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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Radiotherapy for Soft Tissue Sarcomas after Isolated Limb Perfusion and Surgical Resection: Essential for Local Control in All Patients?

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ABSTRACT

Background. Standard treatment for localized soft tissue sarcoma (STS) is resection plus adjuvant radiotherapy (RTx). In approximately 10% of cases, resection would cause severe loss of function or even require amputation because of the extent of disease. Isolated limb perfusion (ILP) with tumor necrosis factor alpha (TNF-α) and melphalan can achieve regression of the tumor, facilitating limb-saving resection. RTx improves local control but may lead to increased morbidity.

Methods. In our database of over 500 ILPs, 122 patients with unifocal STS were treated by ILP followed by limb-sparing surgery. All included patients were candidates for amputation.

Results. Surgery resulted in 69 R0 resections (57%), and in 53 specimens (43%) resection margins contained microscopic evidence of tumor (R1). Histopathological examination revealed >50% ILP-induced tumor necrosis in 59 cases (48%). RTx was administered in 73 patients (60%). Local recurrence rate was 21% after median follow-up of 31 months (2–182 months). Recurrence was significantly less in patients with >50% ILP-induced necrosis versus ≤50% necrosis (7% vs. 33%, $P = 0.001$). A similar significant correlation was observed for R0 versus R1 resections (15% vs. 28%, $P = 0.04$). In 36 patients with R0 resection and >50% necrosis, of whom 21 were spared RTx, no recurrences were observed during follow-up.

Conclusions. In patients with locally advanced primary STS, treated with ILP followed by R0 resection, and with >50% ILP-induced necrosis in the resected specimen, RTx is of no further benefit.

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Soft tissue sarcomas (STSs) are a heterogeneous group of rare malignancies. In the USA, 8,680 new cases of STS are diagnosed annually, of which approximately 60% are located in the extremities.[1] STSs are associated with early metastasis and a high disease-specific mortality rate of approximately 50%. Moreover, STS of the extremity is often large at time of presentation, making local resection and tumor control difficult.[1] Local control may require extensive surgery, resulting in loss of limb function or amputation in 10% of cases. Amputation, however, is not associated with prolonged survival, because survival is determined by the occurrence of systemic disease.[2,3] Since amputation has no beneficial effect on survival, growing interest in limb-salvaging techniques has arisen. Isolated limb perfusion (ILP) is a technique that results in perfusion of a tumor with high concentrations of tumor necrosis factor alpha (TNF-α) and melphalan under hyperthermic conditions. Following introduction of the technique in the early 1990s, Eggermont et al.[4] reported encouraging results in a large European multicenter study. Subsequent studies showed high local response and limb salvage rates and acceptable local and systemic toxicity.[5]

Currently, use of ILP followed by resection and RTx is an established strategy for limb salvage in Europe. Long-term morbidity has been described after ILP.[6] A contributing factor to morbidity is adjuvant RTx.[6] However, whether adjuvant RTx is necessary for all patients treated with ILP remains unclear. The aim of this study is to identify a specific

group of patients in whom adjuvant RTx was of no further benefit for tumor control. All patients in our hospital undergoing ILP for unifocal STS of the extremity followed by local resection were identified. Subsequently, we determined whether patients with STS of the extremity may be spared adjuvant RTx under specific circumstances.

PATIENTS AND METHODS

Patients

From August 1991 to March 2009, 511 ILPs were performed in our hospital. These 511 cases comprised 168 melanomas, 306 STS, and 37 miscellaneous malignancies (Fig. 1).

ILP was the treatment strategy in 74 cases of multiple STS, while 232 patients were treated for unifocal disease. In this retrospective study we evaluated all 122 consecutive ILPs (in 120 patients) for unifocal STS followed by limb-sparing surgical resection. The minimal tumor–node–metastasis (TNM) stage was IB, while the vast majority of STS was staged as IIB. Liposarcoma was the most common treated type of STS in our study, of which 3 were well differentiated, 2 were dedifferentiated, 7 were pleomorphic, and 16 were of myxoid subtype. Patient characteristics are summarized in Table 1.

Perfusion

The technique of ILP with TNF-α and melphalan has been described previously.[4,5] Briefly, the procedure is performed with patients under general anesthesia. After heparinization, a targeted blood circuit is isolated by clamping and cannulation of the major artery and vein and connection to an oxygenated extracorporeal circuit. A tourniquet compresses collateral vessels and prevents leakage. Using a precordial scintillation probe to detect technetium-labeled albumen, leakage is monitored for the length of the procedure. Patients underwent ILP via axillary ($n = 9$), brachial ($n = 19$), iliac ($n = 54$), femoral ($n = 24$) or popliteal ($n = 16$) approach.

