Combined Therapy of Gastrointestinal Stromal Tumors

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KEYWORDS

• Gastrointestinal stromal tumor • Neoadjuvant therapy • Adjuvant therapy • Imatinib • Surgery

KEY POINTS

- Preoperative (neoadjuvant) therapy in locally advanced GIST may facilitate resection with microscopically clear margins, decrease the risk of perioperative tumor spill, and decrease extent and morbidity of the surgical procedure.
- Existing evidence-based clinical practice guidelines suggest adjuvant imatinib for at least 36 months for patients with high-risk GIST (tumor >5 cm in size with high mitotic rate [>5 mitoses/50 high-power fields] or tumor rupture or a risk of recurrence that is >50%).
- Surgical removal of residual disease during imatinib treatment may allow for complete remission (in approximately 20%) in selected patients with GIST after response to therapy, probably prolonging durable remission.
- The time of the implementation of surgical treatment warrants further studies; mutilating surgery in metastatic GIST should be avoided, as systemic therapy is the mainstay of treatment in this setting and surgery is only adjunctive to tyrosine kinase inhibitors therapy.

INTRODUCTION: GASTROINTESTINAL STROMAL TUMORS GENERAL OVERVIEW

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract. Morphologically and clinically they are a heterogeneous group of tumors, with a biological behavior that is difficult to predict, ranging from clinically benign to malignant. Radical surgery is the treatment of choice in primary resectable GIST. Nevertheless, approximately 40% to 50% of patients will develop recurrent or metastatic disease after curative resection.[1–4] Understanding

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the molecular mechanisms of their pathogenesis demonstrated that most GISTs are associated with activating, constitutive, mutually exclusive mutations of 2 genes: *KIT* and *PDGFRA* (platelet-derived growth factor receptor-α). These are the early oncogenic events during GIST development and result in overexpression and activation of oncoproteins KIT and PDGFR.[2,5–8] A significant subset of GIST is still diagnosed at a locally advanced, unresectable and/or disseminated stage of disease. Metastases preferably occur in the peritoneal cavity and/or the liver.[3,5] Conventional cytotoxic chemotherapy treatment is ineffective in advanced cases of GIST. Radiotherapy is also of limited value in the management of GIST, mainly because these tumors are often located in close proximity with dose-limiting vital organs.[3,5] However, advances in the understanding of molecular mechanisms of GIST pathogenesis have recently resulted in the development of a treatment modality that has become a model of targeted therapy in oncology. Imatinib mesylate is a tyrosine kinase inhibitor of KIT, BRC/ABL fusion protein, FMS (receptor for colony stimulating factor 1), Abl-related gene, and PDGFR-alpha and PDGFR-beta. It has revolutionized the treatment of advanced GIST and was the first effective nonsurgical treatment in inoperable and/or metastatic cases.[1,2,5–8] Current survival in advanced GIST is strikingly superior to historical clinical data, with a reported median overall survival (OS) of 5 to 6 years[4,9] and median progression-free survival (PFS) ranging from 2 to 3 years.[10–13] In case of progression during imatinib treatment (which is mainly related to occurrence of new secondary *KIT*/*PDGFRA* mutations) there are currently several therapeutic strategies, such as escalation of the dose of imatinib to 800 mg daily, surgical removal of focally progressive lesions, and therapy with registered second-line drug sunitinib malate and third-line drug regorafenib (both are multitargeted tyrosine kinase inhibitors with anti-angiogenic properties).[14–18] Recently, imatinib has been registered for adjuvant therapy in patients after resection of primary GIST with high risk of recurrence based on the results of 2 randomized trials (ACOSOG Z9001 and Scandinavian Sarcoma Group XVIII = SSGXVIII/AIO).[19,20] Currently in selected cases of locally advanced GISTs, a strategy of neoadjuvant imatinib therapy has become a common approach.

In this review article we have focused on the evolving role of combined therapy with surgery and tyrosine kinase inhibitors in GIST management.

RISK ASSESSMENT OF PRIMARY GASTROINTESTINAL STROMAL TUMORS

The treatment of choice in primary, resectable, localized GISTs is radical surgery with negative margins, but virtually all GISTs are associated with a risk of recurrence, and approximately 40% of patients with potentially curative resections will ultimately develop recurrent or metastatic disease.[2–4] The identification of the risk factors for recurrence after primary surgery is crucial for reliable prognosis, follow-up schedule, and the selection of patients who may potentially benefit from the adjuvant therapy, aiming for a decrease in disease recurrences. The main criteria of aggressive behavior of GISTs are based on the presence of invasion of adjacent structures and/or the presence of metastases (overtly malignant cases), as well as on primary tumor site, size, and mitotic index.[21] Several risk-stratification systems have been proposed in the recent years. In 2001, a Consensus Conference held at the National Institutes of Health (NIH) provided the first evidence-based definition and a practical scheme for the risk assessment in the clinical course of this disease. The risk categorization was based on evaluation of the tumor size and mitotic rate (evaluated per 50 high-powered fields [HPF] or mm^2) as the most reliable prognostic factors.[22–24] Additional analysis in patients with primary tumor after complete macroscopic resection

confirmed the significance of tumor anatomic location as the independent prognostic factor. Miettinen and Lasota created the classification for risk assessment in gastric, duodenal, intestinal, and rectal GISTs (National Comprehensive Cancer Network-American Forces Institute of Pathology [NCCN-AFPI]),[2,21,25–28] which constituted the basis for new staging system of American Joint Committee on Cancer (**Table 1**).[29,30] It combines 3 crucial features (ie, size, site of origin, and mitotic index) and it reflects the fact that gastric GISTs show a much lower rate of aggressive behavior than jejunal and ileal GISTs of comparable size and/or mitotic rate.[21,27,28] Recently it was established that tumor rupture (spontaneous or iatrogenic) is an additional important risk factor strongly associated with the increased recurrence rates.[4,31] Therefore, in 2008 Joensuu and colleagues[32–34] proposed another simplified classification system based on 4 prognostic factors (tumor size, site, mitotic count, and the presence of tumor rupture). Furthermore, completeness of resection is an independent prognostic risk factor; rather obviously patients with resectable primary GIST who undergo R0 resection have a significantly longer survival than patients undergoing incomplete resection.[4,35,36]

