Aggressive surgical resection for the management of hepatic metastases from gastrointestinal stromal tumours: a single centre experience

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Abstract

Background: The outcome of surgical intervention for hepatic metastases from gastrointestinal stromal tumours (GIST) is still uncertain. This study evaluated the outcome of patients following aggressive surgical resection and Imatinib mesylate therapy (IM). *Patients and methods:* This was a retrospective analysis of patients managed with hepatic metastases from GIST over a 13-year period (January 1993 to December 2005). *Results:* Twelve patients were identified with a median age at diagnosis of 62 (32−78) years. The primary sites of GIST were stomach ($n=5$), jejunum ($n=4$), sigmoid ($n=1$), peritoneum ($n=1$) and pancreas ($n=1$). Eleven patients underwent surgical resection with curative intent and one patient had cytoreductive surgery. Following surgery with curative intent ($n=11$), the overall 2- and 5-year survival rates were both 91%, whereas the 2- and 5-year disease-free rates following primary hepatic resection were 30% and 10%, respectively. The median disease-free period was 17 (3−72) months. Eight patients had recurrent disease and were managed with further surgery ($n=3$), radiofrequency ablation (RFA) ($n=2$) and IM ($n=8$). Overall, there are four patients who are currently disease-free: two patients following initial hepatic resection and two patients following further treatment for recurrent disease. There was no significant association in clinicopathological characteristics between patients with recurrent disease within 2 years and patients who were disease-free for 2 years or more. Overall morbidity was 50% ($n=6$), with one postoperative death. The follow-up period was 43 (3−72) months. *Conclusion:* Surgical resection for hepatic GIST metastases may improve survival in selected patients. Recurrent disease can be managed with surgery, RFA and IM.

Key Words: *gastrointestinal stromal tumour, hepatectomy, surgical resection, liver metastasis*

Introduction

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours, and account for 1−3% of all gastrointestinal malignancies [1−3]. These tumours demonstrate a broad spectrum of biological behaviours, from indolent to rapidly progressive malignancies [4,5]. The liver is known to be a common metastatic site for GIST and previous studies have reported that 55−72% of patients develop hepatic metastasis following complete resection of the primary tumour [6−8].

Previously described treatment modalities for hepatic metastases from GIST include anthracycline- and ifosfamide-based chemotherapy regimes [9,10], hepatic arterial chemoembolization [11], surgical resection [12,13] and hepatic transplantation [14].

However, high recurrence rates and poor survival outcomes following hepatic transplantation have been reported [14]. Previous studies have described radical surgical resection, including hepatectomy, as a potential treatment modality for this clinical condition [8,12].

More recently, the emergence of Imatinib mesylate (STI571, Glivec™), a tyrosine kinase inhibitor, has been reported to induce a good response in cases of GIST [15,16]. In the clinical setting, Imatinib mesylate has been successfully tested in patients with metastatic and/or irresectable GIST [17−19]. Currently, large randomized clinical trials are ongoing to determine the effectiveness, safety, duration and inclusion criteria of adjuvant Imatinib mesylate therapy for patients with GIST.

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This study presents a retrospective review of the management of patients with hepatic metastases from GIST and their clinical outcome evaluated at a single institution.

Patients and methods

Patients

Patients referred with hepatic metastasis from GIST to the Hepatobiliary Unit, St James's University Hospital during the 13-year period, from January 1993 to December 2005 were identified using the Hepatobiliary database. The medical records of these patients were retrospectively reviewed for demography, clinical presentation, radiological investigations, treatment and clinical outcome (morbidity and mortality). Preoperative radiological assessment included thoracic, abdomen and pelvis CT and MRI of the liver.

Surgery and follow-up

Surgical resection was classified as resection with curative intent and palliative surgery. Surgical resection with intent to cure involved the complete resection of all tumours identified at operation, including the primary tumour, hepatic metastases and other intra-abdominal disease. Palliative surgery was defined when resection of all tumours was not feasible. Hepatic resection was performed using the Cavi-Pulse Ultrasonic Surgical Aspirator (CUSA, Model 200T, Valley Lab., Colorado, USA). Intraoperative ultrasound was performed to confirm the findings of preoperative imaging and to assist in surgical planning.

