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SPECIAL ARTICLE

Gastrointestinal stromal tumors (GISTs): SEAP–SEOM consensus on pathologic and molecular diagnosis

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Abstract Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the digestive tract, with an incidence of 1.1 cases/100,000 inhabitants/year. A group of experts from the Spanish Society of Pathology and the Spanish Society of Oncology met to discuss a brief update on GISTs and agree on aspects relating to the pathological and molecular diagnosis of these tumors. GISTs are generally solitary, well-circumscribed lesions of variable size (<10 mm–35 cm) that may present with intra- or extraluminal parietal growth or a mixed-type (hourglass) growth pattern. Histologically, they are unencapsulated neoplasms displaying expansive growth and spindle-shaped (70%), epithelioid (20%), or mixed cellularity (10%). Mitotic activity is generally moderate or low and should be evaluated only in areas with high cellularity or higher mitotic frequency. The great majority of GISTs harbour mutually exclusive activating mutations in genes coding for the type III receptor tyrosine kinases KIT and PDGFRA; less commonly, GISTs have also been reported to display mutations elsewhere, including *BRAF* and *NF1* and SDH-complex genes. The method most widely used to detect *KIT* and *PDGFRA* mutations is amplification of the exons involved by polymerase chain reaction followed by direct sequencing (Sanger method) of these amplification products. Molecular analyses should always specify the type of analysis performed, the region or mutations evaluated, and the sensitivity of the detection method employed.

Keywords Gastrointestinal stromal tumor · GIST · Pathologic diagnosis · Molecular diagnosis · Consensus

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Introduction

Conceptual evolution and current status

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the digestive tract [1]. Although initially considered smooth-muscle tumors (leiomyoma, leiomyoblastoma, and leiomyosarcoma) [2], ultrastructural and immunohistochemical studies have revealed evidence of considerable morphological heterogeneity and the presence of lesions with a null phenotype. The term "stromal tumor" was introduced by Mazur and Clark (1983) to reflect this variability in stomach tumors and was soon widely applied to denote for similar lesions in other areas of the digestive tract; henceforth, these tumors became known as gastrointestinal stromal tumors or GISTs [3].

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Current understanding of GISTs draws mainly on the work of two independent research groups. Hirota et al. demonstrated that most GISTs harbored activating mutations in the *KIT* gene, and that interstitial cells of Cajal (ICC), in the digestive tract wall, as well as GISTs, stained positive for the KIT protein (CD117) [4]. In contrast, Kindblom et al., using a combination of electron microscopy and immunohistochemistry, concluded that GISTs differentiate toward cells with an ICC phenotype and proposed, albeit with a little success, that the most appropriate term to designate them was "gastrointestinal pacemaker cell tumor (GI-PACT)" [5].

Once it was established that GISTs constitute a well-defined clinicopathological entity, characterized by the expression of CD117 and, in most cases, mutations in the *KIT* gene, mutations in other genes were reported in a subgroup of tumors not displaying *KIT* mutations (*KIT wild type* [WT]). Heinrich et al. described activating mutations in the *PDGFRA* gene in 35% of KIT *WT* tumors [6], while Agaram et al. observed mutations in the *BRAF* gene in 5% of patients with *KIT/PDGFRA WT* and in 2% of GISTs with mutations in *KIT/PDGFRA* that had acquired resistance to imatinib [7]. Finally, McWhinney et al. reported mutations in several genes of the SDH enzymatic complex (*SDHB*, *SDHC*, *SDHD*) [8]. In recent decades, attention has focused on molecular studies of GISTs with *KIT*/*PDGFRA WT* and on multiple familial GISTs.

An important milestone in the redefinition of GISTs was the integration of an understanding of the molecular features of GISTs and treatment with imatinib, reported by Heikki Joensuu. In 2001, they published a case of metastatic GIST showing an impressive response to imatinib, a medication approved for chronic myeloid leukemia [9]. This clinical finding led to a paradigm shift in the diagnosis, risk definition, radiologic evaluation, and treatment of GISTs.

A group of experts from the Spanish Society of Pathology [Sociedad Española de Anatomía Patológica (SEAP)] and the Spanish Society of Medical Oncology [Sociedad Española de Oncología Médica (SEOM)] met recently in Seville to provide a brief update on GISTs and agreed on aspects of their pathologic and molecular diagnosis.

