

Survival After Resection of Gastrointestinal Stromal Tumor and Sarcoma Liver Metastases in 146 Patients

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Abstract

Background We investigated outcomes by primary tumor type in patients who underwent resection of liver metastases from gastrointestinal stromal tumors (GIST), leiomyosarcomas, and other sarcomas.

Method Our institutional liver database was used to identify patients who underwent resection from 1998 through 2013. Histopathological, clinical, and survival data were analyzed.

Results One hundred forty-six patients underwent resection of liver metastases from GIST ($n=49$), leiomyosarcomas ($n=47$), or other sarcomas ($n=50$). The 5-year overall survival (OS) rates in patients with GIST, leiomyosarcomas, and other sarcomas were 55.3, 48.4, and 44.9 %, respectively, and the 10-year OS rates were 52.5, 9.2, and 23.0 %, respectively. The 5-year recurrence-free survival (RFS) rate was better for GIST (35.7 %; $p=0.003$) than for leiomyosarcomas (3.4 %) and other sarcomas (21.4 %). Lung recurrence was more common for leiomyosarcomas (36 % of patients; $p<0.0001$) than for other sarcomas (12 %) and GIST (2 %). For GIST, the findings support a benefit of imatinib regarding the 5-year RFS rate compared to resection alone (47.1 vs. 9.5 %; $p=0.013$). For leiomyosarcoma, primary tumor location did not affect the 5-year RFS rate (intraabdominal 14.5 %; other location 0 %; $p=0.182$).

Conclusion Liver metastases from GIST, leiomyosarcomas, and other sarcomas should be assessed separately as their survival and recurrence patterns are different. This is especially important for GIST, for which imatinib is now available.

Keywords Gastrointestinal stromal tumors · Leiomyosarcoma · Sarcoma · Surgery · Neoplasm metastasis · Resection · Liver metastases

Introduction

The safety of liver resection is improving, allowing for broader application of resection of noncolorectal liver

metastases.^{1–3} However, as the definition of technically resectable liver disease is expanding, it remains important to determine the survival benefit from liver resection given that tumors of different origins have different growth rates, invasiveness, and migratory potential.⁴

Among the tumors that can metastasize to the liver are gastrointestinal stromal tumors (GIST) and leiomyosarcomas (LMS). GIST, arising from interstitial cells of Cajal of the gastrointestinal tract or other intraabdominal sites, account for 90 % of gastrointestinal mesenchymal neoplasms.⁵ GIST may or may not possess features of smooth muscle cells but are uniformly characterized by immunoreactivity to the transmembrane tyrosine kinase receptor CD117 (KIT).⁶ LMS, on the other hand, generally lack expression of CD117 but reliably demonstrate high levels of smooth muscle actin and desmin.^{7,8} Distinguishing between GIST and gastrointestinal LMS (GI-LMS) was difficult before the introduction of KIT immunohistochemistry.⁵ Consequently, early studies of GI-LMS were comprised largely of patients with GIST, and the

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unique patient outcomes after resection of liver metastases from GIST and LMS remain poorly described. This problem became especially important after the introduction of imatinib mesylate (imatinib) for treatment of GIST because imatinib has improved outcomes significantly for patients with GIST, whereas targeted therapy for LMS remains experimental and LMS respond poorly to chemotherapy.^{9,10}

There are a number of published studies on outcomes after resection of liver metastases from GIST and sarcomas of various origins (Table 1). However, most of these studies are limited by small patient numbers (<40 patients)^{11–18} and/or poor distinction between pathological types, some even including non-GI-LMS and sarcomas of other or indeterminate origin (SRC) in the survival analyses.^{1,2,19,20}

The aim of the present study was to determine outcomes after resection of liver metastases from GIST, LMS, and SRC as unique groups in a large series of patients from a single center. We performed subanalyses to determine the survival impact of imatinib treatment in GIST, the survival impact of the location of LMS (intraabdominal vs. other location), the survival impact of radiofrequency ablation (RFA) in all pathological types, the risk factors for recurrence, and the patterns of recurrence according to pathological type.

