

Imatinib as Preoperative Therapy for Primary Large Gastrointestinal Stromal Tumor

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ABSTRACT

AIM: This study aimed to explore whether preoperative imatinib mesylate (IM) can improve the surgical safety and prognosis of patients with large gastrointestinal stromal tumor (GIST).

METHODS: Patients with large GIST in a single medical institution (Department of General Surgery, West China Hospital, Sichuan University, China) from February 2007 to November 2011 participated in this study. Patients were divided into two groups (preoperative treatment group and control group) based on whether they have taken IM preoperatively. All patients underwent laparotomy and postoperative adjuvant therapy. Recurrence/metastasis-free survival (RFS) and overall survival (OS) were calculated based on Kaplan–Meier analysis.

RESULTS: A total of 50 patients were enrolled in this study, of whom 17 patients were classified in the preoperative treatment group and 33 patients were in the control group. No significant differences in clinical pathologic features and demographic data before starting any treatment ($P>0.05$) were observed between the two groups. The preoperative treatment group was superior to the control group with respect to intraoperative bleeding volume, multivisceral resection rate, and R0 resection rate ($P<0.05$). Lower recurrence or metastasis rates were reported in patients in the preoperative treatment group

compared with those in the control group two years after surgery ($P=0.026$). However, no statistically significant difference was observed in the two-year OS between the two groups ($P=0.347$).

CONCLUSIONS: Preoperative IM in patients with large GIST was safe and feasible. Moreover, preoperative IM could reduce the intraoperative bleeding volume and multivisceral resection rate, and improve the R0 resection rate. It also significantly improved the RFS at two years post-operation.

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Key words: Imatinib mesylate; Gastrointestinal stromal tumor; Preoperative therapy; Adjuvant therapy

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INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor in the alimentary canal, and is considered to originate from Cajal cells (located in gastrointestinal pacemaker cells between the smooth muscle cells of the gastrointestinal muscular layer) or precursor cells^[1,2]. The annual incidence of GIST is about 10 to 15 cases per million^[3,4]. GIST can be found in any part of the alimentary canal, but mostly occurs in the stomach and small intestine^[5]. The current standard treatment of GIST is complete surgical resection to obtain a negative margin. However, complete surgical resection is difficult because of the immense diameter and rich blood supply of a large GIST. A tumor recurrence of 50% two years after surgery was reported among patients who had GIST diameters greater than 10 cm and underwent complete GIST resection, thereby affecting the long-term survival of patients^[6,7].

Imatinib is a small molecule tyrosine kinase inhibitor (TKI) that can effectively inhibit KIT and PDGFR. Many previous studies reported that treatment with imatinib as adjuvant therapy benefits GIST patients. However, clinical studies on the preoperative treatment of GIST with imatinib are rare. Preoperative treatment can reduce tumor size, surgical range, and intraoperative bleeding risk; avoid unnecessary resection of joint organs; and increase the opportunity of radical resection^[8,9]. The clinical experimental results of the first preoperative treatment with imatinib of stage II Eisenberg proved that imatinib is safe and effective^[10].

We conducted this study to examine whether preoperative imatinib treatment in patients with large GIST will improve operation safety, recurrence/metastasis-free survival (RFS), and overall survival (OS).

METHODS

Patient selection

All patients who were diagnosed with large GIST were recommended to take imatinib mesylate (IM) preoperatively by clinicians. A total of 33 patients who refused to take IM and opted for direct surgical treatment comprised the control group. By contrast, 16 patients who took IM before surgery comprised the preoperative treatment group. The inclusion criteria were as follows: (1) GIST patients with tumor diameters greater than 10 cm, without other malignant tumors; (2) patients who were pathohistologically and immunohistochemically diagnosed with GIST; (3) all patients received regular postoperative medication; and (4) patients who were at least older than 18 years. The exclusion criteria were as follows: (1) patients with metastasis and severe cardiopulmonary, liver, and kidney diseases; (2) patients subjected to single surgical or medical treatment; and (3) pregnant and lactating women.

Patients' gender, age, tumor site, tumor diameter, and intraoperative and postsurgical conditions were recorded. After hospital admission, the patients actively underwent electronic gastroscopy, whole abdominal enhanced CT, gastrointestinal barium radiography, and chest plain film. Frozen slices of incisional margin and tumor were conventionally obtained during surgery. Based on the NCCN guide, endoscopic ultrasound-guided fine needle aspiration biopsy or needle biopsies guided by abdominal CT were carried out to clarify the diagnosis of the preoperative treatment group^[11]. The protocol was approved by the Institutional Review Board and Committee of West China Hospital of Sichuan University. All patients signed informed consents and voluntarily accepted the treatment.

