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ORIGINAL ARTICLE

Response to preoperative chemotherapy in patients undergoing resection of pulmonary metastasis from soft tissue sarcoma – a predictor of outcome?

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ABSTRACT

Approximately 50% of patients with high-grade soft tissue sarcoma (STS) will develop pulmonary metastasis. This is the most frequent cause of death and improving treatment is warranted. Preoperative chemotherapy is used for selected patients, usually those with less favorable prognosis and mainly outside clinical trials. The predicted value of histological and radiological response to preoperative chemotherapy on outcome was the main focus for this investigation.

Patients and methods. This retrospective study comprises 93 patients with metachronous lung metastasis from STS who underwent complete metastasectomy alone ($n = 41$) or metastasectomy following preoperative chemotherapy ($n = 52$). Clinical data, histological and radiological responses to chemotherapy were recorded and survival analyses performed.

Results. The time from initial STS diagnosis to the appearance of metastasis was shorter in the preoperative chemotherapy group than in those treated with surgery alone ($p = 0.02$). However, no statistical differences in post-metastasis disease-specific survival (DSS) or progression-free survival (PFS) between the groups were demonstrated. Patients in the preoperative chemotherapy group with good (complete) histological response had improved PFS compared with poor responders ($p = 0.04$). Radiological partial response was an independent, favorable prognostic factor for improved PFS and DSS ($p = 0.003$).

Conclusion. Despite having unfavorable disease characteristics, some patients may benefit from preoperative chemotherapy. Both histological and radiological responses to preoperative chemotherapy seem to be prognostic in STS patients undergoing complete pulmonary metastasectomy.

Soft tissue sarcomas (STS) encompass a wide spectrum of rare tumors accounting for approximately 1% of all adult malignancies. The lungs are the most frequent metastatic site [1]. With metastatic disease the prognosis is poor with a median survival of approximately 10 months [2]. Overt metastasis at diagnosis (synchronous metastasis), metastatic relapse (metachronous metastasis) with a short interval from primary disease, more than three pulmonary

nodules and bilateral involvement are related to inferior outcome [3,4]. Patients with long progression-free interval from diagnosis face a more favorable prognosis and selected patients can be cured if the metastases are completely resected [2,4]. Long-term survival may be feasible even with repeated metastasectomies [4].

Nevertheless, more than 60% of patients undergoing pulmonary metastasectomy will experience

subsequent recurrences due to co-existing micro-metastatic disease [4], and the strategy of eliminating such micrometastases by chemotherapy is tempting. Preoperative chemotherapy in patients with lung metastasis from osteosarcoma has resulted in approximately one third long-term survivors [5]. This has led some to explore a similar approach also in STS [2,6]. Previous retrospective studies, however, have not shown improved outcome in patients with STS undergoing chemotherapy prior to resection of pulmonary metastases [7,8]. Furthermore, randomized trials in this setting have been difficult to conduct due to low enrollment [9]. Importantly, two publications report long-term survivors among highly selected subsets of advanced STS patients with complete remission after surgery and/or chemotherapy (13 of 38 and 17 of 66 patients, respectively) [10,11].

In our institution preoperative chemotherapy has generally been reserved for patients < 70 years of age with good performance status and aggressive tumor biology; i.e. < 12 months metastasis-free interval (from diagnosis until first appearance of pulmonary metastasis), multiple pulmonary nodules, extrapulmonary- or bilateral pulmonary disease. Postoperative chemotherapy has been administered after radiological response evaluation according to WHO criteria [12] and histological evaluation [13]. Disease progression, poor histological response, or unacceptable toxicity often resulted in altered or no postoperative chemotherapy.

Radiological response evaluation in high grade STS has limitations due to stromal components that may keep the tumor volume unchanged post-treatment [14]. This emphasizes the importance of histological evaluation of chemotherapy effectiveness. Well-defined histological criteria for assessing response have been established in osteosarcoma, and in this disease histological response has a clear relationship to outcome [15]. To our knowledge, except one study [10], this has only been examined in localized STS with disparate results [10,16–20].

This retrospective study includes all patients in our institution between 1980 and 2007 who underwent complete surgical removal of lung metastases occurring more than six months from first STS diagnosis. Attempts were made to address the impact of response to preoperative chemotherapy on long-term outcome.