Methods

Study Population

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved the study protocol, PA14-0761. Patients who underwent resection of first-time liver metastases from GIST, LMS, or SRC from 1998 through 2013 were identified from the institutional liver database. Resection of nonliver metastatic disease prior to liver surgery was not an exclusion criterion. The following data were recorded or updated with data found in electronic patient medical records: sex, age, disease-free interval between resection of the primary tumor and presentation of liver metastases, number of liver metastases, diameter of the largest liver metastasis, type of liver resection, resection margin status (no viable tumor cells <1 mm from the resection margin, or viable tumor cells <1 mm from the resection margin [R1]), use of RFA, pathological type, use of chemotherapy and targeted therapy, site of recurrence, and overall survival. The patients were grouped according to pathological type: GIST, LMS, or SRC. The following groups were

Table 1 Summary of studies reporting resection of liver metastases from GIST, LMS, and SRC

First author	Study period	No. of patients	Pathological type(s)	TKI, no. of patients treated	RFA	Predictor(s) of positive outcome	Overall survival rate
Lang	1982–1986	34	LMS	0	No	None	5 years: 13 %
DeMatteo	1982–2000	56	GIST/GI LMS (n=34), non-GI LMS (n=11), SRC (n=11)	0	No	Disease-free interval >2 years	5 years: 30 %
Shima	1989–2001	10	GIST	0	±RFA	None	Median: 39 months
Nunobe	1984–2003	18	GIST and/or LMS	0	No	None	5 years: 34 %
Pawlik ^a	1996–2005	66	GIST (n=36), LMS (n=18), SRC (n=12)	26	±RFA	No RFA; adjuvant therapy; imatinib	5 years: 27.1 %
Adam ^b	1983–2004	158	GIST (n=33), SRC (n=125)	NA	NA	None	GIST 5 years: 70 % SRC 5 years: 31 %
Rehders	1993–2003	27	LMS/GIST/hemangiopericytoma	0	NA	Disease-free interval >2 years	5 years: 49 %
Xia	2005	19	GIST	19	NA	Resection improved survival in imatinib-poor responder	3 years: 89.5 %
Turley ^c	1995–2005	39	GIST	27	6	TKI and resection better than TKI alone	3 years: 67.9 %
Cananzi	2006–2010	11	GIST	11	NA	TKI improved overall survival	2 years: 70.7 %
Current study	1998–2013	146	GIST (n=49), LMS (n=47), SRC (n=50)	39	±RFA	GIST, LMS, and SRC have different outcomes and predictors of outcome	10 years: 52.5, 9.2, and 23.0 % for GIST, LMS, and SRC, respectively

GI gastrointestinal, GIST gastrointestinal stromal tumor, LMS leiomyosarcoma, NA not available, RFA radiofrequency ablation, SRC sarcoma of other or indeterminate origin, TKI tyrosine kinase inhibitor

^a Study included 13 patients who underwent RFA only

^b Multicenter study involving 41 centers

^c Multicenter study involving three centers

used for subanalyses: use of tyrosine kinase inhibitor (TKI) or not in patients with GIST, intraabdominal, or other primary tumor location in patients with LMS, and use of RFA or not in all patients.

Patient Care

Resectability and extrahepatic disease were assessed with helical computed tomography of the chest, abdomen, and pelvis with a triphasic liver protocol. Intraoperative ultrasonography was used to assess the vascular anatomy and to assess known and possibly undetected lesions. Parenchymal transection was performed using the Cavitron Ultrasonic Surgical Aspirator (Valleylab, Boulder, CO) and saline-linked cautery (Dissecting Sealer DS 3.0, Tissue Link Medical, Inc., Dover, NH) and performed with control of hepatic inflow.²¹ GIST diagnosis was confirmed by immunohistochemistry or PCR-based DNA sequencing analysis to detect mutations in *PDGFR α* (exon 18) or *c-KIT* (exons 9, 11, 13, and 17). Adjuvant treatment, (i.e., chemotherapy or targeted treatment) was used in 96 of the 146 patients (65.8 %). Imatinib was used to treat patients with GIST, and combinations of doxorubicin, docetaxel, gemcitabine, ifosfamide, and/or dacarbazine were used to treat patients with LMS and SRC. Radiological follow-up was performed every 4 months after resection of liver metastases to assess for recurrence.

