Oncological Outcome of Primary Non-Metastatic Soft Tissue Sarcoma Treated by Neoadjuvant Isolated Limb Perfusion and Tumor Resection

JENS JAKOB, MD,[1]* PER-ULF TUNN, MD,[2] ANDREW J. HAYES, MD, PhD,[3] LOTHAR R. PILZ, PhD,[4] KAI NOWAK, MD,[1] AND PETER HOHENBERGER, MD[1]

[1]Division of Surgical Oncology and Thoracic Surgery, Department of Surgery, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany
[2]Department of Orthopedic Oncology, Helios Klinikum Berlin-Buch, Sarcoma Center Berlin-Brandenburg, Berlin, Germany
[3]Sarcoma and Melanoma Unit, Department of Surgery, Royal Marsden Hospital NHS Foundation Trust, London, UK
[4]Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

Background: Isolated limb perfusion (ILP) is an effective limb salvage strategy in patients with advanced soft tissue sarcoma (STS) where surgery alone would result in significant functional morbidity or mandate an amputation. Most previous reports of patients undergoing ILP focus on limb salvage rates rather than local and distant relapse rates. Here, we report the oncological outcome of sarcoma patients treated by ILP and surgery.
Methods: Data were retrieved from prospective ILP databases from two ILP centers following similar ILP techniques and surgical approaches. Only patients with primary, intermediate, or high grade non-metastatic STS were included.
Results: The cohort comprised 90 patients. Median follow-up was 39 months (range 3–165 months). Median tumor size was 11 cm (range 5–34). Twenty of 90 (22%) patients underwent prior debulking surgery outside the centers. Twenty-nine of 90 (32%) had postoperative irradiation. Four of 90 underwent amputation either related to local recurrence or irresectability, 4 of 90 underwent amputation for treatment-related complications. Fifteen of 83 (18%) patients had local recurrences after ILP and limb sparing surgery, 39 of 90 (43%) developed metastatic disease. Twenty-two of 90 (24%) died of disease.
Conclusion: Preoperative ILP and tumor resection resulted in good local control in a cohort of high-risk STS patients.
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KEY WORDS: soft tissue sarcoma; TNF; ILP; local recurrence; neoadjuvant; preoperative

INTRODUCTION

Isolated limb perfusion (ILP) was introduced 1958 as a new modality for the treatment of extremity tumors [1]. During the procedure, the tumor-bearing limb is isolated from the systemic circulation, heated until mild hyperthermia is reached and then anti-tumor drugs are added to the isolated limb circuit. Although it proved effective in patients with advanced in-transit metastases from melanoma, the results of ILP in sarcoma patients with standard cytotoxic drugs were disappointing until the introduction of recombinant tumor necrosis factor alpha (TNF) [2]. TNF is a multifunctional cytokine involved in apoptosis, cell survival and inflammation [3,4]. TNF leads to increased vascular permeability resulting in increased concentrations of cytotoxic drug within the tumor, blood cell extravasation, and selective destruction of tumor-associated vessels by endothelial apoptosis and inflammation [5,6].

The indication for use of TNF in an ILP is locally advanced, limb threatening soft tissue sarcoma (STS) and therefore the most common primary outcome in previous cohort studies was limb salvage rate. A number of ILP cohort studies demonstrated that ILP is an effective induction strategy for locally advanced extremity STS and might allow function preserving operations that might otherwise not have been possible [7–17]. These previous reports, however, did not differentiate between amputation candidates and those who were at risk functional morbidity after tumor resection and irradiation. They also included patients with both, primary and recurrent tumors, and finally they did not report oncological outcome (local and distant relapse rates) [18]. Furthermore, ILP has never been compared to other (neo-) adjuvant treatment strategies such as irradiation; perioperative chemotherapy combined with heat or intensified preoperative chemotherapy in a controlled trial. In the consequence, the role of ILP in multimodal therapy of locally advanced STS still remains unclear.

