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Liver Resection for Hepatic Metastases from Soft Tissue Sarcoma: A Nationwide Study

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Keywords
Liver metastasis · Sarcoma · Liver resection · Hepatic resection

Abstract
Background: This study aims to evaluate the feasibility and safety of resection of sarcoma liver metastases, and to identify possible prognostic factors for long-term survival. ***Methods:*** All patients who underwent resection of liver metastases of sarcoma in the Netherlands from 1998 to 2014 were included. Study data was retrospectively collected from patient files. Survival rates were calculated using Kaplan-Meier survival analysis. ***Results:*** Some 38 patients treated in 16 hospitals were included (15 male, 23 female). The median age was 57 years (37–80 years). The most common histological subtype was leiomyosarcoma (63%). The predominant site of primary tumour was the abdomen (59%). R0 resection was achieved in 16 patients. Mortality was 3 and 16% of included patients had 1 or more complications. The median follow-up period was 18 months (range 1–161). After liver resection, 1-, 3-, and 5-year survival were 88, 54, and 42% respectively. Median overall survival was 46 months (1–161 months). One- and three-year progression-free survival (PFS) after liver resection were 54 and 19% respectively. Median PFS was 16 months (1–61 months). ***Conclusions:*** Liver surgery for sarcoma metastases is safe and leads to a relatively good survival. The choice for surgical treatment should always be discussed in a multidisciplinary sarcoma and liver team.

Introduction

Sarcomas are held accountable for less than 1% of all solid malignancies and approximately 80% of all sarcomas originate from soft tissue. Prognosis depends mainly on histological factors and patient characteristics. Of all patients with soft tissue sarcoma (STS), 25–40% will develop distant metastases [1, 2]. Predominant sites of me-

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tastases are the lungs and liver. Up to 16% of all patients with retroperitoneal sarcomas and 62% of all patients with visceral sarcomas will develop hepatic metastases [2]. The current standard treatment for patients with metastatic STS (excluding gastrointestinal stromal tumours, Ewing-like sarcomas, and other small blue round cell tumours) is systemic therapy with doxorubicin or ifosfamide, both resulting in poor survival rates [3, 4].

Resection of liver metastases arising from neuroendocrine or colorectal carcinoma in patients with liver-only disease is widely accepted and effective [5–7]. The role of surgery in the treatment of STS with hepatic metastases remains unclear.

Current literature on this subject consists of small, heterogeneous cohorts, including patients with metastases from gastro intestinal stroma cell tumours (GIST) or other non-colorectal, non-neuroendocrine tumours. These studies demonstrate a possible improved survival after resection of metastases [2, 8–12]. To date, no data from a population-based national database is reported.

The objective of this study was to evaluate all patients in the Netherlands who underwent liver resection for hepatic metastases of STS since 1998. Primary outcomes were progression-free survival (PFS) and overall survival (OS). Secondary aims were demonstrating the safety of the procedure, and identification of factors that may influence long-term survival.

Materials and Methods

Patients and Data

All patients who underwent a liver resection of metastatic STS between January 1998 and July 2014 in the Netherlands were identified via the Dutch nationwide histology database (PALGA). Since 1991, all reports generated by every pathology department in the Netherlands are collected in this nationwide database [13]. All Ewing-like sarcomas and other small blue round cell tumours were excluded, since these types of sarcomas respond well to chemotherapy. Furthermore, GIST were also excluded. Standard demographic and clinicopathologic data, including histopathological information about the primary tumour and metastases, intraoperative details and use of chemo- and/or radiotherapy, were retrospectively collected from the patient files in 16 different hospitals in the Netherlands. Prior ethical approval was granted for the current study, with the medical Ethic Committee waiving the requirement for informed consent to be obtained for the use of anonymized patient data.

