Outcome and Prognostic Factor Analysis of 217 Consecutive Isolated Limb Perfusions with Tumor Necrosis Factor-α and Melphalan for Limb-Threatening Soft Tissue Sarcoma

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BACKGROUND. Extensive and mutilating surgery is often required for locally advanced soft tissue sarcoma (STS) of the limb. As it has become apparent that amputation for STS does not improve survival rates, the interest in limb-preserving approaches has increased. Isolated limb perfusion (ILP) with tumor necrosis factor-α (TNF) and melphalan is successful in providing local tumor control and enables limb-preserving surgery in a majority of cases. A mature, large, single-institution experience with 217 consecutive ILPs for STS of the extremity is reported.

METHODS. At a prospectively maintained database at a tertiary referral center, 217 ILPs were performed from July 1991 to July 2003 in 197 patients with locally advanced STS of the extremity. ILPs were performed at mild hyperthermic conditions with 1-4 mg of TNF and 10-13 mg/L limb-volume melphalan (M) for leg and arm perfusions, respectively.

RESULTS. The overall response rate was 75%. Limb salvage was achieved in 87% of the perfused limbs. Median survival post-ILP was 57 months and prognostic factors for survival were Trojani grade of the tumor and ILP for single versus multiple STS. The procedure could be performed safely, with a perioperative mortality of 0.5% in all patients with no age limit (median age, 54 yrs; range, 12-91). Systemic and locoregional toxicity were modest and easily manageable.

CONCLUSION. TNF+M-based ILP can provide limb salvage in a significant percentage of patients with locally advanced STS and has therefore gained a permanent place in the multimodality treatment of STS. ***Cancer* 2006;106:1776–84.**

KEYWORDS: isolated limb perfusion, soft tissue sarcoma, TNF, melphalan.

In the US, 8680 new cases of soft tissue sarcomas (STS) are diagnosed annually, and approximately 60% of these tumors occur in the extremity.[1] Although the propensity of the tumor to develop systemic metastases is the primary cause of the high disease-specific mortality rate (up to 50%), the extremity tumors are often large at time of presentation, causing a local management problem.[1] The local situation in the limb may require extensive and mutilating surgery (± radiotherapy), which can cause severe disability of the limb, whereas in some 10% of cases amputation may be inevitable. With the emergence of evidence that amputative surgery does not improve survival,[2–4] the tendency to perform more limb-preserving surgery has led to the exploration of isolated limb perfusion (ILP) as

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a procedure enabling limb salvage at time of surgery in cases of primarily unresectable STS.

ILP was fist described by Creech et al. in 1958[5] and since then primarily melphalan has been used as the cytostatic drug in patients with melanoma in-transit metastases. In contrast to high response rates in melanoma patients, the results in STS patients were uniformly disappointing.[6,7] The introduction of tumor necrosis factor-α (TNF) in ILP by Lienard et al.[8] changed this situation dramatically, as they reported not only high response rates in 13 melanoma patients, but also in 4 patients with advanced extremity STS. This led to multicenter studies evaluating response and limb-salvage rates using TNF-based ILPs with or without interferon-gamma, showing consistently overall response rates of 75% to 85% and limb salvage in a similar percentages of the patients.[9,10] These results led to the approval of TNF in Europe.[11] At present, TNF-based ILP for extremity STS is used as induction biochemotherapy to obtain local control and to make limb-sparing surgery possible. Here we report on the mature results of a large single-center experience of 217 consecutive ILPs with TNF and melphalan (TM-ILPs) for locally advanced STS.

