BULGARIAN SOCIETY OF MEDICAL SCIENCES journal

Bulgarian Society of Medical Sciences Journal
8: e174054 (2026)
DOI: 10.3897/bsms.8.174054

Review Article | General Adult Cardiac

The role of surgery in the multimodal treatment of gastrointestinal stromal tumors

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Academic editor: Teodor Atanassov ♦ **Received:** 6 October 2025 ♦ **Accepted:** 18 December 2025 ♦ **Published:** 16 February 2026

Citation: Dimitrov P, Kjossev K, Popivanov G, Ivanov V, Tabakov M. The role of surgery in the multimodal treatment of gastrointestinal stromal tumors. Bulgarian Society of Medical Sciences Journal 2026;8:e174054. doi: 10.3897/bsms.8.174054.

Abstract

Introduction: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. Radical resection remains the only curative treatment for primarily resectable disease, whereas the extent of surgery should be carefully tailored to tumor location and biology. Given the heterogeneity in tumor size, location, and biology, the tailored surgical approach based on the imaging and molecular assessments is essential.

Aim: This narrative review aims to highlight the evolving role of surgery in the multimodal management of GIST, outlining key principles of operative strategy and integration with systemic therapy.

Main findings: Complete R0 resection is the cornerstone of treatment, while lymphadenectomy is unnecessary. Organ-preserving limited resections are oncologically adequate in most cases, provided rupture is avoided. In challenging anatomical sites, neoadjuvant imatinib may improve resectability. For advanced disease, tyrosine kinase inhibitors have reshaped outcomes, and surgery retains a role in selected responders.

Conclusion: Surgery continues to play a pivotal role in the treatment of GIST, but optimal outcomes rely on tailoring the extent of resection to tumor size, location, and biology, while integrating systemic therapy where appropriate. The future of GIST management lies in increasingly individualized multimodal strategies, combining precise surgical techniques with targeted molecular approaches.

Keywords

GIST, multimodal therapy, organ-preserving surgery, surgery, radical resection

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract [1]. They arise from the interstitial cells of Cajal or related stem cell precursors and most frequently occur in the stomach (40–60%) and small intestine (25–35%), while less commonly in the colon, rectum (≈5%), and oesophagus (<1%) [2–5]. Rarely, extra-gastrointestinal STs are found in the omentum, mesentery, or retroperitoneum (<5%).

A key molecular hallmark is the activation of mutations in the KIT proto-oncogene, reported in the majority of cases, with PDGFRA mutations accounting for the remainder [2]. These discoveries established GIST as a distinct clinicopathological entity, providing the rationale for targeted therapies.

GISTs are generally resistant to radiotherapy and conventional chemotherapy, highlighting the significance of tyrosine kinase inhibitors (TKIs). Imatinib is the standard of care for metastatic disease. It is also used as neoadjuvant therapy for initially unresectable or borderline resectable tumors, as well as adjuvant therapy in high-risk patients [6]. Nevertheless, surgery remains the cornerstone of treatment for localized, primary GIST and is potentially curative in many cases [7, 8].

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Rationale for specific surgical approach

gISTs exhibit biological and anatomical features that dictate their surgical management. Metastases typically involve the liver and peritoneum, whereas regional lymph node spread is exceedingly rare [9]. Their predominantly exophytic growth leads to displacement rather than infiltration of adjacent structures. However, these soft and friable tumors are prone to intraoperative rupture, which substantially increases the risk of recurrence.

The surgical goal is complete resection with negative margins. Unlike gastrointestinal adenocarcinomas, lymphadenectomy is not required, making extensive procedures such as D2 dissection or total mesorectal excision unnecessary. The extraluminal growth pattern of GISTs also facilitates minimally invasive approaches, provided careful handling prevents rupture.

Esophagus

GISTs of the oesophagus are rare, occurring less frequently than leiomyomas, the predominant submucosal neoplasm at this site [10]. Patients most often present with dysphagia, though some lesions are discovered incidentally.

