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

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Background: Therapy for gastrointestinal stromal tumors (GIST) has changed significantly with the use of imatinib mesylate (IM). Despite the success of this drug in metastatic GIST, disease progression remains a perplexing clinical issue suggesting the need for multimodality management. There have been no prospective studies either evaluating the neoadjuvant use of IM in primary GIST or as a preoperative cytoreduction agent for metastatic GIST.
Methods: RTOG 0132/ACRIN 6665 was a prospective phase II study evaluating safety and efficacy of neoadjuvant IM (600 mg/day) for patients with primary GIST or the preop use of IM in patients with operable metastatic GIST. The trial continued postop IM for 2 years.
Results: Sixty-three patients were entered (52 analyzable), 30 patients with primary GIST (Group A) and 22 with recurrent metastatic GIST (Group B). Response (RECIST) in Group A was (7% partial, 83% stable, 10% unknown), in Group B (4.5% partial, 91% stable, 4.5% progression). Two-year progression free survival (Group A 83%, Group B 77%). Estimated overall survival (Group A 93%, Group B 91%). Complications of surgery and IM toxicity were minimal.
Conclusion: This trial represents the first prospective report of preop IM in GIST. This approach is feasible, requires multidisciplinary consultations, and is not associated with notable postop complications.
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KEY WORDS: GIST; neoadjuvant imatinib; locally advanced GIST; metastatic GIST

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal malignancy found in the GI tract. The recognition of these malignancies as an exclusive entity within the classification of soft tissue tumors and the subsequent delineation of their pathobiology has lead to a notable treatment breakthrough in the use of oncoprotein targeted therapy. Historically these tumors were resistant to medical management and patients with metastatic or recurrent GIST had an average survival of between 6 and 18 months [1]. Retrospective single institutional surgical series for primary GIST have consistently noted a 5-year survival of 50% overall with significantly worse outcome for those patients considered in the high risk category, those with large tumors or tumors with high mitotic rates [2,3]. Imatinib mesylate (IM), a small molecule inhibitor of the GIST oncoprotein KIT and PDGFRA, has proven efficacy in phase II and III metastatic disease trials with reported clinical benefit of over 80% [4]. However, despite the success of this drug, it is apparent that disease progression remains a perplexing problem and that multimodality management may provide added value.

Recently completed adjuvant trials of imatinib for primary GIST have indicated a benefit for this drug principally in patients with larger tumors and manifested by enhanced disease free survival [5]. However, ideal dose and duration of imatinib in this setting remain a question. Other than retrospective small institutional reports, the neoadjuvant use of imatinib in GIST has not been investigated. In addition, the use of imatinib with the intent of cytoreduction followed by surgical resection in patients with potentially resectable metastatic disease has not been evaluated in prospective clinical trials. Radiation Therapy Oncology Group (RTOG) 0132 was designed as a nonrandomized prospective phase II trial to evaluate the neoadjuvant use of imatinib (600 mg/day) for patients with advanced primary GIST and the preoperative use of imatinib in a group of patients with potentially operable metastatic/recurrent disease to provide preliminary data regarding the efficacy and

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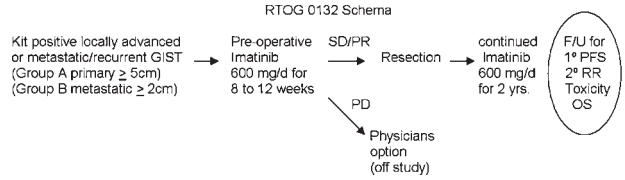

Fig. 1. Schematic representation of RTOG 0132/ACRIN 6665 trial—Phase II Trial of Neoadjuvant/Adjuvant Imatinib Mesylate for Advanced Primary and Metastatic/Recurrent Operable Gastrointestinal Stromal Tumor.

safety of this approach (Fig. 1). In all patients, the trial was designed to continue imatinib (600 mg/day) for a postoperative time frame of 2 years. This report provides a short-term analysis of these clinical trial patients.

