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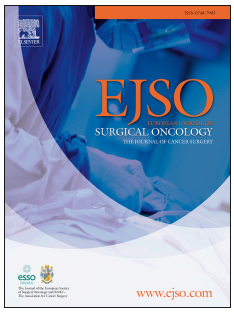

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Unraveling the role of local ablative therapies for patients with metastatic soft tissue sarcoma – A retrospective multicenter study of the Bavarian university hospitals

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Abstract

Background: Local ablative therapies (LAT) are increasingly used in patients with metastatic soft tissue sarcoma (STS), yet evidence-based standards are lacking. This study aimed to assess the impact of LAT on survival of metastatic STS patients and to identify prognostic factors.

Methods: In this retrospective multicenter study, 246 STS patients with metastatic disease who underwent LAT on tumor board recommendation between 2017 and 2021 were analyzed. A mixed effects model was applied to evaluate multiple survival events per patient.

Results: Median overall survival (OS) after first metastasis was 5.4 years with 1-, 2- and 5-year survival rates of 93.7, 81.7, and 53.1%, respectively. A treatment-free interval ≥12 months and treatment of liver metastases were positively correlated with progression-free survival (PFS) after LAT (HR=0.61, p=0.00032 and HR=0.52, p=0.0081, respectively). A treatment-free interval ≥12 months and treatment of metastatic lesions in a single organ site other than lung and liver were positive prognostic factors for OS after first LAT (HR=0.50, p=0.028 and HR=0.40, p=0.026, respectively) while rare histotypes and LAT other than surgery and radiotherapy were negatively associated with OS after first LAT (HR=2.56, p=0.020 and HR=3.87, p=0.025). Additional systemic therapy was independently associated with a PFS benefit in patients ≤60 years with ≥4 metastatic lesions (for max. diameter of treated lesions ≤2cm: HR=0.32, p=0.02 and >2cm: HR=0.20, p=0.0011, respectively).

Conclusion: This multicenter study conducted at six German university hospitals underlines the value of LAT in metastatic STS. The exceptionally high survival rates are likely to be associated with patient selection and treatment in specialized sarcoma centers.

Keywords: Soft tissue sarcoma, Metastasis, Local ablative therapy, Surgery, Radiotherapy, Systemic therapy

1. Introduction

Soft tissue sarcoma (STS) encompasses a heterogeneous group of mesenchymal malignancies accounting for approximately 1% of all malignancies in adults.[1] Up to 50% of STS patients will develop metastatic disease, mainly within the lungs, followed by the liver, the peritoneum and the bones while metastases affecting the lymph nodes are relatively rare.[2,3] With survival rates of one to two years, prognosis remains dismal for metastatic STS patients.[4,5]

Oligometastatic disease has been proposed as an intermediate state between localized and widespread metastatic disease. It is characterized by a limited number of metastases and their amenability to a curative approach. [6,7] Local ablative therapies (LAT), such as surgical resection and radiotherapy, are increasingly used in patients with oligometastatic cancer based on randomized phase II trials: A tumor-agnostic trial, mainly involving patients with breast, lung, colorectal, and prostate cancer, demonstrated an overall survival (OS) benefit by metastasis-directed stereotactic body radiation therapy (SBRT) in addition to palliative standard-of-care treatment.[8] For patients with non-small cell lung cancer (NSCLC) a prolonged progression-free survival (PFS) and OS could be demonstrated by adding LAT (surgery or SBRT) to systemic therapy.[9,10] In patients with oligometastatic prostate cancer, SBRT led to a benefit in androgen deprivation therapy-free survival compared to surveillance alone.[11] The randomized clinical trials referenced above included patients with a maximum of three to five metastases according to the common definition of oligometastasis of up to five metastases in up to three organ sites.[12] As a small number of metastases can represent different clinical situations with a different prognosis, the *European Society for Radiotherapy and Oncology* (ESTRO), along with the *European Organisation for Research and Treatment of Cancer* (EORTC) developed a new classification system of oligometastasis. In this dynamic model, oligometastasis is classified into nine different states based on several clinical characterization factors, such as previous poly- or oligometastatic disease and diagnosis of oligometastasis in a treatment-free interval or during systemic therapy.[13]