Surgery

Decisions about surgical approaches were tailor-made for every single patient. Hepatic metastases were defined according to Couinaud's liver segments [14]. Radicality was defined according to the Union Internationale Contre le Cancer standards; R0: complete microscopic resection, R1: microscopic residual disease or R2: macroscopic residual hepatic or extrahepatic disease. Liver metastases were considered metachronous when they were diagnosed at least 6 months after diagnosis of the primary tumour.

Outcome Variables

Primary outcomes in this study were PFS and OS. PFS was defined as the time between resection of liver metastases and the first diagnostic proven recurrence or progression of disease in liver or any other tissue. OS was defined as the time from first liver resection till the date of death, regardless of the cause of death. Incidentally, the date of death could not be traced; in that case, the last date of follow-up was used. Secondary outcomes included the safety of metastasectomy and the prognostic impact of gender, age, the type of resection (minor; ≤2 segments or major; >2 segments), radicality (R0, R1 or R2), the extent of PFS, the number of metastases, the time of diagnosis of liver metastases (synchronous or metachronous) on PFS and OS.

Statistical Considerations

PFS and OS were estimated by Kaplan-Meier survival analysis. According to Cox proportional hazards regression methodology, prognostic factors for long-term survival were identified by univariable survival analysis. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 23.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Demographics and Histological Characteristics

Thirty-eight patients underwent hepatic resection of metastatic STS between January 1998 and July 2014. Patient characteristics are described in Table 1. Liver resection took place in 16 different hospitals. Twenty-three female and 15 male patients were included in this study. The median age at liver resection was 57 years (range 37–80 years). In total, 5 histological types of sarcoma were described, 7 cases were described as "not otherwise specified". All diagnoses were confirmed histologically. The median follow-up was 18 months (range 1–161 months) after liver resection.

Preoperative Evaluation of Liver Metastases

All liver metastases were preoperatively diagnosed by ultrasound, CT-, MRI-, PET-scanning or a combination of these means. In 14 patients, multiple liver metastases were found; 20 patients had a solitary metastasis. In 8 patients, metastases were spread bilobar and in 28 patients, unilobar. Liver metastases were synchronous in 11 patients and metachronous in 23. In 4 patients data on the number and location of lesions were missing.

Surgical Procedure

In 3 cases, intraoperative radio frequent ablation (RFA) was combined with liver resection. A minor resection (≤2 segments) was performed in 24 patients and 13 patients underwent a major (>2 segments) resection. There was no intra-operative mortality; nevertheless, 3 patients had intra-operative complications, including a perforation of the small bowel, tumour rupture and bleeding. In 16 patients, an R0-resection was achieved, 5 patients underwent an R1-resection and in 15 patients, surgery resulted in an R2-resection. In 7 patients, R2-resection was achieved due to extra hepatic disease. In 2 patients, information about radicality was not available.

Postoperative Complications

Six patients encountered postoperative complications, for which 2 patients underwent secondary surgery due to intra-abdominal sepsis. One of these patients died due to sepsis after a gastrointestinal perforation. Median hospital stay was 9 days (range 2–20 days).

Progression-Free Survival

Median PFS was 16 months (range 1–161; Fig. 1). One- and three-year PFS after liver resection were 54.2 and 18.9% respectively. Follow-up was conducted according to the preference of the local centre. One patient did not experience progression of disease after 5 years. Median PFS after resection of metachronous metastases was significantly longer with 19 months (range 1–161 months) versus 5 months (range 2–54 months) for synchronous metastases ($p = 0.02$). When an R0- or R1-resection could be achieved, median PFS was 16 months (range 2–161 months); for an R2-resection, median PFS was 10 months (range 1–161 months; $p = 0.87$). Eight patients underwent secondary liver resection. Median PFS was 19 months (range 1–161 months) for patients younger than 60 and 9 months (range 2–34 months) for patients older than 60 ($p = 0.06$).

PFS was also not significantly different in terms of gender, number of metastases, primary intra- or extra-abdominal tumour, minor/major resection or uni- or bilobar metastases. Factors that may influence PFS are described in Table 2.

