REVIEW ARTICLE

Recent advances in gastrointestinal stromal tumors: where are we going?

Avances recientes en tumores del estroma gastrointestinal: ¿hacia dónde vamos?

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Abstract

Gastrointestinal Stromal Sarcomas (GIST) are mesenchymal neoplasms whose incidence accounts for 1-2% of digestive tumors, being located in the stomach (55-60%) and small intestine (30%). The most important advances in recent years are focused on four areas: molecular biology, laparoscopic surgical approach, technical management of GIST in unusual locations, and treatment and integration of surgery in the management of advanced GIST. Advances in the knowledge of the molecular biology of GIST have led to the progressive identification of new oncogenic mutations that make the concept wild type obsolete. These advances have allowed the development of two new drugs, avapritinib and ripretinib, which allow the treatment of patients with mutations resistant to the three classic therapeutic lines. The surgical treatment of GIST is governed by well-established technical principles that the laparoscopic approach must comply with, an approach that is limited by two key factors: location and size. Infrequently located GIST (esophagus, duodenum or rectum, or extradigestive) represents a therapeutic challenge. These patients must be managed in a multidisciplinary context. Surgery is integrated into the management of advanced GIST, being considered as an adjuvant to tyrosine kinase inhibitors.

Keywords: *Gastrointestinal stromal tumor (GIST). Tyrosine kinase inhibitors (ITQ). Imatinib. Laparoscopy. Multidisciplinary team.*

Resumen

Los sarcomas del estroma gastrointestinal (GIST) son neoplasias mesenquimales cuya incidencia representa el 1-2% de los tumores digestivos, localizándose en el estómago (55-60%) e intestino delgado (30%). Los avances en su conocimiento y gestión logrados en los últimos años han sido espectaculares. Esta revisión tiene como objetivo resumir los más importantes para los cirujanos. Identificamos cuatro áreas de interés: oncología molecular, abordaje laparoscópico, manejo de GIST ubicados en lugares inusuales y manejo de GIST avanzado. Los avances en el campo de la oncología molecular conducen al descubrimiento de nuevas mutaciones oncogénicas que hacen obsoleto el término Wil Type GIST. Además, estos avances permiten el desarrollo de 2 nuevos fármacos: avapritinib y ripretinib, que sumados a los 3 fármacos anteriores disponibles comercialmente (imatinib, sunitinib y regorafenib) hacen posible el manejo de los GIST con mutaciones resistentes. Están bien establecidos los principios del manejo quirúrgico de los GIST primarios que debe cumplir el abordaje laparoscópico.

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Este enfoque está limitado por 2 factores principales: ubicación y tamaño. El diagnóstico de GIST en localizaciones inusuales como esófago, duodeno, recto o fuera del tracto gastrointestinal (EGIST), implica un extraordinario desafío terapéutico, siendo imperativo su manejo por parte de cirujanos y oncólogos entre otros en el marco de un equipo multidisciplinario. El manejo de los GIST avanzados/metastásicos ha cambiado de manera revolucionaria porque ahora la cirugía es parte de su tratamiento como adyuvante de los inhibidores de la tirosina quinasa.

Palabras clave: *Tumores del estroma gastrointestinal (GIST). Inhibidores de la tirosina quinasa (TKI). Imatinib. Laparoscopia. Equipos multidisciplinarios.*

Introduction

This review tries to summarize the advances that have occurred in the field of gastrointestinal stromal tumors (GIST) in recent years. This text is aimed at general surgeons with an interest in this pathology.

The main advances are circumscribed to four well-defined areas: tumor molecular biology and development of new drugs; consolidation of the technical principles of GIST surgery and the role of laparoscopy; and management of GIST in rare locations and advanced GIST.

Advances in the molecular biology and pharmacology of gastrointestinal stromal tumor

Molecular biology of the gastrointestinal stromal tumor

The identification of the oncogenic mutation in GIST is essential, both from a prognostic and therapeutic point of view. Most GISTs present alterations in the c-KIT sequence that in most cases affect exon 11, followed by alterations in exon 9, with mutations in exons 13 and 17 being less frequent, which are associated with resistance phenomena[1]. In 2003, alterations were identified in PDGFRA, which are exclusive with respect to those of c-KIT, and which are located in exons 12, 14 and 18, with a greater presence of the primary resistance mutation, D842V, located in exon 18[2]. Those cases in which alterations in these genes are not identified are known as *wild type* (15%). Alterations along the sequence of these two receptors influence the diagnosis, prognosis, and prediction of response to treatment, so their initial determination is considered essential for the management of these patients[3].

The 15% of cases without alterations in c-KIT or PDGFRA include a wide variety of molecular alterations (Table 1). The two most frequent are those of the BRAF pathway and the SDH complex[4]. Tumors without alterations in KIT, PDGFRA, BRAF, or SDH are called quadruple *wild type*. This group includes alterations such as the presence of fusions that affect the neurotrophic receptor type 3 (NRTK3) and the fibroblast growth factor (FGFR1), or the ETV transcription factor[5]. Thus, the GIST term *wild type* has evolved and divided over time, first encompassing those tumors without alterations in c-KIT, and later including tumors without alterations in PDGFRA, BRAF and SDH. Therefore, it seems more appropriate to abandon the GIST terminology *wild type* and replace it with "tumors without identified mutations" (GIST NOS)[6].

New drugs and combination strategies

Oncogenic activation of KIT or PDGFRA receptor tyrosine kinases is the central event that governs the evolutionary course of GISTs. The role of KIT or PDGFRA continues to be essential in the maintenance of the tumor phenotype[1], to the point that the pharmacological strategies approved today, and also those that are under investigation, are focused on its inhibition.

The oncogenic mutation in c-KIT or PDGFRA is the fundamental event in the biology of GIST. Its blockade with imatinib has shown great clinical benefit, reporting response rates (TR) of 51% with 90% clinical benefit and progression-free survival (PFS) of close to two years[7]. This drug has also been approved for adjuvant use after surgical resection[8].