Taking into account that some of prognostic features (such as mitotic index and tumor size) are continuous (not categorical) variables, prognostic nomograms for prediction of tumor were developed.[37–39] Joensuu and colleagues'[32] prognostic contour maps resulting from nonlinear modeling may be appropriate for estimation of individualized outcomes. The comparison of different classification systems shows that patients with intermediate risk have a clinical course more similar to the low-risk group, which implies that only the high-risk patients would likely benefit from adjuvant therapy after primary tumor resection.[32]

In addition to the clinicopathological factors mentioned previously, *KIT* and *PDGFRA* mutational status may also have a prognostic significance in primary GIST. However, currently available data are insufficient to incorporate the kinase mutation status into the risk stratification of primary tumors. Several studies have indicated a more favorable prognosis for patients carrying exon 11 point mutations or insertions, as well as *PDGFRA* exon 18 mutations, whereas tumors harboring *KIT* exon 9 duplications as well as *KIT* exon 11 deletions (especially involving codons 557 and/or 558 or in homozygous state) were associated with more aggressive behavior.[40–47] Recent analysis of clinicopathologic and molecular data from 1056 patients with localized GIST who underwent surgery with curative intention (R0/R1) and were registered in the European Contica GIST database confirmed the independent prognostic significance of the *KIT* deletions involving codons 557 and/or 558, especially in GIST of gastric origin.[24] Population-based series of patients with primary

Table 1
Relevant risk parameters for primary gastrointestinal stromal tumor including molecular data

Parameters	Lower Risk	Higher Risk
Surgery	R0	R1, tumor rupture
Localization	Stomach	Small or large intestine
Size (cm)	≤5	>5
Mitotic index	≤5/50 HPF	>5/50 HPF
Gene mutation	PDGFRA	KIT, wild-type (nn-PDGFRA, non-KIT)
Type of *KIT* mutation	Duplications/insertions in exon 11	Exon 11 deletions (especially involving codons 557–558), exon 9

Abbreviations: HPF, high-power field; PDGFRA, platelet-derived growth factor receptor-α.

resectable GIST confirmed more favorable outcomes of PDGFRA mutations and KIT exon 11 duplication mutations or deletions of 1 codon.[48] Further developments in molecular analysis (such as inclusion genomic index) may further optimize the individual risk assessment and inclusion criteria for adjuvant therapy after primary tumor resection.[49]

PRIMARY LOCALIZED GASTROINTESTINAL STROMAL TUMORS

Neoadjuvant Strategy

Locally advanced GISTs are defined as those tumors that can potentially benefit from neoadjuvant treatment with imatinib through a decrease in size and vulnerability. If the tumor is localized at a critical anatomic site, such as the gastroesophageal junction, juxtapancreatic duodenum, or lower rectum, the surgical procedure can be downsized from an extensive multiorgan or full-organ resection to a more limited surgical procedure, without compromising local radicality. Very large tumors also can be potential candidates for preoperative therapy, because they tend to be extremely fragile and hypervascular, with a substantial risk of intraoperative rupture and/or bleeding.

Thus, based on the spectacular activity of imatinib on metastatic GIST, neoadjuvant therapy seems an attractive treatment strategy in locally advanced and/or marginally resectable GIST. Although current European (European Society of Medical Oncology [ESMO]) and US (NCCN) guidelines recommend this neoadjuvant strategy in selected cases,[50,51] it seems that is not yet fully implemented in routine practice. This neoadjuvant cytoreductive and tumor cell inactivating treatment in localized GIST aims to facilitate resection with microscopically clear margins, to decrease the extent and morbidity of the surgical procedure, and to minimize tumor micrometastases, thus increasing the patient's chance for cure.[52,53] Neoadjuvant therapy can reduce the need for extensive, multiorgan resections and diminish the intraoperative risk of rupture of devitalized tumor and spillage of active tumor cells into the peritoneal cavity (which is closely related to the risk of disease dissemination). Furthermore, it decreases the necessity of blood transfusions as a consequence of intraoperative tumor bleeding.[54,55] **Fig. 1** illustrates a locally advanced gastric GIST, detected due to gastrointestinal bleeding, which responded to imatinib 400 mg daily, resulting in a significant shrinkage of tumor. This enabled a complete tumor removal via wedge resection.

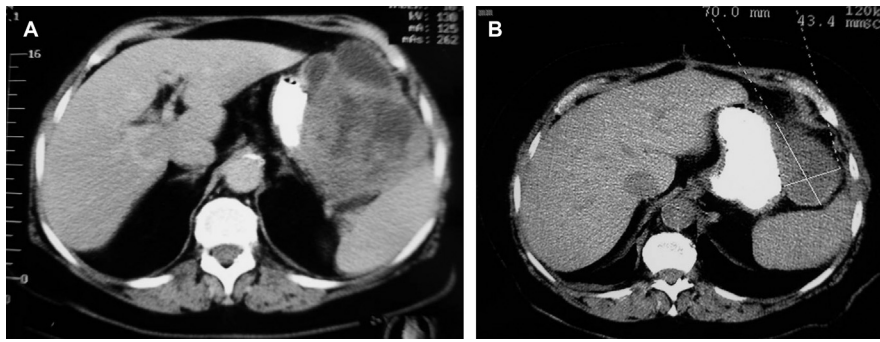

Fig. 1. CT images demonstrating response of locally advanced gastric GIST detected due to gastrointestinal bleeding with significant shrinkage of tumor allowing for complete tumor removal via wedge resection. (*A*) Before and (*B*) after treatment with imatinib (400 mg daily).

When used as a neoadjuvant treatment, imatinib is administered until maximal response is achieved. The duration of treatment can vary between 6 and 12 months. Usually, after 6 to 9 months, when 2 consecutive images (mostly computed tomography [CT]) show no further tumor regression, this is considered the point of maximal response. At that moment, a plateau in tumor shrinkage is reached, whereas the risk of developing secondary resistance to imatinib therapy is still very low.[56–58] A study by Tirumani and colleagues[59] confirmed that the best response to neoadjuvant imatinib is reached after approximately 28 weeks of treatment, with a plateau response at 34 weeks. Therefore, continuation of imatinib beyond this time span is probably not beneficial.

To avoid missing the optimal timing for surgery, careful response assessment should be undertaken. In selected cases, especially if mutational status was not determined in advance, this assessment should include imaging with PET/CT, as this modality may more adequately predict short-term treatment responses. Moreover, there is clear evidence that treatment with imatinib should always be followed by surgical resection. In the BFR-14 trial, Blesius and colleagues[60] demonstrated that patients with potentially resectable GIST who are treated with imatinib alone (ie, without resection) have a similar disease-free survival (DFS) and OS to that of patients with metastatic GIST. Thus, imatinib cannot replace surgery.