For STS, there is no prospective randomized data on the value of metastasis-directed LAT. A randomized clinical trial on the value of pulmonary metastasectomy in addition to chemotherapy in STS patients was terminated prematurely due to poor recruitment (NCT00002764). Retrospective analyses show an improvement in the prognosis of patients with metastatic STS within the last decades as well as an increase in LAT, suggesting an association.[4,13]

Pulmonary metastasectomy potentially leads to long-term survival in STS with 5-year survival rates of 18-58% being reported in two systematic reviews by Treasure et al. and Stamenovic et al. which collectively examined 13 retrospective studies involving 1282 soft tissue sarcoma patients.[14,15] Prognostic factors primarily include a prolonged disease-free interval, a small

number of metastatic lesions, the ability of complete resection, the absence of extrapulmonary disease, and control of the primary tumor.[15,16] Repeat pulmonary metastasectomy proved to be a feasible option resulting in a survival benefit.[17,18] With regard to LAT of extrapulmonary metastatic sites in STS, there are only a few retrospective studies available. Surgical resection of liver metastases yielded a pooled 5-year survival rate of 31% according to a systematic review including six studies with a total of 212 patients.[19] A large observational study conducted by the French Sarcoma Group identified LAT of different metastatic sites as a positive prognostic factor with 83.5% of metastatic STS patients being alive after 5 years.[3] In a study by two European tertiary centers including 135 STS patients with metachronous metastasis, a propensity-matched comparison demonstrated an OS benefit in the group treated with metastasectomy (adjusted 10-year-OS in patients with vs. without metastasectomy: 17% vs. 3%).[20] In several studies, the combination of LAT with chemotherapy did not lead to a survival benefit or even impaired outcome of metastatic STS patients.[21,22,23,24]

To date, decisions on LAT in metastatic STS are taken situationally in multidisciplinary tumor boards without recommendations based on randomized trials.[25] Despite some prognostic factors originating from retrospective studies, it remains challenging to identify patients suitable for LAT. As randomized studies are difficult to perform due to a lack of patient compliance, systematic retrospective studies are of high clinical relevance to establish treatment algorithms. This study aimed to evaluate the value of LAT in metastatic STS at the six Bavarian university hospitals in the context of a multicenter project of the Bavarian Cancer Research Center (BZKF).

2. Materials and Methods

2.1 Patient selection and data extraction

An exploratory retrospective multicenter study was performed at the six Bavarian university hospitals in Germany: Ludwig Maximilian University (LMU) of Munich, Technical University (TU) of Munich, Augsburg, Erlangen, Regensburg and Würzburg.

Eligible patients (age ≥18 years) had pathologically confirmed STS with distant metastasis and received a metastasis-directed LAT after recommendation in one of the participating institutions' sarcoma tumor boards between January 1, 2017, and December 31, 2021. Local therapy was defined as ablative if it aimed for tumor clearance or high disease control. The following LAT were included in all participating institutions: Surgical metastasectomy, radiotherapy, brachytherapy, selective internal radiotherapy (SIRT), radiofrequency ablation (RFA) and high-intensity focused ultrasound (HIFU). No specific number or size of metastatic lesions were defined. Patients with gastrointestinal stroma tumors (GIST), primary bone

tumors and patients that received local therapies with sole palliative intent were excluded. In the case of more than one LAT being performed without a tumor recurrence or progression in between therapies, treatments were regarded as one LAT with multiple interventions. Of the patients evaluated, all local and systemic therapies following first diagnosis were longitudinally recorded. The end of follow-up was December 31, 2022. Clinical, pathological, and outcomes data were extracted from the prospectively maintained databases of the respective institutions. The current World Health Organization (WHO) tumour classification system and the French grading system at first diagnosis were applied.[26,27,28,29] Dates of death were determined with the help of the Cancer Registry of Bavaria. At each study site, data collection was performed on the biomedical research portal CentraXX by KAIROS (KAIROS GmbH, Bochum, Germany) in accordance with local security standards.