Statistical Analysis

Continuous data were expressed as median with range and compared with Mann–Whitney U test. Categorical data were compared by Pearson Chi-squared tests or Fisher's exact test if the expected cell count number of any cell was less than 5. A *p* value of less than 0.05 was considered statistically significant. Cox regression survival analyses with enter method for the covariates were conducted to determine factors associated with overall survival. Kaplan–Meier analysis was used to assess recurrence-free survival (RFS) and overall survival (OS) from the hepatectomy, and groups were compared using log-rank analyses. The statistical analyses were performed using SPSS v. 19.0 (SPSS Inc., IBM, Chicago, IL, USA).

Results

Clinicopathological Characteristics and Pathological Types

A total of 146 patients underwent resection of liver metastases from GIST ($n=49$), LMS ($n=47$), or SRC ($n=50$) during the study period (Fig. 1). Patient characteristics by pathological type are summarized in Table 2. The median age was 55 years for patients with GIST, 57 years for those with LMS, and

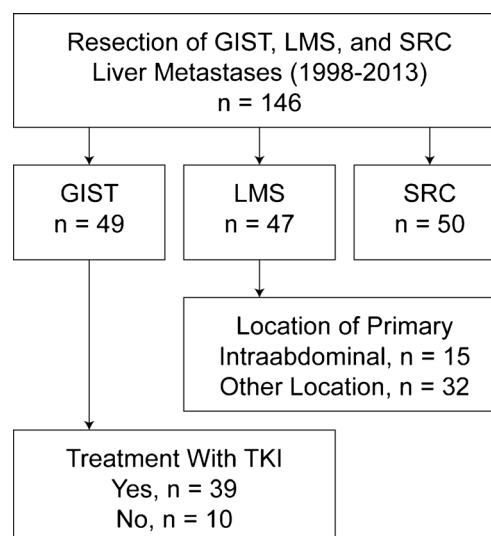


Fig. 1 Flow chart of study population and selected characteristics

54 years for those with SRC; the proportion of males was 59 % for GIST, 28 % for LMS, and 56 % for SRC. Of the 49 GIST, 20 were located in the small bowel, 14 in the stomach, 13 in the mesentery, and 2 in the large bowel. Of the 47 LMS, 14 were located in the abdomen, 10 in the uterus, 10 in the retroperitoneum, 4 in the kidneys, 3 in the adrenal glands, 3 in the vena cava, and 3 in other locations. Among the 50 SRC, there were ten cases of unclassified sarcoma; seven cases of liposarcoma; four cases each of desmoplastic small round cell sarcoma and pleomorphic sarcoma; three cases each of angiosarcoma, chondrosarcoma, fibrosarcoma, and hemangiopericytoma; two cases each of hemangioendothelioma, osteosarcoma, and spindle cell sarcoma; and one case each of clear-cell sarcoma, epithelioid sarcoma, Ewing sarcoma, myxofibrosarcoma, perivascular epithelioid cell tumor, phyllodes sarcoma, and synovial sarcoma.

RFS According to Pathological Type

The 5-year RFS rate was 35.7 % for GIST, 3.4 % for LMS, and 21.4 % for SRC, and median time to recurrence was 17.8 months for GIST, 7.9 months for LMS, and 8.8 months for SRC ($p=0.003$; Fig. 2a). The liver was the most common site of recurrence for all groups (GIST, 41 % of patients had recurrence in the liver; LMS, 40 %; SRC, 34 %), and there were no differences regarding the sites of recurrence except that lung recurrence occurred in 2 % of patients with GIST, 36 % of those with LMS, and 12 % of those with SRC ($p<0.001$; Table 3).