MATERIALS AND METHODS

Patients

From July 1991 to July 2003, 217 TM-ILPs were performed in 197 patients for locally advanced STS. Fourteen patients underwent a second ILP after recurrence of the tumor in the limb; 2 patients had 3 ILP procedures. In 4 patients (1 with Stewart-Treves lymphangiosarcoma, 2 with Kaposi sarcoma, and 1 with neurofibrosarcoma), a second ILP procedure was performed on the other leg because of bilateral disease. Thus, a total of 201 limbs were treated with an ILP. There were 101 men and 96 women, with a median age at the time of ILP of 54 years (range, 12-91 yrs). Patient and tumor characteristics are summarized in Table 1. All patients were candidates for amputation of the limb, as resection of the tumor was impossible, or only possible at the cost of severe functional morbidity, due to either fixation of the tumor to neurovascular structures or bone, multifocality of the tumor, or location of the tumor in a previously irradiated area without the possibility to perform a complete radical resection. Median follow-up of all patients was 22 months (range, 0.1-130).

TABLE 1
Patient and Tumor Characteristics of 217 TM-ILPs in 197 Patients

	N	%
Gender		
Female	108	50
Male	109	50
Age		
≤ 50	93	43
> 50	124	57
Size		
< 5 cm	67	31
5–10 cm	58	27
> 10 cm	92	42
Trojani grade		
1	41	19
2	60	28
3	116	53
Site		
Upper arm	31	14
Lower arm	29	13
Upper leg	108	50
Lower leg	49	23
Histology		
Liposarcoma	31	14
Synovial Sarcoma	34	16
MFH	34	16
Leiomyosarcoma	18	8
Desmoid/Agg Fibro	12	6
St-T/Kaposi sarcoma	23	11
Other (16 tumor types)	65	30
Primary/recurrent		
Primary	132	61
Recurrent	85	39
Previous treatment		
None	161	74
XRT	34	16
CT	21	10
ILP	11	5
Single/multiple		
Single	153	71
Multiple	64	29
Post- ILP treatment		
None	145	67
XRT	59	27
CT	10	5
XRT + CT	3	1

TM-ILP: isolated limb perfusion with TNF and melphalan; MFH: malignant fibrous histiocytoma; Agg Fibro: aggressive fibromatosis; St-T: Stewart-Treves lymphangiosarcoma; XRT: radiotherapy; CT: chemotherapy.

Treatment

Patients underwent an ILP via the axillary ($n = 25$), brachial ($n = 35$), iliac ($n = 94$), femoral ($n = 38$), or popliteal ($n = 25$) approach. ILP technique has been described previously.[9,10] Briefly, recombinant human TNF (Boehringer Ingelheim, Ingelheim/Rhein, Germany) and the cytostatic drug melphalan (L-PAM, Alkeran, Burroughs Wellcome, London, UK), obtained as a sterile powder, were dissolved aseptically using solvent and diluents (Burroughs Wellcome). Isolation of the blood circuit of a limb was achieved by clamping and cannulation of the major artery and vein, connection to an oxygenated extracorporeal circuit, and application of a tourniquet to compress the re-

maining collateral vessels. TNF was injected as a bolus into the arterial line, provided limb tissue temperature had reached 38°C. Melphalan was administered after 30 minutes at limb temperatures between 38 and 39.5°C. The administration of melphalan changed during the studied period from injection as a bolus (1991-1996) to infusion by pump over a period of 20 minutes (1996-present), because of reports that melphalan peak concentration is correlated with regional toxicity.[12] ILP consisted of a 90-minute perfusion with 1-3 mg (arm) or 1-4 mg (leg) TNF, and a 10-mg/L (leg) or 13-mg/L (arm) volume of melphalan at mild hyperthermia (tissue temperatures of maximally 39.5°C in the leg and 38.5°C in the arm). Median dose of melphalan was 70 mg (mean, 73.3; range, 0-160); median dose of TNF was 4 mg (mean, 3.5; range, 1-4). In the first 25 ILPs, performed between 1991 and 1994, interferon-γ (IFN) was added to the schedule according to trial prescriptions consisting of the subcutaneous injection of 0.2 mg IFN on days -2 and -1 before the ILP and the injection of 0.2 mg IFN during the ILP procedure into the arterial line before the administration of TNF. During the procedure, continuous leakage monitoring was performed by using a precordial scintillation probe to detect leakage of radiolabeled albumen injected into the perfusion circuit. At the end of the ILP, the limb was washed out with at least 1 L (arm) up to 4 L (iliac perfusion) of physiologic saline solution and 6% dextran 70 (Macrodex Pharmacia, Uppsala, Sweden). ILPs were performed under general anesthesia and normally took 2.5 to 4 hours. Median hospital stay of the patients was 8 days (mean, 12; range, 2-136).

