



Review article

Controversies in the surgical treatment of primary gastrointestinal stromal tumours (GIST)

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It is estimated that 50% of GIST are located at the time of their diagnosis. A complete surgical resection can be performed in up to 95% of these cases, making this the most important prognostic factor. This surgery must fulfil a series of technical requirements so as to be really effective, as it has to be R0, with no tumour rupture, with preservation of the pseudo-capsule, etc. Although the majority of GIST are gastric, their location in other anatomical areas, such as the oesophagus, duodenum or rectum, require the surgeon to use more complex techniques. Laparoscopy is increasingly used; however, we must avoid its use, due to there being few experienced groups or if there are large tumours. The use of neoadjuvant therapy has revived great interest by allowing to resection tumours that were once non-resectable or in very compromised anatomical locations, with less aggressive surgery. The use of pre-surgical biopsy is not exempt from serious risks, thus it should only be used for establishing a neoadjuvant treatment or if there are diagnostic doubts with other diseases in high risk patients.

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Controversias en el tratamiento quirúrgico de los tumores del estroma gastrointestinal (GIST) primarios

R E S U M E N

Se calcula que un 50% de los tumores del estroma gastrointestinal están localizados en el momento de su diagnóstico. Hasta en el 95% de estos casos es posible efectuar una resección quirúrgica completa que se convierte en el factor pronóstico más importante. Esta cirugía debe cumplir una serie de requisitos técnicos para que sea realmente efectiva, como que debe ser R0, sin rotura tumoral, con preservación de la pseudocápsula, etc. Si bien la mayoría de los tumores del estroma gastrointestinal son gástricos, su localización en otras zonas anatómicas, como el esófago, duodeno o recto, obligan al cirujano al empleo de técnicas más complejas. La laparoscopia es cada vez más usada; sin embargo, debemos evitar su uso por grupos poco experimentados o en caso de tumores de gran tamaño. El empleo

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de la neoadyuvancia ha suscitado un gran interés al permitir resear con cirugías poco agresivas tumores antes irresecables o en localizaciones anatómicas muy comprometidas. El empleo de la biopsia preoperatoria no está exento de grandes riesgos, de ahí que sólo deba emplearse en caso de plantearse un tratamiento neoadyuvante o en caso de existir dudas diagnósticas con otras patologías en pacientes de alto riesgo.

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Introduction

Surgery is the key therapeutic weapon in the management of localised, non-metastatic primary gastrointestinal stromal tumour (GIST). Various guidelines^{1,2} not only confirm this fact but also detail a series of characteristics that this surgery must bring together as well as a series of recommendations regarding its use. Furthermore, since the complete characterisation of GIST tumours, multiple series have been published. All this may make many people think that surgical management of these tumours is perfectly defined. Nothing could be further from the truth. GIST tumours continue being tumours with poorly understood natural history, especially when their size is <2 cm. The role of laparoscopy is not completely clear, nor of pre-operative biopsy. Finally, some anatomical locations make surgery more difficult, requiring significant modifications in technique.

The objective of this review is to detail the main limitations and controversies surrounding surgical management of primary localised GIST.

Objectives and surgical technique

GIST tumours have a number of features that facilitate their surgical treatment.¹⁻³ These are tumours that develop liver and peritoneal metastases but rarely lymphatic ones,⁴ making lymphadenectomy unnecessary. They show exophytic extraluminal growth, which makes them easy to find and they have an expansive, not infiltrative growth, limiting the resection to be performed. However, they are very fragile, highly vascularised tumours, so great care must be taken in their handling in order to prevent breakage.¹⁻³

The main objective of primary localised GIST surgery is resection,^{1,3,4,8} since when complete, is the most important prognostic factor, with survival rates from 40%-55% at 5 years³⁻⁷ (Table 1).