TABLE 1 Patient and tumor characteristics

	N	%
Gender		
Female	55	45.1
Male	67	54.9
Age		
≤50 years	56	45.9
>50 years	66	54.1
Size		
<5 cm	20	16.4
5–10 cm	34	27.9
>10 cm	68	55.7
Trojani grade		
1	11	9.0
2	31	25.4
3	73	59.8
Missing	7	5.7
Site		
Upper arm	8	6.6
Elbow	5	4.1
Lower arm	10	8.2
Wrist or hand	5	4.1
Upper leg	46	37.7
Knee	20	16.4
Lower leg	22	18.0
Ankle or feet	6	4.9
Histology		
Liposarcoma	28	23.0
Synovial sarcoma	24	19.7
HGPS NOS	16	13.1
Leiomyosarcoma	12	9.8
Other (16 types)	43	34.4
Primary/recurrent		
Primary	102	83.6
Recurrent	20	16.4
Adjuvant RTx		
No	49	40.2
Yes	73	59.8

HGPS NOS high-grade pleomorphic sarcoma not otherwise specified

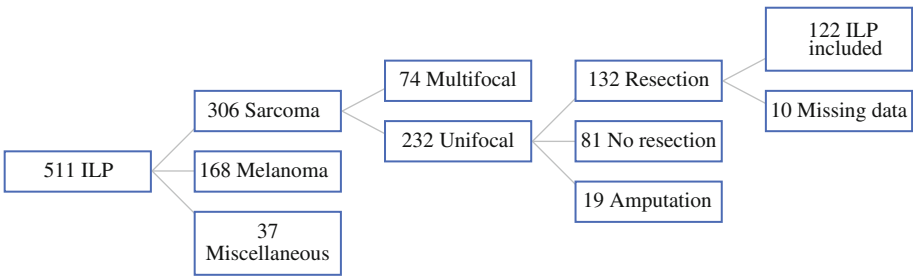

FIG. 1 Inclusion flow chart

A dose of 1–3 mg (arm) or 1–4 mg (leg) recombinant TNF-α (Boehringer Ingelheim GmbH, Ingelheim/Rhein, Germany) was injected as a bolus once the temperature of the limb reached 38°C. Subsequently, 13 mg/l (arm) or 10 mg/l (leg) melphalan (L-PAM; Alkeran, Burroughs Wellcome Ltd., London, UK) was administered 30 min after the limb temperature reached 38–39.5°C. The median dose of TNF-α administered was 4.0 mg (mean 3.2 mg, range 1–4 mg), while the median dose of melphalan was 75 mg (mean 79.8 mg, range 18–160 mg). Several studies reported successful use of reduced doses of TNF-α in ILP for STS with comparable local recurrence rates and no systemic toxicity.[7,8] Thereafter, perfusion was executed with 1 mg TNF-α in the arm and 2 mg in the leg. Consequently, since 2005 the median dose of TNF-α has been 2.0 mg (mean 2.09 mg, range 1–3 mg). After 90 min of perfusion, the limb was washed out with 1 l (arm) to 4 l (Iliac perfusion) physiological saline solution and 6% dextran (Macrodex Pharmacia, Uppsala, Sweden). Patients were observed in intensive care unit (ICU) for one night. Median length of hospital stay was 8 days (mean 11 days, range 2–136 days).

Clinical response was defined using clinical findings and magnetic resonance imaging (MRI). Complete response (CR) was defined as complete remission of tumor tissue, while partial response (PR) was defined as 51–99% remission. No change (NC) was defined as 0–50% remission. Clinical evidence of new lesions or growth of the tumor was defined as progressive disease (PD).

Local Control

Whenever the response of the tumor to ILP appeared to facilitate local resection without major limb function loss, local resection was attempted. Local resection was performed at median of 84 days (mean 91 days, range 14–260 days) after ILP. Margine status of the resection was defined using the criteria according to Pisters et al.[9] In each surgical specimen the peripheral margins were inked. A microscopically positive (R1) margin was defined as unequivocal tumor extension to the inked margin on permanent section. Cases in which tumor was close to but did not reach the inked margin were considered to have microscopically negative margins (R0). The percentage of the tumor that was necrotic due to ILP was estimated by the pathologist by macroscopic inspection and microscopic confirmation. Two categories were defined: 51–99% necrosis of the tumor and 0–50% necrosis of the tumor.