Epidemiology and etiology

The incidence of clinically relevant GISTs in the Spanish population is 1.1 cases/100,000 inhabitants/year [10], but the actual incidence may be much higher, since 20–30% of the population aged over 50 may have microscopic gastric GIST lesions [11]. Although they can present in children and adolescents, the median age at diagnosis is approximately 60, with no gender differences.

Prior to the incorporation of adjuvant treatment, the global 5-year survival rate in patients with surgically treated localized tumors was approximately 70% [12]. Before the administration of tyrosine kinase inhibitors (TKIs), the median overall survival of patients with metastatic disease was around 20 months [13]. The introduction of TKIs has notably modified the natural history of this disease, and the median overall survival in patients with metastatic GIST now exceeds 5 years [14].

Clinical presentation and diagnostic methods

GISTs are typically located in the digestive tract wall, and more specifically in the stomach (50–60%), ileum and jejunum (20–30%), duodenum (3–5%), rectum-anus (2–4.4%), colon (1.2%), esophagus (<1%), and appendix (<1%). They may appear outside the gastrointestinal tract, and are then termed extra-gastrointestinal GISTs (EGISTs); these tend to be located in the omentum, mesentery, and retroperitoneum. More rarely, cases have also been reported in other locations, such as the pancreas, liver, gallbladder, female reproductive organs, prostate, mesoappendix, abdominal wall, and thoracic cavity (pericardium and pleura) [1].

Although symptoms depend on location, most reported cases have non-specific findings, such as postprandial fullness and abdominal distension; ulcerated tumors often present with active, visible or occult bleeding, and with associated anemia. Larger tumors may cause abdominal pain, or even intestinal obstruction (25–40%), although intestinal perforation is uncommon [10, 13]. Although infrequent, paraneoplastic syndromes, such as hypoglycemia secondary to IGF-II production, have been reported [15]. Multifocality and regional lymph-node metastasis are rare. Liver and peritoneum are virtually the only sites of metastatic dissemination.

The following are exceptions to these general clinical characteristics:

- Micro-GIST: lesions <1 cm, asymptomatic. Diagnosis is incidental and usually occurs during a radiologic or endoscopic study or during surgery for an unrelated issue [16].
- Pediatric-type GIST: most cases are seen in females during infancy or early childhood. These tend to be frequently mutifocal *KIT/PDGFRA WT* tumors located in the stomach, with metastasis to lymph nodes (29%) and liver (25%). Their clinical course is typically indolent, and despite dissemination, survival tends to be long [17].
- GIST associated with Carney's triad: this non-hereditary condition displays the same characteristics as the pediatric-type GISTs, but should also have at least one

of the following components: extra-adrenal paraganglioma, pulmonary chondroma, esophageal leiomyoma, or adreno-cortical adenoma [17].

- GIST associated with Carney–Stratakis syndrome: shares clinical and morphological characteristics with Carney triad-associated GISTs but without pulmonary chondroma or gender predominance. Genetically, this syndrome is characterized by autosomal-dominant inheritance and incomplete penetrance [17].
- GIST associated with neurofibromatosis type 1: presents in adults (median age 46) and is characterized by ICC hyperplasia and multiple small GISTs in the small intestine [18].
- Familial GIST: families carrying hereditary germline mutations in *KIT* and less frequently in *PDGFRA* have been reported. Penetrance is higher, and middle-aged patients present with one or more GISTs. The majority of these tumors are benign. Patients with *KIT* exon 11 mutations may develop hyperpigmentation of the skin and mastocytosis [18].

The clinical diagnosis of GIST requires evaluation of tumor size and location. Endoscopy and echo-endoscopy are especially useful in more proximal (esophagus, stomach, and duodenum) and more distal locations (colon and rectum). Contrast-enhanced computed tomography (CT) scan is the imaging technique of choice. Nuclear magnetic resonance (NMR) is useful in pelvic tumors (especially in the rectum), for the anatomical definition of hepatic metastasis and for mesenteric and peritoneal extensions [19, 20].

Positron-emission tomography (PET) offers no advantages over CT or NMR, but is useful for the early evaluation of the response to neoadjuvant therapy [19, 20].

The standard procedure for histologic diagnosis is endoscopic ultrasound-guided core biopsy; where this is not possible, CT-guided percutaneous biopsy is to be preferred [20, 21]. In certain circumstances, CT-guided fine-needle aspiration cytology and ultrasound-guided endoscopy are of great diagnostic value [22].

