

Advanced Extremity Soft Tissue Sarcoma: Prognostic Effect of Isolated Limb Perfusion in a Series of 88 Patients Treated at a Single Institution

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Purpose: To explore the prognostic impact of isolated limb perfusion (ILP) in locally advanced extremity soft tissue sarcomas (ESTS).

Methods: From August 1982 to April 2005, 1,119 patients affected by ESTS (girdle excluded) were observed and treated at our institution. Eighty-eight (7.9%) were judged non-resectable or locally advanced and underwent ILP. Thirty-seven patients received antineoplastic alone (non-TNF-ILP) while 51 had anti-neoplastic + recombinant-tumor necrosis factor alpha (TNF-ILP). Local disease-free survival (LDFS) was calculated by the Kaplan-Meier method and was reported separately in the two subgroups.

Results: Limb salvage was achieved in 83% (73/88) of the patients. The observed overall (complete + partial) response rate was 59%. In the TNF-ILP group a complete response (CR) was achieved in 21 (41%) patients, while in the non-TNF ILP group a CR was obtained in seven (19%) cases ($P < 0.05$). Patients with in-transit metastases (epithelioid sarcomas and clear cell sarcomas) had a significantly worse long-term outcome (LDFS at 5 years was 40.9 vs 67.3%, $P < 0.05$). A trend towards a better LDFS at 5 years could be observed in the patients receiving TNF (63.6 vs 57.1%) and post-operative radiation therapy (RT) (79.3 vs 55.4%).

Conclusions: Isolated limb perfusion is an active treatment. By adding TNF a better local control seems to be obtained, possibly due to a higher rate of CR. It should therefore be considered as a valid option for patients affected by limb-threatening STS, save for in-transit metastases from epithelioid and clear cell sarcoma. Post-operative RT should always be considered.

Key Words: Sarcoma—Limb—Isolated limb perfusion—TNF- α —Surgery—Prognosis.

Soft tissue sarcomas (STSS) are a group of neoplasms, characterized by a wide range of biological

behavior. A multimodality approach has been more and more employed for the treatment of the more aggressive ones.

Pre-operative chemotherapy and/or radiotherapy are used as a means of cytoreduction for limb-sparing surgery, with a potential impact on long-term outcome.¹

Unfortunately, even with multiregimen high-dose chemotherapy, response rates of large high-grade

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sarcomas reach only approximately 40% in the most favorable studies.² Although the response to multimodality treatment can afford physicians the opportunity to preserve extremities as well as limb function, clearly, a significant number of patients still require physically disabling and function-limiting surgery.² About 60% of STSs occur in the limbs; of these 6–10% are locally advanced on presentation. It was reported that 80–90% of patients affected by locally advanced STSs of the extremities are treated by limb-sparing surgery without significant impairment of limb function. The remaining are deemed unresectable and thus referred for amputation.

In this setting, isolated limb perfusion (ILP) is used as a limb-sparing cytoreductive treatment, followed by surgery on the residual tumor in order to prevent amputation.

The regional administration of high-dose chemotherapy by ILP has been attempted mainly as a limb-sparing alternative in patients with locally advanced soft-tissue sarcomas of the extremity, which would have otherwise required amputation as a ultimate procedure.

ILP has been used in patients with extremity sarcomas for over 40 years.

One of the more controversial questions during the early period of investigation involved selection of the proper drug to be used in the perfusion circuit for the treatment of sarcomas. A wide variety of drugs were initially employed, including melphalan, dactinomycin, nitrogen mustard, and cisplatin.

Because of the rarity of this tumor and the variety of chemotherapeutic agents used in those patients who did undergo ILP, there were few investigators from sarcoma-specific trials reporting on the results of ILP for extremity sarcoma.

The use of loco-regional treatments is also supported by the evidence that amputation does not improve life expectancy, as prognosis is related to distant metastases.³

In our institution, we retrospectively reviewed patients who underwent ILP with or without recombinant-tumor necrosis factor alpha (TNF) for locally advanced STSs of the extremities, in order to analyze possible prognostic factors and the final local outcome.

PATIENTS AND METHODS

At Istituto Nazionale dei Tumori of Milan, from 1982 to 2005, 98 consecutive patients affected by advanced extremity STSs underwent ILP. Eighty-

eight received Doxorubicin or Melphalan, with or without TNF, and therefore make up the series of this study. There were 47 males and 41 females, with a median age of 54 years (range 18–85).

The tumors were considered locally advanced when local control was achievable only with mutilating surgery which could result in functional morbidity or with major amputation.

Resectability with adequate margins was judged on the basis of clinical examination and of computed tomography scans or magnetic resonance imaging.