Imatinib can generally be stopped safely the day before surgery and restarted (when indicated) as soon as postoperative oral food intake is restored.[55,61,62] However, some centers prefer to stop the drug 1 week before surgery and do not restart it until 1 week after surgery.

Although preoperative therapy has become a common approach in individualized GIST cases, formal evidence from clinical trials regarding the outcome of neoadjuvant treatment with imatinib is limited.[53,63] Several articles report on small series of patients treated with imatinib before tumor resection, but they often have a mixed population of patients with primary, nonmetastatic GIST, as well as patients with metastatic GIST operated for residual disease.[57,61,64–77] The largest cohort of patients with GIST treated with neoadjuvant imatinib followed by resection was a series of 161 patients from 10 sarcoma centers of the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG). This study reported excellent safety data and long-term results, with a 5-year DFS (calculated from date of resection) and OS (calculated from start of preoperative imatinib) of 65% and 87%, respectively.[53] Only 1% of patients progressed during preoperative therapy. Microscopically radical resection (R0) was obtained in 83.2% of cases. Postoperative complications were recorded in 15% of cases, but only 3% required surgical intervention. One patient died postoperatively after total gastrectomy. Tielen and colleagues[78] analyzed a series of 57 patients with locally advanced GIST treated with neoadjuvant imatinib, with a median treatment duration of 8 months. Microscopically radical resection (R0) was possible in 84% of patients. Five-year DFS and OS of 77% and 88% were reported, respectively. Median tumor size of 12.2 cm before treatment was reduced to 6.2 cm after imatinib treatment. No tumor rupture was recorded.[78] Goh and colleagues[69] analyzed 37 patients preoperatively treated with imatinib, and concluded that radical resection was possible in 33 (89%) cases. Postoperative complications were recorded in only 4 (11%) of cases. A Dutch study presented data of 57 patients with locally advanced GIST who underwent surgery after a median time of 8 months of treatment with imatinib.[78] Tumor perforation did not occur in any of the patients and R0 resection was achieved in 84% of cases. Forty-four patients did not develop recurrence during follow-up. Recent reports indicate the possibility of successful laparoscopic resection of locally advanced gastric or esophageal GIST treated with neoadjuvant imatinib.[79,80]

Only 3 small, nonrandomized phase II trials are available evaluating neoadjuvant therapy with imatinib in locally advanced GIST (**Table 2**).[81–85] In the Radiation Therapy Oncology Group (RTOG), the National Cancer Institute, and the American College of Radiology Imaging Network (ACRIN)–RTOGS-0132/ACRIN 6665 phase II trial, 31 patients with primary, localized GIST received imatinib at the dosage of 600 mg daily preoperatively for 8 to 12 weeks and in case of objective response or stable disease they underwent elective surgery, followed by 2 years of adjuvant imatinib.[81] Results of this trial confirmed the safety of this approach and a high percentage of relapse-free survival was observed after surgery.[82] Two-year DFS and OS rates were 83% and 93%, respectively,[81] but discontinuation of adjuvant imatinib decreased the outcome to 5-year DFS and OS rates of 57% and 77%, respectively.[82] This study may have also identified gene expression signatures that are predictive for response to imatinib.[86] The German phase II CST1571-BDE43 study is the largest trial on neoadjuvant treatment with imatinib. After 6 months of imatinib, only 1 patient was inoperable at planned surgery and 26 (64%) of 41 patients had less extensive surgery than initially planned before administration of imatinib.[83]

These results imply that neoadjuvant therapy with imatinib increases the possibility of complete tumor resection and decreases the need for extensive and/or multivisceral resections. The median time of preoperative imatinib in the EORTC STBSG data was 10 months.[53] With longer neoadjuvant therapy, approximately 80% of cases demonstrate objective response to imatinib therapy. This is higher than the response rates reported in the phase II RTOG 0132 trial,[81] in which a maximum of 12 weeks of preoperative imatinib only was used. Goh and colleagues[69] as well as Doyon and colleagues[87] reported similar data. Furthermore, neoadjuvant imatinib seems to be a safe treatment strategy. In the EORTC STBSG series only 3% of patients were reported to require surgical reintervention due to postoperative complications.[53]

The proper candidates for preoperative imatinib are those patients who may benefit from tumor downstaging before operation; that is, patients in whom preoperative therapy with imatinib enables an organ-sparing resection with negative margins, avoiding mutilating surgery, intraoperative tumor rupture, and/or extensive blood loss (**Box 1**). Obviously, this neoadjuvant strategy is especially attractive in surgically demanding tumor sites, such as distal rectum, gastroesophageal junction, duodenum or esophagus, where preservation of vital functions is pivotal.[53,55,88] Resection of advanced primary tumors at these sites may be related to significant morbidity and functional defects. In some selected cases, downstaging of the primary tumor may sometimes even allow laparoscopic surgery instead of open surgery through an extensive midline laparotomy. Of course, these patients must be selected carefully by multidisciplinary assessment to optimize clinical outcomes. Before starting neoadjuvant therapy, a biopsy is obligatory (preferentially core-needle biopsy) and ideally the selection process should also be based on tumor genotyping results. The assessment of molecular status before neoadjuvant therapy is obligatory according to current ESMO guidelines,[50] but this may sometimes be difficult on a small biopsy sample. Nevertheless, it is clear now that the presence of primary gain-of-function mutations in *KIT* or *PDGFRA* genes strongly correlates with outcome of imatinib therapy in advanced GIST. The mutational status of the primary tumor is related to PFS and it predicts the probability of response to imatinib. Tumors harboring exon 11 *KIT* mutations demonstrate the best response to imatinib (70%–85% objective response rate) and these patients have the longest overall and PFS.[89–92] On the other hand, several clinical and laboratory studies confirmed that tumors with exon 18 *PDGFRA* D842V mutations are insensitive to imatinib, whereas other *PDGFRA*-mutant GIST show variable response.[89,93] In GIST harboring exon 18 *PDGFRA* D842V mutations (which are relatively frequent in the

Table 2
Summary of trials and major series with neoadjuvant imatinib therapy in GIST