For small tumors, presurgical biopsy is not necessary if the lesion is highly suspicious and its location allows for surgical removal without risk. Biopsy is, of course, required in cases of disseminated disease and localized advanced tumors when neoadjuvant therapy is proposed.

Histopathologic diagnosis

Macroscopy and microscopy

GISTs are well-circumscribed solitary lesions of variable size (<10 mm–35 cm), which develop in the gut wall with an intra-luminal, extra-luminal, or mixed-hourglass growth pattern. On cut sections, they are firm and gray–white in color, and may display focal hemorrhage, cystic change, or necrosis [1, 18, 23–25]. On external inspection, special attention should be paid to the integrity of the tumor surface and surgical margins. On rare occasions, GISTs present as multiple lesions, mainly localized in the stomach (pediatric GISTs and micro-GISTs) or small intestine (familial GISTs and GISTs associated with neurofibromatosis).

Histologically, they are unencapsulated neoplasms displaying expansive growth and fusiform (70%), epithelioid (20%), or mixed (10%) cellularity.

Spindle-cell GISTs (70%) are composed of elongated cells with scant cytoplasm and oval nuclei, arranged in interlacing short fascicles or in a storiform pattern. The number of cells and their stromal characteristics varies considerably. Some histological details are especially relevant in certain locations; nuclear palisades and cytoplasmic perinuclear vacuolization, for example, are more often seen in gastric lesions, while skeinoid fibers and the "paraganglioma-type" pattern are more common in intestinal lesions [1] (Fig. 1a).

Epithelioid GISTs (20%) comprise polygonal or rounded cells with clear or eosinophilic cytoplasm arranged in cohesive nests and diffuse sheets with scant interposed stroma. Nuclei are rounded or oval, but sometimes display focal pleomorphism or multinucleation. Roughly, a third of gastric lesions are epithelioid. Elsewhere, epithelioid cells are almost always associated with an aggressive clinical course [1, 23] (Fig. 1b).

Mixed GISTs (10%) are composed of both spindle-shaped and epithelioid cells in abrupt transition, or by cells with an intermediate morphology [23].

On rare occasions, atypical forms with marked pleomorphism and bizarre cellularity (2%) or undifferentiated forms with focal or total loss of immunohistochemical markers may be found [1].

Mitotic activity is generally moderate or low, and should be evaluated only in areas of greater cellularity or a higher incidence of mitosis. Although traditionally expressed as number of mitoses per 50 high-power fields (HPF), it is advisable to count mitoses in areas of 5 mm^2 [1, 26, 27], equivalent to 25 HPF with a 20x lens or 21 HPF with a 22x lens.

Tumors in imatinib-treated patients show a marked reduction in the number of cells, stromal changes (presence of sclerosis or fibrohyalinosis; appearance of myxoid or pseudochondroid component), and/or necrosis. Cells are similar to those of the primary lesion but smaller due to cytoplasmic depletion. Lesions with secondary resistance to imatinib display tumor progression with phenotypic (mixed or epithelioid), changes, formation of pseudopapillae, and, more sporadically,

