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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Long-Term Outcome of Isolated Limb Perfusion in Advanced Soft Tissue Sarcoma of the Extremity

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ABSTRACT

Background. Isolated limb perfusion with tumor necrosis factor alpha and melphalan (TM-ILP) has proven to be a successful option in treating advanced soft tissue sarcomas (STS), where amputation otherwise is needed to achieve safe surgical margins.

Methods. From 2000 to 2009, 54 patients with locally advanced STS, who all were candidates for amputation, were treated with totally 57 TM-ILP procedures and then followed prospectively. The median follow-up time was 30 months. Median tumor size was 10 cm, and 94% of the patients had high-grade tumors.

Results. The clinical overall response after TM-ILP was 71% (including 21% CR), and 60% of the patients underwent resection of the tumor remnant after a median of 2 months. The histopathologic response rate in the resected specimens was 76%. Local recurrence/progress occurred in 37% of the patients after a median of 7 months. Thirteen patients finally underwent amputation after a median of 11 months, giving a long-term limb salvage of 76%.

Conclusions. TM-ILP of advanced soft tissue sarcoma of the extremities makes limb-sparing surgery possible in a high proportion of patients.

Soft tissue sarcoma (STS) is a heterogeneous group of mesenchymal neoplasms that account for approximately 1% of malignant tumors. They can develop at any anatomic site, but approximately 60% appear in the extremities.[1] The primary treatment strategy for extremity sarcomas is a wide local excision, either alone or together with radiotherapy or adjuvant chemotherapy. In 5–10% of the patients, the tumors cannot be resected with adequate surgical margin or with preserved limb function, and the patients are then candidates for amputation.[1,2] An other alternative is isolated limb perfusion with tumor necrosis factor alpha and melphalan (TM-ILP). After the pioneering work by Lejeune and Lienard, the results from a European multicenter study were reported in 1996 by Eggermont.[3] This study included 186 patients with locally advanced STS where amputation or functional amputation was the only surgical option. The patients were treated with TM-ILP before limb saving resection was attempted and the results showed an overall response of 82% and a limb salvage rate of 82%.[4] Later studies have confirmed these results, reporting response rates of 65–92% and limb salvage rates of 77–87%.[5–9] The aim of the present study was to analyze the long-term effects of TM-ILP in a consecutive series of patients with locally advanced STS treated at Sahlgrenska University Hospital, Göteborg, Sweden.

PATIENTS AND METHODS

Patients

Fifty-four patients with locally advanced STS, where the primary surgical option was amputation, were treated with TM-ILP during the period November 2000 to August 2009. Forty-four patients (81%) underwent TM-ILP in a neoadjuvant setting as a downstaging treatment before planned resection. Ten patients (19%), who were elderly and who either had advanced metastatic disease or who refused any

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kind of mutilating surgery, received TM-ILP in a palliative setting not primarily aiming at resection. There were 32 men and 22 women, with a median age of 70 years. Tumors were graded according to Broders,[10] most tumors were high grade tumors (40 grade IV, 11 grade III) but there were also three grade II tumors (all large and deep-seated). Tumor and patient characteristics are summarized in Table 1. Fourteen patients received radiotherapy (mean dose 50 Gy) after tumor resection. Eighteen patients received chemotherapy, 12 of these as a result of systemic progressive disease (PD),

TABLE 1 Patient and tumor characteristics

Characteristic	Primary STS ($n = 32$)	Recurrent STS ($n = 22$)	n (%)
Sex			
Female	16	6	22 (41%)
Male	16	16	32 (59%)
Median age, y	70 (15–90)	69 (14–94)	70 (14–94)
Localization			
Elbow	3	0	3 (6%)
Lower arm	1	4	5 (9%)
Upper leg	15	6	21 (39%)
Knee	5	6	11 (20%)
Lower leg	3	4	7 (13%)
Ankle or feet	3	0	3 (6%)
Whole leg	2	2	4 (7%)
Vessels cannulated			
Axillary	1	3	4 (7%)
Brachial	3	1	4 (7%)
Femoral	11	5	16 (30%)
External iliac	17	13	30 (56%)
Median size	12 cm	5 cm	10 cm
Multifocality	3	10	13 (24%)
Indication for TM-ILP			
Involving the neurovascular bundle	18	7	25 (46%)
Concern about the surgical margin	10	9	19 (35%)
Palliative reason	4	6	10 (19%)
Tumor stage			
T1b	1	0	1 (2%)
T2a	1	2	3 (6%)
T2b	30	20	50 (93%)
General metastasis	3	5	8 (15%)
Grade			
II	3	0	3 (6%)
III	6	5	11 (20%)
IV	23	17	40 (74%)
Subtype			
Malignant fibrous histiocytoma	6	6	12 (22%)
Synovial sarcoma	6	2	8 (15%)
Sarcoma unclassified	4	3	7 (13%)
Myxofibrosarcoma	1	4	5 (9%)
Fibrosarcoma	1	3	4 (7%)
Angiosarcoma	2	1	3 (6%)
Spindle cell sarcoma	3	0	3 (6%)
Epithelioid hemangioendothelioma	1	1	2 (4%)
Extraskeletal myxoid chondrosarcoma	2	0	2 (4%)
Other sarcoma[a]	6	2	8 (15%)

