with the possible exclusion of < 2 cm non-rectal GISTs)

Management of local/locoregional disease
- The standard treatment of localised GISTs is complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes [II, A]
- If laparoscopic excision is planned, the technique needs to follow the principles of oncological surgery [II, A]
- When R0 surgery implies major functional sequelae, and preoperative medical treatment is not effective, the decision can be made with the patient to accept possible R1 resection [IV, B]
- Adjuvant therapy with imatinib for 3 years is the standard treatment of patients with a significant risk of relapse [I, A]
- *PDGFRA D842V*-mutated GISTs should not be treated with adjuvant imatinib [IV, D]
- Adjuvant treatment should be avoided in NF1-related and SDH expression-negative GISTs [IV, D]
- Patients at a very high risk of peritoneal relapse (in case of tumour rupture at the time of surgery) should be considered for imatinib therapy [IV, A]
- If R0 surgery with no expected major sequelae is not feasible, pre-treatment with imatinib is standard [II, A]

Management of advanced/metastatic disease
- Imatinib is the standard treatment of locally advanced inoperable and metastatic disease [I, A]
- Imatinib is also the standard treatment for patients with metastatic disease who have had all lesions removed surgically, although surgery is not recommended as a primary approach in the metastatic setting. The standard dose of imatinib is 400 mg daily [I, A]
- Standard treatment of patients with *KIT* exon 9 mutation is 800 mg daily of imatinib [II, B]
- In the metastatic setting, treatment with imatinib should be continued indefinitely, unless intolerance or specific patient request to interrupt [I, A]
- Surgery of residual metastatic disease should be individualised after making the decision with the patient in the case of uncertainty [II, C]
- Surgical excision of progressing disease should be considered for an individual patient with limited progression, while continuing imatinib [IV, C]
- In the case of tumour progression on 400 mg of imatinib, the dose can be increased to 800 mg daily [III, B] (with the exception of insensitive mutations)
- In the case of confirmed progression or rare intolerance on imatinib, standard second-line treatment is sunitinib [I, A]
- Regorafenib, at the dose of 160 mg daily for 3 out of every 4 weeks, is the standard third-line therapy for patients progressing on or failing to respond to imatinib and sunitinib [I, A]
- Rechallenge or continuation of treatment beyond progression with imatinib to which the patient has already been exposed is an option [II, B]

GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type 1; PDGFRA, platelet-derived growth factor alpha; R0, no residual tumour; R1, microscopic residual tumour; SDH, succinate dehydrogenase.

Table 4. 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 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 groups, case reports, 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