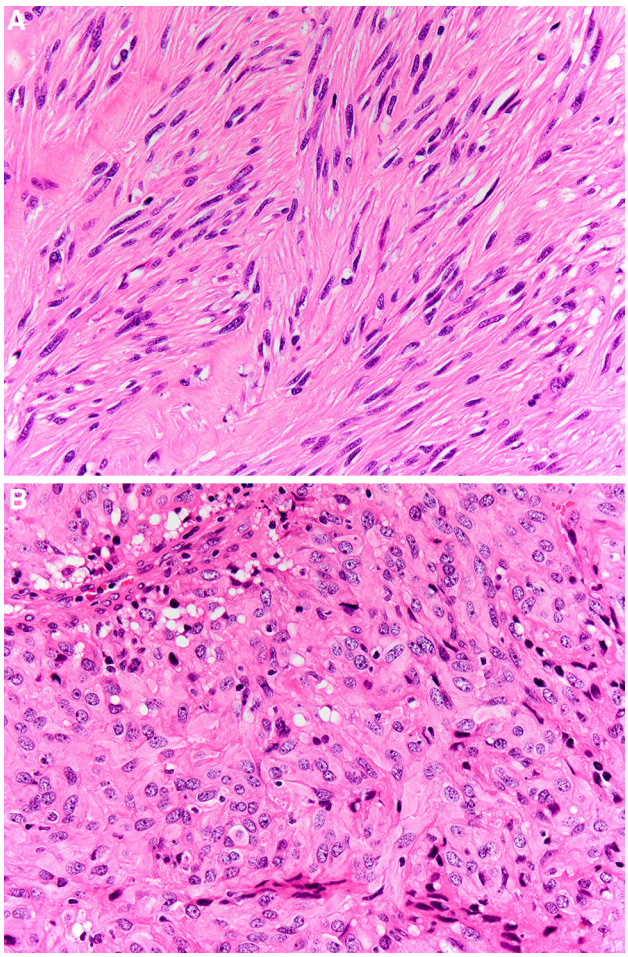

Fig. 1 **a** Spindle-cell GIST. *Spindle-shaped* cells display scant eosinophilic cytoplasm and elongated nuclei, often with sharp ends—H&E 40×. **b** Epithelioid GIST. Cells are *polygonal* with abundant eosinophilic cytoplasm and *rounded* or *oval* nuclei. Some cells contain cytoplasmic vacuoles. H&E. 40×

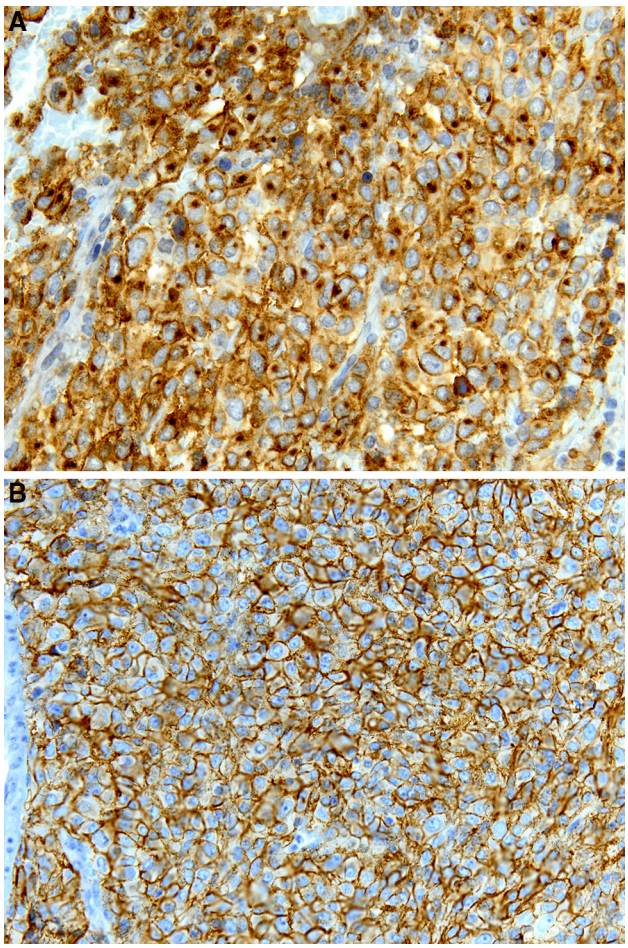

Fig. 2 **a** CD117. Appreciable immune reaction, particularly in the cytoplasmic membrane and the paranuclear region in the form of dot-like staining (Golgi pattern). IPX 60×. **b** DOG1. Immunoreactivity is seen primarily in the membrane and, to a lesser extent, in the cytoplasm. IPX 40x

rhabdomyosarcoma-type heterologous differentiation. Reports on the efficacy of imatinib treatment should indicate the percentage of viable tumor cells [25, 28].

Certain histological features are linked to specific forms of GIST. GISTs associated with neurofibromatosis type 1 display spindle-shaped cellularity, low mitotic activity, and frequent skenoid fibers, and seldom have an aggressive clinical course [18, 25]. Pediatric-type GISTs (sporadic forms, Carney-Stratakis syndrome, and Carney's triad) are characterized by a multinodular architecture, a plexiform growth pattern, and epithelioid or mixed cellularity; occasionally, they may display nuclear pleomorphism or necrotic areas. Lymphovascular invasion and metastasis to regional lymph nodes and liver may also be fairly frequently [18, 25]. Micro-GISTs are composed exclusively of spindle-shaped cells with very low mitotic activity and a varying degree of sclerosis and calcification [16].

