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Hepatic Metastasectomy for Soft-Tissue Sarcomas: Is It Justified?

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Abstract
Background Except for patients with gastrointestinal stromal tumors (GIST), systemic chemotherapy in patients with liver metastasis of soft-tissue sarcoma (STS) is not effective. Therefore, all patients with resectable liver metastases underwent surgical therapy. We present our experience with this approach during the last 13 years.
Methods All patients (n = 45) with liver metastasis of STS undergoing surgical therapy were prospectively analyzed. Clinical and histopathological parameters as well as the postoperative course were recorded. Survival data were analyzed by using the Kaplan-Meier method and the log-rank test.
Results Twenty-seven of 45 patients with liver metastasis underwent hepatic resection; 59% of these patients had a solitary metastasis, 22% had two metastases, and 18% had three or more metastatic nodules. The surgical perioperative mortality was 7%. The median survival was 44 (range, 1–123) months, and the 5-year survival was 49%. Repeated resection for recurrent tumor was performed in eight patients, which yielded a median survival of 76 months.
Conclusions Patients who have hepatic metastases that are functionally and technically resectable should be considered for surgery because this treatment offers the chance for long-term survival (>5 years).

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Introduction

Soft-tissue sarcomas (STS) are a heterogeneous group of malignant tumors that account for approximately 1% of all malignancies. Despite excellent rates of local disease control, 25–40% of all patients with STS eventually develop distant metastasis [1]. Abdominal and pelvic STS predominantly metastasize to the liver. Because systemic chemotherapy and chemoembolization do not prolong survival remarkably [2], hepatic metastasis is generally associated with a poor prognosis. Only patients with gastrointestinal stromal tumors (GIST) tumors who receive Gleevec® have a more optimistic prognosis; however, advances in both surgical techniques and perioperative care have made hepatic resection a safe surgical option for patients with metastatic disease [3].

During the last decades, several reports have shown promising results and prolonged survival after surgical treatment of hepatic STS metastasis [4–6]. However, the question of which patients benefit from surgical intervention is still being debated. Several authors state that hepatic recurrence is a manifestation of a more generalized disease and conclude that surgical therapy in most patients should

be confined to the relief of symptoms [7–10]. Alternative concepts with minimally invasive radiofrequency ablation yielded a median survival of 25 months in selected patients with hepatic STS metastasis [11]. This technique is clearly limited by factors, such as tumor size and proximity to large vessels. These parameters significantly correlate with an increased rate of local recurrence [12].

Unless severe comorbidity was present, in our institution all patients with resectable liver metastasis underwent radical resection regardless of site, size, or number of metastatic nodules. We report the analysis of 13 years of our experience in treating these patients, with emphasis on prognostic factors and long-term results.

Material and methods

Assessment

Between January 1993 and May 2003, 329 consecutive patients with STS were operated on at our hospital. All patients were entered into a computerized database during their hospitalization. Furthermore, follow-up was recorded for each patient. All patients presenting with hepatic metastases were evaluated for surgical therapy unless contraindications existed. Potential contraindications were insufficient control of the primary tumor, unresectable or diffuse hepatic involvement, unresectable local recurrence, as well as nonhepatic metastatic disease. Diffuse involvement was defined as multiple small lesions in both hepatic lobes and most segments; these precluded oncologic resection with clear margins. Further contraindications were liver cirrhosis or insufficient liver function as well as other concomitant comorbidities that indicated that the resection of all hepatic nodules would not be tolerated by the patient.

Before surgery a complete staging examination was performed, including chest radiography, thoracic computed tomography, abdominal ultrasound examination, as well as magnetic resonance imaging of the previous primary tumor site, if the primary tumor was located at the extremities. All patients were assessed by a multidisciplinary sarcoma board consisting of oncologic surgeons, oncologists, radiotherapists, pathologists, and radiologists.

