





Neoadjuvant and adjuvant therapy for gastrointestinal stromal tumors

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Abstract

Gastrointestinal stromal tumors (GIST) are rare and mesenchymal in origin with a yearly incidence of 10-15 cases per million people. If it is technically resectable, surgical resection is the mainstay of therapy regardless of tumor location. Although complete (R0) resection can be achieved in up to 85% of patients with primary disease, approximately 50% of patients experience recurrence or metastases within 5 years of primary resection. Moreover, prior to 2000, the prognosis of patients with advanced, inoperable GIST was poor because the molecular mechanism had not sufficiently been elucidated, thus effective therapy was lacking. The tyrosine kinase inhibitor imatinib, which selectively inhibits tyrosine kinase KIT, has shown substantial clinical benefit for patients with GIST. In clinical trials, imatinib treatment resulted in response rates of 40%-55% and longer progression-free survival for patients with a KIT-positive unresectable or metastatic GIST. Furthermore, recent clinical trials have shown that giving imatinib after curative resection for high-risk cases prolonged recurrence-free survival and overall survival in an adjuvant setting. Several clinical trials of imatinib treatment in a neoadjuvant setting are ongoing; however, in clinical settings, there are problems to resolve, such as optimal agents, duration of administration, and postoperative management. In this review, we discuss the application of surgical options, combined with adjuvant/neoadjuvant or perioperative imatinib treatment and their potential impact on survival for patients with primary, recurrent, or metastatic GIST.

KEYWORDS

adjuvant, GIST, imatinib, neoadjuvant

1 | INTRODUCTION

Gastrointestinal stromal tumors (GIST) are rare and mesenchymal in origin that are derived from the interstitial cells of Cajal in the gastrointestinal tract.¹ With a yearly incidence of 10-15 cases per

million people, GIST are the most common sarcomas of the intestinal tract, accounting for approximately 80% of all gastrointestinal mesenchymal neoplasms.² Prior to 2000, there was no effective therapy for unresectable or metastatic GIST, because the molecular mechanisms of GIST development were not well understood. A significant

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breakthrough was achieved with the identification of the expression of the CD117 antigen, which is part of the KIT transmembrane receptor tyrosine kinase (RTK).³ Approximately 80% of GIST have *KIT* gene mutations that lead to constitutive activation of the KIT receptor.³⁻⁵ Therefore, targeted therapy with imatinib, which is a small-molecule inhibitor of RTK that was originally approved for the treatment of chronic myeloid leukemia, induced dramatic, rapid, and sustained clinical improvement in patients with GIST.⁶ Many clinical trials have subsequently been conducted to confirm the utility of imatinib for patients with metastatic or unresectable GIST, leading to an improved prognosis for these patients.

For patients with a primary localized GIST, complete resection with negative microscopic margins remains the mainstay of therapy and should be the initial therapy if the tumor is technically resectable.^{7,8} However, about half of patients who had a curative complete resection subsequently experienced recurrence after several years.⁹ However, the precise factors responsible for malignant progression and aggressive clinical behavior have been debated for years.¹⁰ Several risk classifications have been established, which include tumor size, mitotic index, tumor location, and presence of tumor rupture.^{11,12} Most recently, a nomogram was developed to predict recurrence after surgery to help guide patient selection for adjuvant therapy.¹³ To improve the prognosis for patients with a high risk of recurrence after curative surgery, for several years, attempts to use imatinib perioperatively have been made based on the success of this agent in advanced or metastatic GIST. Although these multidisciplinary treatments can improve the prognosis of patients with advanced or high-risk GIST, in the clinical setting, there are several problems to resolve.

In the present review, we update and discuss recent progress in the perioperative use of imatinib and other agents for localized GIST. These new data improve our understanding of the multidisciplinary approach for treating advanced and localized GIST. This new information may lead to development of novel clinical targets and improve clinical management of GIST patients.