2.2 Outcomes

The primary objective of the study was to explore the impact of LAT in patients with metastatic STS. The endpoints of this analysis included PFS and OS. PFS was calculated as the time from start of LAT to the first of either disease progression, relapse or death of any cause. OS was estimated by the time from first metastasis or start of LAT to death of any cause. Both PFS and OS were censored at the date of last follow-up. Baseline characteristics, variables regarding the disease stage at date of LAT and LAT-specific details were analyzed regarding their impact on survival. A metastatic event was defined as first evidence, progression or recurrence of distant metastasis. Primary tumor control was defined as absence of progression or new primary tumor/local recurrence at date of LAT. Treatment-free interval was defined as the time between the end of any last therapy at previous tumor diagnosis/progression/recurrence and the start of LAT. To categorize different metastatic states, we applied a modified classification of the *ESTRO* and *EORTC* consensus recommendation.[30] Polymetastasis was defined as more than five metastatic lesions.

2.3 Statistics

OS and PFS were analyzed with Cox proportional hazards regression. To analyze PFS after multiple LAT per patient a mixed effects model was applied. Since OS is censored at the time of the subsequent LAT in this model, PFS and OS after first LAT were additionally analyzed. The results with a p-value of ≤0.05 were considered statistically significant.

To investigate if there are subgroups of patients who benefit from additional systemic therapy, we performed interaction analyses between systemic therapy and various risk factors. For continuous variables, cutoffs between the 0.1 and 0.9 quantiles were considered, and the cutoff with the lowest p-value of the interaction term with systemic therapy was chosen as optimal. Because of the purely explorative nature of these analyses, the p-values were not

adjusted for multiple testing. Statistical analysis was performed using R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

2.3 Ethics

The internal review board and the ethics committee at the LMU University Hospital of Munich, Germany, approved the study protocol (Protocol Nr. 22-0822). In addition, the respective local ethics committees at each study site approved the present study. As the collected patient data was sufficiently anonymized, no informed consent was required for data acquisition.

3. Results

3.1 Patient cohort

In total, 246 patients with metastatic STS were analyzed. A flowchart of patient evaluation is available in Supplementary Material (1). The patient demographics and disease characteristics are presented in Table 1. The most common histologic subtypes were leiomyosarcoma (LMS), liposarcoma (LPS), synovial sarcoma (SySa) and undifferentiated pleomorphic sarcoma (UPS).

Factor	**Value**	**n**	**%**
Total		246	100
Age (years)	Median [Range]: 56 [19-86]		
Sex	Male	119	48
	Female	127	52
Grading according to FNCLCC (primary histology)	G1	13	5
	G2	82	33
	G3	123	50
	N/A	28	11
Histotype	Leiomyosarcoma	55	22
	Liposarcoma	38	15
	UPS	37	15
	Synovial sarcoma	34	14
	(Myxo)fibrosarcoma	13	5
	MPNST	9	4
	Endometrial stroma sarcoma	8	3
	Solitary fibrous tumor	7	3
	Angiosarcoma	6	2
	Clear cell sarcoma	5	2
	Other (max. 4 patients)*	34	14
Site of primary tumor	Extremities	107	43
	Intra-/retroperitoneal	67	27
	Trunk	27	11
	Head/Neck	5	2
	Uterus	22	9
	Other	18	7
Date of first metastasis	<12 months after first diagnosis	117	48

	≥12 months after first diagnosis	129	52
Treated metastatic sites	Lungs	158	64
	Liver	40	16
	Soft tissue	36	15
	Intra-/retroperitoneal	23	9
	Lymph nodes	21	9
	Bone	16	7
	Brain	13	5
	Other	9	4
	Concurrent LAT of 2 organ systems	18	7
Number of LAT	≤2	167	68
	>2	79	32
Number of treated metastatic lesions at first LAT	≤5	209	85
	>5	37	15
Local recurrence	Yes	74	30
	No	172	70

Table 1: Patient characteristics

FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer, N/A: Not applicable, UPS: Undifferentiated pleomorphic sarcoma, MPNST: Malignant peripheral nerve sheath tumor, LAT: Local ablative therapy
*Detailed list in Supplementary Material (2)

3.2 Local ablative therapies

In total, 516 LAT were analyzed between 2006 and 2022. Patients received in median two LAT (range 1-12). 26% of LAT (n=119) were applied in combination with a systemic therapy. Surgical metastasectomy and external beam radiotherapy represented the most common LAT (67% of all interventions, n=381 and 23%, n=128, respectively). Furthermore, brachytherapy (3%, n=17), SIRT (1%, n=5), RFA (1%, n=3) and HIFU (0.2%, n=1) were reported. Pulmonary, soft tissue, hepatic, intraabdominal and lymph node metastases were most commonly treated by surgery while for brain, bone and other rarer sites radiotherapy was the most frequently applied LAT (Figure 1). The median number of treated lesions was 1 (range 1-56), and the median size was 2cm (range 0.25-34cm).