Criteria for unresectability were (1) multifocality, (2) recurrences in a previously irradiated area, (3) pluricompartimental disease.

The tumor was localized in the upper limb in 32% of the patients, in the lower limb in 68% of the patients.

Tumor characteristics regarding histologic subtypes and tumor grade at the time of ILP are shown in Table 1.

The median tumor size was 6 cm (range 1–30 cm). For a multifocal localization, this concerned the largest lesion.

Fifty-one patients (58%) received TNF; in 33 cases TNF was associated with Melphalan and in 18 cases it was associated with Doxorubicin.

Thirty-seven patients (42%) received drug alone: in 18 cases Melphalan and in 19 cases Doxorubicin (Table 2).

ILP Technique and Drug Schedules

Isolated limb perfusion is usually undertaken in specialized centers by experienced surgical teams.

The procedure is conducted under general anesthesia; it is important to prevent large fluctuations in systemic blood pressure, which can affect leakage between systemic circulation and the perfusion circuit.

During ILP, central venous pressure and arterial pressure are monitored. For the prophylaxis of shock, patients should be hydrated prior to, during, and after the procedure.

Our ILP methodology is the one previously described in detail.⁴

Shortly describing the procedure, during ILP the major artery and vein are clamped at the desired level, collateral vessels are ligated, and a tourniquet is applied around the limb, proximal to the region of ILP.

After insertion of the catheters, the isolated limb is perfused by an extracorporeal circulation that is oxygenated and propelled by a heart–lung machine. During ILP, adequate tissue temperatures are

TABLE 1. Main patient and disease characteristics, according to tumor presentation

	No. (%)
Total	88
Age (years)	
Median	54
IQ range	18–85
Gender	
Males	41 (46.5)
Females	47 (53.4)
Site	
Upper extremity	28 (31.8)
Lower extremity	60 (68.2)
Size (cm)	
Median	6
IQ range	1.0–30
Histotype	
Liposarcomas	15 (17.05)
Clear cell sarcomas	8 (9.1)
Synovial sarcomas	10 (11.4)
MPNSTs	7 (7.9)
MFHs	15 (17.05)
Epithelioid sarcomas	13 (14.8)
Others	20 (22.7)
FNCLCC Grade	
I	11 (12.5)
II	17 (19.3)
III	60 (68.2)
Post-ILP surgical procedure	
Limb-sparing resection	61 (69.3)
Amputation	19 (21.5)
No surgery due to distant pro.	8 (9)
Post-ILP radiation	
Not done	70 (79.5)
Done	18 (20.5)
Post-ILP systemic chemotherapy	
Not done	75 (85.2)
Done	13 (14.8)

TABLE 2. Drug schedules

	TNF [no. (%)]	No-TNF [no. (%)]
Melphalan	33 (37.5)	18 (20.5)
Doxorubicin	18 (20.5)	19 (21.5)
Total	51 (58%)	37 (42%)

achieved and maintained by heating the heparinized perfusate and by the application of a warm water blanket around the limb.

In the group of patients who received TNF, after a heating phase to a temperature of 38–40° C (mild hyperthermia), TNF- α is added to the perfusate and is circulated for 90 min, at a dose of 1 mg, irrespective of limb volume.

Melphalan is injected 30 min after the administration of TNF- α and is circulated for the remaining 60 min, at a dose of 50 mg in the upper limb and 100 mg for the lower limb, irrespective of iliac or femoral approach. In five patients, interferon- γ was

added: it was injected subcutaneously 2 days before surgery (0.2 mg IFN- γ), and the same dose was given during ILP.

In the group of patients who did not receive TNF, the drug is injected when the temperature is about 40–41° C and the perfusion lasts 60 min.

At the end of the procedure, the perfusate is drained out, and the limb is rinsed with an electrolyte solution. The tourniquet is then released, and the catheters are removed.

Twenty-eight ILPs procedures were at the axillary isolation level, five procedures were at the popliteal isolation level, 42 procedures were at the iliac isolation level, and 13 procedures were at the femoral isolation level.

Leakage from the isolated circuit into the systemic circulation is monitored continuously with a radioactive-labeled human serum albumin.

All patients signed a written informed consent prior to the procedure.