Here, we present a retrospective cohort study of patients with primary non-metastatic but locally advanced STS only treatable by amputation or in whom traditional limb conserving radical operations and postoperative irradiation would result in severe functional consequences for the limb. All these patients have been treated by preoperative ILP with the intent to perform tumor resection while preserving acceptable function of the limb. The purpose of the study was to evaluate the oncological outcome of this cohort of patients.

PATIENTS AND METHODS

Data Collection

Data were collected from prospectively maintained databases comprising all consecutive sarcoma patients treated by ILP at the

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*Correspondence to: Jens Jakob, MD, Division of Surgical Oncology and Thoracic Surgery, Department of Surgery, University Medical Center Mannheim, University of Heidelberg, Th.-Kutzer-Ufer 1-3, 68137 Mannheim, Germany. Fax: 0049-621-383-1479. E-mail: jens.jakob@umm.de

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participating centers from January 1998 until December 2010. Missing data were retrieved from medical records.

Patient Selection

Patients with intermediate or high grade STS of the extremity were eligible if the tumor was considered either irresectable other than by amputation or resectable only by functionally mutilating surgery. This included patients with very large tumors, multifocal tumors, tumors invading of neurovascular bundles or fixed to bone or a combination of these factors. Only primary STS patients were included. Patients with local recurrence or distal metastases at the time of presentation were excluded from the study. Patients who had undergone unplanned debulking (R2) resections outside the study centers were included. In each case, the tumor and its resectability was judged by one out of three sarcoma surgeons at one of the two participating tertiary referral centers in Germany (Mannheim or Berlin).

Treatment Strategy

Treatment strategy was to perform neoadjuvant ILP with TNF and melphalan and then to perform either a wide or compartmental R0 resection of the tumors 6–10 weeks later. Adjuvant irradiation was not given on a regular basis but considered in case of R1 resections and/or insufficient pathologic response (defined as less than 90% histopathological necrosis of the tumor). In these cases, external beam radiation therapy was given with a dose of 60–66 Gy. No neoadjuvant or adjuvant chemotherapy was given.

Isolated Limb Perfusion

ILP was performed under general anesthesia. After surgical exposure, the major vessels of the tumor-bearing limb were clamped and cannulated and the limb was separated from the systemic circuit by a tourniquet. An oxygenated limb circulation was maintained using a standard cardiopulmonary bypass machine. Hyperthermia was established by heating the isolated circuit, with a targeted tumor temperature of 38–39.5°C. TNF (Beromun®, Boehringer Ingelheim, Ingelheim, Germany) was administered after a stable limb isolated circulation with minimal leakage to the systemic circulation had been established. The TNF dose was 1–2 mg for ILP in the upper limb and 2–4 mg for the lower limb. Melphalan was administered to the limb circulation 15 min after TNF administration. The dose of melphalan for ILP of the upper limb was 13 mg/L of perfused limb volume, and 10 mg/L of perfused limb volume for the lower limb. The total perfusion time was 90 min. The limb was then washed out by perfusing the circuit with hydroxyl ethyl starch to ensure that the limb circulation was free of either melphalan or TNF prior to cannulae removal, vascular repair, and return of the limb to the systemic circulation. Local toxicity of ILP was classified according to Wieberdink et al. [19].

Surgery for Tumor Resection

Surgery to resect the tumor was planned 6–10 weeks after ILP. We aimed to perform en-bloc resections with wide margins (1–2 cm of uninvolved tissue or intact adjacent fascial layer) whenever possible. When the tumor was abutting major vessels (e.g., superficial femoral artery) or motor nerves (e.g., sciatic nerve) the adventitia or epineurium was taken as the margin of resection vascular reconstruction (using autologous vein graft or prosthetic vascular graft) was undertaken only if there was encasement of the vessels. When the tumor was abutting bone, the periosteum was taken en bloc with the tumor as clearance. Plastic reconstruction with pedicled or free flaps was performed when skin involvement was too great for primary skin closure.