MATERIALS AND METHODS (TRIAL DESIGN)

RTOG 0132/ACRIN 6665 was open to accrual from February 2002 through June 2006. Patients were entered from 18 RTOG institutions after institutional IRB approval. Sixty-three patients were entered into the trial with 52 analyzable (3 withdrew, 8 ineligible). For the purpose of the study trial design advanced primary GIST was defined as ≥5cm. The trial eligibility included documented (KIT positive) GIST patients with either primary disease (≥5cm) or metastatic/recurrent (≥2cm) disease. Patients were treated with the study drug for a period of 8–12 weeks prior to surgery. Frozen and fixed paraffin tumor tissue were collected both pre- and post-imatinib and, in most cases, the second tumor specimen was acquired from the surgical resection. The study included correlative endpoints of planned tissue analyses for mutation and genomic arrays from each patient's GIST. Clinical endpoints included drug related toxicity and surgical complication assessment, tumor response to preoperative therapy, time to progression and progression free and overall survival. Imatinib was stopped on the day prior to surgery and resumed as soon as possible postoperative and then continued for 2 years as a postoperative adjuvant (Fig. 1). FDG-PET scans were obtained pretreatment within one week after starting IM and before surgery. CT scans were also obtained pretreatment, and postoperative and then every 3 months postsurgery. The selected duration of 8–12 weeks for the intended pre-surgical administration of imatinib was conceptualized based on the early results of the phase II study of imatinib for metastatic disease [4]. This study concluded a median time to partial response of 2.7 months and therefore RTOG 0132 extrapolated these data to arbitrarily assign this time frame for preoperative therapy.

STATISTICS

Time to progression, progression-free survival, and overall survival were measured from the date of registration. Time to progression was estimated by the cumulative incidence method to account for the competing risk of death without progression [6]. Failure was defined as local or distant recurrence or progression. Progression-free and overall survival were estimated with Kaplan–Meier method [7]. Failure for progression-free survival was defined as local or distant recurrence or progression, or death due to any cause. Failure for overall survival was death due to any cause. RECIST was used to measure objective response to preoperative imatinib [8]. Adverse events were scored using the Common Toxicity Criteria (CTC) version 2.0; only events scored as definitely, probably, or possibly related (or unknown relationship) were considered related to protocol treatment. Only patients eligible per protocol criteria that started protocol treatment were included in analysis.

TABLE I. ROTG 0132 Patient and Tumor Characteristics (n = 52)

	Primary patients (n = 30)	Recurrent/ metastatic patients (n = 22)
Age (years)		
Median	64	53
Range	42–84	24–77
Gender		
Male	15 (50.0%)	13 (59.1%)
Female	15 (50.0%)	9 (40.9%)
Zubrod performance status		
0	9 (30.0%)	18 (81.8%)
1	18 (60.0%)	4 (18.2%)
2	3 (10.0%)	0 (0.0%)
Tumor size, largest diameter (cm)		
Median	8.9	5.8
Range	5.0–24.5	2.0–15.5
Disease location		
Abdomen	1 (3.3%)	1 (4.5%)
Duodenum	1 (3.3%)	0 (0.0%)
Intra-abdominal periumbilical	1 (3.3%)	0 (0.0%)
Large intestine	1 (3.3%)	0 (0.0%)
Liver	0 (0.0%)	6 (27.3%)
Liver and perirectum	0 (0.0%)	1 (4.5%)
Pancreas	1 (3.3%)	0 (0.0%)
Pelvis	0 (0.0%)	2 (9.1%)
Perirectum	2 (6.7%)	0 (0.0%)
Peritoneum	0 (0.0%)	10 (45.0%)
Rectum	1 (3.3%)	0 (0.0%)
Small intestine	6 (20.0%)	2 (9.1%)
Stomach	16 (53.3%)	0 (0.0%)

RESULTS

The median follow-up for this study is 3 years. Of the 52 patients, median age was 58.5 (24–84). There were 28 males (54%) and 24 females (46%) with a Zubrod performance status at study entry of 0 in 52% (27), 1 in 42% (22), and 2 in 6% (3). There were 30 patients (58%) in Group A—primary GIST and 22 patients (42%) in Group B—metastatic/recurrent GIST. The majority of primary GIST presented in the stomach (53%) followed by small bowel (20%), and for patients with metastatic/recurrent GIST the most common location was abdominal/peritoneum (49.5%) (Table I). Unusual locations for primary GIST in Group A included pancreas, duodenum, colon, and rectum, with these anatomic sites possibly reflecting the individual investigator's rationale for including these patients in the trial. The median tumor size in Group A was 9 cm (5–25) indicating that this patient group had at least an intermediate recurrent risk profile (Table I).