Patients and methods

Searching the institution's Sarcoma Database identified 350 STS patients with metachronous pulmonary metastasis treated between 1980 and 2007 (Figure 1). Among these, 112 were subjected to lung surgery following a metastatic relapse more

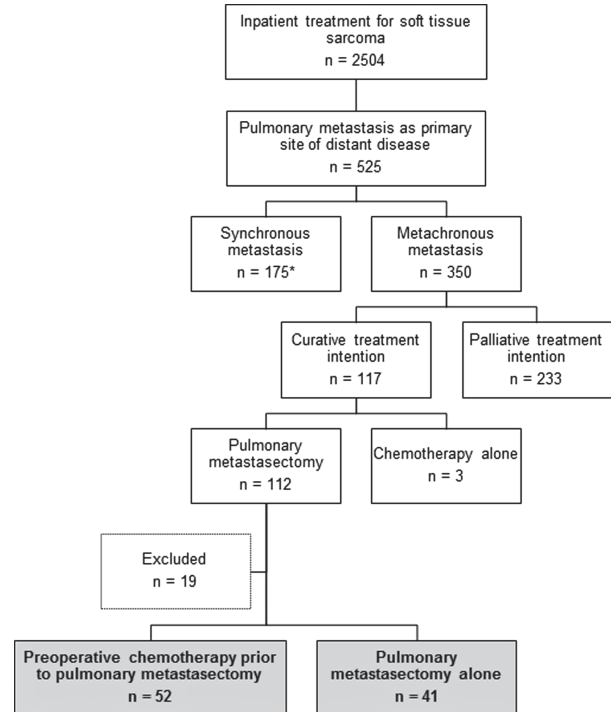


Figure 1. Flow chart demonstrating the subgroups of patients chosen for analysis (study population in filled boxes). *Not included in this study.

than six months from their primary STS diagnosis. A retrospective review of the medical records was performed based on informed consent to sarcoma research in general obtained at time of primary diagnosis. Only patients with good performance status (ECOG 0–1), curative treatment intention and subsequent pulmonary metastasectomy were included. Reasons for exclusions were incomplete/palliative thoracoscopy/thoracotomy ($n = 15$), malignancy not conclusive ($n = 2$) and solely pleural metastasis ($n = 2$). This left a total of 93 patients for further analysis of survival, among which 52 had received preoperative chemotherapy and could be subjected to histological and radiological response evaluation (Figure 1). The study was approved by the Institutional Review Board.

Response evaluation

Previously, histological response to preoperative chemotherapy in advanced STS has been divided into four grades based on the percentage of viable cells [10]. The method was partly derived from the four-grade system defined by Huvos [13] and was applied in the present study: Huvos grade I–II (I: no necrosis, II: < 90% necrosis) was considered poor, grade III ($\geq 90\%$ necrosis) intermediate and grade IV (100% necrosis) good histological response (i.e. complete). All specimens from patients treated with preoperative chemotherapy (except four cases with

insufficient tissue for analysis) were histologically re-examined. The percentages of tumor necrosis were evaluated on routine slides stained with hematoxylin and eosin. All available slides were reviewed. If multiple metastases were resected and evaluated with variable histological responses ("mixed"), the definitive response was scored according to the poorest chemotherapy response.

Radiological response rates were classified according to standardized WHO criteria [12]. Pre-chemotherapy measurements were done close to initiation of chemotherapy and pre-surgery measurements close to surgery. The number and dimension of metastases were determined based upon review of cross-sectional imaging studies (7.5–8mm CT slices) in lung window setting. When CT scans were not accessible (n = 18), plain x-rays were used. A maximum of five lesions were measured in each case. For single lesions multiplication of the longest diameter by the greatest perpendicular diameter was used. In multiple lesions the average of sum of products was applied. Relevant images were missing in seven cases, thus excluded from radiological analysis.

Principally, all preoperative evaluations were done by the institution's same multidisciplinary sarcoma team. Postoperatively, the patients were followed with radiological and clinical control every three months.

Statistical methods

The data were analyzed with respect to progression-free survival (PFS, i.e. next pulmonary metastasis, extrapulmonary metastasis or sarcoma related death) and disease-specific survival (DSS). Disease-free interval (DFI) was calculated from the date of primary diagnosis until first metastatic relapse, whereas PFS and DSS were defined from the date of first metastasis.

