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Tailored Management of Primary Gastrointestinal Stromal Tumors

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Abstract

Gastrointestinal Stromal Tumor (GIST) is the most common human sarcoma, and can form along the entire GI tract. Over the last 20 years, considerable advances have been made in our understanding of the biology of GIST. The advent of tyrosine kinase inhibitors has provided effective medical therapy for the first time. In fact, given that GIST typically is driven by either a *KIT* or *PDGFRA* gene mutation, it has become a paradigm of targeted molecular therapy. In addition, diagnostic and surgical techniques have been refined. Here, we summarize the critical aspects of primary GIST and how it is now managed with an integrated approach. Treatment plans are developed based on specific pathologic and molecular features of the tumor. We outline the general principles of therapy and highlight some of the nuances. Particular focus is given to diagnosis, surgical considerations, and use of preoperative and postoperative tyrosine kinase inhibitors.

Precis:

The multidisciplinary management of primary gastrointestinal stromal tumor has evolved considerably over the last 20 years. Here, we review the surgical and medical considerations.

Keywords

Gastrointestinal stromal tumor; Imatinib; Surgery; primary; adjuvant

Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms with variable malignant potential that can form along the entire length of the gastrointestinal (GI) tract, including some extra-intestinal sites. They are thought to arise from the interstitial cells of

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Conflicts of Interest Statement:
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Cajal, smooth muscle-derived pacemaker cells in the wall of the luminal GI tract.[1] GIST is the most common human sarcoma subtype,[2] but has only been recognized as a distinct entity since the late 20th century.[3] In the late 1990s, GISTs were shown to highly express mutated oncogenic forms of KIT, a receptor tyrosine kinase (RTK) protein responsible for cell survival and proliferation.[4, 5] This discovery ignited a rapid expansion of knowledge and literature on GIST for the past two decades. Most (70–80%) of GISTs contain mutations in *KIT*, but about 10% contain mutations in *PDGFRA* (the gene for platelet-derived growth factor receptor alpha, another RTK),[6] and the remaining 10% has defects in succinate dehydrogenase or a mutation in *BRAF* or other oncogenes.[7] The most common tumor location is the stomach (50–70%), followed by small intestine (25–35%), rectum (5–10%), and esophagus (<5%).[8] GISTs are extraordinarily rare in the colon. Extra-intestinal GISTs (~6%) are found most commonly in the omentum, but can also arise in the mesentery or retroperitoneum. The most common sites of metastasis are the liver and peritoneum.[9] GISTs are diagnosed by morphology and immunohistochemical staining for the KIT receptor (CD117) and DOG1, a highly expressed chloride channel protein.[10]

Imatinib mesylate (IM) is a small molecule tyrosine kinase inhibitor (TKI) that is active against most mutated forms of KIT and PDGFRα oncoproteins. IM has prolonged 5-year overall survival in advanced GIST from a historical 16–19 months[9, 11, 12] to 5 years.[13–17] IM is the first line therapy for advanced GIST. Sunitinib and regorafenib are multikinase inhibitors that are FDA-approved for IM resistance or intolerance.[18, 19]

How do patients typically present?

GISTs are discovered in a variety of ways. About 70% of patients have symptoms. The remainder have incidental findings on imaging, endoscopy, or during surgery for other conditions. Patients can have intraluminal bleeding that ranges from occult to massive. Tumor rupture can result in an acute abdomen with or without massive bleeding, necessitating an emergency operation. Some patients have vague abdominal pain or are found to have a palpable abdominal mass. Rarely, GISTs may erode into the gastrointestinal tract with the subsequently infected tumor resulting in fever. Strangely, intestinal obstruction almost never occurs in primary GIST.

Is preoperative tissue confirmation mandatory?

Proving the diagnosis of GIST preoperatively is recommended but can be problematic. Cross-sectional imaging may be highly suggestive of GIST. We prefer to use computed tomography (CT) with oral and intravenous contrast of the abdomen and pelvis. The classic features of GIST are an enhancing mass arising from the wall of the GI tract with exophytic or endophytic extension (Figure 1).[20] Air-fluid levels indicate the presence of a fistula with the lumen of the GI tract (Figure 1A). Magnetic resonance imaging (MRI) scan is an alternative to CT. It is preferable for defining the anatomy in rectal GIST, slightly better at detecting and characterizing small liver lesions, but less sensitive in demonstrating peritoneal metastasis. PET scans are almost never necessary.