Overall Survival

Median OS was 46 months (1–161 months; Fig. 2). One-year survival, 3-year survival and 5-year survival after liver resection were 88.1, 53.9 and 41.1% respectively. In the R0- or R1-group, 54.6% of the patients were alive after 5 years. Median OS in the R0- or R1-group was 77 months (range 6–142) and median survival in the R2-group was 20 months (range 1–161; $p = 0.19$). Factors that may influence outcome are described in Table 2. None of the factors mentioned above could be included in multivariable analysis for OS, since all factors had a p value of >0.05 in univariable analysis.

Table 1. Patient and tumour characteristics

Variable	($n = 38$)
Gender	
Male	15 (40)
Female	23 (60)
Age	57 (37–80)
Sarcoma subtype	
Leiomyosarcoma	24 (63)
Liposarcoma	3 (8)
Hemangiopericytoma	2 (5)
Angiosarcoma	1 (3)
PEComa*	1 (3)
Not otherwise specified	7 (19)
Primary tumour site	
Abdomen	22 (59)
Organ (bowel, stomach)	9 (23)
Retroperitoneum	7 (18)
Gynaecologic	6 (15)
Pelvis	1 (3)
Extremity	5 (13)
Head	2 (5)
Other	9 (24)
Interval primary tumour – hepatic metastases	
Synchronous	11 (28)
Metachronous	23 (59)
Missing	4 (10)
Number of hepatic metastases	
Solitary	20 (51)
Multiple	14 (36)
Missing	4 (10)
Distribution metastases	
Unilobar	28 (74)
Bilobar	8 (21)
Missing	2 (5)
Extrahepatic metastases prior to liver resection	
Absent	25 (67)
Present	12 (30)
Missing	1 (3)
Type of resection	
Minor	24 (63)
Major	13 (34)
Missing	1 (3)

For continuous variables data shown represent median (range), all other data is presented as numbers (%).

* PEComa, perivascular epithelioid cell tumour.