Response Evaluation and Toxicity

Clinical response evaluation was performed 2, 4, 8, and 12 weeks after ILP and thereafter every 3 months for the first year both by clinical examination and by magnetic resonance imaging (MRI) (4-6 and 8-12 wks after ILP, and thereafter every 3-6 mos),[13] and reported according to World Health Organization (WHO) criteria. In 130 patients the histologic response could be assessed and in these patients response rates were adjusted if the pathologic response (complete response [CR] if 100% necrosis, partial response [PR] if 50% to 99% necrosis, and no change [NC] if $<$ 50% necrosis) differed from clinical response. New lesions or growth of the tumor at first response evaluation is reported as progressive disease (PD), and if occurring during follow-up, as local progression.

Acute local toxicity of the ILP procedure was classified according to Wieberdink et al.[14]: (I) no reaction; (II) slight erythema or edema; (III) considerable erythema or edema with some blistering, slightly disturbed motility permissible; (IV) extensive epidermolysis or obvious damage to the deep tissues, causing definite functional disturbance, and threatening or manifest compartmental syndrome; and (V) reaction that may necessitate amputation. Systemic toxicity is reported according to WHO criteria.

Statistical Evaluation

Overall survival (OS) and time to local/systemic progression (TTLP/TTSP) were defined as time from ILP to death, local progression, or systemic progression, respectively, and estimates were made using the method of Kaplan and Meier. We evaluated the prognostic value of some baseline categories on overall response (CR or PR) achievement using the Fisher exact test for univariate analysis and logistic regression for multivariate analysis. A log rank test and Cox regression were used for TTLP, TTSP, and OS. Based on previous reports on prognostic factors in patients with extremity STS,[15,16] we chose to evaluate gender and age of the patient, size, Trojani grade,[17] and histology of the tumors and presentation with recurrent disease at time of ILP. We added previous irradiation therapy and presence of multifocal tumors to these baseline categories, as these conditions are often present when ILP treatment is considered. After univariate analysis, all these factors were included in a multivariate model. We used a stepwise backward algorithm in order to exclude factors without prognostic value starting with the factor with the highest P-value, to $P < .05$. All tests were done at a significance level of 5%.

RESULTS

Tumor Response

Of 217 TM-ILPs for STS, a clinical complete response was obtained in 38 (18%) ILPs, PR in 111 (51%) ILPs, NC in 62 (29%), and PD in 4 (2%) ILPs. Clinical response was not assessed in 2 patients (1%, 1 patient died shortly after ILP, 1 reason unknown). In 130 patients (60%), ILP had made a complete resection of the tumors possible (71% in patients with single tumors, 34% in patients with multiple tumors; Fig. 1). In these patients (and in a minority of patients, especially with multiple sarcomas, in whom a core biopsy was performed to assess histologic response), the final outcome was adjusted according to the necrosis percentage found on histologic evaluation. Final outcome, therefore, was: 56 (26%) CR, 106 (49%) PR, 49 (23%) NC, and 5 (2%) PD, resulting in an overall response percentage of 75%. One patient died 3 days after ILP, so the final response to ILP could not be assessed. On univariate analysis, the presence of multiple tumors ($P = .006$) and ILP for Stewart-Treves lymphangiosar-

