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Isolated limb perfusion with tumor necrosis factor and melphalan for non-resectable soft tissue sarcomas: long-term results on efficacy and limb salvage in a selected group of patients

THESE

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par

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Isolated limb perfusion with tumor necrosis factor and melphalan for non-resectable soft tissue sarcomas: long-term results on efficacy and limb salvage in a selected group of patients

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pour Le Doyen
de la Faculté de Biologie et de Médecine

Madame le Professeur Stephanie Clarke
Directrice de l'Ecole doctorale

Rapport de synthèse

Introduction :
La perfusion isolée de membre (isolated limb perfusion, ou ILP) par TNF-alpha et melphalan, utilisés en association, est une stratégie de prise en charge chirurgicale des sarcomes non opérables des extrémités. Elle a été en partie développée au CHUV dans les années 1990, sous l'impulsion du Professeur F. Lejeune, ancien Chef du Service d'oncologie médicale (CePO). Les résultats des 31 premiers patients ont été publiés en 2000 dans l'European Journal of Surgical Oncology.
Les données dans la littérature manquant sur les résultats à long terme, nous avons revu tous les patients traités au CHUV depuis 1992 pour tenter des de déterminer ces résultats à long terme, en se focalisant sur l'efficacité du traitement, symbolisée par le taux de sauvetage de membres, autrement condamnés à l'amputation ou à une chirurgie mutilante.

Matériel et méthode :
Etude rétrospective.
De 1992 à mars 2006, 51 patients ont été traités par ILP dans notre institution, certains à deux reprises (58 ILP au total). Quatre-vingt-huit pour cent présentaient un sarcome de haut grade de malignité, et 84% une tumeur localement avancée (T2b N0 Mo ou plus).

Résultats :
Le follow-up moyen est de 38.9 mois (4-159, médiane 22 mois), on note 21% de complications immédiates et 23% de complications tardives ou chroniques.
Une réponse complète (nécrose totale ou disparition de la tumeur) a été observée dans 25% des cas, une réponse partielle (>50% de nécrose ou de diminution de taille tumorale) dans 42%, une stabilité de la maladie dans 14% et une progression tumorale dans 14%.
Un traitement adjuvant a été entrepris dans 31% des cas, une résection des résidus tumoraux a pu être effectuée chez 65% des patients.
On note un taux de récidive locale de 35% (après 20,3 mois en moyenne) et un taux de récidive à distance de 45% (après 13,4 mois en moyenne). Le disease-free survival est de 14,9 mois et la survie à 5 ans de 43,5%.
Le taux d'amputation s'élève à 24%.

Conclusion.
La perfusion isolée de membre est un traitement grevé d'un taux élevé de complications, mais il peut être entrepris dans les sarcomes les plus sévères avec un succès significatif. Ainsi, dans notre série, une chirurgie mutilante (en général l'amputation) a pu être épargnée à 76% des patients.

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Isolated Limb Perfusion With Tumor Necrosis Factor and Melphalan for Non-Resectable Soft Tissue Sarcomas: Long-Term Results on Efficacy and Limb Salvage in a Selected Group of Patients

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Background and Objectives: Isolated limb perfusion with TNF-alpha and melphalan (TM-ILP) is a limb salvage therapy for non-resectable soft tissue sarcomas (STS) of the extremities. It is indicated for patients for whom amputation or debilitating surgery is the only alternative. It can be used either as an exclusive therapy (in palliation) or as a neo-adjuvant treatment, followed by marginal resection of tumor remnants with minimal functional impairment.

Methods: Between February 1992 and March 2006, 57 TM-ILPs were performed on 51 patients with 88% high grade and 84% advanced stage tumors.

Results: Mean follow-up is 38.9 months (4–159, median 22 months). Twenty-one percent patients had significant early complications, with 3 major re-operations, and 23% suffered long-lasting complications. Complete response was observed in 25%, partial response in 42%, stable disease in 14% and progressive disease in 14%. Resection of the tumor remnants was possible in 65%. A complementary treatment was necessary in 31%, mostly radiation therapy. A local recurrence was observed in 35%, after a mean of 20.3 months (2–78), and distant relapse was seen in 45%, after a mean of 13.4 months (5–196). Mean Disease-free survival was 14.9 months, and overall 5-year-survival 43.5%. Amputation rate at 5 years was 24%.

Conclusions: TM-ILP is a conservative treatment with a high complications rate, but it can be successful even for the most severe STS of extremities. As a consequence the limb can be spared from amputation or debilitating surgery on the long term in about 75% of patients.
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KEY WORDS: **advanced extremity sarcomas; local treatment; multidisciplinary team work; prevention of amputation**

INTRODUCTION

Soft tissue sarcomas (STS) account for approximately 1% of all newly diagnosed tumors; over 50% arise in the extremities [1,2]. Limb-sparing surgery, generally associated with radiation therapy, can be successfully performed in up to 90% of these tumors, whereas amputation was the rule in nearly 50% before the 1980s [3–5]. Moreover, it has been proven that amputation does not improve overall survival, especially for large deep-seated high grade tumors [6–9]. Treatment of the latter is challenging, because of the size and location that often makes a surgical extirpation difficult or impossible without severe functional impairment. Multiple strategies have been developed to improve limb salvage, comprising radiation therapy, chemotherapy (intra-arterial or systemic), or both, delivered pre- or post-operatively [10–15].

