Review

Surgical management of gastrointestinal stromal tumours

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Background: **Over the past decade, gastrointestinal stromal tumours (GISTs) have served as a model for the application of tyrosine kinase inhibitors in the treatment of solid neoplasms. Operative and medical management of GISTs is rapidly evolving, but current guidelines appear restricted to basic non-organ-specific recommendations.**

Methods: **A PubMed search was made of the English literature from 1998 to 2008 for references containing the terms 'gastrointestinal stromal tumours' and 'surgery'. This paper reviews the various operative strategies so far reported for GISTs within the digestive tract.**

Results: **Many original procedures tailored to the specific characteristics of these rare sarcomas have been reported. GISTs exhibit distinct features, in particular an absence of metastases within locoregional lymph nodes. Operations requiring extended lymph node dissection, typically designed for adenocarcinomas, such as gastrectomy with extended lymph node dissection, Whipple's procedure and total mesorectum excision, are inappropriate for treating GISTs originating from the stomach, duodenum and rectum respectively.**

Conclusion: **GISTs allow the possibility of performing oncologically adequate but limited (wedge; segmental) resections. Such surgery can be carried out in a variety of ways, such as open, laparoscopic, trans-sacral or endoscopic.**

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Introduction

Gastrointestinal stromal tumours (GISTs) are the commonest mesenchymal tumours in the digestive tract, with a worldwide incidence of approximately 15 per million[1]. In 1998, Hirota and colleagues[2] investigated the molecular biology of these sarcomas and demonstrated that a mutation in the juxtamembrane domain of CD117 (c-kit) resulted in constitutive activation (gain-of-function) of the c-kit receptor tyrosine kinase. This mutation is present in 90 per cent of GISTs, and one-third of GISTs lacking c-kit mutations have a mutation in a related tyrosine kinase, platelet-derived growth factor receptor α (PDGFRA)[3]. Subsequently, Kindblom and co-workers[4] and Sircar and colleagues[5] demonstrated that GISTs share a common precursor with the interstitial cells of Cajal, which regulate autonomous gut peristalsis and are intercalated between the longitudinal and circular layer of the muscularis propria throughout the gastrointestinal tract. GISTs occur most commonly in the stomach (60 per cent), followed by the small intestine (25 per cent), colon and rectum (10 per cent) and oesophagus (5 per cent)[6].

In 2001, the initial report of activity of the tyrosine kinase inhibitor (TKI) imatinib mesylate in a patient with chemotherapy-resistant metastatic GIST[7] prompted clinicians to conduct a multicentre trial. This established the efficacy and safety of this molecule for treating patients with advanced GISTs[8]. Since then, various TKIs have been developed, in parallel with a growing clinical interest in these rare tumours; a previously obscure disease rose to prominence with the concept of targeted molecular therapy for cancer[9]. However, many GISTs are of 'uncertain malignant potential', oncologists being reluctant to use the term 'benign'[10]. A large proportion of patients with a primary localized GIST do not require TKIs; they require adequate surgical resection.

Population-based data from the USA[11] and Sweden[12] before the TKI era indicate, first, that 50–60 per cent of tumours are localized at the time of diagnosis and, second, that complete removal of tumour can be achieved in 95 per cent of patients with non-metastatic disease. These

results suggest that surgery alone is likely to achieve cure in 50 per cent of patients with a GIST. In contrast, curative (R0) resection is possible in only a small minority of patients presenting with recurrent or metastatic disease. Such patients had a median survival of only 12 months before the introduction of imatinib mesylate[13].

The present article is based on a PubMed search of the English literature from 1998 to 2008 for references containing the terms 'gastrointestinal stromal tumours' and 'surgery'. The reference lists of identified papers were also searched and preference was given to papers published in English. What follows is a review and critical assessment of existing surgical strategies for GISTs according to tumour location.

Rationale for a specific surgical management

GISTs are not like carcinomas. They have specific features that affect surgical management. First, metastases commonly develop in the liver and peritoneum, but are extremely rare in locoregional lymph nodes[14]. Second, GISTs typically show a tendency to grow opposite the intestinal lumen, or towards the abdominal cavity (*Fig. 1*). Third, even when overtly malignant, they have a tendency to displace, but not to invade, surrounding organs. Finally, they are soft, fragile tumours, which may rupture within the abdomen during surgery, with a significant risk of subsequent peritoneal dissemination.

Obviously, the aim of surgery must be to achieve complete gross resection with negative histological margins. However, the most relevant characteristic in the surgical management of GISTs is that, in contrast to surgery for gastrointestinal adenocarcinomas, lymphadenectomy is unnecessary. Procedures such as extended lymph node dissection (D2) and total mesorectum excision for gastric and rectal carcinomas respectively are inappropriate in the treatment of GISTs originating from the stomach and rectum. Similarly, extensive resections of the duodenum may be advantageously replaced by more conservative, pancreas-sparing procedures. Finally, the extraluminal growth of these tumours renders their localization straightforward and enhances the possibility of their treatment using minimally invasive techniques.

