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Tumour Review

GEIS guidelines for gastrointestinal sarcomas (GIST)

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ABSTRACT

Gastrointestinal stromal sarcomas (GISTs) are the most common mesenchymal tumours originating in the digestive tract. They have a characteristic morphology, are generally positive for CD117 (c-kit) and are primarily caused by activating mutations in the *KIT* or *PDGFRA* genes*(1)*. On rare occasions, they occur in extravisceral locations such as the omentum, mesentery, pelvis and retroperitoneum.

GISTs have become a model of multidisciplinary work in oncology: the participation of several specialties (oncologists, pathologists, surgeons, molecular biologists, radiologists…) has forested advances in the understanding of this tumour and the consolidation of a targeted therapy, imatinib, as the first effective molecular treatment in solid tumours. Following its introduction, median survival of patients with advanced or metastatic GIST increased from 18 to more than 60 months. Sunitinib and Regorafenib are two targeted agents with worldwide approval for second- and third-line treatment, respectively, in metastatic GIST.

Prologue

Gastrointestinal stromal sarcomas (GISTs) are the most common mesenchymal tumours originating in the digestive tract. They have a characteristic morphology; are generally positive for CD117 (c-kit) and are primarily caused by activating mutations in the *KIT* or *PDGFRA*. On rare occasions, they occur in extra-visceral locations such as the omentum, mesentery, pelvis and retroperitoneum.

GISTs have become a model of multidisciplinary work in oncology: the participation of several specialities (oncologists, pathologists, surgeons, molecular biologists, radiologists…) has allowed advances in the understanding of this tumour and the consolidation of a targeted therapy: Imatinib, as the first molecular treatment that is effective in solid tumours. Following the introduction of this drug, median survival of patients with advanced stage GIST has increased from 18 to more than 60 months. Other drugs such as Sunitinib or Regorafenib have been subsequently registered as second-line treatment for metastatic GIST.

Diagnostic evaluation

Radiology

Radiological diagnosis of GIST is similar to that of other digestive tract tumours. In several studies, GISTs appear as submucosal lesions [1] and in ultrasound studies as hypoechogenic masses that, when large, can displace neighbouring structures and show cystic, necrotic or haemorrhagic areas.

A computerized tomography [2] scan and magnetic resonance imaging (MRI) are the first choice to study location and extension [3]. A CT scan with contrast and image acquisitions of the arterial and portal phases allows identification of hypervascular hepatic lesions that would otherwise go unnoticed and become evident when they become hypodense with treatment. The latter could

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wrongly suggest progression due to the development of new lesions. On the contrary, a CT scan without endovenous contrast allows detection of haemorrhage or intratumoral calcification.

In a CT scan, tumours appear as well circumscribed exoluminal masses that, after the contrast, show heterogeneous enhancement, especially large tumours, which may have necrotic-haemorrhagic areas or degenerative components [4].

An MRI is useful for the local study of tumours located in the pelvic area [5] as well as for the study of the mesenteric and peritoneal extension.

Histology

Techniques for histological diagnosis

The technique of choice for providing histological diagnosis is echoendoscopy-guided-biopsy or a CT-guided percutaneous biopsy when the first option is not possible. Although FNA (fine needle aspiration) endoscopy could be performed on oesophagogastric tumors, this technique does not usually provide sufficient material to carry out a proper, definitive histological diagnosis and molecular analysis, thus a biopsy would also be called for [6–9]. If the biopsy become complex a laparoscopic incision or laparotomy is required in order to obtain diagnosis. However, the use of biopsy forceps for polypectomy increases the risk of perforation and should be avoided and performed only in exceptional cases.

Preoperative endoscopic biopsy is not necessary when a lesion is considered suspicious, resectable or operable. On the other hand, it would be needed for patients with disseminated disease or in locally advanced cancers, when considering neoadjuvant therapy, in order to start the treatment according to mutational analysis [10].

Pathology

GIST is the most common mesenchymal tumor originated in the digestive tract. They have characteristic morphological features and are generally positive for CD117 (c-kit), and have active KIT o PDGFRA mutations [11].

Macroscopic characteristics.

Most common sites. They are usually found in stomach (60%), small intestine, jejunum and ileum (30%), duodenum (5%), rectum (2–3%) and colon (1–2%). They are much less frequent in the esophagus (<1%). In some cases there is presence of disseminated tumor with unknown primary tumor and a small number originates in the omentum, mesentery and retroperitoneum [12,13]. Metastases are typically intra-abdominal involving the peritoneum and liver. From a distance they are odd-looking and usually found on skin, bones and soft tissue.

Morphology. The size of GIST is variable (up to 38 cm). Most tumors measure around 5 cm at the time of diagnosis. They typically originate in the digestive track and can be submucosal, intramural or subserosal. They are rarely invasive and there is often ulceration of the mucous membrane with poor prognosis [12]. Necrotic, hemorrhagic and cystic degeneration areas are usually displayed [14]. They are usually solitary, but in sporadic cases have multiple lesions [15] in familial or neurofibromatosis GIST and Carney Triad [16]. Its growth pattern is extensive (21%) and pseudoextensive (45%) or infiltrative (24%). The pathology report must always include three-dimensional tumor measurement, the existence of quantification of necrosis and distance between lesion and margin, as incomplete resection is associated with poor prognosis [17].

Microscopic characteristics. Three histological types can be distinguished according to the cellular appearance: fusiform cells (77%), epithelioid cells (8%) and mixed cells (15%) [11]. The epithelial type is more frequently observed in stomach and omentum [18].

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 is equivalent to the former 50 high-power fields) [19,20]. Strict criteria should be followed as pyknosis and karyorrhexis must not be overlooked.

Immunohistochemistry. Over 95% of GISTs have CD117 (c-kit) expression with diffuse cytoplasmic staining pattern but rarely in the membrane or Golgi apparatus. There is intense staining in 75% of cases. Moreover, 70–90% also express CD34, 20–30% actin, 8–10% S-100 and desmin in 2–4% [11]. The immunohistochemical positivity for CD117 is independent from the mutational status of KIT and PDGFRA [21]. The almost pathognomonic IHC marker DOG1, corresponding to the potassium transporter ANO1, can optionally be included in the initial IHC panel and is highly recommended in negative c-kit [22] in which DOG1 is expressed in over 35% of cases. IHC expression of CD117 and/or DOG1 confirms GIST diagnosis.

In KIT/PDGFRA wild type (WT) GIST, immunohistochemistry for SDHB protein may be done [20,23].

Differential diagnosis. The main differential diagnosis in fusiform GIST comprises mainly smooth-muscle tumors (leiomyoma and leiomyosarcoma); schwannoma and malignant peripheral nerve sheath tumor; inflammatory myofibroblastic tumour; solitary fibrous tumor, sarcomatoid carcinoma; inflammatory fibroid polyp and desmoid fibroidmatosis. Differential epithelioid GIST diagnosis includes poorly differentiated carcinomas; endocrine cancers and variants of epithelioid leiomyosarcoma and malignant peripheral nerve sheath tumor. Luckily, morphological features together with an adequate immunohistochemical panel allow proper diagnosis [14].