	Eligibility Criteria	Trial Design	Patient Numbers, n	Endpoints and Results				
				DFS/RFS	OS	ORR	PFS	Toxicity/SAE
Phase II RTOG-S0132/ACRIN 6665[82]	Cohort A: Locally advanced GIST ≥5 cm Cohort B: potentially resectable metastatic/ recurrent GIST KIT-positive	Nonrandomized Neo-adj. imatinib 600 mg/d. for 8–12 wk and adj. imatinib for 2 y [R0 resection: 67%]	Total: n = 52 Cohort A: n = 30 Cohort B: n = 22	5-y. RFS: 57%	2-y. OS: 92% 5-y. OS: 77%	—	2-y. PFS: 80.5%	Grade 3: 29% Grade 4: 16% Grade 5: 4%
Phase II MD Anderson Cancer Center[85]	GIST at size ≥1 cm KIT-positive	Nonrandomized Neo-adj. imatinib 600 mg/d. for 3, 5 or 7 d and adj. imatinib for 2 y	n = 19	1-y. DFS: 94% 2-y. DFS: 87%	—	—	—	—
Phase II APOLLON CST1571-BDE43[83]	Locally advanced GIST KIT-positive	Nonrandomized Neo-adj. imatinib 400 mg/d. for 6 mo [R0 resection: 87%]	n = 41	3-y. RFS: 85%	Mean OS: 74.9 mo Mean OS: 83%	—	Mean PFS: 67% Mean TTP: 64 mo	—
EORTC STBSG collaborative series[53]	Locally advanced, nonmetastatic GISTs KIT-positive	Retrospective study Neo-adj. imatinib 400 mg/d. for median time of 40 wk [range: 6–190 wk] [R0 resection: 83%]	n = 161	5-y. DFS: 65%	5-y. OS: 87% 5-y. DSS: 95% Median OS: 104 mo	80%	—	—

Abbreviations: adj, adjuvant; DFS, disease-free survival; DSS, disease-specific survival; GIST, gastrointestinal stromal tumor; neo-adj, neoadjuvant; OS, overall survival; RFS, recurrence-free survival; TTP, time to progression.

Box 1
Current recommendations for preoperative imatinib therapy

- Locally advanced tumor, not a priori amenable for surgery without mutilating/multivisceral operation (eg, abdominal-perineal resection, pelvic evisceration, Whipple procedure, esophagogastric resection)
- When a negative resection margin of the organ of origin is difficult to obtain, a high risk of tumor rupture can be expected or complication due to the extensive surgery can be foreseen
- When function-sparing resection, minimizing the extent of surgery and reducing postoperative morbidity and mortality can be expected after tumor shrinkage (wedge resection instead of total gastrectomy with splenectomy, local excision instead of Whipple procedure, one cavity approach instead of abdominal-thoracic resection).

stomach) neoadjuvant treatment with imatinib is futile, as these tumors are not sensitive to this drug. Furthermore, it has been demonstrated that patients with advanced and metastatic GIST harboring *KIT* exon 9 mutations may benefit from an increased imatinib dose (escalated to 800 mg daily).[91,92] This indicates that patients with this mutation may be undertreated, when applying standard 400-mg daily dosage, but so far no clinical trial explored the outcome of an increased imatinib dose in this subset of patients in a neoadjuvant setting.

Based on assessment of size, location, and mitotic index, most primary GISTs treated with preoperative imatinib are considered high-risk or intermediate-risk tumors. This makes them candidates for adjuvant treatment with imatinib. According to current guidelines, imatinib should be administered postoperatively for 36 months (see also the next section). The EORTC STBSG series demonstrated the significant difference in DFS in favor of patients receiving imatinib, especially in patients with small-bowel GIST, who have an intrinsically higher risk of developing recurrence.[32]

Adjuvant Strategy

Postoperative recurrence of moderate and high-risk GIST is frequently observed. This led to the idea of using imatinib as an adjuvant treatment after primary surgery to prevent or delay recurrence and thus prolong survival. In 2008, imatinib was registered for use in adjuvant therapy after resection of primary GIST at significant risk of relapse. This was based on the results of clinical trials demonstrating a significant reduction in the risk of recurrence.[19] However, the data did not provide a clear guidance as to optimal duration of treatment.

The role of imatinib in the adjuvant treatment setting has been evaluated in several phase II and III clinical trials: ACOSOG Z9000 and Z9001 (conducted by the American College of Surgeons Oncology Group), SSGXVIII/AIO (conducted by the Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie XVIII), RTOG S0132 (conducted by the Radiation Therapy Oncology Group), and EORTC 62024 (conducted by the European Organization for Research and Treatment of Cancer) (**Table 3**).[82,94–99] Data from the ACOSOG Z9001 phase III study, comparing 1 year of adjuvant therapy with imatinib 400 mg daily to placebo in patients after R0 resection of GIST of at least 3 cm in diameter, have shown a significant reduction in the risk of recurrence from 17% to 2% at 1 year (20 months of follow-up; $P = .0001$, hazard ratio = 0.35).[94] The treatment was well tolerated. However, no significant impact on OS was observed; many patients recurred shortly after adjuvant imatinib cessation and they then received imatinib as a rescue therapy in the metastatic setting. This implies that adjuvant imatinib delays rather than prevents the

relapse. Moreover, this trial enrolled many patients with low risk of recurrence according to current criteria. Substantial clinical benefit of adjuvant therapy was most obvious in the group of patients with high risk of relapse according to NCCN-AFIP criteria, with an improvement of 2-year recurrence-free survival (RFS) from 41% to 77% ($P<.0001$).[19,100] This raised interest in the assessment of a more long-term administration of adjuvant imatinib in high risk GIST.