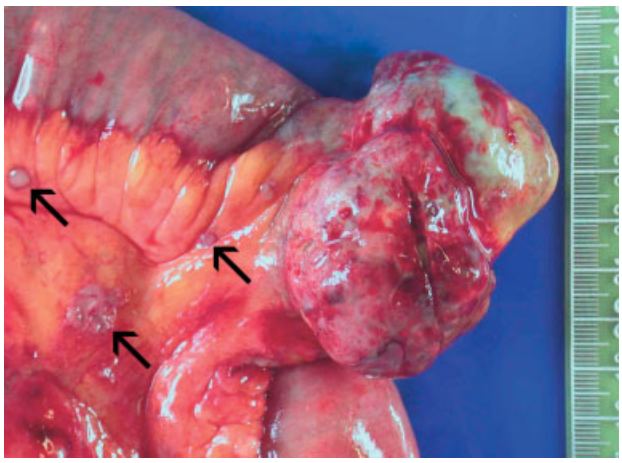


Fig. 1 Extraluminal growth of a small bowel gastrointestinal stromal tumour, with high malignant potential. Note the presence of small tumour deposits in the surrounding mesentery (arrows)

Oesophagus

In the oesophagus the commonest mesenchymal tumours are leiomyomas, which are three times as common as GISTs[15]. Only 50 reports of oesophageal GISTs, mostly originating from the lower third, have been recorded in the US National Cancer Database since 1999. Their endoscopic and radiological appearance being similar, leiomyomas and GISTs should be differentiated before surgery using immunohistochemical staining for c-kit[16]. Although the former are clinically indolent tumours with no associated mortality, oesophageal GISTs carry a risk of malignant behaviour and should be resected. Most patients complain of dysphagia, but bleeding may be the initial symptom. A significant number of GISTs are detected incidentally during endoscopy or barium swallow.

It is hardly surprising that the largest surgical series of oesophageal GISTs includes only four patients, and that the technical issues pertaining to adequate resection are poorly recognized. Surgical enucleation using a thoracoscopic, laparoscopic or combined approach is the treatment of choice for oesophageal leiomyomas[17], but this minimally invasive resection is inappropriate for oesophageal GISTs, which may be difficult to enucleate because of adhesions with the muscularis propria. Blum and co-workers[18] recommended that local resection is restricted to small (less than 2 cm) oesophageal GISTs, with the condition that negative margins of resection can be obtained. Larger tumours and those located close to the gastro-oesophageal junction are best treated by Ivor Lewis oesophagectomy, as there is no need for regional lymphadenectomy[19]. This aggressive strategy appears justified in the light of the 14 per cent 5-year survival rate reported by the Surveillance, Epidemiology, and End Results database[11]. In high-risk patients, and for distal lesions only, the Merendino procedure, which includes vagal-sparing segmental oesophageal resection, jejunal interposition and gastric preservation, appears

oncologically safe. It is functionally superior to the classic Ivor Lewis oesophagectomy[20]. Both procedures require the preoperative differentiation of GIST from leiomyoma using c-kit immunohistochemical staining on biopsies obtained through endoscopic ultrasonography-guided fine-needle aspiration.

Stomach

The stomach is the commonest site for GIST development, and extensive data regarding clinicopathological features and prognosis at this location are available. In a series of 1765 patients, gastrointestinal bleeding was the most frequent presentation, and prognosis was usually good. The overall tumour-specific mortality was 17 per cent, and less than 2 per cent for tumours smaller than 10 cm; even tumours over 10 cm with a low mitotic count were associated with a surprisingly low (12 per cent) risk of developing subsequent metastatic disease[21]. The authors also noted that patients with GISTs of the stomach rarely developed locoregional recurrence, which supports the practice of limited gastric resection with clear margins. However, care should be taken to avoid tumour rupture, which is equivalent in prognostic terms to incomplete surgical resection[22].

Several recent surgical series have reported that laparoscopic wedge resection of gastric GISTs is safe and oncologically adequate[23–26]. In these series, the mean tumour diameter was 3–4 cm, and follow-up was short. Current guidelines from expert panels in Europe[27] and the USA[28] suggest that laparoscopic resection for gastric GISTs should be restricted to tumours smaller than 2 cm that are intramural and so have a low risk of rupture and subsequent peritoneal seeding. These small, submucosal GISTs may benefit from a dual laparoscopic–endoscopic approach, intraoperative endoscopy (with or without endoscopic ultrasonography) facilitating exact tumour localization and circumferential dissection of both mucosal and submucosal layers around the lesion[29,30].