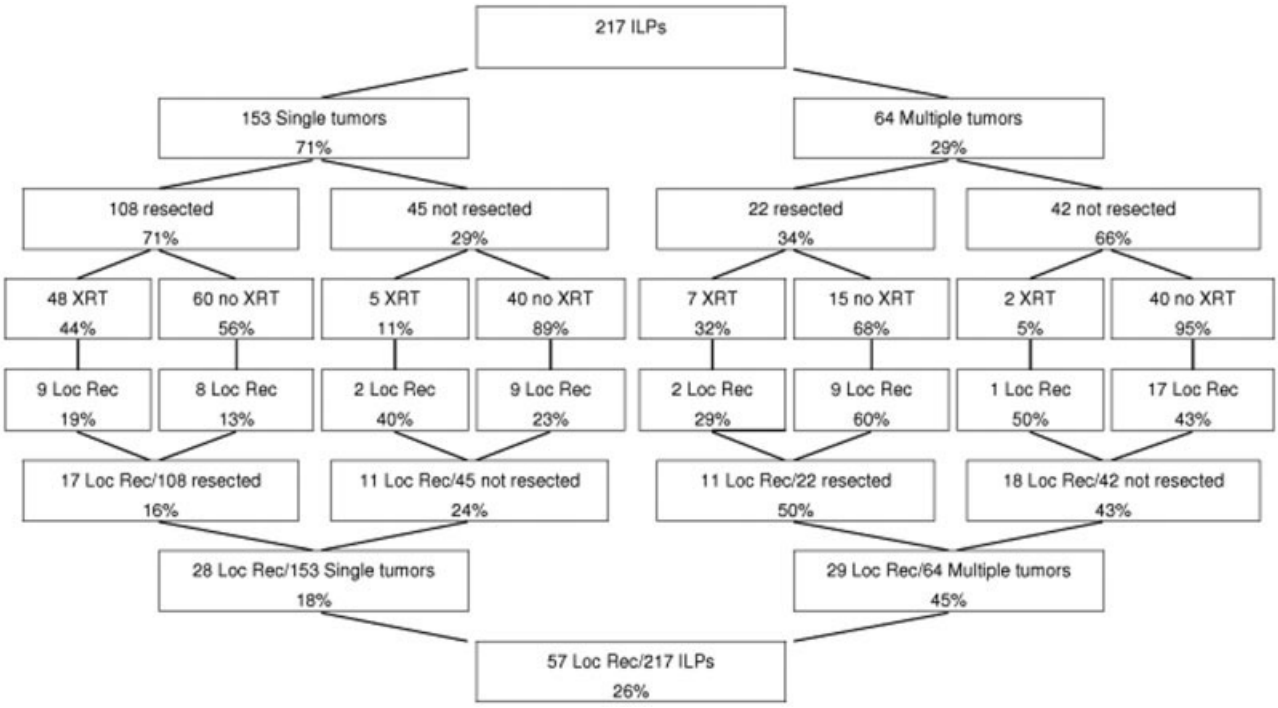

FIGURE 1. Flow-chart of management after ILP and its implications for local control. ILP: isolated limb perfusion; XRT: radiotherapy; Loc Rec: local recurrence.

TABLE 2
Univariate Analysis of Clinical Prognostic Factors for CR/PR Achievement, Local Progression, Systemic Progression, and Survival

Variable	CR/PR	Local Progression	Systemic Progression	Survival
Gender	NS	NS	NS	NS
Age	NS	NS	NS	NS
Size of the tumor	NS	P < .001	NS	NS
Trojani grade	NS	NS	*P* = .001	*P* = .020
Histology	*P* = .041*	*P* < .001	*P* = 0.006	NS
Primary/recurrent	NS	*P* = .009	NS	NS
Previous XRT	NS	*P* = .011	NS	NS
Single/multiple tumors	*P* = 0.006	*P* < .001	NS	NS

CR: complete response; PR: partial response; XRT: radiotherapy NS: not significant.
* Overall, histology is a borderline significant prognostic factor for response (*P* = .041), but Stewart-Treves lymphangiosarcoma/Kaposi sarcoma is associated with higher response rates (*P* = .002, see text).

coma or Kaposi sarcoma (*P* = .002) were both related with a significantly better response rate (Table 2). Only the latter remained statistically significant in multivariate analysis. There were no histologic tumor types that were significantly worse or did not respond to ILP. After ILP (± tumor resection), 72 patients received adjuvant therapy consisting of radiotherapy in 59 patients, systemic chemotherapy in 10 patients, and a combination of both in 3 patients.