Kit-negative GIST. Between 4% and 5% of GIST with typical morphological features are negative for CD117 [24,25]. Those with negative stains or weak staining less than 10% of tumor extension, are to be considered as such. Kit-negative GIST is clinically, pathologically and genetically different from kit-positive GIST. Although they are more frequently found in stomach, they can also be observed in the omentum and peritoneal surface. They are less commonly CD34 and actin positive, while curiously, desmin expression is approximately 30%, especially in stomach lesions and epithelioid morphology [22]. DOG1-positive was observed in slightly over one third of tumors [22].

Kit-negative GISTs present a true diagnostic challenge. It is recommended to refer these cases to a reference center, extend the immunohistochemical panel with other markers such as DOG1 and a mandatory study for KIT and PDGFRA mutation, being mindful that there is a small percentage of GIST with typical morphology, negative for CD117 and DOG1 and wild type for KIT and PDGFRA genotype [25]. It should be taken into consideration that dedifferentiation in GIST may occur either de novo or after chronic imatinib exposure and can represent a diagnostic pitfall. This phenomenon is not related to additional KIT mutations, but might be secondary to genetic instability, either represented by loss of heterozygosity or low level of KIT amplification [26].

Final recommendations

- Pathologic diagnosis is based on both unique microscopic features and ancillary techniques (CD-117, CD34, actin, desmin, S-100 and DOG1), which are very important to confirm diagnosis.
- The pathology report must include information for risk assessment guidelines (Table 1) [27]: location, tumor size, number of mitoses on a total area of 5 mm^2 counted in the most active regions and margins status.

Table 1
Primary gastrointestinal stromal tumors (GIST) risk assessment guidelines.

Tumor parameters		Risk of progression[b] (%)	
Mitotic index[a]	Size	Stomach[d]	Small bowel[d]
≤5	≤2 cm	No (0%)	No (0%)
	>2 to ≤5 cm	Very low (1.9%)	Low (4.3%)
	>5 to ≤10 cm	Low (3.6%)	Moderate (24%)
	>10 cm	Moderate (10%)	High (52%)
>5	≤2 cm	No[c]	High[c]
	>2 to ≤5 cm	Moderate (16%)	High (73%)
	>5 to ≤10 cm	High (55%)	High (85%)
	>10 cm	High (86%)	High (90%)

[a] Number of mitoses on a total area of 5 mm^2.
[b] Defined as metastasis or cancer-related death.
[c] Small number of cases.
[d] See stomach for omentum and other locations (esophagus, colon, peritoneum and mesentery) see small bowel.

- It is advisable to refer the complex or unusual cases to experienced centers.
- Regarding tumors with atypical morphology, an extended phenotype of DOG1 as well as KIT and PDGFRA gene mutation analysis is required.
- 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.

Molecular biology

GISTs are characterized by activating mutations in KIT and PDGFRA genes which are shown to be mutually exclusive, encoding a tyrosine kinase receptor type III (TKR) [14,15]. KIT mutations are found in 60–85% of GIST tumors while PDGFRA mutations are found in 5–10%. Approximately 10–15% of GIST do not have detectable mutations in any of these receptors (GIST wild type), suggesting that other molecular routes can also be involved in the pathogenesis of these tumors [21,28–30].

Spectrum of mutations in GIST

Mutations found in GISTs mainly affect exons that codify functional domains of KIT and PDGFRA receptors. Among the main types of mutation we find the following: deletions, point mutations, duplications, insertions and complex mutations [29].

Mutation detection before tyrosine kinase (TK) inhibitor therapy such as Imatinib is known as primary mutation (and mainly affects exons 11, 9, 13 and 17 of KIT, and exons 18, 12 and rarely affects 14 of PDGFRA). Meanwhile, mutations detected during treatment, which are to a large degree responsible for resistance to TK inhibitors, are known as secondary mutations (generally detected in exons 13, 14 and 17 of KIT and 18 of PDGFRA) [28,29].

KIT mutations. The most common KIT mutations affect exon 11 (juxtamembrane domain). Approximately 70% of GISTs present some type of mutation in this exon [28,31]. The most frequent mutations in this exon are interstitial deletions, commonly affecting the beginning of exon 11 (between codons 550 and 579) and especially codons 557–559. Then there are point mutations, albeit with a lower incidence and limited to four codons (557, 559, 560 and 576). Lastly, at the extreme end of the exon (between codons 571 and 591) and in a much smaller proportion of patients, tandem duplications associated to GIST gastric site and epithelioid or mixed cell morphology are found [21,32–34].

In exon 9 (extracellular domain) only duplication of residues 502–503 have been described and is present in 9–20% of cases depending on the study. This mutation is mainly associated with GIST of small bowel location and greater malignant potential [29,34].

The KIT-TK domains are encoded by exons 13 and 17. Only point mutations have been found in these exons, the frequency being between 0.8 and 4.1% for exon 13 lower than 1% in the case of exon 17 [21,29,34–36].

PDGFRA mutations. Overall, the estimated frequency rate of PDGFRA mutations in GIST is 5–10% [21,28,37], which are associated with localized gastric GIST and epithelioid morphology [21,31,37]. Mutations are concentrated in the juxtamembrane domain (0.7%) encoded by exon 12; in TK domain (6%) encoded by exon 18, D842V mutation being the most frequent (65%-75%); and very rarely in exon 14 (0.1%) [21,28,31,37].

Comparison between localized and advanced GISTs has shown that the mutations of PDGFRA exon 18 as well as KIT exon 11 substitutions are more likely to be seen in patients with localized GISTs (odds ratio 7.9, 3.1, 2.7 and 2.5, respectively), while KIT exon 9 502_503dup and KIT exon 11 557_559del are more frequent in metastatic GISTs (odds ratio of 0.3 and 0.5, respectively) [38].

GIST wild type. Around 12–15% of adult GIST and 90% of pediatric GIST lack KIT and PDGFRA mutations [29]. Other intracellular signaling pathways as the one controlled by BRAF with mutations described in 7% of wild type GIST [39] and mutations in the succinate dehydrogenase enzymatic complex subunit genes (SDH), most associated with germline mutations [40], have been involved in these tumors.

Approximately 7.5% of GIST (30% GIST WT) are SDH-deficient and not driven by KIT/PDGFRA mutations. The occurrence of SDH-deficient GISTs is restricted to stomach, and they typically occur in children and young adults representing a spectrum of clinical behavior from indolent to progressive. Slow progression is a common feature even after metastatic spread has taken place, and many patients live years with metastases. SDH-deficient GISTs have characteristic morphologic features including multinodular gastric wall involvement, often multiple separate tumors, common lymphovascular invasion, and occasional lymph node metastases. Diagnostic is the loss of succinate dehydrogenase subunit B (SDHB) from the tumor cells and this can be practically assessed by immunohistochemistry. SDHA is lost in cases associated with SDHA mutations. Approximately half of the patients have SDH subunit gene mutations, often germline and most commonly A (30%), and B, C or D (together 20%), with both alleles inactivated in the tumor cells according to the classic tumor suppressor gene model. Half of the cases are not associated with SDH-mutations and epigenetic silencing of the SDH complex is the possible pathogenesis. SDH-loss causes succinate accumulation and activation of pseudohypoxia signaling via overexpression of HIF-proteins. Activation of insulin-like growth factor 1-signaling is also typical of these tumors. SDH-deficient GISTs are a unique group of GISTs with an energy metabolism defect as the key oncogenic mechanism [30,41].