Subgroup analysis showed that patients with GIST who received imatinib had a higher 5-year RFS rate than patients with GIST who underwent surgical resection alone (47.1 vs. 9.5 %; $p=0.013$; Fig. 3a). Patients with LMS and SRC who received adjuvant chemotherapy had

Table 2 Patient characteristics by pathological type

Characteristic	GIST (n=49)	LMS (n=47)	SRC (n=50)	p Value
Male, n (%)	29 (59)	13 (28)	28 (56)	0.003
Age, median (range), year	55 (35–79)	57 (23–75)	54 (4–79)	0.709
Disease-free interval < 12 months, n (%)	26 (53)	22 (49)	26 (52)	0.807
Tumor size, median (range), mm	40 (6–250)	29 (6–148)	50 (3–230)	0.006
Number of tumors, median (range)	2 (1–9)	1 (1–10)	1 (1–10)	0.161
Major hepatectomy > three segments, n (%)	22 (45)	25 (53)	28 (56)	0.519
Concomitant RFA, n (%)	13 (27)	10 (21)	7 (14)	0.301
R1 resection, n (%)	2 (4)	2 (4)	4 (8)	0.627
Adjuvant treatment, n (%)	41 (84)	27 (57)	28 (56)	0.005
Tyrosine kinase inhibitor, n (%)	39 (80)	0	1 (2)	<0.001

GIST gastrointestinal stromal tumor, LMS leiomyosarcoma, SRC sarcoma of other or indeterminate origin, RFA radiofrequency ablation, R1 resection viable tumor cells < 1 mm from the resection margin

similar median RFS as patients who did not receive adjuvant chemotherapy (LMS: 7.9 vs. 9.0 months, $p=0.434$; SRC: 7.4 vs. 9.4 months, $p=0.805$). Patients with LMS with intraabdominal primary tumors had a 5-year RFS rate (14.5 %) similar to that of patients with LMS with primary tumors at other locations (0 %; $p=0.182$; Fig. 3b). Patients with any pathological tumor type who underwent RFA as part of their treatment (GIST, 27 %; LMS, 21 %; SRC, 14 %; $p=0.301$) had a lower 5-year RFS rate than patients whose disease could be cleared by resection alone (10.9 vs. 24.7 %; $p=0.009$; Fig. 3c). Patients who underwent resection and RFA had similar size of the largest metastasis, but more metastases than patients who underwent resection only: 45 and 55 mm (mean; $p=0.291$) and two metastases vs. one metastasis (median; $p=0.005$), respectively.

OS According to Pathological Type

The 5-year OS rates and median survival times did not differ significantly by pathological type, although there was a clear trend toward better 5-year survival for patients with GIST (Table 3). However, the 10-year OS rate was significantly better in patients with GIST (52.5 %) than in patients with LMS (9.2 %) or SRC (23.0 %; Fig. 2b; $p=0.016$). In univariate analyses (Table 4), after resection of liver metastases from GIST, age greater than 55 years (HR, 2.798; $p=0.027$) was associated with reduced OS, male sex (HR, 0.447; $p=0.071$) exhibited a trend toward increased OS, and concomitant RFA (HR, 2.179; $p=0.085$) and R1 resection (HR, 4.100; $p=0.066$) exhibited trends toward reduced OS. After resection of liver metastases from LMS, disease-free interval less than 12 months (HR, 2.253; $p=0.033$) and diameter of the largest