For preoperative estimation of the hepatic reserve after metastasectomy, parameters of liver function, such as serum albumin, serum bilirubin, and prothrombin time, were measured. When the number, size, or site of the metastatic lesions required major hepatectomies, computed tomography was used to validate residual liver volumes, which were determined by a formula that was related to the body surface area [13]. When preoperative imaging indicated that metastasectomy required an extended hepatectomy >70% of the total liver volume, portal vein embolization was considered [14].

The prospectively gathered data included histopathological parameters, such as primary tumor stage, grading, histological type, and the assessment of the resection margin at primary surgery. Moreover, clinical parameters with potential prognostic impact were analyzed [15]. We focused on such parameters as age, grading, histological type, localization of the primary tumor, number of hepatic metastases, time until liver metastases occurred, extrahepatic recurrence, incidence of local recurrence, number and type of surgical interventions, and intra- and postoperative morbidity.

Postoperative follow-up was performed at 3-month intervals for the first 2 years and then every 6 months until the end of the fifth postoperative year; this was followed by yearly examinations thereafter. It consisted of a baseline chest x-ray, abdominal ultrasound examination, and computed tomography of the chest and abdomen. In patients with primary STS of the extremities, an imaging study (computed tomography scan or magnetic resonance imaging) of the respective extremity was performed. When recurrent hepatic metastasis was diagnosed during follow-up, patients underwent repeated liver resection unless an unresectable relapse was found or multiple unresectable metastases at other sites were found. In these cases, patients were transferred to the oncology department for further palliative therapy.

Statistical analysis

The primary end points were relapse-free survival or tumor-related death, respectively. Survival and follow-up times were calculated from the time of resection of the primary tumor and from the time of the first metastasectomy to the last date of follow-up. Probabilities of survival were calculated according to Kaplan and Meier [16] and compared by using the log-rank test. The data from patients who were still alive and without evidence of tumor relapse at the end of the observation period were censored. Fisher's exact test and, whenever appropriate, χ^2 test were used for the comparison of median values. The level of significance was set at $p < 0.05$. Statistical analysis was performed by using SPSS® software (SPSS Inc., Chicago, IL).

Results

Characterization of patients and primary tumors

Between January 1993 and May 2003, 329 patients with soft-tissue sarcoma were operated on at the Department of

Surgery, University Hospital of Hamburg-Eppendorf. Forty-five patients presented with synchronous or metachronous hepatic metastasis. All patients underwent surgical therapy with curative intent, unless a contraindication existed. Whereas 30 of 45 patients (67%) were eligible for surgical exploration, in 15 patients a resection was not performed because of contraindications that were found during preoperative evaluation. Palliative chemotherapy was offered to these patients. In three patients (10%), surgical exploration revealed diffuse micronodular metastatic disease, which had not been recognizable in preoperative imaging studies. After hepatic biopsy confirmed the intraoperative finding, these patients were transferred to the department of oncology for evaluation of palliative treatment. The remaining 27 patients underwent surgical therapy with curative intent and constitute the basis of this study. Due to the recommendations of our multidisciplinary sarcoma board, four of these patients received adjuvant doxorubicin-based chemotherapy subsequent to hepatic metastasectomy. All patients who presented with metastases of GISTs were treated before Gleevec® was available and, therefore, did not receive this therapy. There were 11 men (41%) and 16 women (59%; median age, 47 (range, 34–78) years). The predominant histological subtypes of STS were leiomyosarcoma, followed by GIST, malignant fibrous histiocytosis (MFH), and hemangiopericytoma, as well as malignant peripheral nerve sheath tumors (MPNST). Fourteen patients (52%) had a visceral primary tumor site, and nine (33%) had a retroperitoneal or pelvic sarcoma; four patients (15%) had a primary sarcoma of the extremities. Further characteristics of the primary tumors are summarized in Table 1.