Limb Function

Limb function of the 201 perfused limbs was assessed in 194 (97%) cases and was without functional loss in 145 (72%) limbs, mildly disturbed in 14 (7%), and severely diminished leading to the use of crutches in 9 (4%) limbs. An amputation could not be avoided in 26 perfused limbs (13%). Fifteen patients had an insufficient clinical response (PD/NC) and underwent immediate amputation. Notably, histologic examination of the amputated limb showed PR in 3 of these patients. Nine amputations had to be performed due to rapid progression (2-9 months) after ILP: 5 after PR and 4 after CR. One patient with a histologic PR but with sufficient local control of a synovial sarcoma of the lower leg developed a late local progression after 36 months, necessitating amputation. One other pa-

tient had to undergo a late amputation: delayed resection of a 100% necrotic malignant fibrous histiocytoma of the lower leg caused osteomyelitis because of a period of inadequate soft tissue coverage of the bone, resulting in a pathologic fracture 17 months after ILP. Two patients had to undergo leg amputation during the follow-up period due to preexisting vascular disease. Although the ILP procedure might have altered the course of the vascular disease in these patients, these amputations were not considered Wieberdink V local toxicity nor tumor-related amputations for analysis in this study.

Leakage and Toxicity

Leakage of TNF and melphalan, as reflected by the leakage of radioactively labeled albumen to the systemic circulation, was absent or minor (<10%) in 192 (88%) ILPs. Median leakage was 0%, mean 2.6%. Six procedures were complicated by significant leakage of > 20% (21%, 23%, 25%, 29%, 34%, 64%), but no serious systemic toxicity occurred in these patients and none of the patients required an intensive-care stay of more than 24 hours. The 64% leakage in 1 ILP was attributable to snapping of the tourniquet 35 minutes after administration of TNF, just after adding melphalan to the perfusate. All other high-leakage ILPs were terminated when leakage exceeded 20%, but melphalan circulation time was at least 45 minutes in all these cases.

Local toxicity of the procedure was absent or mild (Wieberdink I-II) in 165 cases (76%), Wieberdink III in 45 patients, and Wieberdink IV in only 4 patients. No treatment-related amputation had to be performed. In 3 patients local toxicity could not be assessed (1 rapid amputation due to PD, 1 rapid death, and 1 reason unknown). Systemic toxicity was restricted to a transient rise in core temperature > 40°C in 8 patients, lasting over 24 hours in 1 patient. No toxic shock-like syndrome necessitating the use of vasopressors occurred. One 91-year-old patient with significant arteriosclerosis and an excessively large high-grade liposarcoma of the leg developed a thrombosis of the mesenteric artery and died 3 days post-ILP (perioperative mortality 0.5%).

Local Progression

Local progression of STS in the limb was observed after 57 (26%) ILPs. If progression occurred, median time to local progression was 8.9 (range, 1-54) months. Of these local failures, 28 occurred after resection of the tumor remnants post-ILP and are therefore true local recurrences (28 in 130 resections: 22%). Twenty-nine patients developed new lesions after ILP, or late regrowth of the known lesion(s), but in these patients the tumor was not resected after ILP (29 in 87 cases: 33%). The implications for local control of the management of the tumors post-ILP (resection, post-ILP irradiation) are outlined in Figure 1.

Univariate prognostic factors for developing a local recurrence included size and histology of the tumor, ILP for recurrent STS, previous radiotherapy, and the presence of multiple tumors. Prognostic factors for local progression after multivariate analysis were: tumor type (synovial sarcoma, malignant fibrous histiocytoma, leiomyosarcoma, and Stewart-Treves/Kaposi associated with higher local recurrence rates) and multiple sarcomas at presentation ($P < .001$). Prognostic factors are listed in Tables 2 and 3.

