

# World Journal of *Gastroenterology*

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## Gastrointestinal stromal tumors: A multidisciplinary challenge

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### Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors located in the alimentary tract. Its usual manifestation is gastrointestinal bleeding. However, small asymptomatic lesions are frequently detected as incidental finding. Characteristically, most GISTs (> 95%) are positive for the KIT protein (CD117) by IHC staining and approximately 80%-90% of GISTs carry a mutation in the c-KIT or PDGFRA genes. Mutational analysis should be performed when planning adjuvant and neoadjuvant therapy, due to its possible resistance to conventional treatment. The arise of tyrosine kinase inhibitor has supposed a revolution in GISTs treatment being useful as adjuvant, neoadjuvant or recurrence disease treatment. That is why a multidisciplinary approach to this disease is required. The correct characterization of the tumor at diagnosis (the diagnosis of recurrences and the evaluation of the response to treatment with tyrosine kinase inhibitors) is fundamental for facing these tumors and requires specialized Endoscopist, Radiologists and Nuclear Medicine Physician. Surgery is the only potentially curative treatment for suspected resectable GIST. In the case of high risk GISTs, surgery plus adjuvant

Imatinib-Mesylate for 3 years is the standard treatment. Neoadjuvant imatinib-mesylate should be considered to shrink the tumor in case of locally advanced primary or recurrence disease, unresectable or potentially resectable metastatic tumors, and potentially resectable disease in complex anatomic locations to decrease the related morbidity. In the case of Metastatic GIST under Neoadjuvant treatment, when there are complete response, stable disease or limited disease progression, complete cytoreductive surgery could be a therapeutic option if feasible.

**Key words:** Gastrointestinal stromal tumors; Surgery; Oncology; Radiology; Endoscopy; Nuclear medicine; Pathology; Disease management; Tyrosine kinase inhibitors; Gastroenterology

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**Core tip:** The treatment of gastrointestinal stromal tumors with tyrosine kinase inhibitors represents the paradigm of the new era of molecular targeted therapy against cancer. During the last years, there have been improvements in the control of this disease and in the prognosis of these patients, deriving in hopeful perspectives in the management of these tumors partly thanks to the numerous specialists. In this work, we define the role of each specialist in the different clinical scenarios.

Sanchez-Hidalgo JM, Duran-Martinez M, Molero-Payan R, Rufian-Peña S, Arjona-Sanchez A, Casado-Adam A, Cosano-Alvarez A, Briceño-Delgado J. Gastrointestinal stromal tumors: A multidisciplinary challenge. *World J Gastroenterol* 2018; 24(18): 1925-1941 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i18/1925.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i18.1925>

## INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor located in the gastrointestinal (GI) tract. Most studies have reported the incidence of clinically relevant GIST between 10 and 15 cases per million; however, it is common to detect small asymptomatic lesions as incidental findings during abdominal surgery or in radiological or endoscopic studies, so GIST cases are often misdiagnosed<sup>[1,2]</sup>.

The majority of studies have reported an increase in incidence since 2000; nevertheless, this may be a consequence of improvements in diagnostic criteria rather than a true increase in incidence<sup>[3]</sup>.

GISTs are more often located in the stomach (56%) followed by small bowel (32%), colorectum (6%), and esophagus (< 1%). Sporadically, it may affect the omentum, mesentery, and peritoneum<sup>[4]</sup>. Liver and

peritoneum are the most common locations for distant metastases where they appear up to 47% at the time of diagnosis<sup>[5]</sup>. Pulmonary metastases, which are highly frequent in soft tissue sarcomas, are uncommon in the case of GISTs.

Interstitial cells of Cajal (ICCs) are recognized as the precursor cells of GISTs being implicated in the regulation of gut peristalsis. They are considered the pacemaker cells of the gastrointestinal tract and are immunostained by antibodies against CD117 (KIT) like GISTs<sup>[6,7]</sup>. ICCs are located between the layers of the muscularis propria in the interface between the autonomic innervation of the gastrointestinal wall and the smooth muscle, having immunophenotypic and ultrastructural features of smooth muscle and neuronal differentiation<sup>[8]</sup>.

Characteristically, most GISTs (> 95%) are positive for KIT (CD117) protein staining. Approximately 80%-90% of GISTs carry a mutation in the *c-KIT* gene (80%) or platelet-derived growth factor receptor alpha (PDGFRA) gene, which code for type III receptor tyrosine kinases<sup>[9]</sup>.

Traditionally, GIST tumors have been characterized by their resistance to conventional chemotherapy and radiotherapy treatments. Nevertheless, in 2002, the appearance of the tyrosine kinase inhibitor, Imatinib-Mesylate, was the first to be used to treat metastatic disease and currently has been introduced as an adjuvant or neoadjuvant. This drug was suggested to revolutionize treatment of these tumors that normally requires a multidisciplinary approach, which involves numerous specialists such as physicians, endoscopist, surgeons, radiologists, oncologists, nuclear medicine physicians, or pathologists<sup>[10]</sup>.

## ROLE OF CLINICIAN

A high proportion of GISTs are asymptomatic, and frequently, they are discovered incidentally during an endoscopic study (It is common to notice the presence of a sub epithelial mass) or on radiological images obtained for another purpose. Incidental finding can cause a significant diagnostic delay. Currently, a significant number of patients presents with metastases at the time of diagnosis (up to 50% in some series)<sup>[5]</sup>. It is essential that physicians include GISTs in differential diagnosis due to the importance of early diagnosis in these cases.

Clinical manifestations depend on the location of the primary tumor. There is no difference between gender and mean age reported is approximately 60-70 years old<sup>[1,11]</sup>.

Usually, these tumors are associated with nonspecific symptoms (early satiety, swelling) unless they ulcerate, bleed or grow enough to cause pain, obstruct, or present other manifestations related to their disproportionate size<sup>[12,13]</sup>. In the case of esophageal GIST, dysphagia represents the first specific symptom in this location<sup>[14]</sup>.

In general terms, the most frequent manifestation is gastrointestinal bleeding, either evident or hidden, which may be associated with anemia and sometimes melena or hematemesis<sup>[15]</sup>; bleeding is the most frequent symptom in case of small intestine GISTs and often require urgent surgical intervention<sup>[16]</sup>. Because their silent growth tumors may be particularly large causing abdominal distention or a palpable mass and sometimes provoking intestinal obstruction (25%-40%); however, intestinal perforation has rarely been described<sup>[16,17]</sup>.

Paraneoplastic syndromes are unusual in case of GISTs; however, some have been reported as consumptive hypothyroidism or hypoglycemia secondary to IGF-II production, so they should be included in the differential diagnosis when endocrine-metabolic symptoms appear<sup>[18,19]</sup>.

Patients with multifocal disease are generally classified as advanced (metastatic) stage, but it should be taken into account, particularly in those cases with hereditary conditions, that multiple primaries may be possible<sup>[20]</sup>.