Laparoscopy for gastric GISTs lacks any evidence-based recommendation, but it is probable, in the hands of an experienced surgeon, that laparoscopic resection of a 5-cm GIST located on the greater curvature would carry little risk of tumour spillage or inadequate resection margins[31]. Indeed, many surgeons might reasonably argue that the question of conventional *versus* laparoscopic approach is of minor importance, provided oncological precautions are strictly observed. The surgeon should be prepared to convert quickly to an open procedure when confronted with a fragile, haemorrhagic tumour[32]. Interestingly, two instances of port-site metastasis following diagnostic[33] or therapeutic[34] laparoscopy for gastric GISTs have been reported. Preoperative identification of tumour site is more important than tumour size for deciding the optimal surgical strategy, including the extent of gastric resection[35]. Endoscopy might deceive in this respect, underlining the need to obtain a spiral computed tomogram and barium upper gastrointestinal x-ray before planning laparoscopy.

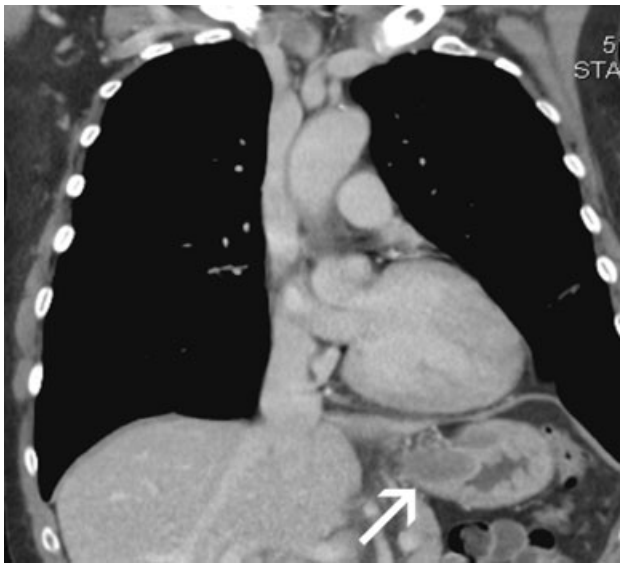
Lesser curvature and gastro-oesophageal junction

GISTs located near the oesophagogastric junction are rare and may be difficult to resect with adequate margins. In a series of 111 patients with gastric GISTs, An and colleagues[36] reported a 42 per cent local recurrence rate for tumours located in the upper stomach. In this specific location, laparoscopic wedge resection, although possible[37,38], is not always feasible because of the proximity of the lower oesophageal sphincter. Many surgeons in Western countries would typically approach these tumours by means of a laparotomy, or be prepared to convert quickly after a laparoscopic exploration[39,40] (*Fig. 2*). Limited resection, when possible, is the preferred procedure using a 'cut and sew' technique and reconstruction over an oesophageal bougie, with the aim of preserving patency of the gastro-oesophageal junction.

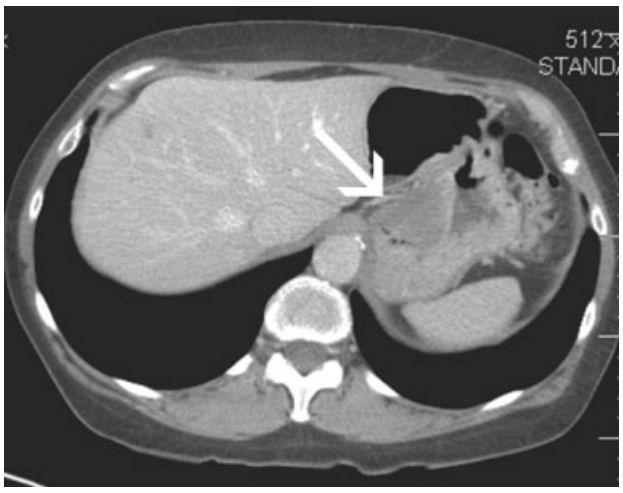
This approach, however, may prove inadequate for larger tumours, which may require proximal gastrectomy with reconstruction by jejunal interposition (Merendino procedure)[20,41]. Extensive resections, classically recommended for carcinomas of the gastric cardia, such as oesophagogastrectomy, should really be considered only in a very small subset of patients with locally advanced GISTs of the gastro-oesophageal junction. Such patients may benefit from neoadjuvant imatinib therapy to downsize the tumour volume, thereby making a complete resection easier and safer. Finally, two small series have suggested a role for a combined endoscopic and laparoscopic approach, using two or three intragastric trocars. This proved feasible for resection of GISTs of the oesophagogastric junction[42,43]. Still, it is a technically demanding procedure that requires advanced laparoscopic skills and instrumentation. It should be considered experimental and restricted to tumours smaller than 3 cm in diameter.