Most patients with advanced or metastatic GIST eventually develop resistance to imatinib treatment, usually within 2 years of initiation, although up to 33% of patients have disease controlled for 5 years or more, and up to 6-9% for 10 years or more[7]. The main mechanism of resistance (90% of cases) consists of the growth of cell subpopulations or clones with secondary mutations that confer resistance to the drug[9]. Over the last 15 years, tyrosine kinase (ITQ) inhibitors with a broader spectrum of activity against various

Table 1. Gastrointestinal Stromal Tumor (GIST) fragmentation and subdivision *wild type*

GIST *wild type* (KIT/PDGFRA)			
SDH Deficientes			
BRAF			
NF-1			
Quadruple WT	Somatic mutations	CBL APC CTDNN2 TP53 ARID1A	MAX MEN-1 BCOR CHD4
	Gene fusion	FGFR1 p.N546K FGFR1-KOOK3 FGFR1-TACC1 ETV6-NTRK3	KIT-PDGFRA MARK2-PPFIA-1 SPRED2-NELFCD

Adapted from Liegl et al[9].

Table 2. Approved or investigated tyrosine kinase inhibitors after progression to imatinib

ITQ	Therapeutic line	Response rates (%)	SLP (months)	Status (phase)
Sunitinib	2.[a]	7	6.1	Approved
Regorafenib	3.[a]	4.5	4.8	Approved
Dasatinib	2.[a]	ND	2.0	II
Dovitinib	≥ 2nd	5	4.6	II
Masitinib	2.[a]	ND	3.7	II
Nilotinib	3.[a]	0	6.0	II
	3.[a]	3	3.7	II
	3.[a]	< 1	3.6	II
Pazopanib	≥ 2nd	0	1.9	II
	≥ 2nd	0	3.4	II
Ponatinib	≥ 2nd	8	4.3	II
Sorafenib	≥ 2nd	13	4.9	II
	≥ 3rd	13	5.2	II

SLP: progression-free survival; ND: not defined.

Table 3. Therapeutic strategies under development in gastrointestinal stromal tumor (GIST)

Strategy	Example(s)
Pan-KIT inhibitors	Ripretinib (DCC-2618)
Selective mutation inhibitors	Avapritinib (BLU-285)
KIT protein stability	HSP90 or HDAC inhibitors
KIT signaling pathways	PI3K or MEK inhibitors
Adaptation to KIT inhibition	MET or FGFR inhibitors
KIT heterogeneity	ITQ Quick Turnover

ITQ: tyrosine kinase inhibitors.

secondary mutations in KIT have been developed. Thus, in 2006 sunitinib was approved[10] and in 2012 regorafenib[11], both with a broad spectrum of inhibition. After progression to imatinib, RT is poor (< 10%), with a progression-free interval of 4-6 months regardless of the line of treatment used (Table 2)[10,11].

In 2020 we witnessed the development of multiple ITQs (Table 3) and FDA approval *(Food and Drug Administration)* of two revolutionary new ITQs: avapritinib and ripretinib.

Avapritinib (BLU-285) binds specifically, and with great inhibition power, to the active form of KIT and PDGFRA, being highly specific against mutations in the activation domain, which is highly relevant in GIST with the D842V mutation in exon 18 of PDGFRA. This mutation is inherently resistant to any ITQ approved to date. Thus, it is observed that up to 95% of the patients with this mutation treated with avapritinib obtained a reduction in tumor size, exhibiting TR of 86%, the majority for > 12 months. Avapritinib is effective in patients with primary mutations in progression to all lines of standard treatment, with an TR of 22% with a mean duration of 10 months[12].

Ripretinib (DCC-2618) is a pan-KIT inhibitor that interferes with kinase activation regardless of the type of secondary mutation present. Its use in patients refractory to all types of treatment for metastatic disease has been shown to achieve PFS rates of 6.3 months with RT close to 10%[13].

The possibility of treating these patients with five lines of treatment (Table 4) will mean an increase in the overall survival of these patients, which will make us consider their management over time, the order in which these drugs are used and the possibility of making surgical decisions throughout the course of the disease.

Advances in gastrointestinal stromal tumor surgery

Principles of gastrointestinal stromal tumor surgery and its laparoscopic management

Surgery for localized primary GIST consists of removal of the lesion with free surgical margins (R0)

Table 4. Mutations and sensitivity to treatment of gastrointestinal stromal tumor (GIST) according to type of mutation

Mutation	Treatment (sensitivity)
KIT exon 11	Imatinib, regorafenib
KIT exon 9	Imatinib (800 mg/day). Sunitinib
KIT exon 13	Sunitinib, ripretinib
KIT exon 14	Sunitinib, regorafenib, ripretinib
KIT exon 17	Regorafenib, ripretinib
KIT exon 18	Dasatinib, ripretinib
PDGFRA D842V	Avapritinib, crenolanib
exon 18	Imatinib resistance. Regorafenib
No KIT/PDGFRA	(if SHD deficiency). Dasatinib
WT mutation	

Table 5. Technical considerations in localized primary gastrointestinal stromal tumor (GIST) surgery

Objectives and general technical principles of GIST surgery
Complete abdominal examination
Grossly complete resection with negative margins (R0)
Unnecessary wide margins (1 cm)
Intact pseudocapsule without tumor rupture
Lymphadenectomy is not indicated
If microscopic margins are affected (R1) consider re-resection on a case-by-case basis

without lymphadenectomy[14]. In this context, the laparoscopic approach to GIST has been greatly favored, since both the characteristics of these tumors and the principles that govern their surgery (Table 5) are easily applicable[14,15]. To these principles[14], which are the same as in open surgery, a series of considerations should be added (Table 6)[14]:

- Its use should be avoided if it is not possible to obtain an R0 resection.
- It should not be used in tumors > 10 cm due to the high risk of tumor rupture. Its use should be restricted to GIST < 5 cm in favorable anatomical locations[16].
- It should be limited to tumors located on the greater curvature, *fundus* and anterior gastric face. Locations with the gastroesophageal junction, cardia, lesser curvature, posterior face, or antrum/pylorus pose technical problems that favor the use of the open approach.
- The extraction of the surgical piece must always be carried out in a bag in order to avoid implants in the abdominal wall at the level of the extraction hole.
- The experience of the surgical team is key. It is not only the experience in laparoscopic surgery that counts, but also in these tumors in particular.