Tumor Response

Clinical tumor responses were assessed according to the standardized World Health Organization criteria.⁵ A complete response (CR) was defined as the complete disappearance of tumor in the extremity for a period >4 weeks, a partial response (PR) was defined as regression of tumor size by >50% for >4 weeks, no change (NC) was defined as regression of tumor size <50% for >4 weeks, and progressive disease (PD) was defined as progression of >25%. After resection of the tumor remnant, at pathologic examination, the percentage of necrosis was estimated on the basis of macroscopic evaluation of necrotic tissue and histologic examination of tissue surrounding the necrotic tissue area. A tumor in CR was 100% necrotic. If the tumor had 50–99% necrosis, then the response was considered a PR. If the tumor was <50% necrotic, then the response was classified as NR. Final tumor response was based on a combination of clinical and pathological responses and, for the purpose of this study, we considered only the final (clinical + pathologic) response. If a clinical PR proved to be 100% necrotic on pathologic examination, then the response was upgraded to a CR. Besides the immediate responses, the ORs were evaluated, as the sum of CRs and PRs.

Statistical Methods

Local disease-free survival and disease-specific survival curves were calculated by the Kaplan–Maier method and compared with the logrank test.

TABLE 3. Tumor responses: immediate responses

Immediate response	No.	%
CR	28	31.8
PR	52	59.1
NC	7	8
PRO	1	1.1
Total	88	100

TABLE 4. Tumor responses

	TNF		No-TNF	
	No.	%	No.	%
CR	21	41	7	19
No-CR	30	59	30	81
Total	51	100	37	100
Chi square, $P = 0.0269$				
OR (CR + PR)	49	96	31	84
No response	2	4	6	16
Total	51	100	37	100
Chi square, $P < 0.05$				

Locoregional recurrence analysis was also carried out using multiple variable Cox regression model.

Toxicity

Acute regional toxicity was graded from 1 to 5 according to Wieberdink et al.⁶ Systemic toxicity was measured according to Common Toxicity Criteria⁵. Signs that were evaluated were nausea/emesis, fever, hypotension, rhythm disturbances, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, white blood cell count, and platelet count.

RESULTS

Tumor Response

Regarding the final tumor response, a CR was attained in 28 patients (32%), 52 patients (59%) had a PR, seven patients (8%) had NC, and one patient had PD (1%) (Table 3).

To evaluate the impact of the adjunct of TNF in the drug schedule, we considered the CR rate and OR rate in both groups who did receive, or who did not, TNF.

Concerning CR, we observed a 41% rate in the TNF group compared to a 19% in the non-TNF group, and this resulted statistically significant in an univariate analysis ($P < 0.05$) (Table 4).

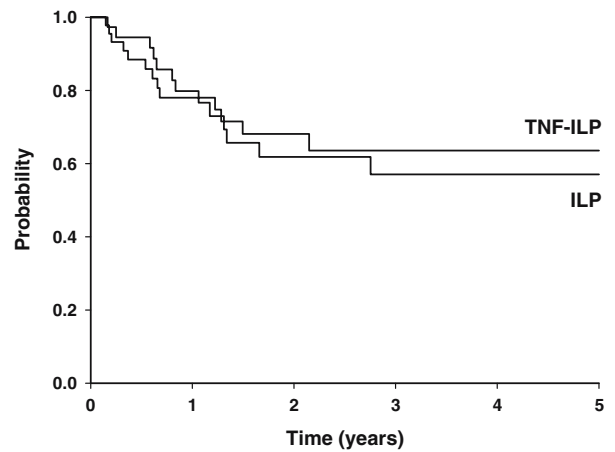


FIG. 1. Local disease-free survival according to the drug schedule (with or without r-TNF- α).

On the other hand, when considering OR, we observed 96% in the TNF group and 84% in non-TNF group ($P < 0.05$).

Neither initial tumor size nor tumor grade influenced final response in a univariate analysis.

Amputations and Locoregional Recurrence

Overall 15 patients (17%) underwent amputation of the limb. In the non-TNF-ILP subgroup the amputations were six (16.2%) while in the TNF-ILP group were nine (17.6%).

One patient underwent amputation of the extremity because of toxicity secondary to ILP; in seven cases amputation was after an insufficient response to ILP and in seven patients amputation was due to local relapse after ILP.

Overall limb salvage rate was 83% (73/88 patients).

Although in 73 of 88 patients (83%) the limb was not amputated, 20/73 (27%) patients had a local relapse after ILP, after a mean interval of 13 months (range 2–80 months), so that in the entire series local relapse was observed in 27/88 patients (31%), respectively, in 13 patients who received TNF and in 14 patients who received drug alone. In the group of patients who experienced local relapse after ILP, 41% of cases (11/27) had a multifocal disease (30% had a multifocal epithelioid sarcoma, 11% had clear cell sarcoma).

Isolated limb perfusion therefore resulted in an overall local tumor control with preservation of the affected limb in 53 of 88 patients (60%), 51% in the non-TNF-ILP group and 67% in the TNF-ILP group (Fig. 1).