Pathologic Analysis

Pathologic analysis included both margin assessment measurement of the extent of pathologic response defined by the extent of tumor necrosis. A macroscopically positive margin was defined as R2 resection. If the tumor extended into the resection margin on microscopic examination, the margin was defined as R1 resection and margins without actual involvement of the resection margin were considered microscopically negative (R0) even if there was a close proximity to the tumor (tumor invading surrounding tissue <1 mm from nearest margin).

Follow-Up

Clinical examination and cross-sectional imaging of the tumor site and lungs were usually performed every 4 months for the first 2 years and every 6 months thereafter. If patients were not seen in the tumor centers, missing follow-up was retrieved by contacting general practitioners.

Analysis

Patient, tumor, and treatment variables are presented descriptively with median values and ranges where appropriate. Survival times were calculated from the date of ILP. Local and distant recurrences were defined by clinical, radiographic, and histological findings. Patients who underwent amputation for treatment-related complications were not included in local disease-free survival analysis. Actual survival statistics were calculated using the method of Kaplan and Meier. Univariate analysis of survival using the log-rank test was performed to determine the relation between the occurrence of local recurrence, metastases, death and the following factors: age (<65 years vs. ≥ 65 years), tumor site (upper vs. lower extremity), tumor size (<10 cm vs. ≥ 10 cm), tumor grade (2 vs. 3), resection margin (R0 vs. R1), necrosis in the resected specimen ($\geq 90\%$ vs. $<90\%$), postoperative irradiation (yes vs. no), and local recurrence (only for survival, yes vs. no), respectively. Hazard ratios were calculated using the maximum likelihood estimation method. Cox-regression multivariate analyses were performed for the occurrence of metastases and death. Input probability was chosen at 0.25 and the stay was limited by probability 0.15. Hazard ratios of the multivariate model were given only for those parameters, which stayed in the model and χ^2 test was used for those parameters. SAS statistical software (SAS 9.2 TS Level 2M3, 2012, SAS Institute, Inc., Cary, NC) was used for statistical analysis.

RESULTS

Patients

Ninety patients were included in the study. Table I summarizes patient and tumor characteristics in detail. The median age was 55 years at the time of ILP. We treated 16 of 90 (18%) tumors of the upper limb and 74 of 90 (82%) tumors of the lower limb. The median tumor size was 10 cm. The most common histological subtype was STS not otherwise specified. Most tumors were high grade. Twenty of 90 (22%) patients underwent prior R2 resection outside the study centers before ILP.

Treatment and Pathologic Response

Eighty-six of 90 (96%) underwent limb sparing tumor resection after ILP. Four of 90 (4%) underwent amputation after ILP (see below). Sixteen of 90 (18%) patients had an R1 and 70 of 90 (82%) an R0 resection. Tumor response measured as fraction of non-viable tumor in the resected specimen revealed necrosis of 90% or more in 33 of 90 (37%) patients. Twenty-nine of 90 (32%) patients received postoperative external beam radiotherapy. Twenty of 90 (22%) patients required pedicled or free flaps and 11 of 90 (12%) patients

TABLE I. Patient and Treatment Characteristics

N		90 (100%)
Age	Median (range), years	55 (16–84)
Site	Arm	16 (18%)
	Leg	74 (82%)
Size	Median (range), cm	10 (5–34)
Histology	NOS	35 (39%)
	Liposarcoma	17 (19%)
	Synovial sarcoma	11 (12%)
	Leiomyosarcoma	7 (8%)
	Myxofibrosarcoma	7 (8%)
	Other	13 (14%)
Grade	2	23 (26%)
	3	67 (74%)
Prior R2 resection	Yes	20 (22%)
	No	70 (78%)
Response to ILP	≥90% necrosis	33 (37%)
	<90% necrosis	48 (53%)
	Not available	9 (10%)
Resection margin	R0	74 (82%)
	R1	16 (18%)
Adjuvant RTX	Yes	29 (32%)
	No	61 (68%)
Local recurrence	N	16 (18%)
Distant metastases	N	39 (43%)
Dead of disease	N	22 (24%)
Amputations	N	8 (9%)
Follow-up	Median (range), months	39.5 (3–165)

required vascular reconstruction. Epineurectomy of the sciatic nerve or motor nerve resection (tibial or fibular nerve) was performed in 10 of 90 (11%) patients (Table I).