Imatinib therapy

The dose of imatinib (Glivec, Novartis Pharmaceuticals, Basel, Switzerland) taken by patients in the preoperative treatment group was 400 mg/d. The treatment effect was assessed according to Choi criteria^[12] combined with tumor size and density (CT value). Tumors were surgically resected when signs of advanced tumor were observed or IM treatment effects reached the maximum (two continuous CT results indicate no improvement). All patients conventionally underwent outpatient review once every two to four weeks, including routine blood tests; liver, kidney, and cardiac function evaluations; and abdominal enhanced CT. Seventeen cases in the preoperative treatment group stopped medication one week before surgery. Medication resumed after the surgery upon the recovery of gastrointestinal functions and drug tolerance. One-year and three-year adjuvant were recommended for patients with intermediate and high risky, respectively.

Operation procedures

All patients underwent traditional surgery in the General Surgery of West China Hospital, Sichuan University. The surgical principles were as follows: (1) the surgery aimed to maintain as many residual organ functions as possible, and achieve R0 resection; (2) during complete tumor resection, tumor rupture and intraoperative spreading were avoided whenever possible; (3) unless signs of metastasis in surgery were observed, conventional cleaning was unnecessary because of the few lymph node metastases of GIST; and (4) considering the large tumor diameter and surgical difficulty, intraoperative probing should be performed carefully and gently. According to the surgical conditions for tumors that infiltrate adjacent tissues and organs in some patients, combined organ resection should be conducted, including combined splenectomy and resection of pancreatic tail, gallbladder, and kidney. The operator recorded surgical resection as follows: R0 resection (complete gross and microscopic resection) and R1 (complete gross resection).

Postoperative follow-up

Every three months after surgery, outpatient follow-ups or calls were conducted until December 2013. Follow-up included a review of abdominal CT or MRI, routine blood test and classification, evaluation of liver and kidney functions, and specific information of medication. RFS is defined as the recurrence or metastasis of tumors from the surgical day to the time when the tumor advances. OS refers to the time from the surgical day to death. The median follow-up time was 29.2 months (range: four to 71 months).

Statistical analysis

Data are expressed as the mean±SD. Categorical data were analyzed by the Chi-square test or Fisher's exact probability test. Wilcoxon test was used to test ranked data. Student's *t*-test was used to compare continuous variables between the two groups. The OS and RFS were estimated by the Kaplan–Meier method. Statistical analyses were performed using SPSS 17.0 software package. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 50 cases with primary large GIST without metastasis from February 2007 to November 2011 were included in this study. Seventeen patients chose to take IM as a preoperative treatment, and the median medication time was 3.5 months (range: one to 7.5 months). The remaining 33 patients refused preoperative medication and chose direct surgery. Both groups consisted mostly of male patients. Eleven cases of males (65%) and six females (35%) comprised the preoperative treatment group, with a median age of 56 years (range: 29 to 80 years). Nineteen male cases (58%) and 14 females (42%) comprised the control group, with a median age of 52 years (range: 29 to 74 years). During follow-up, five cases were lost, namely, two cases in the preoperative treatment group and three cases in the control group. Table 1 shows a summary of the clinical pathologic features of both groups. No statistical differences in population data, tumor sites, mitotic counts, tumor diameter during the first visit, and postsurgical hospital stay time were observed between the groups. Specific data are shown in table 1.

IM therapy and surgical outcome

The median time of patients taking IM in the preoperative treatment group was 3.5 months (range: one to 7.5 months). One patient chose