In adults, GIST tumors have been associated with multiples syndromes as neurofibromatosis type 1 (NF1), Carney Triad syndrome and Carney Stratakis syndrome; GISTs associated with NF1 usually appear in the gastrointestinal tract and are usually multicentric. In these tumors, the KIT mutation is not characteristic, and they are usually positive for the CD117 antigen<sup>[21]</sup>; on the other hand, Carney's triad consists of epithelioid GISTs is associated with extra-adrenal paraganglioma and pulmonary chondroma. It lacks the conventional KIT and PDGFRA gene mutations and tends to present an indolent course<sup>[22]</sup>; the Carney Stratakis syndrome is extremely rare and is similar to Carney's Triad syndrome but lacks pulmonary chondroma and follows a benign course. Mutations have been identified in KIT or PDGFRA. The tumors are generally small, lack mitotic activity and arise in interstitial cells of Cajal<sup>[23]</sup>.

Pediatric GISTs are assumed to be 1%-2% of all GISTs. Two subgroups exist: (1) with mutations (KIT or PDGFRA) or (2) without mutations (the most frequent). The patients are almost exclusively young women who develop gastric epithelioid GISTs, which are KIT types. Unlike adult GISTs, these tumors can spread to lymph nodes<sup>[24,25]</sup>.

## ROLE OF RADIOLOGIST

Computed tomography (CT) is the gold standard for imaging that is used to characterize any abdominal mass in addition to assessing its extent and the presence/absence of disease at a distance (GIST metastasize more frequently to the liver, omentum, and peritoneal cavity). Therefore, with suspicion of a tumor in the digestive tract, as in the case in question, an initial CT scan should be done. It should be noted that for the optimal performance of CT, oral and intravenous

contrast should be administered in order to define the intestinal margins<sup>[26,27]</sup> (See Figure 1 and 2).

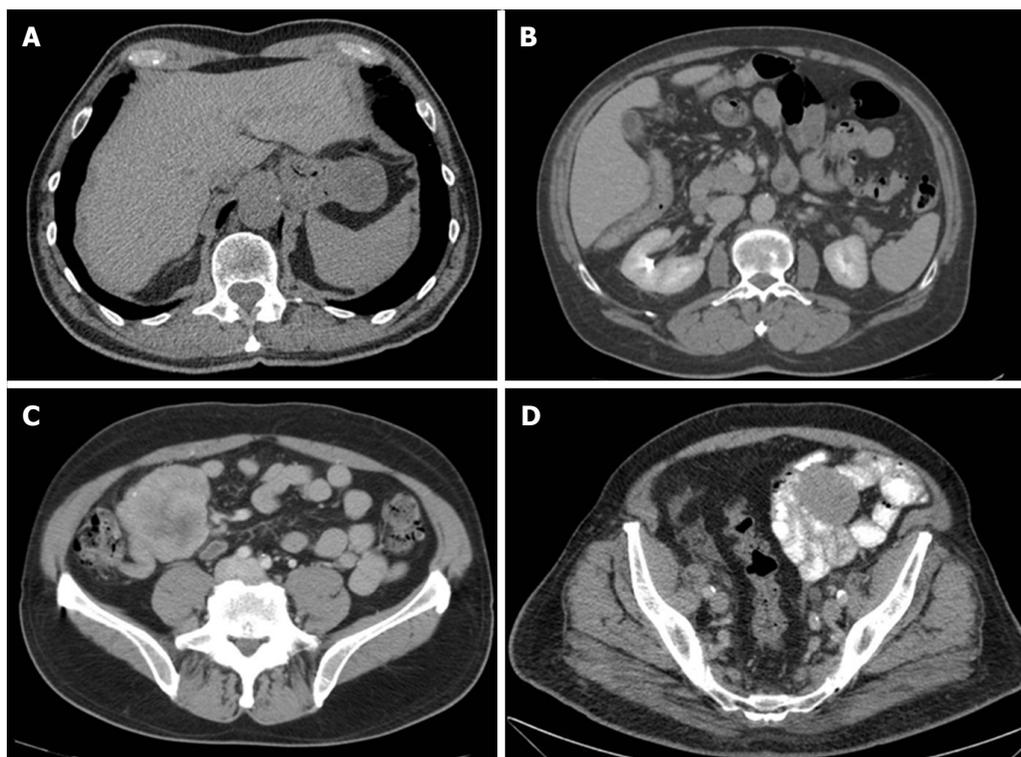
Magnetic resonance imaging (MRI) has a diagnostic performance comparable to CT and the advantage of lacking ionizing radiation; however, CT is the preferred initial imaging study for screening and staging of the disease. There are exceptions to this process; for example, there are patients who cannot receive intravenous contrast for various reasons (allergies, IR). In addition, MRI can sometimes be the choice for GISTs found in specific locations (such as the rectum) and is especially useful for evaluating the anatomical degree of surgery or for evaluating the suspicion of liver metastases<sup>[26]</sup> (See Figure 3).

The usual characteristic images seen on these images include the presence of a solid mass with a soft contour that is enhanced with intravenous contrast in the case of CT<sup>[28]</sup>. Very large tumors may appear more complex due to necrosis, haemorrhage, or degenerative components, and it may be difficult to identify the origin of a large mass due to exophytic growth<sup>[27]</sup>.

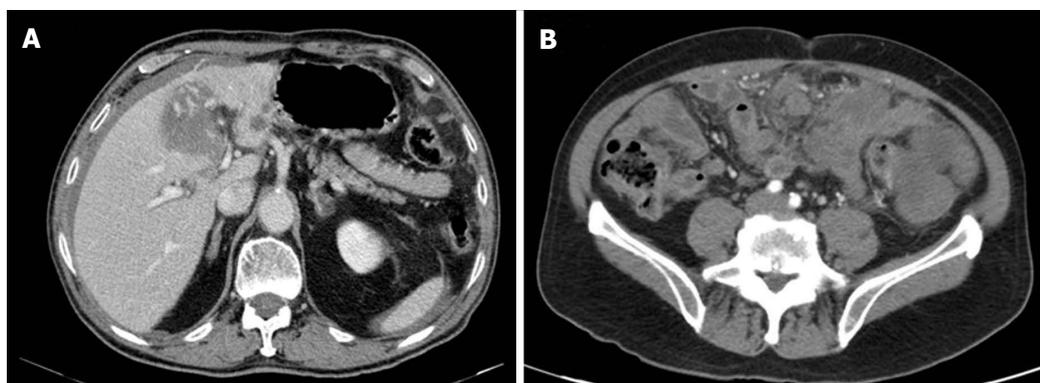
With regard to the evaluation of response to treatment, patients are routinely subject to CT, and two-dimensional measurements are used to determine response, stability, or progression.