Data from the SSGXVIII/AIO trial, comparing 12 versus 36 months of adjuvant imatinib treatment after resection of GIST with a high risk of recurrence, were initially presented in 2011 at the 47th Annual Meeting of the American Society of Clinical Oncology (ASCO).[96] The results showed significant improvement in the 36-month arm compared with the 12-month arm, both in RFS (5-year RFS: 65.6% vs 47.9%; $P<.0001$) and OS (5-year OS: 92.0% vs 81.7%; $P = .01$). The best results were obtained in GIST harboring *KIT* exon 11 mutations. Imatinib was generally well tolerated with anemia, periorbital edema, fatigue, nausea, diarrhea, leucopenia, and muscle cramps as the most common adverse events. More patients discontinued imatinib therapy in the 3-year arm in comparison with the 1-year arm (for reasons other than GIST recurrence) (26% vs 12%; $P<.001$).[20,32,96,101] Based on these data, the Food and Drug Administration and the European Medicines Agency, as well as ESMO and NCCN recommended 36 months of treatment with imatinib after surgery for adult patients with CD117-positive GIST considered at high risk of relapse.[50,51,102] Subsequent analyses confirmed the cost-effectiveness of prolonged adjuvant therapy in patients with GIST at high risk of disease recurrence.[103,104] The second, planned analysis of the SSGXVIII/AIO trial after a median follow-up time of 7.5 years confirmed the superior and sustained effect on RFS and OS of 3 years of adjuvant imatinib versus only 1 year of therapy.[105] Nevertheless, even after 3 years of adjuvant imatinib, a clear trend toward relapse occurs when imatinib is stopped. This implies an even further prolongation of adjuvant therapy in high-risk GIST and a very close follow-up after cessation of adjuvant therapy (especially in patients with higher mitotic index, who are especially susceptible for relapse).[94,105,106] The same observation was done for intermediate-risk and high-risk GIST in the EORTC 62024 trial,[97] suggesting that delaying relapse without a clear decrease in the relapse rate might actually exert a limited impact on survival. The highest impact is seen in the high-risk subgroup, probably with appropriate genotype profile. Recently reported interim results of an ongoing, nonrandomized phase II trial, evaluating the efficacy and safety of 5-year adjuvant imatinib in high-risk (based on modified NIH criteria) GIST after curative surgery, suggested a benefit of extended adjuvant imatinib therapy.[107] Currently, another nonrandomized phase II trial called PERSIST-5 (Post-resection Evaluation of Recurrence-free Survival for Gastrointestinal Stromal Tumors) is investigating 5 years of adjuvant imatinib therapy (400 mg daily) in patients with completely resected GIST (R0-resection) with significant risk of recurrence, with RFS as its primary endpoint.[108]

Characterizing the precise benefit of adjuvant imatinib in patients with moderate and high risk of recurrence by one of the new classifications, stratified by mutational subtype, is the next step in defining which patients should be treated. When using different risk-stratification schemes, such as the NCCN-AFIP, MSKCC (Memorial Sloan Kettering Cancer Center) nomogram, or the heat map, there is a consensus to treat all patients having at least 30% risk of recurrence, if their tumor carries a sensitive genotype.[30,34,37,50,51] Mutational status also has a predictive value for the clinical outcome after adjuvant treatment with imatinib and may help to tailor the treatment to patients with more sensitive mutations, such as *KIT* exon 11 mutants, or to exclude patients with imatinib-resistant mutations, such as *PDGFRA* D842V mutation. The data from randomized clinical trials ACOSOG Z9001 and SSGXVIII/AIO clearly demonstrated

Table 3
The most important clinical trials of adjuvant therapy with imatinib in primary GIST

Trial	Imatinib Dose and Duration	Inclusion Criteria	Efficacy Results	
			Primary Endpoints	Secondary Endpoints
ACOSOG Z9001[94] Randomized, phase III, placebo-controlled	400 mg daily (n = 359) vs placebo (n = 354) for 1 y	• KIT + primary GIST • Tumor size ≥3 cm • R0-resection • Low, intermediate or high risk of recurrence	1-y RFS: 98% with imatinib vs 83% placebo (83%) median FU: 19.7 mo HR 0.35, *P*<.0001	No significant difference in 1-y OS median FU: 19.7 mo HR 0.66, *P* = .47
ACOSOG Z9000[95] One-arm, open-label, phase II	400 mg daily (n = 107) for 1 y	• KIT + primary GIST • R0-resection • High risk of relapse ◦ Tumor size ≥10 cm *OR* ◦ Tumor rupture *OR* ◦ Peritoneal metastases <5	1-y OS: 99% 2-y OS: 97% 3-y OS: 97% Median FU: 4 y	1-y RFS: 94% 2-y RFS: 73% 3-y RFS: 61% Median FU: 4 y
SSGXVIII/AIO[96] Randomized, open-label, phase III	400 mg daily for 1 y (n = 200) vs 3 y (n = 200)	• KIT + primary GIST • High risk of recurrence[b]: ◦ Tumor size >10 cm *OR* ◦ Mitotic rate >10/50 HPFs *OR* ◦ Mitotic rate >5/50 and tumor size >5 cm *OR* ◦ Tumor rupture	5-y RFS: 65.6% after 3 y vs 47.9% after 1 y of imatinib (71.1% vs 52.3% in Intention-to-treat population) Median FU: 54 mo HR 0.46, 95% CI 0.32–0.65; *P*<.0001	5-y OS: 92% after 3 y vs 81.7% after 1 y of imatinib Median 54-mo FU HR 0.45, 95% CI 0.22–0.89; *P* = .019
EORTC 62024[97] Two-arms, open-label, randomized, phase III	400 mg daily vs observation (n = 908) for 2 y	• KIT + primary GIST • R0-resection • Intermediate or high risk of relapse[a]: ◦ Tumor size> 5 cm *AND/OR* ◦ Mitotic index >5/50 HPF	5-y imatinib failure-free survival (IFFS): 84% with imatinib arm vs 84% in control arm HR = 0.80, *P* = .23 5-y IFFS in high-risk GIST: 89% vs 73%; *P* = .11	RFS (at 3 y): 84% after 2 y vs 66% in control arm Median FU: 4.7 y HR 0.45, 95% CI 0.22–0.89; *P* = .019 OS: no significant difference

Kang et al[98] Single-arm, prospective, phase II	400 mg daily (n = 47) for 2 y	• Primary GIST with *KIT* exon 11 mutation • R0-resection • High risk of recurrence: ○ Tumor size ≥10 cm *OR* ○ Mitotic rate ≥10/50 HPFs *OR* ○ Tumor size ≥5 cm and mitotic rate ≥5/50 HPFs	1-y RFS: 97.7% 2-y RFS: 92.7% Median FU: 26.9 mo	—
Li et al[99] Open-label, nonrandomized, phase II	400 mg daily (n = 56) vs no treatment (n = 49) for 3 y	• KIT + primary GIST • R0-resection • Intermediate or high risk of recurrence[a]: ○ Tumor size >5 cm and/or ○ Mitotic rate >5/50 HPFs	RFS with imatinib vs no treatment: 1-y RFS: 100% vs 90% 2-y RFS: 96% vs 57% 3-y RFS: 89% vs 48% Median FU: 45 mo HR 0.188, 95% CI 0.085–0.417; *P*<.001	Significantly reduced risk of death with imatinib vs no treatment Median FU: 45 mo HR 0.254, 95% CI 0.070–0.931; *P* = .025

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; AE, adverse event; AIG, Arbeitsgemeinschaft Interistisch Onkologie; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; FU, follow-up; GIST, gastrointestinal stromal tumors; Gr, Grade; HPF, high-power microscope field; HR, hazard ratio; NIH, National Institutes of Health; OS, overall survival; RFS, recurrence-free survival; RTOG, Radiation Therapy Oncology Group; SSG, Scandinavian Sarcoma Group.