2 | GENERAL SURGICAL PRINCIPLES

For a resectable GIST (as confirmed by histological examination), surgical resection is the mainstay of therapy regardless of tumor location. The goal of surgery is to remove the tumor macroscopically with an intact pseudocapsule. Lymph node dissection is routinely unnecessary because lymph node metastases are extremely rare. Organ-preserving and function-preserving surgery is oncologically allowed if negative resection margins can be achieved. Bischof et al demonstrated recently that a laparoscopic approach for gastric GIST was associated with low morbidity and a high rate of R0 resection, and the long-term oncological outcome was acceptable. Therefore, they recommended that a laparoscopic approach should be the preferred approach for gastric GIST in well-selected patients.¹⁴ However, it remains unclear whether this procedure is applicable for larger GIST and for GIST at other sites because the tumor should be handled carefully to avoid rupture, which markedly increases the risk

of disease recurrence. Therefore, laparoscopic resection for GIST should currently only be carried out by surgeons with expertise, and prospective studies are required to confirm the utility of the laparoscopic approach for GIST. Furthermore, even if complete resection is achieved for a larger tumor, the rate of recurrence increases with increasing size.¹⁵ Therefore, adjuvant therapy with imatinib is recommended, as discussed below. For patients with a very large localized GIST, which is considered unresectable without risk of unacceptable morbidity or functional deficit (so-called marginally resectable GIST), preoperative imatinib may be recommended. Preoperative imatinib treatment is also an option to facilitate organ- and function-preserving surgery because esophagectomy for esophageal GIST, pancreaticoduodenectomy for duodenal GIST, and abdominoperineal resection for rectal GIST may be invasive and impair quality of life. Although the goals of neoadjuvant therapy involving imatinib are to preserve organ function, to avoid tumor rupture and to reduce the risk of complication, evidence of safety and efficacy for preoperative imatinib treatment remains to be established.

3 | NEOADJUVANT THERAPY

The high response rate of advanced GIST to imatinib has made it possible to adapt imatinib to the neoadjuvant setting. It is expected that neoadjuvant therapy can achieve organ- or function-preserving surgery, avoid tumor rupture, and reduce postoperative complications. Furthermore, the shrinkage of tumors treated with imatinib permits conservative and less invasive R0 resection, especially for GIST located at the esophagogastric junction, and in the duodenum and rectum. However, as there are few clinical trials of neoadjuvant therapy for GIST, evidence of the efficacy of neoadjuvant therapy remains to be established (Table 1). NCCN guidelines state that neoadjuvant chemotherapy is considered if surgical morbidity could be reduced by downstaging the tumor.⁷ Furthermore, there are several important clinical concerns in the neoadjuvant setting, but not in the adjuvant setting.

3.1 | Clinical trials of neoadjuvant therapy

3.1.1 | Prospective study

The multicenter Radiation Therapy Oncology Group (RTOG) 0132/ American College of Radiology Imaging Network (ACRIN) 6665 trial is the only prospective phase II study yet conducted for neoadjuvant imatinib.¹⁶ Sixty-three patients with KIT-positive GIST were enrolled, including either primary GIST ≥ 5 cm or resectable recurrent or metastatic GIST ≥ 2 cm, who received preoperative imatinib (600 mg/day for 8-12 weeks). All patients received adjuvant imatinib for 2 years after surgery. Median follow-up period was 5.1 years. The 5-year progression-free survival and overall survival (OS) rates for localized GIST were 57% and 77%, respectively.¹⁷

Recently, a phase II study for a neoadjuvant setting for large gastric GIST was reported from Asia.¹⁸ Patients with a large gastric GIST (≥ 10 cm) received imatinib (400 mg/day) for 6-9 months before