Regarding the metastatic state according to a modified classification of the consensus recommendation of the *ESTRO* and *EORTC*, most LAT were performed for metachronous oligorecurrence and repeat oligorecurrence (26%, n=133 and 40%, n=206, respectively). Additionally, 9% (n=48) were carried out in synchronous oligometastatic patients, while 3% (n=13), 2% (n=11), and 2% (n=10) were applied for induced oligorecurrence, induced oligopersistence, and induced oligoprogression, respectively (induced oligometastasis: history of polymetastatic disease). Furthermore, 1% (n=7), 6% (n=30), and 1% (n=4) of LAT were performed in patients with metachronous oligoprogression, repeat oligoprogression, and repeat oligopersistence, respectively. In 10% of LAT (n=54), polymetastasis, defined as >5 metastases, was treated.

The most common decision factors for the use of LAT, reported in the respective sarcoma tumor board, were number of metastases in 36% (n=188), localization of metastases in 29% (n=148), response to systemic therapy in 16% (n=84) and general state of patient's health in 16% of LAT (n=84).

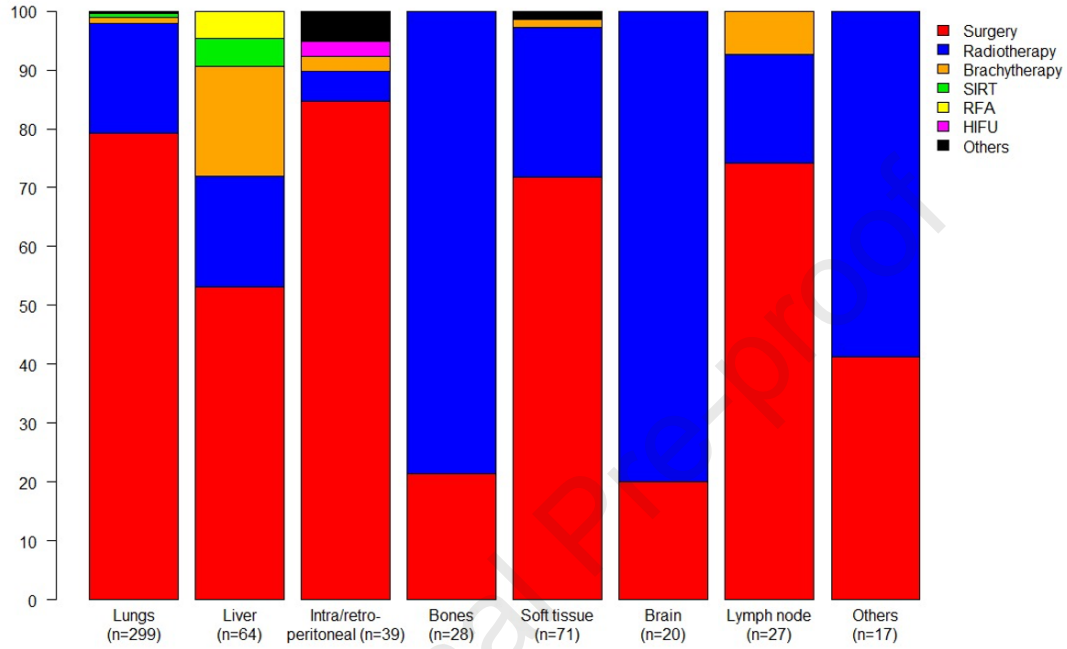

Figure 1: Sites of metastasis and types of local ablative therapy (number of interventions).
SIRT: Selective internal radiotherapy, RFA: Radiofrequency ablation, HIFU: High-intensity focused ultrasound.

3.3 Overall survival (OS) after occurrence of first metastasis

The median follow-up after first metastasis was 3.8 years (95% CI 3.1-4.2) for the overall population. The median OS after first metastasis was 5.4 years (95% CI 4.4-7.8 years). 1-, 2- and 5-year survival rates were 93.7% (95% CI 90.7-96.9), 81.7% (95% CI 76.6-87.0) and 53.1% (95% CI 45.4-62.2), respectively. Multivariate analysis demonstrated patient's age >60 years, histotype "SySa" and "Others" compared to LMS as poor prognostic factors for OS (p=0.047, HR=1.75; p=0.028, HR=2.72; p=0.029, HR=2.50). The absence of a local recurrence of the primary tumor was associated with an OS benefit (p=0.016, HR=0.51). For the detailed analysis see Supplementary Material (3).