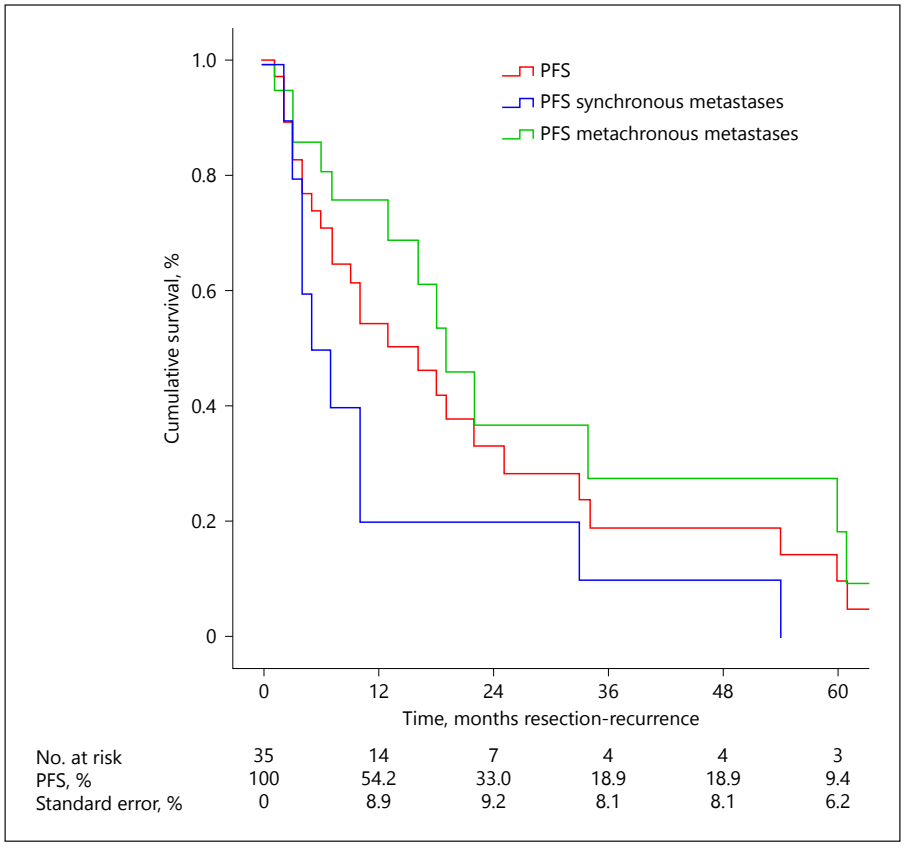

Fig. 1. Progression-free survival (PFS).

Discussion

In the current study, liver resection for metastatic STS resulted in a median OS of 46 months (1–161 months). Median PFS after liver resection was 16 months (1–161 months). Development of metachronous metastases was the only beneficial prognostic factor for PFS. The sample size of the current study clearly illustrates the scarcity of liver resection for hepatic metastases of STS, resulting in a scarcity of studies published on this topic. This study is the first nationwide report of all patients who underwent liver surgery for sarcoma metastases during a period of more than 15 years in the Netherlands.

Current treatment options for patients with STS metastatic to the liver include chemotherapy, trans-arterial chemotherapy embolization, radiofrequency or microwave ablation and hepatectomy. Liver metastasectomy has been previously described to be a curative treatment option in a highly selected group of patients [10, 15–18].

According to analyses conducted by the European Organization for Research and Treatment of Cancer (EORTC), treatment of patients with hepatic STS metastases with chemotherapy alone, resulted in a median OS of 10 months with a 1-year survival of 42% and a 2-year survival of 13% [15]. Combined chemotherapy (doxorubicin + ifosfamide) has demonstrated not to improve OS [4]. Median OS in our, highly selective, cohort was 46 months with a 1-year survival of 88% and a 2-year survival of 62% respectively. Hepatectomy should therefore be considered a treatment option for a selected group of patients.

During the past decades, liver surgery has become safe, thereby liberalizing its indications [19]. Especially, colorectal liver metastases are frequently operated on in the Netherlands, whereas surgery for non-colorectal metastases is still rare [20]. However, it is pivotal to meticulously select patients who are candidates for potentially curative resection. Discussion in multidisciplinary tumour boards has demonstrated to be essential in selecting patients who might benefit from surgery [21]. The results of the current study are comparable to other cohort studies (Table 3). Only Groeschl et al. [9] and Chua et al. [22] reported a substantially higher OS, with a median OS of 71 and 103 months respectively.

Table 2. Potential prognostic factors for survival

Variable	(*n* = 38)	PFS, months	Univariable *p* value	OS, months	Univariable *p* value
Gender					
Male	15 (40)	19	0.794	62	0.522
Female	24 (60)	10		35	
Age					
<60 years	23 (61)	19	0.057	62	0.196
≥60 years	15 (29)	9		35	
Interval primary tumor – hepatic metastases					
Synchronous	11 (28)	5	0.021	40	0.508
Metachronous	23 (59)	19		20	
Number of hepatic metastases					
Solitary	20 (51)	10	0.367	62	0.360
Multiple	14 (36)	16		46	
Distribution metastases					
Unilobar	28 (74)	13	0.684	56	0.960
Bilobar	8 (21)	18		20	
Resection status					
RO or R1	21 (55)	16	0.869	77	0.192
R2	15 (39)	10		20	
Type of resection					
Minor	24 (63)	10	0.854	18	0.321
Major	13 (34)	16		56	
Primary tumour site					
Intra-abdominal	22 (58)	9	0.364	19	0.099
Extra-abdominal	16 (42)	17		Not reached	

PFS, progression-free survival; OS, overall survival.