A tissue diagnosis can be obtained with an endoscopic or percutaneous biopsy. The feasibility of these techniques depends on the tumor location and operator skill. Endoscopy

for esophageal, gastric, proximal small intestinal, and rectal GISTs will typically reveal a submucosal mass with normal overlying mucosa (unless ulceration has occurred) and well-defined margins. Endoscopic ultrasonography (EUS) provides further clarification, showing a hypoechoic lesion that most commonly arises from the muscularis propria layer. EUS-guided fine needle aspiration or core biopsy may not yield a definitive diagnosis as there may be no actual tumor tissue or only enough to conclude that spindle cells are present, which could represent GIST or leiomyoma. Percutaneous fine needle aspiration or biopsy is reserved for masses not reachable by endoscopy, but this approach has a small risk for hemorrhage or perforation. In patients without histologic proof of a GIST, especially those who have already undergone an inconclusive biopsy, we do not necessarily pursue another biopsy if the radiographic features are highly suggestive of GIST. The patient is counseled about the possibility of a "GIST masquerade", such as schwannoma, leiomyoma, leiomyosarcoma, synovial sarcoma, or even ectopic pancreas.

When should neoadjuvant therapy be used?

Several factors contribute to decision-making for a patient with a proven or suspected GIST (Figure 2). The first priority is to stage the patient with cross-sectional imaging to identify the presence of metastases, which would lead to IM therapy and then surgery in the future only if all the tumor could be removed. (Note: Metastatic disease would mandate lifelong medical therapy and is not the focus of this review.) Gastric tumors less than 2 cm in diameter can be observed.[21] For tumors 2 cm or greater, the patient is taken directly to surgery unless sacrifice of a lot of normal tissue is necessary because of large tumor size or difficult location.[22]

If neoadjuvant therapy is being considered it is generally standard practice to confirm the diagnosis via biopsy. Some institutions can even perform a tumor mutation analysis on small samples, although this usually takes several weeks. We generally perform a CT scan 2–3 weeks after starting IM to assess tumor response. A reduction in tumor density *or* size indicates response, as defined by the Choi criteria.[23] If the tumor has responded, we generally obtain the next scan 4 months later and operate between 6–9 months on IM, the time of maximal tumor shrinkage. IM can be safely continued up until the day before operation. If the tumor has grown on the early scan after IM initiation, the diagnosis may be incorrect or the specific GIST mutation may not be sensitive. Additional pathologic analysis of the biopsy may be indicated.

There have been a number of single-arm and non-controlled clinical trials demonstrating the safety and feasibility of neoadjuvant IM.[24, 25] However, whether it improves the rate of R0 resection or overall survival is not proven. IM can be useful to arrest slow intraluminal bleeding. It is clear that responsive tumors have much less blood flow and usually reduced tumor size, rendering surgery easier to perform. This is particularly relevant in challenging anatomic locations. Reducing the size of a tumor at the gastroesophageal junction can convert a total gastrectomy to a local resection with primary closure. Downsizing of a duodenal GIST near the ampulla may avoid the need for pancreatoduodenectomy. GISTs at the duodenal/jejunal junction (Figure 1A) are typically close to the superior mesenteric artery and tumor shrinkage is often desirable. Neoadjuvant IM can facilitate sphincter

preservation in certain rectal GISTs. Indeed, patients with GISTs in all of these sites have been commonly selected for neoadjuvant treatment in retrospective series.[26–28]

The current recommendation for those at moderate to high risk of recurrence is 3 years of adjuvant therapy, whether neoadjuvant therapy was used or not. The problem is that in many patients, risk cannot be fully evaluated since pre-treatment mitotic rate is often not available. The large, multi-institutional experiences suggest that 1–3 years of adjuvant therapy after neoadjuvant IM is safe and replicates the standard of RFS seen in the randomized trials of adjuvant IM. [25, 29, 30] With the emergence of data supporting increasingly longer durations of TKI therapy in the adjuvant setting, we may ultimately find that chronic adjuvant therapy is indicated for some patients who received neoadjuvant therapy.[31]

As our familiarity with specific primary *KIT* and *PDGFRA* mutations increases and preoperative tumor sequencing becomes faster and more widespread, neoadjuvant therapy will become more precise. For instance, though the most common *KIT* exon 11 mutants will respond to IM, *PDGFRA D842V* mutation is resistant to IM, *KIT* exon 9 mutations may respond better to higher doses of IM,[32, 33] and *SDH* and *NF1* mutations do not respond to TKIs. Primary *KIT* exon 13 and 14 mutations are rare and data is lacking, however it is known that secondary exon 13 and 14 mutations exhibit IM resistance and respond better to sunitinib.[34]

What are the fundamentals of GIST surgery?