In most cases these resections can be carried out through very limited resections of segments or 'wedges' of the tumour focus (>65%). In other cases the surgeon must make more extensive anatomical resections, even including resection of adjacent organs as a unit or "block".⁹ It has been shown that surgical extension or aggressiveness is not related to survival of patients.^{10,11}

The resection of a GIST must not be disruptive, that is, it must preserve the pseudo-capsule and not break the tumour. The preservation of the pseudo-capsule is the key to avoid leaving tumour foci. In fact, breaking it would result in the

need for an R2 resection; hence simple enucleation is not recommended. Nishimura^{12,13} reports a local recurrence rate of 33% in enucleated tumours. Tumour rupture also amounts to an R2 resection, reducing average survival from 46 to 17 months.¹³⁻¹⁷

When treating expansive tumours, we frequently find them inextricably attached to neighbouring structures, but without infiltrating them. In these cases block resection is required.¹⁻³

As mentioned earlier, these tumours rarely metastasise to lymph nodes,^{13,18-20} so routine lymphadenectomy is unnecessary unless there is evidence of severe lymph node involvement.⁷ What is necessary, as some authors recommend, is a local peritonectomy, in order to eliminate potential local peritoneal tumour seeding.^{6,13,15,21}

To these specific technical aspects we can add others of a more general nature, including those that require a complete abdominal exploration to rule out the presence of peritoneal and/or liver metastasis at the level of the epiploic foramen or the pouch of Douglas.^{1,2}

Table 2 shows the results of the main published series.^{6,9,17,22-34} Their analysis reveals that large series and

Table 1 – Technical considerations for localised primary GIST surgery. Taken and modified from Raut et al.⁸

Surgical approach	Main technical objectives
Laparotomy	Macroscopically complete resection with negative margins (R0) Unnecessary large margins Intact pseudo-capsule Block resection of adjacent organs, if necessary Extensive resection, if required Lymphadenectomy is not indicated Complete abdominal examination If microscopic margins are affected (R1), consider re-resection case by case
Laparoscopy	Same technical principles as for laparotomy Acceptable if it enables R0 resection Extraction of the piece in protective bag Limit its application depending on tumour size Only for teams with experience in large tumours (>5cm)
Endoscopy	Valid for monitoring <1 cm gastric GIST Valid in support of laparoscopy Endoscopic resection in contraindicated
GIST indicates gastrointestinal stromal tumours.	

Table 2 – Major surgical series (n>50) since 2000

Author (ref.)	Year	n	G (%)	Rx (%)	Size, cm	Mon, m	DFS/S, % (5 years)	Rcd, %
Dematteo ⁶	2000	200	39	86	29%<5/34%>10	24	51/55	40
Crosby ²²	2001	50	100*	70	11 (2.5-27)	24	18/41	59
Pierie ¹⁷	2001	69	61	59	7.9 (1.8-25)	38	–/29 (42%R0)	41
Langer ²³	2003	39	51	90	6.8 (0.9-30)	2.2 years	100-0/65-0**	26
Wong ²⁴	2003	108	–	100	–	–	42	–
Lin ²⁵	2003	81	54	77	7.5+5.7	–	90-25**/–	39
Kim ²⁶	2004	86	–	85	6 (0.4-23)	35.7	29-78	34
Martin ⁶⁴	2005	162	57	100	6 (2-26)	42	68/–	26
Wu ²⁸	2006	100	100*	85	–	44%/50%	52	–
Bumming ²⁹	2006	259	55.2	–	–	–	95-0/–	17
Bucher ³⁰	2006	80	58	90	5 (0.5-26)	42	100-0/95-19**	–
Rutkowski ²⁰	2007	335	45.7	100	29%<5/30%>10	31	37.8/–	45
An ⁹	2007	111	100	–	17-26	23	–/77 (R1)-100 (R0)	35
Richter ³³	2008	54	50	100	61%<5	–	76/65	21
Hassan ³²	2008	191	54	95	–	63	90-40/80-25**	–
Ahmed ³¹	2008	185	52	83	6.7 (10-45)	6.8 years	–/100-55**	11
Das ³⁴	2009	50	64	94	–	–	100-45/100-58**	–

DFS indicates Disease-Free Survival; G (%), percentage of gastric cases; Mon (m), average monitoring in months; n, number of patients; Rcd, recurrence rate; ref, references; Rx (%), percentage of patients resected; S, survival.