TABLE 1 Clinical relevance of neoadjuvant treatment for GIST

Author	Journal	Year	Cases	Agent/Dose	Patients	Duration	Notes
Prospective study							
Eisenberg et al ¹⁶	J Surg Oncol	2009	63	Imatinib/600 mg	GIST (>5 cm)	8-12 wks	5-y PFS: 57%, 5-y OS: 77%
Wang et al ¹⁷	Ann Surg Oncol	2012					
Kurokawa et al ¹⁸	Br J Cancer	2017	53	Imatinib/400 mg	Gastric GIST (>10 cm)	6-9 mo	2-y OS: 89%
Retrospective study							
Rutkowski et al ¹⁹	Ann Surg Oncol	2012	161	Imatinib/400 mg	Locally advanced GIST	40 wks	5-y DFS: 65%, 5-y DSS: 95%
Tielen et al ²⁰	Eur J Surg Oncol	2013	57	Imatinib/400 mg	Locally advanced GIST	8 mo	5-y PFS: 77%, 5-y OS: 88%

DSS, disease-specific survival; GIST, gastrointestinal stromal tumor; OS, overall survival; PFS, progression-free survival.

surgery. Forty-six of 53 patients enrolled in this study completed at least 6 months of dosage. The response rate was 62%, and R0 resection was carried out in 91% of patients. The 2-year OS was 89%. These findings suggest that neoadjuvant imatinib therapy can be beneficial for larger gastric GIST. Operative morbidities of any grade occurred in nine (18%) patients (postoperative bleeding: 2, surgical site infection: 3, anastomotic leakage: 2, bowel obstruction: 1, pyloric stenosis: 1) without treatment-related deaths. However, this study was limited to gastric GIST in a single-arm non-randomized study with a short follow-up period; furthermore, mutation analysis was not carried out before imatinib treatment. Phase III trials are required to confirm the significance of neoadjuvant therapy for advanced GIST. We will discuss the neoadjuvant setting below.

3.1.2 | Retrospective study

Several retrospective studies of neoadjuvant therapy have been reported.^{19,20} However, few data are available for primary GIST in the neoadjuvant setting, because most of these studies included both primary and recurrent or metastatic resectable GIST. Recently, in a larger retrospective study, 161 patients with locally advanced GIST who received preoperative imatinib (400 mg daily) was reported.¹⁹ The primary tumor was located in the stomach (55%), rectum (20%), small intestine (11%), duodenum (10%), or esophagus (3%). Median duration of preoperative imatinib was 40 weeks. Although the rate of R0 resection was 83%, two cases had disease progression before surgery. Five-year disease-specific survival and disease-free survival rates were 95% and 65%, respectively. Only 56% of patients received imatinib after surgery for at least 1 year. The findings of this study suggested that neoadjuvant imatinib therapy was feasible and effective for locally advanced GIST. It is possible that the benefit from neoadjuvant therapy depends on tumor location. Neoadjuvant therapy can be beneficial for GIST located at the esophagogastric junction, duodenal, and rectum because complete resection for these tumors requires extensive organ disruption through esophagectomy, pancreatoduodenectomy, or abdominal perineal resection. For rectal GIST, in particular, several studies indicated the efficacy of neoadjuvant imatinib therapy. Jakob et al showed that the rate of the negative surgical margin in patients after neoadjuvant therapy was significantly higher than that in patients

without neoadjuvant therapy.²¹ Also, all patients with a positive surgical margin who experienced recurrence after surgery did not receive imatinib before surgery. Tielen et al also showed that complete resection was achieved in 77% of patients given preoperative imatinib for rectal GIST.²² Furthermore, sphincter-preserving surgery is achieved more often in patients who received imatinib, also leading to a reduction of local recurrence. Although Wilkinson et al also showed that neoadjuvant imatinib therapy can decrease both tumor size and mitotic activity,²³ suggesting that neoadjuvant therapy is a promising strategy for locally advanced GIST, a larger prospective study is required to resolve the clinical questions.

