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Gastrointestinal stromal tumor (GIST) with liver metastases

An 18-year experience from the GIST cooperation group in North China

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Abstract

Approximately 40% to 50% of gastrointestinal stromal tumor (GIST) patients will have recurrence or metastases after resection of the primary lesion, and the most common affected sites will be liver and peritoneum. Imatinib has been considered as the first-line therapy of metastatic GIST. Surgery for metastases is proposed when possible. Furthermore, there are controversies concerning hepatic resection and systemic tyrosin kinase inhibitors (TKIs). The therapeutic conditions and long-term outcome of GIST patients with liver metastases in northern China remain unknown.

The clinical, pathological, and follow-up data of 144 GIST patients, who had liver metastases between June 1996 and June 2014 from 3 tertiary cancer centers in northern China, were reviewed.

Thirty-two cases (22.2%) had hepatectomy with 23 (23/32, 71.9%) R0 resections and 9 (9/32, 28.1%) R1/R2 resections, respectively. Twenty-three patients were given imatinib postoperatively. Furthermore, 98 (68.1%) patients were given TKIs only to control disease progression, and sunitinib was considered after imatinib failure in 12 patients. The 1-, 3- and 5-year survival rate was 82%, 51%, and 24%, with a median overall survival of 48 months for all patients. Patients who had hepatic resection combined with TKIs had a tendency of improved outcome, and the median survival time was 89 months. This was in contrast to patients who received TKIs only, in which median survival time was 53 months. Patients who received imatinib plus sunitinib had a tendency of longer survival time, compared with patients who received imatinib only (not reached vs 50 months).

TKIs combined with hepatic resection had a role in improving the outcome of GIST patients with liver metastases.

Abbreviations: CT = computed tomography, DCR = disease control rate, GIST = gastrointestinal stromal tumor, HR = hazard ratios, OS = overall survival, TKIs = tyrosin kinase inhibitors, UICC = Union Against Cancer.

Keywords: gastrointestinal stromal tumor, hepatectomy, imatinib, liver metastases, tyrosine kinase inhibitor

1. Introduction

Gastrointestinal stromal tumor (GIST) is the most frequent mesenchymal tumor that occurs in the gastrointestinal tract, accounting for 1% to 3% of all gastrointestinal tract neoplasms,[1] following gastric and colorectal cancer. Gain-of-function mutations of c-KIT and PDGFRa were found to play a role in the pathogenesis of the disease. It was reported that approximately two-thirds of patients with recurrence had liver metastases and 50% of these patients had peritoneal disease,[2] with a median time of recurrence of 2 years.[3] Before the prevalence of effective systemic therapies, hepatic resection was the only possible therapy for patients with liver metastases. However, surgery could not be curative all the time; and prognosis with 5-year overall survival (OS) rates of 27% to 34% and a median survival time of 36 to 47 months have been reported.[4] The emergence of tyrosine kinase inhibitors (TKIs), such as imatinib mesylate, has radically altered the outcome of metastatic GIST patients, with an 80% response rate and a median survival time which has increased to 5 years.[5] Since then, GIST became the quintessential model for targeted therapy. Nonetheless, resistance to imatinib as a result of secondary gene mutations developed approximately 18 to 24 months after systemic therapy, and has become a significant clinical problem.[6,7]

Editor: Weina Chen.

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The authors report no conflicts of interest.

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Medicine (2017) 96:46(e8240)

Received: 1 August 2017 / Received in final form: 13 September 2017 / Accepted: 15 September 2017

http://dx.doi.org/10.1097/MD.0000000000008240

Metastatic liver disease is a major determinant of patient survival, and controversies exist in the management of GIST metastases in the liver. According to NCCN guidelines, surgery was recommended for the limited disease progression or locally advanced or previously unresectable tumors after a favorable response to preoperative imatinib in GIST patients.[8] Therefore, observations and studies that concern the combination therapy of imatinib and surgery have been carried out. In this multicenter study, we retrospectively investigated the role of hepatic resection and systemic TKIs among Chinese GIST patients with liver metastases during the past 2 decades, and described the survival rate of patients with combination therapy, as well as with TKIs only therapy; aiming to find factors associated with the prognosis of GIST patients with liver metastases, and to seek for an optimal therapy.

