Role of Surgery in the Management of Liver Metastases From Gastrointestinal Stromal Tumors

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Background: The clinical benefit of hepatectomy in patients with liver metastases from gastrointestinal stromal tumors (GIST) has not been well defined in this era of tyrosine kinase inhibitor (TKI). Our study aims to demonstrate the survival advantage of adding hepatectomy in patients with GIST liver metastases.

Methods: Information on patients with metastatic GIST treated or consulted between January 2006 and December 2018 was retrieved. Patients without extrahepatic metastases were included and classified into the surgical (S group) and non-surgical (NS group). Clinicopathological features were compared and their association with survival was assessed.

Results: A total of 119 patients were included in this retrospective analysis, 62 in the S group and 59 in the NS group. Comparison of clinicopathological features showed that a markedly higher proportion of patients in the S group had ≤3 hepatic lesions (79.0% vs. 29.8%, $p<0.001$). After a median follow-up duration of 56 months, patients in the S group had significantly better progression-free survival (PFS) and marginally improved overall survival (OS) than those in the NS group (3y PFS:86.2% vs. 64.6%, $p=0.002$; 5y OS: 91.5% vs. 78.3%, $p=0.083$). After propensity score matching, multivariate analysis identified hepatectomy as the only significant prognostic factor for PFS while age, hepatectomy and max tumor diameter were significant predictor for OS.

Conclusions: Addition of hepatectomy provided longer disease control in patients with metastatic GIST confined to the liver. Upfront hepatectomy followed by imatinib therapy is worthwhile trying in patients with single and easily removable lesions.

Keywords: gastrointestinal stromal tumor, liver metastasis, surgery, imatinib, survival

INTRODUCTION

Gastrointestinal stromal tumors (GIST) constitute the most frequent mesenchymal malignancy of the gastrointestinal tract, with an estimated incidence of 10–20 per million population (1, 2). Surgery is the only curative modality for GIST, yet about 15–50% of newly-diagnosed patients present with metastatic disease, most frequently in the liver (3, 4). Even in patients with localized

GIST completely removed, approximately half would experience recurrence in 18 to 24 months (5). Before the introduction of tyrosine kinase inhibitors (TKI), surgical resection had long been the only treatment expected to prolong the life of patients with metastatic GIST, but yielded a dismal 5-year overall survival (OS) rate of 27–34% (6, 7). Imatinib mesylate, the first-line TKI for treating GIST, has been highly effective in patients with advanced/metastatic disease and tripled the median survival duration to nearly 5 years (8). Controversy thus arose over the necessity of surgery and imatinib therapy has been proposed as a substitute considering its effectiveness and non-invasiveness. Despite a high response rate of up to 80%, complete response is rarely observed while the majority of patients progress on imatinib therapy (9). Unfortunately, the efficacy of subsequent lines of TKI in treating refractory GIST is limited, with a median progression-free survival (PFS) of 6.8 months for sunitinib and 4.8 months for regorafenib (10, 11).

Since disease progression on imatinib is inevitable, addition of surgical resection to reduce the risk of acquired resistance became an attractive investigatory approach. Though the therapeutic effect of hepatectomy is widely recognized in patients with liver metastases from colorectal carcinoma or neuroendocrine tumors (12, 13), there are limited data on the clinical benefit of hepatectomy in treating metastatic GIST in the era of imatinib. Most retrospective studies performed were underpowered due to their vague entry criteria and imbalanced patient characteristics. In the current study, we sought to evaluate the survival benefit of adding hepatectomy in patients receiving imatinib for liver metastases from GIST.

MATERIALS AND METHODS

Patient Selection

The study protocol was approved by the institutional review board of Zhongshan Hospital, Fudan University and the requirement for informed consent was waived due to its retrospective nature. Patients who received surgical resection, imatinib medication or medical consultation for metastatic GIST in our institution from January 2006 through December 2018 were identified from the institutional medical records. The inclusion criteria were as follows (1): complete resection of primary tumors (2), biopsy-proven or radiological evidence of metastases confined to the liver (3), no history of local recurrence or distant metastasis, (4) receiving imatinib therapy for metastatic GIST, and (5) adequate liver, kidney and bone marrow function. We excluded patients with liver metastases emerging during imatinib therapy, age <18 years, prior malignancy and severe underlying disorders.