There are several specific considerations in GIST surgery. Foremost, the tumors are soft and friable compared to adenocarcinomas and therefore easy to rupture, which risks peritoneal dissemination. Tumor rupture is an independent predictor of poor prognosis.[35, 36] Meticulous dissection is necessary as GISTs are particularly vascular tumors and prone to bleed during resection. It is rare for GISTs to grow into adjacent structures, but rather they tend to push them aside. However, if a GIST is adherent to a nearby structure, the involved tissue should be removed en bloc. GISTs rarely metastasize to lymph nodes, so routine lymphadenectomy is unnecessary. However, when nearby nodes are enlarged, they should be removed and alternative diagnoses should be considered. The exception to this rule is patients with SDH-deficient GIST, who commonly have nodal metastasis.[7]

The optimal margin of tumor resection in GIST is not well defined. Since GISTs do not tend to spread submucosally, a grossly negative margin is generally sufficient and a 1 cm margin should be adequate. The prognostic impact of an R1 (microscopically positive) resection was unclear in the pre-IM era.[9, 37] The American College of Surgeons Oncology Group (ACOSOG) Z9000 and Z9001 trials of adjuvant IM failed to show a significant effect of R1 resection on recurrence-free survival (RFS).[36] It should be pointed out that true local recurrence is rare in GIST. Instead, peritoneal metastasis occurs. In the setting of an R1 resection, a discussion with the pathologist should take place since the resection edges can retract after surgery or staple lines are removed during tumor processing, which can make an initially negative margin appear either grossly or microscopically involved. Ultimately, the management of a patient with an R1 resection should involve a multidisciplinary approach with discussion of patient-specific risk factors and consideration of the risks of reoperation versus watchful waiting or IM therapy.

When should minimally invasive surgery be performed?

Laparoscopy is indicated for diagnosis and resection of smaller GISTs. We performed a size-matched comparison and found that laparoscopic resection was oncologically safe.[38] In contrast, the limited published series of endoscopic resection for small GISTs have mixed results with perforation rates up to 13%.[39] There are insufficient data to recommend routine endoscopic resection at this time. However, endoscopy can be helpful during a laparoscopic operation to facilitate identification of small, endophytic GISTs that may not be otherwise readily apparent at laparoscopy.[40]

What are the technical considerations for specific resections?

Because GISTs occur in diverse locations, the surgeon has to be familiar with a variety of techniques. GISTs arise most frequently in the stomach. Laparoscopic resection is favored for small to medium-sized gastric GISTs, especially those that are exophytic. Small tumors that grow endophytically may require concomitant intraoperative endoscopy. Posterior tumors are more difficult to remove as they may require extensive mobilization of the stomach, which may include division of the greater omentum and preservation of the gastroepiploic arteries to enter the lesser sac. Sometimes, the short gastric arteries must be sacrificed. Partial gastrectomy can often be achieved with surgical staplers, taking care to avoid narrowing the gastric lumen. A majority of the time a formal anatomic gastrectomy is not required, even for proximal tumors. We prefer an open approach for tumors near the gastroesophageal junction (Figure 1B). If there is concern about gastric lumen compromise, a gastrotomy can be made and the GIST is resected with a 1cm radial margin circumferentially with cautery. Although some patients present with massive gastric tumors, total gastrectomy is rarely required if neoadjuvant IM is utilized (Figure 1C, D). Preoperative discussion should include the possibility of total gastrectomy for certain tumors and also include the potential for removing nearby organs if they are attached to the tumor, such as the distal pancreas, spleen, or splenic flexure of the colon.