Table 1 Demographic data and clinical pathologic features between two groups

Variables	preoperative treatment group (n=17)	control group (n=33)	P value
Gender			0.626
Male	11	19	
Female	6	14	
Age (years)			0.336
Median	56	52	
Range	29-80	29-74	
Tumor location			0.850
Stomach	8	17	
Small intestinal	5	11	
Extra GIST	4	5	
Tumor diameter (cm)	13.76±4.40	14.71±5.67	0.341
10cm to 15cm	14	26	
>15cm	3	7	
Mitotic counts			0.766
≤5/50 HPF	8	15	
6 to 10/50 HPF	6	10	
>10/50 HPF	3	8	
Preoperative medication time (month)			
Median	3.5	-	-
Range	1-7.5	-	-
Postoperative hospital stay	17.45±3.65	18.25±2.52	0.440

surgical treatment after 4.5 months of regular medication because of disease progression. No case was completely relieved, 14 cases were partially relieved, and two cases demonstrated stable conditions. Figure 1 shows the changes in tumors using abdominal CT scan after preoperative IM therapy. All cases started medication once intestinal functions recovered and drugs were tolerated after surgery. The median medication time of all patients after surgery was 14.5 months (range: five to 31 months). During medication, some patients reported of slight edema, gastrointestinal reactions, fatigue, discomfort, and anemia. No patient stopped medication because of severe drug side effects.

Table 2 summarizes the intraoperative and postsurgical complications for the two groups. The intraoperative bleeding volumes of the preoperative treatment and control groups were 691.18±290.60 and 887.88±276.71 mL ($P=0.023$), respectively. Two cases (11.8%) in the preoperative treatment group underwent joint organ resection, whereas 13 cases (39.4%) in the control group underwent combined organ resection ($P=0.043$). In the preoperative treatment group, one case underwent gastrectomy+cholecystectomy, and another case underwent gastrectomy+partial hepatectomy. In the control group, four cases underwent gastrectomy+cholecystectomy, and the other nine cases underwent surgical resection (Table 3). Fourteen cases (82.3%) in the preoperative treatment group and