[a] Hemangiopericytoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, myxoid liposarcoma, pleomorphic liposarcoma, rhabdomyosarcoma, and sclerosing epithelioid fibrosarcoma

four patients as an adjuvant therapy (high-grade tumors) and two young patients with synovial sarcoma as a neoadjuvant therapy. The median follow-up for the whole group was 30 months (range 1–116 months). The study was approved by the Human Ethics Committee of Sahlgrenska Academy, Göteborg, Sweden.

Isolated Limb Perfusion

The TM-ILP technique has been described previously.[11,12] Briefly, the blood circuit of a limb was isolated by cannulation and clamping of the major artery and vein, and then connected to an oxygenated extracorporeal circuit. The remaining collateral vessels were compressed with an inflatable tourniquet (Zimmer disposable tourniquet) in femoral perfusions or an Esmarch bandage, secured around a Steinman pin, in iliac and upper extremity perfusions (placed into either the anterior superior iliac spine or the humeral head). TNF-alpha (3 mg in upper limb, 4 mg in lower limb) was injected as a bolus into the arterial line, provided limb tissue temperature had reached 38°C. After 30 min, melphalan (13 mg/L in upper limb, 10 mg/L in lower limb) was administered and the temperature was held at mild hyperthermia with a perfusion time of 90 min in total. During the procedure, continuous leakage monitoring was performed with a precordial scintillation probe (MedicView, Göteborg, Sweden) to detect and measure leakage of technetium-99m labeled human serum albumin (Vasculosis, Cis Bio, France) injected into the perfusion circuit. After perfusion, the limb was washed out with at least 1–2 L (upper limb) or 3–4 L (lower limb) of Ringer's solution (Ringer Acetat, Baxter).

Response Evaluation and Toxicity

Clinical response was evaluated according to World Health Organization (WHO) criteria in which complete response (CR) means complete disappearance of all lesions with no new lesions appearing within the field of TM-ILP.[13] Partial response (PR) is defined as a more than 50% decrease in total tumor size; PD is defined as a more than 25% increase in existing lesions or the appearance of new lesions; no change (NC) is defined as if neither PR or PD criteria was met. Response evaluation was done 6–8 weeks after treatment with clinical examination and magnetic resonance imaging (MRI), thereafter the patients were clinically evaluated every third month for the first 2 years, every fourth month the third year, every sixth month up to 5 years, and then yearly. MRI was used in follow-up at the discretion of the treating doctor. The histopathologic response on the resected specimens was defined as CR if more than 99% of the tumor was necrotic, PR when 50–99% was necrotic, and NC if less than 50% was necrotic. Acute local toxicity of the TM-ILP procedure was classified according to Wieberdink et al., and systemic toxicity was graded according to the WHO criteria scale.[13,14]

Statistical Analysis

Overall survival (OS) was defined as time from TM-ILP to death. Local progression-free survival (LPFS) was defined as time from TM-ILP to local progress or recurrence. Progression-free survival (PFS) was defined as time from TM-ILP to local/general progress or death. Survival estimates were made by the Kaplan–Meier method and compared by the log rank test. Perfusion variables were analyzed by the Mann–Whitney *U*-test. All statistics were calculated by SPSS statistical software, version 19 (SPSS, Chicago, IL), at a significance level of 5%.

RESULTS

Response

Clinical response was evaluable in 52 patients, two patients died before evaluation was possible. The overall response was 71%, including 11 patients with CR (21%) and 26 patients with PR (50%); 14 patients showed NC (27%); and one patient had PD (2%). The histopathologic response was evaluable in 33 patients (27 resected specimens and six early amputation specimens) and showed an overall response rate of 76%, including six CR (18%) and 19 PR (58%). No correlation was found between the response and the histologic subtype of the tumor.