Following initial postoperative review at 1 month, all patients were examined in the outpatient clinic at 3, 6, 12, 18 and 24 months and annually thereafter. At each clinic review at 3, 6, 12, 18 months, 2 years and annually thereafter CT of chest, abdomen and pelvis was performed. Liver MRI was used to define suspicious lesions demonstrated on CT or in cases of negative CT with recurrence of endocrine-related symptoms.

Clinicopathological characteristics

Histopathological data of the primary tumour (location), hepatic metastases (number and size of hepatic metastases) and extrahepatic involvement were also recorded and analysed. Patients were considered to have incidental hepatic metastasis if the lesion was discovered during a work-up for a different medical problem. Synchronous hepatic metastasis was defined as simultaneous identification of hepatic metastases and primary GIST. Histopathological diagnosis of GIST was based on the expression of CD117 antigen (*c-kit* proto-oncogene protein product) on resected specimens, which showed differentiation towards the intestinal cells of Cajal on immunohistochemical analysis [20].

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows™ version 12.0 (SPSS Inc., Chicago, IL, USA), and statistical significance was defined as $p < 0.05$. The Kaplan−Meier method was used to assess the actuarial survival and disease-free rate. Univariate analysis (Mann-Whitney U test, χ^2 test and Fisher's exact test) was performed to assess for a difference in clinicopathological characteristics between patients with recurrent disease within 2 years and patients that were disease-free for 2 years or more.

Results

During the study period, 12 patients with hepatic metastases from GIST were identified from the database. The median age at diagnosis was 62 (32–78) years and the male to female ratio was 5:7.

The localization of the primary tumour was the stomach ($n = 5$), jejunum ($n = 4$), sigmoid ($n = 1$), peritoneum ($n = 1$) and pancreas ($n = 1$). One patient presented with synchronous primary GIST with hepatic metastases and the remaining 11 patients had metachronous hepatic metastases. The median time interval between hepatic metastases and primary tumour resection in these cases was 18 (5–168) months.

The most common symptom at presentation of hepatic metastases was abdominal pain ($n = 7$). One patient presented with an abdominal mass and the remaining four patients with hepatic metastases were detected by surveillance imaging. All patients underwent a complete imaging assessment, including ultrasound examination, abdominal and thoracic CT and MRI of the liver. In addition, five patients had a bone scan. Radical surgery with intent to cure was performed in cases where metastatic hepatic tumours were judged to be resectable on imaging studies.

One patient underwent a left lateral segmentectomy as a cytoreductive procedure for the removal of selected hepatic metastases that were resistant to Imatinib mesylate therapy. Eleven patients underwent surgical resection with intent to cure, which consisted of right hepatic trisegmentectomy ($n = 5$, three cases having additional contralateral non-anatomical metastectomies), right hepatectomy ($n = 1$), right hemihepatectomy with contralateral non-anatomical metastectomies ($n = 1$), left hepatectomy with contralateral non-anatomical metastectomies ($n = 1$) and multiple non-anatomical metastectomies ($n = 3$). In addition, synchronous peritoneal tumours were identified in four patients, and combined resection of these tumours was also performed (Table I).

Table I. Characteristics of the 12 patients in this study.