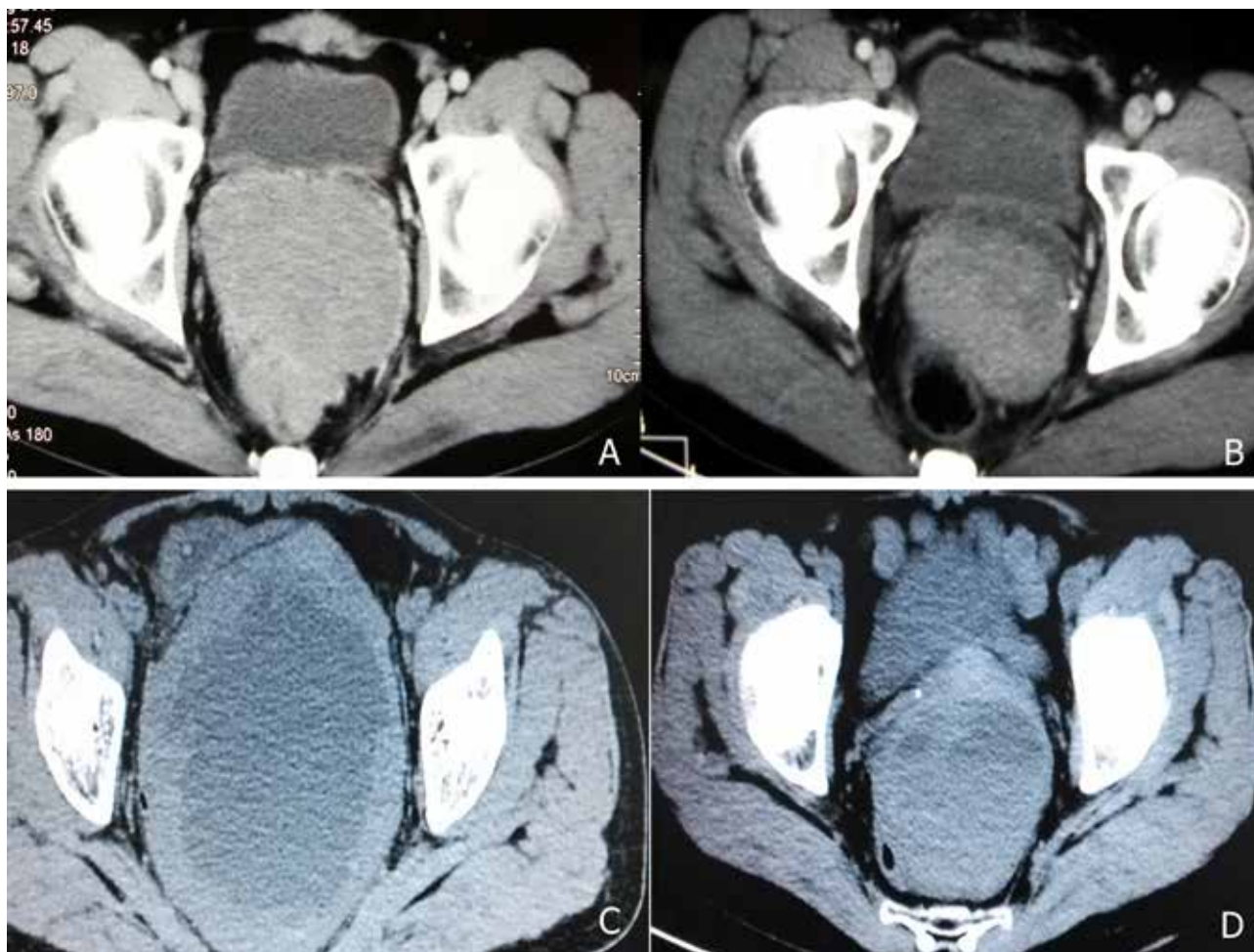


Figure 1 Abdominal CT scan (A) showed a soft-tissue tumor (11 cm × 9.0 cm in size) located in the excavatio rectovesicalis. Abdominal CT scan (B) obtained five months after imatinib treatment showed that the mass became smaller (6.7 cm × 5.1 cm × 4.0 cm in size), and CT density decreased. CT scan (C) showed a huge pelvic cystic or solid mass with relatively clear boundaries and adjacent organs affected by extrusion, approximately 11.9 cm × 11.2 cm × 10.6 cm in size. Based on images obtained two months after drug therapy, the tumor decreased in size (8.2 cm × 7.1 cm × 5.9 cm) and multiple punctual calcification foci were visible (D).

17 cases (51.5%) in the control group underwent R0 resections, with a statistically significant ($P=0.033$) difference. Reoperation, perioperative death, or anastomotic leak did not occur in both groups. No statistical significances were found in the differences of intraoperative blood transfusion, intraoperative tumor rupture, postsurgical intestinal ileus, postsurgical metastasis, or number of recurrence cases between the two groups ($P>0.05$).

Postoperative pathological diagnosis

Spindle cells or a mixture of spindle cells and epithelioid cells were observed by endoscopic examination. Immunohistochemical staining showed the following results: positive rates for CD117 (90%, 45/50), CD34 (72%, 36/50), S-100 (4%, 2/50), SMA (32%, 16/50), and Desmin (6%, 3/50), as shown in table 4. According to the NIH risk

Table 2 Information of surgery and postoperative complications in two groups.

Variables	Preoperative treatment group (n=17)	Control group (n=33)	P value
Operation time	255.29±27.41	270.61±27.12	0.066
Intraoperative bleeding volume (mL)	691.18 ± 290.60	887.88 ± 276.71	0.023
Intraoperative transfusion			0.474
Yes	4	11	
No	13	22	
Intraoperative tumor rupture			0.650
Yes	1	4	
No	16	29	
Multivisceral resection			0.043
Yes	2	13	
No	15	20	
Lymph node dissection			0.650
Yes	1	5	
No	16	28	
Tumor excision status			0.033
R0 resection	14	17	
R1 resection	3	16	
Postoperative ileus			
Wound/abdominal infection	0	1	1.000
Reoperation			
Perioperative death	0	0	-
Anastomotic fistula	0	0	-
Postoperative metastasis/recurrence	6	18	0.197

Table 3 Summary of combined multiple organs resection between the two groups.

Variables	Preoperative treatment group	Control group
Gastrectomy+splenectomy	-	2
Gastrectomy+distal pancreatectomy	-	1
Gastrectomy+cholecystectomy	1	4
Gastrectomy+Partial hepatectomy	1	2
Bowel resection+cholecystectomy	-	2
Duodenectomy+right nephrectomy+cholecystectomy	-	1
Retroperitoneal tumor resection +ascending colon resection+cholecystectomy	-	1
Total cumulative patients with multivisceral resection	2	13

Table 4 The data of postoperative pathological examination.

Variables	No of patients (n=50)	Percentage (%)
CD117	45	90%
CD34	36	72%
S-100	2	4%
SMA	16	32%
Desmin	3	6%

assessment criteria^[13], four cases were at intermediate risk and 13 cases were at high risk in the preoperative treatment group, whereas 33 cases in the control group were at high risk.