KIT-negative GIST

Approximately 5% of GIST are c-kit negative, leading to diagnostic difficulty. Between 30% and 50% of these tumors present mutations in KIT or PDGFRA [31,42–44], which may have therapeutic implications. The notion that a GIST can be negative for c-kit as well as wild-type for KIT and PDGFRA mutations is not entirely clear considering that current diagnosis is by exclusion [31]. Furthermore, the last European consensus proposed using a mutational analysis of KIT and PDGFRA to confirm GIST diagnosis, especially in CD117/DOG1 negative cases [20].

Syndromes associated with GIST

At present, there are many syndromes associated with GIST, most of them in which a germline mutation in a predisposition gene is identified (SDH, KIT or NF1 genes). In these cases it is highly recommended that these patients and their relatives are advised in a genetic counseling unit.

The following syndromes are associated with GIST:

(1) Associated with SDH-deficiency:
   - Carney Triad: characterized by gastric GIST, paraganglioma, pulmonary chondroma, which may develop in any age group, making it difficult to discard this condition in pediatric wild-type GIST [45].
   - Carney-Stratakis syndrome: characterized by germline mutations in some subunits of the SHD enzyme complex. Characterized by a dyad of GIST and paraganglioma [46,47].

(2) Neurofibromatosis Type-1 (NF1): caused by inactivating mutations in NF1 gene. Associated with wild-type GIST predominantly located in the small intestine [48]. Loss of NF1 leads to high levels of active RAS and hyperactivation of MAPK pathway [30].

Final recommendations

We strongly recommend including a molecular systematic analysis in the diagnosis of all GIST, given the type of relevant predictive and prognostic information provided and required in cases of GIST without CD117 and DOG1 expression. In these cases, it is recommended to refer patients to a center of reference with their own laboratory, integrated in quality assurance programs and proven experience.

Localized disease

Surgery

Complete surgical resection is the standard treatment for localized GIST. Radiological criteria for unresectability include infiltration of the celiac trunk, the superior mesenteric artery or mesenteric artery-to-portal vein. Lymphadenectomy is unnecessary given the low frequency of lymph node affectation or metastasis. Some exceptions could be SDH deficient GIST especially in pediatric population.

The aim is to achieve a R0 type surgery (optimal surgery), complete removal leaving an intact capsule. Segmental resection of intestine and stomach is accepted, thus, aggressive and a more extensive surgery to remove unaffected tissue is unnecessary. It is therefore necessary, in some cases, to remove neighboring organs and perform a surgical "block excision" although a multivisceral resection should be avoided and multidisciplinary consultation is first indicated. Endoscopic removal is not recommended on oesophagus and gastric tumors because of the difficulty to get R0 complete resections. Peritoneal and hepatic surfaces should be carefully examined during a laparotomy to rule out tumor spread. Tumor resection must be carefully performed to avoid tumor rupture [10].

Regarding R1 resection (marginal excision containing tumor cells), re-excision could be offered, and shared with the patient, if this does not imply major functional sequelae. If the context of R1 surgery is a very low to low-risk tumor, the physician should communicate the wait-and-see approach to the patient as opposed to aggressive surgery with permanent damage since there is no clear evidence that R1 margins entail a worse prognostic in such cases [10,49,50].

A laparoscopic approach may be considered for tumors in favorable anatomic locations by expert surgeons, only in situations where a complete resection without capsule rupture is feasible, and should be removed in a plastic bag. In this regard, a laparoscopic approach is strongly discouraged in patients with voluminous tumors [10,51,52].

Prognostic factors after surgery in localized GIST

Relapse-risk assessment for primary GIST is paramount not only providing prognostic information when trying to determine risk factors but also estimating the potential benefit of adjuvant imatinib. In 2002, an index was proposed (NIH Consensus NIH or Fletcher) [18] based on studies of prognostic factors studies for patients with localized GIST, to estimate the risk of recurrence (Table 2; Fig. 1), based on the number of mitosis per 50 high-power fields (HPF), the size of the primary tumor and the two variables with the greatest prognostic significance. Principally, it seems that any GIST has malignant potential and the index makes it possible to classify GIST patients according to risk factors and complete resection.

Subsequently, Miettinen et al., analyzed data of 1.765 patients with gastric GIST and observed that patients only developed metastasis in 2–3% tumors with <10 cm and <5 mitosis/50 HPF, compared with 68% of those who presented >10 cm and >5 mitosis/50 HPF [12]. A second series including 906 patients with <10 cm and <5 mitosis/50 HPF tumor located in the jejunum and ileum, presented recurrence in 24% compared to 90% which presented >10 cm and >5 mitosis/50 HPF tumor.

Table 2
Group risk according to Fletcher et al. [18].

	Size[a]	Mitotic index (50 HPF)[b]
Very low-risk	<2 cm	≤5 mitosis
Low-risk	2–5 cm	≤5 mitosis
Intermediate-risk	≤5 cm	6–10 mitosis
	5–10 cm	≤5 mitosis
High-risk	>5 cm	>5 mitosis
	>10 cm	Any number of mitosis
	Any size	>10 mitosis

[a] Size takes into account the maximum dimension. Variation is accepted with the measurement of tumors before or after fixation and the existing differences among observers.

[b] 50 HPF represent between 10 and 12 mm^2 in current optical density. Ideally, the mitotic index should be expressed according to the surface to be examined based on the power field magnification (HPF).

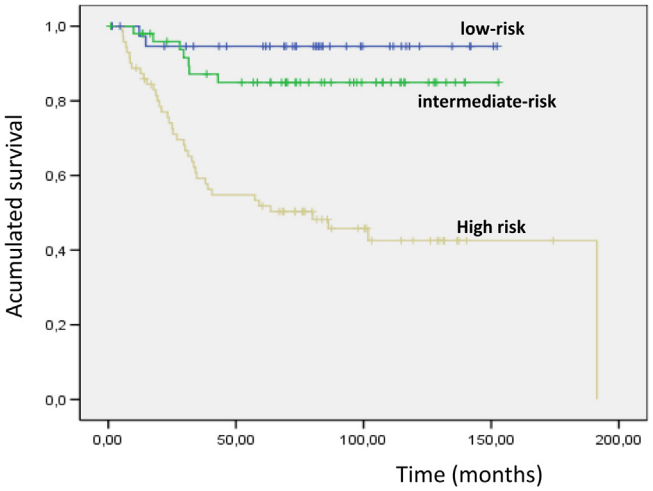

Fig. 1. Relapse free survival according to 162 patients in GEIS database.