Radiotherapy

Adjuvant RTx was administered to 73 (60%) patients, while 49 (40%) patients did not receive RTx. Like all other decisions concerning STS, decisions on the subject of adjuvant RTx were made in a multidisciplinary board containing a surgical oncologist, a medical oncologist, a radiation oncologist, a pathologist, and a radiologist. Before 1998, there was little evidence that adjuvant RTx was beneficial after local resection of STS. Since Olieman et al.[10] reported improved outcome after adjuvant RTx in 1998, our center has administered significantly more RTx ($P = 0.04$). Reasons for refraining from administering adjuvant RTx after 1998 are summarized in Table 2.

TABLE 2 Reasons for no RTx after 1998

	N	%
Systemic disease	8	40
Joint/hand/foot	3	15
Age/comorbidity	2	10
Refused by patient	1	5
Reason not specified	6	30
Total	**49**	**100.0**

RESULTS

Clinical Response

Clinical response after ILP was complete in five cases (4%). PR was obtained in 80 patients (66%), NC in 35 patients (29%), and PD in 1 patient (1%). Clinical response was not assessed in one patient (1%) for unknown reason.

Local Control

Results are summarized in Table 3. Local resection of the STS resulted in R0 resection in 69 patients (57%), while 53 (43%) patients had R1/R2 resection. The overall local recurrence rate was 21% (25 patients) after median follow-up of 31 months (mean 48 months, range 2–182 months); 5-year recurrence-free survival (RFS) was 75% (±5% standard error, SE). If recurrence occurred, median time to recurrence was 15 months (mean 27 months, range 3–170 months). After R0 resection, 5-year RFS was 80%, while patients with R1 resection had 5-year RFS of 72%. This difference reached significance ($P = 0.04$, Fig. 2).The local recurrence rate was 15% in the R0 group (10 patients), while the R1 group had a local recurrence rate of 28% (15 patients). In 13 cases (11%), amputation, after limb-saving resection, was deemed necessary during follow-up. Median time between limb-sparing resection and amputation was 29 months (mean 25 months, range 2–60 months). Consequently, the limb salvage rate was 89%.

TABLE 3 Results for all STS

	R	Histology (%)	*N*	Recurrence	Recurrence rate (%)
No RTx	R0	≤50	7	1	14.3
	R0	>50	28	1[a]	3.6
	R1	≤50	8	4	50.0
	R1	>50	6	2	33.3
Total			**49**	**8**	**16.3**
RTx	R0	≤50	19	8	42.1
	R0	>50	15	0	0.0
	R1	≤50	29	8	27.6
	R1	>50	10	1	10.0
Total			**73**	**17**	**23.3**
Total	R0		69	10	14.5
	R1		53	15	28.3
		≤50	63	21	33.3
		>50	59	4	6.8
Total			**122**	**25**	**20.5**

[a] One patient with local recurrence of a secondary diagnosed STS

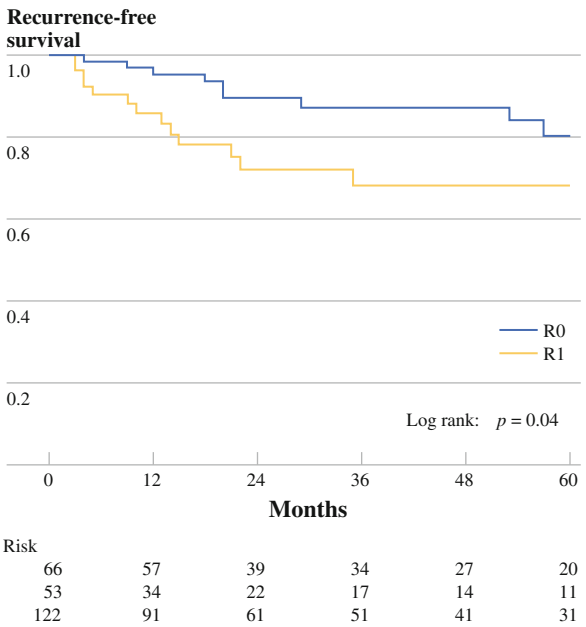

FIG. 2 Local recurrence versus R0/R1

Histopathological examination of the resection specimens revealed >50% ILP-induced tumor necrosis in 59 cases (48%). In 63 (52%) cases the response to ILP was 50% or less. Patients with >50% necrosis in specimen after resection had 5-year RFS of 92%, while patients with ≤50% necrosis had 5-year RFS of 61%. As can be seen in Fig. 3, this difference was significant ($P = 0.001$). In the group with >50% necrosis of the tumor, the local recurrence rate was 7% (4 cases), compared with 33% (21 cases) in the group with ≤50% tumor necrosis. None of the