The statistical analysis was conducted using the software SPSS (version 16.0; SPSS, Inc., Chicago, IL, USA). Pearson's correlation test, Fisher exact test and independent two-tailed t-tests were employed to compare categorical and continuous variables, respectively. Factors previously reported to have prognostic effect on DSS and PFS were tested univariately with the Kaplan-Meier method, and the significance of detected differences estimated with log-rank test or Cox proportional hazard model. Changes were considered significant when $p < 0.05$.

Results

Patient and treatment characteristics

Among the 93 patients who underwent thoracotomy, 52 patients received preoperative chemotherapy

(Figure 1). When comparing these patients with the surgery alone group (41 patients), several differences were evident (Table I): In the surgery alone group there were longer DFI, less bilateral disease and more females. There were no differences between the two groups as regards age, histological subtypes or additional presence of pleural- or extrapulmonary metastasis.

Forty-two patients in the preoperative chemotherapy group were chemotherapy-naïve when lung metastasis occurred versus 30 in the surgery alone group. Several chemotherapy regimens were administered in the metastatic setting, but combinations of adriamycin and cyclo-/ifosfamide dominated (n = 32), then ifosfamide alone (n = 17) or other regimens (n = 3). In the latter groups, seven patients had received adriamycin adjuvantly. The median number of chemotherapy courses given was five (range 2–10). In the preoperative chemotherapy group 22 patients received postoperative chemotherapy. Five patients were allocated to a different chemotherapy regimen postoperatively due to either disease progression (n = 4) or unacceptable side effects (n = 1). Four patients in the no neoadjuvant group received postoperative chemotherapy.

Response to chemotherapy

Histology. Of 52 preoperatively treated patients, 48 cases were available for histological response assessments. The majority of these patients (n = 37) were poor responders to preoperative chemotherapy, but four were complete histological responders with no viable tumor tissue in the resected metastases.

Radiology. Forty-five cases were re-evaluated for radiological response to preoperative chemotherapy. One patient had no visible tumor [complete response (CR)], and this response was in accordance with the observation preoperatively and subsequent histological examination (fibrous scar with no evident tumor). All patients with radiological progressive disease (PD) were poor histological responders, while patients with partial response (PR) and stable disease (SD) displayed histological responses within all categories (Table II). Consequently, there was no statistically significant correlation between radiological and histological chemotherapy responses.

Survival analysis. The median follow-up after first pulmonary metastasis was 39 months (range 4–241). Seventy-five patients died including 65 from sarcoma and three from postoperative complications related to thoracotomy (two lung embolisms and one postoperative arrhythmia). The other causes of death were

Table I. Comparison of clinicopathologic and treatment characteristics in study population.

Characteristics	Preoperative chemotherapy N = 52	Surgery alone N = 41	p
Gender			
Male	27	13	
Female	25	28	0.05
Median age at diagnosis (range), years	48 (14–72)	51 (10–81)	0.49
Primary site			
Lower extremity	17	17	
Upper extremity	11	8	
Thoracic wall	10	7	
Intraabdominal	10	7	
Other	4	2	0.92
Histology			
FS	6	3	
LMS	8	6	
LS	4	2	
MFH	16	13	
MPNST	2	2	
SS	7	6	
Other	9	9	0.99
Grade			
Low	5	8	
High	43	29	
Unknown	4	4	0.32
Depth			
Superficial	9	6	
Deep	40	34	
Unknown	3	1	0.77
Primary tumor size			
< 5 cm	15	12	
5–10 cm	22	11	
> 10 cm	14	13	
Unknown	1	5	0.15
Local recurrence			
Yes	10	8	
No	42	32	
Unknown	0	1	0.68
Median DFI (range), m	17.5 (6–108)	35 (6–219)	0.02
Median no. of met * (range)	3 (1–50)	1 (1–52)	0.56
Pulmonary sides involved			
Unilateral	27	35	
Bilateral [§]	25	6	0.001
Additional pleural met			
Yes	14	8	
No	38	33	0.47
Additional extrapulm met			
Yes	10	6	
No	42	34	
Unknown	0	1	0.57
Radiotherapy to primary tumor			
Yes	17	19	
No	35	22	0.20
Chemotherapy to primary tumor			
Yes	10	11	
No	42	30	0.46

DFI, disease-free interval; FS, fibrosarcoma; LMS, leiomyosarcoma; LS, liposarcoma; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor; SS, synovial sarcoma. Other (histology): phyllodes tumor, alveolar soft tissue sarcoma,

Table II. Distribution of patients among histological and radiological response to preoperative chemotherapy.