*All in the small intestine.

**The first percentage corresponds to low-grade tumours while the second corresponds to tumours with high-grade recurrence.

retrospective studies that include primary tumours as well as local recurrences or even metastases are rare, making data analysis significantly difficult. Very rare indeed are series that include GIST from specific locations, with the majority of these focusing on gastric GIST.⁹ There is a high resection rate (>80%) with low rates of morbidity and mortality, although from the oncology point of view there is great intercentre variability due to differences in incidence risk factors such as location, mitotic index or the use of imatinib.

Anatomic tumour location and surgical technique

Next we will describe the role of surgery in the management of GISTs according to their location.

Oesophagus

This location is extremely rare, with only 50 cases reported since 1999 in the U.S. National Cancer Database.³ Moreover, oesophageal GIST represent only 1% of the 1458 GISTs in the Surveillance Epidemiology and End Results database.^{35,36}

Oesophageal GISTs are easily confused with leiomyomas. They lack a serosal covering, so the risk of breakage is extremely high, and oesophageal resection is a technique that involves high morbidity and mortality. These facts, along with the rarity of this tumour, enormously complicate the surgical treatment.^{3,36}

Blum et al³⁶ analysed four cases, all in the distal oesophagus, arguing for the oesophagectomy alternative to enucleation for large tumours and those close to the gastroesophageal junction (GEJ). Small tumours (<2 cm), confined to the

oesophageal wall in patients at high risk, could be locally resected as long as negative resection margins are obtained. For this author, the difficulty of differential diagnosis with regard to leiomyoma and the different therapeutic approach force, despite its risks, pre-operative biopsy by ecoendoscopy.³⁶ Contrary to this view, a recent study on seven patients³⁷ argues for thoracoscopic enucleation in well-defined, benign <5 cm tumours, whereas for tumours >5 cm, opts for oesophagectomy as the technique of choice. Unlike Blum,³⁶ he uses PET as the method for differential diagnosis between leiomyoma and GIST.

To summarise, enucleation is not a therapeutic option that we can recommend across the board except for groups with extensive experience.³⁷ preferring to opt for local resection of tumours <2 cm, provided that we can ensure an R0 resection, or a standard resection in tumours>2 cm.^{3,36}

Stomach

As this is the most common location and with which we have the most experience, there is much available clinical, pathological, and prognostic data.¹⁻³ In general the surgical technique most commonly used is 'wedge' resection. Following this approach, in a series of 140 patients,^{38,39} 68% were treated by 'wedge' resection, 28% with partial gastrectomy and only 4% required a total gastrectomy. Most surgical series did not find differences in terms of long-term survival between gastrectomy and 'wedge' resection.^{14,38-41}

The 'wedge' resection, often via laparoscopy, is most commonly used.¹⁻³ Occasionally, the surgeon may find that large gastric tumours are firmly adhered to neighbouring

structures, forcing them to perform very aggressive and extensive 'block' resections.^{6,9,39,40} The possibility has been raised of neoadjuvant therapy to reduce tumour size and thus the extension of the surgery.⁴²

Duodenum

They account for 4.5% of all GISTs^{43,44} and are usually located in the 2nd duodenal portion.⁴⁵

Three basic surgical techniques have been described: local 'wedge' excision with primary duodenal closure, segmental duodenal resection plus duodenojejunostomy and pancreaticoduodenectomy (PCD).⁴⁴ In a review by Miettinen,⁴⁵ 45% of cases were treated by local excision, 20% were treated with a PCD, and 20% by segmental resection. In the published series, between 20%-80% of patients are treated with a PCD.⁴⁵⁻⁴⁸ If we consider that only 30% of these GISTs pose a high risk of recurrence and that PCD is a high-morbidity/mortality procedure, it raises the possibility of over-treatment.⁴⁴