Immunohistochemistry

CD117 (KIT) is the immunohistochemical marker most widely used in the diagnosis of GIST, positive staining being recorded in >95% of cases. The staining pattern is generally cytoplasmic (75%) and, more occasionally, Golgi-like (dot-like) or membranous (Fig. 2a). Given its diagnostic importance, it is crucial to follow certain guidelines on immunostaining and evaluation, including use of polyclonal antibodies, avoidance of antigen exposure, and checking antibody suitability by means of internal controls (mastocytes). CD117 is a highly sensitive marker but offers relatively low specificity, since it is frequently expressed in other tumors, especially melanomas [1, 29, 30].

Anti-DOG1 antibodies (anoctamin1, ANO1) are more sensitive than anti-CD117 antibodies, but also display relatively low specificity (expression has been reported in various types of carcinoma and more rarely in certain sarcomas).

Table 1 Differences between SDHB-positive and SDHB-negative GISTs

	SDH-positive Type 1	SDH-negative Type 2
Location	Entire digestive tract	Stomach
Somatic mutations in KIT/PDGFR	Yes (85–90%)	No
SDH germline mutation	No	Sometimes (30–50%)
Sex	Women = men	More often women
Age	Older adults	Young adults, sometimes children
Prognostic stratification	Yes	No
Multifocality	Rare	Frequent
Multinodularity	Rare	Frequent
Predominant cell type	Spindle (PDGFR-mutated gastric epithelioid GISTs)	Epithelioid
Lymph-node metastasis	Rare or never	Common
Metastatic behavior	Aggressive	Indolent
Response to imatinib	Habitual	Never
Syndromic presentation*	Very rare	More common, though infrequent

Type 1: Neurofibromatosis type1 (mutations in *NF1*; *KIT/PDGFRA WT*), familial GIST associated with germline mutations in *KIT* and *PDGFR* (less frequent)

Type 2: Carney's triad (methylation of *SDHC* promoter), Carney–Stratakis Syndrome (*SDHB, C, D* germline mutations)

* Associated syndromes

The staining pattern may be cytoplasmic or membranous (Fig. 2b). Currently, DOG1 is regarded as the best marker of GISTs, since it identifies 36% of CD117-negative cases [31]. Concomitant negativity for DOG1 and CD117 is exceptional, being is reported in <1% of GISTs [32, 33].

Other antibodies are of great value in establishing a differential diagnosis: expression of CD34 is observed in 70–90% of cases, smooth-muscle actin in 20–30%, S-100 in 8–10%, and desmin in 5–10% [1, 29].

New immunohistochemical markers for GIST introduced over recent years (PKCθ, carbonic anhydrase, nestin, PDGFRA, SDHB, insulin growth factor 1 receptor, etc.) have achieved a little success to date, since most fail to provide any additional relevant information [34–38]. SDHB warrants special mention, however, in that identifies the pediatric GIST subtype [39]. Clinicopathological differences between SDH-negative (pediatric GISTs) and SDH-positive GISTs are shown in Table 1. Loss of immunoreactivity to SDHB denotes a dysfunction in the SDH complex; despite some exceptions (e.g., GIST associated with Carney's triad), this is typically related to mutations in one of the four subunits (SDHA, SDHB, SDHC, and SDHD) [39].

Differential diagnosis

Key lesions for the differential diagnosis of GISTs, and the immunohistochemical stains used for their recognition, are listed in Tables 2 and 3. Given the special predilection of

Table 2 Differential diagnosis of gastrointestinal stromal tumors

True smooth-muscle tumors
Leiomyomas
Intramural
Of the muscularis mucosae
Uterine-type leiomyomas (women)
Glomus tumor
Leiomyosarcoma
Neural-sheath and melanocytic tumors
GI Schwannoma
Metastatic melanoma
White-cell sarcoma/GI neuroectodermal tumor
Fibroblast tumors
Desmoid
Inflammatory myofibroblastic tumor
Inflammatory fibroid polyp
Undifferentiated sarcoma

disseminated melanoma for the digestive tract, it is important to bear in mind, especially when managing small biopsies, that many of these tumors can be CD117-positive.

Molecular diagnosis

GIST is characterized by activating mutations in *KIT* and *PDGFRA* genes coding for type III receptor tyrosine kinases [24].