[a] NIH classification.

[b] Modified NIH classification.

that patients with GIST with KIT exon 11 mutation benefited mostly from adjuvant therapy.[94,96,101] Although controversial in the adjuvant setting, patients with metastatic GIST harboring mutations in *KIT* exon 9 may benefit from an increase of the imatinib dose up to 800 mg daily. Thus, *KIT* and *PDGFRA* genotyping in GIST should be mandatory also in the adjuvant setting.[109,110] In our centers, we routinely use tumor mutation analysis as a predictive tool in the adjuvant setting. There is also a consensus not to treat patients having 10% or less risk of recurrence, even if their tumor carries a sensitive genotype. Although the concept that only high-risk patients derive benefit from adjuvant imatinib has not been prospectively validated, based on these data, it would seem reasonable to offer adjuvant therapy to all patients who fall into a "high-risk" category, regardless of the risk-stratification model used.

The EORTC 62024 trial, which compared 2-year adjuvant treatment with imatinib versus observation only, provided some data on imatinib resistance on rechallenge after disease relapse in the patients with intermediate-risk and high-risk GIST who had undergone resection of the primary tumor. In the high-risk subgroup, a non–statistically significant trend in favor of the adjuvant arm was observed in terms of imatinib failure-free survival. This implies that adjuvant therapy does not lead to the development of secondary imatinib resistance.[97,111] This observation confirms observations from a subgroup analysis of the SGXVIII/AIO trial, which demonstrated that most patients who received prior adjuvant imatinib treatment do respond to a rechallenge with imatinib to treat recurrence.[112] Thus, a rechallenge with imatinib is indicated in case of disease recurrence after adjuvant imatinib. In rare cases of disease progression on imatinib, second-line therapy with sunitinib should be used.[113]

RECURRENT/METASTATIC GASTROINTESTINAL STROMAL TUMORS

Imatinib mesylate at initial dose of 400 mg daily is the first-line standard treatment of patients with metastatic, recurrent, and/or inoperable GIST.[9,114] Approximately two-thirds of patients with GIST achieve an objective response during imatinib treatment with a standard dose of 400 mg daily, and further 20% of patients show durable disease stabilization[4,9,10]; however, complete remissions are rare. A recently emerging issue is the surgical removal of disease remnants during imatinib therapy, which may lead to complete remission in selected patients with GIST after the achievement of a partial response (PR). This policy appears attractive, because the excision of the tumor would be performed before the development of imatinib resistance, thus reducing the risk of resistant clone selection, which theoretically might prolong durable remission. The dramatic efficacy of imatinib is time-limited, with a common persistence of viable GIST cells after imatinib therapy and the probability of developing resistant clones of GIST cells is proportional to the tumor mass.[61,115]

The optimal time for the implementation of surgical treatment is probably the moment of disease stabilization; that is, the radiological observation of maximal remission. Usually, this point is reached after a time interval of 6 to 18 months from the onset of imatinib therapy.[61] Several series of patients treated surgically during imatinib therapy have been published, although randomized trials to formally confirm a survival benefit did not prove feasible. Therefore, the ESMO consensus guidelines advise that for metastatic disease the surgical option during imatinib treatment should be individualized after sharing the decision with the patient in cases of uncertainty.[50]

Systemic therapy should be continued indefinitely, as its interruption is followed by relatively rapid tumor progression in virtually all cases, even after successful metastasectomy.[61,116,117] Two trials, 1 in Europe (EORTC 62023) and 1 in China, attempted to address the question of which patients with metastatic or recurrent GIST might benefit

from resection after upfront response to imatinib, but both were stopped prematurely due to poor accrual. The Chinese randomized trial reported data on 41 patients of 210 planned and showed a 2-year PFS of 88.4% in the surgery arm versus 57.7% in imatinib-alone arm (P = .08; median follow-up: 23 months).[118]

Despite the absence of randomized controlled trials, some general conclusions might still be drawn from the results of some single-institution retrospective studies examining disease control after resection in selected patients with limited metastatic disease (**Table 4**).[61,62,113,117,119–121] Generally, the conclusions of these studies were consistent. They demonstrated that complete excision of residual metastatic lesions was associated with improved prognosis, but outcome remained dependent on satisfactory responses to imatinib. Recently, the Spanish Group for Research in Sarcomas analyzed 2 cohorts of patients with advanced GIST: treated (n = 27) or not treated (n = 144) with surgery after PR or stable disease (SD) by imatinib. With a median follow-up time of 56.6 months, they concluded that median OS was strikingly superior in the group treated surgically during imatinib therapy (87.6 months) compared with 59.9 months in the imatinib-only group (P = .022). The 5-year OS rates were 79% and 50%, respectively. The effect of surgery remained significant in multivariate analysis. Median PFS differences were also superior for surgically treated patients: 73.4 months versus 44.6 months.[122] Researchers from Korea studied the role of surgery in patients with metastatic/recurrent GIST, who had at least 6 months of SD or response under imatinib. At a median follow-up of 58.9 months, median OS was not reached in patients who underwent surgery (n = 42), compared with 88.8 months in those who did not undergo surgery (n = 92) (P = .001). PFS was 87.7 and 42.8 months, respectively (P = .001). Surgery remained an independent factor for better PFS and OS in multivariate analysis.[123] Similarly, a data analysis from the Polish Clinical GIST Registry of 430 consecutive patients with inoperable/metastatic/recurrent GIST initially treated with imatinib showed that surgery of residual disease (n = 94) was an independent prognostic factor associated with longer OS and PFS. Eight-year OS and PFS rates were 67.4% and 50.4%, respectively, for patients undergoing resection of residual disease during imatinib therapy.[114] Systematic review of surgery and imatinib mesylate in treatment of advanced GIST also concluded that patients with stable or responding disease tend to have better PFS and OS after surgery when compared with those patients who have focal or generalized preoperative disease progression.[124] This was also supported by data from the prospective phase II RTOG 0132 trial for patients who underwent surgical debulking in the context of perioperative tyrosine kinase inhibitor (TKI) therapy.[81] The EORTC STBSG performed a cross-matched comparison of patients who underwent surgical resection at disease response (complete response, PR, or SD) with patients who were in response at the same time interval from imatinib start, but did not undergo surgery.[125] Fifty-eight patients were available for postsurgery survival analysis: 29 patients underwent resection of their metastatic disease while in response and they were matched with 29 nonoperated patients. Patients who underwent surgery for residual disease had a better survival after surgery than those who did not, especially during the first 3 years. Two-year postsurgery survival was 95.5% (95% confidence interval [CI] 87.2–100.0) versus 82.5% (95% CI 74.4–90.6) and 5-year postsurgery survival was 63.9% (95% CI 52.4–75.3) versus 56.0% (95% CI 43.3–68), respectively. A similar result was seen for postsurgery PFS, during the first year after surgery.[125]