2. Materials and methods

2.1. Patients

Between June 1996 and June 2014, a total of 813 patients from the 3 institutions (Shanxi Cancer Hospital Affiliated to Shanxi Medical University, Tianjin Cancer hospital, and the Fourth hospital Affiliated to Hebei Medical University) were previously pathologically diagnosed with GIST. Among these patients, 144 cases were found to have liver metastases. Patients with additional concurrent malignant tumors and pregnancy were excluded from the analysis. Hepatic metastases were detected by computed tomography (CT), magnetic resonance imaging, and/or positron emission tomography. Patients with primary and hepatic lesions diagnosed at the same time were defined as synchronous liver metastases, whereas other patients had nonsynchronous liver metastases. Record data of patient demographics, clinicopathological characteristics, and the nature of the surgical and medical treatment were reviewed.

2.2. Surgery

Surgical resection was performed through the open or laparoscopic approach, and the final diagnosis was obtained through clinicopathological findings. The extent of the hepatic resection was at the discretion of the operating surgeon, with the aim of achieving negative surgical margins and a liver remnant of sufficient volume, to maintain hepatic function. According to the International Union Against Cancer (UICC) criteria, patients were divided into R0/R1/R2 resections: microscopically complete (R0), macroscopically complete with positive microscopic margins (R1), or macroscopically incomplete (R2). Postoperative risk stratifications of GIST were evaluated according to the modified National Institute Healthcare 2008 criteria.[9]

2.3. TKI medications

Patients with multiple metastases in both liver lobes who could not have the chance of radical hepatectomy after evaluation and those who had completed the hepatic resection surgery were given the TKIs. Patients were administered with 400 mg of imatinib (100-mg capsules) taken orally daily with food postoperatively or when they were evaluated to have unresectable hepatic lesions. A daily dose of 37.5 mg of sunitinib was given to patients intolerant or refractory to imatinib. The dose escalation of imatinib or the switch to sunitinib was decided by the local investigators. Response to TKIs was evaluated according to the criteria described by Choi.[10]

2.4. Patients follow-up

All included patients were mainly followed up on an outpatient basis or through telephone. The clinical data presented in this study are updated up to February 2016, and included a median follow-up time of 48.2 months (range: 1–139 months) from the documentation of liver metastases. Follow-up assessments included abdominal enhanced CT, whole blood count and classification, evaluations of liver and kidney functions, clinical examination, and medication compliance assessment. OS time was calculated from the date of liver metastases until death. Date of last follow-up or date of death was collected from all patients.

2.5. Ethics statement

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the three tertiary caner centers. Written informed consent was obtained from all participants.

2.6. Statistics

Data were presented as percentages of patients or median with interquartile range. Pearson χ^2-test and Fisher exact test were used for nominal variables. OS analysis was carried out using the Kaplan-Meier method, and statistical difference between groups was evaluated using the log-rank test. A multivariable analysis of OS from the date of diagnosis for liver metastases was performed using Cox regression model; the results were shown as hazard ratios (HR), corresponding 95% confidence intervals and P values at Wald test. All statistical analyses were performed using SPSS software package (Version 19.0; SPSS, Inc, Chicago, IL). $P < .05$ was considered statistically significant.

3. Results

3.1. Demographics

From 1996 to 2014, a total of 149 GIST patients with liver metastases were involved in this study; and the median age of these patients was 56 years (range: 21–81 years). The majority of these patients were male (90/144, 62.5%). Furthermore, the median follow-up for surviving patients was 48.2 months (range: 1–139 months) after liver metastases, in which there were 5 missing cases during the follow-up period.

3.2. Clinical and pathological characteristics

The most common clinical manifestation was abdominal mass (67/144, 46.5%), followed by GI obstruction (16/144, 11.1%) and bleeding (27/144, 18.8%). The stomach and small intestine were the most common sites that had the primary disease (68/144, 47.2% and 55/144, 38.2%, respectively). Furthermore, 41 (28.5%) patients were confirmed as synchronous liver metastases, while the remaining patients developed metastasis and/or recurrence after surgery for the primary disease. Peritoneum and other metastatic sites, as well as the liver, were found in 43 (29.9%) cases.

Thirty-two patients (32/144, 22.2%) had hepatectomy, in which 23 (71.9%) were R0 resections and 9 (28.1%) were R1/R2 resections, respectively. Among the patients who had hepatectomy, 23 (71.9%) patients received imatinib postoperatively and

Table 1

Characteristics of GIST patients with liver metastases.