Based on this data, these same authors put forward a new risk index (AFIP/Miettinen) that includes anatomic site [27]. This classification better reflects the high-risk population than the Fletcher index Table 3; Fig. 2), especially between the intermediate and low-risk groups. The risk of gastric cancer relapse varies from 2% in tumors with <5 mitosis per 50 HPF to 90% in gastrointestinal tract GIST with tumors more than <10 cm and <5 mitosis/50 HPF. The casuistry of GEIS group has shown that the Miettinen's classification exhibited statistical significance for discriminating low, intermediate and high-risk groups. This was not the case when the Fletcher classification was used [33]. The main differences between both classification systems lies in patients with gastric GIST, larger than 10 cm but with <5 mitosis per HPF. Using Fletcher's classification, the latter would be in the high-risk group with a recurrence-free survival (RFS) of 50% at 5 years. Nevertheless, they would fall within the intermediate-risk category with a RFS of 80% according to the Miettinen group classification. On the other end of the spectrum we find GIST tumors with extragastric location of <5 cm and more than 5 mitosis per HPF. According to Fletcher's classification, they would fall within the intermediate group with a RFS probability of 85% versus being in the high-risk group with 45% RFS in the Miettinen group classification. It is important to note that Miettinen considered a total area 5 mm^2 in 50 fields HPF characterized by the use of different optical components, while in practice 50 HPF typically corresponds to a total area of 10 mm^2. Therefore, if we use Miettinen's risk classification, we should also make the correction of dividing the number of mitosis by half including the current optical elements by 50 HPF. Other

Table 3
Group risk in GIST adapted from Miettinen et al.

	Size	Mitotic index (50 HPF)[a]	Location
Very low-risk	2–5 cm	≤5 mitosis	Gastric
Low-risk	>5 y ≤10 cm	≤5 mitosis	Gastric
	2–5 cm	≤5 mitosis	Intestinal
Intermediate-risk	>10 cm	≤5 mitosis	Gastric
	>5 y ≤ 10 cm	≤5 mitosis	Intestinal
	2–5 cm	>5 mitosis	Gastric
High-risk intestinal	2–5 cm	>5 mitosis	Intestinal
	>10 cm	≤5 mitosis	Intestinal
	>5 y ≤ 10 cm	>5 mitosis	Gastric
	>10 cm	>5 mitosis	Gastric
	>5 y ≤ 10 cm	>5 mitosis	Intestinal
	>10 cm	>5 mitosis	Intestinal

[a] 50 HPF represent an area of 5 mm^2 in the optical fields used by Miettinen.

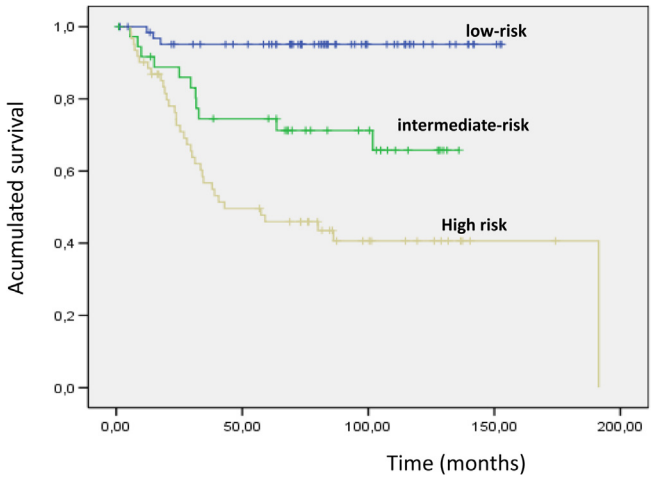

Fig. 2. Disease free survival according to 162 patients in GEIS database.

succeeding risk classifications such as the American Joint Committee on Cancer (TNM) [53] or the nomogram [54] for the individual risk assessment show some differences such as the anecdotal evidence of ganglionic extension or the selection bias that encumber studies in some large centers and magnify the likelihood of relapse. Joensuu H. recently introduced a capsule rupture classification known as modified NIH that simplifies the site classification (gastric/non-gastric) but at the same time renders heat maps to be more complex as categorization of continuous variables is not used [55].

The NCCN [56] and ESMO [20] guidelines tend to favor Miettinen's classification when capsular rupture is considered comparable to peritoneal dissemination.

A further problem posed, at least theoretically, is regarding adjuvant imatinib clinical trials designed using Fletcher's risk classification. If we were to adopt a more liberalized stance on drugs, we would recommend adjuvant imatinib treatment for patients with gastric GIST for tumors of 10 cm or larger with <5 mitosis/HPF (considered as high risk according to Fletcher), when the risk of recurrence is 65%. Therefore, the most rational approach should bear in mind the most current prognostic information in which the high risk of recurrence category is more accurate. Although GIST tumors are a model for the so-called molecular target therapies, molecular prognostic factors have not been incorporated in the risk of recurrence classifications.

There is available evidence indicating that the type and location of the mutation has an effect on the risk of recurrence. Deletions affecting exon 11, codon 557/558 (from now on we will referred as critical mutation of the c-KIT gene, have a higher recurrence risk and it will occur within the first 3–4 years after surgery [33,57]. The leading role of "critical mutation" has been confirmed in recent series [55,58].

Additionally, two studies confirm the independent prognostic value of mutations carrying deletions on 557 and/or 558 codons within KIT gene. In a retrospective collection of series conducted by Conticanet network summarizing 1.056 localized GIST cases, authors found that intermediate risk gastric cases harboring "critical mutations" had significantly worse prognosis than other mutational grouping and this prognostic value was also significant in the multivariate analysis [59]. Similarly, in other series from GEIS group with almost 400 patients, patients with critical mutations had significantly worse relapse free survival within intermediate risk, 26% compared with 64%. In the same line, this prognostic value showed to be independent in multivariate analysis [60]. In both studies, mutations within PDGFRa showed a trend towards a better prognosis.

Final recommendations

(1) The standard treatment of localized GISTs is complete surgical resection (III, A)
(2) We recommend the use of the risk group classification proposed by Miettinen as it is the best at identifying low, intermediate and high-risk populations. Spontaneous or intraoperative capsule rupture should be considered as a very poor prognostic factor.
(3) Deletion type of mutations affecting codons 557 and 558 confers a risk for recurrence regardless of its previous classification, according to different series. The risk is greatest within the first 30 months after surgery and then drops drastically. (IV,A)

Adjuvant treatment

Despite the fact that complete resection is feasible in most localized GIST cases, there is still a recurrence rate of up to 50%

according to some series. The role of imatinib as adjuvant treatment to prevent recurrence has therefore been assessed in several clinical trials. Evidence derived from the large Phase III randomized trials ACOSOG Z9001 [61,62] and SSGX-VIII/AIO [63], has shown a relapse-free survival (RFS) benefit with imatinib. Moreover, the SSGX-VIII/AIO study showed an increase of overall survival (OS) with 3 years of imatinib administration over 1 year in high-risk patients (in accordance with NIH modifications). In a 2016 follow-up analysis with median follow up of 90 months, 5 year RFS was 71% for 3 years of imatinib vs 52% for 1 year of imatinib, and 5 year OS was 92% vs 85% respectively (HR 0.60; 95% CI, 0.37 to 0.97; $p = 0.036$) [64].