The choice of any of these techniques depends on the cancer value, tumour size and the distance from the ampulla of Vater at which the tumour is found, as well as its relationship with pancreatic duodenal face.⁴³⁻⁴⁹ Local 'wedge' resection, although technically possible in small duodenal tumours, appears to be worse than segmental resection due to a greater number of local recurrences.¹⁴ However, survival and recurrence between PCD and segmental resection are similar.^{48,50-52} These data favour the use of segmental resection since it is better than local excision without the morbidity/mortality of PCD.⁴⁴ On this subject, some authors do segmental resections even in tumours that are adjacent to the ampulla of Vater, with various complex technical modifications and potential complications when trying to avoid the stenosis of the ampulla.^{3,44,50,53,54}

In general and in very small tumours (<1 cm) and more than 2 cm from the ampulla, it is possible to use a 'wedge' excision,^{3,50} while large tumours (>3 cm) located in the 3rd-4th duodenal portion are treated with segmental resections.^{3,54} The PCD is reserved for periampullary tumours or those >3 cm located in the 1st-2nd part of the duodenum, where segmental resection is technically impossible. The preferences and experience of each surgeon, together with local factors, will determine the technique to use.³

Small intestine

The small intestine is the second location by order of frequency and the technique of choice is segmental resection with end-to-end anastomosis without lymphadenectomy.³ In special locations such as the Treitz angle, it is preferable to perform resection followed by duodenojejunostomy.³ The small jejunoileal tumours pose the problem of their location. To locate the tumours, the use of double-balloon endoscopy is recommended as it helps pinpoint them by means of pre-operative tattoo and differential diagnosis of the lymphoma through biopsy.^{3,55-59} For large tumours (>5 cm) or those close to the Treitz, an open approach is preferable.

Many of these tumours often invade adjacent organs,

which requires extensive resections.²² Given its exophytic growth along with its impact on the serosa, there is a high potential for peritoneal tumour dissemination. This explains the high rates of peritoneal metastasis that these patients develop in the medium term (41%-66%).^{22,6,60} Indeed, these tumours are considered to have a bad prognosis,^{3,61-66} with a tumour-related mortality rate of 39%.^{3,67}

Colon

The colon is a very infrequent location (<5% of the total)^{3,68} and the technique of choice is segmental colectomy without lymphadenectomy.³ These tumours have extraordinary malignancy (70% of these GISTs are malignant).^{3,69,70} A recent publication by the Memorial Sloan Kettering Cancer Center^{3,63} calculated that the disease-free survival rate for these tumours was only 20% at six years.³

Rectal

The rectum is the third location in order of frequency.^{3,71} A high rate of incomplete resections (R1) is associated with this location, reaching in some series, such as that of the MSKCC, up to 38% of cases.^{3,63,72}

The technique of choice depends on tumour size and location.⁷¹⁻⁷⁴ The most common technique is anterior resection without excision of the mesorectum in the absence of lymph node involvement. This not only facilitates the technique but also avoids potential damage to the autonomic nervous system of that region. For small tumours (<3 cm) with low extra-rectal growth trans-anal excision can be performed.^{3,75} For large tumours (>5 cm) that have a large anterior or posterior extra-luminal component, a trans-sacral (Kraske)^{3,76,77} or trans-vaginal^{3,78} approach is recommended. For larger tumours and those distally located, the technique of choice is a Miles abdomino-perineal amputation.³

The potential role of neoadjuvant imatinib therapy prior to surgery has been examined in an attempt to make a tumour technically resectable and to perform a less aggressive surgery with lower morbidity/mortality, with the particular aim of preserving the sphincter.⁷⁹⁻⁸³ The available literature consists mainly of individual cases and very few case series.⁸⁴ The interesting series of Haller⁸⁵ presents their experience with 10 rectal GISTs, of which six were locally advanced and four were low rectal. In all cases an R0 resection was achieved without requiring the use of colostomy in any of them. Most authors note that neoadjuvant therapy improves tumour resectability and the possibility of organ preservation, thanks to a reduction in tumour size.⁸⁴