Imatinib was a well tolerated drug in this series with preoperative toxicity profile of 21% grade 3, 12% grade 4, and 2% grade 5 (Table III). The median number of days that patients received preoperative imatinib was 65 and the median time of imatinib discontinuation prior to planned surgery was 2 days indicating that the majority of patients tolerated drug up to the surgical date. The preoperative response in Group A by RECIST was partial in 2 patients (7%), stable in 25 (83%), and unknown in 3 (10%); in Group B partial in 1 (4.5%), stable in 20 (91%), and progression in 1 (4.5%).

The surgical complications listed in Table II were consistent with a surgical patient series involving both extensive and reoperative abdominal surgery. These complications were recorded on an RTOG data form and represent events in the postoperative time frame from the initial hospitalization. The respiratory complications consisted of two cases of bacterial pneumonia and three nonspecific respiratory related complications (fever and atelectasis). The reported anastomotic disruption followed a colectomy and resulted in re-operative surgery and a diverting colostomy. The anastomotic breakdown in this patient

TABLE II. Surgical Complications (n = 45)

	Number	Percent
Wound infection	3	6.7
Hemorrhage requiring blood or blood product	2	4.4
Respiratory event	5	11.1
Cardiac event	3	6.7
Surgical death	1	2.2
Anastomotic disruption	1	2.2
Other surgical complication	15[a]	33.3
Abscess (intra-abdominal)	2	4.4

Recorded post-operative surgically induced complications during the initial hospitalization.
[a]Other surgical complication: 5, jaundice or elevated LFTs; 4, renal dysfunction or UTI; 1, pancreatitis; 1, persistent ileus; 1, DVT; 1, severe malnutrition requiring TPN; 1, sepsis; 1, bile leak.

was felt to be secondary to ischemia. The 4% incidence of hemorrhage resulted in intra-operative blood volume replacement. However, the median surgical blood loss for the entire group was 475 ml with a range of minimal to 2,000 ml. There were no instances of re-operative surgery for postoperative hemorrhage. The three postoperative listed cardiac complications consisted of arrhythmia (2), and a non-ST elevation biomarker documented MI. The median length of post-operative hospital stay was 9 days. There was 1 post-surgical death on day 64 secondary to sepsis and this occurred in Group B following a debulking procedure where gross tumor was left behind. Of the 52 evaluable patients in this series only 7 patients (13%) were not operated on. The reason surgery was not performed was inoperable or unresectable disease in 5, physician refusal in 1, and unknown in 1.

The type of surgical resection performed consisted of a single or partial organ resection in 53% (24), multiple organ resection in 36% (18) and a variety of combinations of organ resection along with peritoneal implants in the remaining. In addition, 7 patients had radio-frequency ablation of hepatic lesion(s). This resulted in the following classification of surgical procedures: In Group A the majority (20) had R0 resections (77%) (removal of all gross and microscopic disease), there were 4 (15%) R1 resections (removal of all gross disease but with microscopic disease left behind), and 2 (8%) R2 resections (gross disease left behind); in Group B there were 11 (58%) R0 resections, 1 (5%) R1 resection, 6 (32%) R2 resections, and 1 (5%) unspecified.

The postoperative Imatinib related toxicities are listed in Table III. There were 29% grade 3, 16% grade 4 and a 4% grade 5 (one grade 5 occurred in a Group A patient with a fatal postoperative CNS bleed which was thought to be drug related.) Postoperative imatinib was given for a median 638 days with 67% of surgical patients receiving at least 18 months of a planned 2 years of therapy. In 7 patients (16%) postoperative Imatinib was delayed for a median of 69 days secondary to a surgical complication. In the remaining 38 patients the median time to postoperative Imatinib was 24 days.

The estimated 2-year rate of time to progression is 13.8% overall with 13.9% in Group A and 13.6% in Group B. The 2-year estimated progression free survival (PFS) is 80.5% overall with 82.7% in Group A and 77.3% in Group B (Fig. 2). Of the 17 patients with documented progressive disease 9 were on imatinib at the time of progression: 3 out of 9 progressing patients in Group A and 6 out of 8 progressing patients in Group B. The 2-year estimated overall survival (OS) in Group A was 93.3% and 90.9% in Group B with median follow-up of 3 years for surviving patients (Fig. 3).