Table 1 Characterization of primary tumors

	Patients (%)
Histological subtype	
Leiomyosarcoma	8 (30)
GIST	6 (22)
MFH	3 (11)
MPNST	3 (11)
Hemangiopericytoma	3 (11)
Liposarcoma	2 (7)
Others	2 (7)
Grading	
G1	2 (7)
G2	17 (63)
G3	8 (30)
Tumor site	
Visceral	14 (52)
Retroperitoneal/pelvic	8 (30)
Extremities	5 (18)
T-stage	
pT1	6 (22)
pT2	21 (78)
N-stage	
pN0	26 (96)
pN1	1 (4)
R-stage	
R0	21 (78)
R1	6 (22)

GIST, gastrointestinal stromal tumors; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor

Primary treatment

Eleven of the patients (41%) with hepatic involvement had undergone resection for the primary tumor in our institution, and 16 patients (59%) who presented to us with liver metastases had been primarily operated on at other hospitals.

At primary surgery, 21 patients (78%) had received a completely adequate resection of the primary tumor with microscopically tumor-free margins. In the remaining six patients (22%), the margins after the primary surgery were classified as R1 by histopathological examination or were considered to be insufficient because residual tumor was seen during the primary surgery (R2). In two of these patients, reexcision of the primary tumor site was performed to achieve wide tumor-free margins. The remaining four patients had declined additional surgery and were followed up closely. Two of them developed local recurrence, which then was resected to achieve wide tumor-free margins. The other two patients were initially treated elsewhere, and on presentation at our institution, no evidence of local tumor disease was revealed by preoperative imaging.

Local recurrence and metastasis at other sites

During the follow-up period after resection of the primary tumor, local recurrence occurred in 4 of 27 patients (15%). In all patients, the local recurrence had been diagnosed and resected before the development of hepatic metastasis. In four patients (15%), extrahepatic metastasis occurred before liver metastases were diagnosed. Two patients had been diagnosed with pulmonal metastasis and had undergone pulmonal metastasectomy 8 and 16 months before the detection of hepatic involvement. The remaining patients had lymph node metastases, which had been resected as well. In seven patients (26%) with intra-abdominal primary tumors, intra-abdominal recurrence and hepatic metastasis were discovered at the same time and were resected simultaneously.

Hepatic metastasis

Four patients (15%) had synchronous hepatic metastases. In the remaining 23 patients (85%), metachronous metastasis occurred in a median time of 44 (range, 7–166) months. Eighteen patients (67%) had a disease-free interval (DFI) of more than 24 months after resection of the primary tumor. Sixteen patients (59%) had solitary hepatic metastasis, six patients (22%) had two metastatic nodules, three patients (11%) had three, and two patients (7%) had four metastatic liver lesions. Bilobar disease was present in eight patients (30%).

Surgical therapy

In three patients, surgical exploration and intraoperative ultrasound examination revealed diffuse metastatic involvement, which precluded metastatic resection with clear margins.

Hepatic metastasectomy in the remaining 27 patients included wedge resections in 8 patients (30%), segmentectomies in 4 patients (15%), right hemihepatectomies in 7 patients (27%), left hemihepatectomies in 3 patients (11%), extended right hemihepatectomies in 2 patients (7%), and complex central resections in 3 patients (11%; Table 2).

Results of metastasectomy

Hepatic metastasectomy resulted in tumor-free resection margins (R0) in 25 patients (93%). Twelve patients had perioperative complications, which resulted in a perioperative morbidity of 44%. There were seven minor complications (26%), including three wound infections, two pleural effusions, one minor bile leakage, which did not necessitate surgical intervention, and one case of prolonged hepatic insufficiency. Five patients (18%) had major complications, including three bilary leakages that required reoperation, one hematoma at the hepatic resection site, which required surgical removal, and one fatal pulmonary embolism. The perioperative mortality was 7%. Apart from the fatal pulmonary embolism, another patient died of abdominal sepsis due to bilary leakage despite surgical intervention and repeated open abdominal lavage.

Table 2 Surgical treatment

	Patients	(%)	R0 (%)
Wedge resection	8	30	87.5
Segmentectomy	4	15	100
Right hemihepatectomy	7	27	100
Left hemihepatectomy	3	11	100
Extended right hemihepatectomy	2	7	50
Central hepatic resection	3	11	100

Survival data

The follow-up time in this series was calculated from the date of the primary surgery, and the primary end point was death. The median overall follow-up time after primary surgery was 84 (range, 4–231) months. The median survival time after metastasectomy was 44 (range, 1–123) months. Five- and ten-year survival rates were 49% and 33%, respectively (Fig. 1). Moreover, there was a significant proportion of long-time survivors; nine patients (33%) survived more than 60 months after hepatic metastasectomy.