Table 6. Technical considerations in laparoscopic surgery of localized primary gastrointestinal stromal tumor (GIST)

Objectives and general technical principles of laparoscopic surgery for GIST
Same technical principles as in open surgery
Only for experienced groups
Extraction of the piece in a protective bag
Accepttable if it allows R0 resection
Limit of its application marked by the tumor size (> 5 cm?)

The use of this approach provides a series of advantages typical of any laparoscopic approach: use of smaller incisions, less intestinal manipulation, reduction of postoperative pain, faster recovery of digestive functionality and a reduction in hospital stay[14-17].

Currently, there are no prospective randomized studies comparing the open versus the laparoscopic approach. However, there are several meta-analyses[17,18] which show, firstly, the existence of a strong selection bias in favor of the laparoscopic group: these patients have a smaller tumor size; and also, the location of the tumors is usually more favorable as they are located more frequently on the greater curvature. On the contrary, in the open group there is a tendency for GISTs to be located in unfavorable positions, which, together with their larger size, more frequently requires larger gastric resections. Secondly, a shorter operating time is observed in the laparoscopic approach, which is explained because the «wedge» resection is technically simpler, with a lower rate of postoperative complications and low rates of conversion to open surgery (4.7-5.2%), which emphasizes the reproducibility and safety of the laparoscopic procedure. In addition, this approach is associated with a reduction in hospital stay, with less postoperative pain and a rapid reincorporation into society and work. Finally, when an analysis of the oncological results is carried out by groups in the same surgical technique, size or location, no differences are observed in the disease-free interval or in overall survival[17,18].

The evidence available in jejuno-ileal GIST is much less[19]. In this situation, early surgery is recommended to avoid intestinal obstruction or severe bleeding.

Wedge surgery is only feasible in lesions < 1 cm, segmental resection being indicated for the rest. The main factors that discourage the laparoscopic approach in this location are the presence of adhesions, tumor perforation, proximity to the duodenum, the presence of advanced disease, and the need for concomitant resections[19].

Finally, comment on the boom experienced in recent years in laparoscopic surgery aided by intraoperative endoscopy[20]. Its use facilitates the localization of intragastric GISTs, not objectifiable on the gastric surface; allows to ensure an oncological resection with optimal margins; it allows the checking of the mechanical suture and allows, finally, to verify the absence of postoperative stenosis. Other highly complex approaches recently described include intragastric or intraluminal surgery[21], performed through a gastrotomy in the anterior face, which allows management of tumors of the posterior wall and the *fundus*, a technique that can be performed hand-assisted or combined with endoscopy, and robotic surgery[22].

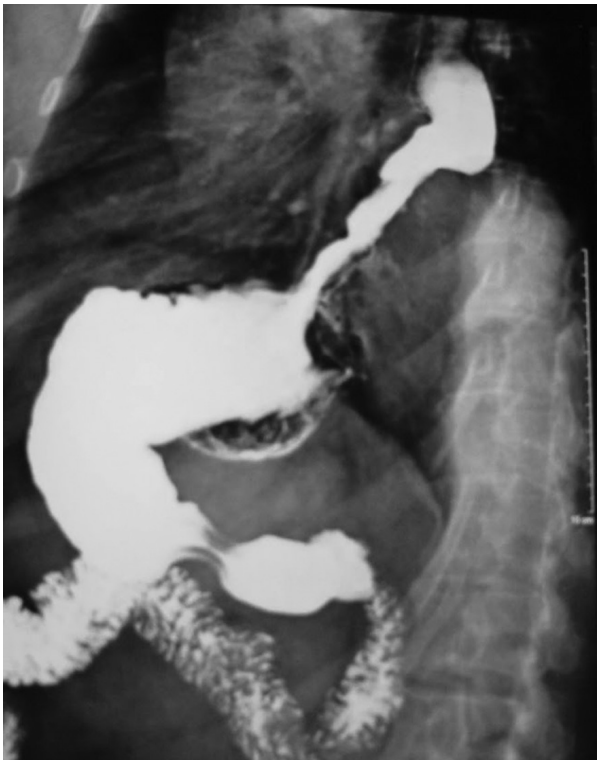

Figure 1. *Esophageal-gastric transit where there is evidence of a filling defect in 1/3 of a large esophageal medium that corresponds to an esophageal gastrointestinal stromal tumor.*

Management of gastrointestinal stromal tumor in uncommon locations

GISTs are usually located in the stomach (55-60%) and small intestine (30%). Other very rare locations are the esophagus, duodenum, or rectum, and extradigestive locations such as the omentum, mesentery, pelvis, or retroperitoneum. In these cases, there are no clear recommendations regarding their diagnosis and treatment, so their management is an extraordinary challenge.

In a recent review, esophageal GIST accounted for 23% of tumors in this location, having been described in the last 15 years around 150 cases worldwide[23]. It predominantly affects males with a mean age of 60 years. Most patients manifest dysphagia (36-51%) and weight loss (20%), 30% of them being asymptomatic[23].

Differential diagnosis[41] arises with various tumors, although the most important is leiomyoma[24]. The esophago-gastric transit (Fig. 1) and echoendoscopy (EE) help to differentiate between submucosal and mucosal lesions[24], noting that mucosal ulceration is characteristic of GIST. EE allows us to assess size, shape, intratumoral appearance and relationship with the muscular layers of the esophagus. Computed tomography (CT) and magnetic resonance imaging (MRI) describe GISTs, unlike leiomyomas, as large, distal, hypervascularized tumors with a heterogeneous appearance (Fig. 2). On positron emission tomography, GISTs have strong and homogeneous uptake that leiomyomas rarely have[25]. EE-guided fine needle aspiration biopsy (FNA/PAB) allows histological and immunohistochemical study of the tumor[42]. 80% of these tumors are located in the distal third of the esophagus, are usually > 5 cm and with > 5 mitoses/50 HAC, so they should be considered as tumors with a high risk of recurrence[22,25].