Greater curvature and fundus

Most GISTs in this location are approached laparoscopically and treated with wedge or sleeve resection, depending on tumour size. In the larger series of gastric GISTs, usually from Japan, around two-thirds of patients had wedge resection[44]. In a series from the Mayo Clinic



a Sagittal scan



b Transverse scan

Fig. 2 **a** Sagittal and **b** transverse computed tomography scans of a 65-year-old woman showing a 3 × 3-cm gastrointestinal stromal tumour (arrows) of the gastric cardia (incidentally detected)

of 191 GISTs resected between 1978 and 2004, about one-third of tumours were located within the greater curvature[45]. Laparoscopic wedge resection for a tumour of the greater curvature is, therefore, the commonest procedure performed for GISTs. The long-term safety of wedge resection for gastric GISTs has been established recently. At a mean follow-up of 36 months, Novitsky and co-workers[23] reported a 92 per cent disease-free survival rate in 50 patients who had laparoscopic gastric resection. Similarly, at 5-year follow-up, Choi and colleagues[26] reported no recurrences or liver metastases in 23 patients who had wedge resection. As the mean time to recurrence after surgery for GISTs is 12–24 months[46,47], the relatively short follow-up in these series probably allows an adequate assessment of outcome.

Although wide margins are unnecessary, care should be taken to achieve an R0 resection. When in doubt, intraoperative endoscopic assistance may be useful to confirm that an oncologically adequate procedure has been performed. Ideally, the staple line should be oriented longitudinally with the axis of the stomach to avoid luminal narrowing. GISTs located on the posterior wall of the stomach can be excised using a transgastric approach[23]. Again, this technique, with stapler firing on the inside of the stomach, should be considered experimental.

Antrum (prepyloric)

A minority of GISTs located in the antrum or prepyloric area can be safely resected laparoscopically using a 'cut and sew' technique. However, stapled wedge resection of tumours larger than 3 cm in this location carries the risk of gastric outlet stenosis. If a limited approach is not feasible, distal gastrectomy is the best alternative, whether open, laparoscopic or hand assisted. Tumour size is the most important criterion for selecting the best technique, and most surgeons would concur that a laparotomy is required for tumours over 10 cm in diameter (*Fig. 3*).

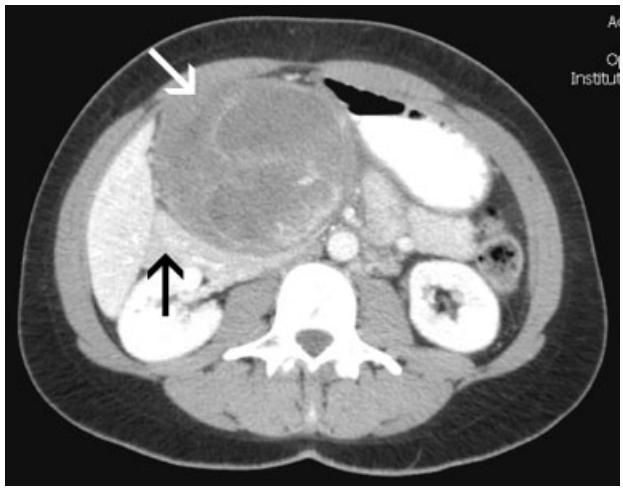


Fig. 3 Computed tomography scan of a 46-year-old patient presenting with a 10 × 12-cm gastrointestinal stromal tumour of the stomach (white arrow). At operation, the tumour was found to displace, without infiltrating, the head of the pancreas (black arrow). A distal gastrectomy was performed