During neoadjuvant and adjuvant treatment, radiologists are mainly involved in the evaluation of the response to treatment with tyrosine kinase inhibitors (TKI). On the one hand, Response Criteria in Solid Tumors (RECIST) is the standard method used to measure the way in which a cancer patient responds to treatment. In order to apply the RECIST criteria, it is necessary to first identify representative and reproducible target lesions during follow-up; it should be taken into account that its great variability (fragmentation, poor definition, imaging technique, appreciation) in addition to the difficulty in measuring them, as occurs in mobile organs, cause intra-observer and inter-observer discrepancies. Assessments of the response will be made with the same technique used in the initial study, stating the duration of the response. The sum of the target lesions in the baseline study can be used to objectively monitor and assess the response. When a target lesion fragments during treatment, its parts will be measured, added up, and considered as a single lesion. The RECIST criteria are a series of published rules to establish the response to treatments and indicate when cancer patients improve ("respond"), stay the same ("stable"), or get worse ("disease progression"<sup>[29,30]</sup>).

In the other hand, the Choi Criteria<sup>[31]</sup> are useful in the evaluation of imatinib treatment of GISTs. In this case, the most characteristic feature is a decrease in the density of lesions associated with myxoid degeneration, hemorrhage, or necrosis. These criteria, based on CT studies, include tumor size, its density, and the appearance of intratumoral hypervascular nodules. They present a high correlation between the results obtained in CT and positron emission tomography (PET). CT



**Figure 1 Localized gastrointestinal stromal tumors on computed tomography scan.** A: Gastric; B: Duodenal; C: Ileal; D: Jejunal. A and B show respectively a gastric tumor and a duodenal tumor of exophytic growth with well-defined borders. Appreciate in C the different densities inside the tumor due to necrosis, haemorrhage, or degenerative components. D shows a jejunal GIST in left iliac fossa.



**Figure 2 Metastatic gastrointestinal stromal tumors on computed tomography scan.** A: Liver metastasis; B: Peritoneal metastasis “Gistosis”. In A, it is appreciated a large hepatic metastasis in segment IV. B shows the CT of a patient with disseminated peritoneal disease “GISTosis”.

should be performed in arterial phases (to see changes in vascularization and uptake) and portal (to measure tumor density)<sup>[32]</sup>.

**Role of interventional radiologist**

As described previously, GISTs usually manifest as gastrointestinal bleeding. Transcatheter arterial embolization has proven to be a safe option for controlling gastrointestinal bleeding, thus preventing emergency surgery that would probably allow a more accurate diagnosis to be made and the best possible surgical plan to be executed<sup>[33]</sup>.

Traditionally, preoperative percutaneous biopsy has

not been used due to the possibility of tumor rupture or peritoneal spread of disease<sup>[8]</sup>. There are data supporting the finding that it may not increase the risk for GIST recurrence in those patients who receive adjuvant Imatinib after the biopsy was obtained. Percutaneous biopsy should be considered when it is necessary to plan preoperative treatment with TKI and endoscopic biopsy is not feasible<sup>[17,34]</sup>.

In the case of patients with unresectable liver metastases, some local interventional modalities, such as transarterial embolization or radiofrequency ablation may be used; however, further studies are necessary to evaluate its effectiveness as adjuvant therapy or

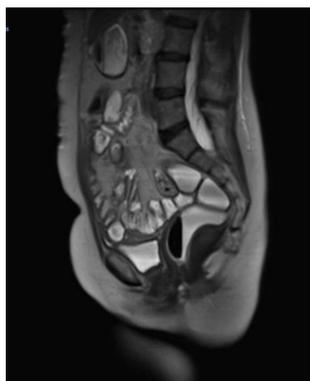


Figure 3 Rectal gastrointestinal stromal tumor on magnetic resonance.



Figure 4 Characteristic endoscopic image of gastric gastrointestinal stromal tumor.

combined with TKI<sup>[35-37]</sup>.

## ROLE OF ENDOSCOPIST

In the presence of a gastric mass, endoscopy is indicated to characterize the lesion. GISTs and leiomyomas may appear as a submucosal mass with smooth margins and a normal overlying mucosa that protrudes in the gastric lumen, but sometimes, a central ulceration may be observed<sup>[38]</sup> (See Figure 4).

Simple endoscopy lacks the ability to accurately distinguish between intramural and extramural tumors. In this sense, Endoscopic Ultrasonography (EUS) has proved to be a valuable technique, being able to characterize such masses by identifying the layer of origin and allowing for acquisition of tissue by a guided puncture for anatomopathological diagnostic studies, which is suitable for immunohistochemical tests<sup>[39,40]</sup>. Standard endoscopic biopsies generally do not obtain enough tissue for a definitive diagnosis, and loop biopsies can cause a perforation and should generally be avoided<sup>[34]</sup>.

Most GISTs originate within the muscularis propria although small lesions may originate in the muscularis mucosae. By EUS, GISTs are typically hypoechoic and present as homogeneous lesions with well-defined margins although there are a small number of described

tumor cases of tumors that may have irregular margins and ulcerations (See Figure 5). Ultrasound (US)-guided biopsy forceps may also not obtain enough tissue, but its main utility is to exclude other lesions arising from the submucosa<sup>[39]</sup>.

Preoperative biopsy is not generally recommended for a resectable lesion if there is high clinical and radiological suspicion of GIST, and the lesion is completely resectable. However, a preoperative biopsy is preferred to confirm the diagnosis if metastatic disease is suspected, if the neoadjuvant Imatinib is considered, or in cases in which there exists high operative morbidity or the diagnosis is not clear.

If a preoperative biopsy is performed, an US-guided biopsy is preferred to a percutaneous biopsy because of the risk of tumor capsule rupture and consequent peritoneal dissemination<sup>[34]</sup>.

The combined use of cytological analysis and immunohistochemistry for KIT protein detection and expression and polymerase chain reaction (PCR) to detect KIT mutations allow the diagnosis of most of these lesions obtained by EUS - fine- needle aspiration Biopsy (FNAB). In a study of 65 patients undergoing EUS-FNAB for a submucosal lesion of the upper GI tract, among the 28 lesions with a definitive pathological diagnosis, the sensitivity for the diagnosis of GIST was 82% and the specificity 100%<sup>[41]</sup>.

## ROLE OF THE NUCLEAR MEDICINE SPECIALIST

PET with fluorodeoxyglucose (FDG-PET) is highly sensitive detection of very metabolically active tumors resulting from a significant glycolysis (See Figure 6); however, this test is not considered to be specific enough to obtain a preoperative diagnostic, so it has not replaced CT as the initial imaging modality of choice in patients suspected of having a mesenchymal tumor in the GI tract. FDG-PET may be useful for detecting an unknown primary site or resolving ambiguities on the CT (inconclusive CT findings or inconsistent with clinical findings)<sup>[42]</sup>. The reported sensitivity of PET for GIST (including metastatic lesions) is 86%-100%<sup>[43]</sup>.

The FDG-PET response, which is characterized by a mark in the glycolytic metabolism of tumors, may be seen one month after starting treatment with Imatinib-Mesylate and an early response may be seen in the first 24 h<sup>[44]</sup>. FDG-PET may detect an early response to a tyrosine kinase inhibitor, which may be important when the treatment is administered and would allow identification of patients with primary resistance to treatment or even identify secondary resistance in the case of patients already treated with Imatinib-Mesylate<sup>[45]</sup>.