Epiploic and mesenteric GISTs and those adhered to adjacent organs

For these cases, limited surgery should not be considered but instead a 'block' resection of the entire visible disease and all structures involved.^{2,13,20,86} This is clearly a very complex surgery that carries with it significant morbidity and mortality, which should be measured against its oncology benefit.^{13,87}

Main controversies

Neoadjuvant therapy

One of the major limitations of surgical treatment of primary GIST is its "difficult" anatomical location or to its large size. There are four factors that determine the applicability of neoadjuvant therapy^{1,42}: achieve tumour resectability, decrease the extent of surgery needed to achieve a R0 resection, improve the expected functional outcome and reduce the risk of tumour rupture.

Oesophageal tumours require surgery with high perioperative risk. While neoadjuvant therapy is not going to modify the technique, it will reduce the risks by hardening the tumour and decreasing the risk of rupture and tumour seeding.⁴² Duodenal GIST can benefit from a reduction in tumour size by allowing limited duodenal resections.⁴² In the case of large gastric GIST, massive 'block' resections are usually necessary. Neoadjuvant therapy could result in the use of more limited gastric resections.⁴² Where we see a difference in the technical approach is in rectal tumours, since a tumour reduction could facilitate a sphincter-sparing surgery.⁴² As regards the risk of tumour rupture, factors such as hypervascularity, the presence of intratumoural cystic areas and large tumours are associated with a high risk of rupture and neoplastic cell dissemination. In these cases neoadjuvant therapy significantly reduces the risk of rupture.^{3,42,89}

All these recommendations are to be taken with caution since they are based on data supplied by series with small numbers of patients and carried out by teams with extensive experience. Moreover, this approach is not without risk, we can "lose" the patient in the attempt to reduce the tumour size or the tumour may not respond, meaning that it is impossible to remove it. That is why our recommendation, like that of the GEIS guide, is to refer these patients to experienced centres in the context of well-designed prospective studies.⁸⁸

Laparoscopy

The role of laparoscopy has been facilitated by the fact that these tumours are frequently located in the gastric region, which makes them technically very accessible. They are easy to locate due to their exophytic growth and because they do not require lymphadenectomy.¹⁻³ Nevertheless, there are three major controversies about its application: 1) the handling of tumours >2 cm; 2) the location and treatment of intraluminal submucosal tumours,⁹⁰⁻⁹² and 3) the resection of tumours located in the GEJ, pyloric antrum and posterior gastric wall.⁹⁰

Initially, the 2004 NCCN guide⁸⁶ restricted the use of laparoscopy to gastric tumours <2 cm due to the high risk of tumour seeding by manipulation or tumour rupture. Various publications forced a re-evaluation of these recommendations. Novitsky,⁹³ in a series of 50 cases of resection by laparoscopy with an average size of 4.4 cm (Table 2), showed no differences in terms of recurrence or effectiveness compared to an historical open series. This

author, as do others,^{13,94-96} suggests that the indications of the NCCN should be expanded because they were aimed at avoiding the use of laparoscopy by inexperienced teams in an attempt to avoid an increase in the rate of intra-operative tumour rupture. Otani et al.,¹⁰ based on their results, believe that 2-5 cm tumours or <2 cm growing tumours should be treated solely with laparoscopy, while tumours >5 cm located near the pylorus or the cardia are ideal candidates for hand-assisted laparoscopy.⁹⁷ These results, as well as others, led to the recommendation in the 2007 NCCN guide¹ for the use of laparoscopic surgery for tumours up to 5cm while assisted laparoscopy would be indicated for those with greater diameters. Once again, the limitations imposed in the case of sizes >5 cm are based on the fact that these tumours are more fragile, more vascularised, have a greater necrotic component, a greater pseudocapsule and a greater probability of being attached to adjacent structures.^{13,93} For this reason, only centres with extensive experience in laparoscopic surgery should remove large GISTs. Under any other circumstance, switching over to open surgery is mandatory.^{13,93,98,99} The main factors associated with this switch are: tumours located in the GEJ, local invasion of adjacent organs, association with other tumour lesions, pre-operative tumour perforation, firm adhesion and large tumour size.^{7,12}