The EORTC 62024/GEIS-10 study has recently been published [65]. This phase-III trial included intermediate and high-risk patients randomized at 2 years with imatinib over observation. Although the initial endpoint was OS, it was changed to time to imatinib failure (TIF) in 2009 due to the small number of relapses in the control group. No significant statistical differences were found in either arms (OS and TFI) after a 4.7 year follow-up. Nevertheless, there was an objective tendency to an improved TFI in high-risk patients (in both NIH 2002 as well as modified NIH classifications). A benefit was also observed in RFS as previous reported studies favouring adjuvant treatment with imatinib in high-risk patients.

In view of these results, both NCCN and ESMO guidelines as well as consensus of the scientific community, recommend 3 years of adjuvant treatment with imatinib in high-risk patients. Adjuvant treatment for low-risk patients is not indicated. However, currently there is not enough scientific evidence to support adjuvant treatment with imatinib in intermediate-risk patients. Based on these considerations, for uncertain cases it is important to carry out an assessment of risk of recurrence and properly classify them by using modified classification tools (modified Miettinen classification of H Joensuu).

There are still many unclear areas concerning duration of adjuvant treatment and whether more than 3 years of treatment would increase benefit in patients at higher risk. Mature data of PERSIST-5 (NCT00867113) may shed some light on this issue. The SSG XXII is a new intergroup phase III randomized trial of 3 years vs 5 years of imatinib in the highest risk tumors, defined as gastric GIST with mitotic count >10/50 HPF, or non-gastric GIST with mitotic count >5/50 HPF, or tumor presenting with rupture. This study is currently recruiting -also en Spain through GEIS- and its results could refine the imatinib treatment duration (NCT02413736).

Moreover, another aspect which needs to be clarified is whether relapse is actually avoided or just delayed, given the relapses observed in SSGX-VIII/AIO following adjuvant treatment interruption at 6–12 months in both arms [63].

Special cases

- Capsule break: These are generally accepted as disseminated patients given that 100% will relapse, at least on a peritoneal level. Therefore, imatinib administration is recommended as advanced disease setting.
- Specific genotypes: Adjuvant imatinib is not recommended in patients with D842V PDGFRα mutation given its known resistance to it. There is no consensus regarding the benefit of a daily dose of 400 mg of imatinib for carriers of an exon 9 mutation in the KIT gene. The efficacy of a daily dose of 800 mg of imatinib was extrapolated from the evidence of disseminated disease. Nonetheless, in this scenario, it has not been proven in clinical trials and therefore, has not been approved for adjuvant treatment. Survival in patients with Wild-type does not seem to increase with the use of adjuvant imatinib, thus there is still controversy over imatinib administration and each case must be considered individually, although in NF-1 related GISTs there is consensus in avoiding adjuvant treatment.
- Patients with R1 surgery: There is no evidence confirming the benefit of adjuvant imatinib in low-risk patients with affected microscopic margins. Surgical re-excision could be considered for these cases (see surgical section).

Final recommendations

(1) High-risk patients: 3 years of adjuvant treatment with imatinib is recommended (I,A)
(2) Low-risk patients: adjuvant treatment is not indicated (I,A).
(3) Intermediate-risk patients: currently there is not enough scientific evidence to support adjuvant treatment with imatinib (III,B). For uncertain cases it is important to carry out an assessment of risk of recurrence and properly classify them by using modified classification tools (modified Miettinen classification of H Joensuu) and consider the genotype.
(4) Finally, GISTs with D842V PDGFRα mutation should not be treated independently of the risk classification (IV,A)

Advanced disease

Treatment of unresectable or metastatic disease

Dose and efficacy of imatinib treatment

Gastrointestinal stromal tumors have been a paradigmatic example of chemo-resistant tumors with less than 5% of responses and 14 months as the median of survival reported in the literature. Imatinib mesylate (STI571, GleevecTM, Novartis Pharmaceuticals, Basel, Switzerland) is a selective tyrosine kinase inhibitor (TKI), whose targets include ABL, BCR-ABL, KIT and PDGFR, and constitutes a very effective agent for the treatment of clinically advanced, metastatic or surgically unresectable GIST [66,67].

The standard dose of Imatinib of 400 mg per day was established from two different randomized phase III trials in metastatic GIST with positive immunostaining for kit (EORTC-ISG-AGITG y NASG-S0033). In both trials daily doses of 400 mg versus 800 were compared without any survival difference and with a more favorable toxicity profile favoring lower doses. The clinical benefit rates (CR, PR and SD) for 400 mg and 800 mg were 90% and 88% respectively in NASG-S0033 study. These figures were 91% and 87% respectively in EORTC-ISG-AGITG study. Furthermore, there was statistically significant difference, in terms of progression free survival (PFS), favoring 800 mg dose in European trial: Progression free rate at 2 years 52% vs 44% (HR 0.78) [68,69]. In a meta-analysis analyzing 1640 patients enrolled in the mentioned trials, a slight but still significantly advantage was found in terms of PFS for the high-dose arm [70]. Nevertheless, no survival advantage was detected and thus the standard dose, as for general recommendation, is 400 mg daily.

Predictive value of genotype for imatinib efficacy

Interestingly, one of the notable features of the clinical studies of imatinib for treatment of GIST is the consistent observation that defined subsets of GISTs according to their mutational status have different outcomes during treatment and therefore should be considered in devising treatment strategies.

Responses to imatinib depend on the functional domain affected [71]. Table 4 lists the correlation between tumor genotype and objective response (both complete and partial responses) in four trials (phase I-III). On the basis of 768 genotyped GISTs, the objective response rates for KIT exon 11, exon 9 mutants and GISTs WT were 72%, 38% and 28% respectively [72–74]. Likewise, the probabilities of primary resistance to imatinib for KIT exon 11, KIT exon 9, and WT GISTs were 5%, 16% and 23% respectively (Table 1). An

Table 4
Relationship between KIT mutational status, response rate and outcome on imatinib therapy.

	European phase I/II (n = 37)	B2222 phase II (n = 127)	European/AustralianAsian phase III (n = 363)	North American SWOG S0033 phase III (n = 324)	Weighted average
Objective response	% (n)	% (n)	% (n)	% (n)	% (n)
KIT exon 11	83 (24)	83b (85)	70b (248)	67b (211)	71 (568)
KIT exon 9	25 (4)	48 (23)	35 (58)	40 (25)	38 (110)
No mutation	33 (6)	0 (9)	25 (52)	39 (33)	28 (100)
Progressive disease					
KIT exon 11	4%	5%	3%	8%	5%
KIT exon 9	0%	17%	17%	16%	16%
No mutation	33%	56%	19%	21%	23%

[a]Defined as complete or partial response by SWOG (B2222) or RECIST criteria (all other trials); excluded non-evaluable patients.
[b]Statistically difference versus KIT exon 9 and no mutation groups.

even more striking observation is that KIT and PDGFRA mutational status correlates with time to progression (TTP) and overall survival (OS), with superior survival seen for patients with GIST carrying an exon 11 KIT mutation. For example, in the American phase-III trial, the median TTP for patients with GISTs harbouring KIT exon 11, KIT exon 9 and WT was 25, 17 and 12.8 months respectively. A similar OS benefit was seen for patients with KIT exon 11 mutations (60 months) compared with those observed for KIT exon 9 (38 months) or WT (49 months) genotypes. Comparable results regarding TTP, OS and KIT mutational status were also observed in the European/AustralAsian phase III trial [73].