3.2 | Agents as neoadjuvant therapy

Only imatinib has been evaluated in previous studies. It remains unclear whether other agents including sunitinib and regorafenib are effective in the neoadjuvant setting as well as the adjuvant setting, although there is one case report using sunitinib as an active neoadjuvant therapy as a result of severe adverse events from imatinib.²⁴ Regarding the dose of imatinib, in the RTOG0132A/ACRIN6665 trial, 600 mg was given daily.¹⁶ Most retrospective studies of neoadjuvant therapy used a dose of 400 mg daily. However, in the European Society For Medical Oncology (ESMO) guidelines, 800 mg imatinib daily is recommended for KIT exon 9 mutation cases, based on the finding that cases with KIT exon 9 mutation have an inferior response to imatinib in metastatic disease.²⁵ Therefore, it is necessary to evaluate the optimal dose of imatinib as neoadjuvant therapy in the context of the safety of subsequent surgery.

The optimal duration of imatinib treatment also remains unclear. The best timing of surgery is the point of best response by the agent before secondary resistance to the agent is acquired. Median time of response to imatinib is 3 months, as reported in a phase II trial of imatinib for unresectable GIST, and the rate of response reached a plateau at 6 months.²⁶ Given these data, the optimal duration of neoadjuvant imatinib therapy appears to be 3-6 months.

3.3 | Evaluation of response

It remains controversial as to which is the best modality to evaluate the response of GIST to tyrosine kinase inhibitors (TKI). Contrast-

enhanced computed tomography (CT) is useful to assess not only tumor size but also tumor viability, evaluated by blood supply. When imatinib is effective, it is often observed that tumor density decreases without a change in tumor size. Therefore, it is possible that the response evaluation criteria in solid tumors (RECIST) criteria are likely to underestimate the efficacy of imatinib. Choi criteria, which consider CT density, are useful to evaluate the response to imatinib for GIST.²⁷ Positron emission tomography scanning using fluorodeoxyglucose (FDG-PET) is highly sensitive for GIST, which have high glucose metabolism. A prompt response is often observed (within days) without a change in tumor size. Recently, Farag et al reported that carrying out PET for early evaluation of response can result in a change of treatment strategy in GIST patients treated with neoadjuvant intent.²⁸ However, it is critical to conduct FDG-PET evaluation before treatment because in baseline surveillance, 20% of GIST do not display abnormal FDG uptake by the tumor. An earlier radiological assessment may be required in the neoadjuvant setting, because curative resection or sunitinib as second-line therapy should be considered if imatinib is not effective.

3.4 | Postoperative management

There is no consensus on postoperative management for patients receiving neoadjuvant therapy. High-risk GIST patients are recommended to receive adjuvant imatinib therapy, as described above. However, it may be desirable that patients with neoadjuvant therapy receive adjuvant imatinib therapy for several years, because the behavior of the original tumor before treatment may require adjuvant therapy. Notably, most patients in the RTOG0132 trial experienced recurrence within 2 years after discontinuation of imatinib.¹⁶ Therefore, further study is needed to determine the risk factor for recurrence after neoadjuvant therapy.

3.5 | Clinical concerns for neoadjuvant therapy

Although neoadjuvant therapy appears beneficial for locally advanced GIST, several clinical problems need to be resolved as follows. First, histological confirmation of a GIST is necessary prior to neoadjuvant therapy according to the National Comprehensive Cancer Network (NCCN) and ESMO guidelines.^{7,8} Furthermore, testing for mutation in c-kit and platelet-derived growth factor receptor alpha (PDGFRA)

mutational analysis is strongly recommended before neoadjuvant therapy to ensure the tumor has a genotype that is likely to respond to treatment.⁷ However, tissue samples can sometimes be obtained by an endoscopic procedure, depending on tumor location. Sampling tissues by laparotomy should be avoided because of the possibility of intraoperative tumor spillage, leading to peritoneal dissemination. Second, risk stratification cannot be reliably evaluated after neoadjuvant therapy because tumor size and mitotic count can differ from those of the tumor before treatment. Therefore, the neoadjuvant strategy can make it difficult to select appropriate patients. Finally, we should provide patients with the following information: (i) we may miss the opportunity for curative resection as a result of disease progression if the GIST does not respond; (ii) postoperative complications may increase as a result of neoadjuvant therapy; and (iii) preoperative complications may arise, including tumor necrosis, perforation, and/or hemorrhage. In these circumstances, it is possible that surgery will be required when the patient is in poor condition. It is critical to establish a system to promptly deal with an emergency situation.