Items	N	% or IQR
Median age*	56	47.6–68.4
Gender		
Male	90	62.5
Female	54	37.5
Primary location of tumor		
Stomach	68	47.2
Small intestine	55	38.2
Large intestine	10	6.9
Mesenterium and retroperitoneum	11	7.6
Clinical manifestations		
Abdominal mass	67	46.5
Obstruction	16	11.1
GI bleeding	27	18.8
Abdominal Distention	14	9.7
Anorexia	9	6.3
Pain	11	7.6
Synchronous liver metastases		
Yes	41	28.5
Nonsynchronous	103	71.5
Metastases sites		
Liver only	101	70.1
Peritoneum and other sites	43	29.9
Median size of primary tumor, cm*	9.3	6.1–17.0
Median liver metastatic size, cm*	3.2	2.6–7.8
Hepatic resection margin status		
R0	23	71.9
R1/R2	9	28.1
Risk stratification (modified NIH criteria)		
Very low risk	0	0
Low risk	5	3.5
Intermediate risk	13	9.0
High risk	126	87.5
Median mitotic rate per 50 HPF*	16.2	4.8–37.4
Immunohistochemistry		
CD34 positive	117	81.2
CD117 positive	127	88.6
Dog-1 positive	134	93.4
Combination therapy	23	16.0
R0 + TKI	14	9.7
R1/R2 + TKI	9	6.25
Surgery only (R0)	9	6.25
TKIs only	98	66.7
Imatinib	86	59.7
Imatinib + sunitinib	12	8.3
Best supportive care	14	9.7

* Interquartile range (25–75%).

9 patients had surgery only. TKI therapy was given to the 98 (68.1%) patients who did not receive surgery to control disease. The best supportive care was administered in 14 (9.7%) terminally ill patients. Details of the characteristics of these patients are presented in Table 1.

Two patients had sunitinib due to intolerance to imatinib. For patients who received imatinib, the initial disease control rate (DCR) was 81.2% (78/96). Among these responders, 3 (3.8%) patients had CR, 44 (56.4%) patients had a PR, and 31 (39.7%) patients had an SD after a median of 14 months (range: 3–49 months) of systemic therapy. In the remaining 18 nonresponders, 8 patients had a dose escalation to 600 mg/d of imatinib; while the remaining 10 patients received an alternative therapy of sunitinib since the progression of the disease.

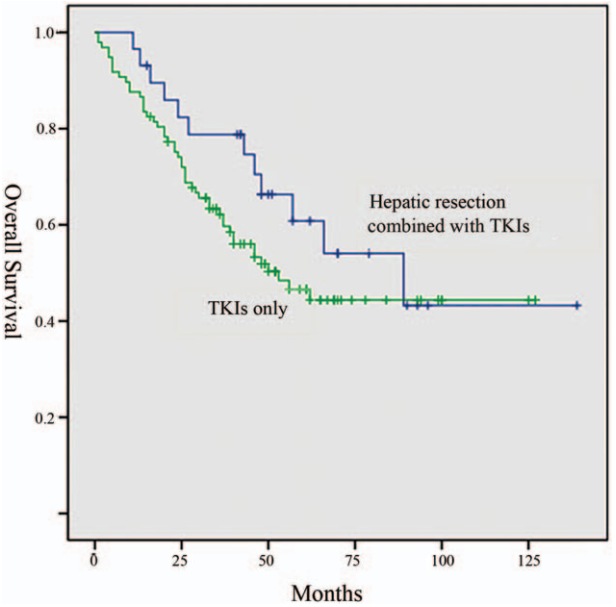

Figure 1. Survival analysis of patients administrated with hepatic resection combined with TKIs versus those having TKIs only.

3.3. Survival analysis

Complete follow-up data were available for 144 patients, with a median follow-up time of 48.2 months (range: 1–139 months). Five patients were lost to follow-up. Tumor recurrence and progression was noted in 14 patients after hepatectomy.

For all liver metastases patients, the 1-, 3- and 5-year survival rate were 82%, 51%, and 24%; and median OS was 48 months. In the subgroup analysis, median OS for patients with TKI only therapy was 53 months. In contrast, patients who received surgery combined with TKIs had a tendency to have an improved median OS of 89 months (Fig. 1). However, differences between these 2 subgroups were not statistically significant ($P=0.225$). The 1-, 3- and 5-year survival rates in the TKIs only and TKIs +surgery groups were 88%, 42%, and 25%, respectively, and 91%, 69%, and 31%, respectively.

Among the 98 patients who received TKIs only, median OS in the imatinib group was 50 months. Furthermore, there was also a tendency of better survival for patients who received sunitinib as a second-line therapy after imatinib resistance, in which median OS was not reached during the follow-up period (Fig. 2). The 1-, 3- and 5-year survival rate of each group are presented in detail in Table 2. The difference in OS between the imatinib and imatinib+sunitinib groups was not statistically significant.