On the other hand, the meta-analysis also confirmed the observations previously reported in the European/AustralAsian trial and therefore it was concluded that KIT exon 9 mutations constituted a dose-dependent predictive factor for imatinib treatment identifying patients with a better response to high doses of imatinib (400 mg twice daily). Consequently, the estimated risk of progression for patients with KIT exon 9 mutations was drastically reduced (42%; $p = 0.0017$) in the 800-mg/day arm compared with the 400-mg/day dose of imatinib. In the same direction, the risk of death was also reduced in a 31% in this subgroup of patients.

Only small numbers of patients with GISTs harbouring PDGFRA mutations were included in the original phase I-III trials. On the basis of in vitro data, the most common PDGFRA mutation in GIST, D842V, is fully resistant to the effects of imatinib [37]. Among the patients whose GIST harboured a PDGFRA D842V mutation in the American phase III trial, there were no objective responses and stable disease was observed for a few months in some of the patients. From in vitro experiments Dasatinib showed activity in GIST cell lines with this specific mutation [75], somewhat recently confirmed in the clinical setting [76].

Practical issues on imatinib as first line in GIST

(1) How long should the therapy last? The BFR14 trial which randomized patients with nonprogressive GIST to continuation versus interruption of imatinib after 1, 3, or 5 years of treatment showed that treatment interruption was associated with a high risk of progression even in patients with a complete response [77]. Interestingly, although Imatinib rechallenge could control the disease in most patients, the quality of the tumor response rarely reached that before treatment interruption [78]. Consequently, in patients with metastatic or unresectable GIST, Imatinib should be continued until disease progression even when metastatic lesions have been previously surgically excised or until unacceptable toxicity. (I,A).

(2) Compliance. Although Imatinib is usually a well tolerated drug with as few as 2 per cent of grade III-IV adverse events, the long duration of therapy and persistent grade I-II side effects could impact in treatment compliance and consequently in disease outcome. Therefore, a good education of patients regarding the importance of compliance and potential interactions with other drugs or foods as well a proper and prompt management of side effects is crucial.

(3) Although seldom, some patients experience Imatinib intolerance. In this setting, treatment with second line agents like Sunitinib [7] should be discussed. In some patients, Nilotinib could also be contemplated (IIB) [79].

(4) Imatinib plasma levels. Although it remains to be demonstrated in a prospective setting, retrospective data suggest that low plasma levels at steady- state are associated with a worse outcome. So, the median time to progression was 11.3 months for patients with Imatinib plasma levels <1110 ng/mL compared with more than 30 months for patients with plasma levels above that threshold (80). Plasma levels could be especially useful in case of suspected poor compliance as the cause of tumor progression, in patients at risk of potentially important interactions with other concomitant drugs or unexpected toxicities. (IV,B)

(5) Rechallenge of Imatinib after adjuvant treatment. For patients recurring during adjuvant treatment, second line treatments including Imatinib 800 mg/day and sunitinib should be discussed, as explained in the next sections. For those patients relapsing with metastatic or unresectable disease after Imatinib interruption, although no direct prospective evidence is available, based on the data from the previously mentioned BRF14 trial, and the indirectly observed 84% response rate to imatinib rechallenge of patients that recurred following completion of adjuvant imatinib treatment in the SSGXVIII/AIO trial, the general recommendation is that Imatinib should be reintroduced at the same dose as recommended for first line. (IV,B)

Final recommendations

(1) Genotype is mandatory for treating advanced/metastatic GIST patients. Evidence II,A.

(2) Imatinib 400 mg/day is the recommended dose in first line in advanced/metastatic GIST. Evidence I,A.

(3) In exon 9 mutants, Imatinib 800 mg/day is the recommended dose. Evidence II,A.

(4) In PDGFR/KIT WT GIST is not clear enough that Imatinib should be the standard. In these patients, enrolment in specific clinical trials should be encouraged (ie. Regorafenib for WT GIST; NCT02638766).

(5) In Imatinib resistant D842V mutant, alternative treatments other than Imatinib could be taken into account (i.e. Dasatinib). (IV,B). But, if available, clinical trial should be the first option in this subset of patients (ie. the forthcoming trials with the PDGFRα D842V inhibitors Crenolanib or BLU-285 (NCT02508532).

Surgery as part of first line therapy in metastatic GIST

Although systemic treatment with Imatinib is the mainstay of metastatic GIST, several retrospective studies have demonstrated survival benefit of cytoreductive surgery following response to initial Imatinib, compared with historical controls in similar patient population treated with imatinib alone [81,82]. In the largest of these studies [81], there was no evidence of disease after surgery in 78% of the patients with stable disease before surgery, and only 4% remained with bulky disease. Twelve-month progression-free survival and overall survival was 80% and 95% respectively. Unfortunately, a phase III EORTC prospective trial assessing this issue was prematurely closed due to poor accrual. Thus, it could be considered in selected patients with good response to initial Imatinib, whose metastatic disease is deemed resectable. Although note that Imatinib should be maintained after surgery. Evidence V, C.

Response evaluation

Initial work-up and evaluation criteria (Fig. 3).

An abdominal and pelvic triphasic CT consists of a non-enhanced phase, an arterial phase, and a portal venous phase of the liver. This allows identification of hypervascular hepatic lesions that would otherwise go unnoticed and become evident when they become hypodense with treatment. Due to low metastatic frequency of pulmonary metastases (2%) [83] thoracic imaging study is only indicated based on clinical suspicion.

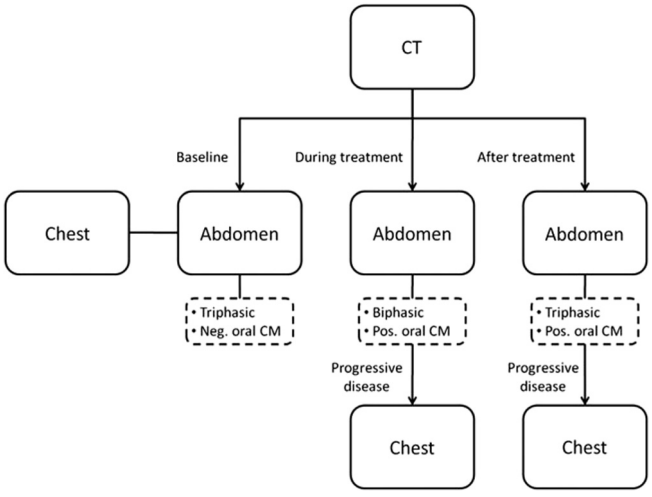

Fig. 3. Algorithm of imaging techniques in GIST [89].

Choi criteria [84] combine changes in both size (RECIST1.1) and density measures (Hounsfield Units: HU) (Table 5). Changes in lesion density should be assessed quantitatively and qualitatively by ROI (Region of Interest). Responses can mimic progression due to the increasing size of some lesions that can only be interpreted if HU are considered [85].