Toxicity of ILP, Surgical Complications After Tumor Resection and Amputations

Most patients experienced mild to moderate local toxicity after ILP (Table II). Four of 90 (4%) had severe toxicity that necessitated amputation in two cases. Twenty-two of 86 (26%) patients had postoperative complications after limb sparing tumor resection following ILP. Re-operation, re-intervention, or deep wound packing was necessary in these cases. Complications included occlusion of vascular grafts (2), hematomas (n = 2), wound infections or dehiscences (n = 10), and lymph fistulas or wound seromas (n = 8).

Amputation of the tumor-bearing limb was performed in 8 of 90 (9%) patients. In detail, the reason to perform amputation surgery was compartment syndrome after ILP (n = 1), severe infection of a necrotic tumor after ILP (n = 1), occlusion of a vascular graft after ILP and limb sparing tumor resection with vascular reconstruction (n = 2), unresectable tumor after ILP (n = 2), broad positive resection margin with almost absence of necrosis in the resected specimen (n = 1), and local recurrence (n = 1).

TABLE II. Local Toxicity After Isolated Limb Perfusion

Wieberdink grade	n (%)
No reaction	18 (20)
Slight erythema and/or edema	57 (63)
Considerable erythema and/or edema, disturbed mobility	11 (12)
Extensive epidermiolyses and/or damage to deep tissue causing definitive functional deficits and/or compartment syndrome	2 (2)
Reaction that may necessitate amputation	2 (2)

Oncological Outcome and Statistical Analysis

Fifteen of 83 (18%) patients developed local recurrence after ILP and successful limb sparing surgery, the estimated 2- and 5-year local recurrence-free survival rates were 86% and 78%, respectively (Fig. 1). Thirty-nine of 90 (43%) patients developed metastatic disease. The estimated 2- and 5-year distant metastasis-free survival rates were 63% and 55% (Fig. 2), respectively. Ten of 90 (11%) patients developed local recurrence and metastatic disease. Twenty-two of 90 (24%) patients died of disease. Estimated 2- and 5-year disease-specific survival rates were 89% and 69%, respectively (Fig. 3). Results for the HR in the univariate case and of the Cox-regression analyses are summarized in Table III.

DISCUSSION

We report the results of a retrospective cohort study of 90 patients with high-risk primary nonmetastatic but locally advanced STS treated by ILP and tumor resection at two German sarcoma centers. In all patients, we aimed to perform tumor resection after ILP induction therapy. All patients had Grade 2 or 3 tumors and median tumor size was

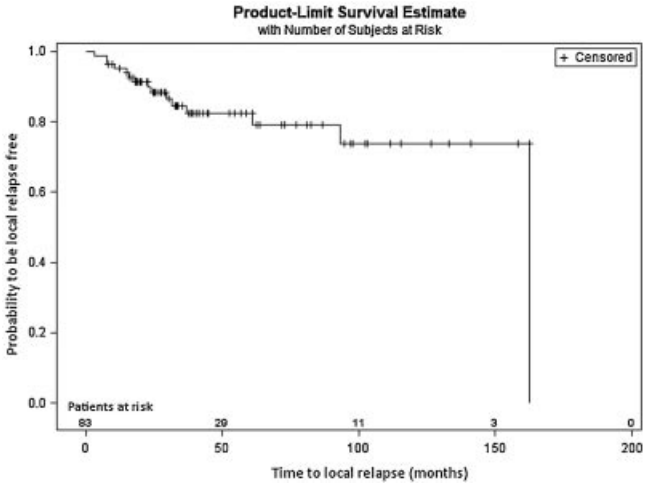

Fig. 1. Kaplan–Meier plot of local recurrence-free survival.