Isolated limb perfusion (ILP) consists in surgically isolating the affected extremity by cannulating its vessels and connecting them to a heart-lung machine. A tourniquet is then applied at the root of the limb and an extra-corporeal circulation is achieved in mild hyperthermia. Drugs can be perfused in concentrations up to 30-fold the level tolerated in systemic infusion [16]. Leakage is monitored with radiolabeled albumin or erythrocytes injected in the circuit and then measured in the precordial region with a scintillation probe [17].

Creech et al. [18] first described ILP in 1958. The first series showed promising results in the management of malignant melanomas, but poor response rates for advanced STS [19–21]. Dramatically

Abbreviations: TM-ILP, TNF-melphalan isolated limb perfusion; TNF, tumor necrosis factor-alpha; STS, soft tissue sarcoma; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NA, not assessable; R0, radical resection; R1, marginal resection; R2, intra-lesional resection; MFH, malignant fibrous histiocytoma; MRI, magnetic resonance imaging; FNCLCC, Fédération Française des Centres de Lutte Contre le Cancer (French Federation of Cancer Centers).

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better results were obtained with the combination of high dose tumor necrosis factor-alpha (TNF-alpha) with melphalan, a low regional toxicity alkylating agent, first reported in 1992 [22]. Several multicenter and institutional studies confirmed the high efficacy of TNF and melphalan-ILP (TM-ILP). Complete response (CR) rates near 100% were obtained for melanomas and objective response rates as high as 80–90% were reported for non-resectable STS, with CR between 28% and 70%, and limb salvage reaching 81–90% [23–27]. Interferon gamma was initially added for its synergy with TNF-alpha, but was then abandoned for it did not prove to give significant better results than the double association in TM-ILP [23].

The mechanism whereby TNF-alpha works has been partially deciphered (reviewed in Ref. [28]): in the early phase (within minutes), it improves penetration of anticancer agents in cancer cells by enhancing permeability of neo-endothelial cells and pericytes. In the second phase (days), it induces destruction of neo-angiogenic vessels by apoptosis of the endothelial cells, and intravascular thrombocytes aggregation by local procoagulant activity.

Over time, different drugs (cisplatin, doxorubicin, etc.) and conditions have been experienced (true hyperthermia, hypoxia, varying duration of perfusion) to improve the efficiency of ILP, never reaching as high response rates with such a low toxicity profile as with TNF-alpha and melphalan in mild hyperthermia (<40°) for 90 min [29,30].

Our center actively participated to the development of TM-ILP for the treatment of locally advanced melanomas and sarcomas, with around 300 TM-ILPs performed since 1992. The results of the first 24 patients with STS was previously published in 2000 [31]. The goal of the present paper is to discuss the results of TM-ILP for STS on the long term. We report here that even for the most severe STS of the extremities, ILP with TNF and melphalan is a conservative treatment that can be successfully undertaken and the limb be saved from amputation or debilitating surgery in a great proportion of patients.

MATERIALS AND METHODS

Between February 1992 and March 2006, 51 patients, 27 women and 24 men, were treated in our institution for a locally advanced limb STS. Mean age was 54.9 years [range 20–84]. Fifty-seven TM-ILP were performed, 6 patients being treated twice.

All patients were selected through the multidisciplinary sarcoma board of our University Hospital (referral center for an approximate one million population), where about 120 new cases of soft tissue or bone tumors are discussed each year. As our center was one of the few in Europe offering this treatment in the 1990s, only a minority of patients were coming from the usual referring population of our hospital (12 patients = 24%). The remaining were referred from different oncologic or orthopaedic centers in Switzerland (21 patients = 42%) and from other countries: France (12 patients = 24%) or Germany (5 patients = 10%).

The Faculty of Medicine's ethic committee gave its approval for the treatment procedure.

The data were obtained from our Multidisciplinary Oncology Center. For the patients not followed in our institution, referring practitioners were contacted by mail or phone to collect the data. For most of the patients, because of the distance between treatment and review, only the most important follow-up data were available, and it was generally not possible to assess daily living activities or functional and satisfaction score.

Histopathologic Diagnosis, Grading, and Staging

Table I shows histolopathological diagnoses. Undifferentiated sarcomas (former malignant fibrous histiocytomas MFH) and liposarcomas represent more than half of cases with 17 (33%) and 13 (27%), respectively. All histopathologic analyses were performed by the sarcoma specialist of our Pathology Department, who is a member of the French Federation of Cancer Center's Sarcoma Group (FNCLCC). In three instances tissue blocs and microscopy slides were sent to the French Sarcoma Group for diagnosis review.