Surgical Treatment

Thirty patients (60%) underwent tumor resection after a median time of 2 months (range 0–14 months). The surgical margin was wide in four patients (13%), marginal in 24 patients (80%), and intralesional in one patient (3%). One specimen could not be properly evaluated for surgical margin.

Local Recurrence/PD

Local recurrence/PD developed in 20 patients (37%) after a median time of 7 months (Fig. 1). Among the 30 resected patients, there were nine local recurrences (30%) after a median of 12 months. Two of the recurrences occurred in the 19 patients with primary tumor (11%), and seven recurrences occurred in the group of 11 patients with recurrent disease (64%), a difference in LPFS (Fig. 2) that is statistically significant ($P = 0.007$). Among the 24 patients not resected, local recurrence/progress occurred in

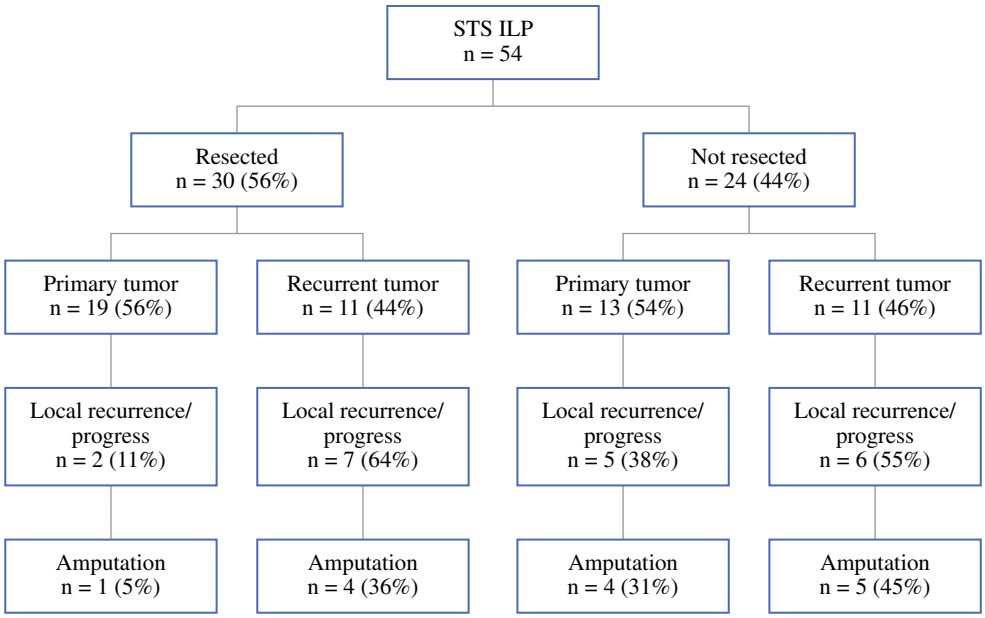

FIG. 1 Flow-chart of outcome after TM-ILP

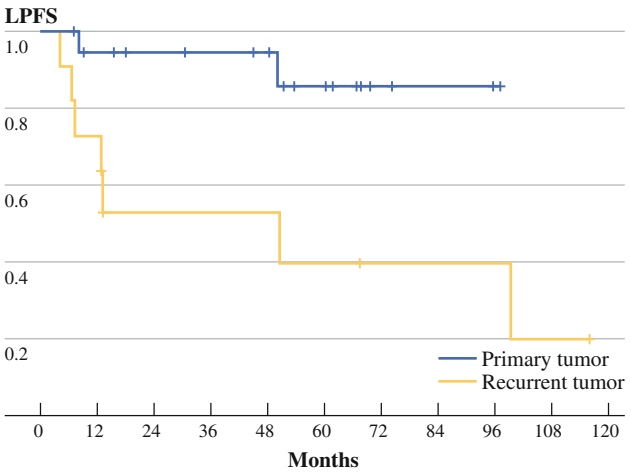

FIG. 2 LPFS for resected primary ($n = 19$) or recurrent ($n = 11$) STS with a statistically significant difference ($P = 0.007$) by log rank test