Radiological response (WHO)	Histological response (Huvos)					Total
	I	II	III	IV	na	
CR	0	0	0	1 ⁷	0	1
PR	8 ^{2,4-7}	5 ^{3,7}	1 ¹	2 ^{3,7} , [§]	0	16
SD	15 ^{1-4,6,7,§}	3 ^{2,3,7}	1 ^{3,*}	1 ^{2,*}	1 ^{2,*}	21
PD	4 ^{3,6,§}	3 ^{3,6,§}	0	0	0	7
na	3 ^{3,§}	1 ^{5,§,*}	0	0	3 ¹⁻³	7
Total	30	12	2	4	4	52

CR, complete response (the disappearance of all known disease, determined by two observations not less than four weeks apart); na, not applicable; PD, progressive disease (25% or more increase in the size of one or more measurable lesions or the appearance of new lesions); PR, partial response (50% or more decrease in total tumor load of the lesions that have been measured to determine the effect of therapy by two observations not less than four weeks apart); SD, stable disease (a 50% decrease in tumor size cannot be established nor has a 25% increase in the size of one or more measurable lesions been demonstrated). ¹Synovial sarcoma; ²Fibrosarcoma; ³Malignant fibrous histiocytoma; ⁴Malignant peripheral nerve sheath tumor; ⁵Liposarcoma; ⁶Leiomyosarcoma; ⁷Other histotypes; [§]1–5 patients with adjuvant chemotherapy in primary setting; ^{*}No postoperative chemotherapy. In bold characters, Adriamycin-based chemotherapy to all patients.

one postoperative bleeding after brain metastasectomy, one from other cancers and five from unknown cause or other diseases. Of the remaining 18 patients in study population, two were alive with persistent disease while the 16 patients with no evidence of disease had a median follow-up of 117 (range 29–243) months from date of first metastasis. The median DSS for the entire study population was 41 months whereas the median PFS was 20 months.

Cumulative survival probability for study population, as illustrated in Figure 2a, showed no statistical differences between the preoperative chemotherapy and surgery alone group (median DSS 38 months vs. 49 months and median PFS 17 vs. 25 months, respectively).

The histological response system showed that poorer response resulted in inferior survival with one important exception: Huvos grade III had inferior survival rate compared to Huvos grade I/II (Figure 2b and see below). In contrast, patients with complete good histological response (Huvos grade IV, n = 4 of 48) were long-term survivors (three of four patients alive more than 10 years after the first metastasectomy) and with significantly longer PFS than the

clear cell sarcoma, Ewing's sarcoma, primitive neuroectodermal tumor, rhabdomyosarcoma, other small cell tumor, angiosarcoma, extraskelatal chondrosarcoma or unclassified. ^{*}Median number of metastasis at first event. [§]When handled sequentially, no more than three months between thoracotomies. Statistical significance in italic characters.