TABLE I. Histological Diagnoses (n = 51)

	n	%
Undifferentiated sarcoma (so-called MFH)	17	34
Liposarcoma	14	27
Leiomyosarcoma	3	6
Epithelioid sarcoma	3	6
Neurofibrosarcoma	3	6
Rhabdomyosarcoma	3	6
Angiosarcoma	3	6
Synovial sarcoma	2	4
Clear cell sarcoma	1	2
Osteosarcoma of the soft tissues	1	2
Unknown	1	2
Total	51	100

Tables II, IIIa and IIIb display histopathological grading and staging of the tumors. All tumors were classified for histological grading according to the FNCLCC classification [32,33]. There were 88% high grade tumors (II or III). Staging was done according to TNM classification of soft tissue sarcomas [34,35]. In 65% of cases the initial stage was T2b N0 M0, that is, a single large (>5 cm) deep-seated tumor. There were 84% stage II–IV tumors (high grade or any grade with local or distant spread).

Patients Characteristics and Past Medical History

Table IV summarizes the initial characteristics of the patients and tumors. Forty-six patients (90%) had tumors located on the lower extremity. Sarcoma presentation included 38 primary tumors (75%) 13 local recurrences (25%). Forty patients (79%) presented with a single tumor and 11 had multiple nodules (21%). The mean time between first symptoms and diagnosis was 22.7 months (0–128).

Eighteen patients (35%) had prior surgery of their tumor: 4 were marginal (R1) and 14 intratumoral (R2) resections. Eleven patients had a surgical biopsy, 8 a core needle biopsy (most of them in our hospital, who favors this diagnosis method) and 2 a cutaneous biopsy. In 12 cases the diagnosis method was not specified. A large amount of patients were referred to our center after initial non-oncological resections for misdiagnosed soft tissue tumors, which explains the low rate of specific oncologic diagnostic biopsy performed.

Twenty-seven patients (53%) had no past surgical or oncological treatment for their sarcoma, while prior treatments had been performed in 24 patients, 5 of them being referred after multiple resections and 8 after multimodal treatments including surgery, chemotherapy, and radiation therapy.

Indication for TM-ILP

In 39% of patients TM-ILP was indicated because of local spread after previous excisions. In 39%, extracompartmental location of the tumor (Fig. 1) or its close relationship to the neurovascular bundle

TABLE II. Histological Grading (FNCLCC, Ref. [32])

	n	%
Grade 1	5	10
Grade 2	17	33
Grade 3	29	57
Total	51	100

TABLE IIIa. TNM Classification of the Tumors (UICC TNM Classification of Malignant Tumors, New York, 2002)

TNM	n	%
T1a N0 M0	3	6
T2a N0 M0	4	8
T2b N0 M0	33	64
T1b N1 M0	1	2
T2a N1 M0	1	2
T2b N1 M0	1	2
T1b Nx M1	2	4
T2b Nx M1	2	4
Tx Nx M1	1	2
Unknown	3	6
Total	51	100

TABLE IIIb. Staging of the Tumors (WHO Classification of Tumors, Lyon, 2002)

	n	%
Stage IA	0	0
Stage IB	5	10
Stage IIA	3	6
Stage IIB	4	8
Stage III	28	54
Stage IV	8	16
Unknown	3	6
Total	51	100

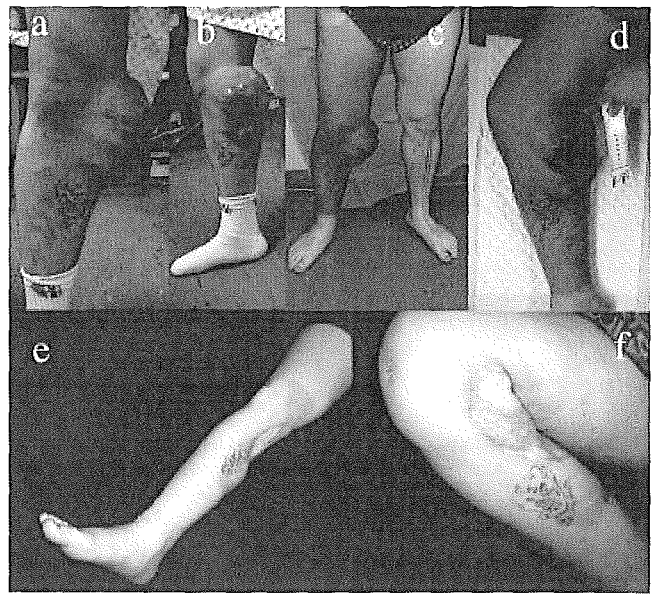

Fig. 1. Twenty-five-year-old male patient with a subcutaneous undifferenciated sarcoma near the knee joint, grade III, stage T2a, N0, M0. **a**,**b**: day 0, **c**,**d**: day 45, **e**,**f**: 18 months after tumor remnant excision, with good function and no recurrence.

made it non-resectable. In the last 22%, the size of the tumor, without regard to its location was such that no resection was conceivable. All indications for TM-ILP were discussed at our Sarcoma Board. In all patients the only alternative would have been amputation or surgery with unacceptable loss of function. Tumor location in the 51 patients were wrist and hand in 2, forearm in 3, elbow in 2, foot and ankle in 6, leg in 9, knee or popliteal fossa in 7 and thigh in 19, while 3 were unknown.