The main therapeutic controversy is whether enucleation or esophagectomy is the surgical technique of choice. Thus, enucleation offers greater technical safety, although it may favor incomplete resections[26]; while esophagectomy offers greater oncological safety at the expense of greater morbidity and mortality. In published series, enucleation has better long-term results than esophagectomy, since it treats smaller tumors and is therefore associated with a lower risk of recurrence. In other words, the key prognostic factor in esophageal GIST is tumor size and the number of mitoses[26]. In the case of tumor rupture or R1 resection, regardless of the surgical technique used, the recurrence rate reaches 35-50%, while it is 0% in the absence of these factors. The choice of one technique or another will depend, therefore and above all, on the size of the tumor and the experience of the surgical

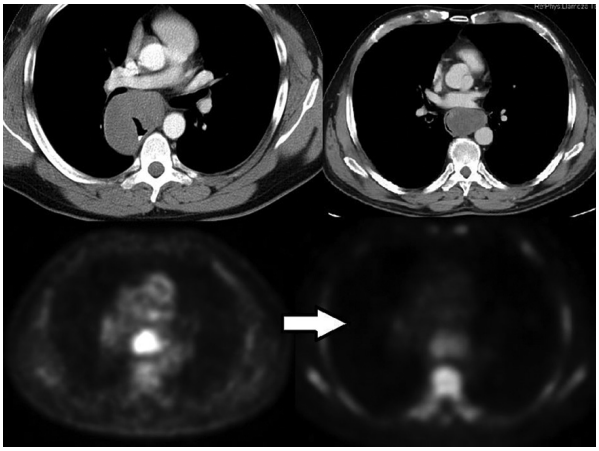

Figure 2. *Computed tomography images showing discretely homogeneous space-occupying masses at the esophageal level.*

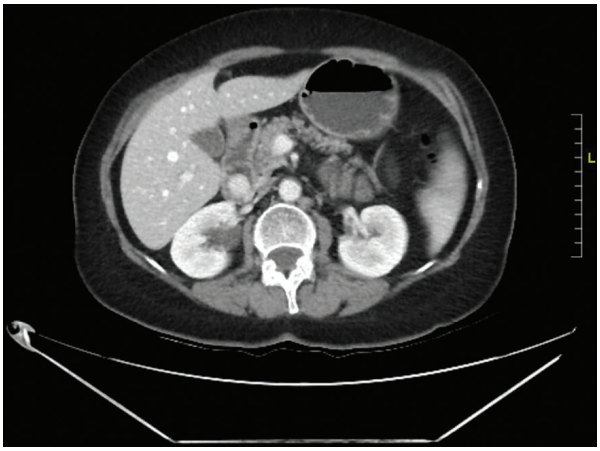

Figure 3. *Computed tomography image showing duodenal gastrointestinal stromal tumor in 2.nd portion.*

group. In general, enucleation is recommended in asymptomatic patients with tumors < 2 cm[27]. In experienced groups, thoracoscopic enucleation is even possible in tumors up to 5 cm. When the esophageal GIST is > 10 cm, esophagectomy is recommended. Management of cases with an intermediate size, between 2 and 10 cm, is much more controversial and will depend on the presence of mucosal ulceration, the mitotic index, and its proximity to the esophagogastric junction. Therefore, the determining factors for the selection of the technique are the size, location, presence or absence of mucosal ulceration, surgical risk and experience of the surgical team.

In GISTs close to the gastroesophageal junction there is a clear controversy among defenders of enucleation, who rely on the efficacy of preoperative ITQs; and those who defend esophagogastrectomy[23-27]. The neoadjuvant use of ITQ can improve the local situation of the tumor and favor a more conservative resection. Patients with significant individual high-risk factors may benefit from exclusive, lifelong treatment with ITQ[23-27].

Globally, the observed survival is 45-85% at five years, with a recurrence rate of 22-39%, with tumor size (> 5 cm) and mitotic index (> 5/5 mm^2)[26] being identified as the main risk factors.

Duodenal GISTs, usually located in the 2nd portion (Fig. 3), account for 30% of all duodenal tumors and only 2-3% of all GISTs[28]. In case of localized or locally advanced disease, treatment with neoadjuvant ITQ is recommended in order to reduce tumor size[29]. Ideal candidates will be those patients in whom the initial surgery to be performed is a cephalic duodenopancreatectomy; and those with tumors in which a reduction in tumor volume favors a resection with negative margins and even the possibility of performing limited resections[29].

The surgical techniques to be used depend on the size of the tumor, its relationship with the head of the pancreas, the ampulla of Vater, and the terminal common bile duct, and its mesenteric or antimesenteric location. Different surgical options include:

- Limited wedge resection of the wall or *wedge resection*. Applicable in small tumors (< 3-4 cm), located at a distance > 2 cm from the papilla and that sit on the antimesenteric edge[30].
- Duodenal segmental resection. Used in tumors located in the third or fourth duodenal portion, its reconstruction involves the use of a Roux-en-Y loop anastomosed to the 2nd duodenal portion. It is a potentially executable procedure laparoscopically[30,31].
- Pancreatic-sparing duodenectomy. It consists of resection of the entire duodenum and subsequent placement of a jejunal loop to which the juxtapyloric duodenum, the bile duct, and the pancreatic duct are anastomosed[32].
- Cephalic duodenopancreatectomy. Indicated in GIST > 5 cm located in the 2nd portion of the duodenum with invasion of the papilla of Vater or pancreas. They are usually tumors with a high mitotic index and more aggressive behavior, which explains their worse prognosis, not related to surgery *per se*[29,33].