In comparison to leiomyomas, oesophagal GISTs adhere to the muscularis propria, making simple enucleation generally inappropriate. Minimally invasive enucleation may be considered only for very small tumors (<2 cm) when R0 resection is feasible [11, 12]. Larger lesions, especially those near the gastroesophageal junction, are best managed by esophagectomy, most commonly through an Ivor-Lewis approach, without the need for lymphadenectomy [13]. In selected distal tumors and high-risk patients, alternatives such as the Merendino procedure may be applied. Accurate preoperative differentiation between leiomyoma and other conditions using endoscopic ultrasound-guided biopsy and immunohistochemistry is critical for surgical planning.

Stomach

The stomach is the most common site for GISTs. In large series, gastrointestinal bleeding is the leading presentation, with overall tumor-specific mortality around 17%, but below 2% for tumors <10 cm [14]. Locoregional recurrence is uncommon, supporting the use of limited gastric resections with negative margins. Intraoperative rupture, however, carries the same adverse prognostic impact as incomplete resection [15].

Laparoscopic wedge resection is well established as safe and oncologically sound for appropriately selected tumors, typically ≤5 cm and favourably located [16]. Combined laparoscopic–endoscopic approaches may further assist in the precise localization of small submucosal lesions [17]. While no universal size limit exists, many authors accept that tumors up to 5 cm on the greater curvature can be removed laparoscopically with low risk of rupture, provided oncological principles are strictly observed. Surgeons must remain prepared for conversion to open surgery.

GISTs at the gastroesophageal junction and lesser curvature

GISTs near the gastroesophageal junction are rare and technically demanding due to the difficulty of securing negative margins while preserving function. Reported recurrence rates are higher for proximal gastric tumors, up to 40% in some series [18]. Laparoscopic wedge resection is often not feasible in this location, and many patients require upper midline laparotomy or conversion after attempted laparoscopy [19]. Limited resections using "cut-and-sew" techniques over a bougie are preferred when achievable (Fig. 1a, b).

Larger tumors may necessitate proximal gastrectomy with reconstruction, such as the Merendino procedure [20]. In borderline cases, neoadjuvant imatinib can downsize tumors, improving the likelihood of R0 resection and reducing surgical morbidity. Small case series have also described combined laparoscopic–endoscopic resections for

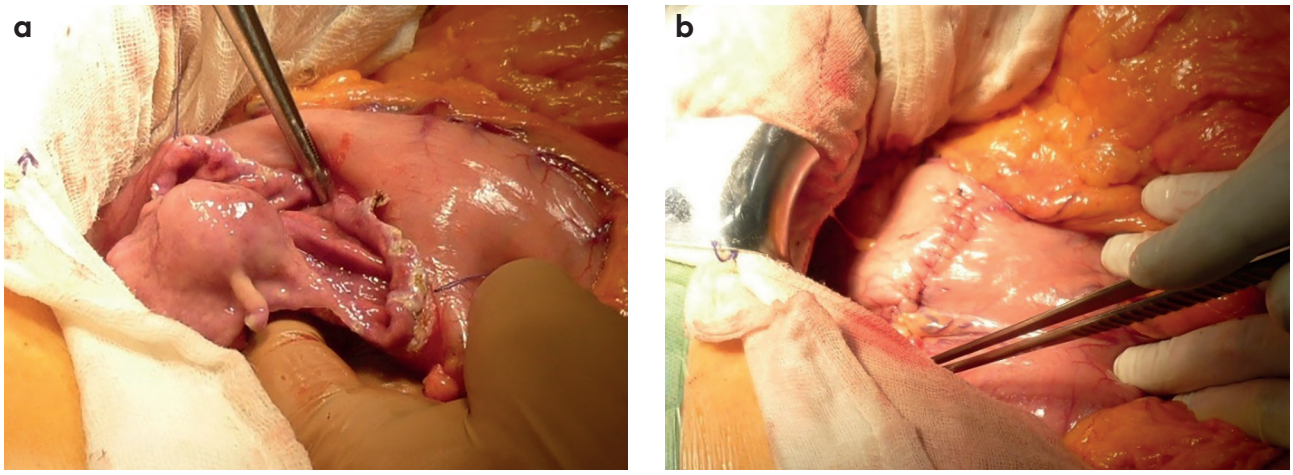

Figure 1. a, b. Intraoperative view along the lesser curvature showing an intraluminal soft-tissue mass (GIST) before and after limited "cut-and-sew" resection.