## ROLE OF SURGEON

Surgery is the only potentially curative treatment for

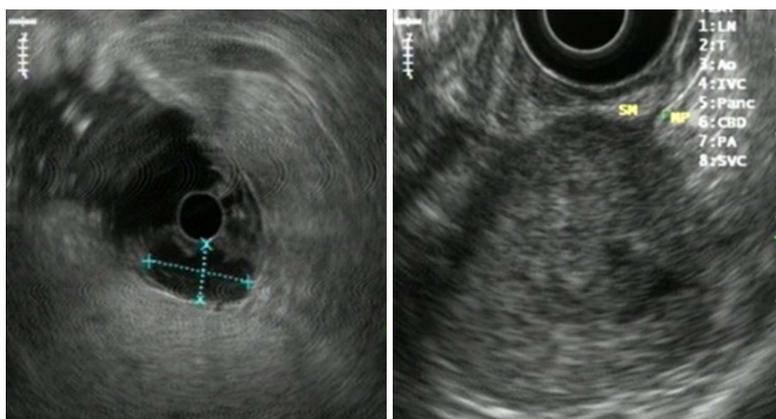


Figure 5 Endoscopic ultrasonography images of gastrointestinal stromal tumors.

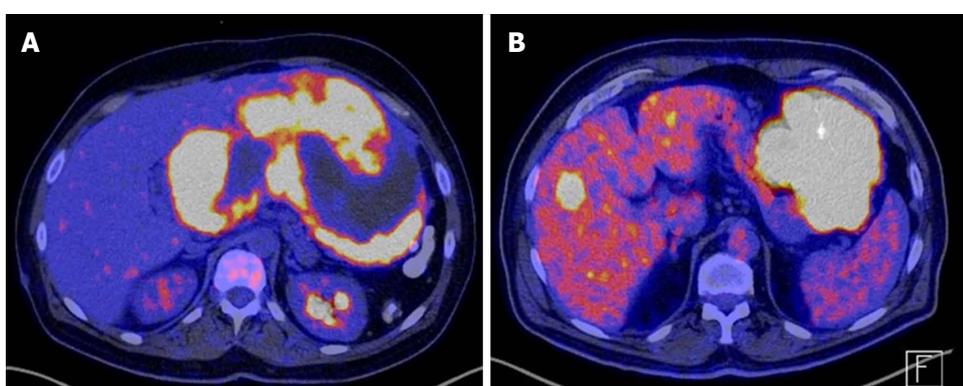


Figure 6 Gastrointestinal stromal tumors on positron emission tomography with fluorodeoxyglucose. A: Giant gastric GIST on a patient with neurofibromatosis type 1; B: Gastric GIST with an unique liver metastasis. GIST: Gastrointestinal stromal tumor.

suspected resectable GIST. The primary objective of this process is to ensure that clear resection margins are obtained in a complete resection of the tumor, and it can be extirpated without tumor pseudocapsule rupture; nevertheless wide margins have no benefit in disease control<sup>[5]</sup>. Conservative surgery must be the procedure of choice due to local GIST infiltrative behavior; lymphadenectomy is not necessary due to lymphatic affection, which is rare<sup>[46]</sup>. A thorough exploration of the liver and parietal peritoneum is important in order to objectify possible metastases.

At least 40%-50% of patients who have undergone optimal surgery may experience a tumor recurrence; however, with the appearance of TKI, a new option disease control has been offered<sup>[47,48]</sup> (See Figure 1).

The management of GISTs < 2 cm is controversial; in spite of the fact that an active follow-up of the lesion could be an option, surgery should be considered because there is no data concerning growth behavior and metastatic potential<sup>[49,50]</sup>.

## RESACTABLE DISEASE

### Stomach

In the case of gastric GISTs, which is the most common location, wedge resections are preferred to

classic gastrectomies<sup>[51]</sup>. Currently, there are multiple studies comparing laparoscopic wedge resection for gastric GISTs versus open surgery showing multiple benefits that patients could obtain resulting from this less invasive approach as reducing postoperative discomfort or shortening the length of postoperative hospital stay. In this sense, laparoscopy wedge resection is considered the standard treatment for gastric GIST<sup>[52-55]</sup>. In a multi-institutional analysis performed by Bischof *et al.*<sup>[56]</sup>, minimally invasive surgery for gastric GIST was shown to reduce length of the hospital stay, blood loss, and morbidity with same R0 and tumor rupture rates. The main limitation to laparoscopy resection is technical difficulty due to tumor size and location; nevertheless, multiple studies have demonstrated that laparoscopy wedge resection for gastric GISTs > 5 cm is feasible<sup>[54,57,58]</sup>.

Incidental GIST finding in bariatric surgery is rare with a reported incidence between 0.3%-1.2% in different series of sleeve gastrectomy and gastric bypass<sup>[59-61]</sup>. In many cases, the performed procedure may be curative; however, the finding of GISTs in certain locations such as the gastroesophageal junction or lesser curve could require abandoning the proposed technique in favor of a suitable and complete tumor excision<sup>[59]</sup>.

**Small bowel**

For patients who have primary localized small bowel GIST, segmental bowel resection remains the first choice of treatment. Emergent resections are more often needed in patients diagnosed with small bowel stromal tumors secondary to hemorrhage, obstruction, or perforation<sup>[62]</sup>. Laparoscopic segmental resection with intra- or extracorporeal anastomoses, when possible, is the elective approach achieving comparable oncologic results<sup>[63-65]</sup>. Tabrizian *et al*<sup>[66]</sup> reported that in their series, laparoscopic removal of tumors up to 85 mm shows low rates of morbidity (10%), mortality (1.3%), and conversion (19%); the main reason for conversion was the tumor's proximity to the gastroesophageal junction, local invasion of adjacent organs, association with another malignant lesion, preoperative tumor perforation, extensive adhesions, and large tumor size<sup>[66]</sup>.

**Colon**

In spite of the fact that the colon is an uncommon location for GISTs, patients with tumors in this location present a much poorer prognosis with a higher rate of disease-specific mortality and a higher percentage of patients with distant disease<sup>[67,68]</sup>.

Due to intrinsic characteristics of GIST tumors, a wide resection is not required and segmental colectomy is the standard approach; Moreover, as previously mentioned, GIST does not metastasize through lymphatics thus mesocolic resection is unnecessary<sup>[69]</sup>.

**GISTs in complex anatomical locations**

In cases of potentially resectable disease that are located in complex anatomic locations and require extensive organ disruption, neoadjuvant therapy with Imatinib has been proposed to downstage tumors and facilitates complete resection or decrease the morbidity of resection<sup>[67]</sup>.

**Esophagus:** Esophageal location of a GIST is infrequent<sup>[16]</sup>. Robb *et al*<sup>[14]</sup> proposed that enucleation of the tumor is safe for esophageal GISTs < 65 mm as long as negative margins and intact pseudocapsule can be achieved, while in tumors of > 90 mm with evidence of mucosal ulceration and/or a high mitotic activity, an esophagectomy should be performed. The choice between esophagectomy and enucleation for tumors of between 65 and 90 mm needs further clarification with the decision being influenced by the location, malignant risk, patient comorbidity, and the presence of mucosal affection<sup>[14,70]</sup>. Neoadjuvant therapy is indicated with the aim of shrinking the primary tumor<sup>[70]</sup>.