RFS and OS

In the preoperative treatment group, six cases experienced regional recurrence or distant metastasis, with a median recurrence/metastasis-free time of 42 months. One case of liver metastasis received surgical treatment again. During follow-up, four cases died as a result of the disease. In the control group, recurrence or metastasis was found in 18 cases, with a median recurrence/metastasis-free time of 25 months, and 10 patients died because of the disease. Recurrent tumors after drug withdrawal were reported for most patients, and only a few patients experienced metastasis or recurrence during medication. Kaplan–Meier analysis showed that the preoperative treatment group had a higher RFS rate than the control group two years after surgery (87.5% vs 51.5%, $P=0.026$) (Figure 2 A). No statistical significance in the differences of the OS rate was observed between the two groups (Figure 2 B).

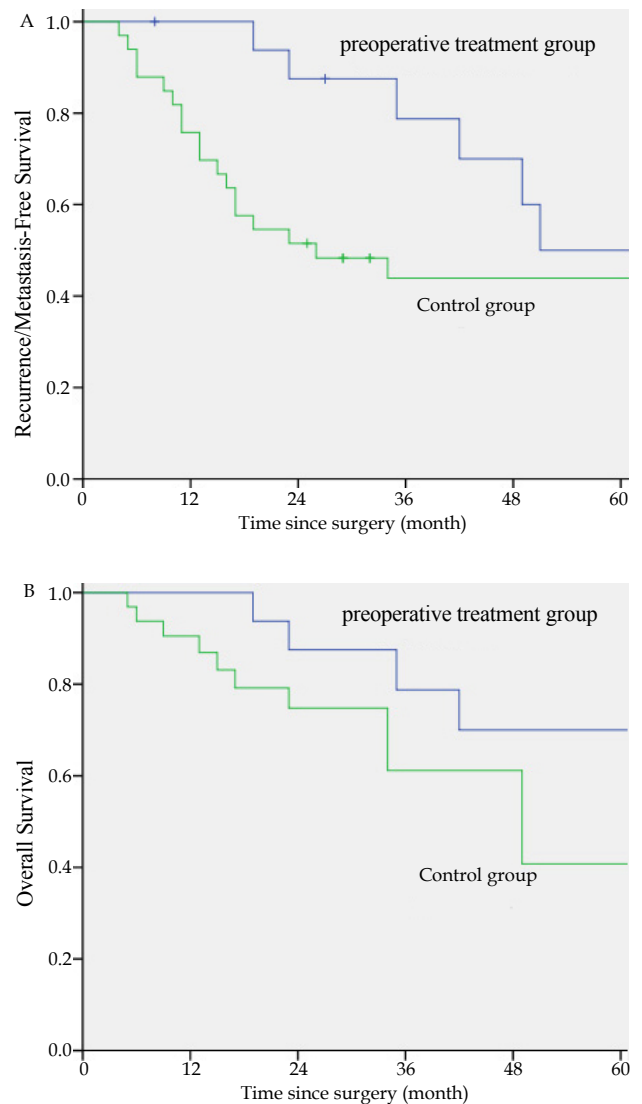


Figure 2 RFS curves of the two groups. (A) The preoperative treatment group had a higher RFS rate than the control group two years after surgery (87.5% vs 51.5%, $P=0.026$). Kaplan–Meier curves of OS of the two groups. No statistical significance in the differences of the OS rate ($P=0.347$) was observed (B).

DISCUSSION

In 1983, Mazur named a group of tumors without smooth muscle differentiation or neurogenic differentiation as GISTs for the first time^[14]. In recent years, further understanding of GISTs and development of diagnosis and treatment methods led to an increase in diagnosed cases. Before the application of TKI in GIST treatment, surgical resection was the only effective treatment method for tumors. However, most patients suffered from postsurgical recurrence even when tumors were completely resected. The published results showed that adjuvant therapy, which is postsurgically administered to patients at intermediate and high recurrence risks, can effectively increase RFS and OS^[15-17]. However, data from clinical research on adjuvant therapy after preoperative TKI treatment and surgical resection are highly limited.