Bauer and colleagues[120] analyzed the largest series of 239 consecutive patients with GIST who had undergone surgery for metastatic GIST in 4 large institutions from EORTC STBSG. In 79% of patients, R0/R1 resection was performed. OS data of patients in whom macroscopically complete resection could be achieved (R0/R1

Table 4
Series of patients with unresectable/metastatic GIST treated with surgery during imatinib therapy

	Number of Cases, Clinical Indications	Key Results
Raut et al,[62] 2006	n = 69 • Group I: Surgery at stable disease • Group II: Surgery at limited progression • Group III: Surgery at generalized progression	• Group I: 1-y PFS: 80%, 1-y OS: 95% • Group II: 1-y PFS: 33%, 1-y OS: 86% • Group III: 1-y PFS: 0%, 1-y OS: 0%
Rutkowski et al,[61] 2006	n = 141 unresectable/metastatic GIST treated initially with imatinib: • Group I (n = 24, 17%): resection of residual disease after complete/partial response or lack of further response to imatinib • Group II (n = 8, 6%): surgery as salvage therapy for progression after initially successful imatinib therapy	• Group I: 5 patients: imatinib not continued after surgery → 4 recurrences, 19 patients: imatinib continued after surgery → 1 recurrence 89.6% alive at last follow-up • Group II: 5/8 patients progressed Median follow-up time 12 mo
Gronchi et al,[117] 2007	n = 159 advanced/metastatic GIST treated initially with imatinib: • Group I (n = 27): surgery at response • Group II (n = 8): surgery at progression	• Group I: postsurgery PFS 96% at 12 mo and 69% at 24 mo; 100% alive at 12 mo (secondary progression: mainly related to postsurgical imatinib discontinuation, irrespective of pathologic or molecular variables) • Group II: postsurgery PFS 0% at 12 mo, 60% alive at 12 mo
DeMatteo et al,[119] 2007	n = 40 metastatic GIST treated with tyrosine kinase inhibitors • Group I (n = 20): response • Group II (n = 13): surgery at focal progression • Group III (n = 7): surgery at multifocal progression	• Group I: 2-y PFS of 61% and 2-y OS of 100% • Group II: 2-y PFS: 24% and the 2-y OS: 36%, median TTP: 12 mo • Group III: 1-y OS: 36%, median TTP: 3 mo Median follow-up 15 mo
Mussi et al,[113] 2010	n = 80 metastatic GIST after imatinib therapy: • Group A (n = 49): surgery at best response • Group B (n = 31): surgery at focal progression	• Group A: 2-y PFS: 64.4% and 5-y DSS: 82.9%, median PFS and DSS were not reached • Group B: 2-y PFS: 9.7%, median PFS: 8 mo and 5-y DSS: 67.6%, median DSS was not reached Morbidity: n = 13 patients (16.3%)
Bauer et al,[120] 2014	239 patients with GIST undergoing surgery for metastatic GIST • Group I (n = 177): Complete resection (R0/R1) • Group II: incomplete resection (R2)	• Group I: Median OS: 8.7 y, median OS was not reached when surgery was performed at remission, median TTP was not reached. • Group II: Median OS: 5.3 y, median OS was 5.1 y when surgery was performed at remission, median TTP: 1.9 y when surgery was performed at response. • Group I & II: No difference in median PFS was seen in patients progressing at time of surgery
Tielen et al,[121] 2012	n = 55 advanced/metastatic GIST after imatinib: • Group I (n = 35): responders • Group II (n = 20): nonresponders	• Group I: 48% recurrence/progression, Median PFS and OS were not reached 5-y OS: 78%. • Group II: 85% recurrence/progression, median PFS: 4 mo, median OS: 25 mo, 3-y OS: 26%.

Abbreviations: GIST, gastrointestinal stromal tumor; n, number of patients; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

group, 79% of patients) were compared with those with residual tumor after resection (R2). Median OS was 8.7 years in the R0/R1 group versus 5.3 years in the R2 group ($P = .0001$). When patients with progressing disease (focal or general progression) at time of surgery were excluded, median OS was not reached in the R0/R1 group and it was 5.1 years in the R2 group ($P = .0001$). Female gender, short interval of imatinib to surgery, resection status (R0/R1), remission at time of surgery (ie, non–progressive disease [PD]), and liver site were identified as positive prognostic factors. Median survival was not reached in R0/R1 patients with hepatic-only metastases compared with 8.7 and 5.9 years in patients with peritoneal ($P = .064$) versus peritoneal and hepatic metastases ($P = .001$ and $P = .024$). Similarly, when patients with PD at time of surgery were excluded, the median PFS was not reached for those patients with complete resection (R0/R1) versus 3.9 years in those in whom surgery resulted in incomplete resection (R2).[120]