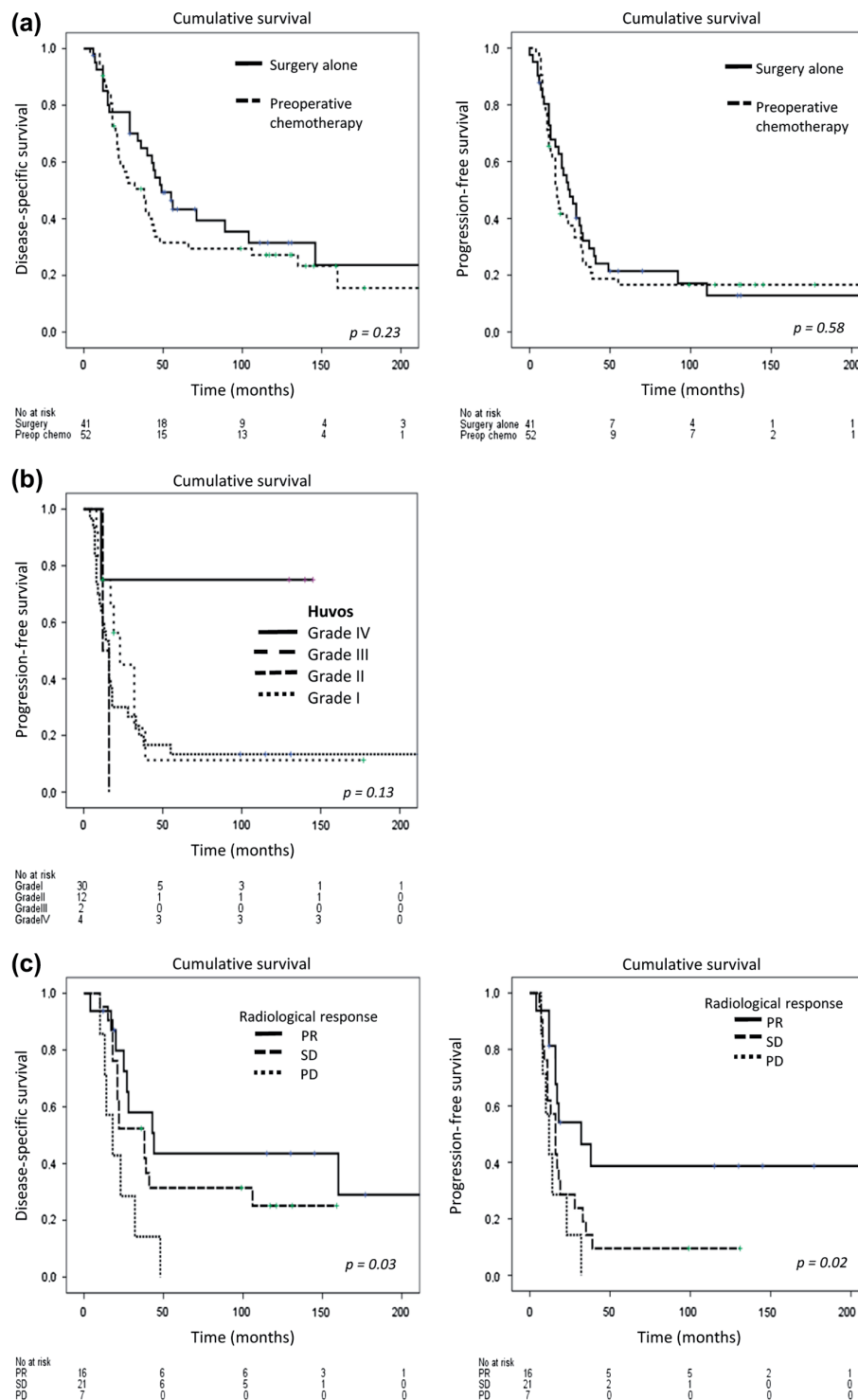


Figure 2. Kaplan-Meier curves depicting (a) DSS and PFS for the two cohorts in study population; preoperative chemotherapy and surgery alone. (b) PFS comparing various histopathologic responses to chemotherapy assessed by Huvo's grading system and (c) DSS and PFS for various radiological responses; partial response (PR), stable disease (SD) and progressive disease (PD).

poor response group (median PFS for Huvo's grade IV not reached vs. 16 months for Huvo's grade I/II, $p = 0.04$). They also displayed longer PFS than the surgery alone group ($p = 0.05$). The impact of histological response on survival was significant in uni-

and multivariate analyses where presence of Huvo's grade IV improved progression-free survival together with unilateral pulmonary disease and absence of pleural metastasis. The histological subtype MPNST, however, was a significant adverse prognostic factor,

as outlined in Table IIIa. Albeit being a small group of tumors ($n = 3$), the group of long-term survivors included both presumed chemo-responsive (PNET, angiosarcoma) and less responsive (MFH) tumors with diverse disease aggressiveness ($n = 1$ unilateral pulmonary metastasis and DFI < 1 year) and extensiveness ($n = 2$ additional metastases).