Contraindications

Metastatic disease does not necessarily preclude TM-ILP. There is a consensus that such patients in good performance status could avoid unnecessary mutilation thanks to TM-ILP. Five patients with locoregional and three with distant spread were submitted to TM-ILP in our institution.

Patients with known severe arterial occlusive disease (stenosis on angiogram or Fontaine stage IIb or more) of the implied limb were not eligible because perfusion could be shunted, loosing the desired antitumoral effect on the hypoperfused part of the limb and increasing the side effects on the overperfused part of it.

Patients with severe heart failure (NYHA class III and IV) were not eligible because of the inability to afford the expected transient distributive shock (see Leakage Monitoring and Early Complications Section).

ECOG status >1, severe organ dysfunction, infection (local or systemic), immunosuppression (allograft recipients, drug-induced, disease-linked) and significant autoimmune disease patients were also not eligible for TM-ILP.

TABLE IV. Characteristics of the Patients at Diagnosis

	n	%; range
Female/male	27/24	53/47%
Mean age at ILP procedure (yo = years old)	54.8 yo	20–84 yo
Upper/lower extremity	5/46	10–90%
Primary tumor	38	75%
Local recurrence	13	25%
Mean tumor size (cm)	13.2	2–38
Single tumor	40	79%
Multiple nodules	11	21%
Lymph nodes	3	6%
Distant metastases	3	6%
Delay between 1st symptoms and diagnosis (m = months)	22.7 m	0–128 m

Leakage Monitoring and Early Complications

Throughout perfusion, leakage was monitored using radiolabeled albumin injected in the extracorporeal circulation and measured in the precordium with a scintillation probe [36]. No patient suffered life-threatening leakage. In the early post-operative phase (hours to days), all the patients experienced some transient distributive shock due to leakage of small amounts of TNF in the systemic circulation after discontinuation of the extracorporeal circulation [37]. All patients were admitted in the Intensive Care Unit for at least 24 hr.

Regional toxicity was described by Wieberdink et al. in 1982 [38]. We used this classification to evaluate toxicity of the treatment on the perfused extremity and the WHO classification [39] to monitor the side effects of the treatment on general health.

Systemic leakage, when important, may yield hematological complications due to systemic effects of chemotherapeutic drugs [40]. Some patients experienced cytopenia, with rare cases of agranulocytosis. In the present series, this kind of complications didn't generate significant consequences and will not be discussed any further.

Response Assessment

TM-ILP response was assessed by measuring variation of the longest diameter and necrosis estimate on monthly MRI, according to the RECIST criteria [41]. After tumor remnants excision up- and

down-grading were then considered, depending on the amount of tumoral necrosis determined at microscopic examination as described by Eggermont et al. [23]. Thus the single most important factor, that determined tumor response, was tumor cells necrosis on microscopic examination.

Resection of the Tumor Remnants and Complementary Treatments

All patients were reevaluated in our multidisciplinary Sarcoma Board. Resection of the tumor remnants was done whenever possible, depending on clinical response and general status of patients. Monthly MRI examinations were repeated until best tumor response was obtained; resection was then performed, either in our center, or by the oncologic orthopaedic surgeon of the referring center.

Complementary treatments (radiation therapy, chemotherapy or combined chemo- and radiotherapy) were discussed according to tumor grade, response to TM-ILP and resection margins mainly.

Late Complications

Due to TNF and melphalan perfusion, surgery and/or radiation therapy, long-lasting locoregional complications are often observed after TM-ILP. Actually, all the patients presented with some degree of skin redness or pigmentation, some amount of edema and skin atrophy. We have focused on severe long-lasting complications, including skin necrosis, neurological complaints and other issues that might have notable consequences on daily living or have necessitated new treatments. As half of the patients were dead by the time of the review, and as most of them were coming from all parts of Switzerland, France and Germany, it was not possible to examine them and determine a functional limb score.

Limb Salvage, Local, Loco-Regional and Distant Recurrences, Amputations and Survival

In calculation of amputation rate, primary amputations were those performed directly after TM-ILP for unsatisfactory response to treatment or local complications. Secondary amputations were those performed later, either after a local relapse or after late progression of an unremoved primary tumor.

Recurrences were considered as local when they presented in or near the resection bed of the primary tumor, for example in the same segment (thigh, leg, arm, forearm, etc.) or compartment of the limb, and loco-regional when located in the next segment (for example skip metastases in the thigh from a primary tumor of the leg) or in the known regional lymph nodes of the limbs (popliteal, ilio-inguinal, elbow, or axillary nodes). Local recurrences were always located within the perfused area, whereas loco-regional recurrences might appear within or outside the perfused area.

Metastases were considered as distant in all other situations (controlateral limb, other extremity or girdle, cerebral or thoraco-abdominal locations).