Generally, the data mentioned previously support the role of surgery for residual metastatic disease in patients with GIST responding to imatinib, but it has never been clearly demonstrated prospectively whether this is due to the surgery itself or to patient selection. Nevertheless, as the available data point to surgery of residual disease in the absence of disease progression as the most independent prognostic factor for better outcomes in advanced GIST, a real impact on the natural course of the disease can be expected from this treatment strategy. Surgery for residual disease, based on individual decisions within a multidisciplinary tumor board, is estimated to be an option in approximately 20% of patients responding to systemic therapy.[61,117,126] It also should be mentioned that cytoreduction before treatment with imatinib does not seem to improve the prognosis.[127] Therefore, surgery should not be the first treatment step for first recurrence, with the exception of emergency indications. Elective surgery should be considered only as a treatment option after imatinib therapy has been initiated. Data from several series have shown surgery after tyrosine kinase inhibitors to be a feasible and safe procedure.[57,61,62,117,119,126] Under elective circumstances, overall complication rates varied from 12% to 33%, with bleeding, prolonged ileus, anastomotic leakage, and fistulae as the most frequently reported postoperative complications. Nevertheless, the need for reintervention due to postoperative complications remains low and no postoperative mortality was reported in these series. In case of surgery for emergency complications during tyrosine kinase inhibitors therapy, on the other hand, complication rates may increase to up to 50% and postoperative mortality has been reported.[57,62] Furthermore, emergency surgery for GIST seems to increase the chances of obtaining an R2-resection.[57] Mutilating surgery in metastatic GIST should be avoided, as systemic therapy is the mainstay of treatment in this setting and surgery is only adjunctive to tyrosine kinase inhibitors therapy. As mentioned earlier, continuation of imatinib after surgery is crucial.[61,116,117] **Fig. 2** illustrates an example of a carefully selected patient with oligometastatic disease confined to the liver, who derived long-term benefit from surgery on imatinib.

Another field for surgery in advanced GIST during treatment with tyrosine kinase inhibitors comprises the resection of focally PD to delay resistance to systemic therapy. In patients who develop limited resistance to imatinib, surgery might be considered, although the benefit is unknown. In cases of generalized progression, currently available data do not support a clinical benefit of surgery.[61,119] Raut and colleagues[62] reported that the 1-year PFS was 80%, 33%, and 0% for patients with SD, limited progression, and generalized progression, respectively. Similarly, we found that patients with responsive or SD had significantly improved RFS and OS when compared with patients with PD.[61] Surgery for focally progressive lesions on imatinib results is a median time to secondary progression of 6 to 14 months,[61,128] which in some cases

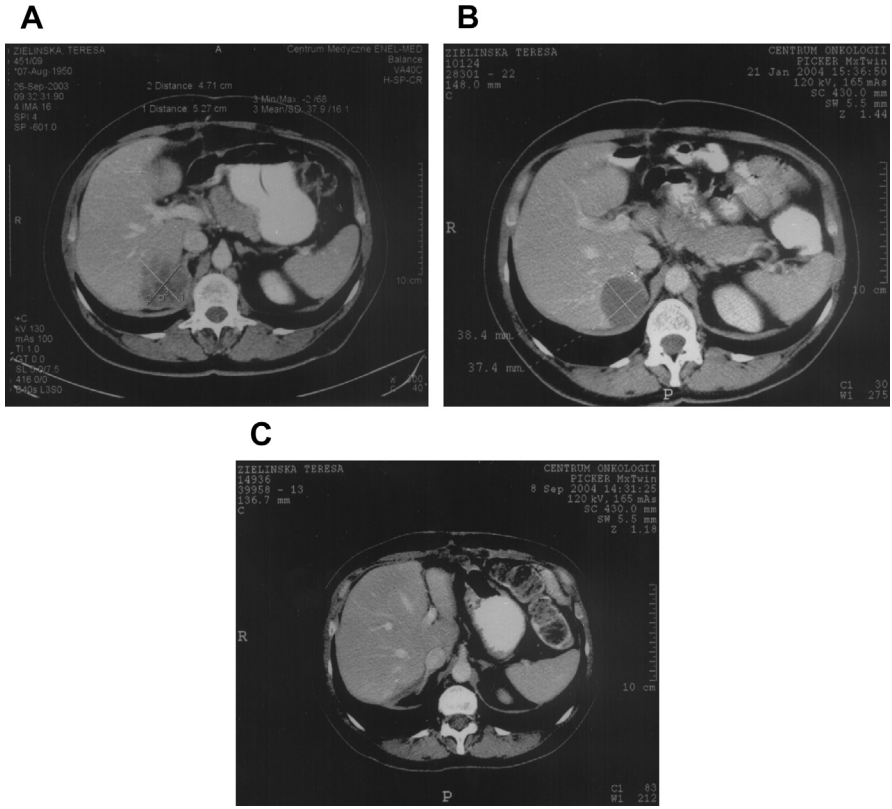

Fig. 2. (*A*) Oligometastatic GIST to the liver. (*B*) CT scan shows response after treatment with imatinib; metastasectomy was performed after response to imatinib. (*C*) Patient continues imatinib and remains in CR 11 years after surgery.

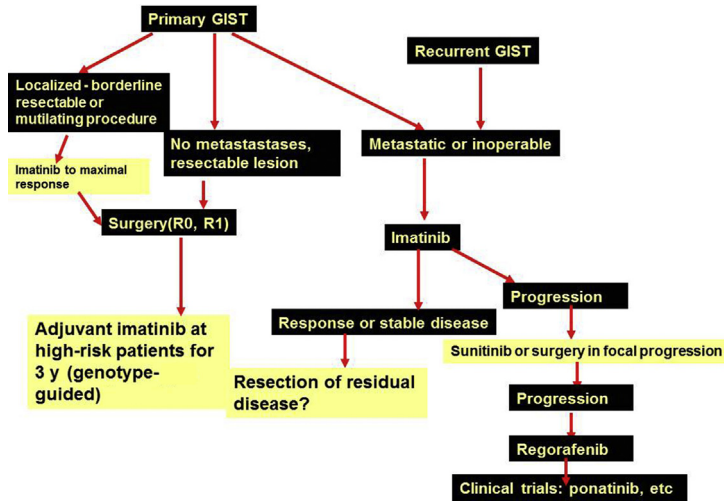

Fig. 3. The current algorithm of therapy in GIST, boxes with light background indicate the fields for combined therapy for surgery and tyrosine kinase inhibitors.

may delay a switch to treatment with sunitinib. Nevertheless, the final impact of this strategy on survival as well as the time of implementation of surgery is still controversial. Generally, the role of elective surgical therapy of advanced GIST during further lines of systemic treatment beyond imatinib is very limited and should be carefully individualized. Only few data are available on this matter.[129,130]

SUMMARY

Fig. 3 summarizes the current algorithm for the treatment of GIST.

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