Many small bowel GISTs of the jejunum and ileum can be removed laparoscopically with an approach that emphasizes segmental resection with minimal direct handling of the tumor. The tumor is identified by laparoscopically running the small bowel from the ligament of Treitz to the ileocecal junction. Large tumors should be removed via an open approach to minimize risk of rupture. Duodenal GISTs are more complex and their management depends on which portion of the duodenum is affected. Periampullary tumors of the second portion may be treated with neoadjuvant IM but may still require pancreatoduodenectomy due to their medial location, whereas those of the lateral duodenal wall, if small or exophytic enough, may be resected locally with either primary closure or Roux-en-Y reconstruction using an isoperistaltic duodenojejunostomy.[28] Large tumors of the more distal duodenum/proximal jejunum may be in close proximity to the SMA and neoadjuvant IM may be of benefit (Fig. 1A).

Rectal GISTs can be particularly challenging. Typically, neoadjuvant IM is employed to facilitate a sphincter-preserving operation and avoid an abdominoperineal resection and permanent end-colostomy. A full thickness resection of the rectal wall is desirable and may sometimes be performed via the transanal approach if distal enough.[27]

There are also select mutation-specific surgical considerations. *SDH*-deficient[41] and *NF1*[42] associated GIST can both present as multifocal disease, and their management is not well defined. These tumors have malignant potential, but because of their multifocality the role of surgical resection must be balanced with the extent of potential tissue loss and potential long-term surgical morbidity. Therefore, surgery is often indicated when, on surveillance imaging, one or a few tumors are found to be growing faster than the others, or have become symptomatic. For example, partial gastrectomy may be performed for a dominant tumor in favor of total gastrectomy, leaving other smaller, indolent tumors in situ. Also, as noted above, regional lymphadenectomy should be performed for *SDH*-deficient GISTs, due to their ability to metastasize to lymph nodes.

How is the risk of recurrence determined?

It should be emphasized that we now know that over 70% of patients with primary GIST are cured by surgery alone, as demonstrated by the ACOSOG Z9001 placebo arm.[43] Prognosis after resection of a primary, localized GIST depends on tumor size, location, and mitotic rate. There are 2 main prognostic systems based on these variables. Miettinen and Lasota originally used mitotic rate (>5 or ≤5 mitoses per 50 hpf), tumor size (cutoffs of 2cm, 5cm and 10cm), and tumor location (stomach is more favorable than small intestine or rectum).[21, 44] Subsequently, we created an online nomogram to estimate 2- and 5- year RFS after resection (http://www.mskcc.org/mskcc/html/98103.cfm).[45] The nomogram has been validated by others.[46, 47] The Miettinen criteria are the basis for the most recent version of the American Join Commission on Cancer (AJCC) Staging system, which incorporates mitotic rate and anatomic location into their standard TNM system.[48]

Mutation status of the primary tumor should also be considered in assessing patient prognosis. In the pre-IM era, patients did worse if their tumor had a *KIT* exon 11 deletion or insertion versus a point mutation.[49] Moreover, deletions specific to KIT amino acids 557 and 558 indicated poor prognosis.[50, 51] However, there is less clarity regarding the impact of these mutations in the IM era. One analysis of the Scandinavian Sarcoma Group XVIII (SSGXVIII) multicenter clinical trial concluded that the *KIT* exon 11 deletions were associated with poorer RFS in patients treated with 1 year of IM, but that effect was ameliorated with 3 years of treatment.[52] Additionally, ACOSOG Z9001 data determined that exon 11 deletions were associated with improved RFS in the 1 year IM arm, compared to placebo.[53] Less common *KIT* exon mutation sites include exons 9, 13, 14, and 17. Exon 9 mutations may respond better to higher doses of IM in metastatic GIST,[33] but there are inadequate data for this in the adjuvant setting. Primary mutations in exons 13 and 14 are rare, though they may still respond to IM treatment. However, secondary mutations in exons 13, 14, and 17 are usually responsible for IM resistance[54] and heightened awareness of this fact should guide surveillance practice and transition to sunitinib or another appropriate TKI upon progression. Of note, the D842V subset of *PDGFRA* mutant GISTs is resistant to IM therapy. GISTs without mutations in *KIT* or *PDGFRA* are unlikely to benefit from adjuvant IM therapy. Lastly, the Complexity Index in Sarcoma (CINSARC) profile of 67 genes related to chromosome integrity, mitotic control, and genome complexity has been applied to GIST and was shown to further help stratify patients of intermediate risk.[55]

Adjuvant Therapy – Who, why, and how long?