3.4 Progression-free survival (PFS) and overall survival (OS) after local ablative therapy (LAT)

Median PFS after first, second and third LAT was 6.9 months (95% CI 5.9-8.5), 5.0 months (95% CI 3.7-7.1) and 5.7 months (95% CI 4.1-7.9), respectively. Median OS after first, second and third LAT was 4.87 years (95% CI 3.96-7.83), 4.14 years (95% CI 3.61-6.41) and 4.36 years (95% CI 2.41-NA), respectively (Figure in Supplementary material (4)). Median PFS and OS after first LAT according to the different organ sites is included in the Supplementary material (5). The median interval between occurrence of first metastasis and first LAT was 36 days (range 0-428 days). Overall, 419 LAT were available for multivariate analysis in a mixed effects model with regard to PFS after LAT. Treated metastatic lesions restricted to the liver and a treatment-free interval of ≥12 months were associated with a PFS benefit while ≥1 prior metastatic event had a negative impact on PFS (Table 2). This analysis was also performed with continuous variables (Supplementary material (6)).

Since OS must be censored at the time of the subsequent LAT in a mixed effects model, multivariate analysis was additionally performed for PFS and OS after first LAT. This analysis is presented in Supplementary Material (7). Histotype other than LMS, LPS, SySa and UPS as well as type of LAT other than surgery and radiotherapy proved to be adverse prognostic factors (p=0.020, HR=2.56 and p=0.025, HR=3.87, respectively), while a treatment-free interval ≥12 months was positively associated with OS after first LAT (p=0.00032, HR=0.61). Patients with an OS after first LAT of ≥8 years are presented in Figure 2 for illustrative purposes.

Factor	Strata	p-value	HR (95% CI)
Age (years)	>60 vs. ≤60	0.36	1.14 (0.86-1.51)
Sex	Female vs. Male	0.58	1.81 (0.82-1.42)
Histotype	LPS vs. LMS	0.64	0.90 (0.58-1.40)
	SySa vs. LMS	0.71	0.92 (0.60-1.42)
	UPS vs. LMS	0.77	0.93 (0.59-1.49)
	Other vs. LMS	0.24	1.23 (0.87-1.74)
Treated metastatic site	Liver only vs. Lung only	**0.0081**	0.52 (0.32-0.85)
	Other single organ site only vs. Lung only	0.54	0.91 (0.66-1.24)
	≥2 organ sites vs. Lung only	0.86	0.94 (0.51-1.74)
Prior metastatic events	≥1 vs. 0	**0.042**	1.33 (1.01-1.75)
Treatment-free interval (months)	≥12 vs. <12	**0.00032**	0.61 (0.47-0.80)

Primary tumor control	Yes vs. No	0.58	0.88 (0.56-1.39)
LAT of all known lesions	Yes vs. No	0.097	0.74 (0.52-1.06)
Type of LAT	RT vs. Surgery	0.20	0.79 (0.56-1.13)
	Other vs. Surgery	0.058	1.84 (0.98-3.46)
	≥2 types of LAT vs. Surgery	0.54	0.85 (0.49-1.45)
Systemic therapy	Yes vs. No	0.070	0.76 (0.56-1.02)
Number of treated lesions	>5 vs. ≤5	0.77	1.06 (0.72-1.57)
Maximal diameter of treated lesions (cm)	>2 vs. ≤2	0.058	1.29 (0.99-1.69)

Table 2: Prognostic factors for progression-free survival (PFS) after local ablative therapy (LAT), multivariate analysis in a mixed effects model.

LPS: Liposarcoma, LMS: Leiomyosarcoma, SySa: Synovial sarcoma, UPS: Undifferentiated pleomorphic sarcoma, RT: Radiotherapy

3.5 Prognostic factors for local ablative therapies (LAT) of pulmonary metastases

In a subgroup analysis, LAT in patients with pulmonary metastases were evaluated. Overall, 219 surgical metastasectomies and 43 radiotherapies were included in the multivariate analysis. A treatment-free interval ≥12 months was associated with an improved PFS while the largest maximal diameter of lesions >2cm resulted in a worse PFS (Table 3). This analysis was also performed with continuous variables (Supplementary material (8)).