4 | ADJUVANT THERAPY

The standard treatment for a primary resectable GIST without distant metastasis is surgery, with the aim of macroscopically complete resection with a negative margin. However, most high-risk patients experience recurrence within the first 5 years, despite complete curative surgery.²⁹ Therefore, adjuvant therapy is necessary to improve the prognosis for these patients. The success of imatinib in an advanced disease setting means that it is possible for high-risk patients to adapt to adjuvant therapy after curative surgery. NCCN and ESMO guidelines strongly recommend adjuvant therapy with imatinib for 3 years for patients with a significant risk of relapse.^{7,8} Several clinical trials have indicated the benefit of imatinib in an adjuvant setting, as shown in Table 2.

4.1 | ACOSOG Z9000 (phase II)

The ACOSOG Z9000 trial was the first trial to evaluate the efficacy of imatinib as adjuvant therapy.³⁰ One hundred seven patients with complete resection of GIST >10 cm in size, tumor rupture, hemorrhage, or multifocal GIST received 400 mg imatinib daily for 1 year. Primary

TABLE 2 Clinical relevance of adjuvant treatment for GIST (prospective trials)

Phase	Journal	Year	Cases	Agent/Dose	Patients	Duration	Notes
Prospective study							
ACOSOG Z9000 (P- II)	Ann Surg	2013	107	Imatinib/400 mg	High-risk GIST	1 y	5-y RFS: 40%
ACOSOG Z9001 (P- III)	J Clin Oncol	2014	713	Imatinib/400 mg	GIST (≥ 3 cm, mitosis $> 5 \geq 50$ HPF)	1 y	1-y RFS: 98% (imatinib) vs 83% (placebo)
SSGXVIII/AIO (P- III)	JAMA	2012	400	Imatinib/400 mg	High-risk GIST (>10 cm, high mitosis)	1 vs 3 y	5-y RFS: 66% (3 years) vs 48% (1 y)
EORTC 62024 (P- III)	J Clin Oncol	2015	908	Imatinib	Intermediate- or high-risk GIST	2 y	5-y RFS: 69% (imatinib) vs 63% (surgery alone)

GIST, gastrointestinal stromal tumor; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival.

endpoints, namely the rates of 1-, 2-, and 3-year recurrence-free survival (RFS), were 96, 60, and 40%, respectively. In an analysis according to specific mutations, the median RFS of patients with KIT exon 9 mutation and exon 11 mutation were 19 months and 42 months, respectively. In a multivariate analysis for prognosis, KIT exon 9 mutation and high mitotic rate were significantly associated with poorer prognosis. This latter finding is consistent with a previous report that some mutations, including KIT exon 9, were associated with a poorer response to imatinib in the setting of advanced or metastatic disease.

4.2 | ACOSOG Z9001 (phase III)

In this trial, 713 patients who underwent a complete resection for KIT-positive primary GIST ≥ 3 cm were randomly assigned to a 1-year dosage of either imatinib (400 mg daily) (N = 359) or placebo (N = 354). When an interim analysis showed that few patients in the imatinib group experienced recurrence, this trial was stopped. The 1-year RFS rate, the primary endpoint, was 98% in the imatinib group and 83% in the placebo group (HR: 0.35, 95% CI: 0.22- 0.53). In subgroup analysis, imatinib significantly improved RFS in all categories, including tumor size, mitotic rate, and tumor location. Notably, however, adjuvant imatinib therapy did not affect OS, perhaps because of the short duration of follow up, the limited number of relapses, or the high efficacy of imatinib for patients experiencing recurrence. Importantly, the findings in this trial bring several key clinical questions to light. One is the appropriate duration of imatinib treatment after complete resection; another is the definition of subsets of patients who should receive adjuvant imatinib therapy.