Both RECIST 1.1 and Choi [84] criteria must be taken into account to avoid confusion with pseudoprogression due to myxoid degeneration or intratumoral hemorrhage (Table 2).

Other techniques

MRI is strictly limited to hepatic studies, complex locations such as the rectum [86] and allergic reactions to iodine contrast, since evaluation of HU is not feasible. PET is reserved for inconclusive cases by other techniques such as CT or MRI or the early assessment of response to imatinib [87] when a baseline PET is available. However PET is useful for early detection of responses [88] and it is mandatory in some neo-adjuvant indications.

Treatment for patients with disease progression following imatinib failure

In patients with advanced GIST who progress on imatinib treatment, the first measure to carry out is to check treatment adherence and rule out potential drug interactions that might decrease efficacy. Consideration may be given to determine plasma imatinib concentrations, to better analyze these issues [80]. If treatment compliance is correct, systemic treatment should be changed.

Imatinib dose escalation. An option to consider could be to increase the dose of imatinib to 800 mg/daily. This approach is based on the results of the crossover to 800 mg after disease progression on 400 mg in the EORTC phase III trial [90] and the American Intergroup (study S0033) [69]. In both cases, 30% of patients who crossed-over to high-dose imatinib achieved disease control. In the EORTC study, the median time to progression was short, 81 days. However, 18% of patients remained free of progression one year after cross-over. The incidence of anemia and asthenia increases significantly with this dosage; therefore, a strict follow-up is required. Some retrospective studies suggested that patients with KIT exon 9 mutations may especially benefit from this approach. However, the benefit appears to be lower in patients with KIT exon 11 mutation [91–93].

Sunitinib is a multitargeted or selective TKI active inhibitor that is active against alpha-type and beta-type PDGFR and VEGFR receptors. Results of a randomized phase III trial versus placebo revealed a prolongation of the time to progression from 1.5 to 6.3 months in patients with GIST who progressed on imatinib treatment [94]. It was approved by the EMA and the FDA for the treatment of patients with GIST resistant to imatinib therapy and for those who do not tolerate it. The recommended dose is 50 mg

Table 5
Response evaluation criteria.

	RECIST	PET	Choi criteria
Complete response (CR)	All lesions must disappear	Lack of FDG uptake Unable to distinguish it from surrounding tissue	All lesions must disappear No new lesions
Partial response (PR)	Decreasing size 30% of sum of target lesions	Decreasing size 15–25% of SUV after 1 cycle and more than 25% after subsequent cycles	Decreasing size >10% or decreasing density ≥15% HU
Stable Disease (SD)	Between PR and PD	<25% increase or SUV decreases <15%	Does not fulfill CR, PR or PD criteria No symptom deterioration due to tumor progression
Progressive disease (PD)	Target lesions increase >20%	SUV increases >25% or new lesion uptake	Size Increases >10% without density decreasing New intratumoral nodules, Size or tissue part of hypodense lesion increases

FDG: Fluorodeoxyglucose; PET: Positron Emission Tomography; SUV Standardized Uptake Volume; HU: Hounsfield Units.

orally once a day over 4 weeks followed by a 2-week rest period, although an uninterrupted daily dose of 37.5 mg could be a valid alternative [95]. The most common side effects were asthenia, skin toxicity, diarrhea, hypertension and hypothyroidism. The development of hypertension seems to be correlated with the benefit of sunitinib [96]. Therefore, active treatment of this adverse effect without interruption of sunitinib therapy, when feasible, is recommended. A retrospective study showed an increased drug efficacy in patients with wild-type KIT GIST or mutations in exon 9 and 11 [97,10]. Likewise, patients who benefited most from sunitinib treatment were those with secondary KIT mutations in exon 13 and 14 compared to those with exon 17 and 18 mutations.

Final recommendations

(1) The first recommended measure to carry out when a patient with metastatic GIST progresses on imatinib is to check adherence to treatment and to rule out drug interactions. (III, B).
(2) After failure of imatinib, sunintib at 50 mg orally once a day over 4 weeks followed by a 2-week rest period is the recommended therapy. (I, A).
(3) Before sunitinib, however, imatinib dose scalation to 800 mg/day is an option that could be considered, especially in patients with GIST harboring KIT exon 9 mutations (III, B).

Resistance to imatinib and sunitinib

Regorafenib

Regorafenib (Stirvarga, Bayer HealthCare Pharmaceuticals Inc.), an orally active multikinase inhibitor with activity against several kinases including KIT, was recently approved by the FDA and the EMA for the treatment of patients with unresectable or metastatic GIST after failure or intolerance to imatinib and sunitinib. A multicenter phase III trial randomized (2:1) 199 GIST patients previously treated with at least imatinib and sunitinib to regorafenib ($n = 133$) or placebo ($n = 66$) [98]. This trial met the primary endpoint demonstrating an improvement in mPFS from 0.9 months in the placebo group to 4.8 months in the treatment arm. No difference was observed in mOS between the groups due to the crossover design. As observed with sunitinib, the majority of the benefit was in form of SD, with a disease control rate, defined as CR, PR or SD at 12 weeks of 52.6% for patients treated with regorafenib and 9.1% of those treated with placebo. The recommended dose is 160 mg taken orally once daily for the first 21 days of each 28-day cycle. Cycles are typically continued until disease progression or unacceptable toxicity. The toxicity profile of regorafenib was consistent with that of other kinase inhibitors with similar target spectrum. Adverse events grade 3 or higher were reported in 61% of patients receiving regorafenib, and the most common were hypertension, hand–foot skin reaction and diarrhea. Dose interruptions and dose reductions for adverse events were required in 58% and 50% of patients receiving regorafenib, although the rate of treatment discontinuation was low (2.3%). According to a preliminary report from the phase II trial [99], regorafenib, unlike sunitinib, appears to be active against some KIT secondary mutations in exon 17, although further data is still warranted.

Other treatment options after progression to regorafenib

Treatment options following imatinib, sunitinib and regorafenib administration are still in experimental phase. Any patient at this stage should first be considered for enrollment in a clinical trial, if appropriate drugs are available.

Imatinib rechallenge may be also considered for symptom palliation in addition to best supportive care. There is randomized evidence supporting the use of imatinib rechallenge after tyrosine kinase inhibitor (TKI) failure [100]. Significant but little improvement was observed in mPFS, and no differences were shown in terms of response rate, OS, and quality of life [100,101]. Maintenance or rechallenge of TKIs to which the patient had already progressed may be considered [100,102], although benefits and risks should be carefully addressed.

Several other multikinase inhibitors have shown activity in multi-TKI resistant GIST, the majority of them in the pre-regorafenib era. Most of these data comes from small phase II studies, and therefore the level of evidence is low.

Sorafenib (Nexavar, Bayer Healthcare Pharmaceuticals and ONYX Pharmaceuticals) is TKI structurally-related to regorafenib. Two single-arm phase II clinical trials have demonstrated activity in patients with GIST after progression to at least imatinib and sunitinib, with a disease control rate and a mPFS similar to that of sunitinib and regorafenib [103,104]. In addition, in vitro studies have demonstrated a wide spectrum of inhibition of KIT secondary mutations, with the exception of kinases resulting from substitutions at KIT codon D816 [105]. Sorafenib might be considered in GIST patients after sunitinib progression and intolerance to regorafenib, given the high possibilities of sharing similar activity profile.