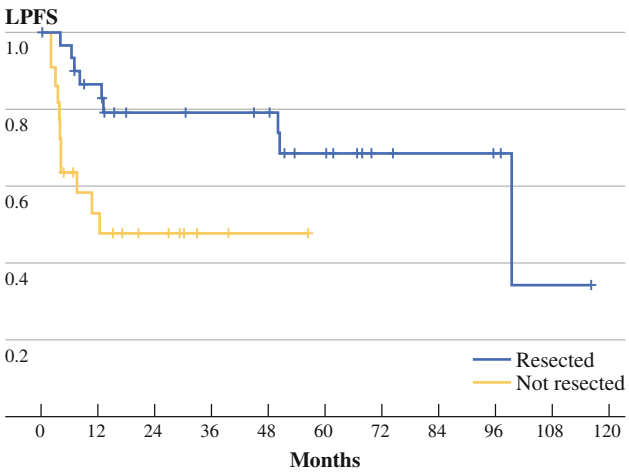

FIG. 3 LPFS for resected ($n = 30$) or nonresected ($n = 24$) STS with a statistically significant difference (median time 99 months vs. 12 months, $P = 0.01$ by log rank test)

11 (46%) of the patients and there were no significant difference in LPFS between primary and recurrent tumors. There was a significant difference in LPFS between resected and nonresected patients (12 months vs. 99 months, $P = 0.01$, Fig. 3) where local recurrence in the resected group of patients occurred during the whole observation period, while PD was an early event in the group of patients not resected. Out of the 19 patients with primary tumor that underwent resection, 16 patients (84%) underwent marginal resections; notably there was only one local recurrence (after 50 months) in this group. Three patients were reperfused because of local recurrence after 3, 4, and 5 months, respectively, for palliative reasons.

Palliation

In the 10 patients receiving TM-ILP mainly as a palliative measure, 40% had general metastases and 60% had a recurrent disease at the time of perfusion. Three patients developed local PD after a median of 4 months after TM-ILP. Two of these patients underwent amputation after 13 and 14 months, respectively. The first patient died after 2 years, but the second patient is still alive after 7 years with no evidence of disease. Eight patients (80%) died with a functional limb after a median time of 18 months.

Amputation

Thirteen patients finally underwent amputation after a median of 11 months (range 3–36 months), which gives a 76% limb salvage rate. Ten patients underwent amputation as a result of local recurrence/PD, one patient as a result of peripheral artery disease, where the patient had both a clinical and histopathologic CR, and one patient as a result of complications to the resection of the primary tumor. One patient with a malignant fibrous histiocytoma underwent amputation after 13 months as a result of MRI findings that indicated viable tumor without any shrinkage in tumor size. However, the histopathologic examination later showed CR with more than 99% tumor necrosis.

Survival

Eight patients (15%) had general metastases at the time of TM-ILP, and another 20 patients (37%) developed general metastases after a median of 8 months (range 2–45 months). Median survival was 30 months with a 2-year and 5-year survival of 59% and 44%, respectively; median PFS was 11 months with a 2-year and 5-year PFS of 40% and 29%, respectively (Fig. 4).

Perfusion and Leakage

During TM-ILP, the temperature was held at mild hyperthermia with a median subcutaneous/intramuscular temperature of 39.7°C/39.8°C and 39.9°C/39.8°C in the thigh and in the calf, respectively. Median flow rate during perfusion was 398 ml/min/L (range 167–1056 ml/min/L) in the lower extremity and 237 ml/min/L (range 175–454 ml/min/L) in the upper extremity. The leakage from the perfusion circuit to the patient during the perfusion was evaluable in 51 patients and was below 1% in 41 patients (80%). In the remaining 10 patients, the median leakage was 2.5%, with one patient with a leakage above 10% (range 1.0–10.6%). After washout and reconnection of the limb circulation, the leakage had further increased with a median of 0.9% (range 0–4.3%), resulting in a total leakage below 1% in 22 patients (43%). In the remaining patients, the total median leakage was 2.4% with one patient with a leakage above 10% (range 1.1–12.5%). The leakage from the patient to the perfusion circuit at the end of the procedure was in median 400 ml (range 0–2000 ml).