No.	Age* (sex)	Disease site (at primary surgery)		Time interval to hepatic metastases (months)	Surgery		Recurrence[?] (months)†	Treatment for recurrence	Current status (follow-up, months)‡
		Primary tumour	Others		Hepatic resection?	Additional procedures			
1	64 (F)	Jejunum	None	168	R hepatectomy	None	None	None	Disease-free (72)
2	33 (M)	Stomach	None	12	R trisegmentectomy	None	27	IM	Stable disease (60)
3	32 (F)	Sigmoid	None	10	R trisegmentectomy + NAM	None	17	IM and surgery	Disease-free§ (43)
4	43 (F)	Peritoneum	None	36	R trisegmentectomy	None	19	IM and surgery	Stable disease (54)
5	78 (F)	Stomach	None	36	L hepatectomy + NAM	Peritoneum resection	15	IM	Stable disease (41)
6	61 (M)	Pancreas	None	24	NAM	Peritoneum resection	17	IM and surgery	Stable disease (54)
7	61 (M)	Stomach	None	12	R hemihepatectomy+NAM	Peritoneum resection	5	IM and RFA	Stable disease (37)
8	39 (F)	Jejunum	None	72	R trisegmentectomy+NAM	Peritoneum and SB resection	None	None	Disease-free (44)
9	67 (M)	Jejunum	None	5	NAM	None	3	IM and RFA	Stable disease (36)
10	45 (F)	Stomach	Liver	0	NAM	Gastrectomy	6	IM	Disease-free§ (29)
11	55 (M)	Jejunum	None	12	R trisegmentectomy+NAM	None	POD	NA	NA
12	69 (F)	Stomach	None	41	L lateral segmentectomy	None	NA	NA	Stable disease (3)

F, female; M, male; R, right; L, left; NAM, non-anatomical metastectomy/metastectomies; SB, small bowel; POD, postoperative death; IM, Imatinib mesylate; RFA, radiofrequency ablation; NA, not applicable.

*Age refers to age at diagnosis at time of identification of hepatic metastases from GIST.

†Recurrence refers to disease recurrence following primary hepatic resection.

‡Follow-up period is from the time of primary hepatic resection to last clinical follow-up.

§These patients are currently disease-free having following treatment of recurrent disease with further surgery, radiofrequency ablation and/or Imatinib mesylate (patient 3: disease-free for 13 months and patient 10: disease-free for 8 months).

Hepatic metastases specimens in all cases were positive for CD117 (*c-kit*) expression on immunohistochemical analysis. Multiple hepatic metastases were present in 11 patients and 1 patient had a solitary hepatic metastasis. Overall, the median number of hepatic metastases was 5.5 (1–21) and the median largest size of hepatic metastatic tumours from each patient was 5 (0.7–14) cm. In five cases, there was evidence of hepatic tumour on the resection margin. The median hepatic resection margin to the tumour in the remaining cases was 1 (0.5–7) mm. Statistical analysis did not reveal a significant difference in clinicopathological variables between patients who were disease-free for less or more than 2 years (Table II). There was also no association between the involved resection margin and disease recurrence in the remnant liver.

Recurrence within the remnant liver following surgical resection occurred in eight patients, with five of them having synchronous extrahepatic disease – peritoneal ($n = 5$) and lung ($n = 1$). Three patients with recurrent disease underwent further surgery including multiple hepatic metastectomies, resection of right lower lobe of lung for solitary metastasis and excision of peritoneal GIST, respectively. Two patients were treated with open RFA for recurrent hepatic metastases.

Ten patients in this series were treated with Imatinib mesylate therapy, with four patients treated preoperatively over a median period of 13.5 (3–55) months. Three of the four patients proceeded to have surgical resection with curative intent and the remaining one patient had selected resection of hepatic metastases that were resistant to Imatinib mesylate therapy. Patients who were not managed with pre-operative Imatinib mesylate therapy were not commenced on this therapy following primary hepatic resection until detection of recurrence. Following the detection of recurrent disease post-resection, eight patients (including the two patients who had neoadjuvant therapy) were commenced on Imatinib mesylate therapy. Currently, seven patients are receiving Imatinib mesylate therapy for a median period of 36 (31–55) months. Following a combination of treatment modalities that included surgical resection, RFA and/or Imatinib mesylate therapy for recurrent disease, there are two patients who are currently disease-free (8 and 13 months, respectively) (Figure 1).