TABLE III. Imatinib Related Toxicities

Category	Toxicity	Grade
a: Pre-operative (4+)		
Blood/bone marrow	Neutropenia	4
Blood/bone marrow	Neutropenia	4
Blood/bone marrow	Neutropenia	4
Blood/bone marrow	Neutropenia	4
Infection febrile neutropenia	Infection with unknown ANC	4
Metabolic/laboratory	Hyponatremia	4
Pulmonary	Pneumonitis	5
Cardiovascular (general)	Thrombosis NOS	4
Gastrointestinal	Colitis NOS	4
Category	Toxicity	Grade
b: Post-operative (4+)		
Gastrointestinal	Anorexia	4
	Tracheo-oesophageal fistula NOS	4
Gastrointestinal	Anorexia	4
	Ileus	4
Gastroinestinal	Vomiting NOS	4
Constitutional symptoms	Constitutional symptoms—other	5
Pulmonary	Pyrexia	4
	Hypoxia	4
	Pulmonary—other	4
Cardiovascular (general)	Edema NOS	4
Metabolic/laboratory	Hypocalcemia	4
Metabolic/laboratory	Blood amylase increased	4
Hemorrhage	Hemorrhagic stroke	5
Blood/bone marrow	Hemoglobin decrease	4

All grades 4 and 5 IM related toxicities using the common toxicity criteria version 2.0.

DISCUSSION

Imatinib, an oral KIT tyrosine kinase inhibitor, has proven efficacy in the majority of patients with advanced metastatic/recurrent GIST. The reported significant clinical benefit based on this rationally designed drug has become a paradigm for the use of molecular targeted therapeutics in solid tumors [9,10]. The combined use of imatinib and surgical resection has been the subject of initial investigations but with the exception of the American College of Surgeons Oncology Group (ACOSOG) postoperative adjuvant studies, this information is based on retrospective data collected from small single institutional reports [11–14]. To our knowledge there have been no prospective reports utilizing imatinib for primary GIST in a neoadjuvant regimen or with planned surgical resection following drug administration in the metastatic/recurrent disease setting. The objective of Radiation Therapy Oncology Group Protocol 0132 was to determine the outcome and toxicity of imatinib given for 8–12 weeks as a neoadjuvant agent

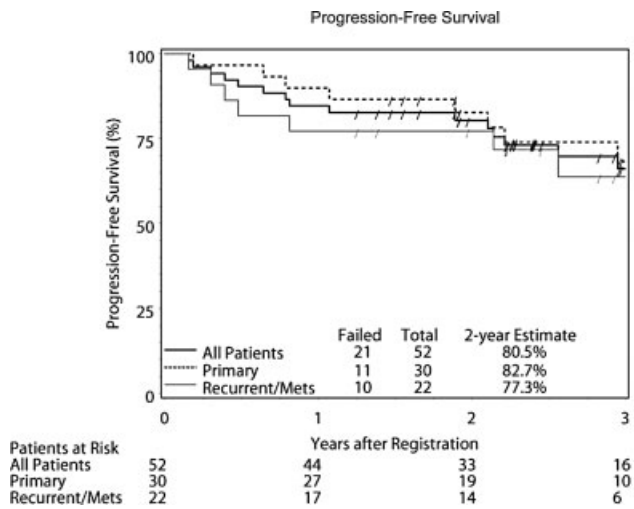

Fig. 2. Progression free survival with a median F/U of 3 years.

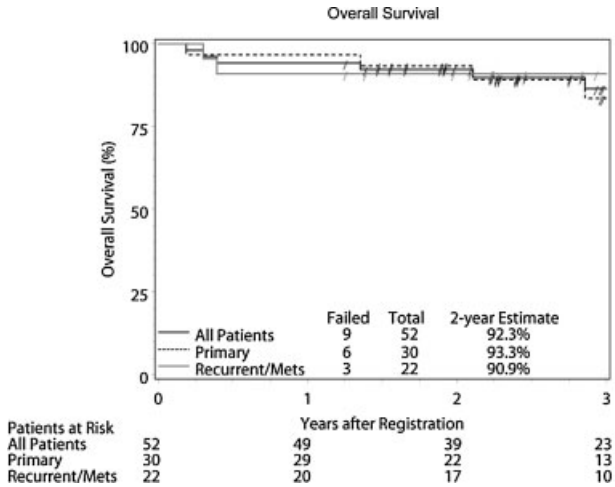

Fig. 3. Overall survival with a median F/U of 3 years.

prior to a planned resection of intermediate/high risk primary GIST or given as a cytoreductive agent prior to planned resection of metastatic/recurrent GIST. This study was designed as a phase II feasibility trial prospectively evaluating the combination of imatinib and surgery in this clinical setting. Although RECIST was used to quantitate response in this study, in the last few years clinical experience has suggested that cytoreduction induced by imatinib may not be reflective by the strict use of RECIST criteria [15]. Therefore it is likely that future design consideration of induction imatinib trials may require modifications to consider a longer duration of preoperative therapy as well as non-traditional methodology for response verification.