Factor	**Strata**	**p-value**	**HR (95% CI)**
Age (years)	>60 vs. ≤60	0.86	1.04 (0.70-1.54)
Sex	Female vs. Male	0.55	1.13 (0.76-1.66)
Histotype	LPS vs. LMS	0.94	0.97 (0.49-1.93)
	SySa vs. LMS	0.18	0.69 (0.40-1.18)
	UPS vs. LMS	0.66	0.87 (0.48-1.60)
	Other vs. LMS	0.74	1.09 (0.66-1.80)
Prior metastatic events	≥1 vs. 0	0.46	1.15 (0.80-1.66)
Treatment-free interval (months)	≥12 vs. <12	**0.016**	0.63 (0.43-0.92)
Primary tumor control	Yes vs. No	0.34	0.69 (0.32-1.49)
LAT of all known lesions	Yes vs. No	0.42	0.76 (0.40-1.47)

Type of LAT	RT vs. Surgery	0.71	0.91 (0.54-1.51)
Systemic therapy	Yes vs. No	0.46	0.84 (0.53-1.34)
Number of treated lesions	>5 vs. ≤5	0.97	0.99 (0.60-1.63)
Maximal diameter of treated lesions (cm)	>2 vs. ≤2	**0.044**	1.47 (1.01-2.14)

Table 3: Prognostic factors for progression-free survival (PFS) after local ablative therapy (LAT) of lung metastasis, multivariate analysis in a mixed effects model.

LPS: Liposarcoma, LMS: Leiomyosarcoma, SySa: Synovial sarcoma, UPS: Undifferentiated pleomorphic sarcoma, RT: Radiotherapy

3.6 Combination with systemic therapy

Number of treated lesions ≥4, a maximal diameter of treated lesions >2cm and age >60 years had a significant interaction with the combination of LAT with systemic therapy. In additional subgroup analyses, systemic therapy was independently associated with better PFS in patients aged ≤60 years with ≥4 treated lesions. This effect was enhanced when the maximal diameter of treated lesions was >2cm (Table 4). Adjustment for further variables possibly influencing the use of systemic therapy (treatment-free interval, primary tumor control, histotype, site of treated lesions, LAT of all known lesions) did not change the association. These findings could be confirmed in the subgroup of LAT for pulmonary metastases (Supplementary Material (9)).

Number of LAT with / without systemic therapy	**Number of treated lesions**	**Maximal diameter of treated lesions (cm)**	**Age (years)**	**p-value**	**HR (systemic therapy: yes vs. no)**
19 / 88	<4	≤2	≤60	0.71	0.89
9 / 60	<4	≤2	>60	**0.0001**	5.5
38 / 56	<4	>2	≤60	0.13	0.65
18 / 69	<4	>2	>60	0.38	0.58
22 / 13	≥4	≤2	≤60	**0.02**	0.32
5 / 11	≥4	≤2	>60	0.68	1.30
15 / 11	≥4	>2	≤60	**0.0011**	0.20
9 / 11	≥4	>2	>60	0.56	1.33

Table 4: Subgroup analysis of local ablative therapies (LAT) with and without combination with systemic therapy and the impact on PFS.