Duodenum

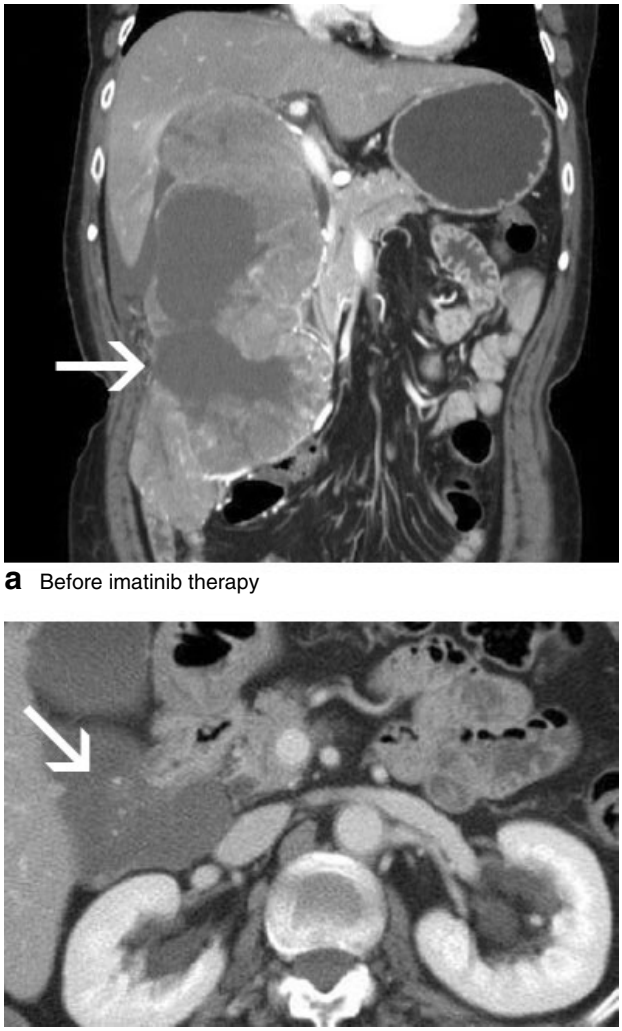
GISTs account for approximately 30 per cent of all primary duodenal tumours and present in the vast majority of patients with gastrointestinal bleeding. Except for the obvious need for clear surgical margins, there are no guidelines to help the surgeon in managing these rare malignancies[48]. In a series from the pre-imatinib era, Miettinen and co-workers[49] reported the outcome of 156 patients who had surgery for duodenal GISTs. Local recurrence, metastasis or both developed in 35 per cent. The commonest procedures were segmental resection, wedge resection and Whipple's operation. Clearly, duodenal GISTs have a wide range of aggressiveness, from small indolent tumours to overt sarcomas. The main question here is whether limited resection is an oncologically adequate alternative to pancreaticoduodenectomy. So far, there have been few data regarding the oncological results of either procedure[50–53]; the only series advocating the use of Whipple's procedure did not assess the outcome of other, more limited approaches[54].

The feasibility of wedge resection for duodenal GISTs is mainly related to tumour size and the distance from the ampulla of Vater. Large tumours arising from the second part of the duodenum and involving the ampulla are best treated by pancreaticoduodenectomy, but high-risk patients might benefit from neoadjuvant treatment with imatinib mesylate to decrease tumour size. This may make a more limited pancreas-preserving resection possible (*Fig. 4*). A recent series by Goh and colleagues[55] demonstrated that limited resections were associated with a low (14 per cent) rate of recurrence, but the authors also recognized that reconstruction after segmental duodenal resection is not free from complications. End-to-end anastomosis after segmental duodenectomy or a Roux-en-Y duodenojejunostomy is recommended whenever the resulting defect is too large to be closed primarily[56,57].

In summary, wedge resection is indicated for small (less than 1 cm) GISTs of the duodenum, as long as they are located more than 2 cm away from the ampulla of Vater. Segmental duodenectomy is indicated for large (over 3 cm) tumours located on D3/D4, when reconstruction is performed using a side-to-side duodenojejunostomy opposite to the ampulla. Pancreaticoduodenectomy remains the best option for periampullary GISTs, as well as for large tumours of D1/D2, which may be inadequately resected through a pancreas-preserving duodenectomy.

Small bowel

The small intestine is the second commonest location of GISTs and as early as 1999 clinicians suspected this anatomical site to be associated with a poor prognosis[58]. In a large series of 906 patients with jejunal or ileal GISTs, Miettinen and co-workers[59] reported an overall 39 per cent tumour-associated mortality that was twice as high as that for gastric GISTs. Two series from the USA[60] and Spain[61] have since demonstrated that the small bowel location is an independent predictor of poor outcome on multivariable analysis (hazard ratio 3·3, with reference to stomach). Despite conflicting data from the post-imatinib era[62], gastric and small bowel GISTs with similar size and mitotic activity have a strikingly different prognosis. For example,



a Before imatinib therapy

b After imatinib therapy

Fig. 4 A large (21 × 12 cm) gastrointestinal stromal tumour (arrows) of the second part of the duodenum **a** before and **b** after imatinib therapy. After 2 years' treatment, tumour size was 6 × 7 cm, and neither the ampulla nor the pancreas was involved, making a segmental duodenal resection possible

tumours larger than 10 cm with up to five mitoses per 50 high-power fields had 49 and 11 per cent tumour-related mortality when located in the small bowel and stomach respectively[63]. A series from a single tertiary cancer centre in the pre-imatinib era clearly confirmed that small bowel GISTs are aggressive tumours, with overall disease-free survival rates of 59, 24 and 18 per cent at 1, 3 and 5 years respectively[64].

Most patients present with bleeding, and in one series 28 per cent had non-elective procedures for either severe haemorrhage or tumour perforation[65]. Segmental resection of the small bowel without lymphadenectomy, which is the recommended treatment for jejunal and ileal GISTs, is a straightforward procedure in most patients. An exception is the occasional large GIST located close to the origin of superior mesenteric vessels at the duodenojejunal junction (*Fig. 5*). In this patient, a stapler was applied at the level of the ligament of Treitz, and reconstruction was achieved by a side-to-side duodenojejunostomy performed opposite the papilla.