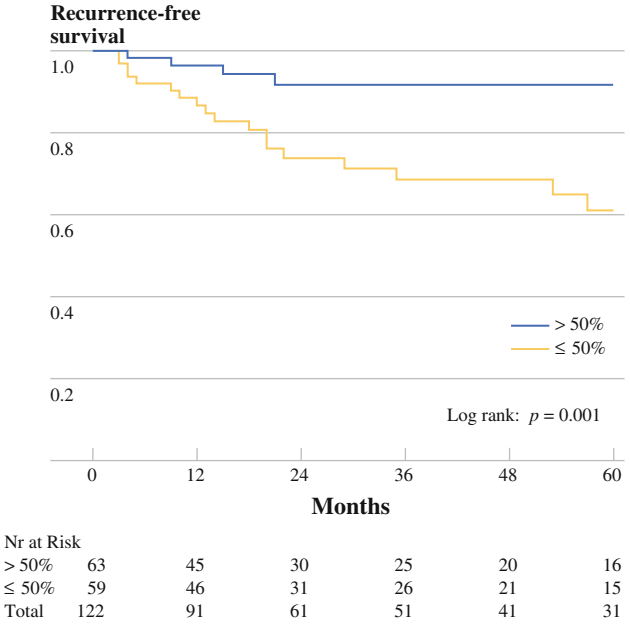

FIG. 3 Local recurrence versus histopathological response

patients were treated with adjuvant systemic chemotherapy or any other treatment modality in the time interval between ILP and resection. Combining these results we could define a group of 43 patients (35%) with R0 resection and >50% tumor necrosis, with a single case of local recurrence. This concerned a patient who was treated for local recurrence. This female, aged 44 years, had no signs of residual vital tumor in the resected specimen. Since the tumor had been small and difficult to locate preoperatively, the completeness of the resection was deemed doubtful. Therefore, RTx was proposed, but refused by the patient. In retrospect, we believe that the tumor was not resected during surgery.

None of the patients with R0 resection and >50% necrosis who were treated for primary STS ($n = 36$) developed local recurrence. Patients with R0 resection but less than 50% necrosis of tumor ($n = 26$) showed recurrence in nine cases (35%).

The local recurrence rate for patients treated with adjuvant RTx was 23%, while patients not treated with RTx had local recurrence in eight cases (16%). Whether patients with R0 resection had RTx was not based on main tumor characteristics (Table 4).

DISCUSSION

Our results suggest that patients with primary and unifocal STS of the extremity, in whom R0 resection is achieved after successful ILP (induction of >50% necrosis), may not benefit from adjuvant RTx. In these patients, the recurrence rate was 0%. Patients treated for recurrence

TABLE 4 R0 resection ± RTx

	RTx	
	No	Yes
Size		
<5 cm	7	5
5–10 cm	11	8
>10 cm	17	21
Trojani grade		
1	5	1
2	14	9
3	16	22
Missing	0	2
Histology		
Liposarcoma	9	7
Synovial sarcoma	4	8
HGPS NOS	7	3
Leiomyosarcoma	4	2
Other (16 types)	11	14
Primary/recurrent		
Primary	26	29
Recurrent	9	5

HGPS NOS high-grade pleomorphic sarcoma not otherwise specified

of STS ($n = 7$), who had R0 resection and >50% tumor necrosis, showed local recurrence in one case.