Evaluation of Primary and Metastatic GIST

The electronic patient records were searched for information regarding patient characteristics (age and gender), primary tumors (location, interval from primary tumor resection to liver metastases), liver metastases (onset, number and location of metastatic tumors, max tumor diameter, response to preoperative imatinib, and date of hepatectomy). According to the time of occurrence, liver metastases were classified as synchronous (simultaneous with primary GIST or within 6 months after the diagnosis of primary tumors) or metachronous (beyond 6 months after the diagnosis of primary tumors).

Surgical Management

For patients with resectable lesions, the choice whether to undergo hepatectomy was made by patients and surgeons jointly. Patients who had liver metastases primarily unresectable or needing extensive R0 organ resection but exhibited positive response to imatinib therapy were re-evaluated for surgery by dynamic radiological examinations. Major hepatectomy was defined as resection of three or more hepatic segments while every other resection was designated as minor hepatectomy. Surgical margins were classified as microscopically complete (R0), macroscopically complete with microscopic residual tumor cells (R1), or macroscopically incomplete (R2). Radiofrequency ablation was applied for highly-suspected or unfavorably located lesions and its curative effect was confirmed by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Postoperative complications were scored according to the Clavien-Dindo classification, with grade III and above considered major (14).

Treatment With TKIs

Patients who had unresectable lesions or refused surgery were offered imatinib therapy after the diagnosis of liver metastases was made by liver biopsy or radiographic examination. Response to imatinib was assessed by contrast-enhanced CT or MRI at every 2 to 3 months and classified according to the Choi criteria (15). PFS was calculated as the length of time from the initiation of imatinib for liver metastases or date of hepatectomy to the date of documented recurrence or progression. OS was defined as the length of time from the date of imatinib administration or surgery for liver metastases to the date of last follow-up or tumor-related death, which ever occurred first. All the patients enrolled were mainly followed up on an outpatient basis or *via* telephone.

Statistical Analyses

Continuous data are expressed as medians with ranges and compared using the Mann-Whitney *U* test. Categorical data were compared using Pearson's chi-squared test or Fisher's exact test, as appropriate. To minimize the impact of selection bias, potential pre-treatment parameters that may influence treatment decision were included in a 1:1 propensity score matching (PSM) with a caliper width of 0.1. Survival curves were plotted using the Kaplan–Meier method and intergroup differences were compared using the log-rank test. Univariate and multivariate analyses of the association between survival and potential prognostic factors were performed using the Cox proportional hazard regression models. All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL,

USA). A two-tailed *p* value of less than 0.05 was considered statistically significant.

RESULTS

Identification of Study Population

Between January 2006 and December 2018, 186 patients were diagnosed with hepatic metastases from GIST in our institution and they were further reviewed for eligibility. Thirty-seven patients were then excluded for the existence of previous or simultaneous extrahepatic metastases, 9 excluded for not having undergone surgical resection of primary tumors, 5 excluded for refractory liver lesions emerging during imatinib therapy, 6 excluded for less than 6 months of imatinib administration and 10 excluded for incomplete follow-up or medical information (**Figure 1**). A total of 119 patients were ultimately included in this study, 62 in the surgical group (S group) and 57 in the non-surgical group (NS group).

Patient Characteristics

Liver metastases were diagnosed in 71 (59.7%) males and 48 (40.3%) females at a median age of 56 (range, 26–82) years. Primary tumors were located in the small intestine in 67 (56.3%) patients, stomach in 46 (38.7%) patients and elsewhere in 6 (5.0%) patients. 44 (40.0%) patients presented with initially metastatic GISTs (synchronous) and the other 75 (60.0%) patients experienced liver metastasis more than 6 months after primary tumor resection (metachronous). The number of metastases were three or fewer in 66 (55.5%) patients and four or more in 53 (44.5%) patients, with a median diameter of the largest lesion measuring 4 (range 0.5–20.4) cm. Mutational analyses revealed mutations of *c-kit* exon 11 in 87 (77.7%) patients, *c-kit* exon 9 in 19 (17.0%) patients and *c-kit/PDGFRα* other exons in 3 (2.7%) patients. A comparison of baseline clinicopathological features between the surgical and non-surgical groups is shown in **Table 1**. A markedly higher proportion of patients in the surgical group had three or fewer metastatic nodules in the liver (79.0% vs. 29.8%, *p*<0.001).