Toxicity data were evaluated collectively, however because there were two distinct patient groups in this series (Group A—primary GIST and Group B—metastatic/recurrent GIST), the outcome data were analyzed for each group separately. The protocol directed the extent of the pre-operative imatinib to 600 mg/day for 8–12 weeks. The median was 9.9 weeks in Group A and 8.9 weeks in Group B. The reported postoperative complications were quite uniform for both groups and not out of the ordinary for a surgical series representing extensive abdominal surgery. The most common complications were wound infection and cardio-respiratory events with minimal drug effects on wound disruption or anatomatic breakdown despite discontinuing imatinib within 48 hr of surgery and re-initiating within a median of 24 days. Postoperative postponement of imatinib administration was documented due to a surgical complication in only seven patients.

Group A consisted of 30 patients with primary GIST of intermediate to high risk disease (median size of 9 cm) with the majority of the non-gastric GIST measuring 5–10 cm in diameter. The treatment recommended for patients with primary GIST is generally expeditious and complete surgical resection. Thus surgery, as the first treatment modality, remains the gold standard at present even after the noted clinical success of the tyrosine kinase inhibitors for GIST. However, when RTOG 0132 was conceptualized in 2001, the potential benefit of neoadjuvant imatinib in these primary GIST surgical patients, as well as adjuvant therapy after surgical resection was unknown. In addition to the obvious potential advantages of enhanced PFS and OS in a GIST patient population with a recurrence risk historically of up to 80% [16], the rationale for the neoadjuvant use of imatinib was that this approach might result in less short- and long-term surgical morbidity, and in organ preservation and function sparing. In addition surgical manipulation of smaller responding tumors could result in less intraoperative extravasation of viable cells as well as provide for an in vivo drug sensitivity evaluation and rationale for continuation of postoperative adjuvant therapy [17,18].

In our series of primary GIST patients delaying surgery for the imatinib induction duration does not appear to have had any adverse effects, in that no patient experienced progression and there were two documented measured partial responses using RECIST. A complete gross and microscopic resection was performed in 77% of the patients and the majority of these had single organ resections. In addition, smaller diameter tumors in this group of patients were located in uncommon GIST sites such as duodenum, rectum, GE junction and partial organ preservation and function sparing was reported in the majority of these cases. With a median follow-up of 3 years there have been nine patients with disease progression in Group A, with an estimated 1-, 2-, and 3-year progression-free survival of 90%, 83%, and 68% respectively (Fig. 2). Of the nine failures, three were noted in patients while on imatinib (one gastric and two small intestine). Estimated overall survival at 1, 2, and 3 years was 97%, 93%, and 84%, respectively (Fig. 3). Of the six cumulative deaths in this group, one was treatment related (CNS bleed) and only three were related to progressive GIST. The other two deaths in this patient group were from causes unspecified or unknown.

This prospective series represents a relatively small group of patients. It is to date, however, the only multi-institutional trial to address the question of neoadjuvant followed by adjuvant therapy in GIST. The progression and survival results are quite favorable in comparison to historical single institutional surgical series for high risk GIST patients where median disease-free survival ranged from 7 to 20 months [2]. In addition there are just a few retrospective reports in the literature evaluating neoadjuvant imatinib for primary GIST. The group from the MD Anderson reported 1 recurrence in 11 such patients with a median follow-up of 19.5 months [19]. A group from Milan reported on three patients after neoadjuvant imatinib with no recurrences after a median of 21 months [20].