In patients that underwent surgery with intent to cure, the overall 2- and 5-year actuarial survival rates were both 91%, whereas the 2- and 5-year disease-free rates following primary hepatic resection were 30% and 10%, respectively. The median disease-free period was 17 (3–72) months (Figure 2). Overall, there are four patients that are currently disease-free: two patients following initial hepatic resection and two patients following further treatment for recurrent disease.

Overall morbidity was 50% ($n = 6$). Four patients (33.3%) had abdominal collection and three patients (25%) developed a wound infection. There was one postoperative death due to multi-organ failure and sepsis secondary to small bowel perforation. The overall follow-up period was 43 (3–72) months.

Discussion

There are significant prognostic implications in GIST cases with hepatic metastasis [6]. Recent studies on hepatic resection for metastases from GIST have

Table II. Clinical and pathological characteristics of patients with metastatic GIST in this study.

	Disease-free period		
Clinical and pathological characteristics	Less than 2 years ($n = 7$)	More than 2 years ($n = 3$)	*p* value*
Demographics			
Male:female ratio	3:4	1:2	1.000
Age at diagnosis: median (range) years	67 (32–78)	39 (33–64)	0.424
Time interval between hepatic metastasis and primary resection: median (range) months	12 (0–36)	72 (12–168)	0.108
Pathological analysis			
Primary site	3	1	0.516
Stomach	1	2	
Jejunum	1	0	
Sigmoid	1	0	
Peritoneum	1	0	
Pancreas	1	1	
Extrahepatic metastatic disease at presentation	3	1	1.000
Size of hepatic metastasis: median (range) cm	3.3 (0.7–14)	3.7 (2–12)	0.909
No. of hepatic metastases: median (range)	3 (2–7)	6 (1–21)	0.728
Resection margin: median (range) mm	1 (0.5–1.8)	1 (0–7)	0.726

*Statistical analysis was performed on 10 patients that had surgical resection of metastatic disease with curative intent (2 patients were excluded from analysis: 1 patient with early postoperative death and 1 patient with cytoreductive surgery).
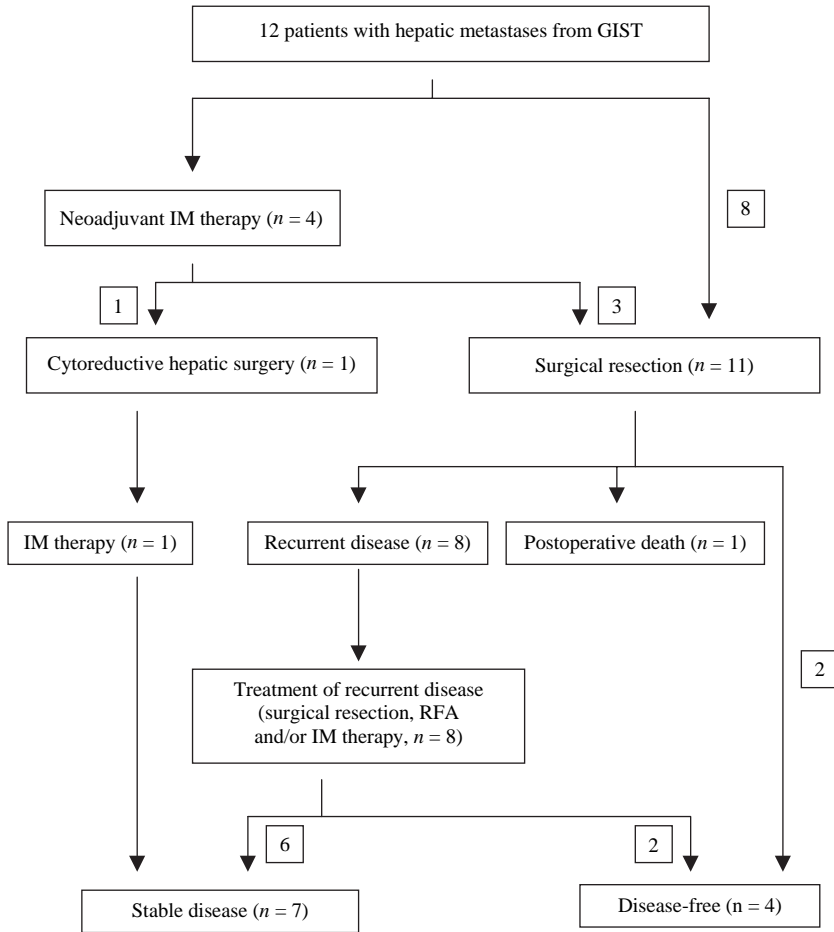
Figure 1. Management and clinical outcomes of patients with hepatic metastases from GIST in this study. GIST, gastrointestinal stromal tumour; RFA, radiofrequency ablation; IM, Imatinib mesylate (STI571, Glivec™).