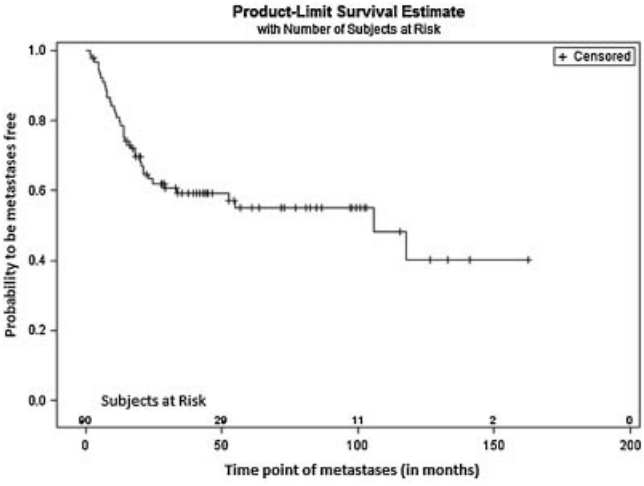

Fig. 2. Kaplan–Meier plot of metastases-free survival.

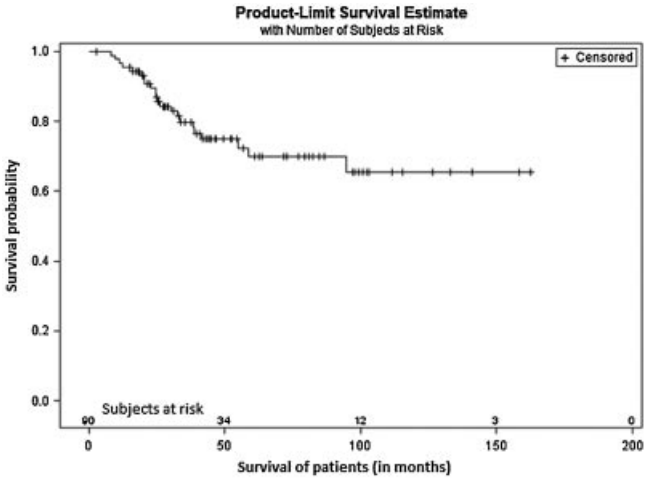

Fig. 3. Kaplan–Meier plot of disease-specific survival.

10 cm. Twenty-two of 90 patients (24%) had undergone inadequate surgery before ILP outside the centers. Systemic chemotherapy was not used and postoperative irradiation was only administered to patients who underwent either R1 resection or had no response to ILP or both. At both sarcoma centers, this strategy was generally used for patients with sarcomas who were treatable only by amputation or surgery that would have major functional consequences. This approach resulted in a good 2-year local recurrence-free survival rate of 86%. Two-year metastasis-free and disease-specific survival rates were 63% and 89%, respectively, which is to be expected in this patient cohort with large, intermediate, and high grade tumors.

Outcome after ILP has been described nonuniformly in the past. In fact, we are aware of only two cohort studies documenting oncological outcome of primary STS after ILP. Deroose et al. [16] summarized the experience of the Rotterdam ILP center comprising 208 STS patients who underwent ILP and tumor resection reporting an estimated 5-year local disease-free survival rate of patients with primary M0 STS (n = 134) of 73%. Hoven-Gondrie et al. [11] described the outcome of patients treated at the Groningen ILP center. Of 98 patients who underwent ILP, 87 had primary STS. The estimated 5-year local recurrence-free survival rate of patients who underwent ILP and resection of that had a complete remission after ILP (n = 71) was 87%. In both cohorts, the local progression rate of patients who underwent ILP for local recurrence was greater compared to that in primary M0 STS. All other cohort ILP studies included primary and recurrent tumors without exact differentiation between the two groups [7–10,12–15,17]. Furthermore, the authors frequently chose "limb salvage" as primary end-point and included patients who were candidates for "functional amputation". Although the selection criterion "functional amputation" and the outcome parameter "limb salvage" may be adequate to describe the indication and outcome of ILP, these terms are not well-defined and hardly ever used with regard to other treatment modalities, which makes comparison of ILP to other treatment strategies difficult. Therefore, we chose to report the more standard oncological outcomes of local disease-free, metastasis-free, and disease-specific survival in this study.