Statistical Methods

Confidence intervals for all data were based on the binomial law [42]. Amputation Rate, Disease-Free Survival (DFS) and Overall Survival curves were established according to the Kaplan–Meier (K–M) methods [43]. Survival and local or distant recurrences, as well as disease-free interval were measured from the date of the TM-ILP. Patients still alive were considered as censored observations at the date of the last follow-up. All data were reviewed by our clinical epidemiologist, who determined the K–M curves and the recurrence and survival rates by using the software "R" [44].

TABLE V. Response Rates (51 Patients, 57 ILP)

	Grade 1	Grade 2	Grade 3	Total (n)	Total (%)
Complete response = CR	0	9	5	14	25
Partial response = PR	2	6	16	24	41
No change = NC	2	3	3	8	14
Progressive disease = PD	0	2	6	8	14
Unmeasurable	0	0	0	0	0
Not evaluable: ILP<3 months	1	1	1	3	6
Total	5	21	31	n = 57	100

RESULTS

This retrospective study has a mean follow-up of 38.9 months [range 4–159, median 22 months]. TM-ILP were performed between February 1992 and march 2006. The data were collected and reviewed until June 2006. No patient was lost to follow-up.

Tumor Response and Grade-Related Response

Table V displays the response rates and responses according to the histological grade. In 67% of all 57 TM-ILPs, a major tumor response was observed with 14 (25%) complete response (CR, disappearance of all measurable disease for >4 weeks on MRI or necrosis 98–100% on histopathology analysis) and 24 (42%) partial response (PR, regression of >50% on MRI or necrosis >50%). Eight patients (14%) showed no evolution of the disease (no change NC), 8 patients (14%) progression of the tumor (progressive disease PD) and 3 were not fully assessed due to a too short follow-up (not assessable NA).

The six patients undergoing a second TM-ILP showed 1CR, 2 PR, 1 NC, 1 PD, and 1 NA (short follow-up). All but one (who showed twice a CR) had a worse response following the second TM-ILP.

A response rate (CR + PR) was observed in 40% grade I, 74% grade II and 68% grade III sarcomas. No CR was observed in grade I tumors, which elicited only PR or NC. Six PD out of 8 were observed in grade III tumors.

Toxicity and Complications

The mean Intensive Care Unit stay was 2 days (0–11), with 4 patients staying more than 3 days.

Twelve patients (21%) presented with serious early complications, of which four had a transient nerve palsy (Wieberdink grade 3) and one had a compartment syndrome of the thigh (grade 5) who eventually was amputated due to ongoing severe sciatic nerve palsy combined with extensive skin necrosis. Other severe complications included 3 patients with hematologic disorders (WHO grade 2 or more), 2 reoperations in emergency for retroperitoneal bleeding, one extensive tumor necrosis with early debulking after 13 days, 2 temporary renal failures, one temporary liver failure and 1 thrombo-embolic disease, some of them in the same patient. All patients sustained at least a Wieberdink grade 2 local reaction (limb edema, skin redness).

Thirteen patients (23%) suffered from late complications: 8 cutaneous, 7 long-lasting neurologic (comprising pain and algodystrophy), 1 articular (elbow stiffness), 1 orthopedic (femoral nail fatigue fracture) and one septic shock. Among 8 patients with cutaneous complications, 4 needed multiple plastic surgery procedures to cover defects, and 4 had a chronic skin ulcer. Two of them had received complementary radiation therapy.

Two patients sustained both early and late complications, uncorrelated one with the other.

Tumor Remnants Excision and Complementary Treatment

Following the first TM-ILP tumor remnants were resected in 33 patients (65%), while 7 (14%) had to be amputated. Ten distant en bloc resections (R0), 20 marginal (R1) and 3 intra-tumoral (R2) were performed. On six patients, because of early appearance of distant metastases, no operation was performed.

After the second TM-ILP, 1 R1, 1 R2 resection and 2 amputations were performed; while 2 patients were treated conservatively.

Sixteen (31%) patients received a complementary treatment: radiation therapy in 9, systemic chemotherapy in 3 and combined radio- and chemotherapy in 2.

Recurrence

Thirty-two patients (63%) suffered from recurrence. Ten patients had distant recurrence alone, 6 local recurrence alone and 4 loco-regional recurrence alone. Eleven patients sustained both local and distant relapse (5 synchronously, 3 locally first, and 3 distantly first), and one patient had synchronous local, loco-regional and distant relapse.

Recurrence within perfusion area occurred in 19 patients (37%) and outside perfusion area in 25 patients (49%). Figure 2 summarizes location and distribution of recurrences.

Local recurrence was diagnosed in 18 patients (35%). Mean local recurrence time from TM-ILP was 20.3 months [range 2–78]. Only high grade tumors recurred locally, from which had elicited a 5 CR, 10 a PR, 2 a NC, and 2 a PD after the first TM-ILP. A R0 resection had been performed in 5 patients, a R1 in 7, a R2 in 2, an amputation in one and no resection in 4. Six patients (30% of the patients with a local recurrence) were eligible for a second TM-ILP.