Median tumor-free survival after metastasectomy was 23 (range, 3–123) months. Sixteen patients (59%) developed metastatic recurrence. Intrahepatic recurrence occurred in seven patients (26%). Three of them developed additional lung metastases during the further course of the disease. Four patients had solely a pulmonal recurrence, three patients had extrahepatic abdominal recurrence, and two patients were diagnosed with lymph node metastases.

Prognostic parameters

The presence of 33% long-term survivors (>10 years) in our series indicates the existence of two populations with a different risk profile for tumor recurrence. Therefore, it was interesting to search for criteria that might help to identify which patients were likely to benefit from this treatment.

Prognostically relevant parameters were identified in several studies [15, 17–19]. We analyzed the prognostic impact of clinicopathological parameters, such as stage, grade, histology, location of the primary tumor, residual tumor after primary resection, local recurrence, number

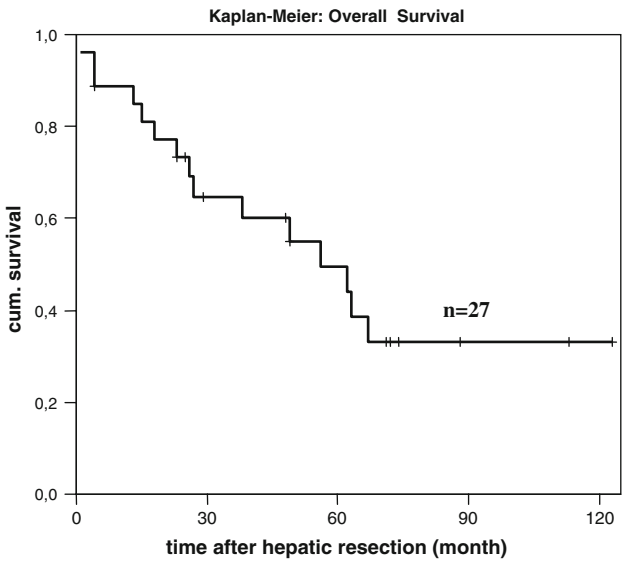

Fig. 1 Kaplan-Meier: Overall survival curves after hepatic metastasectomy

and site of metastases, and duration of the disease-free interval (DFI). Amongst all of the parameters that were evaluated in this series, the only characteristic with significant prognostic impact was the duration of the DFI (Table 3; Fig. 2). Patients with a DFI of more than 24 months had a median survival time of 81 months compared with 31 months for patients with a shorter DFI ($p = 0.0134$). Furthermore, no prognostic impact of the operative approach was seen. There was no significant difference between those patients who received an atypical wedge resection of their hepatic metastases and those who underwent an anatomical resection. Furthermore, the application of an adjuvant chemotherapy after hepatic metastasectomy (n = 5) had no significant prognostic impact (Table 3).

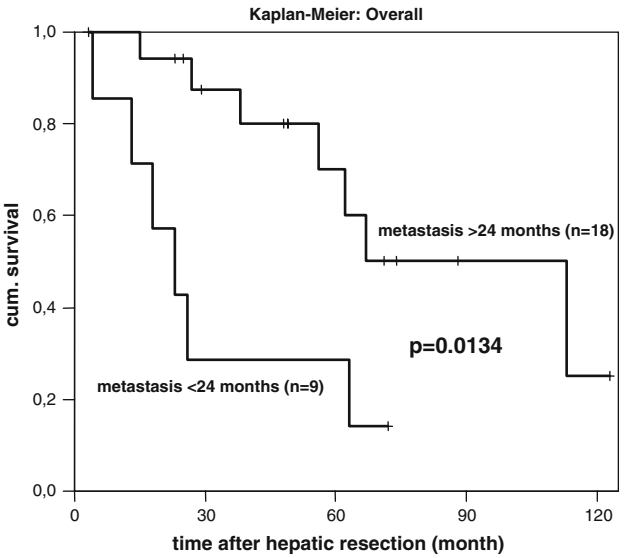

Fig. 2 Kaplan-Meier: Overall survival curves according to the duration of DFI. Patients with a DFI < 24 months had a significantly shorter overall survival (p = 0.0134, log rank test)