4.3 | SSGXVIII/AIO (phase III)

The Scandinavian Sarcoma Group (SSG) XVIII trial was a large randomized controlled trial comparing 1 vs 3 years of adjuvant imatinib (400 mg daily) in high-risk resected GIST patients.³¹ In this trial, high

risk was defined as having at least one of the following: tumor size >10 cm, mitotic count $>10/50$ high-power field (HPF), tumor size >5 cm with mitotic rate $>5/50$ HPF, or tumor rupture. There was a significant improvement in primary endpoint RFS in patients who received imatinib for 3 years compared with 1 year (5-year RFS: 66% vs 48%, HR: 0.46, 95% CI: 0.32-0.5). OS in patients treated for 3 years was also significantly improved compared to those patients treated for 1 year. Recent long-term follow-up results demonstrated that patients who received imatinib for 3 years had significantly greater RFS (71% vs 52%) and OS (92% vs 85%).³² Adverse events related to imatinib treatment were observed more frequently in patients treated for 3 years and included periorbital edema and muscle cramps. Most adverse events were grade 1 or 2, and the rate of severe adverse events \geq grade 3 was similar in both groups. However, the rate of discontinuation of imatinib for reasons other than disease progression was more frequent in patients treated for 3 years (26% vs 13%). Based on this trial, 3 years of adjuvant imatinib treatment is standard for high-risk GIST patients.

4.4 | EORTC 62024 (phase III)

The EORTC 62024 trial was an open-label randomized study comparing 2 years of adjuvant imatinib therapy (400 mg daily) or observation after complete resection for intermediate or high-risk GIST patients.³³ Nine-hundred eight intermediate- or high-risk patients, including those having experienced tumor rupture or intraoperative tumor spillage, were randomly assigned. Primary endpoint was imatinib-free survival (IFS: the time to death or starting treatment with other TKI). Five-year IFS was 87% in the treatment arm compared with 84% in the observation arm (HR: 0.79, 95% CI: 0.52-1.25). The difference in 5-year IFS between the treatment arm and the observation arm was not statistically significant even in limited high-risk or high-risk patients based on the modified National Institutes of Health (NIH) risk criteria, including tumor site.

TABLE 3 Clinical concerns of neoadjuvant and adjuvant treatment for GIST

Clinical concern	Note
Neoadjuvant therapy	
Agent	Only imatinib evaluated in previous studies. No trials whether sunitinib and regorafenib are effective in the neoadjuvant setting.
Optimal duration	At least 3-6 months prior to surgery may be required, but before secondary resistance (within 2 y).
Evaluation of response	PET may give indication of imatinib activity after 2-4 weeks of therapy for early evaluation of response.
Postoperative management	There is no consensus on adjuvant therapy for patients receiving neoadjuvant therapy. It may be desirable because the behavior of the original tumor before treatment may require adjuvant therapy.
Adjuvant therapy	
Optimal imatinib dose	Only the 400 mg daily dose was given in all previous phase III trials.
Optimal duration	At least 3 y of imatinib treatment is recommended for high-risk GIST patients, but phase II trial of 5-year dose of adjuvant imatinib was reported.
Patient selection	High-risk patients based on tumor size, mitotic rate, tumor location, and tumor rupture, mutation subtypes should also be considered during patient selection (PDGFRA exon 18 D842V mutation).

GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha; PET, positron emission tomography.

Collectively, the data from the above trials suggest that adjuvant imatinib therapy is effective for high-risk GIST patients. However, the following clinical questions remain unclear.

4.5 | Optimal imatinib dose and duration

Only the 400 mg daily dose was given in all previous trials.^{31,33,34} However, an 800 mg daily dose of imatinib led to an improved outcome, compared to 400 mg daily, for patients with KIT exon 9 mutation in an advanced or metastatic setting.³⁵ Further study is needed to clarify the optimal dose according to the molecular features and to evaluate the feasibility of high-dose therapy in an adjuvant setting.