Table 3 Differential diagnosis of GIST by IHC

Diagnostic	KIT	Actin ML	Desmin	S-100	CD34	Keratin
GIST	+++	+ (40)	−	−	+++	−
Leiomyoma	−	+++	+++	−	−	−
Leiomyosarcoma	−	+++	+ a +++ (80)	−	+ (10)	+ (25)
Schwannoma	−	−	−	+++	−	−
Fibromatosis	−	++	−	+ (Occasional)	−	−
Carcinoma	−	+ a +++	−	−	−	+ a +++
Melanoma	+ (50)	−	−	+++	−	−

− No positive cells, + <25% of cells positive, ++ 25–50% of cells positive, +++ >50% of cells positive

(*n*) Approximate percentage of cases

Spectrum of mutations in GIST

Mutations (deletions, point mutations, duplications, insertions, and complex mutations) are found in exons coding for the functional domains of KIT and PDGFRA receptors [40]. Those appearing prior to imatinib treatment are known as primary mutations, and affect exons 9, 11, 13, and 17 of *KIT* and exons 12, 18 and, more rarely, 14 of *PDGFRA*. Mutations appearing after treatment, termed secondary mutations, are largely responsible for resistance to imatinib. Secondary mutations are generally accompanied by a primary mutation in the same gene and are concentrated in *KIT* exons 13, 14, and 17 and *PDGFRA* exon 18 [40].

KIT mutations

Mutations in *KIT* exon 11 (juxtamembrane domain) are the most common, and are observed in 70–75% of all mutation-positive cases [18, 41]. The majority are interstitial deletions located between codons 550 and 579; primarily affecting codons 557–559. Point mutations are mostly confined to codons 557, 559, 560, and 576, but also contribute to the complex mutations associated with interstitial deletions or tandem duplications. Tandem duplications identified between codons 571 and 591 are generally associated with gastric GISTs of epithelial or mixed morphology [40–42].

Duplication of codons 502–503 is the only finding in exon 9 (extracellular domain) and accounts for 9–20% of GIST mutations; this duplication is associated with small intestinal tumors and higher potential malignancy [40, 42].

In exons 13 and 17 (domains with tyrosine kinase activity), point mutations are the only finding, with a frequency of 0.8–4.1% (exon 13) and <1% (exon 17) [40–42].

PDGFRA mutations

PDGFRA mutations are reported in 5–10% of GISTs [41, 43] mostly in gastric locations and displaying epithelioid morphology [18, 41, 43]. They affect exon 12 (juxtamembrane domain) in 0.7% of cases and exon 18 (tyrosine kinase domain) in 6%; mutations in exon 14 are rare (0.1%). The D842 V mutation is the most commonly encountered in *PDGFRA* (56–75%) [18, 41, 43].

WT GIST

Between 12 and 15% of GISTs in adults and 90% of pediatric GISTs lack both *KIT* and *PDGFRA* mutations [40]. Other intracellular signaling pathways affected in these tumors include the BRAF pathway, with mutations reported in 7% of GISTs [44].

At least one-third of WT GISTs display deficiencies in genes coding for subunits of the SDH enzyme complex [45, 46]. SDH-deficient GISTs are a unique group of GISTs with an energy metabolism defect as the key oncogenic mechanism. In 50% of cases, the deficiency arises due to mutations primarily affecting subunit A (30%), while the remaining 20% are distributed among subunits B, C, and D. Many of these mutations, especially those in subunits B, C, or D, are also present in the germline, which may require genetic counseling [8]. In the remaining 50% of cases, SDH-complex deficiency may result from epigenetic silencing (inactivation of the *SDHC* gene promoter) [47]. Loss of SDH results in succinate accumulation and activation of hypoxia-inducing proteins.

CD117-negative GISTs

Although roughly 5% of GISTs do not exhibit positive immunoreactivity for CD117, 30–50% of cases have *KIT* or *PDGFRA* mutations [18, 48], which may have major therapeutic implications. The notion that a CD117-negative GIST may also be wild-type is not well defined, especially given that diagnosis is currently performed by exclusion [18, 21].

Techniques for detecting KIT and PDGFRA mutations

The most widely used method for detecting *KIT* and *PDGFRA* mutations is amplification of the exons of

interest by polymerase chain reaction (PCR) followed by direct sequencing (Sanger method) of amplification products. When performing this procedure, it is essential to bear in mind certain factors that might compromise the results of genetic examination. First, due to the detection limits of this technique, direct sequencing should be performed only on samples containing at least 50% tumor cells, as selected by the pathologist. In cases not attaining this level of cellularity, macrodissection is recommended to enrich the sample for greater tumor content. Second, when examining fixed, paraffin-embedded tissue, in which DNA is typically fragmented, the primers used in PCR reactions need to provide adequately sized products to guarantee the sensitivity of the procedure (<200 base pairs); primers should lie in intronic regions covering the whole of the coding region. Finally, sequencing should be confirmed in both forward and reverse directions.