Fiore reported that imatinib treatment before surgery for adjuvant therapy can reduce intraoperative bleeding and intraoperative tumor rupture, thereby increasing patient prognosis^[18]. Consistent with this report, 17 cases in the preoperative treatment group in the present research exhibited less intraoperative blood loss than cases in the control group. No statistically significant difference was observed in intraoperative tumor rupture between the two groups, but we found a smaller proportion of intraoperative tumor rupture in the preoperative treatment group. Large GISTs are usually supplied by multi-source arteries, and sometimes exhibit plexiform-like layers attached to a meager envelope. Uncontrollable bleeding, which can cause intraoperative bleeding, may occur despite careful surgery. When the tumor is large, its envelope can easily infiltrate the adjacent tissues and organs with unclear intervals. Forced separation can also cause bleeding or tumor rupture. After preoperative IM treatment, 82.4% (14/17) of patients experienced R0 resection, which was consistent with the data reported by Rutkowski^[19]. However, in a research by Andtbacka^[20], 11 cases of locally advanced GIST patients underwent radical resection after preoperative treatment, with a median time of one year, followed by continued adjuvant therapy after surgery; the progression-free survival (PFS) rate was 91% after 19.5 months of follow-up. Our research results indicate that the two-year PFS was slightly low at 87.5% after 3.5 months of median preoperative medication. This result was possibly caused by the different preoperative times of the two studies. In the treatment of large GISTs, the problem of joint organ resection is likely to arise. The separation and removal of tumors to maintain increased organ functions contradict the no-tumor principle. If the life quality of patients is not significantly influenced, joint organ resection should be completely resected with the tumors^[21] to achieve a negative margin and remarkably affect the postsurgical PFS of patients^[22]. In this research, the organ resections were mainly joint cholecystectomy and local liver resection. Although one patient underwent joint kidney resection, it was R0 resection. The metastatic pathways of GIST are mainly liver and intraperitoneal seeding metastases, and clean up of lymph node metastasis is rare^[23]. Consistent with this report, six cases in the present research underwent clean up of lymph node metastasis, and postsurgical pathology indicated no metastasis.

After six to 12 months of preoperative imatinib treatment or when the maximum effects are observed, surgery is performed^[8,24]. Excessive prolongation of preoperative treatment can lead to secondary resistance and disease progression. In the present research, the median time of preoperative treatment was 3.5 months for 17 cases in the preoperative treatment group. One case showed advanced tumor during treatment, whereas the conditions of the other 16 cases were partially relieved or stable. Most patients who underwent preoperative

treatment were preoperatively estimated to experience a difficult R0 resection; these patients had large tumors or tumors at special sites (esophagogastric junction, duodenum, and low rectum) or required combined organ resection. Postsurgical NIH risk assessment of these patients was largely intermediate and extremely risky. Therefore, TKI adjuvant therapy should continue postoperatively in GIST patients who have received preoperative therapy^[20,25,26]. The toxicity and side effects of imatinib are dose-dependent^[27]. The treatment of chronic granulocytic leukemia and GIST shows minimal toxicity and side effects, and patients exhibit good tolerance^[28]. Edema, fatigue, discomfort, and mild anemia only occur in a few patients who are preoperatively and postsurgically medicated, which was consistent with our research. The current consensus of postsurgical adjuvant therapy is to advise patients at high risk to undergo adjuvant therapy, whereas patients with low risk do not require it^[15]. However, whether patients at intermediate risk need adjuvant therapy remains controversial. Li objectively proved that patients at intermediate and high risks can benefit from postsurgical adjuvant therapy^[17]. In our research, 46 cases at high risk and four cases at intermediate risk underwent adjuvant therapy. By contrast, 16 cases in the control group showed recurrent tumors or metastasis, most of which occurred two years after surgery. Compared with postsurgical adjuvant therapy of one year, postsurgical adjuvant therapy of three years in patients at high risk results in improved PFR and OS^[29]. In the 50 cases of our research, the median time of postsurgical adjuvant therapy was 14.5 months. After drug withdrawal, most patients demonstrated recurrence or metastasis, so prolonging medication is necessary.

In conclusion, imatinib treatment of large GISTs, which cannot be locally resected or are at advanced stages, is safe and feasible. IM could reduce intraoperative bleeding, increase R0 resection, and decrease joint organ resection to reduce surgical difficulty. Postsurgical adjuvant therapy significantly increased the two-year RFS rate of patients. The shortcomings and limitations of this research were the small amount of patient samples included, non-randomness in cases, and short adjuvant therapy period. Further studies require rigorous large samples, as well as multi-center randomized controlled experiments.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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