While it is now clear that adjuvant IM increases RFS in patients with intermediate or high-risk primary GIST (Table 1), the optimal duration of treatment is unclear. ACOSOG Z9001, a phase 3 randomized placebo controlled trial of adjuvant IM versus placebo in patients with complete gross removal of GISTs ≥3cm showed prolonged RFS for IM compared to placebo with a median follow-up of 19.7 months, which led to FDA and European Medicines Agency approval for adjuvant IM in GIST.[43] Subsequent long term follow-up (median of 74 months) showed persistently prolonged RFS, even though many patients in the placebo arm did not experience recurrence.[56] However, patients in the treatment arm only received 1 year of adjuvant IM, and some developed recurrence after drug discontinuation.

The SSG XVIII trial, a large Scandinavian prospective randomized phase 3 trial demonstrated superior RFS with three years of adjuvant IM compared to one year. There was significant improvement in overall survival (OS), but not disease-specific survival (DSS).[57, 58] Another European trial by the EORTC randomized 2 years of adjuvant IM versus observation in intermediate or high-risk GIST and evaluated time to IM resistance, finding that in high risk patients there was improved RFS in the IM arm but no difference in IM failure-free survival.[59] The PERSIST-5 trial, a phase 2 study of five years of adjuvant IM therapy was recently reported. It showed that no patient with an IM-sensitive mutation had a tumor recurrence while on IM, but 49% of patients stopped treatment early, mostly due to patient choice rather than adverse events.[31]

Our practice is to clarify the goals of adjuvant IM with intermediate and high-risk patients. There is no doubt that RFS is prolonged. Since recurrence can develop in some patients after IM is stopped at 1 or 3 years, chronic therapy (>5 years) may be indicated for select patients. One example is patients with intraoperative tumor rupture. These GISTs, regardless of tumor location, fall into a high-risk category.[60] These patients should generally be considered to have metastatic disease[61] and therefore treated with chronic IM.

Whether adjuvant IM increases DSS has not been proven. DSS may not be altered since patients are followed closely with serial radiologic scans, resulting in recurrence usually being detected when there is minimal disease that usually responds to initiation of IM. The potential benefits of prolonged RFS have to be balanced against the side effects and cost of the drug. IM is generally well tolerated, but it can be associated with nausea/vomiting, edema of the face, hands and feet, diarrhea, skin rashes, and fever, many of which subside with time. Dose reduction is required in some patients.

There are additionally some mutation-specific considerations to bear in mind when prescribing adjuvant IM. Although patients with a *KIT* exon 9 mutation may benefit from a higher IM dose (i.e., 800 mg daily) in the metastatic setting, there are no data in the adjuvant setting and so 400 mg daily is recommended. *PDGFRA* D842V-mutant GISTs are resistant to IM, as are those with SDH-deficient or NF1 related GISTs, and so adjuvant IM is not used. There are newer targeted therapies emerging for some of these IM resistant primary mutations, though no formal treatment guidelines exist yet.

Conclusions and Future Directions.

The management of primary localized GIST has evolved significantly over the past 2 decades, and now there is an excellent understanding of patient presentation, diagnostic methods, surgical and anatomic considerations, prognostication, and role for neoadjuvant and adjuvant therapy. Nevertheless, there is still room for improvement. Novel RTKs are being developed to treat IM-resistant mutations. Other approaches may include immunotherapy, or combination therapies, with the ultimate goal of eradicating residual, microscopic disease. New advances will lead to further personalization of therapy.