The laparoscopic approach in duodenal GISTs is possible, especially in tumors < 5 cm in favorable anatomical locations (1º and 3º /4º duodenal portion),

although it should only be used by highly experienced groups. Large GISTs (> 5-7 cm) have a higher risk of rupture, so open surgery is more recommended in these cases[31].

Duodenal GISTs are considered to have a less aggressive behavior than GISTs located in other locations, with a 5-year survival rate of 94.9%. Despite this, they have a recurrence rate of 10-20%, even after R0 surgery. The disease-free rate at one and three years after a complete resection ranges from 86 to 100%[33].

Rectal GISTs represent the third most frequent location, although they only account for 1.6-5% of all GISTs[34]. They do not have specific symptoms, so they are frequently confused with other anorectal pathologies. The most frequent symptoms are bleeding (28.9%) and anal pain (17.8%). Sometimes they are incidental findings. CT and MRI (Fig. 4) are very useful for diagnosis and staging, as well as allowing the determination of possible involvement of the pelvic organs. Endorectal ultrasound localizes the tumor and determines its size and its relationship to the sphincters[35,36].

The choice of the type of surgery must be individualized according to the patient's condition, the location and size of the tumor, the degree of local extension and invasion, and the experience of the surgical team[35,36]. Surgical resection can be very difficult in situations with a deep and narrow pelvis, as occurs in men; or in the case of tumors very close to anal sphincters or other neighboring organs. Under these conditions, R0 resection is only achieved in 40-60% of patients.

The technical options are:

- Local split. Indicated for small GISTs (< 2 cm) located in the distal rectum with the possibility of margins > 1 cm without involvement of the anal sphincter. In anterior tumors there is a risk of recto-vaginal fistula in women, or urethral injury in men[37].
- Local resection under direct vision. Indicated in tumors very close to the anal margin. Techniques such as TAMIS (transanal surgery through a single port), TEM (transanal microsurgery) and even robotic TAMIS[37,38] improve vision, facilitating resection. Other local resection routes include the transsphincteric, transvaginal, or transsacral Kraske approach[38,39].
- Wide resections of the rectum. Indicated for larger lesions (≥ 2 cm) with deep invasion and sphincter involvement. In these cases, the patient's comorbidities, the size and location of the tumor, and the possibilities of sphincter preservation must be taken into account[36]. One can choose between radical surgery without excision of the mesorectum, such as low anterior resection, abdominal-perineal amputation (of choice in distal rectal tumors with impossibility of sphincter preservation) and pelvic exenteration, indicated in locally advanced tumors[36].

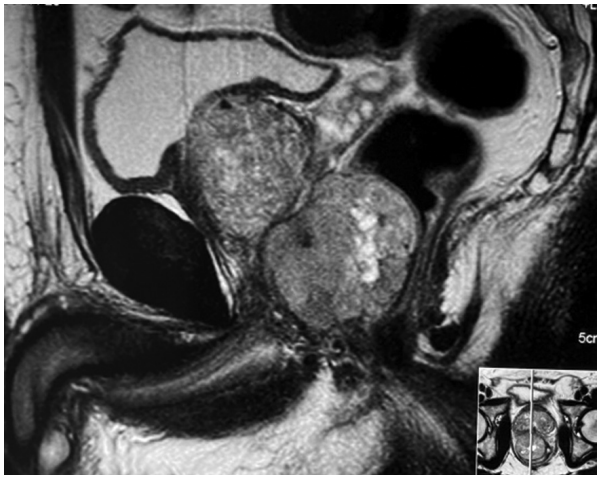

Figure 4. *Magnetic resonance imaging of a rectal gastrointestinal stromal tumor that allows us to appreciate its anatomical relationships in the pelvis.*

Locally advanced rectal GISTs, not candidates for "front-end" resection surgery, should undergo neoadjuvant treatment (Fig. 5) to reduce its size and facilitate sphincter preservation[40,41]. The combination of neoadjuvant therapy and surgery is feasible in more than half of the cases[40,41].

The presence of interstitial cells of cajal (ICC) in various organs or connective tissues of the organism can explain the appearance of GIST in extragastrointestinal locations (EGIST)[42-44]. Mesenteric GIST has a very low incidence (5-12%), is usually solitary and affects more women between 60 and 65 years of age, with an average size of 12 cm[42-44]. The most frequent symptoms are pain and/or the presence of a slow-growing and indolent abdominal mass, which facilitates large tumor sizes (Fig. 6). The treatment of choice for localized EGIST is "in block" excision surgery. In the case of advanced disease, they should be treated initially with ITQ, and only in case of obtaining a good response could rescue surgery be considered. The main factors of poor prognosis are size, the presence of necrosis, a high index of mitosis per field, and a high ki-67[42-44].

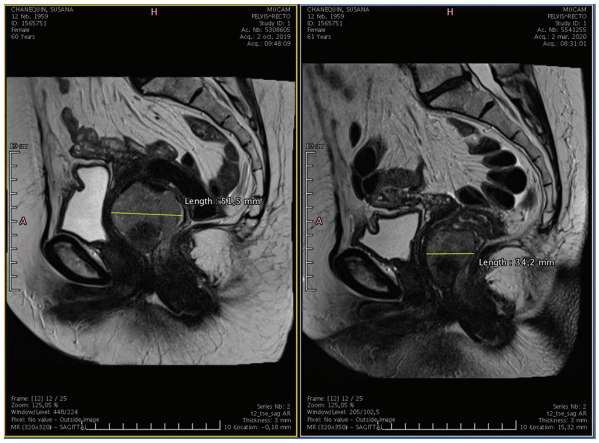

Figure 5. *Effects of neoadjuvant treatment in rectal gastrointestinal stromal tumor, before (left) and after (right) treatment with imatinib, observing a significant reduction in tumor size.*