Rapid technological advances in the field of genetic diagnosis have enabled the introduction of other procedures offering greater sensitivity, including next-generation sequencing (NGS). Panels designed specifically for GIST (e.g., GIST MASTR Multiplicom) and broader panels to test for *KIT* and *PDGFRA* mutations (e.g., TruSight Tumor, Illumina; Ion AmpliSeq Cancer Hot Spot Panel, LifeTech are now commercially available.

In all the cases, the technique used should be appropriate, validated, and performed by specifically trained personnel. Reports on molecular analysis should always specify the type of analysis performed and the region or mutations evaluated, and should indicate the sensitivity of the detection method used.

Prognostic and predictive factors in GIST

Patients with GISTs greater than 2 cm in diameter are in risk of relapse, although the clinical behavior of these tumors varies considerably. It is, therefore, common in daily clinical practice to use prognostic and predictive factors to help estimate the risk of relapse after surgery and/or to predict the potential benefit of adjuvant treatment with imatinib.

The three main prognostic factors in GIST are tumor size, mitotic count, and tumor location. Studies performed in patients with localized GISTs not receiving adjuvant treatment with imatinib have consistently demonstrated that extragastric location, increased tumor size, and high mitotic activity are significantly associated with poor relapse-free survival (RFS) [23]. Rupture of the tumor into the abdominal cavity, whether spontaneous or due to manipulation during surgery, is also associated with a high risk of relapse (80–100%) [12], independently of other prognostic factors. These four factors underlie the three risk-stratification schemes for relapse after surgical excision of localized GISTs [1, 23, 49] summarized in Table 4. The consensus criteria from the National Institutes of Health (NIH) [23] scheme, which is the oldest, stratify risk on the basis of tumor size and mitotic count. The risk criteria of the Armed Forces Institute of Pathology (AFIP) [1] incorporate tumor location as a prognostic factor, which improves differentiation between patients with moderate and intermediate risk. Finally, the revised NIH consensus criteria additionally incorporate tumor rupture [49]. The prognostic prediction capacity of these three systems is similar, with an area under the curve (AUC) of 0.79, 0.82, and 0.78 for the NIH consensus criteria, AFIP risk criteria, and revised NIH consensus criteria, respectively [49]. Both American (National Comprehensive Cancer Network) [27] and European (European Society for Medical Oncology) clinical guidelines [50] tend to favor the AFIP risk criteria. In case series examined by the Spanish Sarcoma Research Group [Grupo Español de Investigación en Sarcomas (GEIS)], AFIP risk criteria proved to be optimal for distinguishing GIST cases with a low, moderate, or high risks of relapse [51]. These risk assessments have been validated only for adult GISTs with primary *KIT* mutations, since other genotypes are under-represented. The presence of deletions in *KIT* exon 11 is associated with a higher risk of relapse; specifically, those patients with deletions in codons 557 and/or 558 have tumors exhibiting particularly aggressive behavior. This may lead to the reclassification of gastric GISTs of intermediate prognosis as high risk with respect to relapse [51–53]. These reports also agree that GISTs with primary mutations in *PDGFRA* exon 18 (D842V) are associated with a more favorable prognosis.

The importance of identifying patients at high risk of relapse using risk-stratification systems also lies in the proper selection of patients likely to benefit from adjuvant treatment with imatinib, given that approximately 60% of patients with GISTs never experience a relapse and are considered cured only with surgery [12].

Therapeutic guidelines

Surgical treatment

Surgery is the cornerstone of treatment for localized disease. The criteria for defining unresectability and/or inoperability should be discussed in a multidisciplinary committee. Criteria for unresectability include infiltration of the celiac trunk, the superior mesenteric artery, or the