A radiological PR or better also correlated significantly with survival (Figure 2c), and patients with PR had median DSS of 44 months, whereas patients with SD or PD had median DSS of 38 and 18 months, respectively ($p = 0.03$). Median PFS was 32, 16 and 12 months, respectively ($p = 0.02$). In multivariate analysis PR improved both DSS and PFS significantly. In addition, PFS was favored by unilateral pulmonary disease whereas presence of MPNST, FS and local relapse were adverse prognostic factors (Table IIIb).

Finally, patients who received additional postoperative chemotherapy ($n = 22$) had median DSS of 39 months and PFS of 18 months compared to 27 and 16 months with preoperative chemotherapy alone ($n = 30$). No statistically differences could be detected

with the small sample sizes available. Similarly, no distinction could be observed between modified postoperative regimens and unchanged regimens (median DSS 21 vs. 45 months, median PFS 16 vs. 24 months, $n = 5$ vs. $n = 17$, respectively).

Discussion

STS in adult patients shows only moderate sensitivity to chemotherapy (e.g. 10% improvement in overall recurrence-free survival at 10 years following adjuvant doxorubicin-based chemotherapy [21]), with lack of evidence for combination treatment of metastasis. In STS the strategy of eliminating micrometastases by chemotherapy is nevertheless tempting. This retrospective study investigates the impact of preoperative chemotherapy on pulmonary metastasis from STS in 52 patients compared with 41 patients treated with surgery alone. Since the patients were treated in a non-randomized manner, obviously there was a selection for more aggressive tumor biology [i.e. shorter time to first metastasis (DFI < 1 year) and

Table III. A. Uni- and multivariate analysis in histological response groups. Progression-free survival.

Univariate				Multivariate			
Variables	Hazard ratio	95% CI	p	Variables	Hazard ratio	95% CI	p
Huvos IV	0.17	(0.02–1.21)	0.08	Huvos IV	0.08	(0.01–0.66)	0.02
MPNST	26.2	(4.31–159)	<i>< 0.001</i>	MPNST	24.6	(3.78–160)	0.001
Unilateral disease	0.51	(0.27–0.98)	0.04	Unilateral disease	0.48	(0.23–0.99)	0.05
No pleural metastasis	0.51	(0.25–1.05)	0.07	No pleural metastasis	0.39	(0.18–0.86)	0.02

B. Uni- and multivariate analysis in radiological response groups. Disease-specific survival.

PR	0.27	(0.10–0.75)	0.01	PR	0.19	(0.06–0.58)	0.003
SD	0.42	(0.17–1.04)	0.06	SD	0.27	(0.10–0.73)	0.01
FS	2.44	(0.90–6.61)	0.08				
Unilateral disease	0.5	(0.24–1.03)	0.06				
1–3 pulmonary nodules	0.31	(0.09–1.09)	0.07				
No pleural metastasis	0.36	(0.17–0.80)	0.01				
No extrapulmonary metastasis	0.49	(0.21–1.16)	0.10				

C. Uni- and multivariate analysis in radiological response groups. Progression-free survival.

PR	0.27	(0.10–0.75)	0.01	PR	0.19	(0.06–0.55)	0.002
MPNST	35	(4.83–254)	<i>< 0.001</i>	MPNST	28.9	(3.67–227)	0.001
FS	2.40	(0.89–6.47)	0.08	FS	3.60	(1.18–10.9)	0.02
LR	2.24	(0.92–5.45)	0.08	LR	3.52	(1.32–9.41)	0.01
Unilateral disease	0.48	(0.24–0.94)	0.03	Unilateral disease	0.45	(0.21–0.93)	0.03
1–3 pulmonary nodules	0.33	(0.09–1.14)	0.08				
No pleural metastasis	0.38	(0.17–0.83)	0.02				

Multivariate Cox regression model with strategy 'Backward LR'. CI, confidence interval; FS, fibrosarcoma; HR, hazard ratio; LR, local relapse; MPNST, malignant peripheral nerve sheath tumor; PR, radiological partial response; SD, radiological stable disease. Age, gender, performance status, primary tumor site, -size, -depth and -grade, other histological subtypes, disease-free interval, number of chemotherapy cycles, presence/absence of postoperative chemotherapy and other histological or radiological chemotherapy responses were not significant in univariate analysis (0.10 significance level), thus not included in multivariate analysis.