shown an overall median survival time of 39 (33–40) months following surgery [6,8,12,13,21,22] (Table III). However, in some of these series, the results included patients with sarcomas and leiomyosarcomas. It is not unreasonable to assume that the majority of such lesions would be reclassified as GIST

Figure 2. Disease-free rate in patients with hepatic metastases from GIST in this study. +, disease-free patients.

in current practice. Nevertheless, these results suggest that surgical resection is a recognized treatment modality for hepatic metastases from GIST and does have a contributory effect on the overall survival rate. In the present study, all patients except one are currently alive, with a median follow-up period of 43 months.
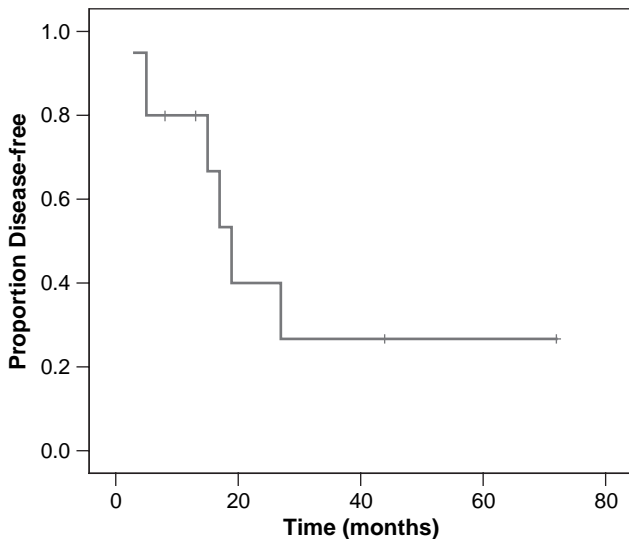
Previous studies have reported high recurrence rates following surgical resection for hepatic metastases from GIST, i.e. median =71.5%, range =50–84% [8,12,13,21,22]. Some clinicians have advocated the use of different treatment modalities to manage recurrent disease following hepatic resection including chemotherapy [13], hepatic arterial chemoembolization [12,16], further resection of the remnant liver [12,13] and peritoneal recurrence [6,8,23], RFA [13] and Imatinib mesylate therapy [13,24,25]. Although complete resection of GIST in the abdominal cavity has been reported to improve the survival outcome [6,8,23], extra-abdominal recurrences have a poor prognosis [12]. In this study, the majority of cases had disease recurrence within 2 years following surgical resection. Eight patients with recurrent disease in the remnant liver (including four with additional extra-hepatic disease), were treated with further surgery, RFA, Imatinib mesylate therapy or a combination of

Table III. Previous published series (1990 to present) of surgical resection for hepatic metastases from GIST, sarcomas and leiomyosarcomas.