Loco-regional recurrence was diagnosed in 5 patients (10%). Mean loco-regional recurrence time from TM-ILP was 8.8 months [range 4–19]. All loco-regional recurrences but one were located in regional lymph nodes outside the perfusion's area. They were observed only in patients with high grade tumors.

Distant recurrence developed in 22 patients (43%). Mean time from TM-ILP to distant metastases was 13.4 months [range 2–43]. Again only patients with high grade tumors presented with distant metastases. Seventy-seven percent of them were located in the lungs. Initial response to TM-ILP had been a CR in 6 (23%), a PR in 11 (42%), a NC in 4 (15%) and a PD in 5 (19%).

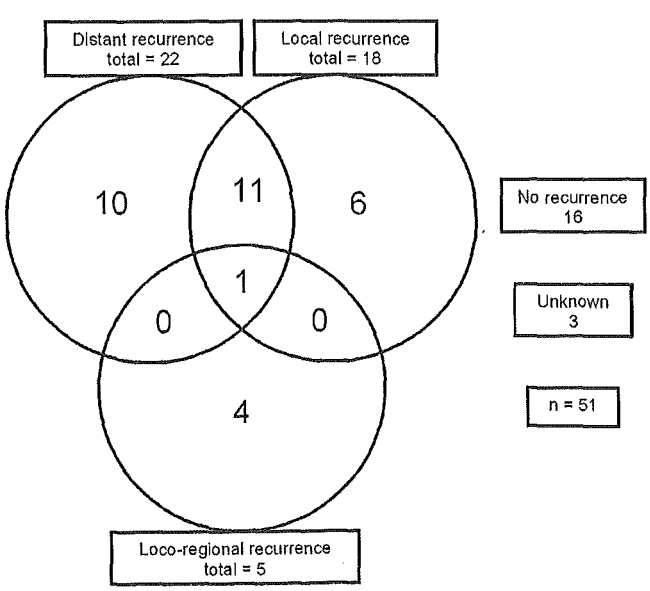

Fig. 2. Location and distribution of recurrences.

Disease-Free and Overall Survival

Mean DFS from TM-ILP was 14.9 months (2–49). Three patients with distant metastases prior to TM-ILP were not considered. Overall survival rates at 2, 5, and 10 years were 60%, 44% and 28% respectively.

Twenty-four patients out of 51 have died (47%) with a mean overall survival of 23.3 months (4–93). All patients but one died of the disease (96%).

Amputations and Limb Salvage

Following TM-ILP limb salvage was not possible in 12 patients (24%), with 7 primary and 5 secondary amputations, as shown in Figure 3, where there is an early steep curve corresponding to the primary amputations after ILP and it is followed by a linear and not steep curve corresponding to the secondary amputations. This illustrates that the secondary amputations were due to the natural outcome of the disease not in relation with ILP.

No specific risk factors could identify patients who finally needed amputation (early or late) in this heterogeneous group of patients. *Primary amputation* was decided in 7 patients: 5 had insufficient treatment response (NC or PD), one patient had a local multi-operated status and one patient had a compartment syndrome with complete sciatic nerve palsy. Five different histological diagnoses and all grades were present.

Secondary amputation was performed in 5 patients (12%): two had an unsuccessful response to a second TM-ILP, two patients had a diffuse local relapse and one patient, who refused excision of the primary tumor after TM-ILP, had a slow progressive disease during 3.5 years.Overall primary limb salvage rate was 86%, and the total limb sparing 76%.

DISCUSSION

This retrospective study is based on a selected group of patients with a very poor prognosis (88% of the patients in this series had a high grade and 84% an advanced staged tumor). It demonstrates that TM-

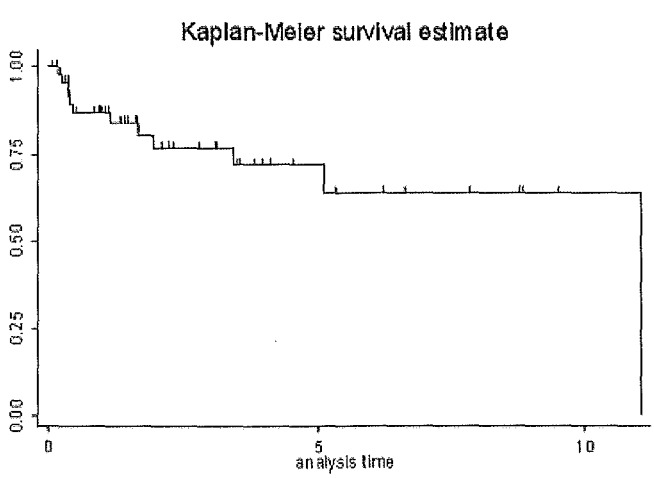

Fig. 3. K–M curves showing the biphasic pattern of amputations after TM-ILP (early versus late events) x-axis = years; y-axis = amputation-free proportion.

ILP is able to offer a limb sparing strategy even for the patients with the most aggressive non-resectable soft tissue sarcoma, observed with a long-term follow-up more than 10 years.