Standard treatment of non-metastatic STS is resection combined with radiation therapy [20,21]. Randomized controlled trials evaluating brachytherapy and external beam radiation in extremity STS resulted 5-year local recurrence-free survival rates of 89–92% [22,23]. In high-risk STS, there is a rationale for preoperative or postoperative chemotherapy

TABLE III. Univariate and Multivariate Analyses of Overall Survival With Hazard Ratios (HR) and 95% Confidence Intervals

	Univariate analysis			Multivariate analysis[a]		
Factors	HR	95% CI	*P*-value*	HR	95% CI	*P*-value**
Local recurrence						
Upper extremity	**4.893**	**1.689–14.177**	**0.0012**			
Age >65 years	1.952	0.707–5.387	0.1885			
Size ≥10 cm	0.427	0.152–1.199	0.0959			
Grade 3	0.745	0.253–2.198	0.5930			
R1 resection	1.236	0.392–3.896	0.7166			
Necrosis <90%	**0.217**	**0.047–1.003**	**0.0322**			
Irradiation	1.212	0.414–3.554	0.7252			
Metastases						
Upper extremity	**1.480**	**0.676–3.239**	**0.3231**	**2.786**	**1.182–6.565**	**0.0191**
Age>65 years	0.932	0.468–1.856	0.8409			
Size ≥10 cm	**1.999**	**0.994–4.021**	**0.0474**	**2.657**	**1.237–5.706**	**0.0122**
Grade 3	0.958	0.472–1.946	0.9067			
R1 resection	**0.348**	**0.123–0.980**	**0.0363**			
Necrosis <90%	0.709	0.350–1.434	0.3355			
Irradiation	1.119	0.574–2.180	0.7408			
Survival						
Upper Extremity	0.882	0.260–2.990	0.8400			
Age >65 years	0.725	0.284–1.854	0.5003			
Size ≥10 cm	1.889	0.739–4.829	0.1766			
Grade 3	0.863	0.350–2.130	0.7492			
R1 resection	**0.154**	**0.021–1.142**	**0.0349**	**0.211**	**0.028–1.570**	**0.1287**
Necrosis <90%	0.543	0.205–1.438	0.2121			
Irradiation	1.445	0.605–3.450	0.4051			
Local recurrence	0.649	0.192–2.194	0.4831			

[a]Multivariate analysis was not performed for local recurrence because the number of local recurrences was too low.
*P-value of the log-rank test.
**P-value of the χ^2-test (maximum likelihood estimation).

because of the high incidence of metastatic disease. Gronchi et al. [24] have reported a 5-year local progression-free survival of 94% for patients undergoing preoperative chemotherapy, surgery, and postoperative radiation therapy. Issels et al. [25] performed a randomized controlled trial evaluating the addition of regional hyperthermia to chemotherapy. The 2- and 4-year local progression-free rates of extremity STS treated with heat, chemotherapy, surgery, and irradiation were 92% and 82%, respectively. The results of the above mentioned studies may not be comparable to the results of ILP cohorts because those may have selected the most challenging cases. Nevertheless, we may state here that ILP as induction treatment does not seem to be inferior to other treatment strategies.

The key question is which role ILP will play in the future of multimodal treatment. What will be the indication for performing an ILP? On the one hand, one can argue that as long as other treatment modalities are available, ILP with TNF should only be performed if the very next necessary treatment was amputation. On the other hand, ILP is obviously an effective modality [20,21]. Currently, no comparative data exist describing extend of surgery, functional, or oncological outcome after ILP and resection versus standard treatment. A comparative trial would be especially interesting for those patients who are not amputation candidates but in whom standard therapy would result in severe functional consequences. Obstacles for such a trial are the low incidence of limb threatening STS, the advent of new tailored treatment strategies and the low availability of ILP [26]. Another reason is that a large proportion of patients with large, high grade STS will develop metastases and die from disease. The most important need for these patients is to prevent overt metastatic disease. Distant disease control will be most probably achieved by improved systemic treatment that may also lead to excellent local disease control. It is possible that novel systemic options may be utilized in conjunction with ILP in further studies.

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