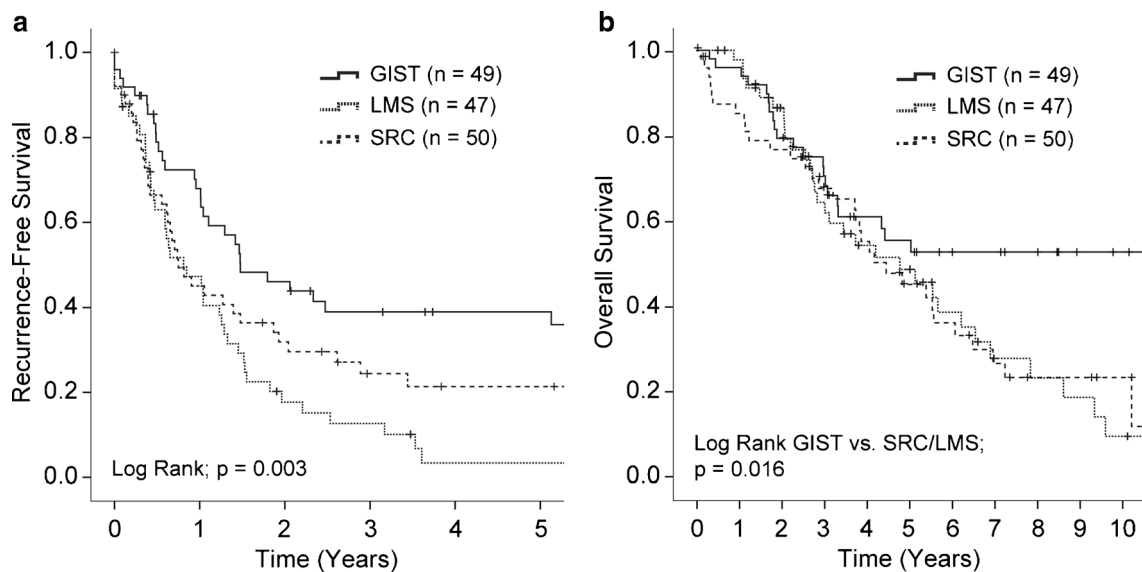


Fig. 2 Kaplan–Meier plot of 5-year recurrence-free survival (a) and 10-year overall survival (b) after resection of liver metastases according to pathological type. GIST gastrointestinal stromal tumor, LMS leiomyosarcoma, SRC sarcoma of other or indeterminate origin

Table 3 Overall survival, recurrence-free survival, and recurrence by site according to pathological type

Outcome	GIST (<i>n</i> =49)	LMS (<i>n</i> =47)	SRC (<i>n</i> =50)	<i>p</i> Value
Overall survival (OS)				0.016
Median survival, month	40.6	42.1	45.5	
3-year OS, %	72.7	64.3	67.5	
5-year OS, %	55.3	48.4	44.9	
10-year OS, %	52.5	9.2	23.0	
Recurrence-free survival (RFS)				0.003
Median time to recurrence, month	17.8	7.9	8.8	
3-year RFS, %	39.0	12.7	24.4	
5-year RFS, %	35.7	3.4	21.4	
Site of first recurrence, <i>n</i> (%)				
Liver	20 (40.8)	19 (40.4)	17 (34.0)	0.736
Lung	1 (2.0)	17 (36.2)	6 (12.0)	<0.001
Lymph node	4 (8.2)	4 (8.5)	4 (8.0)	0.996
Peritoneum	3 (6.1)	1 (2.1)	2 (4.0)	0.615
Abdominal	5 (10.2)	4 (8.5)	3 (6.0)	0.745
Retroperitoneal	1 (2.0)	3 (6.4)	2 (4.0)	0.563
Bone	2 (4.1)	3 (6.4)	4 (8.0)	0.718
Other	2 (4.1)	0	2 (4.0)	0.377

GIST gastrointestinal stromal tumor, LMS leiomyosarcoma, SRC sarcoma of other or indeterminate origin

tumor more than 30 mm (HR, 2.059; $p=0.055$; borderline significant) were associated with decreased OS. After resection of SRC, R1 resection (HR, 12.97; $p<0.001$) was associated with decreased OS, and male sex (HR, 1.962; $p=0.076$) exhibited a trend toward decreased OS (Table 4).