**Duodenum:** GISTs located in duodenum are rarely observed and often manifest as nonspecific abdominal pain, gastrointestinal hemorrhaging, and intestinal obstruction may infrequently have been observed<sup>[71,72]</sup>.

When possible, limited resection should be the

procedure of choice; nonetheless, due to peculiar anatomic location because of proximity of the pancreatic head and papilla of Vater and the difficulties to get an adequate section margin, Pancreaticoduodenectomy is often necessary<sup>[73]</sup>. In the meta-analysis accomplished by Chok *et al*<sup>[74]</sup>, it was appreciated an increase of positive margins in case of Limited resection, although there was no significant difference in local recurrence between Limited Resection and Pancreaticoduodenectomy.

Neoadjuvant treatment with TKI has been proposed to downstage GISTs, and possibly increases the chance of preserving normal biliary and pancreatic anatomy which would otherwise require more aggressive surgery<sup>[74,75]</sup>.

**Rectum:** Outcomes in colonic or rectal locations appear to be worse than those located in the stomach<sup>[67]</sup>. Rectal GIST may require an abdominoperineal amputation to achieve a surgically complete resection. To avoid an extensive and limiting surgery, neoadjuvant Imatinib-Mesylate should be considered to reduce tumor size and facilitate complete surgical resection by increasing negative margins and less radical sphincter-sparing surgery<sup>[76,77]</sup>. Laparoscopic sphincter-preserving surgery is safe and feasible after neoadjuvant treatment of Imatinib Mesylate<sup>[78]</sup>. Mesorectal resection for rectal GISTs is not required due to the absence of lymphatic dissemination. Transanal endoscopic surgery has been employed for local treatment of low rectal GISTs with no evidence of recurrence after an 18-mo follow-up<sup>[79]</sup>.

**LOCALLY ADVANCED DISEASE OR BORDERLINE RESECTABLE**

Most studies define locally advanced primary GIST as the significant involvement of a single organ with large tumor size or extension of the tumor to adjacent organs<sup>[80]</sup>. Neoadjuvant use of imatinib has been demonstrated to be useful in primary locally advanced GISTs by causing a decrease in tumor volume in the majority of the patients. Tumor response may facilitate complete resection of these advanced tumors and could allow less invasive procedures without tumor rupture<sup>[10,16,81]</sup>.

**METASTATIC AND RECURRENT DISEASE**

Metastases may be detected at first presentation or at the time of disease progression. The first line of treatment for patients with metastatic or recurrent GISTs are TKI in the form of neoadjuvant or adjuvant therapy with the choice of treatment being Imatinib-mesylate<sup>[82]</sup>. The appropriate time for surgical intervention is still unknown. It is proposed to consider surgery if a complete cytoreductive resection is feasible after six to nine months with a tyrosine kinase inhibitor.

After treatment with TKI, there are three possible radiological response of the disease<sup>[83]</sup>: (1) Complete response: Non metabolic activity in PET; Disappearance

of disease in CT; Infrequent clinical situation. (2) Partial response or responding to drug therapy; Decrease of metabolic activity in PET and/or decrease of size in CT. (3) Stable disease: Disease is radiographically (CT, PET) stable. (4) Limited/localized disease progression: Progression in spite of drug therapy is seen at one or a few (but not all) sites of disease. Patients with Partial response, stable disease or limited/localized disease progression could undergo cytoreductive surgery. And (5) Generalized disease progression: In this case, disease is progressing at multiple sites while on drug therapy. Debulking surgery does not seem to prolong survival so cytoreductive surgery is not recommended.

### **Peritoneum metastases; “GISTosis”**

Peritoneal GIST metastases may be detected, especially in cases in which the primary tumor ruptured spontaneously or surgically. When disease progression occurs due to Imatinib resistance and GISTs relapse loco-regionally after surgical resection or disease disseminates to peritoneum, prognosis is poor and standard treatments such as conventional surgery, radiotherapy, and systemic chemotherapy are generally ineffective<sup>[84]</sup>.

Imatinib-Mesylate and Sunitib-Malate (used in cases in which GIST develops resistance to Imatinib) have been shown to increase disease control and survival rates; nevertheless, although patients experience durable periods of disease stability to Imatinib lasting months to years, the response is not maintained indefinitely<sup>[85]</sup>.

Aggressive surgical procedures to treat loco-regional relapse and peritoneal metastases have been proposed. These cytoreductive strategies involve peritonectomy procedures and multivisceral resection to remove all macroscopic tumor(s)<sup>[84]</sup>. Cytoreductive surgery has been shown to increase progression-free survival and overall survival rates in patients with metastatic GIST who are receiving Imatinib Mesylate therapy. Patients with stable disease or responsiveness to Imatinib Mesylate had demonstrated an increase in survival rates compared to those with disease progression<sup>[81,85-87]</sup>.

Sugarbaker<sup>[84]</sup> proposes the complete resection of recurrent sarcomas using peritonectomy and visceral resections to complete cytoreduction of disease and perioperative intraperitoneal chemotherapy. The randomized trial performed by Bonvalot *et al.*<sup>[88]</sup> in 2005 demonstrate the importance of the positive impact of complete cytoreductive surgery; however, the use of intraperitoneal chemotherapy didn't increase greatly overall survival of sarcomatosis. Cytoreductive Surgery combined with perioperative intraperitoneal chemotherapy is a promising future approach to sarcomatosis, awaiting new chemotherapy agents.

After the surgical excision of GISTs metastases, it is necessary to continue treatment with TKI<sup>[85]</sup>.

### **Liver metastases**

GIST metastases are often located in liver and may

appear as primary disease or as a recurrence after surgery. In cases of metastatic GIST in which stable disease or localized disease progression exists, hepatic resection is the mainstay of treatment for liver metastasis<sup>[83]</sup>.

In DeMatteo *et al.*<sup>[89]</sup> 56 patients with liver metastasis who underwent complete resection of all gross disease had significantly longer survival (1-,3-,5-year disease-specific survival rate was 88%, 50%, and 30%, respectively) than those 275 patients who did not undergo complete resection (1-, 3-, and 5-year disease-specific survival rates of 50%, 13%, and 4%, respectively). Completing surgical treatment with Imatinib Mesylate showed an increase in disease-free and overall survival<sup>[37,90]</sup>.

There exist few references in the literature concerning liver transplantation in patients with metastatic sarcoma showing uninspiring results<sup>[91,92]</sup>.

## **ROLE OF ONCOLOGIST**

The use of TKI against GIST introduced a new era in molecular-targeted therapies in clinical oncology. The oncologist plays a major role in GIST treatment for carrying out the indication for the TKI for metastatic tumors after a curative surgery or as a neoadjuvant treatment (See Figure 1).