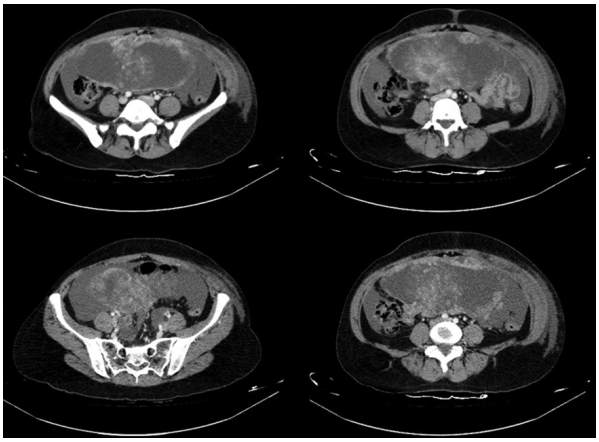

Figure 6. *Magnetic resonance image of mesenteric gastrointestinal stromal tumor.*

Disseminated and/or metastatic gastrointestinal stromal tumor

The main advance in the management of advanced GIST has been the incorporation of surgery as an adjunct to medical treatment. This medical treatment is based on the continued use of ITQ, which has some peculiarities[45,46]:

- Imatinib is the drug of choice, given the most common c-KIT mutation in exon 11. In case of mutations in PDGFRA (exon 18) or without KIT/PDGFRA mutation *(wild type)*, other ITQs should be used (Table 4). Thus, in the case of PDGFRA D842V mutations, drugs such as avapritinib or crenolanib should be used; while the deficient WT SDH subgroup may be a candidate for treatment with sunitinib, but with low RTs.
- Treatment should last a minimum of 6-9 months prior to a re section, because sustained exposure to the drug favors the development of resistance before two years in up to 50% of patients.
- ITQs should also be used adjuvantly even in those patients in whom it has been possible to resect all the metastatic lesions, and also indefinitely until the appearance of resistance, since their suspension is associated with a rapid progression of the disease.
- Treatments such as ablation or palliative radiotherapy may also be useful in well-selected cases with locoregional progression not amenable to surgical resection.

GISTs who develop peritoneal sarcomatosis or GISTosis[47,48], spontaneously or secondary to tumor rupture during surgery, have a poor prognosis. In this situation, the initial cytoreduction surgery does not imply any benefit, being the administration of ITQ the treatment of choice. Cytoreductive surgery would be indicated when complete resection can be achieved in patients with a good response to imatinib. In the event of resistance to imatinib, debulking surgery would only be indicated in those patients with limited progression in whom complete resection can be achieved.

About 20% of GISTs present, at the time of diagnosis or during the course of the disease, liver metastases. It is estimated that surgery for metastatic GIST can be performed in only 30% of cases, with a median survival of 19 months. In this context, adjuvant surgery can prolong survival in selected patients with response to ITQ, being ineffective in case of progression after ITQ administration[49,50]. A study of the *European Organization for Research and Treatment of Cancer* (EORTC)[51] shows the possibility of achieving high rates of R0 resections and greater survival, especially if the surgery is complete (R0) and if it is followed by continued treatment with ITQ. This strategy is clearly accepted when liver metastases are technically resectable[49-51]. In 2015, the Spanish Group for Sarcoma Research (GEIS) published[52] an analysis of 171 patients with unresectable metastatic GIST that was not refractory to treatment with imatinib, concluding that based on the superior survival obtained in the included patients in the group with salvage surgery, this strategy should be evaluated in all patients with metastatic hepatic GIST as long as

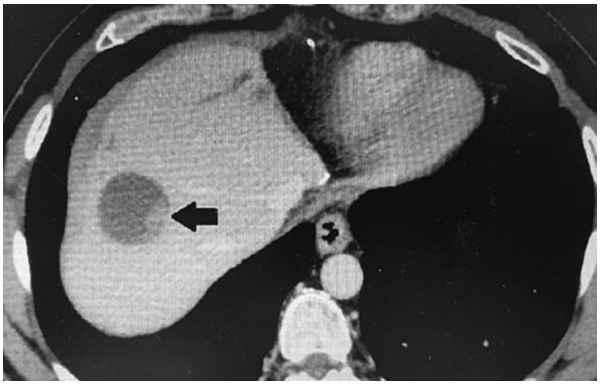

Figure 7. *Radiological image (computerized tomography) where a recurrence is seen within a nodule ("nodule within a nodule").*

they show a good response to preoperative ITQ. The indication for salvage surgery should be made six months after starting treatment with imatinib, since it is at this time that the maximum tumor response appears. This surgery should be performed leaving the shortest possible preoperative and postoperative interval without treatment with imatinib[46]. In patients without stabilization of metastatic lesions, excision of all possible tumor mass *(debulking)*, associated or not with other tissue destruction therapies such as radiofrequency[53], may occasionally achieve better survival, but in no case greater than that of patients with a good response to imatinib. That is why this surgical indication must be restricted and evaluated in exceptional cases in a multidisciplinary context[54].

Patients undergoing excision of liver metastases from GIST, after a good response to imatinib, can create resistance and develop again hepatic progression in the form of a “nodule within a hyalinized nodule” (Fig. 7). In this situation, re-resection of these metastases offers better survival than if they were treated with imatinib alone[54].

Adjuvant surgery to ITQ treatment in metastatic hepatic GIST is a therapeutic strategy of great value in selected patients. Other options such as radio frequency[53] or arterial embolization[55] must also be considered on a case-by-case basis. The possibility of liver transplantation in unresectable metastatic GIST is a recently explored option[56].