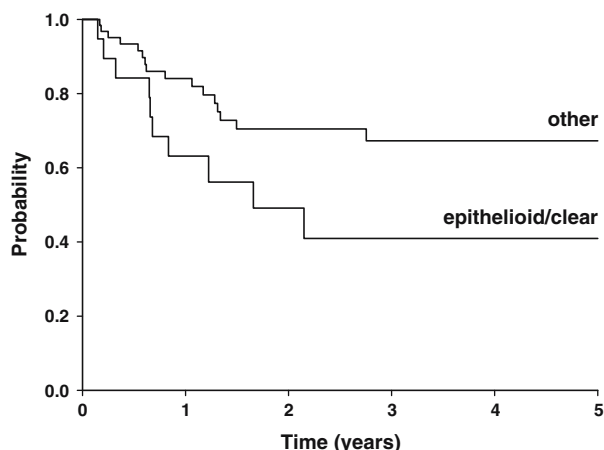


FIG. 2. Local disease-free survival according to histological subtype (epithelioid sarcoma and clear cell sarcoma vs others).

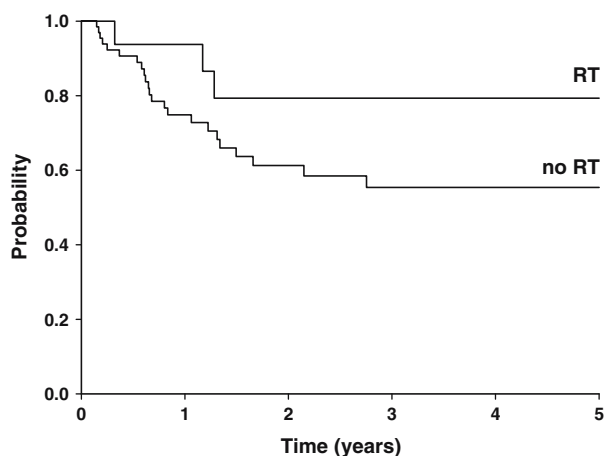


FIG. 3. Local disease-free survival according to performance of post-operative RT.

As patients with multifocal epithelioid sarcoma and multifocal clear cell sarcoma presented clinically with in-transit metastases, we evaluated the final outcome of this group of patients and compared it to that of patients with all other histotypes. The LDFS at 5 years in patients with in-transit metastases resulted 40.9%, while in patients with other histotypes resulted 67.3% (Fig. 2).

Eighteen patients received post-operative radiation therapy (RT), while 70 did not. The LDFS at 5 years for those who received RT was 79.3% versus 55.4% for those who did not (Fig. 3).

A multiple variable Cox regression model including TNF, the presence of in-transit metastases in epithelioid and clear cell sarcomas, and post-operative RT yielded significant results only for in-transit metastases ($P < 0.05$). In particular, patients with

in-transit metastases had a rate of local recurrence more than doubled comparing to the remaining patients (Hazard Ratio, 2.2; 95% confidence limits, from 1.02 to 4.9). As regards the remaining factors, the Cox model showed only a trend towards an event rate reduction in patients receiving TNF (HR 0.8; 95% CL 0.4–1.8) and patients undergoing post-operative radiotherapy (HR 0.5; 95% CL 0.1–1.6).

Toxicity and Complications

Acute regional toxicity was mild (grade I–II reactions) in the most patients (85.5%) and more severe (grade III reactions) in 10% of the patients.

A grade IV reaction was observed in three patients (3.4%) and resulted in definitive functional impairment.

A grade V toxicity which led to amputation of the extremity was observed in one patient (1.1%).

Systemic toxicity was observed in 7% of the patients. No grade III or IV systemic toxicity was observed.

Survival

In the entire series, 38/88 (43%) patients had distant metastases, in 13 (15%) cases when also a local relapse had been evident and in 25 cases (28%) without any local relapse.

The overall disease-specific survival rate at 5 years was 47.1% for the 88 patients.