Surgical Treatment and Outcomes

Of the 62 patients who received hepatectomy, resection of primary tumors was performed during the same procedure in 17 (27.4%) patients, ≤6 months before liver surgery in 7 (11.3%) patients and >6 months in 38 (61.3%) patients. Preoperative imatinib was administrated to 9 (14.5%) patients after the diagnosis of liver metastases, 7 (11.3%) of which exhibited partial response and 2 (3.2%) had stable disease. Thirty-eight (61.3%) patients underwent minor hepatectomy and 24 (38.7%) patients underwent major hepatectomy, while 9 (14.5%) patients received intraoperative radiofrequency ablation (RFA). R0 resection was achieved in 44 (71.0%) patients, R1 resection in 16 (25.8%) patients and R2 resection in 2 (3.2%) patients. Postoperative complications occurred in 8 (12.9%) patients, including abdominal infection in 3 (4.8%) patients, pleural effusion in 2 (3.2%) patients, anastomotic leakage in 1 (1.6%) patient, wound infection in 1 (1.6%) patient and encapsulated effusion in 1 (1.6%) patient. Invasive intervention was required in only one case while the rest were successfully managed by conservative treatment. No postoperative mortality was
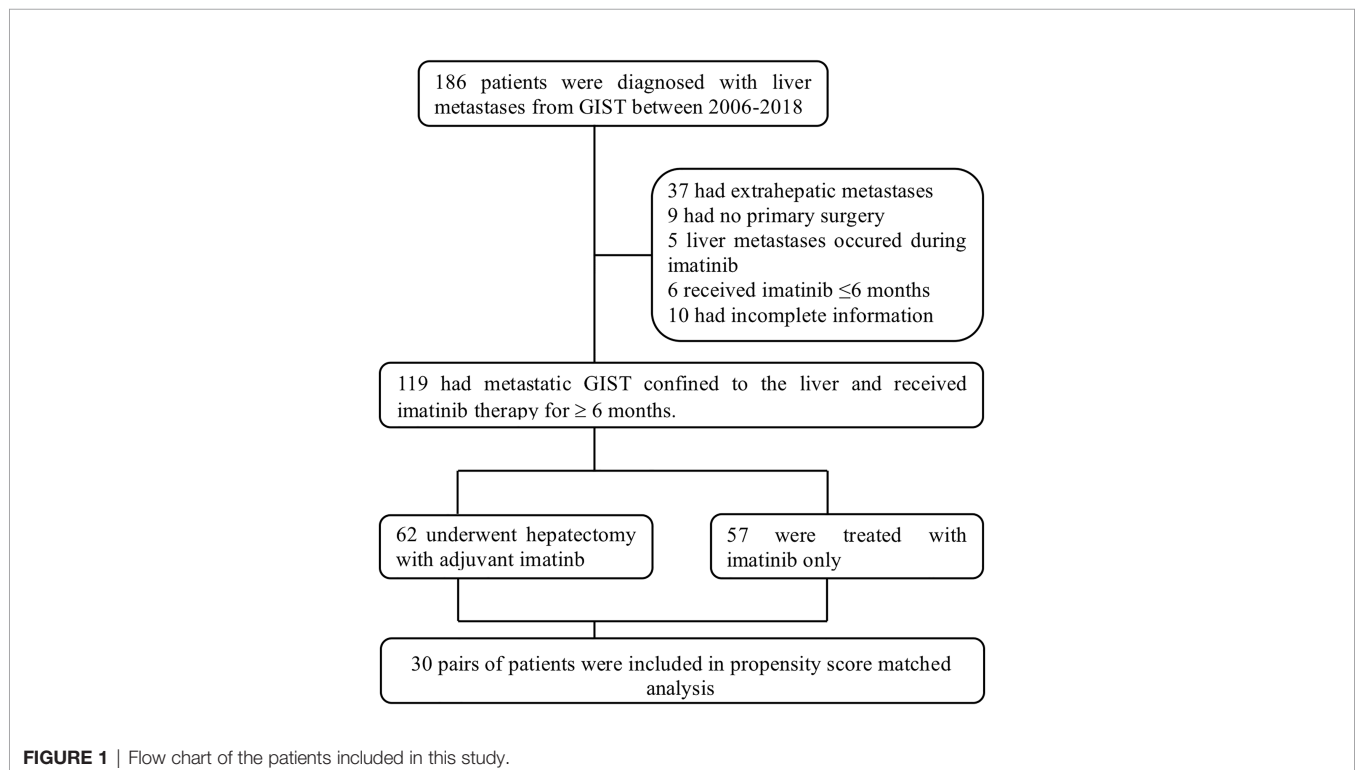

FIGURE 1 | Flow chart of the patients included in this study.