While comparing other publications in the literature, the present series has the longest mean follow-up (38.9 months, 4–159) with Lev-Chelouche's study in 1999 who was referring on six desmoid tumors [45].

It would be difficult to have a much longer follow-up while dealing with advanced high grade sarcoma patients, because most of them recur and die within a few years after treatment as presented in our experience with 40% death rate after 2 years. In our results 44% of patients survived more than 5 years. This is of notable importance, because late relapses and amputations can be observed.

In fact the amputation rate is one of the highest ever published in spite of the fact that 3/12 were submitted to a second TM-ILP. Late amputations up to 3.5 years after TM-ILP have been identified. One may speculate that the real limb salvage in some cohorts is overrated because of a shorter follow-up. Likewise local relapse rate (35%) is high compared with other series, but again 5 recurrences were observed more than 3 years after TM-ILP. The long-term recurrence rate does not seem to be influenced by longer follow-up, as only 2 patients recurred more than 3 years after treatment. Large differences in limb salvage and local relapse can be explained by higher proportion of aggressive tumors and longer follow-up, with consequently difficulties to compare our results with others [23,24,26,29,46,47].

The 25% complete response (CR) rate of this series is comparable to the 28% and 29% CR of the European multicenter study published by Eggermont et al. in 1996 and 1999 [23,48], the 29% CR of the Rotterdam experience with older patients of van Etten in 2003 [49] and the 24% CR in recurrent sarcomas in irradiated fields of Grünhagen in 2005 [50].

CR results reported by Bonvalot et al. in 2005 [51] were also higher than ours, but they were based on a randomized phase IIb study (studying TNF doses) with a consistent proportion of stage Ib and IIa patients. Furthermore CR was considered when 90% necrosis was present on histological examination, whereas 98-100% necrosis were required in our series [48–51]. With 42% PR, the objective response rate is 67%, which is also comparable to the aforementioned studies (57–76%).

Classical early complications related to TM-ILP (local, hemodynamic, hematological, renal, hepatic, etc.) were present in 21% of the patients. In most of the cases they were transient, predictable and successfully managed. They generated a mean Intensive Care Unit stay of 2 days (0–11), with 4 patients staying more than 3 days. They were mainly due to systemic TNF leakage during perfusion distinct from the so called "tourniquet effect," as described by Christoforidis et al. in 2003 [37]. These data are not consistently different from what has already been described in the literature [28,38,39]. With two early re-operations (3.5%) for bleeding on the cannulation site, this series reaches an acceptable complication rate. Scarce data in the recent literature makes a global comparison difficult to establish. No treatment-related death was reported.

With 23% late and long-lasting complications, this series is also comparable to others; local consequences of TM-ILP can be serious, as one patient needed to be amputated one year after treatment because of a Wieberdink grade 5 complication (thigh compartment syndrome and subsequent complete sciatic nerve palsy). Eight patients suffered from permanent skin ulcer or needed iterative surgery to cover a cutaneous defect. It is however difficult to distinguish between tumor-related from TM-ILP-related skin complications. It is worth mentioning that only two of the 13 patients with long-lasting complications had received complementary radiation therapy. Together with Olieman et al. [47] and Vrouenraets et al. [52] we think that complementary radiotherapy is not contraindicated after TM-ILP and excision of tumor remnants, as far as local healing is acquired. In order to improve post-operative edema, we have introduced early systematic lymphatic drainage (in the ICU), mobilization therapy and mild-pressure stockings, with subjective promising results, although no objective measurements have been performed.

Tumor remnants excision was performed in 33 patients (65%) after the first TM-ILP and in two out of 6 after the second one. Marginal resection (R1) is the rule (20/34). TM-ILP often facilitates surgical resection not only because of tumor shrinkage, but also because the sarcoma is better delineated. The previous fragile thin pseudocapsule is replaced by a thick fibrous pseudocapsule. It is constituted by the tumor response itself and by surrounding non-tumoral fibrosing tissue (Fig. 4). The surgeon find this resistant pseudocapsule, which enables a safer marginal resection of the tumor remnant with a lower risk for positive surgical margins or capsule break with tumor spilling in the resection bed.

With 76% total limb salvage, our data are within the range of the recent literature (from 58% for Noorda et al. in 2003 [27] to 89% for