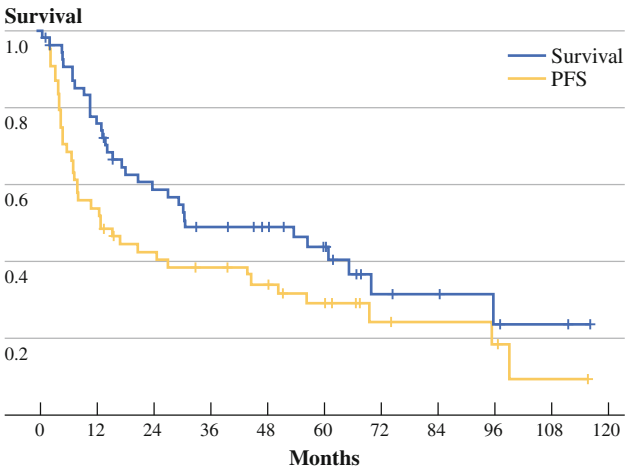

FIG. 4 The median survival was 30 months with a median PFS of 11 months

Hospital Stay

The median hospital stay was 7 days (range 4–99 days), including a median stay at the intensive care unit for 1 day (range 1–10 days).

Toxicity

Acute local toxicity was scored according to Wieberdink, and out of the 57 procedures (including three reperfusions) the majority (53 procedures, 95%) had a toxicity reaction between grade I and III.[14] Grade IV toxicity developed in four patients. This group had a marked increase in peak myoglobinemia with a median of 2770 μg/L (range 812–25700 μg/L) compared to a median of 191 μg/L for the other patients (range 24–2266 μg/L), this difference was statistically significant ($P < 0.001$). There were two acute myocardial infarctions in the immediate postoperative period, leading to death in one of the patients after 2 weeks. Both patients had previously known coronary artery disease and there was 0% and 0.25% leakage during the perfusion, respectively. One patient developed ventricular tachycardia postoperatively (1.06% leakage); all other toxicities (grade I–III) were of a transient nature and required no special intervention. There was no correlation between leakage and systemic or local toxicity. Systemic and local toxicities are summarized in Table 2.

DISCUSSION

For patients with locally advanced STS amputation is still a treatment option, although the trend for many years has been toward more limb-sparing surgery, especially because there seems to be no negative effect on survival. The rationale for limb-sparing surgery is to improve quality of life, although the scientific evidence for this is scarce. An improvement has been shown in physical parameters when comparing amputation with limb-sparing surgery, but without obvious differences in general quality of life.[15] The

TABLE 2 Systemic toxicity

	0	I	II	III	IV
Cardiac	52 (91%)	1 (2%)	1 (2%)	–	3 (5%)
Pulmonary	54 (95%)	–	2 (4%)	1 (2%)	–
Gastrointestinal	57 (100%)	–	–	–	–
Liver	45 (79%)	8 (14%)	2 (4%)	2 (4%)	–
Renal	55 (96%)	1 (2%)	–	1 (2%)	–
Leukopenia	56 (98%)	–	–	1 (2%)	–
Thrombocytopenia	57 (100%)	–	–	–	–
Fever	52 (91%)	3 (5%)	2 (4%)	–	–

Systemic toxicity according to WHO criteria

degree of impediment may also be dependent on the level of amputation, where below-knee amputations seems to be comparable to limb-sparing surgery.[15,16]

To improve local control, different protocols to allow for tumor down-staging or more radical surgery have been explored. Neoadjuvant chemotherapy alone has not proven to be of any greater value, the only prospective randomized trial failed to show any significant benefit in terms of PFS after 7 years of follow-up.[17] Perioperative radiotherapy has been shown to improve local control in the setting of resectable disease, but the timing of the radiation has been debated. Preoperative radiation gives more wound complications than postoperative radiation, but seems to yield better long-term extremity function and better local control.[18] A novel technique of neoadjuvant chemotherapy together with regional hyperthermia was tested in a randomized trial showing a significant increase in response and disease-free survival (32 vs. 18 months) compared to chemotherapy alone.[19] Another option is a wide resection followed by vascular reconstruction, and in a recent publication by Muramatsu et al., a short summary of previous studies show a limb salvage rate of 75–100% and a local recurrence rate of 0–29%.[20] Notably, the sample size was small—in total, 141 patients in nine studies—and there was significant morbidity (25–87%) as well as a questionable functional outcome. In our opinion, radical surgery with advanced vascular reconstruction is more hazardous than using TM-ILP and should be saved for occasions where TM-ILP is not suitable for other reasons. However, comparing these regimens is difficult, and no good data supporting such an analysis exist, mainly as a result of the large heterogeneity in the reported materials and the lack of randomized trials.