TABLE 1 | Baseline clinical characteristics of all patients.

Parameters	Surgery+Imatinib (n = 62)	Imatinib (n = 57)	p-value
Gender			
Male	34 (54.8%)	37 (64.9%)	0.263
Female	28 (45.2%)	20 (35.1%)	
Age (years)			
≤60	35 (56.5%)	34 (59.6%)	0.724
>60	27 (43.5%)	23 (40.3%)	
Primary sites			
Stomach	26 (41.9%)	20 (35.1%)	0.745
Small intestine	33 (53.2%)	34 (59.6%)	
Others	3 (4.9%)	3 (5.3%)	
Metastatic phase			
Synchronous	25 (40.3%)	19 (33.3%)	0.430
Metachronous	37 (59.7%)	38 (66.7%)	
No.of metastases			
≤3	49 (79.0%)	17 (29.8%)	<0.001
>3	13 (21.0%)	40 (70.2%)	
Largest diameter (cm)			
Median (range)	4.5 (0.6-20.4)	3.7(1-14.4)	0.235
≤4	28 (45.2%)	31 (54.4%)	0.315
>4	34 (54.8%)	26 (45.6%)	
Mutation analysis[a]			
c-kit exon 11	45 (76.3%)	42 (79.3%)	0.413
c-kit exon 9	12 (20.3%)	7 (13.2%)	
Other exons or none in c-kit/PDGFRα	2 (3.4%)	4 (7.5%)	

[a]Genetype results were unknown in 7 patients.

observed within 30 days after surgery and the median time from surgery to imatinib resumption was 31 days. Details of the surgical outcomes of patients are shown in **Table 2**.

Survival Analysis

In the non-surgical group, partial response was discovered in 34 (59.6%) patients and stable disease in 22 (38.6%) patients. Liver metastases in 1 (1.8%) patient underwent complete cystic change and was considered complete response. After a median follow-up period of 56 (range, 24-189) months, 14 (22.6%) patients developed recurrence in the surgical group while 35 (61.4%) patients experienced disease progression in the non-surgical group, resulting in a 3-year PFS of 86.2% versus 64.6% (p=0.002). The 5-year OS rate were estimated to be 91.5% for

TABLE 2 | Surgical treatments and outcome.

Total number	62
Resection of primary GIST	
>6 months before liver surgery	38 (61.3%)
≤6 months before liver surgery	7 (11.3%)
During the same procedure	17 (27.4%)
Response to preoperative imatinib	
Partial response	7 (11.3%)
Stable disease	2 (3.2%)
Type of hepatectomy	
Minor (≤2 segments)	38 (61.3%)
Major (>2 segments)	24 (38.7%)
Locoregional intervention	
Intraoperative RFA	9 (14.5%)
Pre-/postoperative RFA/TACE	7 (11.3%)
Resection margin status	
R0	44 (71.0%)
R1	16 (25.8%)
R2	2 (3.2%)
Postoperative complications	
Anastomotic leakage	1 (1.6%)
Wound infection	1 (1.6%)
Encapsulated effusion	1 (1.6%)
Abdominal infection	3 (4.8%)
Pleural effusion	2 (3.2%)

RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

the surgical group, marginally better than 78.3% for the non-surgical group (*p*=0.083). Following a 1:1 propensity score matching for age, metastatic phase, number of metastases and max tumor diameter, 30 pairs of patients with well-matched baseline features were selected (**Table 3**). Patients who underwent surgery in the propensity model still had significantly better PFS and OS when compared with those receiving imatinib only. The estimated 3-year PFS rate was 81.8% for the surgical group and 53.1% for the non-surgical group (*p*=0.001). The estimated 5-year OS rate in the surgical group was 94.4% and in the non-surgical group it was 70.3% (*p*=0.037). Survival graphs are shown in **Figure 2**. Hepatectomy was the only significant predictor for PFS in both the univariate and multivariate analyses. Among the risk factors associated with OS, multivariate analysis identified age, surgery and max tumor diameter as significant prognostic factors (**Table 4**).