Systemic Progression

We observed systemic metastases after ILP in 92 patients (42%). In those patients who developed systemic metastases, they became manifest after a median period of 4.6 (range, 0-80) months. Notably, 34 patients (16%) had Stage IV disease (metastases present) at the time of ILP. On univariate analysis, Trojani grade ($P = .001$) and histology ($P = .006$) were significant prognostic factors for the development of systemic metastases. On multivariate analysis, age of the patient, size, grade, and histology of the tumor and the presence of multiple tumors all were significant prognostic factors (Tables 2, 3).

Survival

The overall, 5-year actuarial survival rate was 49%; median survival was 57 months. Survival after ILP for extremity STS is shown in Figure 2. The prognostic factor for overall survival after ILP was Trojani grade (both on uni- and multivariate analysis, Fig. 2b). Despite the fact that patients with multiple tumors had lower, but not statistically significant lower, survival rates than patients with single tumors (53% vs. 39% at 5 years; $P = .152$), this factor was significant on multivariate analysis ($P = .015$; Tables 2, 3; Fig. 2c).

DISCUSSION

The current study of 217 TM-ILPs in a single center setting shows that limb salvage can be achieved in a large percentage of patients by combining induction biochemotherapy with marginal resection of the tumor. Even by ILP alone, significant tumor response rates can be obtained, providing long-lasting local control in patients with large extremity STS and a limited life expectancy.

Response and Limb Function

The overall response rate in this series of 75% is in accord with previous reports on TM-ILPs for STS, with

TABLE 3
Multivariate Analysis on Local Progression, Systemic Progression, and Survival

	Local Progression		Systemic Progression		Survival	
Variable	**HR**	***P***	**HR**	***P***	**HR**	***P***
Age						
≤ 50			1			
> 50			0.6	.039		
Size of the tumor						
≤ 5 cm			1			
5–10 cm			1.5	NS		
≥ 5 cm			2.4	.005		
Trojani grade						
1			1		1	
2			2.1	NS	2.5	NS
3			3.2	.030	3.6	.003
Histology						
Lipo	0.8	NS	0.5	NS		
Synovial	4.9	.002	1.4	NS		
MFH	5.0	.001	0.7	NS		
Leio	4.6	.004	0.7	NS		
Desmo	0.7	NS	0.0	*		
St-T/Kaposi	2.9	.036	0.2	.005		
Other	1		1			
Single/multiple						
Single	1		1		1	
Multiple	4.6	< .001	2.4	.001	1.7	.015

HR: hazard ratio; Lipo: liposarcoma; synovial: synovial sarcoma; MFH: malignant fibrous histiocytoma; Leio: leiomyosarcoma; Desmo: desmoid/aggressive fibromatosis; St-T: Stewart-Treves lymphangiosarcoma; NS: not significant.

* Perfect prediction: no systemic progression in desmoid tumors.

response rates varying from 63% to 91%.[9,10,18–20] With only 26 amputations in 201 perfused limbs, the limb salvage rate was 87%, which compares to a smaller series reported in the literature.[9,10,18–20] This is in fact an important observation, as we know that a large proportion of the patients will eventually develop systemic metastases and succumb to their disease. However, the local problem of a large tumor in the extremity can be managed with ILP, even if no resection is performed or if the response is not complete. As TNF acts on tumor-associated vasculature by destroying the vessels[21] and increasing the uptake of melphalan in the tumor in the preclinical tumor models,[22] one could expect that response rates would be better in well-vascularized (high-grade) and large tumors. We could not demonstrate such a preferential effect in this study, nor could we identify a negative effect in tumors that lack extensive vascularization. The only prognostic factors for response were ILP for multiple tumors and ILP for Stewart-Treves lymphangiosarcoma or Kaposi sarcoma. As these factors are highly related, only the latter remained statistically significant on multivariate analysis. We know from previous reports that response rates in these tumors indeed are very high (87% to 100%[23,24]), presumably as these are small and highly vascularized tumors, and therefore we speculated that the clinical situation in these tumors resembles more the melanoma than the STS situation.[25]