The different primary locations had little role in affecting the median OS of patients. However, patients with large intestine tumors had relatively short survival time (Table 3). In addition, OS between patients with synchronous liver metastases and nonsynchronous liver metastases was not significantly different; and patients with liver metastases only and those accompanied by other metastatic sites were also not statistically different in terms of median OS (Table 3). Three of 5 patients with low risk based on the NIH criteria did not receive imatinib postoperatively, and died from disease progression. The remaining 2 patients received imatinib only, and had a survival time of 32 months and 49 months, respectively. Terminally ill patients were given the best supportive care, and had a median OS of 8 months.

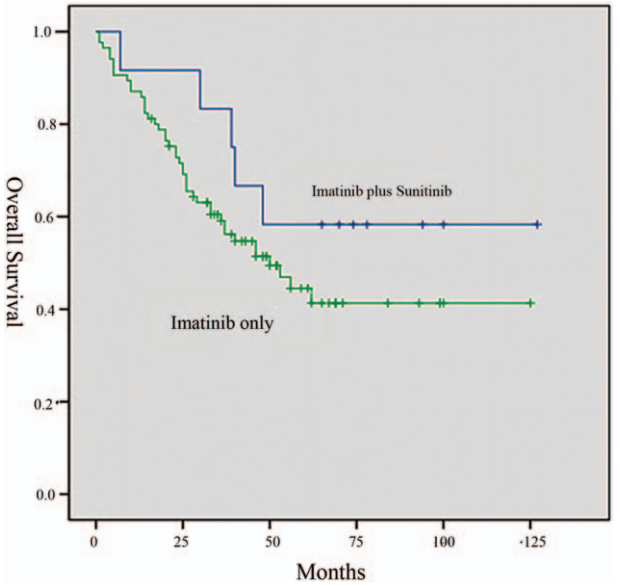

Figure 2. Survival analysis of patients with imatinib plus sunitinib versus patients with imatinib only.

We identified age more than 70 years as prognostic factors for death (Table 4). Gender, primary location of tumor, risk stratification, synchronous liver metastases, peritoneum and other metastases, hepatic resection, and utility of sunitinib were not statistically significant for a survival benefit.

4. Discussion

In this multicenter retrospective study of a population in northern China, we report the clinical manifestations, pathological features, treatment options, and follow-ups of Chinese GIST patients with liver metastases. We observed their 3- and 5-year OS rate, which was 51% and 24%, respectively, with a median survival time of 48.2 months. This was a long-term study of nearly 2 decades of partial patients living in an era before imatinib, a drug that has been used to treat metastatic or recurrent GIST since 2000. The population in our study comprised patients who underwent either single therapy or combination therapy, and terminally ill patients who did not have a chance to receive tumor-specific therapy. On the other hand, multidisciplinary evaluation and management options for metastatic GIST changed gradually in the times of TKIs. In this study, patients who received surgery combined with TKI accounted for 20% (23/144), and the majority of patients had TKI monotherapy for a long period of time. We speculate that some of them might have encountered disease progression before they realized TKI resistance and the chance of hepatic resection. According to the theory that tumor debulking surgery would delay the development of secondary KIT mutations leading to TKI resistance[11]; patients who had good response to imatinib could still have a chance of surgery in recent years. Additionally, neoadjuvant imatinib has been reported to have a role in improving OS for liver metastases in a prospective trial.[12]

DeMatteo et al reported a prognosis with 5-year OS rates between 27% and 34% and a median survival time ranging between 36 and 47 months by hepatic resection for liver metastases.[4] Other observational studies described a median survival of 48 months with imatinib only for GIST liver metastases.[13,14] For the subgroup analysis of this study, patients with both TKI monotherapy and combination therapy achieved long survival after liver metastases, which exceeded 48 months; and was not inferior to the results previously reported. Furthermore, we observed a tendency for patients who received combination therapy to have more favorable outcomes with increased median survival time, when compared with those who received TKI therapy (89 vs 53 months). This indicates that surgical resection combined with postoperative TKI therapy may improve OS. Another investigation has also supported combination therapy for GIST liver metastases, in which surgical resection and TKI therapy to be more effective than surgery or TKIs alone.[1] In particular, patients who received sunitinib as a second-line therapy after disease progression had longer median survival time when compared with patients who received imatinib only (not reached vs 50 months), although the difference was not statistically significant. The evidence of clinical benefit for sunitinib based on the prolonged time to tumor progression after imatinib failure has been reported in a prospective, double-

Table 3

Univariate analysis for patients with different clinicopathological characteristics.