The good results of TM-ILP have been documented in several studies. However, these reports are mainly from the same institutions that originally developed the technique.[3–5,7,21–24] Our study adds to the knowledge concerning TM-ILP in sarcoma patients and confirms that the method very well can be exported to new centers achieving similar results; a finding also supported in other recent publications.[6,8,25–28] The efficacy of the treatment is surprisingly uniform considering the heterogeneity in the reported materials. Our material has a large cohort of high-grade tumors (94% grade III–IV) as well as a long and consistent median follow-up of 30 months. The relatively high local recurrence rate observed in this study (37%) is most likely explained by these two factors, particularly the latter, because three of the recurrences were very late (50, 50, and 99 months). In the group of 19 patients with primary tumors that underwent resection, there were only two local recurrences (11%), and the limb salvage rate was 95%. In the palliative setting, the result of TM-ILP is also encouraging, with 80% of the patients having a functional limb for their remaining lifetime.

One patient underwent amputation as a result of MRI results that revealed no response to therapy, but the histopathologic analysis later revealed a CR. There is a known lack of reliability in the use of both computed tomography and MRI with WHO/Response Evaluation Criteria in Solid Tumors (RECIST) criteria in the response evaluation of STS treatment.[29] In a publication by Stacchiotti et al. the predictive value of no-response according to RECIST criteria compared to histopathologic response was 15–60%.[30] The use of ^{18}FDG-PET (^{18}F-18-fluorodeoxyglucose–positron emission tomography) has increased worldwide and the role in clinical trials are also expanding as new criteria for evaluating response is being developed.[31] False-positive FDG uptake after treatment has to be considered, new tracers such as ^{18}F-FLT (3′-deoxy-3′-^{18}F-fluorothymidine) might be able to better discriminate between viable tumor cells and inflammation and thereby become a valuable tool in the future.[32] Currently we would consider doing an open biopsy before amputation if any doubt exists concerning response.

We had two major postoperative complications with acute myocardial infarctions, with one patient dying after 2 weeks (2% mortality). There was no leakage observed during this TM-ILP and the death was attributed to the surgical stress per se, not the TM-ILP itself. In the literature reviewed two other deaths have been reported (0.5% and 2% mortality) in the immediate postoperative period.[21,22] There were four patients developing Wieberdink grade IV toxicity with manifest neuropathy, predominantly in the peroneal nerve. One of them underwent fasciotomy, the three others had no signs of compartment syndrome. All other patients (95%) had only minor local complications (Wieberdink toxicity grades I–III), which is in line with previous reports.

Our standard treatment for STS is wide or radical surgery without any neoadjuvant treatment.[33] According to the Scandinavian Sarcoma Group guidelines, postoperative radiotherapy is recommended to all deep seated high grade sarcoma and sarcomas with marginal resection.[34] Adjuvant chemotherapy is given to high grade sarcoma if the resected specimen shows vascular invasion and/or at least

two of the criteria; size > 8.0 cm, infiltrative growth or necrosis (according to the Scandinavian Sarcoma Group XX study protocol). In patients with extensive disease or involvement of the neurovascular bundle, amputation or limb-sparing surgery with preoperative TM-ILP is considered. In patients with myxoid/round cell liposarcoma, preoperative radiotherapy and resection is considered a treatment option.[35]

The use of adjuvant radiotherapy after TM-ILP and resection has until now been decided on an individual basis. A recent study by Deroose et al. indicated that patients with primary STS treated with TM-ILP and R0 resection experienced no further benefit of radiotherapy if there is more than 50% necrosis in the resected specimen.[36] Comparing this with our results, there were two local recurrences in the group of 19 patients with primary tumor undergoing resection (one R1 and one R0 resection; both had a histopathologic PR), and neither of the two had received any adjuvant radiotherapy.

Several previous studies have shown that isolated limb perfusion reduces the need of amputation in advanced STS of extremities. This study confirms that TM-ILP is a safe and efficacious technique, provided a strict perfusion technique and monitoring can be guaranteed in order to avoid the risks of serious complications. Hence, this technique should be centralized to major cancer centers with a high load of patients with STS of the extremities. The patients who benefited most from TM-ILP in our series were those with resected primary sarcomas. The recurrence rate was low despite marginal resections of high-grade tumors in unfavorable sites. One of the major benefits with TM-ILP in the treatment of advanced STS seems to be the shift from the adamant demand on wide or radical margins, to allow for marginal resections with tolerable morbidity and without a staggering increase in local recurrences.

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