Endoscopic resection may be considered for small submucosal lesions or lesions with intraluminal growth. However, the high rate of perforations and margins affected (R1) requires rethinking this indication.¹⁰⁰ In these cases it is preferable to use a combined laparoendoscopic approach, which is indicated above all for lesions of the anterior gastric wall. The use of intra-operative endoscopy helps to identify the tumour, facilitates its resection and enables easy control and checking of the suture line.⁹⁰ As such, in some series,⁹⁰ laparoscopic tumour location could only be achieved in 23% of the cases, whereas when it was performed in conjunction with endoscopy, 99% of the lesions were located.^{41,90,101-106} Furthermore, endoscopy can improve tumour exposure thus helping the surgeon to decide which resection technique to use and to better place the staple line through a better viewing, thereby avoiding stenosis of the gastric lumen. It also helps the surgeon to verify the complete excision of the tumour.^{90,107-109} In the case of posterior GIST, it is possible to use a trans-gastric approach, also assisted by a combined or hand-assisted laparoendoscopic approach.^{10,93}

The GEJ and the pyloric antrum involve specific technical problems since at this level laparoscopic 'wedge' resection has^{110,111} a high risk of stenosis,^{112,113} leading many centres to consider the laparotomy approach as the standard.^{3,45,113,114} Recent reports indicate the possibility of a combined laparoendoscopic approach, especially for tumours <3 cm, to be performed by very experienced teams.^{115,116} For other situations, especially for large tumours, partial gastrectomy^{117,118} and more extensive resections³ are required. The pre-pyloric antrum poses similar technical problems and while a laparoscopic resection is possible for tumours <3 cm, a distal, open or laparoscopic gastrectomy is preferable for tumours >3 cm.

Meanwhile, for tumours >10 cm an open entry approach is preferable.³

The laparoscopic approach for GIST should follow the oncology principles described above for open surgery,^{1,119} with a preference for the 'wedge' resection technique.^{6,39,93,120-122} We should note that tumour extraction should be performed in a protective bag to avoid implants in the trocar entry ports and that the staple-line should be aligned longitudinally to the gastric axis to prevent lumen stenosis.^{3,107}

Of course, one should never accept a potentially R1 laparoscopic approach if an open approach would ensure an R0 resection.⁸ While the majority of GISTs are gastric and easy to find, this is not true for small tumours or those located in the small intestine. In these cases, pre-operative location through endoscopic tattoo⁹⁷ or intraoperative location through endoscopy or echo-laparoscopy is required.

An analysis of the available literature (Table 3) showed that in the series analysed, all but one^{97,123} operated on tumours >2 cm, with sizes ranging between 1-7.5 cm.⁹⁷ This

approach has a recurrence rate similar or lower than those of open surgery, with a low conversion rate (0%-3.4%)^{7,110,114,124} although some authors report a rate of 14.5%.⁷ In addition, morbidity and mortality is minimal, hospital stay is greatly reduced and there are no problems related to the surgical wound. We should note that there are no randomised prospective studies comparing open versus laparoscopic surgery,^{114,125} just comparative studies on historical open entry series. Anyway, these results should be assessed with caution as these series focus on gastric GISTs that have better prognosis than extra-gastric tumours and there is also a selection bias toward "better" patients.⁹³

Importance of disease-free margins

The 2004 consensus conference on GIST² stated that positive microscopic margins or R1 were not seen to compromise survival. The 2004 NCCN guide⁸⁶ reached the same conclusion. However, the 2007 update¹ of this same guide did include negative microscopic margins as a surgery goal.