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References

1. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumors: origin and molecular oncology. Nat Rev Cancer. 2011;11(12):865-78.
2. Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and *in vitro* sensitivity to imatinib. J Clin Oncol. 2005;23(23):5357-64.
3. ESMO Guidelines Committee. Appendi×3: Soft tissue sarcoma: MCBS eUpdate published online 5 May 2017(www.esmo.org/Guidelines/Sarcoma-and-GIST). Ann Oncol. 2017;28(suppl 4):iv147-iv148.
4. Daniels M, Lurkin I, Pauli R, Erbstösser E, Hildebrandt U, Hellwig K et al. Spectrum of KIT/PDGFRA/BRAF mutations and Phosphatidylinositol-3-Kinase pathway gene alterations in gastrointestinal stromal tumors (GIST). Cancer Lett. 2011;312(1):43-54.
5. Brenca M, Rossi S, Polano M, Gasparotto D, Zanatta L, Racanelli D et al. Transcriptome sequencing identifies ETV6-NTRK3 as a gene fusion involved in GIST. J Pathol. 2016;238(4):543-9.
6. Nannini M, Urbini M, Astolfi A, Biasco G, Pantaleo MA.The progressive fragmentation of the KIT/PDGFRA wild-type (WT) gastrointestinal stromal tumors (GIST). J Transl Med. 2017;15(1):113.
7. Casali PG, Zalcberg J, Le Cesne A, Reichardt P, Blay JY, Lindner LH et al. Ten-year progression-free and overall survival in patients with unresectable or metastatic GI stromal tumors: Long-term analysis of the european organisation for research and treatment of cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels. J Clin Oncol. 2017;35(15):1713-20.
8. Laurent M, Brahmi M, Dufresne A, Meeus P, Karanian M, Ray-Coquard I et al. Adjuvant therapy with imatinib in gastrointestinal stromal tumors (GISTs)-review and perspectives. Transl Gastroenterol Hepatol. 2019;4:24.
9. Liegl B, Kepten I, Le C, Zhu M, Demetri GD, Heinrich MC et al. Heterogeneity of kinase inhibitor resistance mechanisms in GIST. J Pathol. 2008;216(1):64-74.
10. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329-38.
11. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID): an international, multicentre, randomized, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295-302.
12. Avapritinib. Technical sheet [Internet]. European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_es.pdf
13. Blay JY, Serrano C, Heinrich MC, Zalcberg J, Bauer S, Gelderblom H, et al. Ripretinib in patients with advanced gastrointestinal stromal tumor (GIST): a randomized, double-blind, placebo-controlled phase 3 study (INVICTUS). Lancet Oncol. 2020;21(7):923-34.
14. Fernández JA. General technical principles and objectives of surgery. In: Fernández JA, Martínez-Marín V, editors. Gastrointestinal stromal tumors. GIST. Multidisciplinary management in the 21st century. First edition. Murcia, Spain: Editorial Diego Marín Librero-Editor; 2017. pp. 285-290.