Progression and Survival

Local tumor recurrence in this study occurred in 26%, which again is in accord with results from the literature on ILP, ranging from 11% to 45%.[9,10,18–20] This is slightly higher than the 10% to 20% local recurrence rate reported in the literature for all STS of the extremity,[26–28] supposedly because a large percentage of the patients qualifying for ILP present with recurrent disease (39% in this study), which is a known adverse prognostic factor for local recurrence.[15] Systemic metastases developed in 42% of the patients and the actuarial 5-year overall survival rate was 49%. We determined that Trojani grade and leiomyosarcoma and synovial sarcoma were prognostic factors for systemic recurrence, and that Trojani grade was a prognostic factor for survival, which is virtually equal with known data.[15,16] The fact that size of the tumor is not a prognostic factor for survival in our study, but on multi-

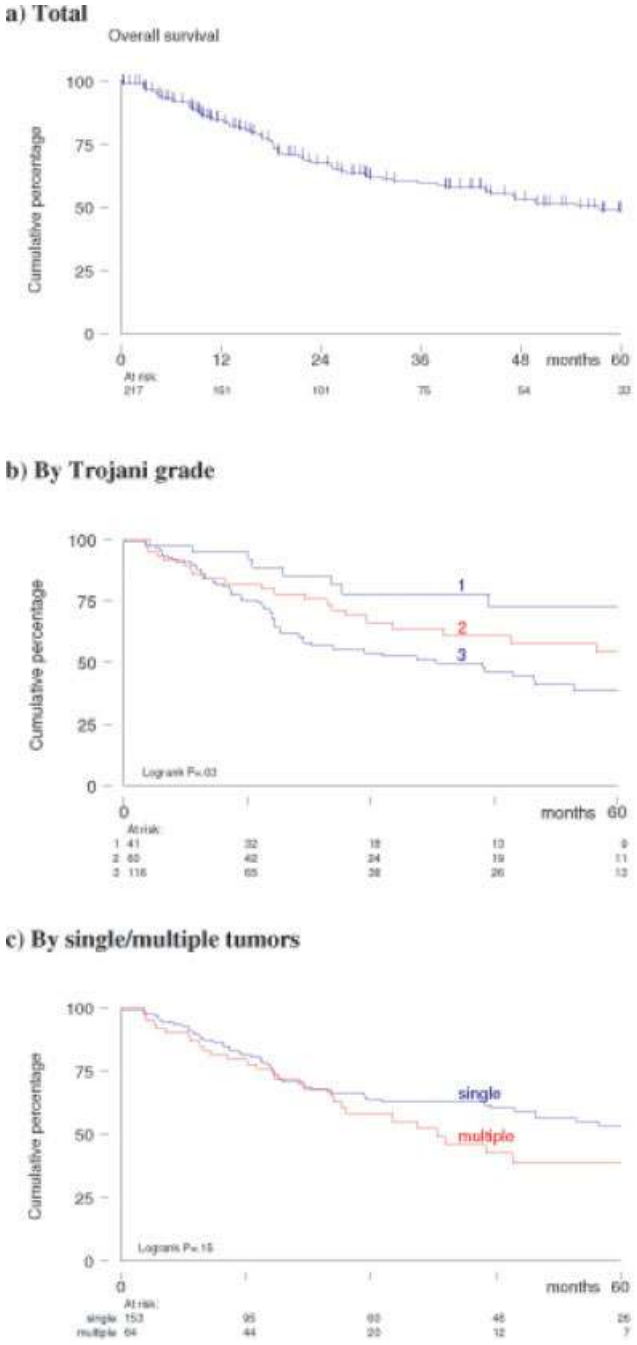

FIGURE 2. Overall survival. (a) Total; (b) by Trojani grade; and (c) by single/multiple tumors. X-axis: time in months; Y-axis: cumulative percentage.

variate analysis presentation with multiple tumors is, reflects the high number of patients presenting with small but numerous tumors who specifically are candidates for ILP, as primary resection is not feasible in these patients.