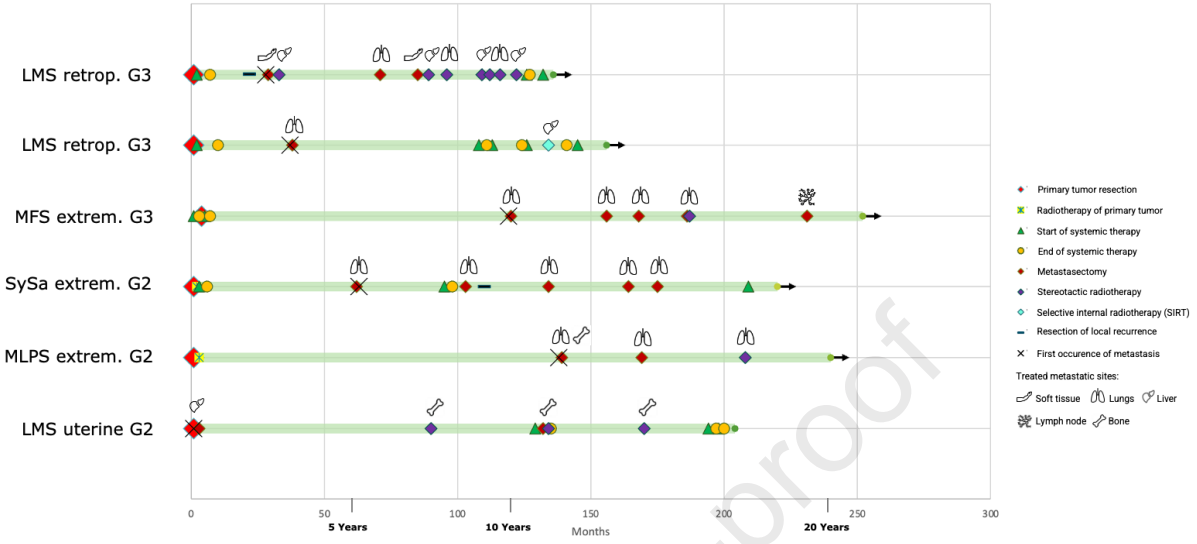

Figure 2: Patients with overall survival (OS) after first local ablative therapy (LAT) of ≥8 years.

LMS: Leiomyosarcoma, MFS: Myxofibrosarcoma, SySa: Synovial sarcoma, MLPS: Myxoid Liposarcoma, retrop.: retroperitoneal, extrem.: extremities

4. Discussion

This series represents a multicenter longitudinal study of 246 patients with metastatic STS and metastasis-directed LAT. Due to the rarity of STS and the difficulties of performing randomized studies, large-scale retrospective studies offer an essential opportunity to generate evidence.

In our overall cohort, the median OS after first metastasis was 5.4 years (64.8 months) with a 5-year survival rate of 53.1%. A previous study conducted by the French Sarcoma Group including STS patients with a maximum of five metastases found a median OS of 45.3 months in patients treated with LAT.[23] Further studies showed a median OS of 12-24 months in patients with metastatic STS.[2,4] The favourable outcome of our cohort is likely to be associated with patient selection and treatment at specialized sarcoma centers. Previous studies demonstrated a survival benefit for patients treated in specialized institutions.[31,32] As our cohort includes patients from four certified sarcoma centers, our results emphasize the value of highly specialized treatment for patients with rare cancers.

In our study, OS after first metastasis was better for LMS compared to most other histotypes. This finding is in accordance with previous literature and might be related to the high chemosensitivity of this subtype.[3] Interestingly, PFS and OS after first, second and third LAT with regard to all patients did not differ significantly underlining the value of repeated LAT which is in line with previous work on pulmonary metastasectomy in STS.[17,18]

Pulmonary metastasectomy is the most established LAT in patients with metastatic STS. As early as 1997, the International Registry of Lung Metastases (IRLM) conducted a retrospective analysis of 5206 patients after pulmonary metastasectomy revealing a 5-year survival of 32% among soft tissue and bone sarcoma patients (n=2173).[16] Long-term survival in a group of patients and clinical prognostic factors, such as a prolonged disease-free interval, were confirmed in subsequent studies.[14,15] With regard to resection of other metastatic organ sites, no clear guideline recommendations are given due to a lack of high-quality systematic studies.[33] In selected studies on pulmonary metastasectomy, extrapulmonary disease was considered a negative prognostic factor.[21,34] Moreover, previous studies identified more than one metastatic organ site as a negative prognostic factor for survival in metastatic STS.[3,4] In our cohort, we found no significant difference in survival after first metastasis with regard to metastatic organ site and involvement of more than one metastatic organ site. LAT of metastatic lesions in the liver was even associated with favourable PFS in the mixed effects model analysis and treated metastatic lesions in a single organ site other than lung and liver led to an OS benefit after first LAT. Studies on LAT of extrapulmonary metastases in STS remain scarce. However, our results align with previous studies indicating promising survival rates after hepatic metastasectomy of up to 49%.[35,36] Our findings further underscore the value of LAT for hepatic and other extrapulmonary metastases.