DISCUSSION

Liver is the most frequent site of metastasis for GIST and liver metastases, once treated exclusively by surgery, pose a major threat to the survival of patients with GIST (5). The advent of imatinib has radically altered the management of GIST and greatly improved the survival of patients with GIST (16). Unlike the case in colorectal carcinoma and neuroendocrine tumors, where chemotherapy and targeted drugs act in synergy with surgery to improve survival, imatinib has more often superseded hepatectomy in patients with GIST liver metastases in view of its safety and effectiveness. Nonetheless, most patients on imatinib therapy eventually develop drug resistance and succumb to disease progression.

Although there is no direct evidence to support the role of surgery in delaying imatinib resistance, it is reasonable to deduce that the incidence of drug resistance is in proportion to the amount of tumor cells exposed and the duration of imatinib administration (17). Since continuous medication of imatinib is the cornerstone for disease control, surgical intervention to eliminate or reduce tumor burden seems a logical strategy. In addition, metastases in the liver are easier to identify and assess than those in the peritoneum, which makes them more appropriate for complete surgical resection. Hepatectomy was thus taken into consideration again to prolong the activity of imatinib. A Japanese prospective, multicenter trial was once conducted to clarify the efficacy and safety of surgery for liver oligometastasis but was prematurely terminated due to the amendment of the guideline and poor accrual (18). Several retrospective studies conducted in the last decade have indicated survival benefit from adding hepatectomy in the treatment of metastatic GIST, but were limited statistically by small sample size as well as their heterogeneity (19–26). To better demonstrate the clinical benefit of hepatectomy, we adopted strict inclusion criteria and collected a relatively homogenous cohort of patients with liver metastases from GIST.

At initial analysis of all patients, we found that hepatectomy plus imatinib was associated with improved PFS compared with imatinib alone (3y PFS, 86.2% vs. 64.6%, *p*=0.002). There was a tendency for better OS in the surgical group but this difference did not reach level of statistical significance (5y OS, 91.5% vs. 78.3%, *p*=0.083). Comparison of baseline clinicopathological characteristics between the two groups revealed that patients undergoing hepatectomy were more likely to have three or fewer metastatic nodules in the liver (79.0% v.s 29.8%, *p*<0.001). Along with age, metastatic phase and diameter of the largest nodule,

TABLE 3 | Baseline clinical characteristics of patients after propensity score matching.

Parameters	Surgery+Imatinib (n = 30)	Imatinib (n = 30)	*p*-value
Gender			
Male	15 (50.0%)	18 (60.0%)	0.436
Female	15 (50.0%)	12 (40.0%)	
Age (years)			
≤60	20 (66.7%)	17 (56.7%)	0.426
>60	10 (33.3%)	13 (43.3%)	
Primary sites			
Stomach	11 (36.7%)	12 (40.0%)	0.885
Small intestine	16 (53.3%)	16 (53.3%)	
Others	3 (10.0%)	2 (6.7%)	
Metastatic phase			
Synchronous	13 (43.3%)	9 (30.0%)	0.284
Metachronous	17 (56.7%)	21 (70.0%)	
No.of metastases			
≤3	17 (56.7%)	17 (56.7%)	1
>3	13 (43.3%)	13 (43.3%)	
Largest diameter (cm)			
≤4	20 (66.7%)	17 (56.7%)	0.426
>4	10 (33.3%)	13 (43.3%)	
Mutation analysis[a]			
c-kit exon 11	20 (71.4%)	22 (75.9%)	0.704
Non-*c-kit* exon 11	8 (28.6%)	7 (24.1%)	