tumors <3 cm, though these require advanced expertise and specialized instruments [21, 22].

More recently, innovative endoscopic techniques have been reported. Submucosal tunneling with bidirectional full-thickness resection has enabled successful removal of small exophytic gastric GISTs, achieving R0 resection without complications and durable control at 21-month follow-up [23].

Greater curvature and fundus

Larger tumors located on the greater curvature or fundus are typically managed via sleeve resection (Fig. 2a, b, c), whereas the smaller ones can be removed by wedge resection (Fig. 3). This is the most common and well-validated procedure, with series reporting disease-free survival rates above 90% at three years [16, 24]. Wide margins are not required, but R0 resection must be ensured. Intraoperative gastroscopy can assist in confirming margins, and staplers should be applied longitudinally along the gastric axis to minimise luminal narrowing.

Giant gastric GISTs, although rare, may present with complications such as bowel obstruction or compression of adjacent structures. Cappellani et al. reported a 40 cm gastric GIST successfully managed by en bloc resection including sleeve gastrectomy, distal pancreatectomy, and splenectomy, followed by adjuvant imatinib, with long-term disease-free survival [25]. Similarly, Yeoh et al. described an 83-year-old patient with a 25 cm gastric GIST invading the transverse colon, who underwent distal gastrectomy with segmental colectomy. In this case, adjuvant imatinib was withheld due to advanced age, yet the patient recovered uneventfully [26]. These reports highlight that radical surgical resection remains the cornerstone of therapy even in giant gastric GISTs, while the use of targeted therapy should be tailored to patient characteristics. (Fig. 4).

Antrum (prepyloric region)

A small proportion of GISTs are found in the antrum or prepyloric region. These can be safely resected using the "cut-and-sew" technique. Wedge resections using a stapler for tumors larger than 3 cm in this area carry a risk of stenosis. If limited excision is not feasible, distal gastrectomy is the safest approach. The most crucial criterion for the proper approach is tumor size. Most authors agree that tumors larger than 10 cm require laparotomy.

Duodenum

GISTs of the duodenum are uncommon and no standardized surgical strategy exists due to their rarity and the complex regional anatomy. Management must therefore be individualized. The three main approaches are pancreaticoduodenectomy (PD), wedge resection, and segmental resection.