DISCUSSION

Amputation of the limb undoubtedly results in the highest local control rate in patients with locally advanced STS of extremities. However, to our knowledge, no survival benefit has been shown so far after amputation compared with limb-sparing treatment modalities in these patients, and, currently, the latter is being pursued increasingly.⁷

The impact of local control on the development of distant metastases is not completely known. Most authors claim that local recurrence is of minor importance for development of metastases in STSs and that an increased local recurrence rate in metastatic tumor is probably due to the aggressiveness of the primary tumor and that highly malignant tumors combine a potential for both local and distant spread.^{3,8}

Most likely, the event of local relapse as source for metastases is also a coexisting factor that might

determine distant disease progression. The latter hypothesis is suggested in some papers that have shown that the most important risk for both local recurrence and survival is the quality of surgical margins in primary surgery.^{9,10} Both these concepts underline the importance of having limb-sparing procedures able to reduce the rate of local recurrence, by improving the quality of surgical margins and therefore possibly, also survival. ILP should be considered as one of the tools for obtaining such results. From our study ILP, as an adjunct to surgery for subsequent tumor removal, seems to obtain local control and prevent amputation in patients with limb-threatening STSs. Our policy was to perform a wide resection of the remnant tumor after ILP and if it was not possible without compromising limb function, then amputation was done. In cases of multifocal disease which obtained a CR after ILP, post-perfusion resection of the tumor was not performed.

The factors that determine tumor response after TNF α -ILP in patients with unresectable STS are unknown. It is assumed that high-grade tumors respond better to ILP than low-grade tumors, although this could not be demonstrated in our series. Also large and highly vascularized tumors, described by others to respond better to treatment, were not significantly affected in relation to smaller tumors.

The limb-salvage rate in our study resulted 83%, which is in line with previously reported limb-salvage rates of 81–86%.^{11–15}

It is definitively difficult to define objectively what is clearly advanced in extremity STSs, and therefore identify those patients who should be irrefutably candidated to pre-operative procedure (ILP included). In our hands, primary amputation for extremity STSs has been 4% in primary tumors and 7% in recurrent diseases, with a local control of approximately 15% at 10 years.⁹ These cases were amputated mostly for multicompartamental extension. This subset of really locally advanced cases is critical also for TNF-ILP, which is unlikely to change significantly the rate of amputation. On the other hand, those patients where an amputation is not dictated by technical reasons, but by oncological reasons (multifocal disease or recurrent disease in a previously irradiated area), could be ideal candidates to ILP, to improve local control after conservative procedures. This effectiveness should be definitely demonstrated in a prospective trial, as difficult as it may be, but is already supported by the prospective experience reported in the literature by Lans et al.¹⁷ and by Grunhagen et al.¹⁸

A high limb-salvage rate does not indicate per se the percentage of patients who had their tumors eradicated, as it is the case when considering the local control. When considering patients who never developed a local recurrence after ILP, a local control in our series was obtained in 60% of patients, which is much lower than what is expected in a general population of extremity STSs, reflecting the high risk category selected in our series.

When comparing ILP drug schedules with or without TNF, it appears that TNF not only improves the number of CRs (Table 3) ($P < 0.05$), but seems to be a factor determining a better local outcome. In fact, in the patients who received ILP without TNF LDFS at 5 years was 57.1%, while in those who received TNF-ILP we observed a LDFS at 5 years of 63.6% (Fig. 1). This trend towards a better local control in the patients treated with TNF-ILP (HR 0.8) is in line with what was already reported by other authors.^{11–18}

The expected local risk in this population of perfused patients if compared to our historical control, with similar characteristics who could not undergo perfusion, would have been roughly around 50% at 5 years.⁹ This difference in local outcome, more evident in the subgroup of patients who received TNF, could be related to ILP, making it not only an active treatment, as already demonstrated in a number of studies,^{11–14} but also effective in terms of local control. This efficacy should be definitively tested prospectively in a randomized fashion, though the feasibility of such a trial is questionable.

We were also able to identify a subgroup of patients, who did not seem to benefit so much from ILP. As a matter of fact, those affected by multifocal epithelioid or clear cell sarcoma had LDFS at 5 years of 40.9%, which was significantly lower than the one of all other histotypes, (67.3% at 5 years), as shown in Fig. 2. This difference in the local outcome was statistically significant even at multivariate analysis (HR 2.2, $P < 0.05$). Therefore, care should be taken when referring patients affected by these particular histotypes for ILP.

Post-operative RT could be administered only in 20% of the patients. These patients had a better local outcome compared with those who did not receive it (Fig. 3). This difference, not significant at multivariable analysis, could reflect both the fact that many of the patients who did not receive post-ILP RT had already received it in the past, as well as the efficacy of the RT itself, as reported in the literature.^{16,19} It is therefore reasonable to evaluate the indication to RT, whenever possible, but the risk of late morbidity

should also be considered¹⁶ and the final decision shared with the patient.

In summary, ILP is an effective option to be proposed to the patients affected by locally advanced soft tissue sarcoma. The employment of TNF seems crucial in determining response and in improving the local outcome after limb-sparing procedures. In-transit metastases, fortunately rare in extremity STS, except for epithelioid and clear cell sarcoma, are unlikely to benefit much from this procedure and deserve further therapies. Post-operative RT should always be considered.

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