Characteristics	Case no	%	m OS, mo	*P* value
Primary location of tumors				
Stomach	68	47.2	57	.818
Small intestine	55	38.2	66	
Large intestine	10	6.9	39	
Mesenterium and retroperitoneum	11	7.6	53	
Synchronous liver metastases				
Yes	41	28.5	56	.734
Nonsynchronous	103	71.5	89	
Metastases sites				
Liver only	101	70.1	57	.831
Peritoneum and other sites	43	29.9	46	

Table 4

Cox regression analyses for patients: multivariable OS analysis.

	P	HR	95% CI
Gender	.392	0.784	0.450–1.368
Age >70 y	.033	2.536	1.078–5.970
Primary location of tumor	.690	1.070	0.769–1.489
Risk stratification	.986	1.006	0.532–1.901
Synchronous liver metastases	.497	1.217	0.691–2.145
Peritoneum and other metastases	.851	1.028	0.770–1.373
Hepatic resection	.130	1.177	0.953–1.456
Utility of sunitinib	.543	0.772	0.335–1.776

Table 2

Survival analysis for patients with imatinib and imatinib+sunitinib.

Subgroup	Case no	%	m OS, mo	1 y OS, %	3 y OS, %	5 y OS, %	*P* value
Imatinib	86	87.8	50	87	50	21	.259
Imatinib+sunitinib	12	12.2	Not reached	92	83	58	

blind phase-III trial.[15] Twelve patients were administered with sunitinib, and more than half of them remained alive by the end of the last follow-up.

Interestingly, we found that patients with different primary tumor locations had similar outcomes. However, patients who had tumors that originated in the large intestine had a relatively shorter survival. The modified NIH criteria have been proven to have a prognostic value of GIST postoperatively.[9] Since 87.5% (126/144) of patients were classified into high risk of recurrence or metastasis, we deduce that other factors such as the distribution of tumors in hepatic lobes, the possibility of R0 resection, the response to TKIs, and second mutations may play a greater role in patient survival, rather than the origin of the tumor. Similarly, whether liver metastases were synchronous or not, and whether this was accompanied by metastases at other sites were not significantly related to patient survival.

There were limitations in this study. First, selection bias in this retrospective study could not be avoided, and the relevance of survival rates was difficult to analyze. Furthermore, the study lasted for a long time, while the therapeutic therapy updated as times. Second, few patients underwent KIT mutation examinations from operational or biopsy specimens, and experimental therapy decisions were made for patients when they had imatinib failure and switched to sunitinib. Third, the compliance of patients during the administration of TKIs was difficult to monitor. Therefore, the progression of the disease might be due to the interruption of imatinib or sunitinib to a certain extent.

In conclusion, we performed a retrospective multicenter study in a population in northern China regarding GIST with liver metastases. Patients who were given imatinib monotherapy and those who underwent combination therapy both achieved a long survival time, and the latter appears to have more clinical benefits. Further prospective studies of GIST liver metastases are needed in the future.

References

[1] Turley RS, Peng PD, Reddy SK, et al. Hepatic resection for metastatic gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. Cancer 2012;118:3571–8.

[2] Bamboat ZM, DeMatteo RP. Updates on the management of gastrointestinal stromal tumors (GIST). Surg Oncol Clin N Am 2012;21:301–16.

[3] DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51–8.

[4] DeMatteo RP, Shah A, Fong Y, et al. Results of hepatic resection for sarcoma metastatic to liver. Ann Surg 2001;234:540–7.

[5] Chaudhry UI, DeMatteo RP. Advances in the surgical management of gastrointestinal stromal tumor (GIST). Adv Surg 2011;45:197–209.

[6] Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res 2005;11:4182–90.

[7] Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342–9.

[8] Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8(suppl 2): S1–41.

[9] Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39:1411–9.

[10] Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol 2007;25:1753–9.

[11] Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364:1127–34.

[12] Xia L, Zhang MM, Ji L, et al. Resection combined with imatinib therapy for liver metastases of gastrointestinal stromal tumors. Surg Today 2010;40:936–42.

[13] DeMatteo RP, Maki RG, Singer S, et al. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. Ann Surg 2007;245: 347–52.

[14] Zhu J, Yang Y, Zhou L, et al. A long-term follow-up of the imatinib mesylate treatment for the patients with recurrent gastrointestinal stromal tumor (GIST): the liver metastasis and the outcome. BMC Cancer 2010;10:199.

[15] Demetri GD, Garrett CR, Schöffski P, et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res 2012;18:3170–9.