Many patients with small bowel GISTs are initially investigated for anaemia secondary to occult gastrointestinal bleeding. GIST was the most frequent tumour type (32 per cent) detected in a series of 5129 patients who had video capsule endoscopy[66]. This modality, however, has three major drawbacks in jejunal or ileal GIST. First, there is a lack of biopsy capability. Second, there is a lack of precise information regarding tumour location within the small bowel. Finally, there is a risk of missing lesions, because of their tendency to grow extraluminally. Some authors believe double balloon enteroscopy to be superior to video capsule endoscopy for identifying small bowel tumours[67,68]. This method provides the possibility of obtaining biopsies (to rule out lymphoma), and of tattooing the site of GIST to make its peroperative localization easy during laparoscopic resection[69,70]. In summary, an integrated approach using double balloon endoscopy and laparoscopically assisted bowel resection appears ideally suited for small GISTs of the jejunum or ileum[71]. Larger tumours (over 5 cm), which are usually detected with standard computed tomography, and those located close to the duodenojejunal junction are probably more difficult to approach with a minimally invasive technique and may require a laparotomy.

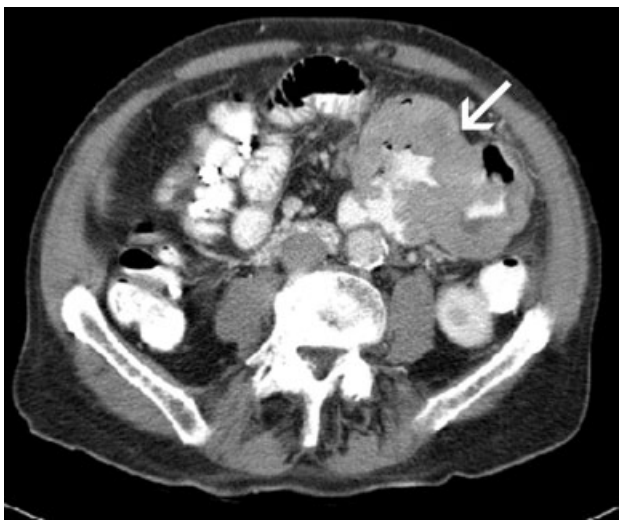


Fig. 5 Computed tomography scan of a 78-year-old patient with a 7 × 11-cm highly malignant gastrointestinal stromal tumour of the proximal jejunum (arrow), closely related to but not infiltrating the mesentery of the transverse colon. The main difficulty in the operation was dissecting the tumour away from the superior mesenteric vessels

Colon

Less than 5 per cent of GISTs are located in the colon and few data are available regarding their management[72]. Colonic GISTs must be distinguished from leiomyomas originating from the muscularis mucosae, which are benign[73]. Most patients present with relatively bulky tumours causing bleeding or abdominal pain. Preoperative diagnosis is generally made by computed tomography, which usually demonstrates a large, lobulated mass, with inhomogeneous enhancement related to haemorrhagic or necrotic components. Colonoscopy is always performed and biopsies might be obtained for diagnosis confirmation. Segmental colectomy without lymph node dissection is the recommended strategy for GISTs of the large bowel. These tumours tend to displace, but rarely infiltrate, surrounding organs or the abdominal wall. An R0 resection is usually feasible, despite an ominous appearance on cross-sectional imaging (*Fig. 6*).

The prognosis is poor, especially for tumours with a high mitotic count. In the pre-imatinib era, more than 80 per cent of patients with tumours larger than 1 cm and high mitotic activity died from their disease, with a median survival time of only 15 months[72]. Data from the Mayo Clinic and Taiwan suggest that about 70 per cent of colonic GISTs are malignant, and at high or intermediate risk of producing distant metastases. Local recurrence on the other hand is rare[74,75]. In a series from the Sloan–Kettering Memorial Cancer Center, patients with colorectal lesions had the poorest prognosis among those affected by GISTs; only 20 per cent were free from recurrence 6 years after surgery[60].

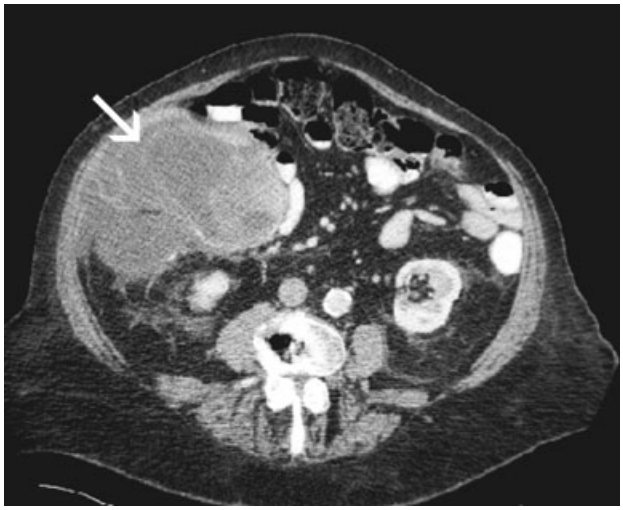


Fig. 6 A 14 × 11 × 9-cm gastrointestinal stromal tumour (arrow) of the ascending colon in an 85-year-old patient who had a right colectomy. The tumour, despite its ominous aspect on computed tomography, did not invade the surrounding structures (abdominal wall, duodenum and right kidney)