Discussion

In the present study, we investigated survival and factors associated with outcome after resection of liver metastases from GIST, LMS, and SRC in a large series of

patients from a single center. The median RFS times for patients with GIST, LMS, and SRC were 17.8, 7.9, and 8.8 months, respectively. Lung recurrence after resection of liver metastases was more common in patients with LMS than in those with GIST or SRC. The 10-year OS rate was 52.5 % in patients with GIST, 9.2 % in those with LMS, and 23.0 % in those with SRC, indicating long-term survival benefits of surgery in selected groups. In contrast to previous studies based on small patient series and/or poorly differentiating between the different pathological types, the current study suggests unique patterns of recurrence and survival for different

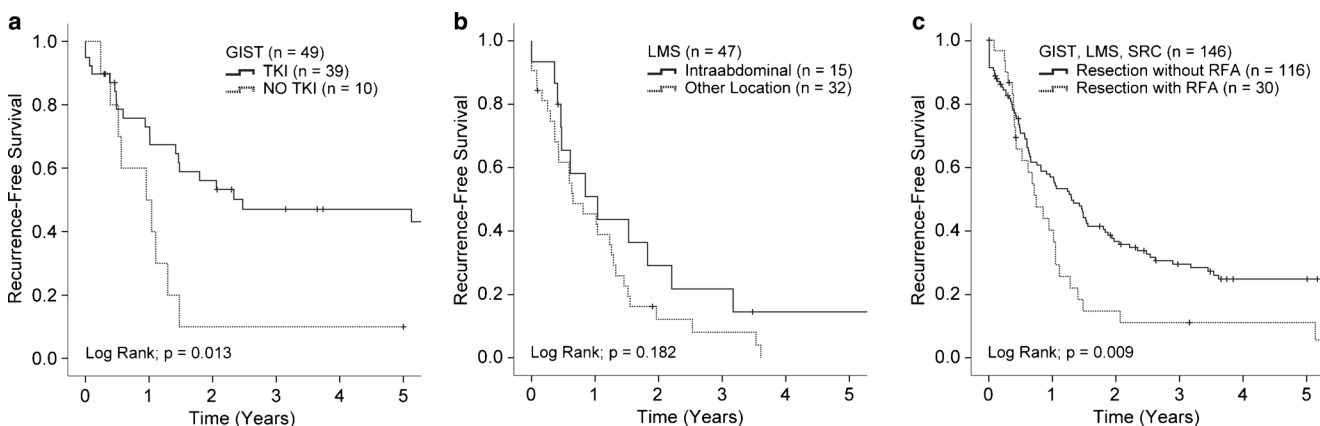


Fig. 3 Kaplan–Meier plots of recurrence-free survival according to subgroup: TKI treatment in patients with GIST (a), primary tumor location in patients with LMS (b), and RFA in all patients (c). GIST gastrointestinal

stromal tumor, LMS leiomyosarcoma, SRC sarcoma of other or indeterminate origin, TKI tyrosine kinase inhibitor, RFA radiofrequency ablation

Table 4 Predictors of overall survival by pathological type

	GIST (n=49)			LMS (n=47)			SRC (n=50)		
	HR	95 % CI	p Value	HR	95 % CI	p Value	HR	95 % CI	p Value
Male	0.447	0.187–1.072	0.071	1.496	0.676–3.312	0.290	1.962	0.932–4.133	0.076
Age>55 years	2.798	1.121–6.981	0.027	0.827	0.402–1.700	0.605	1.238	0.616–2.486	0.548
DFI<12 months	1.489	0.616–3.599	0.376	2.253	1.069–4.747	0.033	1.329	0.653–2.703	0.433
Tumor size>30 mm	2.179	0.798–5.952	0.129	2.059	0.985–4.305	0.055	0.833	0.401–1.732	0.625
Multiple tumors	1.534	0.633–3.716	0.343	0.714	0.346–1.472	0.361	0.693	0.331–1.451	0.331
Major hepatectomy ^a	0.651	0.269–1.571	0.339	1.255	0.599–2.630	0.547	0.777	0.387–1.559	0.477
Concomitant RFA	2.179	0.897–5.293	0.085	1.804	0.759–4.288	0.182	0.593	0.204–1.722	0.337
R1	4.100	0.913–18.41	0.066	1.031	0.241–4.409	0.967	12.97	3.542–47.49	<0.001
Adjuvant treatment	1.044	0.350–3.108	0.939	1.872	0.875–4.002	0.106	1.205	0.598–2.427	0.601
TKI	0.696	0.354–2.650	0.950	–	–	–	–	–	–