Table 3 – Main series (n>20) of laparoscopically resected GIST since 2005

Author, ref. (year)	n	Lap, %	G (%)	Diameter, cm	R1	HS, days	High risk	Morb/mort, %	Mon (months)	DFS, %	S, %
Novitsky ⁹³ (2006)	50	100	100	4.4+2 (1-8.5)	0	3.8+1.6	20	8/0	36	92	96
Otani ¹⁰ (2006)	38	100	100	4.2	–	7.2	–	2.6/2.6	53	96	100
Huguet ¹⁰⁷ (2008)	33	93	100	3.9 (0.5-10.5)	6	3 (1-40)	6	9/0	13	100	100
Tabrizian ⁷ (2008)	76		72	3.5 (0.4-8.5)	–	6 (1-94)		10/1.3	41	66	89
Catena ⁹⁷ (2008)	21	100	100	4.5+2 (1-8.5)	0	4.8+1.6 (3-7)	0	0/0	35	100	100
Nakamori ¹⁴⁶ (2008)	56	100	100	5.1+3 (1-15)	0	6.6+0.5	36	0/0	37	82	96
Sexton ¹¹⁴ (2008)	61	98	100	3.8+1.8 (0.4-9)	1.5	3.9+2.2	15	16.4/1.6	15	95	98
Nishimura ¹² (2007)	39	100	100	3.8 (0.8-7.3)	7.7	–	10	0/0	18.9		100
Basu ¹²⁶ (2007)	21	71	76	5.5 (2-11)	0	7	24	–/–	24 (6-75)	–	81
Wilhelm ⁹⁰ (2008)	93	93	100	2.6 (0.3-6.5)	0	7.5 (2-19)	1	7.5/0	39.5 (2-99)	99	99
Silberhumer ¹¹³ (2009)	22	65	100	3.5+1.4	0	7.8+3.1	9	0/0	30+2	100	100
Choi ¹⁰⁹ (2007)	23	100	100	4.3	0	5.2+2.3	8	4.3/0	61	100	100
Hindmarsh ¹²⁷ (2005)	22	68	100	4.7	0	4.6	14	–/–	18	90	100
Iwahashi ¹²⁸ (2006)	22	–	100	<5	0	–	36	–/–	32	82	82
Lai ¹²⁴ (2006)	28	96	100	3.4+1.6	3.5	6.7+1.8	–	0/0	43	100	100
Nguyen ¹²⁹ (2006)	43	89	67	4.6 (0.4-11.5)	–	–	–	9/2	–	–	–

G (%) indicates percentage of gastric cases; HS, hospital stay; Lap, percentage of case treated laparoscopically; Mon (months): average monitoring in months; Morb/mort, morbidity and mortality; n, number of patients; R1, percentage of patients with microscopically affected margins; ref., references; S, Survival; SFD, Disease-Free Survival.

The available series report conflicting results. De Matteo⁶ compared 65 cases of R0 versus 15 cases of R1. This author, like others,^{15-17,22,28,130,134,135} found no differences in either the recurrence rate (33% versus 30%, respectively) or in survival, thereby emphasising complete macroscopic resection. In sharp contrast, De Gouveia¹³¹ compared 78 cases of R0 versus 18 cases of R1. The recurrence rate for R0 was 9% versus 27.8% for R1. Other authors^{23,31,132} also consider microscopic margins to be very important prognostic factors.^{14,16,19,23,28,39,131,133}

This controversy has no easy solution.¹³¹ There are only a few small series that address this problem and they suffer from selection bias by including, in different proportions, tumours with various risk factors such as size or tumour grade.¹³⁶ There is an association between size, tumour grade and incomplete resection, that is, it is easier to achieve an R0 resection in small, low-grade tumours and vice versa.¹⁹ Since low-grade tumours generally require less aggressive surgeries, this explains why some studies report that local resections have lower recurrence rates than segmental resections.^{14,132} Given that the variables of differentiation degree, surgery type and surgical radicality are always linked, statistical interpretation becomes very complex. Moreover, there is a frequent occurrence of false positives related to retraction of the piece after setting prior to pathological analysis or by resection of the stapled margin. Lastly, data analysis is often distorted by the administration of adjuvant imatinib therapies.^{6,19,137}