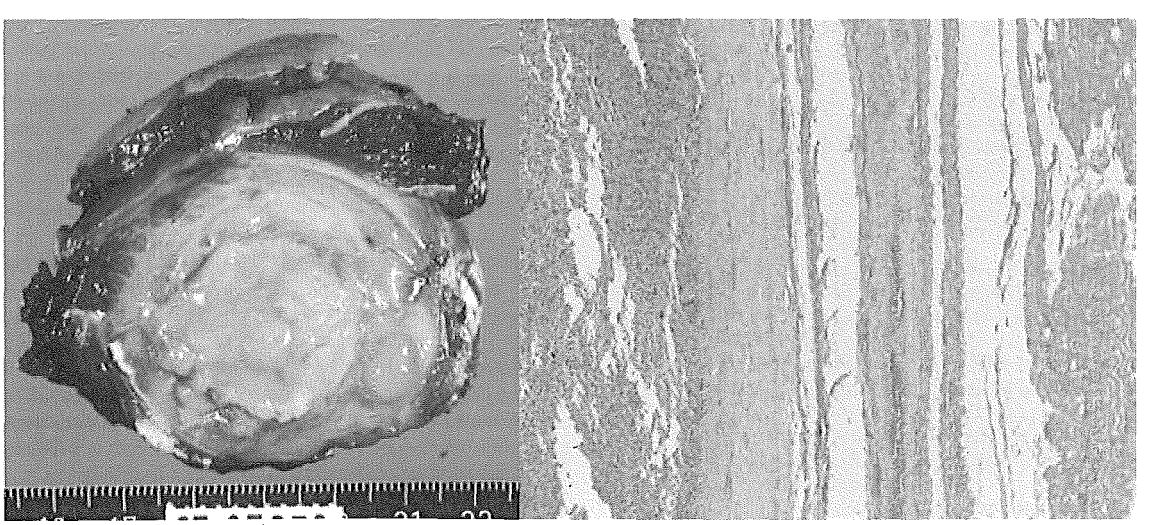

Fig. 4. Macroscopic (**left**) and microscopic (**right**) pictures of an operative specimen showing extensive necrosis and a thick pseudocapsule surrounding the tumor.

Santinami et al. in 1996 [24]). Initial TM-ILP and tumor remnant excision even reach 86% primary limb salvage, which is close to the best results published by Santinami et al. in 1996 [24] with 90% limb sparing for after 15 months follow-up. As the primary treatment end-point is amputation or debilitating surgery prevention, we may consider the present results as satisfactory.

Local recurrence was observed in 19 patients (37%), which compares with others [25,46]. This high rate can be explained on one hand by a longer mean follow-up (>3 years) allowing late recurrences registration and on the other hand by a higher proportion of high grade and high stage tumors. Finally we also get a great amount of recurrences or disseminations in already multi-operated patients, who were referred to our center for TM-ILP.

In most of the cases local and distant recurrences occurred simultaneously. Systemic metastases presented first or synchronously in 68%. All together, a total of 26 loco-regional or distant recurrences (51%) were observed. This indicates that a distant spread was probably already present by the time of TM-ILP. Actually, all patients with recurrence had a high-grade sarcoma. It confirms that the less differentiated the tumor, the more aggressive the biological behavior and the higher the risk for relapse, whatever the stage as already mentioned. It confirms that local control does not correlate with overall survival [6–9].

Five years survival rate after TM-ILP was 44%, with 96% disease-related deaths. In 2003, Noorda et al. [27] reported 48% 5-year disease specific survival rate, but with 20% grade I and 41% stage I and II tumors. Other series do not mention 5-year survival rate because of a shorter follow-up.

For soft tissue limb sarcomas treated by classical surgery, Pisters mentioned 76% survival after 5 years [53]. This corresponds to the fact that a group of patients combining less aggressive sarcomas with all stages together have a better prognosis and cannot be compared with our series of patients, that includes 88% high grade (FNCLCC II and III) and 85% >stage IB STS. Patients who could afford an oncological safe resection were spared TM-ILP in our Sarcoma Board. Our series demonstrates that preservative treatment should be considered in order to prevent the remaining patients with a poor prognosis from mutilation.

Limitations of this retrospective study include difficulties for collecting data. Seventy-six percent of patients were coming from outside the referring population of our University Hospital and more than half had died by the time the data were collected. Following the published review of the first 24 patients (1992–1998) [31], no database or prospective follow-up were available by the time the present review was restarted. Another limitation was the impossibility to evaluate any functional outcome or impact on daily living, which should ideally be part in a study evaluating a local treatment strategy, but this aspect of TM-ILP was thoroughly described by Vrouenraets et al. in 1999 [46]: he demonstrated 25% global limb atrophy and 40% restricted ankle extension after 48 months.

The present study is a retrospective review of all the STS treated by TM-ILP in our center. It is very heterogeneous when regarding 10 different histopathological diagnoses, 11 different TNM and 6 different stages together in the same series. However it is homogeneous and different from other series in that there are almost only high grades (II and III) and high stages (IIa–IV). We might have been more selective and exclude the lower grades and stages in order to determine the outcome of the treatment only for high grade and high stage tumors, considering that indications to TM-ILP do not depend on the histopathologic characteristics of the tumors. However considering that all patients presented criteria of irresectability, we decided not to exclude any patient from the review. It is important in that TM-ILP offers long-term perspectives of limb salvage in all patients with an advanced STS of an extremity, whatever the prognosis. It is not dedicated only to condemned patients for whom an amputation would significantly worsen the quality of life during the last months or years of their existence.

CONCLUSION

TM-ILP is a procedure with a high immediate and late complications rate. Long-term results show that, even for the most severe soft tissue sarcomas of the extremities (88% high grade and 84% advanced stage tumors in the present series), this conservative treatment can be successfully undertaken and the limb be saved on the long term from amputation or debilitating surgery in three quarters of the patients.

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