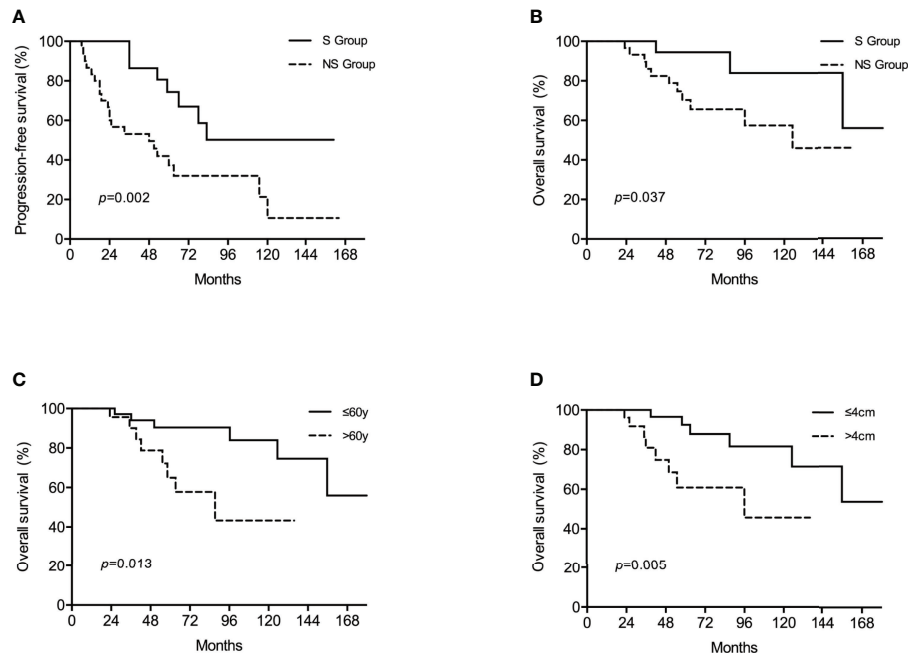[a]*Genotype results were unknown in 3 patients.*

FIGURE 2 | Kaplan–Meier survival analyses showed that in the propensity model, surgery was associated with improved progression-free survival (PFS) **(A)** while surgery **(B)**, age **(C)** and diameter of the largest nodule **(D)** were prognostic factors for overall survival (OS).

factors that may affect the decision for surgery, a 1:1 propensity score matching was performed to minimize the impact of selection bias. In the propensity model, addition of surgery was still associated with better PFS and OS in both univariate and multivariate analyses. Previous studies reported a 3y PFS of 25.6%-77.5% for patients receiving surgery for liver metastases from GIST, which is inferior to our result (17, 19, 22, 25, 26). The difference in survival is probably attributed to the inclusion of

TABLE 4 | Prognostic factors for progression-free survival (PFS) and overall survival (OS) after propensity score matching.

Parameters	PFS			OS		
	p-value (univariate)	*p*-value (multivariate)	95% CI	*p*-value (univariate)	*p*-value (multivariate)	95% CI
Gender						
Male	0.342	–	1.445 (0.677-3.084)	0.280	–	1.799
Female						(0.620-5.217)
Age(years)						
≤60	0.263	–	1.529	0.013	0.043	3.351
>60			(0.726-3.219)			(1.038-10.818)
Primary sites						
Stomach	0.693	–	1.164	0.314	–	1.817
Others			(0.548-2.470)			(0.568-5.811)
Metastatic phase						
Synchronous	0.693	–	1.167	0.748	–	0.840
Metachronous			(0.541-2.520)			(0.289-2.439)
No.of metastases						
≤3	0.309	–	0.676	0.728	–	0.823
>3			(0.317-1.438)			(0.273-2.475)
Largest diameter (cm)						
≤4	0.159	–	1.708	0.005	0.034	3.435
>4			(0.811-3.595)			(1.101-10.716)
Mutation analysis						
c-kit exon 11	0.134	–	1.887	0.157	–	2.371
Non-*c-kit* exon 11			(0.822-4.330)			(0.718-7.827)
Metastasectomy						
Yes	0.004	0.004	3.340	0.037	0.039	4.019
No			(1.476-7.559)			(1.076-15.010)

patients with more advanced disease such as extrahepatic metastases and imatinib resistance in previous studies. All patients enrolled in the current study, however, were diagnosed with liver metastases for the first time and had no previous or simultaneous extra-hepatic lesions. Besides, all patients had primary tumors completely removed and received more than 6 months of imatinib for liver metastases.