Data from the SSG XVIII trial established that at least 3 years of imatinib treatment is recommended for high-risk GIST patients.³¹ Duration of imatinib dose may be a factor influencing the prognosis. Therefore, we anticipate that a longer duration of imatinib treatment may improve the prognosis for high-risk GIST patients. However, adverse events including secondary cancer induced by longer-term imatinib dose should be considered.³²

4.6 | Patient selection

Patient selection was different in all of the above trials, and optimal selection of patients who will derive the most benefit from adjuvant imatinib remains unestablished. Although several risk-stratification tools were available based on tumor size, mitotic rate, tumor location, and tumor rupture, mutation subtypes should also be considered during patient selection. Patients with a KIT exon 9 mutation, PDGFRA exon 18 D842V mutation, and wild-type (lacking KIT or PDGFRA mutation) had an inferior response to imatinib in several clinical trials for advanced or metastatic GIST.^{36–40} In the ACOSOG Z9001 trial, imatinib therapy was associated with higher RFS in patients with a KIT exon 11 deletion of any type, but not with a KIT exon 11 insertion or point mutation, a KIT exon 9 mutation, a PDGFRA mutation, or a wild-type tumor.⁴¹ In clinical practice, there is consensus that patients with PDGFRA D842V mutation should not be treated with adjuvant therapy.^{7,8} Therefore, mutational analysis is critical to make a decision for adjuvant therapy. Joensuu et al investigated the risk factors for GIST recurrence despite adjuvant therapy after curative resection using the SSG XVIII trial database. The factors identified were also validated using the database of the ACOSOG Z9001 trial. Five factors (high tumor mitotic count, non-gastric location, large size, rupture, and adjuvant imatinib for 12 months) were independently associated with unfavorable RFS in a multivariable analysis in the SSG XVIII cohort. These variables were strongly associated with RFS in the Z9001 cohort.⁴² Collectively, further trials are required to elucidate the optimal dose, duration, and patient selection for adjuvant imatinib therapy.

5 | CONCLUSION

We review and summarize the clinical relevance and issues of neoadjuvant and adjuvant therapy for localized GIST (Table 3). Although

imatinib as neoadjuvant and adjuvant therapy clearly contributes to improving the prognosis for high-risk GIST, the optimal dose, duration, and patient selection for clinical settings remain controversial. Furthermore, molecular biological research including detailed mutational analysis will help guide personalized therapy for advanced GIST.

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REFERENCES

- Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol.* 1998;152(5):1259–69.
- Goettsch WG, Bos SD, Breekveldt-Postma N, Casparie M, Herings RM, Hogendoorn PC. Incidence of gastrointestinal stromal tumours is underestimated: results of a nation-wide study. *Eur J Cancer.* 2005;41(18):2868–72.
- Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science.* 1998;279(5350):577–80.
- Lux ML, Rubin BP, Biase TL, et al. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. *Am J Pathol.* 2000;156(3):791–5.
- Rubin BP, Singer S, Tsao C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res.* 2001;61(22):8118–21.
- Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med.* 2001;344(14):1052–6.
- von Mehren M, Randall RL, Benjamin RS, et al. Soft Tissue Sarcoma, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2018;16(5):536–63.
- Casali PG, Abecassis N, Bauer S, et al. Gastrointestinal Stromal Tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018. [Epub ahead of print]. <https://doi.org/10.1093/annonc/mdy096>
- DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg.* 2000;231(1):51–8.
- Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Int J Surg Pathol.* 2002;10(2):81–9.

11. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol.* 2002;33(5):459–65.
12. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol.* 2006;23(2):70–83.
13. Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Lancet Oncol.* 2009;10(11):1045–52.
14. Bischof DA, Kim Y, Dodson R, et al. Open versus minimally invasive resection of gastric GIST: a multi-institutional analysis of short- and long-term outcomes. *Ann Surg Oncol.* 2014;21(9):2941–8.
15. Dematteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). *Cancer.* 2008;112(3):608–15.
16. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol.* 2009;99(1):42–7.
17. Wang D, Zhang Q, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. *Ann Surg Oncol.* 2012;19(4):1074–80.
18. Kurokawa Y, Yang HK, Cho H, et al. Phase II study of neoadjuvant imatinib in large gastrointestinal stromal tumours of the stomach. *Br J Cancer.* 2017;117(1):25–32.
19. Rutkowski P, Gronchi A, Hohenberger P, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. *Ann Surg Oncol.* 2013;20(9):2937–43.
20. Tielen R, Verhoef C, van Coevorden F, et al. Surgical treatment of locally advanced, non-metastatic, gastrointestinal stromal tumours after treatment with imatinib. *Eur J Surg Oncol.* 2012;39(2):150–5.
21. Jakob J, Mussi C, Ronellenfitsch U, et al. Gastrointestinal stromal tumor of the rectum: results of surgical and multimodality therapy in the era of imatinib. *Ann Surg Oncol.* 2013;20(2):586–92.
22. Tielen R, Verhoef C, van Coevorden F, et al. Surgical management of rectal gastrointestinal stromal tumors. *J Surg Oncol.* 2013;107(4):320–3.
23. Wilkinson MJ, Fitzgerald JE, Strauss DC, et al. Surgical treatment of gastrointestinal stromal tumour of the rectum in the era of imatinib. *Br J Surg.* 2015;102(8):965–71.
24. Svetlichnaya J, Huyck TK, Wayne JD, Agulnik M. Neoadjuvant use of sunitinib in locally advanced GIST with intolerance to imatinib. *Chemotherapy.* 2012;58(1):30–3.
25. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2012;23(Suppl 7):vii49–55.
26. Nishida T, Shirao K, Sawaki A, et al. Efficacy and safety profile of imatinib mesylate (ST1571) in Japanese patients with advanced gastrointestinal stromal tumors: a phase II study (ST1571B1202). *Int J Clin Oncol.* 2008;13(3):244–51.
27. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol.* 2007;25(13):1753–9.
28. Farag S, Geus-Oei LF, van der Graaf WT, et al. Early evaluation of response using (18)F-FDG PET influences management in gastrointestinal stromal tumor patients treated with neoadjuvant imatinib. *J Nucl Med.* 2018;59(2):194–6.
29. Joensuu H, Vehtari A, Riihimäki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol.* 2012;13(3):265–74.
30. DeMatteo RP, Ballman KV, Antonescu CR, et al. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. *Ann Surg.* 2013;258(3):422–9.
31. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA.* 2012;307(12):1265–72.
32. Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant imatinib for high-risk GI stromal tumor: analysis of a randomized trial. *J Clin Oncol.* 2016;34(3):244–50.
33. Casali PG, Le Cesne A, Poveda Velasco A, et al. Time to definitive failure to the first tyrosine kinase inhibitor in localized GI stromal tumors treated with imatinib as an adjuvant: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup randomized trial in collaboration with the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas. *J Clin Oncol.* 2015;33(36):4276–83.
34. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2009;373(9669):1097–104.
35. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol.* 2008;26(4):626–32.
36. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J Clin Oncol.* 2005;23(23):5357–64.
37. Debiec-Rychter M, Dumez H, Judson I, et al. Use of c-KIT/PDGFRα mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer.* 2004;40(5):689–95.
38. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol.* 2003;21(23):4342–9.
39. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. *J Clin Oncol.* 2008;26(33):5360–7.
40. Patrikidou A, Domont J, Chabaud S, et al. Long-term outcome of molecular subgroups of GIST patients treated with standard-dose imatinib in the BFR14 trial of the French Sarcoma Group. *Eur J Cancer.* 2016;52:173–80.
41. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J Clin Oncol.* 2014;32(15):1563–70.
42. Joensuu H, Eriksson M, Hall KS, et al. Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. *Cancer.* 2014;120(15):2325–33.

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