Almost 85% of GISTs have a mutation in KIT or PDGFRA that induces an KIT activation, which is a tyrosine kinase receptor that stimulates the growth of cancer cells. Mutational analysis is acquiring a growing importance and should be performed when adjuvant and/or neoadjuvant therapy show possible mutations with a tendency toward Imatinib Mesylate-resistance<sup>[17]</sup>. Tyrosine kinase inhibitor selection based on gene mutations is described in Table 1.

**KIT gene mutations (80%):** KIT exon 11 is the most common mutation and may be observed in approximately 75% of all mutation-positive tumors primarily affecting codons 557-559. These mutations are most commonly observed in gastric GIST. In the Z9001 trial, patients with exon 11 mutation proved to experience greater benefits from adjuvant Imatinib with higher rates of relapse-free survival although these mutations indicate poorer prognosis and high metastatic risk<sup>[17,93,94]</sup>. Exon 9 mutations (approximately 10%) are associated with poor Imatinib response. Mutations in exons 8, 13, and 17 are infrequent and seem to be < 3%<sup>[24]</sup>.

**PDGFRA gene mutations (5%-8%):** GISTs with PDGFRA mutations are regularly located in stomach<sup>[17]</sup>. The D842V mutation in PDGFRA exon 18 is the most common mutation found (65%-75% of PDGFRA mutations)<sup>[94]</sup>; this mutation is associated with Imatinib and Sunitinib resistance<sup>[95,96]</sup>. Non-D842V exon 18, 12, and 14 mutations are rare and sensitive to Imatinib.

**Table 1** Tyrosine kinase inhibitor election based on genes mutations

Gene	Mutation	TKI. Dose
KIT	Exon 11	Imatinib-Mesyate 400 mg/d
	Exon 13	
	Exon 17	
PDGFRA	Exon 9	Imatinib-Mesyate 800 mg/d Sunitinib 50 mg/d Regorafenib 160 mg/d Imatinib-Mesyate 400 mg/d
	Exon 18. D842V mutation	
	Exon 12	
	Exon 14	
Wild-type	Exon 18. Non D842V mutations.	Sunitinib 50 mg/d Regorafenib 160 mg/d

**Wild-type GISTs (12%-15%; 90% of pediatric GISTs):** In these cases, there are no detectable mutations in KIT or PDGFRA genes that are resistant to treatment with Imatinib although tyrosine kinases are still activated. Wild-type GISTs represent a heterogeneous group that includes several oncogenic mutations such as BRAF V600E substitution, NF1 mutation, and defects in the succinate dehydrogenase complex<sup>[97-99]</sup>. Second line TKI are recommended despite poor response by these tumors.

**KIT-negative GISTs (CD117-negative):** Approximately 5% of GISTs do not express CD117 by immunoreactivity but 30%-50% of cases have KIT or PDGFRA mutations<sup>[100]</sup>.

When patients present primary or secondary resistance to Imatinib, second-line treatment with Sunitinib and third-line treatment with Regorafenib are recommended.

## ADJUVANT THERAPY

In spite of performing a complete resection of the tumor without tumor rupture and appearance of negative margins, GISTs still have some malignant potential and may recur or metastasize. It is necessary to identify those patients who may derive benefits from the adjuvant Imatinib-Mesyate because of their high risk of recurrence or metastases following resection. Several risk stratification models have been proposed to estimate the risk of recurrence and identify high risk GISTs after resection, so the indication of adjuvant Imatinib can be individualized. In multiples models, the main predictors of recurrence established were tumor mitotic rate, size, and location<sup>[47,101]</sup>. Increased tumor size, high mitotic activity, or extragastric location such as small bowel, colon, rectum, or mesentery is associated with an increased risk of poor outcomes. The oldest risk stratification model is the consensus from the National Institutes of Health (NIH) which stratifies risk on the basis of tumor size and mitotic count and has demonstrated its usefulness in predicting GIST behavior<sup>[8,102]</sup>. On the other hand, Miettinen *et al.*<sup>[103]</sup> emphasized the importance of location to the risk of

recurrence. The revised NIH consensus criteria by Joensuu *et al.*<sup>[104]</sup> in 2008 included the presence of either spontaneous tumor rupture or that occurring, which worsens the prognosis and location because of the better prognosis of gastric location versus extra gastric GISTs (Table 2)<sup>[105]</sup>. Incomplete resection has demonstrated to adversely affect overall survival (OS)<sup>[106]</sup>.

In a phase II US Intergroup trial ACOSOG Z9000<sup>[107]</sup>, 106 patients with resected high-risk GIST were included. High risk was defined as tumors >10 cm, evidence of capsular rupture, hemorrhage, or multifocal disease with > 5 tumor foci. Patients were treated after a complete resection with daily oral 400 mg Imatinib for one year. The primary endpoint was OS with 1-, 2-, and 3-year OS of 99%, 97%, and 83%, respectively. One-, 2-, and 3-year recurrence-free survival was 96%, 60%, and 40%, respectively.

In the ACOSOG Z9001 randomized phase III multicenter trial, 713 patients with complete gross resection of a primary GIST at least 3 cm in size and showing positive staining for KIT protein were randomly assigned to one year of adjuvant Imatinib (400 mg daily) or placebo<sup>[108]</sup>. Primary endpoint was recurrence-free survival (RFS). Imatinib was shown to increase RFS compared with placebo (98% versus 83% at one year; hazard ratio [HR] 0.35;  $P < 0.0001$ ). Although no differences in the case of OS (99.2% vs 99.7% at one year; HR 0.66;  $P = 0.47$ ), it was considered justified because of short follow-up time and the crossover study design, which allowed patients with tumor recurrence assigned to the placebo arm to receive Imatinib-Mesyate. In this study, patients with exon 11 mutations showed the longest progression-free survival (PFS), while those with an exon 9 mutation had the worst outcomes; however, those patients with exon 9 mutations treated with higher dose of Imatinib showed greater PFS.

In the EORTC 62024 phase III trial<sup>[109]</sup>, 908 patients with intermediate- or high-risk GIST were included and assigned to two years of daily Imatinib 400 mg after complete resection compared to only surgery. The primary endpoint at the origin was OS; however, in 2009, the primary endpoint was changed to Imatinib failure-free survival (IFFS). With a median follow-up

**Table 2 Risk stratification criteria for primary resectable gastrointestinal stromal tumor proposed by Joensuu**

Risk category	Tumour size (cm)	Mitotic index (per 50 HPF)	Primary tumour site
Very low risk	≤ 2.0	≤ 5	Any
Low risk	2.1-5.0	≤ 5	Any
Intermediate risk	≤ 5.0	6-10	Gastric
	5.1-10.0	≤ 5	Gastric
High risk	Any	Any	Tumour rupture
	> 10.0	Any	Any
	Any	> 10	Any
	> 5.0	> 5	Any
	≤ 5.0	> 5	Non-gastric
	5.1-10.0	≤ 5	Non-gastric

HPF: High-power field.

of 4.7 years, 5-year IFFS was 87% in those patients treated with Imatinib versus 84% in the control arm (HR = 0.79; 98.5%CI: 0.50-1.25;  $P = 0.21$ ); RFS was 84% in the Imatinib group vs 66% at 3 years and 69% versus 63% at 5 years (log-rank  $P < 0.001$ ).