Statistical significance in italic characters.

bilateral disease] in the preoperative chemotherapy group. Interestingly, no differences in DSS or PFS could be demonstrated. This is in line with previous reports [2,7,8], and may suggest an impact of chemotherapy in patients with presumed poor prognosis. There were no differences in age distribution or presence of pleural- or extrapulmonary metastasis between the two groups. This is in agreement with the report from Blackmon *et al.* [22] which documented that long-term survival can be achieved if a complete resection is possible for both pulmonary and extrapulmonary metastasis.

Disparate responses are reported between primary tumor and metastasis in patients receiving preoperative chemotherapy [23]. Thus radiological and histological chemotherapy response evaluation should be performed in the metastatic tissue. In the present study a significant concordance between radiological response in lung metastasis and outcome was found, and radiological partial response was one of the good prognostic factors for DSS and PFS. In contrast, radiological progressive disease was associated with dismal outcomes. Hence, additional chemotherapy and subsequent metastasectomies may be questioned in such patients.

A well-known histological response system (Huvos) was applied to evaluate preoperative chemotherapy response of pulmonary metastasis from STS. Poorer response resulted in poorer survival, with one important exception; Huvos grade III had inferior survival rate compared to Huvos grade I/II. Huvos grade III corresponds to more than 90% tumor necrosis, but still with foci of viable tumor present. To avoid interpreting any spontaneous necrosis as chemotherapy response, previous authors have argued that >95% necrosis should be the cut-off for complete histological response [19]. Thus, Huvos III may theoretically consist of more non-responding tumor than indicated by the response system. This might explain why there was no statistically significant correlation between radiological and histological chemotherapy responses.

In the present study only four patients were good histological responders according to the method applied. These patients turned out to be long-term survivors compared to the poor histological responders. Hence, good histological response to preoperative chemotherapy might be a surrogate marker of good clinical outcome. We recognize that the number of patients in this group is small, limiting the statistical power of the results. However, this group displayed diverse demography and disease extensiveness which emphasize the importance of not excluding patients with expected poor prognosis from chemotherapy, in line with a previous report [11]. This observation is in contrast to some long-term survivors with

indolent, lung only disease assumed to have fair prognosis only as a result of surgical complete metastasectomy [4]. Hence, it might be presumed that complete surgical removal of all apparent disease partly explains the good prognosis observed in these patients, as does good histological response to preoperative chemotherapy.

One of the theoretical benefits of preoperative chemotherapy is the *in vivo* test of chemo-sensitivity. However, the gain in modifying postoperative chemotherapy regimen based on the histological response has been questioned for other tumor entities such as osteosarcoma [15]. In the present study postoperative chemotherapy was administered after response evaluation in 22 preoperatively treated patients. This included all long-term survivors. Only five patients received new regimens postoperatively, four due to poor histological or radiological response evaluation. A trend towards increased disease- and progression-free survival by additional postoperative chemotherapy was found. However, no differences could be observed between modified postoperative regimens and unchanged regimens. Unfortunately, the sample sizes were too limited to conclude, but may raise the question of consolidation therapy, such as utilized in osteosarcoma, tentatively without changing regimens postoperatively. Larger studies are obviously needed to draw valid conclusions in this respect.

There are several limitations in the present dataset, primarily the selection bias inherent in the retrospective, non-randomized nature of this report with the selection for more aggressive disease biology in the preoperative chemotherapy group. However, patients with synchronous metastasis were excluded as these represent invariably poor prognosis (median DSS 22 months, PFS 12 months, data not shown). Hence, a cut-off of 6-months disease-free survival was selected. Furthermore, despite separate histological and radiological reviews, these were not blinded. Instead of using the prevailing RECIST criteria, less sophisticated imaging technology and WHO criteria were applied. This might lead to an overestimation of progressive disease [24]. Finally, some patients were not chemotherapy-naïve at time of pulmonary metastasis. Although new drug regimens were administered, the effect might be outweighed by primary chemo-resistance.

In summary, although patients receiving preoperative chemotherapy had unfavorable disease characteristics, no difference in survival was observed compared to the surgery alone group. This might suggest an effect of chemotherapy. Furthermore, histological and radiological responses to such treatment seem predictive of survival. Based on this, selected patients may be offered pre- and postoperative chemotherapy with the aim to improve prognosis.

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