We could confirm a long treatment-free interval (≥12 months) as a positive prognostic factor for survival after LAT which is consistent across different studies and likely to be the most reliable clinical variable for choosing suitable patients for LAT.[15,16] In our analysis, primary tumor control was not associated with a survival benefit after LAT, suggesting that metastasis-directed LAT can also be reasonable in patients with a primary tumor recurrence at the same time. The number of treated lesions was not associated with an impact on survival, whereas the maximal diameter of treated lesions seemed to be more relevant for outcome of LAT in our analysis. While in some previous studies on pulmonary metastasectomy survival benefits were reported in patients with less than two to four metastatic lesions[21,22,37], others did not find a correlation between number of lesions and outcome.[38,39] In our analyses of the total cohort and the subgroup of patients with LAT of pulmonary metastases, number of treated lesions did not have a significant impact on the outcome. Our findings suggest that LAT might be feasible also in patients beyond the common definition of oligometastasis (up to five metastases in up to

three organs).[12] Regarding the maximal diameter of treated lesions, resected pulmonary lesions of ≤2cm were found to be favourable for survival in two studies.[21,22] Furthermore, size of the largest lesion has been proposed as a negative prognostic factor in STS patients with pulmonary metastases who received first-line systemic therapy.[40] In our subgroup analysis of patients with LAT of pulmonary metastases, a size ≥2cm was an adverse factor for PFS. To determine cut-off values up to which number and size of treated lesions LAT is reasonable, randomized prospective trials are required.

To date, it remains unclear when to use which type of LAT. No prospective trials comparing surgery, radiotherapy and other LAT in metastatic STS have been performed. For pulmonary metastasis, SBRT is considered a valid alternative to surgical metastasectomy with similar survival rates.[41,42] In our study, modalities other than surgery and radiotherapy were associated with worse OS after LAT. However, this finding might be related to a less curatively intended approach in these patients.

One of the main remaining questions with respect to LAT in STS is the role of systemic therapy. Previous studies provided varying results with either no or even a negative impact by the combination of LAT with systemic therapy.[21,22,23,24] In our study, additional systemic therapy tended to result in a better PFS. Interaction and subsequent subgroup analysis could demonstrate a maximal PFS benefit of systemic therapy in patients aged ≤60 years with ≥4 treated metastatic lesions, further enhanced when the diameter of treated lesions was >2cm suggesting a benefit of systemic therapy in younger patients with high tumor burden.

Limitations of our study include the retrospective design and the heterogeneous patient cohort, typical for STS studies. Moreover, our study lacks a control cohort preventing us from drawing conclusions regarding the benefit of LAT as the metastatic states and indications for the use of LAT vary widely. However, this is unavoidable when demonstrating real world data. The rather high proportion of soft tissue metastases might arise from the preferred use of LAT for this site leading to a selection bias.[3] It must be noted that our study included highly selected patients which were carefully evaluated in specialized tumor boards before recommendation of LAT. Therefore, our results might not apply to the general population of metastatic STS. In order to best analyze multiple LAT per patient with regard to PFS, a mixed effects model represents a valid method. However, for OS analysis this model is less suitable for our cohort as patients are censored after start of second LAT which would result in a loss of information about patients with multiple LAT. Taking this limitation into account, we added an analysis of survival after first LAT.

5. Conclusion

Given the paucity of large-scale studies, our multicenter study provides significant information about LAT in metastatic STS, which may help to improve treatment decisions. The high survival rates shown in the study underline the value of LAT after multidisciplinary tumor board decision. In addition, our study suggests a benefit of additional systemic therapy for patients ≤60 years with ≥4 treated lesions.

Author Contributions

Conceptualization AB-M, MG and LHL; data curation AB-M and VJ; formal analysis AB-M, VJ, MG and LHL; funding acquisition LHL and MG; investigation AB-M and VJ; methodology AB-M, VJ, MG and LHL; project administration LHL and MG; resources MG and LHL; software VJ and AB-M; supervision LHL, MG, UL, ML, NM, AB-M and AH; validation LHL, MG and AB-M; visualization VJ and AB-M; writing—original draft AB-M; writing—review and editing MG, VJ, LHL, AA, MA, LMB, DDG, HRD, RvE-R, CE, KF, EF, SEG, JSH, AH, FK, AK, CK, JRK, WGK, AML, ML, UL, NM, CM, N-SS-H, SS, WS, MT, JW and AW. All authors have read and agreed to the published version of the manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

Declaration of Interests

None.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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