Series (reference)	Study period (year of publication)	Centre	Sample size (surgical resection)	Median survival (months)	Recurrence (months)*
Ng et al. [6]	1957–1987 (1992)	Houston, USA	5	33	Not recorded
Chen et al. [21]	1984–1995 (1998)	Baltimore, USA	6	39	3 (50%)
Lang et al. [22]	1983–1996 (2000)	Hannover, Germany	18	40	9 (60%)
DeMatteo et al. [8]	1982–1998 (2000)	New York, USA	56	39	47 (84%)
Shima et al. [12]	1989–2001 (2003)	Kochi, Japan	10	39	7 (70%)
Nunobe et al. [13]	1984–2003 (2005)	Tokyo, Japan	18	36	14 (77%)
Present series	1993– 2005	Leeds, UK	12	43	8 (73%)

*Recurrence represents disease recurrence in patients following primary hepatic resection with curative intent.

these modalities. This resulted in two patients with recurrent disease being currently disease-free and the remaining patients having stable disease. This included a patient with lung metastasis who is alive at 54 months following initial hepatic resection. The current data suggest that further surgical resections for recurrent hepatic disease and peritoneal recurrence should be attempted when feasible and a combination with other treatment modalities such as RFA and Imatinib mesylate therapy is thought to be safe and improves clinical outcome.

Due to the difference in its natural history and high recurrence rates, some authors suggest that hepatic metastases from GIST should not be managed in a similar fashion to hepatic colorectal metastasis [13]. Hepatic metastases from GIST could indicate that systemic disease is already present and surgical resection is merely palliative. Nevertheless, results from the present study suggest that recurrent disease managed with further surgery, RFA, Imatinib mesylate therapy or a combination of these modalities does improve prognosis.

Various studies have attempted to determine prognostic factors for hepatic metastases from GIST. The disease-free interval between primary surgery and recurrence, or the duration between hepatic resection and recurrence, has been shown to be a significant prognostic predictor of survival [8,13]. DeMatteo et al. showed that a time interval from the primary tumour to the development of hepatic metastasis >2 years was a significant predictor of survival following hepatectomy [8]. Nunobe and co-workers found that the only significant prognostic factor following hepatectomy was a 5-year period to the development of recurrence [13]. Other investigators have reported similar findings [22]. Another study revealed that primary GIST size and mitotic rate were the most useful parameters to predict malignant potential [25]. Patel and Benjamin demonstrated that prognostic factors associated with improved survival following recurrent disease were disease-free intervals >18 months, recurrence limited to the peritoneal cavity or liver and complete resection of metastatic disease [26]. However, the status of the microscopic resection margin did not alter the survival rate [8]. Other reports have also demonstrated a trend towards an improved survival rate when comparing isolated liver metastasis to all other abdominal recurrences [6,8,27]. Nevertheless, this series did not identify any significant prognostic factors from clinical and pathological characteristics of hepatic metastases from GIST. This may be due to the small sample size in this study.

The underlying mechanism of the development of GIST is thought to be due to the gain-of-function mutation of the *c-kit* gene, resulting in activation of its product, KIT receptor tyrosine kinase [28]. Imatinib mesylate is a selective inhibitor of tyrosine kinase activity of *c-kit* and clinical trials have reported good efficacy and improved survival outcomes in patients with metastatic GIST [16,17,19,29–31]. The clinical response to Imatinib mesylate therapy is determined by the type of *c-kit* mutation [15,16,30–32]. In this series, all patients treated with Imatinib mesylate therapy demonstrated *c-kit* expression. Three patients treated preoperatively with Imatinib mesylate therapy had a significant response and proceeded to have hepatic resection with intent to cure. This may suggest that neoadjuvant Imatinib mesylate therapy could further expand the indications for surgical resection. All patients under adjuvant Imatinib mesylate therapy complementing other treatment modalities for recurrent disease now have stable disease or are currently disease-free. The full potential of Imatinib mesylate therapy is yet to be elucidated and trials are in progress to determine its role in the management of this disease.

Conclusion

Surgical resection with curative intent for hepatic metastases from GIST should be considered when feasible, as it may improve survival outcomes in selected patients. Recurrence of disease can be managed with further surgery, RFA, Imatinib mesylate therapy or a combination of these treatment modalities.

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