In the Scandinavian Sarcoma Group (SSG) XVIII trial comparing 12 mo vs 36 mo of adjuvant 400 mg/d Imatinib, 400 patients with high-risk complete resected GIST were included. Patients who were treated with 36 months of Imatinib showed an increase in RFS compared with those treated 12 mo (HR = 0.46; 95%CI: 0.32-0.65;  $P < 0.001$ ). Five-year RFS was 65.6% in the 36-mo group compared to 47.9% in the 12-mo group. Patients treated with 36 mo of Imatinib showed an increase in OS (HR = 0.45; 95%CI: 0.22-0.89;  $P = 0.02$ ) with 5-year survival of 92.0% versus 81.7% in those patients treated for 12 mo<sup>[110]</sup>. In the 36-mo group, it was observed that a high number of patients discontinued Imatinib for reasons other than GIST recurrence (25.8% vs 12.6%). In this study, patients with KIT exon 11 deletion mutations benefitted most from the 36 mo of adjuvant Imatinib, while in the other mutational subgroups examined there were no significant benefits<sup>[111]</sup>.

Adjuvant treatment is recommended in those patients who have R0 primary high risk GISTs; however, the optimal indication of adjuvant treatment in high risk patients is not clear, so each case must be approached individually in multidisciplinary specialized committees that balance beneficial and negative impacts. The standard treatment for high risk GIST is adjuvant therapy of 400 mg/d of Imatinib-Mesylate over three years. Two randomized trials comparing prolonged adjuvant therapy with Imatinib-Mesylate versus standard treatment (five versus three years in SSG XXII [NCT02413736] and six versus three years ImadGist [NCT02260505]) exist.

## NEOADJUVANT THERAPY

Neoadjuvant Imatinib-Mesylate should be, considered for shrinking the tumor in cases of locally advanced primary or recurrent disease, unresectable or potentially

resectable metastatic tumors, and potentially resectable disease in complex anatomic locations to decrease the related morbidity<sup>[112]</sup>. There is no consensus about duration of the treatment with Imatinib-Mesylate; however, 3-12 mo of treatment with numerous imaging control studies would be an acceptable management<sup>[113]</sup>. Usually, maximal tumor response occurs after 4 to 12 mo of treatment<sup>[114]</sup>.

Tumors located in complex anatomic locations such as the esophagus, duodenum, or rectum may show a major benefit of initial neoadjuvant treatment to produce less extensive organ disruption interventions<sup>[14,78,115]</sup>.

Preoperative Imatinib has demonstrated to facilitate complete resection of locally advanced primary, recurrent, or metastatic GISTs. In Andtbacka *et al*<sup>[80]</sup>, a series of 46 patients, who underwent surgery after neoadjuvant Imatinib, was retrospectively reviewed; 35 patients were treated for recurrent or metastatic GIST obtaining a complete resection in 11 patients. This study showed that those patients with a partial radiographic tumor response to neoadjuvant showed significantly higher complete resection rates than patients with progressive disease (91% vs 4%;  $P < 0.001$ ).

In a study by Bonvalot *et al*<sup>[81]</sup>, 22 of 180 patients with unresectable GIST treated with neoadjuvant Imatinib (19 received imatinib 400 mg/d and three received 800 mg/d) and no radiographic evidence of overall progression underwent surgery. There were five patients with metastases who underwent emergency surgery due to hemorrhaging and three of them died in the early postoperative period. When surgery was planned, 15 of 17 patients (88%) had a complete resection.

In the study by Chandrajit *et al*<sup>[30]</sup>, those patients with advanced GISTs under neoadjuvant therapy with Imatinib showing stable disease or limited progression had an increase in OS rates after cytoreductive surgery.

The analysis realized by European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC STBSG), which included databases from 10 EORTC STBSG sarcoma centers, indicated that the largest group of GIST patients ( $n = 161$ ) were treated with neoadjuvant Imatinib. The most

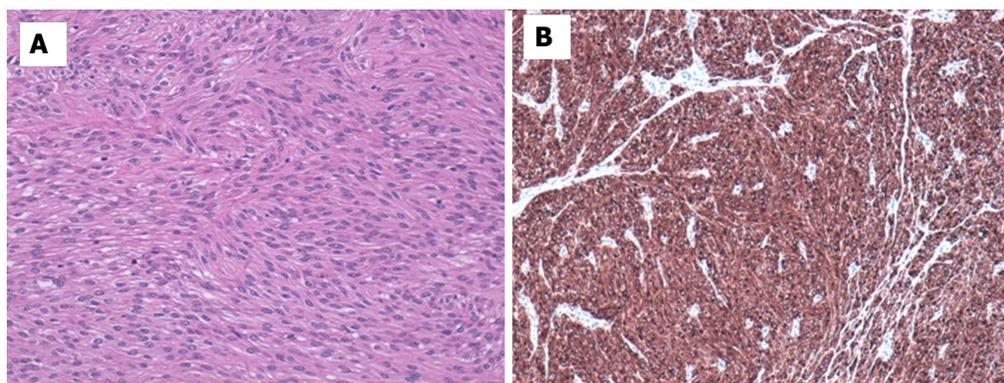


Figure 7 Histological sections of ileal gastrointestinal stromal tumor. A: HE stain; B: Immunohistochemistry with C-KIT.

Table 3 Items that pathology report should include

Pathology report items
Localization
Size
Number of foci
Tumor infiltration
Histologic subtype
Depth of tumor infiltration
Grade of dedifferentiation
Mitotic rate
Ki67
Grade of necrosis
Grade of hemorrhage
Margins
Staging
Mutational study

common location was the stomach (55%) followed by rectum (20%), duodenum (10%), ileum/jejunum/other (11%), and esophagus (3%). Median time on therapy with neoadjuvant Imatinib was 40 weeks, and R0 was obtained in 83% of patients. During follow-up, they observed 37 disease recurrences (23%) and only five patients (3%) presented a local relapse with a 5-year DFS rate of 65% (95%CI: 59.1%-70.9%). Five-year OS was 87% (95%CI: 78%-98%), and median OS was 104 mo. Patients who continued with Imatinib after surgery presented better rates of DFS.

In cases of patients with metastatic or recurrent disease under treatment with second-line sunitinib or third-line regorafenib, the role of debulking surgery is still not clear, and there is only a certain amount of information concerning emergency interventions. It is necessary to bear in mind that in these cases the tumors are advanced and resistant to standard treatment, so the potential benefit of the surgery is not known<sup>[112]</sup>.

## ROLE OF PATHOLOGIST

Pathologic diagnosis has a major impact on GIST management, both at the preoperative time and after complete surgical resection. Data obtained by pathologists need to be stratified according to risk, and

prognoses and possible therapies based on primary and acquired secondary resistance to TKI need to be determined.

GISTs in GI tracts are normally found in the sub-epithelial layer; however, as they become larger, they may cause epithelial ulceration. Currently, GIST's pathological diagnosis depends on the combination of morphology, immunohistochemistry (CD117 and/or DOG1), and molecular analysis (See Role of Oncologist).