ILP with consecutive limb-sparing surgery is considered the alternative for amputation in this study population. This is based on the insight that limb-preserving surgery is equal to amputation in terms of survival,[2–4] although the local recurrence rate of 10% to 20%[26–28] after limb-sparing resection is obviously higher than when an amputation is performed. There is still debate as to whether local recurrence of STS is a determinant of overall survival, with studies that do not find a statistically significant effect,[2,29] and studies that do.[27,30] Although the authors of the latter studies argue that patients who develop a local recurrence need aggressive treatment, a study from the Memorial Sloan-Kettering Cancer Center showed that even in a patient category presenting with recurrent disease, amputation only improves local control, but not survival.[31] We therefore claim that ILP is justified as a treatment option allowing limb preservation in both primary and recurrent STS.

As ILP was applied to make limb-sparing surgery possible in the majority of patients in this study, its effect should be compared with other neoadjuvant treatment regimens. The impact of induction systemic chemotherapy on the resectability of STS was recently studied at the M. D. Anderson Cancer Center.[32] Although a response of the tumor was observed in 43% of the patients, only 13% of the population (consisting of 65% extremity STS and 35% retroperitoneal STS patients) showed a radiographically documented response sufficient to reduce the extent of the operation. Notably, none of the extremity STS patients scheduled for amputation could be treated with limb-sparing surgery after neoadjuvant systemic chemotherapy.[32] These results are sustained by a randomized study on neoadjuvant chemotherapy for "high-risk" adult STS (150 patients, 82% extremity STS). In none of the 9 patients scheduled for amputation in this study could neoadjuvant chemotherapy provide limb salvage.[33] Systemically administered chemotherapy does have the advantage of a possible systemic effect on distant (micro-) metastases, although a large metaanalysis of doxorubicin-based adjuvant chemotherapy only showed a reduction in time to recurrence (both local and distal), but no significant effect on survival.[34] ILP with doxorubicin or melphalan alone in advanced STS has failed to demonstrate adequate activity in studies performed in the Netherlands[35] and in a recent study performed at M. D. Anderson,[36] and is not recommended. Presumably, the poor drug uptake in large tumors without the use of TNF is the cause of this failure.[11,37] Preoperative radiotherapy also has the possible advantage of reducing the tumor to a size that makes resection possible. To our knowledge, no data on this issue exist to date. Preoperative radiotherapy was shown in a randomized trial to be as effective as postoperative irradiation in terms of progression-free survival, but is associated with higher wound-compli-

cation rates.[38] Chemoradiotherapy, a combination of preoperative (intraarterial or intravenous) chemotherapy and radiotherapy, was shown to provide excellent local control rates and improved overall survival with acceptable toxicity both in small exploring studies[39] and in a comparison with a historical control group.[40] However, this treatment option remains investigational and the results of randomized trials are pending. Moreover, to compare chemoradiotherapy with ILP is difficult, as the tumors are primarily resectable in the first case, whereas they are generally not in the second.

As TM-ILP can be of particular value in the palliative treatment of patients with metastatic disease and a rapidly growing tumor threatening the limb, it is of great importance that the procedure is safe and without severe side effects. Systemic toxicity is directly correlated with leakage of TNF (and melphalan) to the systemic circulation.[41–43] In the present time of leakage-free ILPs, it should not be necessary to use vasopressors in order to keep the blood pressure at adequate levels to counteract the systemic inflammatory response syndrome that can occur when significant levels of TNF reach the systemic circulation. Ample hydration and adequate diuresis in order to keep the levels of circulating TNF after ILP low should prevent systemic toxicity even in high-leakage ILPs.[43] The procedure can be safely performed in patients with advanced age[44] and the median hospital stay of 8 days shows that the procedure is relatively mild to undergo. This is also underlined by the perioperative mortality rate of 0.5%.

The results obtained in the 217 consecutive TM-ILPs described here underline that TNF-based ILP can play a major role in the treatment of limb-threatening extremity STS. TM-ILP can provide excellent local control and a high rate of limb salvage. Therefore, TNF+M-based ILP has gained a permanent place in the multimodality treatment of locally advanced extremity STS and is currently available in some 40 referral centers in Europe.

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