Repeated metastasectomy

Of the 16 patients who developed metastatic recurrence during follow-up, 8 (50%) underwent additional surgical treatment. In four (57%) of the seven patients with hepatic recurrence, repeated liver resection was performed. In two patients, subsequent pulmonal recurrences were resected, as well as extrahepatic abdominal recurrence in another two patients. The median survival in the subgroup that underwent repeated metastasectomy was 76 months after the first hepatic resection. The patients with recurrent tumors who solely received conservative therapy had a significantly worse outcome of 26 months of survival ($p = 0.0007$; Fig. 3).

Table 3 Prognostic impact of clinicopathological parameters

	Median overall survival (mo)	*p* value*
T-stage		
pT1 (n = 6) vs. pT2 (n = 21)	70 vs. 59	0.0903
M-stage		
Synchronous (n = 4) vs. metachronous (n = 23)	74 vs. 29	0.1266
Grading		
G1 (n = 2) vs. G2 (n = 17) vs. G3 (n = 8)	81 vs. 63 vs. 48	0.334
R-stage		
R0 (n = 21) vs. R1 (n = 6)	58 vs. 71	0.9052
Localization of primary tumor		
Abdominal (n = 15) vs. pelvic (n = 7) vs. extremities (n = 5)	64 vs. 75	0.2591
Number/site of metastases		
1 nodule (n = 15) vs. >1 nodule (n = 12)	52 vs. 85	0.2586
Unilobar (n = 19) vs. bilobar (n = 8)	70 vs. 62	0.7946
Surgical approach		
Wedge (n = 8) vs. anatomic resection (n = 19)	54 vs. 73	0.6823
Adjuvant therapy		
Yes (n = 4) vs. no (n = 23)	61 vs. 59	0.4533
Local recurrence		
Yes (n = 8) vs. no (n = 19)	71 vs. 69	0.9885
Duration of DFI		
≤24 month (n = 9) vs. >24 month (n = 18)	31 vs. 83	0.0134

* Log-rank test

DFI disease-free interval

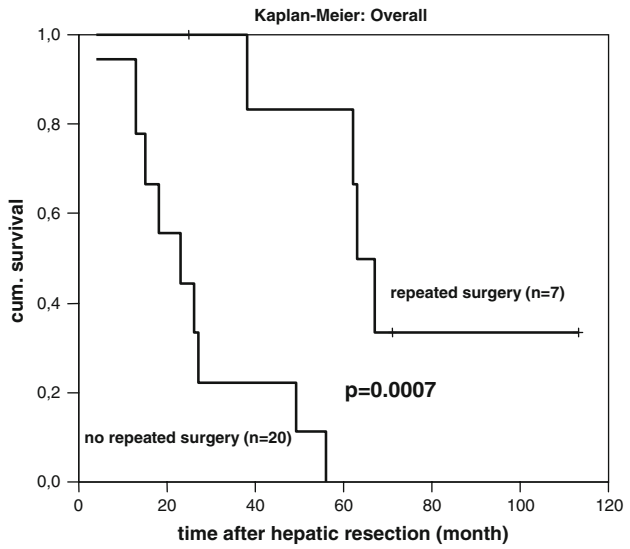

Fig. 3 Kaplan-Meier: Overall survival curves of patients with metastatic relapse, with reference to relapse surgery. Patients who underwent repeated metastasectomy had a significantly longer survival ($p = 0.0007$, log-rank test)

Discussion

Hepatic metastasis is a rare condition in patients with STS, and just a few studies with small series of patients address this issue. Although most patients have primary tumors at abdominal or visceral sites, hepatic metastases also occur in a heterogeneous population of patients who have primary tumors of the extremities or other extraperitoneal sites.