According to the aforementioned assumption that metastectomy would delay acquired resistance to imatinib, surgical resection should be performed as completely as possible to minimize residual tumor cells. Bauer et al. provided evidence that patients with macroscopic complete metastectomy (R0/R1) had a longer median OS compared to those with incomplete metastectomy (R2) (8.7 versus 5.3 years) (23). A retrospective analysis performed by Seesing et al. showed that R0 resection was the only independent prognostic factor for PFS and OS in patients undergoing hepatectomy for GIST liver metastases (22). The impact of surgical margin status was not assessed in the current study due to our high rate of R0/R1 resection but we agree that a thorough preoperative examination is indispensable to avoid unnecessary debulking surgery. Another concern associated with metastectomy is that postoperative complications may counteract the survival benefit as a prolonged recovery would preclude the administration of imatinib. The rate of postoperative complications in our study turned out to be acceptable, with complications of any grade observed in 8 (12.9%) patients. There was no significant difference in postoperative complication between patients undergoing combined or sequential surgery (13.3% vs. 11.7%, p>0.05). Percutaneous peritoneal drainage was required in one case while the rest were successfully managed by conservative treatment. No postoperative mortality was observed within 30 days after surgery and the median time from surgery to imatinib resumption was 31 days.

Given that imatinib may shrink the tumor volume of GIST, its preoperative use has been proposed to minimize the extent of resection and the surgical morbidity (27, 28). Several retrospective analyses suggested that response to preoperative imatinib, partially responsive or stable, were associated with prolonged survival in patients with metastatic GIST (29, 30). One possible explanation is that patients with liver metastases from GIST are more likely to achieve R0 resection after downsizing imatinib therapy (31). In the real world, however, it is not uncommon for patients with responsive disease to refuse surgery and return with signs of disease progression. Frequent surveillance helps to detect early signs of progression, for which surgical resection is still possible and beneficial, but general progression unfortunately contraindicates surgical intervention (30, 32). Therefore, for patients with primarily unresectable tumors or needing extensive R0 organ resection, the focus should be on identifying the optimal timing of surgery and duration of preoperative imatinib, weighing survival benefit against risk of acquired resistance.

The management of initially resectable liver metastases is, on the other hand, different from their "less easily removable" counterparts. There are two strategies for this subset of patients according to the sequence of surgery. Preoperative imatinib followed by surgical resection is appropriate for patients with resectable "high volume" tumors. Upfront liver resection followed by adjuvant imatinib therapy is the other option to be considered, particularly for single and easily removable lesions. This approach is helpful to relieve patients of the need to undergo frequent preoperative radiological reassessment and may also reduce risk of acquired drug resistance by minimizing tumor cells exposed to imatinib exposure. In our series, 53 patients (85.5%) in the surgical group underwent hepatectomy prior to imatinib administration and R0/R1 resection were achieved in 98.1% of cases. The 3y PFS rate was 86.6% for patients with upfront hepatectomy and 83.3% for those responsive to preoperative imatinib. A prospective, real-world, observational study is ongoing in our institution to demonstrate the safety and effectiveness of upfront hepatectomy followed by imatinib in patients with initially resectable liver metastases from GIST (ChiCTR2000035773).

Despite being the largest study with a relatively strict inclusion criteria, our study has several limitations. First, patients with fewer number of metastases were prone to undergo surgery, a selection bias that cannot be avoided in this retrospective study. After propensity score matching, patient characteristics were balanced but the number of cases was relatively small. Second, as a high-volume center with experienced surgeons specialized in liver surgery, patients with liver metastases were more likely to receive surgical resection in our institution, partly accounting for the low proportion of patients receiving preoperative imatinib. Third, the information on treatment modalities after progression or recurrence was unknown in some cases, which is important for survival analysis.

CONCLUSIONS

Hepatectomy combined with imatinib seems to offer better survival than imatinib alone in patients with metastases confined to the liver. Upfront hepatectomy should be considered an option for patients with initially resectable liver metastases, especially single and easily removable lesions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional review board of Zhongshan Hospital, Fudan University. Written informed consent for participation

was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KS and YF conceptualized and designed this retrospective study. AX and XG performed most of the statistical analyses and wrote the draft manuscript. JS, JL, and PS assisted with the data collection. YFH, XH, and YYH made substantive intellectual

contributions to the paper. All authors read and approved the final manuscript.

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