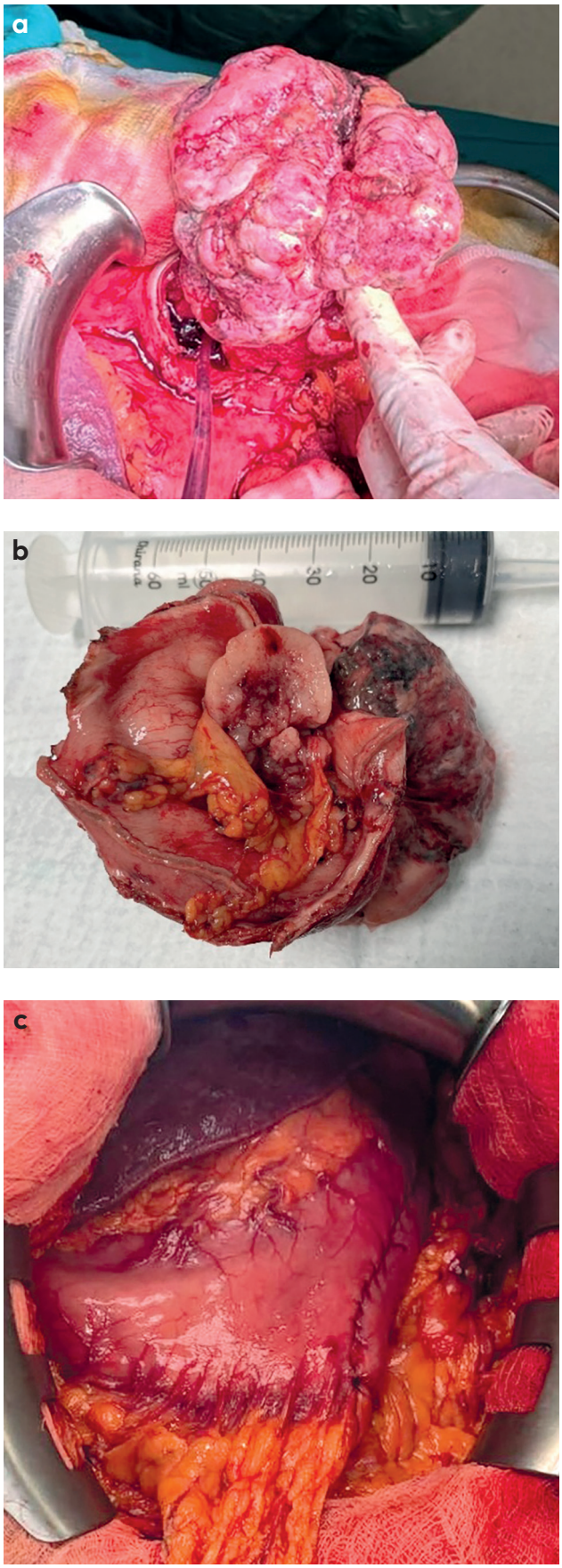

Figure 2. a, b, c. Intraoperative view of an endoluminal gastrointestinal stromal tumour, measuring 71×64 mm in axial dimensions, managed via sleeve resection.

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Although surgical resection remains the standard for duodenal GISTs, recent reports have shown that endoscopic full-thickness resection (FTR) with endoscopic suturing can be performed safely for small, well-selected lesions near the papilla, achieving complete en bloc removal without major complications [27].

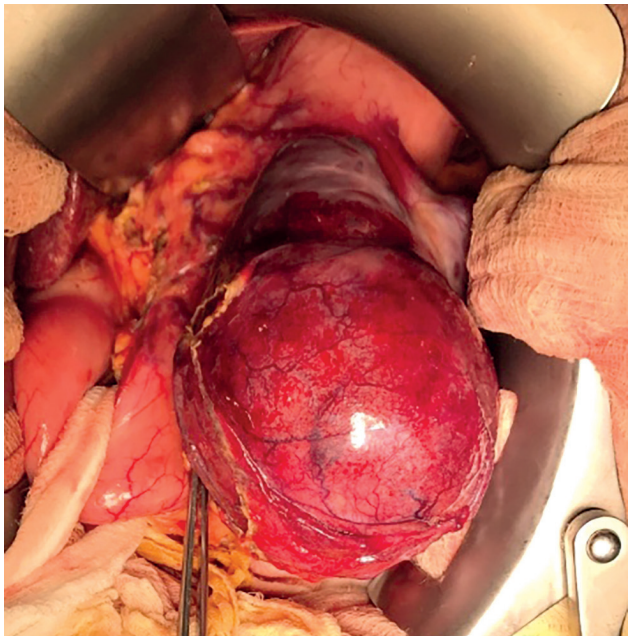

Figure 3. Intraoperative view of a rounded soft-tissue mass (GIST) with predominantly exophytic growth, visualised along the greater curvature, measuring 83 × 52 mm in axial dimensions..

Figure 4. Giant tumor of the fundus requiring gastrectomy with splenectomy.