Our results of consequent metastasectomy in all patients who are eligible for oncologic surgery (67%) are encouraging, because this aggressive surgical treatment protocol yielded a 5-year survival rate of 49% and a 10-year survival rate of 33%, respectively. The subgroup of patients with long DFI seemed to particularly benefit from surgical therapy.

Actually our policy for hepatic metastasectomy was rather liberal. In four patients, extrahepatic metastases had already been resected before the diagnosis of hepatic involvement. In eight patients, extrahepatic abdominal recurrence and hepatic metastases had been diagnosed and resected simultaneously. Nevertheless, our survival data are clearly superior to the results of other series, which reported 5-year survival rates between 20% and 34% [4, 5, 10].

However, the characteristics of our patients were rather heterogeneous. Therefore, these results might be difficult to compare to other series that were only focused on metastasis of gastrointestinal leiomyosarcoma and/or GIST. Our study was designed to reflect the situation of all STS patients who have hepatic metastasis, which distinguishes this report from others. Apart from several histological subtypes of STS, there were different primary tumor sites in our series; 15% of the patients had STS that originated from the extremities and 33% had retroperitoneal or pelvic primary sarcomas, respectively. However, statistical analysis did not reveal any prognostic impact of parameters that were analyzed, such as histological subtype or primary tumor site. Therefore, it is more likely that the different outcomes of our patients might be explained by the high rate of reresection of subsequent metastatic recurrence. If metastatic relapse after hepatic metastasectomy was discovered, reoperation was offered to all patients, unless diffuse or technically inoperable disease was present.

Within the observation period, tumor recurrence occurred in 16 patients, and 50% of them eventually underwent repeated surgery. Although these patients represent a selected subgroup, in our view their significant prognostic benefit demonstrates that the exhaustion of all surgical options seems to enable long-term survival, even in advanced situations.

In contrast to pulmonal metastases of STS, which are treated by aggressive surgery in an increasing number of centers, the attitude toward hepatic metastases seems discouraged. In several reports in the current literature [7–9, 20], the role of surgery is merely confined to the relief of symptoms. The results of our aggressive surgical approach to hepatic STS metastasis seem to contradict these statements.

When metastatic disease is present, there is little doubt that the disease has become systemic; however, little is known about the biological properties of disseminated sarcoma cells and their mechanisms of metastatic progression. By analyzing clinicopathological parameters with respect to prognosis, we determined that a DFI duration of more than 24 months was significantly associated with longer postoperative survival; this is consistent with other reports [21, 22]. However, even patients with a shorter DFI still had a median survival time of 31 months, which is considerably better than the results of palliative chemotherapy or radiofrequency ablation [11, 23].

Conclusions

As a result of advances in surgical and perioperative care, the risks of major hepatic resections have decreased remarkably, thus liberalizing the indications for hepatic resection. Hepatic metastasis of STS has been generally associated with poor prognosis because of the absence of effective therapies. Our aggressive surgical approach toward hepatic metastasis and subsequent recurrences yielded long-term survival in a significant proportion of patients. We conclude that the predominant attitude of pessimism toward surgical therapy of hepatic metastases of STS does not seem to be justified. Our data indicate that

surgery should be offered to all patients who have technically resectable sarcoma lesions of the liver. Furthermore, the subgroup of patients who have a long DFI (>24 months) especially benefit from surgical therapy.

Even surgical therapy of recurrent liver metastases seems to be associated with prognostic benefit, as long as resectability is given. Like most other reports that address the issue of hepatic sarcoma metastasis, this analysis is based on a small number of only 27 patients; however, even the largest study of hepatic metastasectomy is comprised of no more than 56 patients [5].

Although our data support an aggressive surgical approach toward functionally and technically resectable liver metastases, powerful multicenter studies are needed to establish general guidelines for the appropriate treatment of these patients.

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