The randomized phase II trial PAZOGIST compared pazopanib (Votrient, GlaxoSmithKline) with placebo in 81 GIST patients after failure to at least imatinib and sunitinib [106]. The 4-month PFS rate favored pazopanib compared to placebo (45% vs. 18%, respectively; $p = 0.03$). Other single-arm, phase II trial recently reported a mPFS of 1.9 months in a similar population [107]. In any case, these data do not suggest higher activity than sunitinib or regorafenib.

Ponatinib is a third-generation TKI that is highly active in patients with chronic myeloid leukemia with resistance to multiple TKIs. Moreover, is one of the few KIT inhibitors that has been tested in a large panel of mutant KIT variants [108]. Ponatinib potently suppresses all KIT secondary mutations with the exception of V654A. Unlike other approved TKIs, it is active against the KIT exon 17 D816 mutant kinases. Preliminary data from a non-randomized phase II trial has been recently reported [2]. The clinical benefit rate (CR, PR, or SD $\geq$ 16 weeks) was 55% in heavily pretreated (74% had $\geq$4 prior agents, including regorafenib) GIST patients with primary KIT exon 11 mutation. A second phase II trial (POETIG) will further evaluate ponatinib activity and toxicity in imatinib-resistant GIST patients.

Final recommendations

(1) Regorafenib is the current standard for patients with progression or intolerance on imatinib and sunitinib (II, A).
(2) Physicians are encouraged to enroll GIST patients in clinical trials after progression on all current standard treatments for advanced/metastatic disease (imatinib, sunitinib, and regorafenib).
(3) Re-introduction of previously tolerated and effective imatinib for symptom palliation can be considered, but the risk of toxicities should be outweighed (category II, C).
(4) Based on limited data, the guidelines have also included sorafenib, pazopanib, and ponatinib (category IIIC).

Special cases

Capsule break: Those are best considered as disseminated patients, as virtually all of them will relapse, generally as disseminated unresectable peritoneal disease. Therefore, chronic imatinib treatment is recommended. The decision to withdraw treatment in non-progressing patients after many years of KIT-inhibition is a difficult one to be taken on an individual basis. Close monitoring is mandatory during the next years. Most of such patients will

respond again to imatinib rechallenge after an eventual progression.

R1 surgery: There is no evidence confirming the benefit of adjuvant imatinib in low-risk patients with affected microscopic margins. Surgical reexcision could be considered for these cases but is not mandatory (see surgical section).

Neoadjuvant and induction therapy

Systemic induction therapy aims at facilitating surgery through tumour shrinkage, whereas systemic neoadjuvant therapy targets survival advantage in otherwise resectable cases [109].

In locally advanced and unresectable GIST, there are few cases that would eventually become resectable after induction treatment with imatinib [110].

However, a cytoreductive treatment with imatinib can be attempted for those GISTs only resectable at the expense of a mutilating surgery [111]. Examples of such scenario are duodenal GISTs near the ampulla of Vater in need for a Whipple procedure in spite of its small tumour size or rectal GISTs near the sphincter. Early response-assessment is needed, since surgery delay could hamper long-term results after an unsuccessful imatinib treatment. Mutational analysis should be mandatory due to the robust predictive value of some genotypes (IIb). Hence, exon 9 mutants would require 800 mg/day of imatinib; no induction treatment would be active in D842V mutants and it is doubtful that imatinib could be useful as an induction preoperative treatment for PDGFRA-mutated and wild type cases. A CT scan can suffice for early response-assessment, but PET-scan seems advantageous given its ability to verify the efficacy of the treatment within a very short time [112].

The recommended duration of preoperatory treatment cannot be based on objective criteria. However, it is estimated that surgery could be performed within 6–12 months after starting imatinib, since maximal response and minimal risk of secondary resistance is expected in this time interval [113].

Adjuvant therapy is to be indicated taking into account the characteristics in the biopsy prior obtained to neoadjuvant treatment, not on those derived from the surgical specimen. If applied, the total duration of preoperative and postoperative imatinib treatments should sum up the total three year duration of a conventional adjuvant treatment.

Final recommendations

(1) There is a lack of published evidence regarding neoadjuvant treatment in operable GIST and therefore it should not be used outside clinical trials.
(2) Induction treatment can be useful in individual cases where a decrease in tumor size would avoid significant surgical trauma. (III, B).

Small GIST < 2 cm

Many GISTs smaller than 2 cm are incidental findings during surgeries carried out for other reasons. Such a small GIST tumour accidentally found in a surgical specimen does not require any additional treatment.

Those cases still deserve a conventional follow-up.

Focal progression

There is a well-documented type of secondary resistance to imatinib called nodule-within-a-mass. This is a focal kind of disease progression, while most of the tumour burden remains under treatment control. Maintenance of systemic treatment combined with local treatments can keep the patient free of progression for over a year in one-third of cases and should be favoured over second-line systemic treatments. Local treatments usually employed are surgery, radioablation and arterial embolization. In the absence of controlled trials, the choice of a particular local treatment modality should be based disease characteristics and medical experience.

Final recommendations

(1) Systemic therapy should not be interrupted or replaced when progression is limited to a single or few focal foci amenable to local treatment. (III, B).
(2) The treatment of choice for focal progression is maintenance of systemic therapy along with local control techniques appropriate for each case. (III, B).

Follow-up of patient diagnosed with GIST

Level of evidence IV, grade of recommendation C.

There are no studies analyzing the efficacy of different follow-up strategies. Recent recommendations advocate adjustment to risk of recurrence with time [114] based on risk, size, number of mitosis and location, according to the Miettinen [13] classification, adjuvant treatment and time.

Other techniques such as MRI are strictly limited to hepatic studies, complex locations such as the rectum and allergic reactions to iodine contrast given that evaluation of Hounsfield units is not feasible. PET is reserved for inconclusive cases by other techniques such as CT or MRI or the early assessment of response to imatinib [87].

Localized resectable disease

Follow-up after resection according to risk group.

Very low risk: Surgically removed: no follow-up.

Very low risk and low risk. Annual CT scan.

Intermediate risk and high risk: 1–2 year CT scan every 4 months and 3–5 year every 6 months and annually thereafter. Note that once imatinib is withdrawn, since relapses occur most frequently within the following 2 years, follow-up should be maintained.

Localized un-resectable or metastatic disease

Follow-up should be conducted every 3 months from the beginning and can be prolonged up to every 6 months if response is obtained, especially if response remains beyond a five-year period. As mentioned before both RECIST 1.1 and Choi [84] criteria must be taken into account to avoid confounding it with pseudoprogression due to myxoid degeneration or intratumoral hemorrhage as previously described.

Conflict of interest statement

Los autores del presente artículo declaran no tener ningún conflicto de interés en relación con la elaboración de dicho artículo.

The authors of this article declare that they have no conflict of interest in relation to the preparation of the article.

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