PD is indicated when the papilla or pancreas is involved and is performed in up to 40% of cases [28, 29]. Although associated with higher morbidity and more extended hospital stay, several studies and a meta-analysis have shown no survival disadvantage compared with local resections [30, 31]. Patients undergoing PD typically present with larger tumors and higher mitotic indices.

The challenges largely stem from the close relationship of the duodenum to the pancreas, ampulla, and major mesenteric vessels [32]. Local resections should be tailored to tumor site, with meticulous technique to avoid rupture, which carries a near-certain risk of recurrence [33].

Laparoscopic resections, including segmental duodenectomy with duodenojejunostomy, have been reported as safe and comparable to open procedures in selected patients [34, 35].

Robotic-assisted resections of duodenal GISTs have also been reported, including wedge and segmental resections with duodenojejunostomy [36]. While most wedge or segmental resections are technically feasible, they carry risks of serious complications such as pancreatitis, fistula, bleeding, and anastomotic stenosis [29]. The challenges largely stem from the close relation of the duodenum to the pancreas, ampulla, and major mesenteric vessels.

Small intestine

The small intestine is the second most frequent site of GISTs. In an extensive series of 906 patients with jejunal and ileal tumors, the reported mortality was 39%, nearly twice that of gastric GISTs [37]. Patients often present with bleeding, and up to one-third require emergency surgery for haemorrhage or perforation [38]. Segmental resection without lymphadenectomy is the standard approach. Exceptions include large tumours near the duodenojejunal junction, where resection may require stapling at the ligament of Treitz with reconstruction by latero-lateral duodenojejunostomy (Fig. 5a, b).

Many small bowel GISTs are first suspected during evaluation for anaemia. In a series of 5,200 patients undergoing capsule endoscopy, GIST was the most frequent tumor identified (32%) [39]. However, capsule endoscopy has important limitations: it does not permit biopsy, lacks precise localization, and may miss extraluminal lesions. Double-balloon enteroscopy is considered superior, as it allows biopsy to exclude other diagnoses and tattooing to facilitate intraoperative localization [40]. A combined approach of double-balloon enteroscopy and laparoscopic-assisted resection appears optimal for small jejunal and ileal tumors. Larger lesions (>5 cm), especially those near the duodenojejunal junction, are generally best managed through open surgery.

Colon

Fewer than 5% of GISTs occur in the colon, and published data on this topic are limited. Patients typically present with a palpable mass causing pain or bleeding. CT usually