Rectum

According to the Miettinen group, the rectum is the third commonest site for GISTs, comprising approximately 5–10 per cent of all tumours[76]. Symptomatic patients with rectal GISTs usually present with bleeding or perineal pain or discomfort. Because of their location close to the pelvic floor, rectal GISTs represent a challenge even for the specialist. There is evidence that patients with rectal GISTs are at risk of incomplete (R1) resection (38 per cent of patients in the Memorial Sloan–Kettering series) and subsequent locoregional recurrence despite extensive procedures, such as abdominoperineal resection and pelvic exenteration[60,77]. In a series from the Mayo Clinic, nine of 14 patients with rectal GISTs had anterior or abdominoperineal resections and five had a local excision[74].

As rectal GISTs do not metastasize through the lymphatics, total mesorectum excision, the preferred strategy for rectal carcinoma, has little, if any, benefit. In addition, the risks of damaging the autonomic nervous plexuses and of poor functional outcome after proctectomy must be considered, particularly in young men. Transanal excision is an interesting alternative for small (under 3 cm) GISTs with a limited extrarectal component, which are usually incidental findings during endoscopy[78]. This approach, however, is inadequate for larger (over 5 cm) tumours growing outside the rectum, whether anterior towards the prostate or vagina, or posterior towards the sacrum (*Fig.* 7). A posterior trans-sacral (Kraske) approach, with wedge resection of the rectum, has some benefits in this setting, including the possibility of obtaining excellent exposure without the need for a major laparotomy, and of avoiding the risk of urogenital dysfunction following total mesorectum excision[79,80]. Similarly, women with GISTs located on the anterior wall of the lower rectum might benefit from a transvaginal approach[81].

It should be noted that GISTs with a large extrarectal component, when located in the male anterior rectal wall, can give the clinical impression of a prostatic lesion[82,83]. Authors from the Department of Pathology at Johns Hopkins Hospital recently reported eight rectal GISTs that were diagnosed on prostate needle biopsy. They recommend including c-kit in the immunohistochemical panel to exclude GIST before establishing a diagnosis of prostate stromal tumour[84].

In summary, the two preferred approaches for rectal adenocarcinoma, total mesorectum excision and transanal excision, are inappropriate for GISTs, the former because of the problem of lymphatic drainage of GISTs and the latter because of the difficulty of locating the tumour's extrarectal component through a transanal approach. Finally, neoadjuvant therapy with imatinib may play a role in downsizing large pelvic GISTs, especially when the tumour is in the vicinity of the anal sphincters. This might make a more limited sphincter-preserving procedure possible.

Metastatic gastrointestinal stromal tumours

As many as 40 per cent of patients after resection of a primary localized tumour will eventually develop

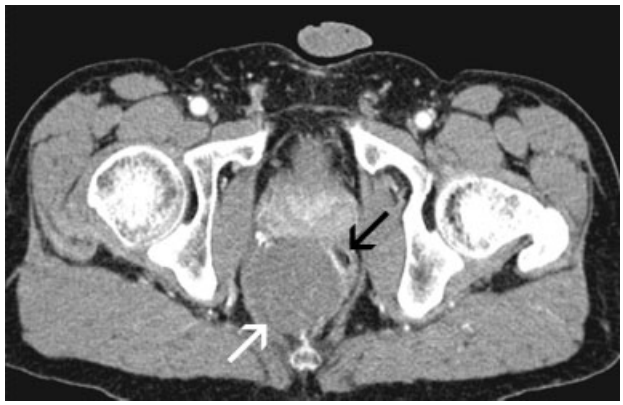


Fig. 7 Computed tomography scan of a 52-year-old patient with a 7 × 7-cm gastrointestinal stromal tumour (white arrow) of the lower rectum with presacral extension, which was displacing the rectum (black arrow) anterior and to the left. The tumour was approached and resected through a posterior trans-sacral (Kraske) incision

recurrent disease, mostly in the liver and peritoneum. Before imatinib, the median survival of these patients was 19 months, with a 25 per cent 5-year survival rate[85]. One series has reported the outcome of 60 patients who had surgery for recurrent or metastatic GIST between 1982 and 1995[86]. The results were disappointing, with a median survival of 15 months, suggesting that surgery should be reserved for symptom control. Imatinib mesylate has become the standard of care for metastatic GIST since 2002, yielding impressive initial tumour response rates[8]. A major limitation of this therapy, however, is the development of secondary tumour resistance related to acquisition of additional c-kit mutations. Neither surgery alone nor imatinib alone is likely to improve outcome dramatically, suggesting a need for multimodal management[87]. The rationale for a combined approach in this setting is that pre-emptive surgical resection of residual disease might enhance tumour response to various tyrosine kinase inhibitors by eliminating or preventing the development of resistant clones.