The overall local recurrence rate in our series was 21%, which is in accordance with several other studies describing ILP as a limb-saving strategy for STS (11–34%), while reported recurrence rates for primarily resectable STS range from 10 to 27%.[5,7,10–18]

A CR rate of 4% seems low compared with the rate of 28% in the multicenter trial published by Eggermont et al. or in comparison with the latest studies of Bonvalot at al. (30%; $n = 100$), Grabellus et al. (15%; $n = 47$), and Pennachioli et al. (41%; $n = 88$).[7,14–16] The discordance is due to selection bias, since we only included patients with limb-sparing surgery after ILP. The vast majorities of patients with MRI-proven CR were not considered for resection and had clinical follow-up for 10 years. Another bias was the exclusion of multifocal tumors in general (Lev–Chelouche, CR = 38, $n = 53$) or Stewart–Treves lymphangiosarcoma (Lans et al., CR = 56%; $n = 16$), which are known to respond well to ILP.[19,20] With the introduction of the use of TNF-α in ILP there was a substantial improvement in treatment for nonresectable extremity STS.[4,5,12,21,22] Nowadays ILP with delayed resection is an established strategy for limb salvage in Europe. Median time span between resection and ILP was 84 days, which was within the range of previous reports (42–117 days).[22,23] Completeness of resection is an important prognostic factor for local recurrence.[14,17,18,24–26] After R0 or R1 resection in patients with over 50% tumor necrosis, a local recurrence rate of only 7% was observed. Of patients with ≤50% necrosis in resection specimen, 33% had recurrence. This highly significant difference suggests that the degree of ILP-mediated tumor necrosis might be an even stronger prognostic factor for local recurrence and supports the findings of Grabellus et al.[14] that improved margin status is achieved after ILP. In patients with R1 resection with >50% necrosis, 19% local recurrence was observed. This is a notable improvement in comparison with the large analysis ($n = 1{,}041$) of Pisters et al. who reported a local recurrence rate of 40% for R1 resection of extremity STS without ILP.[18] Considering the larger proportion of large tumors (>10 cm; 25 vs. 56%) in our series, this result is more remarkable.

It could be argued that determining the degree of necrosis may not necessarily reflect a therapy effect but may be inherent tumor necrosis. Furthermore, macroscopic evaluation is a subjective and therefore imprecise factor. Considering the fact that tumor necrosis in untreated STS is an independent unfavorable prognostic factor, it may be assumed that the necrosis observed in ILP-treated sarcomas is indeed therapy related and prognostically relevant. Second, considering the broad categories defined for tumor necrosis in grading systems (0, <50, and >50%) it is highly unlikely that the degree of necrosis in single cases falls near the cutoff point. Furthermore, in our experience the pattern of necrosis in ILP-treated sarcomas, consisting of large confluent areas of necrosis, is different from the patch pattern of necrosis seen as spontaneous necrosis in untreated sarcomas. Finally, the MRIs that were performed before ILP showed central necrosis in only 7 (12%) of 59 cases with >50% ILP-induced necrosis.

The value of adjuvant RTx after ILP and resection is still unclear. The beneficial effect of irradiation in limb-saving surgery for STS was first demonstrated by Rosenberg et al.[2] Despite reporting a significant decrease in STS local recurrence after irradiation therapy, Yang et al.[27] concluded that, in selected patients with low risk for recurrence, irradiation should not be considered because of important lifetime risk for complications. Other studies claimed that adjuvant RTx in all cases had a significant positive influence in obtaining local control.[10,23]

Complications of RTx should not be underestimated. Hoven-Gonderie et al.[28] reported that two-thirds of all patients experienced serious late toxic problems after combined treatment for STS. Major problems with wound healing and continuous wound infections (8–14%) are described in literature.[29,30] Vascular damage (4–14%) is a common long-term complication of RTx.[6,30,31] Kalman et al.[32] described four cases of long-term vascular side-effects in the axillary artery after mastectomy with adjuvant RTx, 10–27 years after treatment. RTx may cause neuropathy, especially when a boost is given.[28,33]

Although radiation is effective in improving local control, several studies suggest that, after margin-free resection, a subset of patients do not benefit from RTx.[14,34,35] In a prospective study, Pisters et al.[9] reported that patients with T1, R0-resected STS have acceptable long-term local control and may be spared the short- and long-term toxicity of RTx.

In our series, patients were not randomized for adjuvant RTx, so the conclusions based on our findings have to be read with caution. Furthermore, with 36 patients in 18 years, the defined group that can be spared RTx is relatively small. Further studies should be performed to confirm these findings. Nevertheless, our results suggest that patients with R0 resection combined with >50% ILP-induced necrosis may be spared adjuvant RTx. The benefit of adjuvant RTx after ILP followed by limb-sparing surgery for this subset of patients seems limited. The added morbidity, the lack of survival benefit, and the limited effect on local recurrence should be discussed with these patients.

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