Morphologically, GISTs are subdivided into spindle (70%), epithelioid (20%), and mixed-type cells, but it is considered that cell type influence on the outcome is not relevant<sup>[8]</sup>. GIST may be divided into eight different subtypes<sup>[116]</sup>: (1) Spindle cell subtypes: sclerosing, palisading-vacuolated, hypercellular and sarcomatous spindle cell; and (2) Epithelioid cell subtypes: sclerosing, discohesive, hypercellular and epithelioid spindle cell.

The distinction between benign and malignant depends on the presence of nuclear atypia and presence of necrosis, hemorrhaging, and mitotic activity. It is necessary to determine mitotic rate, grade of dedifferentiation, size, location, tumor infiltration, grade of necrosis and hemorrhage, surgical margins, and whether a tumor ruptures because these factors are implicated in the risk of relapse<sup>[117]</sup>. Ki67 is an important prognostic factor that has been implicated in recurrence and survival and should be included in pathologist's report<sup>[118,119]</sup> (See Table 3). The depth of tumor infiltration, including serosal penetration has been proposed as a prognostic factor for patients with GISTs with significantly poorer prognosis compared to its absence<sup>[120,121]</sup>.

Most GIST (> 90%) shows overexpression of the receptor tyrosine kinase KIT (CD117) by immunohistochemistry. On the other hand, a proportion of GISTs (near 5%) which are CD117-negative exists; however, approximately one third of these cases stained with discovered on GIST (DOG)1, which is expressed strongly on GIST and is rarely expressed on other soft tissue tumors<sup>[122,123]</sup> (See Figure 7). PKC- $\theta$  has lower specificity than DOG-1, but it may be a useful biomarker when combined with DOG1. Using both as an important diagnostic tool in the diagnosis of KIT-negative GISTs, even in wild type GISTs may prove useful for diagnosing

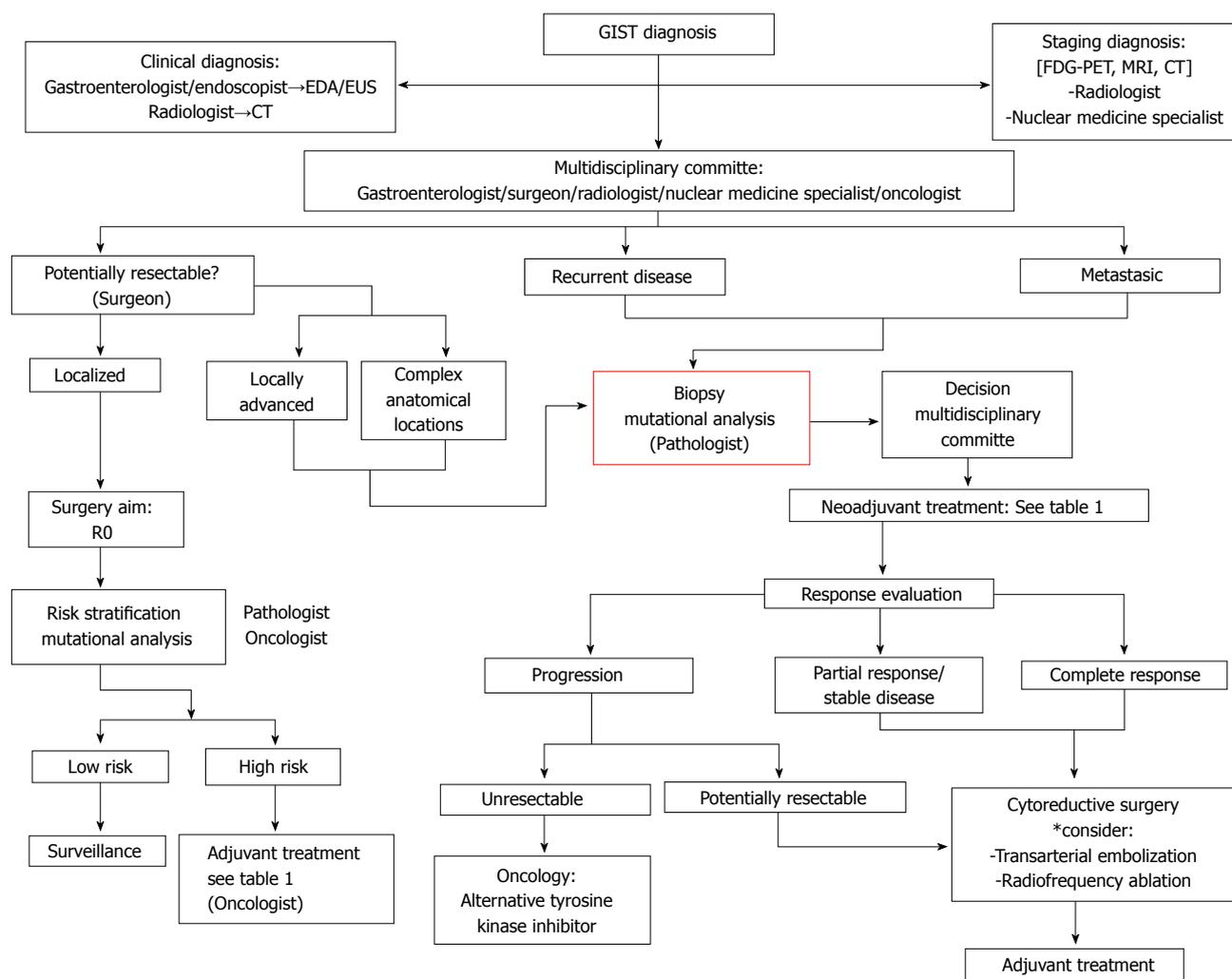


Figure 8 Management algorithm of gastrointestinal stromal tumors. GIST: Gastrointestinal stromal tumor.

GIST<sup>[124]</sup>.

GIST's mutational study is becoming increasingly important. Mutational analyses allow correlations of sensitivity or resistance to molecular-targeted therapies and doses. These types of analyses have prognostic value, so that they play a major role in GIST management<sup>[122]</sup> (see Role of Oncologist).

## CONCLUSION

The diagnosis of GIST has increased in recent years thanks to new imaging techniques which have increased the interest in the management of this type of tumors.

The clinical diagnosis is based on the CT, EDA and/or endoscopic US and staging diagnosis is obtained by CT and FDG-PET. The histological diagnosis is based on US-guided biopsy or percutaneous biopsy prior to surgery; In case of high suspicion in the imaging tests, surgical resection without previous biopsy would be justified.

The biological behavior of the GIST is explained according to the mitotic index, Ki67, anatomical location, size and mutational status.

Surgical resection with free margins of tumor disease

R0 is the only potentially curative therapeutic option.

Therapies with TKI (Imatinib, Sunitinib and Regorafenib) have let a noteworthy improvement in the rates of disease-free survival and overall survival, even in recurrent or unresectable metastatic GISTs.

GISTs are the paradigm of a cancer with molecular targeted therapy and its management requires a multi-disciplinary approach (See algorithm of management in Figure 8).

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