Three recent series have addressed this issue. They reported the outcome of patients with metastatic GISTs who had surgery with a curative intent after imatinib therapy (median duration of 15–17 months)[88–90]. Operations were extensive and usually encompassed hepatectomy, removal of peritoneal deposits with additional small or large bowel resections. Gross tumour clearance was achieved in over 80 per cent of patients with responsive disease. In contrast, complete cytoreduction was achieved in less than 50 per cent of patients with multifocal resistance to medical therapy. Clearly, this subgroup of patients is unlikely to benefit from surgery, and in this regard the response to neoadjuvant therapy with imatinib mesylate can be considered as a means of selecting a subgroup of metastatic disease with a more favourable outcome. In responders, the best time for surgery appears to be 6–9 months after initiating imatinib mesylate treatment, or as soon as the disease is considered to be completely resectable. These data are in accordance with the findings of a previous smaller series of 11 patients. They suggest that an early aggressive surgical approach should be considered for all patients with metastatic GIST who have demonstrated an initial response to medical therapy, provided an R0 resection can be achieved[91]. These encouraging results, however, are likely to reflect the biased experience of tertiary care institutions, with highly selected patients. Many individuals with metastatic GIST present with a combination of multiple peritoneal deposits and bilobar liver metastases, and are poor candidates for any curative approach.

Neoadjuvant imatinib mesylate therapy

A prerequisite for neoadjuvant imatinib mesylate therapy for GIST is a preoperative diagnosis. This is not always feasible because of submucosal tumour development or location within the small bowel. Many clinicians are also concerned that percutaneous fine-needle aspiration biopsy may cause tumour rupture and intra-abdominal seeding, or may be non-diagnostic for tumours with a large haemorrhagic or necrotic content[92]. In addition, a minority of GISTs express kinase oncoproteins, and these are either intrinsically resistant or poorly responsive to imatinib[93,94]. This experimental strategy, however, is becoming increasingly popular, with the rationale of delivering TKIs as preoperative cytoreduction agents in order to facilitate surgical resection of initially irresectable or marginally resectable GISTs. In many instances, endoscopic ultrasonography-guided fine-needle aspiration can help in determining c-kit or PDGFRA mutational status, thereby providing useful predictive information regarding the clinical activity of sunitinib and imatinib[95]. Subsequently, [^{18}F]fluorodeoxyglucose positron emission tomography may provide assessment of any therapeutic response to imatinib as early as 8 days after initiation of neoadjuvant TKI treatment[96].

This approach has proven feasible in two series, with over 80 per cent of patients experiencing a substantial reduction in tumour volume, with subsequent R0 resection[97,98]. In addition, preliminary data from a trial by the Radiation Therapy Oncology Group have established that neoadjuvant imatinib therapy does not increase the risk of postoperative complications[99]. Of note, however, up to 14 per cent of patients on imatinib required emergency surgery for bleeding or tumour perforation[90]. Nevertheless, there is certainly a small subgroup of patients with primary localized GISTs who would have required extensive surgery for poorly situated tumours, and who may, therefore, benefit from TKI-induced tumour downsizing. In the absence of high-level evidence, this approach should rely on three variables[28]: tumour resectability, extent of procedure needed to achieve R0 resection and expected functional outcome after operation. From a surgical standpoint, neoadjuvant imatinib therapy could be considered initially in patients with GISTs at the gastro-oesophageal junction (oesophagogastrectomy), the second part of the duodenum (duodenopancreatectomy) and the lower rectum (abdominoperineal resection). Finally, it is important to distinguish *neoadjuvant* (for primarily resectable tumours) from *induction* (for primarily irresectable tumours) therapy.

Overview

In the near future, novel TKI strategies coupled with the ongoing elucidation of prognostic factors will provide several opportunities for individualizing the medical treatment of those with GISTs. Surgical management of these sarcomas should be tailored according to the tumour location and morphological characteristics. Surgical variables, such as resectability, type of resection and mode of approach, are of paramount importance in the management of primary GISTs. Many patients with primary GISTS can benefit from limited resections performed through minimally invasive approaches. Clinical decision making for marginally resectable or locally advanced GISTs requires multidisciplinary expertise. This is also true for GISTs located at the oesophagogastric junction, second part of the duodenum and lower rectum. Finally, surgery for metastatic, but initially TKI-responsive, GISTs is still under investigation.

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The authors declare no conflict of interest.

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