This clinical treatment paradigm is just beginning to be explored and awaits further evaluation. It is probable, however, that neoadjuvant therapy has no more overall advantage for relapse-free survival than adjuvant therapy in intermediate and high risk patients. The exception to this is the theoretical advantage of neoadjuvant administration in primary GIST patients where a responsive tumor might be downsized to allow for less morbid surgery with organ or function-sparing intent. In addition, there may be benefits in terms of decreased seeding of tumor cells and decreased tumor bleeding at the time of resection. The ACOSOG phase II and III trials of 1 year of postoperative adjuvant imatinib in primary GIST suggest a demonstrative benefit particularly for patients with high risk GIST (>10cm). The phase II Z9000 study (median tumor size 13 cm) recently reported a recurrence-free survival of 94%, 73%, and 61% at 1, 2, and 3 years, respectively [21]. Our trial (median tumor size 9 cm) although smaller in patient numbers compares favorably with 83% progression free survival at 2 years. It is conceivable, however, that this enhanced benefit is likely due to the effect of 2 years of postoperative imatinib rather than the 9.9 weeks of neoadjuvant therapy. The 68% PFS at 3 years in our series may be further evidence of the need to extend the length of adjuvant therapy for a longer duration and whether the drug is given preoperatively or postoperatively in a well defined high risk primary GIST population may not be as significant relative to the total exposure time.

Group B consisted of 22 patients with documented metastatic/recurrent GIST. This represents a rather heterogeneous group and likely subject to some selection bias. However, all of these patients had newly diagnosed, untreated metastatic/recurrent GIST and were initially reviewed by a surgeon for the potential of surgical resection. They were all managed prospectively with intent to treat. Only 1 of the 22 patients had progression during the intended preoperative imatinib time frame. Although less common than in the primary GIST group, the majority of patients in Group B (58%) underwent surgery to

include resection of all gross and microscopic disease. Previous surgical series evaluating this approach for metastatic GIST often retrospectively reviewed a limited subset of all metastatic GIST patients on imatinib and evaluated those patients that were managed by surgical resection either because of prolonged stability, focal progression, drug associated surgical emergency (perforation or bleeding), or generalized progression without other options [22–25]. The recurring theme in these reports is that patients with stable or responding disease tend to have better progression-free and overall survival after surgery when compared to those patients who have focal or generalized preoperative disease progression. Our operative series includes only those patients who have responded to or stabilized on preoperative imatinib. In addition, most retrospective series report a median duration of preoperative imatinib of 12 months or more. Our series had a median duration of imatinib to surgical resection of approximately 2.1 months. Based on recently published data from long term follow-up of the phase II imatinib trial for metastatic GIST their reported median time to response was 2.7 months [26], however, 25% of the patients did not reach measurable partial response until 5.3 months. These data would support the use of a longer pre-surgery duration of preoperative imatinib than in our trial to potentially achieve maximal response and perhaps enhance surgical clearance of metastatic tumor.

Historically surgical intervention for patients with metastatic GIST in the pre-imatinib era was not associated with a good outcome [27]. The combination of surgical resection coupled with imatinib may alter that outcome in certain selected patients. Our prospective series of preoperative imatinib in metastatic GIST patients compares favorably to retrospective reports published from institutional series. A series of 23 patients from Dana Farber Cancer Center with either unresectable primary or metastatic GIST underwent surgical resection following a stable assessment on imatinib with a reported PFS of 80% at 12 months [24]. Similarly, in a series from MSKCC, 20 patients with resectable GIST with responding/stable disease resected after a median of 15 months of imatinib resulted in a 2-year PFS of 61% [22]. The estimated progression free survival in our series at 1 and 2 years was 77% (Fig. 2). There were eight cumulative disease progressions in Group B with only three in the first 2 years. The French phase III imatinib discontinuation study BFR14 demonstrated significant disease progression in the group of metastatic GIST patients where imatinib was stopped after 1 year [28]. Although our series evaluated patients with a planned discontinuation of drug after 2 years, future study design should consider longer duration. With a median follow-up of 3 years the overall survival at 1, 2, and 3 years was 91% (Fig. 3). These results are promising considering that progression in metastatic GIST is an expected occurrence in the majority of patients on imatinib after 2 years without surgical intervention. Because of the small numbers and the phase II trial design these early results in Group B cannot provide a definitive statement regarding the effectiveness of this management. A phase III trial to address this important question is certainly warranted.

The use of neoadjuvant imatinib in the case of locally advanced primary GIST or the use of preoperative imatinib in the case of metastatic GIST was addressed by RTOG 0132 and the short term results are reported. This approach is feasible, requires multidisciplinary considerations, and is not associated with notable postoperative complications.

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