15. Tabrizan P, Nguyen SQ, Divino CM. Laparoscopic management and longterm outcomes of gastrointestinal stromal tumors. J Am Coll Surg. 2009;208:80-6.
16. Xiong H, Wang J, Jia Y, Ye C, Lu Y, Chen C et al. Laparoscopic surgery versus open resection in patients with gastrointestinal stromal tumors: An updated systematic review and meta-analysis. Am J Surg. 2017;214(3):538-46.
17. Chen K, Zhou YC, Mou YP, Xu XW, Jin WW, Ajoodhea H. Systematic review and meta-analysis of safety and efficacy of laparoscopic resection for gastrointestinal stromal tumors of the stomach. Surg Endosc. 2015;29(2):355-67.
18. Piessen G, Lefèvre JH, Cabau M, Duhamel A, Behal H, Perniceni T et al. AFC and the FREGAT working group. Laparoscopic versus open surgery for gastric gastrointestinal stromal tumors: What is the impact on postoperative outcome and oncologic results? Ann Surg. 2015;262(5):831-40.
19. Small bowel gist laparoscopy.
20. Wilhelm D, von Delius S, Burian M, Schneider A, Frimberger E, Meining A et al. Simultaneous use of laparoscopy and endoscopy for minimally invasive resection of gastric subepithelial masses - analysis of 93 interventions. World J Surg. 2008;32:1021-8.
21. Conrad C, Nedelcu M, Ogiso S, Aloia TA, Vauthey JN, Gayet B. Laparoscopic intragastric surgery for early gastric cancer and gastrointestinal stromal tumors. Ann Surg Oncol. 2014;21(8):2620.
22. Arseneaux M, Yarbrough D, Nagamoto T. Robotic-assisted free-handed, full-thickness gastric GIST resection with primary repair in unfavorable locations. J Robot Surg. 2019;13(3):491- 4.
23. Hihara J, Mukaida H, Hirabayashi N. Gastrointestinal stromal tumor of the esophagus: current issues of diagnosis, surgery and drug therapy. Transl Gastroenterol Hepatol. 2018;3:6.
24. Winant AJ, Gollub MJ, Shia J, Antonescu C, Bains MS, Levine MS. Imaging and clinicopathologic features of esophageal gastrointestinal stromal tumors. Am J Roentgenol. 2014;203(2):306-14.
25. Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol. 2007;25:1753-59.
26. Schizas D, Bagias G, Kanavidis P, Moris D, Spartalis E, Damaskos C et al. Prognostic factors affecting mortality in patients with esophageal GISTs. J BUON. 2020;25(1):497-507.
27. von Rahden BH, Stein HJ, Feussner H, Siewert JR. Enucleation of submucosal tumors of the esophagus: minimally invasive versus open approach. Surg Endosc. 2004;18(6):924-30.
28. Lee SJ, Song KB, Kim SC, Hwang DW, Lee JH et al. Clinicopathologic characteristics and optimal surgical treatment of duodenal gastrointestinal stromal tumor. J Gastrointest Surg. 2019;23(2):270-9.
29. Chok AY, Koh YX, Ow MY, Allen JC Jr, Goh BK. A systematic review and meta-analysis comparing pancreaticoduodenectomy versus limited resection for duodenal gastrointestinal stromal tumors. Ann Surg Oncol. 2014;21(11):3429-38.
30. Popivanov G, Tabakov M, Mantese G, Cirocchi R, Piccinini I, D'Andrea V et al. Surgical treatment of gastrointestinal stromal tumors of the duodenum: a literature review. Transl Gastroenterol Hepatol. 2018;3:71.
31. Zioni T, Dizengof V, Kirshtein B. Laparoscopic resection of duodenal gastrointestinal stromal tumour. J Minim Access Surg. 207;13:157-60.
32. Imamura M, Komoto I, Doi R, Onodera H, Kobayashi H, Kawai Y. New pancreas-preserving total duodenectomy technique. World J Surg. 2005;29(2):203-7.
33. Shen Z, Chen P, Du N, Khadaroo PA, Mao D, Gu L. Pancreaticoduodenectomy versus limited resection for duodenal gastrointestinal stromal tumors: a systematic review and meta-analysis. BMC Surg. 2019; 19(1):121.
34. Ijzerman NS, Mohammadi M, Tzanis D et al. Quality of treatment and surgical approach for rectal Gastrointestinal Stromal Tumour (GIST) in a large European cohort. Eur J Surg Oncol. 2020;46(6):1124-30.
35. Kane WJ, Friel CM. Diagnosis and treatment of rectal gastrointestinal stromal tumors. Dis Colon Rectum. 2019;62:537-41.
36. Alavi K. Expert commentary on the diagnosis and treatment of rectal GIST tumors. Dis Colon Rectum. 2019;62:540-1.
37. Spinelli A, Carvello M, Sacchi M, Bonifacio C, Bertuzzi A, Tuynman J et al. Transanal minimally invasive surgery (TAMIS) for anterior rectal GIST. Tech Coloproct. 2019;23:501-2.
38. Shuck RL, Larach SW, Atallah S. Robotic TAMIS for local excision of ultra-distal neoplasia. Tech Coloproctol. 2019;23:395.
39. Centonze D, Pulvirenti E, Pulvirenti D'Urso A, Franco S, Cinardi N, Giannone G. Local excision with adjuvant imatinib therapy for anorectal gastrointestinal stromal tumors. Tech Coloproctol. 2013;17:571-4.
40. Kaneko M, Emoto S, Murono K, Sonoda H, Hiyoshi M, Sasaki K et al. Neoadjuvant imatinib therapy in rectal gastrointestinal stromal tumors. Surg Today. 2019;49(6):460–6.
41. Wang SY, Wu CE, Lai CC, Chen JS, Tsai CY, Cheng CT, et al. Prospective evaluation of neoadjuvant imatinib use in locally advanced gastrointestinal stromal tumors: emphasis on the optimal duration of neoadjuvant imatinib use, safety, and oncological outcome. Cancers (Basel). 2019;11:424.
42. Reith JD, Goldblum JR, Lyles RH, Weiss SW. Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol. 2000;13:577-85.
43. Yi JH, Park BB, Kang JH, Hwang IG, Shin DB, Sym SJ et al. Retrospective analysis of extra-gastrointestinal stromal tumors. World J Gastroenterol. 2015;21:1845-50.
44. Barros A, Linhares E, Valadão M, Gonçalves R, Vilhena B, Gil C et al. Extragastrointestinal stromal tumors (EGIST): a series of case reports. Hepatogastroenterology. 2011;58:865-8.
45. Sánchez-Hidalgo JM, Duran-Martínez M, Molero-Payan R, Rufián-Peña S, Arjona-Sanchez A, Casado-Adam A et al. Gastrointestinal stromal tumors: a multidisciplinary challenge. World J Gastroenterol. 2018;24(18):1925-41.
46. Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S et al. on behalf of the ESMO Guidelines Committee and EURACAN. Gastrointestinal stromal tumors: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(suppl 4):iv68-iv78.
47. Bryan ML, Fitzgerald NC, Levine EA, Shen P, Stewart JH, Votanopoulos KI. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in sarcomatosis from gastrointestinal stromal tumor. Am Surg. 2014;80(9):890-5.
48. Medina Fernández FJ, Muñoz-Casares FC, Arjona-Sánchez A, Casado-Adam A, Rufián Peña S. Peritoneal gistosis: Role of debulking surgery and perioperative intraperitoneal chemotherapy. Cir Esp. 2014;92(4):289-90.
49. Turley RS, Peng PD, Reddy SK, Barbas AS, Geller DA, Marsh JW et al. Hepatic resection for metastatic gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. Cancer. 2012;118:3571-8.
50. DeMatteo RP, Maki RG, Singer S, Gonen M, Brennan MF, Antonescu CR. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. Ann Surg. 2007;245:347-52.
51. Bauer S, Rutkowski P, Hohenberger P, Miceli R, Fumagalli E, Siedlecki JA et al. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib-analysis of prognostic factors (EORTC-STBSG collaborative study). Eur J Surg Oncol. 2014;40(4):412-9.
52. Rubio-Casadevall J, Martinez J, Garcia-Albeniz, Calabuig S, Lopez-Pousa A, Garcia del Muro X et al. Role of surgery in patients with recurrent metastasic, or unresectable locally advanced GIST sensitive to imatinib: a retrospective analysis of spanish group for research on sarcoma (GEIS). Ann Surg Oncol. 2015;22(9):2948-57.
53. Hakimé A, Le Cesne A, Deschamps F, Farouil G, Boudabous S, Aupérin A et al. A role for adjuvant RFA in managing hepatic metastases from gastrointestinal stromal tumors (GIST) after treatment with targeted systemic therapy using kinase inhibitors. Cardiovasc Intervent Radiol. 2014;37(1):132-9.
54. Hasegawa J, Kanda T, Hirota S, Fukuda M, Nishitani A, Takahashi T, et al. Surgical interventions for focal progression of advanced gastrointestinal stromal tumors during imatinib therapy. Int J Clin Oncol. 2007;12(3):212-7.
55. Cao G, Li J, Shen L, Zhu X. Transcatheter arterial chemoembolization for gastrointestinal stromal tumors with liver metastases. World J Gastroenterol. 2012;18(42):6134-40.
56. Lesari S, Mocchegiani F, Nicolini D, Benedetti A, Coletta M, Montalti R, et al. Liver transplantation for metastatic wild-type gastrointestinalstromal tumor in the era of molecular targeted therapies: Report of a first case. Am J Transplant. 2019;19:2939-43.