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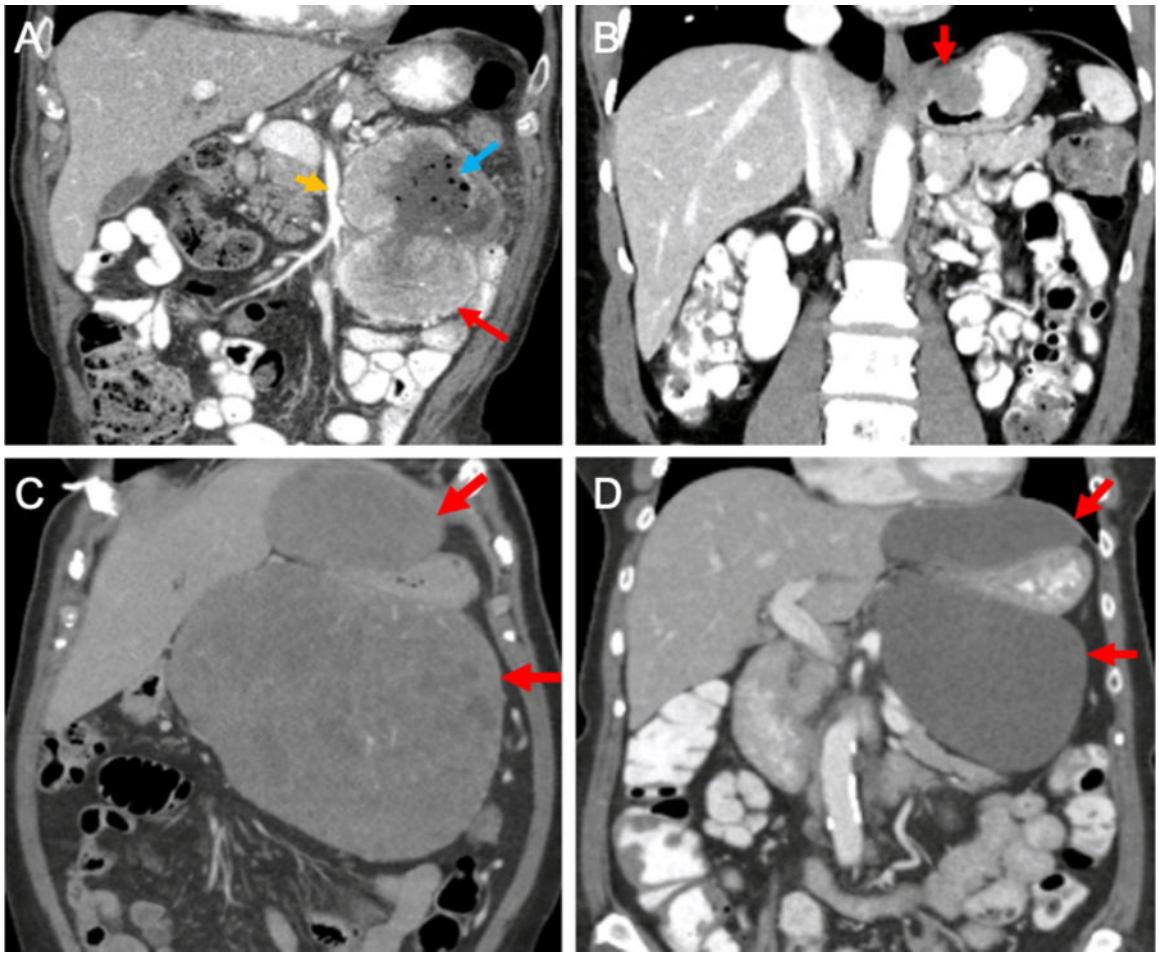

Figure 1 - Examples of primary GISTs.

(A) Coronal CT image of a proximal jejunal GIST (red arrow) near the superior mesenteric artery (orange arrow). Note the air bubbles within the tumor (blue arrow), indicating the existence of a sinus tract between the bowel and the tumor. (B) Coronal CT image of a GIST (red arrow) located at the gastroesophageal junction. (C&D) Coronal CT images of a massive gastric GIST (C) before and (D) after 6 months of neoadjuvant imatinib. Red arrows indicate the bilobed tumor surrounding the stomach. Note the decreased density of the tumor after therapy. At operation, the tumor arose from the gastric cardia and was removed with splenectomy and a limited partial gastrectomy. CT – computed tomography