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or consultation fees from Novartis, Lilly, Pfizer, PharmaMar and Bayer; SBi has reported advisory/consultant roles for Lilly, Bayer, Pfizer, Novartis, Isolfol and Clinigen and conducted studies sponsored by Janssen-Cilag, Eisai and Loxo Oncology; SBo has reported honoraria and travel grants from Nanobiotix and Lilly and received travel grants from PharmaMar; IB has received research funds from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Amgen and has reported advisory roles for AstraZeneca, Roche, Merck Sharp & Dohme, LEO Pharma, Amgen, Bristol-Myers Squibb, Pfizer and Novartis; TB has reported honoraria from Roche and PharmaMar and advisory board and honoraria from Amgen, Bayer, Novartis, Eisai and Eli Lilly; JMB has reported consulting advisory role for PharmaMar, Lilly, Bayer, Novartis and being a member of the speaker's bureau for PharmaMar and received travel grants from PharmaMar and Lilly; APDT is a member of the speakers' bureau for Lilly, Pfizer and Merck Sharp & Dohme; XGDM has reported advisory role for Lilly, PharmaMar and Novartis; PD has reported conducted research sponsored by Eli Lilly; ME has participated in advisory boards for Bayer, Sobi, Lilly, Eisai and Novartis; AMF has conducted studies sponsored by Amgen Dompé, AROG Bayer, Blueprint Medicines, Eli Lilly, Daiichi Sankyo Pharma, Epizyme, GlaxoSmithKline, Novartis, Pfizer, PharmaMar; SG has received research grants and honoraria from Novartis, Pfizer and Bayer; HG has received research grants from Novartis, Daiichi Sankyo Pharma and Pfizer; HG has received research grants from Novartis, Daiichi Sankyo Pharma and Pfizer; AG has reported compensation for advisory boards from Novartis, Pfizer, Bayer, Lilly, PharmaMar and Nanobiotix, honoraria from Novartis, Lilly, PharmaMar and Nanobiotix, and research funds from PharmaMar and travel grants from PharmaMar and Nanobiotix; BH has received research grants from EuroSarc and has conducted research with EIT Health in collaboration with GE healthcare and Philips, he has received reagents from Takeda and Astellas to conduct clinical trials without direct funding; PH has reported conducting research sponsored by Novartis, Blueprint Medicines, Nanobiotix and Lilly and has received honoraria and travel grants from PharmaMar, Eisai and Lilly; HJ has reported co-appointment with Orion Pharma and holds stock in Sartar Therapeutics, Faron Pharmaceuticals and Orion Pharma; RLJ is a consultant for Adaptimmune, Blueprint Medicines, Clinigen, Eisai, Epizyme, Daiichi, Deciphera, Immunedesign, Lilly, Merck and PharmaMar; IJ has received honoraria from Lilly for lectures; PJ has reported being a consultant for Stryker for the design of a new tumour prosthesis; BK has reported honoraria from Novartis, Pfizer and Bayer and advisory role for Bayer; KK has received travel grants from Novartis and Pfizer; ALC has received honoraria from Pfizer, Novartis, Lilly, Amgen, Bayer and PharmaMar; MAP has served on advisory boards for Bayer and Pfizer, and has received research grants from Novartis; PRe has served on advisory boards for Novartis, Pfizer, PharmaMar, Ariad, Merck, Deciphera, Roche, Clinigen and Lilly and has received honoraria from Novartis, Pfizer, Bayer, PharmaMar and Lilly; PRu has received honoraria for lectures from Novartis, Pfizer, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche and has served as a member of advisory board for Novartis, Amgen, Merck Sharp & Dohme, Bristol-Myers Squibb, Blueprint Medicines; PS has received honoraria from Daiichi Sankyo Pharma, Eisai, Eli Lilly, Medspace, Novaris, Swedish Orphan Biovitrium, has reported consulting or advising roles for Sixth Element Capital, Adaptaimmune, Amcure, AstraZeneca, Bayer, Blueprint Medicines, Bristol-Myers Squibb, Boeringer Ingelheim, Cristal Therapeutics, Daiichi Sankyo Pharma, Eisai, Eli Lilly, Epizyme, Genzyme, Ipsen, Loxo Oncology, Medspace, Nektar, Novartis, Philogen, Piqur Therapeutics, Plexxikon, is a member of speaker's bureau of Bayer, Eisai, Eli Lilly, GlaxoSmithKline, Novartis, PharmaMar, Swedish Orphan Biovitrium, has received research grants from Bayer, Blueprint Medicines, CoBioRes, Exelixis, Bristol-Myers Squibb, Novartis, Plexxikon, and has received travel grants from Sixth Element Capital, Adaptaimmune, Amcure, AstraZeneca, Bayer, Blueprint Medicines, Bristol-Myers Squibb, Boehringer Ingelheim, Cristal Therapeutics, Daiichi Sankyo Pharma, Eisai, Eli Lilly, Epizyme, Genzyme, GlaxoSmithKline, Ipsen, Loxo Oncology, Medpace, Nektar, Novartis, PharmaMar, Philogen, Piqur Therapeutics, Plexxikon, Swedish Orphan Biovitrium; SSt has received honoraria from Eli Lilly and PharmaMar, research grants from Amgen Dompé, Advenchen, Bayer, Eli Lilly, Daiichi Sankyo Pharma, Epizyme Inc., Novartis, Pfizer and PharmaMar; travel grants from PharmaMar and has reported advisory/consultant roles for Bayer, Eli Lilly, ImmuneDesign, Maxivax and PharmaMar; WVdG has received research grants from Novartis; EW has reported travel/research grants and/or honoraria from Novartis Oncology, Milestone, Menarini, PharmaMar, Roche, Nanobiotix and Bayer; JYB has declared research grants and honoraria from Novartis, GlaxoSmithKline, Pfizer and Bayer; IL has received honoraria from Bristol-Myers Squibb, MDS, Roche, Novartis and Pfizer for scientific presentations or research; NA, RB, JVMGB, AB, EDA, AFed, VF, AFer, GG, TG, RLH, RI, SK, DAK, RP, PP, SP-N, ALP, OM, MM, MHR, AAS, SSl, KSH, MU, JW and FVC have declared no conflict of interest. SF, AH and OZ have not reported any potential conflicts of interest.

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