Based on the above, we can say that there are insufficient data to justify extensive resection margins for reducing the risk of relapse.^{8,39} We should re-emphasise that a full macroscopic resection with a 1 cm margin is more than sufficient. Indeed, a safety margin of 1-2 cm, which includes the 5 mm of potential microscopic tumour extension, achieves an R0 resection in all cases.^{93,128}

For locally advanced tumours, the recommendation is to attempt macroscopic tumour resection without paying attention to the potential microscopic involvement of the margins, if this avoids resection of vital structures.⁹ An intraoperative analysis of the piece is recommended to confirm that the resection is R0.¹³⁷ Except in cases of palliative surgery, R2 resection is not an option.¹⁵

Another problem that arises is what to do if the final pathology report reveals an R1 resection. To date, there is no evidence that the presence of positive margins after macroscopic resection of a GIST requires re-resection.¹ Still, surgeons' opinions are very important, in terms of whether or not they believe that the pathology report accurately reflects the surgical procedure, and whether or not they are dealing with a false positive.¹ Otherwise, the patient should be carefully re-evaluated and those with low surgical risk, with easily re-identifiable and resectable lesions and with high risk of relapse should be resected.^{31,39}

Microscopic tumours

Lesions that are <1 cm are extremely common, to the point that they are found in 22.5% of cases in autopsy studies and in 35% of pieces from gastrectomies.^{138,139} They are incidental, small, asymptomatic and have an unknown

natural history. Their handling is very controversial and while serial endoscopic control is a logical choice¹⁴⁰ (resection is only recommended in case of increase in size or appearance of symptoms) the endoscopist often resects these lesions.¹⁴⁰ Since this technique has a high rate of positive margins it should therefore not be recommended.⁸

Larger lesions of 1-2 cm are often symptomatic but still have an unknown natural history. In general, they are resected, especially through laparoscopy. Some are in favour of observing these lesions due to their low risk which is estimated based on their small size and easy location (especially if they are gastric). However, we do not know their mitotic rate, a very important risk factor, whose estimation by means of biopsy is very difficult.⁸

Based on the above, we recommend surgical resection for tumours >2 cm; for all extra-gastric tumours, regardless of size; and for tumours <1 cm that are symptomatic or growing. For tumours that are 1-2 cm an individualised treatment can be chosen, although laparoscopic resection is preferable. Observation along with serial endoscopic control is indicated for <1 cm asymptomatic and stable tumours. We should emphasise that there are currently no guidelines to help us manage these patients.¹⁴¹

Pre-operative biopsy

Due to the high risk of rupture, bleeding and tumour dissemination, pre-operative biopsy should be avoided in all potentially resectable tumours in patients at low surgical risk.^{1,6,13} Biopsy would only be indicated in cases of unresectability where neoadjuvant treatment is being considered and in cases where there are serious diagnostic doubts with other tumoural lesions treated differently than GIST, such as ectopic pancreas, lymphomas, oesophageal leiomyomas, etc., and especially in patients with high surgical risk.^{9,13,16,18} Intraoperative frozen biopsy would only be indicated if the possibility of lymphoma or adenocarcinoma is excluded during the course of surgery for a potential GIST.¹³

Conventional endoscopic biopsy tends to be unsuccessful due to the submucosal location of these tumours.¹⁴² Indeed, only 35% of the biopsies are able to obtain submucosal material.¹⁴² In contrast, echo-endoscopic puncture has a success rate of 80%-90%¹⁴³ and identifies the anatomical layer where the tumour originates and the tumour characteristics,^{97,100,144,145} while puncture identifies c-kit positive cells, which are key to the diagnosis.¹⁰⁷ Nonetheless, a diagnosis is difficult to establish based on the few cells obtained by FNAP or because biopsies often only obtain necrotic or haemorrhagic material.^{1,6} One must also add to these limitations the dependency that this technique has on the observer.^{144,145} In a recent review, the rate of successful pre-operative diagnosis was estimated at 50%.⁹⁷ In general, biopsy by means of FNAP performed by echo-endoscopy is preferred to percutaneous FNAP guided by ultrasound/CT, provided that the pathological analysis must be performed at specialised centres.

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