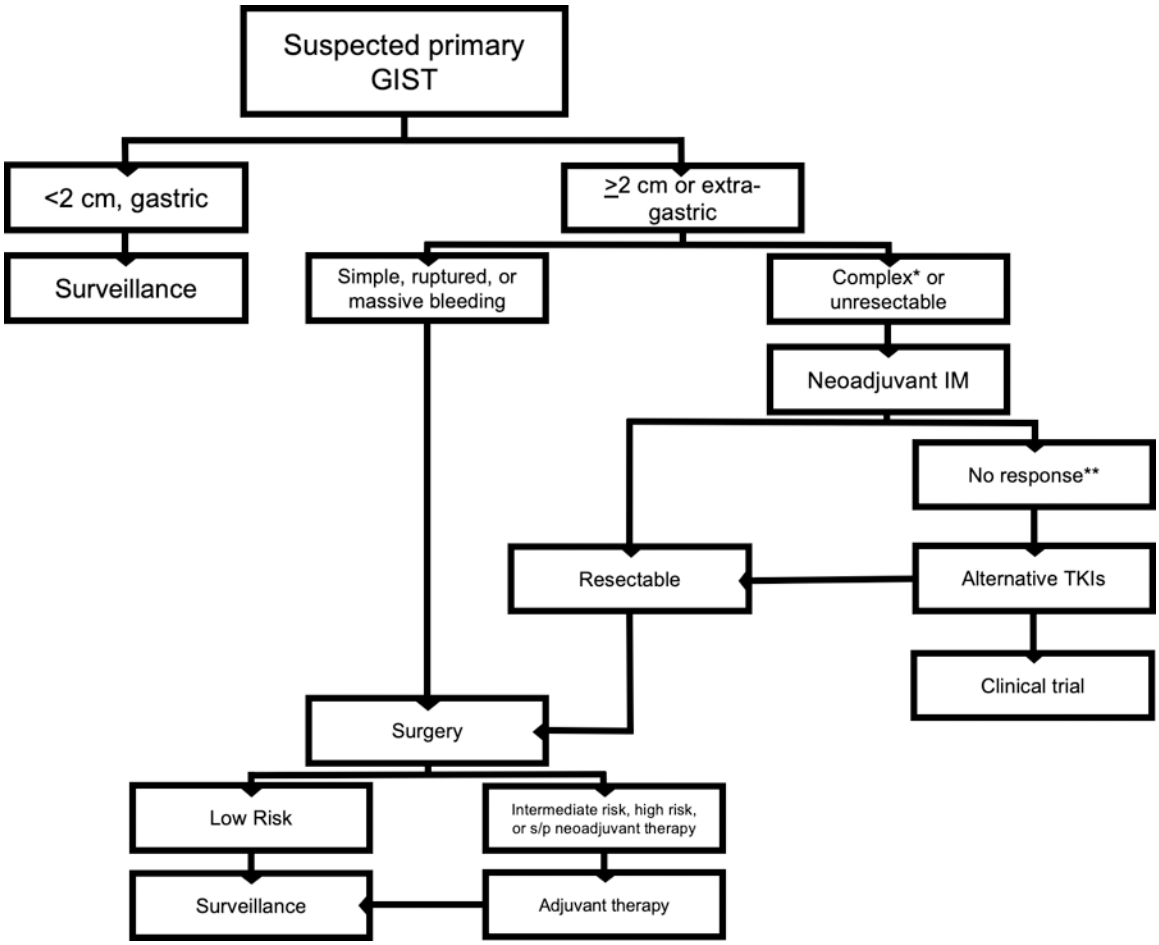

Figure 2 - Management of primary GIST.

*requiring multivisceral resection due to technically challenging location or massive size

**for complex but resectable tumors that do not respond to neoadjuvant IM, one can alternatively proceed directly to surgery IM – imatinib mesylate; TKI – tyrosine kinase inhibitor

Table 1 –

Summary of adjuvant imatinib trials in primary GIST.

Trial	Phase	Entry Criteria	Treatment Dose/Duration	Relevant Findings
ACOSOG Z9001[51]	III	Tumor ≥ 3cm	400 mg daily for 1 year vs placebo	1-year RFS 98% vs 83% No difference in OS
SSG XVIII[52, 53]	III	High-risk tumor	400 mg daily for 1 year vs 3 years	3-year RFS 73% vs 55% 3-year OS 92% vs 85% 3-year DSS 95% vs 89%¶
EORTC 62024[54]	III	Intermediate and high-risk tumor	400 mg daily for 2 years vs no treatment	5-year IFFS 87% vs 84%¶ 3-year RFS 84 vs 66% 5-year RFS 69% vs 63%
PERSIST-5[55]	II	Intermediate or high-risk tumor	400 mg daily for 5 years	5-year RFS 90% 5-year OS 95% 50% in treatment arm discontinued imatinib

¶These findings were not statistically significant. ACOSOG, American College of Surgeons Oncology Group; EORTC, European Organization for the Research and Treatment of Cancer; SSG, Scandinavian Sarcoma Group; PERSIST-5, Postresection Evaluation of Recurrence-free Survival for Gastrointestinal Stromal Tumors With 5 Years of Adjuvant Imatinib; RFS, Recurrence Free Survival; OS, Overall Survival; IFFS, Imatinib-Failure Free Survival