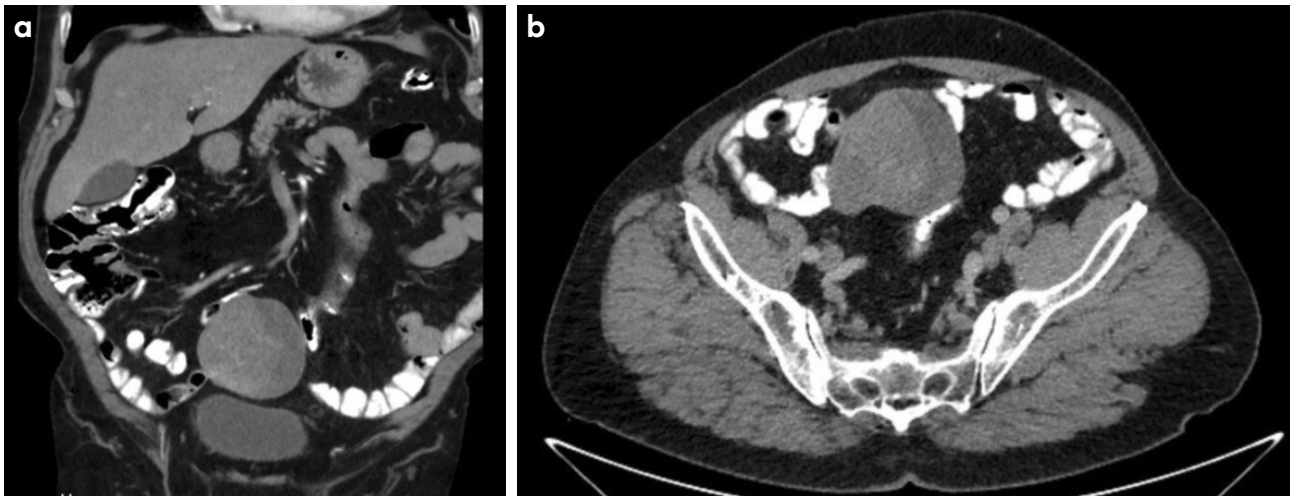

Figure 5. a, b. Sagittal and transverse computed tomography scans of a 67-year-old woman showing a 5 × 6-cm gastrointestinal stromal tumour (arrows) with origin from the jejunal wall, closely related to but not infiltrating the mesentery.

reveals a large, lobulated lesion with necrosis or haemorrhage, and diagnosis is confirmed by colonoscopic biopsy. Segmental colectomy without lymphadenectomy is the standard surgical approach, as these tumors generally displace rather than infiltrate adjacent structures. Prognosis remains poor, particularly for tumors with high mitotic activity, which historically carried a median survival of less than two years [41].

Rectum

The rectum is the third most common site of GISTs, accounting for 5–10% of cases [42]. Patients usually present with perineal pain or bleeding. Rectal GISTs carry a high risk of incomplete (R1) resection and locoregional recurrence, even after extensive procedures [43]. Since nodal spread does not occur, lymphadenectomy is unnecessary.

For small tumors (<3 cm) without an extrarectal component, transanal excision is increasingly employed. Larger lesions or those involving adjacent structures are better managed by alternative approaches such as transsacral resection, which provides good exposure while avoiding laparotomy and preserving urogenital function [44].

Large extrarectal or anterior wall tumors may mimic prostatic lesions. The high rate of misdiagnosis underscores the importance of c-kit immunohistochemistry [45, 46]. Neoadjuvant imatinib is valuable in downsizing rectal or anal sphincter–involving tumors, potentially reducing surgical morbidity.

Metastatic GIST

Around 40% of patients relapse after primary resection, most often with liver or peritoneal metastases. Before the introduction of imatinib, the median survival was 19 months, with a 5-year survival rate of only 25% [47]. Since 2002, Imatinib has become a standard of care, producing high initial response rates. Its effectiveness, however, is limited by secondary resistance due to additional KIT mutations [48].

Neither surgery nor imatinib alone is sufficient; a multimodal strategy is required. Several series report that in patients responding to imatinib, surgery can achieve complete macroscopic resection in >80% of cases, whereas in resistant disease this is <50% [49, 50]. The optimal timing is considered 6-9 months after therapy initiation, once tumors become resectable. However, these favourable results are based on highly selected cohorts from specialised centres. For most patients with disseminated liver or peritoneal disease, a radical surgical approach remains unfeasible.

Conclusion

The radical surgical resection remains the only curative treatment for localised GIST. The operative strategy should be tailored to the tumour size, location, and resectability. Minimally invasive approaches are appropriate for small, favourably located tumors. In contrast, larger or anatomically complex lesions, particularly those involving the gastroesophageal junction, the second portion of the duodenum, or the distal rectum, usually require open surgery, sometimes in collaboration with thoracic or colorectal surgeons. The avoidance of intraoperative rupture is paramount to avoid the iatrogenic dissemination. In metastatic disease, the surgery may offer additional benefit in carefully selected patients tyrosine kinase inhibitor–responsive tumors after downstaging chemotherapy

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

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Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

No use of AI was reported.

Funding

No funding was reported.

Author contributions

Conceptualization: MT, PD, GP; Data curation: PD, VI. Formal analysis: PD; Investigation: PD; Methodology: MT. Project administration: GP, KK; Resources: VI, KK; Supervision: MT, KK; Visualization: VI; Writing - original draft: PD; Writing - review and editing: GP.

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Data availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

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