Table 4 Risk-stratification systems used in GIST

Risk group	GIST characteristics		Tumor location	10-year RFS (%)[b]
	Tumor size (cm)	Mitosis count (50 HPF)		
NIH consensus criteria				
Very low	<2	<5		98.3
Low	2–5	<5		88.2
Intermediate	<5	6–10		79.8
	5–10	<5		30.4
High	>10	Any count		
	Any size	>10		
	>5	>5		
AFIP criteria[a]				
Group 1	<2.0	≤5		95.0
Group 2	2.1–5.0	≤5		89.6
Group 3a	5.1–10.0	≤5		79.7
Group 3b	>10.0	≤5		61.9
Group 4	<2.0	>5		45.7
Group 5	2.1–5.0	>5		48.9
Group 6a	5.1–10.0	>5		25.1
Group 6b	>10.0	>5		9.4
Modified NIH consensus criteria				
Very low	<2	≤5	Any site	94.9
Low	2.1–5.0	≤5	Any site	89.7
Intermediate	≤5.0	6-10	Gastric	86.9
	5.1–10.0	≤5	Gastric	36.2
High	>10.0	Any count	Any site	
	Any size	>10	Any site	
	>5.0	>5	Any site	
	≤5.0	>5	Non-gastric	
	5.1–10.0	≤5	Non-gastric	
	Any size	Any site	Tumor rupture	

AFIP Armed Forces Institute of Pathology, *NIH* National Institutes of Health, *RFS* relapse-free survival

[a] AFIP criteria are available for gastric, duodenal, ileal and jejunal, and rectal locations

[b] 10-year RFS based on pooled data from 10 GIST series [12]

mesenteric-portal confluence. The presence of metastasis does not contraindicate surgery of the primary tumor if it is of clinical benefit. In specific cases, the potential benefits and drawbacks of neoadjuvant treatment need to be discussed, with a view to enabling R0 resection or surgery with lower morbidity (for example, in the rectum, esophagus, or pancreas).

Laparoscopic surgery is acceptable in tumors less than 5 cm in diameter. Total gastrectomy is not required if a partial gastrectomy ensures an R0 resection. Elective lymphadenectomy is not necessary. Essential data to be provided by the surgeon include: surgical technique, presence of hepatic or abdominal-cavity dissemination, involvement of macroscopic margins, tumor size, whether tumor rupture occurred in the abdominal cavity, and multicentricity. Surgical re-intervention in cases of R1 resections may be acceptable if the associated morbidity is negligible.

Systemic treatment

Localized disease

For high-risk GISTs, the standard treatment is adjuvant therapy of 400 mg/day imatinib mesylate over 3 years (STI571, Gleevec™, Novartis Pharmaceuticals) [54–56]. In intermediate- or low-risk cases, this has not been shown to improve survival. As a minimum requirement, genotyping should be performed in intermediate- and high-risk patients, and in case of neoadjuvant therapy is proposed. In cases of intermediate risk and gastric location, since any mutation involving codons 557 and/or 558 is associated

with a relapse-free survival rate of below 30%, administration of imatinib over 3 years should be suggested [51, 57] In patients with the D842V mutation, adjuvant therapy with imatinib is not recommended. A consensus has not been reached in cases with the *KIT/PDGFRA WT* genotype.

Advanced disease

Imatinib mesylate (STI571, Gleevec™, Novartis Pharmaceuticals) at a dose of 400 mg/day is the first-line systemic treatment for metastatic disease and has a median progression-free survival (PFS) of 22 months [58, 59]. Two comparative studies have shown that, except in the context of an exon 9 mutation, a dose of 800 mg/day provides no advantage over that of 400 mg/day [58, 59]; increasing the dose to 800 mg/day after progression at 400 mg/day benefited one-third of patients. Patients with the best PFS after imatinib treatment had tumors with mutations in *KIT* exon 11 [60].

Sunitinib malate (Sutent™, Pfizer) at a dose of 50 mg/day over 4 weeks followed by 2-week off is the standard second-line treatment after progression on imatinib. In a pivotal study of this drug, the median PFS was 6.3 months, and the most sensitive genotypes were those with exon 9 mutations and the *KIT/PDGFRA WT* genotype [61].

Regorafenib (Stirvarga, Bayer HealthCare Pharmaceuticals Inc.) at a dose of 160 mg/day over 3 weeks followed by 1-week off is the standard third-line medication. The median PFS in a pivotal study of regorafenib was 4.8 months [62]. As with sunitinib, the greatest clinical benefit was stabilization.

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Compliance with ethical standards

Conflict of interest The authors declare that, when writing and revising the text, they did not know the names of the pharmaceutical companies that provided financial support for this project, so this support has not influenced the content of this article.

Ethical statement The manuscript does not contain clinical studies or patient data

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