Nevertheless, Chua et al. [22] included only 15 patients with a large OS range (6–200 months) [22] and Groeschl et al. [9] excluded all R1- and R2-resections from their analyses.

Adam et al. [23] identified an age of >60 years, a PFS of <12 months, R2-resection and major hepatectomy as factors associated with poor outcome in a large cohort of patients with noncolorectal nonendocrine liver metastases. In accordance with Adam et al. [23], we have shown a trend towards a better PFS and OS after an R0- or R1-resection compared to an R2-resection (Table 2). The statistical insignificance of this difference may be explained by the relatively small sample size. The deteriorated survival rate after an R2-resection is most likely due to surgery with a palliative intent. However, median OS after R2 resection is 20 months (1–161), which is higher than median survival (10 months) described with chemotherapy in EORTC trial [15].

Moreover, patients from our cohort who were treated for synchronous metastases had a significant shorter median PFS than patients treated for metachronous metastases.

Given the low sample size of this study, no firm conclusions can be made in comparison to other historic cohort studies.

Other treatment options for sarcoma metastatic to the liver are RFA, microwave ablation, trans-arterial chemo embolization (TACE), and radioembolization with yttrium 90 microspheres. Pawlik et al. [16] showed that RFA of metastases resulted in higher recurrence rates than resection alone. In our study, only 3 patients received RFA, in combination with surgery for metastases; therefore, comparisons could not be made. The use of TACE for hepatic metastases of STS is reported in a few studies [17, 18]. Median PFS was reported to be 6 months and median OS was 21 months for responders. Therefore, the authors conclude that TACE should be reserved as a salvage option. However, in the study of Maluccio et al. [17] 6 out of 7 leiomyosarcomas treated did not respond to the therapy.

STSs represent a large and heterogenic group of tumours. A drawback of this study is that biological behav-