GIST gastrointestinal stromal tumor, LMS leiomyosarcoma, SRC sarcoma of other or indeterminate origin, DFI disease-free interval, RFA radiofrequency ablation, R1 viable tumor cells < 1 mm from the resection margin, TKI tyrosine kinase inhibitor

^a Resection of >3 segments

pathological types, indicating the importance of consideration of the tumor type when patients are evaluated for liver resection.^{11–14,19}

The previous practice of analyzing GIST and GI-LMS together has been based on the assumption that metastasizing cells from both pathological entities possibly reach the liver through portal vein circulation. In this view, liver metastases could represent “sentinel metastases” rather than disseminated disease, and surgery may provide a survival benefit and even cure. However, this assumption is hypothetical and does not account for different tumor biology of the pathological entities. Additional reasons for analyzing these pathological entities together have been the fact that these cancers are rare and the fact that they were difficult to distinguish from one another before the routine use of immunohistochemistry or gene analyses.^{1–11}

Previous studies have reported outcomes that could indicate cross-contamination between pathological groups. For example, Nunobe et al.¹³ and DeMatteo et al.¹⁹ did not distinguish between GIST and GI-LMS and reported 5-year survival rates of 34.0 and 40.0 %, respectively. These rates align between the 55.3 and the 21.8 % 5-year survival rates for GIST and GI-LMS in the current study. Furthermore, DeMatteo et al.¹⁹ reported similar survival after resection of GIST/GI-LMS and SRC. This could be attributed to the mixing of pathological entities but most likely reflects the fact that the study included patients treated before the use of imatinib.

Today, discrimination between GIST and LMS is important because patients with GIST are amenable to treatment with imatinib. In GIST, the principal pathological genetic defect has been identified as mutation in the *c-KIT* proto-oncogene or in the platelet-derived growth factor receptor- α (*PDGFR α*)

gene, both leading to expression of proteins causing constitutive activation of tyrosine kinase receptors. Imatinib was initially found as an inhibitor of BCR/ABL, but subsequently also found to be a molecular antagonist of *c-KIT* and *PDGFR α* proteins, and thereby acts as a tyrosine kinase inhibitor (TKI). More than 90 % of GIST express *c-KIT*, and imatinib has revolutionized treatment of these tumors.²² In the current study, most patients ($n=39$; 80 %) with liver metastases from GIST were treated with imatinib perioperatively, and their survival was superior to that of patients who underwent liver resection without imatinib. Liver resection before the 2001 US Food and Drug Administration approval of imatinib was the main reason for absence of treatment in the 10 patients with GIST in our study who did not receive imatinib. The effect of chemotherapy in LMS and SRC, not amenable to treatment with imatinib, is still uncertain and controversial.^{9,10} In the current study, 57.4 % of patients with LMS and 56 % of patients with SRC received some form of perioperative chemotherapy. We did not see the same survival benefit from chemotherapy in patients with LMS and SRC that we saw from imatinib in patients with GIST (data not shown).

Historically, resection of liver metastases from GIST has been controversial, and whether resection actually provided a chance for cure has been questioned. Nunobe et al.¹³ concluded that cure was difficult to achieve with resection in their series of 18 patients with GIST and that repeated surgical resection primarily contributed to palliation. In spite of their conclusion, they reported a 5-year survival rate of 34.0 %, reflecting long-term survivors in their series, which included both GIST and GI-LMS. Our results indicate that the 5-year GIST-specific survival rate could have been even higher had the patients stratified by pathological type.

In the era of imatinib, the role of surgery for liver metastases from GIST has been questioned. However, previous reports indicate that up to 24 % of GIST patients are poor imatinib responders and complete response to imatinib is rare.^{23–25} Xia et al.¹⁶ made the interesting observation that resection of liver metastases from GIST improved survival in patients with poor response to imatinib. Furthermore, resistance to imatinib is seen in more than 50 % of patients after 2 years of treatment.^{23–25} On the basis of our current study, we believe that resection of liver metastases from GIST, even in patients showing radiographic response to imatinib, should remain a vital component of the treatment plan.