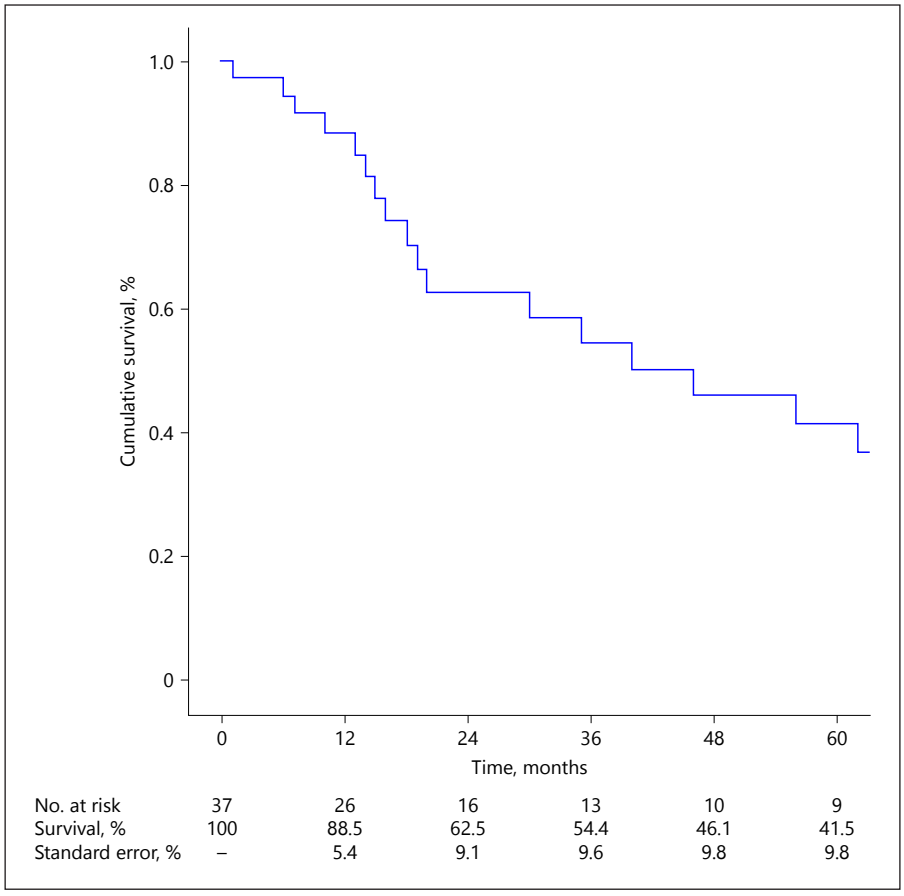

Fig. 2. Overall Survival (OS).

Table 3. Survival after hepatic resection for metastatic sarcoma

Study	*n*	Follow-up, median/months	Survival
Jaques et al. [2], 1995	14	60	Median OS 30 months, 5-year OS was 0%*
Harrison et al. [24], 1997	27	60	Median OS 31 months, 5-year OS was 4%*
Elias et al. [25], 1998	13	Unknown	5-Year OS 18%*
Chen et al. [26], 1998	11	53	Median OS 39 months*
Lang et al. [27], 2000	26	Unknown	Median OS after R0 resection: 32 months, 5-year OS 13%
DeMatteo et al. [8], 2001	22	25	Median OS 30 months
Pawlik et al. [16], 2006	66	35.8	1-Year OS 91.2%, 5-year OS 27%**
Adam et al. [23], 2006	125	Mean FU: 31 months	Median OS 32 months, 5-year OS 31%
Lendoire et al. [28], 2007	23	28	5-Year OS 0%
Rehders et al. [29], 2009	27	84	Median OS 44 months, 5-year OS 49%^
Chua et al. [22], 2011	15	122	Median OS 103 months, 5-year OS: 51%, 10-year OS: 37%^
Marudanayagam et al. [11], 2011	36	24	Median OS 24 months, 5-year OS 32%^
Zacherl et al. [30], 2011	15	Unknown	Median OS 34 months, 5-year OS 27%^
Groeschl et al. [9], 2012	98	32	Median OS 72 months, 1-year OS: 82%, 5-year OS 32%***
Brudvik et al. [10], 2015	50	32	Median OS 45 months, 5-year OS 45%, 10-year OS 23%

* Study population included before 1996.
** Study population included 36 Gastrointestinal stromal tumours, 13 patients were treated with RFA only.
*** Excluded all R1- and R2-resections.
^ Study population included Sarcomas and Gastrointestinal stromal tumours.

iour and response to therapy of the different subtypes could not be determined because of the small number of patients.

As mentioned above and stated in Table 3, most of the previously published studies contain a mixture of information on STS and GIST, or other non-colorectal, non-neuroendocrine tumours [2, 8–11, 16, 22–30]. Due to our more homogeneous study group, the outcomes in this study are more specific, making them poorly comparable to the outcomes of older studies (Table 3).

The strength of our study is the relatively large sample size from a population-based data set. Furthermore, this study provides detailed information on intra- and postoperative complications, which are rare in population-based data sets. However, certain limitations do apply to our current analysis. The current study lacks a proper control group. Also, information on postoperative chemotherapy regimens is lacking. This may explain why synchronous liver metastasis was a prognostic factor for PFS, without influencing OS. Nevertheless, it is the best available evidence since sarcoma, especially with potentially resectable hepatic metastases, is rare and therefore comparative studies and clinical trials are difficult to effectuate. This calls for the need of an international prospective database with results of various treatment modalities for this group of patients to improve the understanding and treatment of the various subtypes of STS.

In conclusion, since current chemotherapy or other treatment options do not lead to cure, resection of sarcoma liver metastases should be considered and discussed in a multidisciplinary sarcoma and liver team for all patients with technically resectable metastases as a potential treatment option. Although this may achieve cure, it remains palliative treatment for the majority of the selected patients.

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Disclosure Statement

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

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