In the current study, the liver was the most common site of recurrence after resection of metastases irrespective of pathological type, and liver metastases were seen in about 40 % of patients. In contrast, lung recurrence presented significantly more often in patients with LMS (36 %) than patients with SRC (12 %) or GIST (2 %). To our knowledge, this difference has not been noted in previous studies reporting recurrence after liver resection, possibly because of lack of differentiation in those studies between GIST and LMS.¹⁹

Because of small patient series and mixing of pathological types, it has been difficult to establish prognostic factors for survival after resection of liver metastases from GIST, LMS, and SRC.¹³ In studies by DeMatteo et al.¹⁹ and Pawlik et al.²⁰, clinicopathological factors such as sex, age, tumor number, and margin status were not prognostic of survival. In contrast, in the current study, male sex was a borderline significant predictor of survival, but with opposite effects in GIST (HR, 0.447; $p=0.071$) and SRC (HR, 1.962; $p=0.076$). In the current study, age more than 55 years was significantly associated with worse survival for GIST (HR, 2.798; $p=0.027$), but not for LMS and SRC. In patients with LMS, overall survival was positively associated with a disease-free interval of more than 12 months, which is in agreement with findings from patients with colorectal cancer liver metastases.²⁶ In contrast, in patients with GIST and SRC, survival was not associated with disease-free interval.

RFA was used in 30 patients (GIST: $n=13$; LMS: $n=10$; SRC: $n=7$) and was associated (borderline significant) with poor survival in patients with GIST but not in patients with LMS or SRC. Patients who underwent RFA alone without surgical resection were not included in the present study, but Pawlik et al.²⁰ previously reported higher rates of recurrence in patients who underwent RFA alone than in patients who underwent resection alone for GIST, LMS, or SRC.

Previous reports have shown that imatinib improves recurrence-free survival more in patients undergoing resection of liver metastases from GIST than in patients undergoing resection of liver metastases from LMS and SRC.²⁰ In the current study, the findings supported a benefit of imatinib on recurrence-free survival in patients with liver metastases from GIST.

The current study has the following limitations. First, the study may have been underpowered for certain analyses, especially subanalyses within the pathological groups. For example, for the analysis of the impact of a positive margin (R1 resection) in patients with GIST and LMS, there were only 2 patients with R1 resection in each of these groups. Furthermore, RFS was similar after resection of liver metastases from intraabdominal primary LMS, which is drained by the portal vein, and resection of liver metastases from primary LMS at other sites, which is drained systemically ($p=0.182$). However, according to the Kaplan–Meier survival plot (Fig. 3b), there could be a trend toward a more favorable outcome with the intraabdominal location of the primary LMS, and our series may have been underpowered to permit firm conclusions to be drawn. Regardless of this limitation, this surgical series is still the largest single-center experience reported to date of these pathological types. Second, while the Kaplan–Meier RFS plots showed significant separation between GIST, LMS, and SRC beginning about 1 year after resection of metastases (Fig. 2a), it was not until about 5 years after resection of metastases that the OS plots showed a survival advantage for GIST over LMS and SRC (Fig. 2b). One possible explanation for the discrepancy between the RFS and OS curves could be more aggressive treatment of recurrence in certain pathological entities. Furthermore, the number of patients with more than 5 years of follow-up was limited and may not have been sufficient to permit conclusions about whether SRC is associated with better OS than LMS between 5 and 10 years.

Conclusion

The current report suggests that patients with GIST, LMS, and SRC should be evaluated separately for resection of liver metastases. Patients with GIST treated with imatinib and resection had a clear survival benefit over patients with GIST undergoing resection alone. This benefit is most likely a synergistic effect and resection should still be the mainstay of treatment as resistance to imatinib is often observed after about 2 years of treatment. The current study demonstrates long-term survivors (5 and 10 years) after resection of liver metastases from LMS and SRC, indicating a role for surgical resection in patients with these pathological entities as well.

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Conflict of Interest The authors report no conflicts of interest relevant to this article.

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