Referral patterns, prognostic models and treatment in soft tissue sarcomas

Seinen, Johanna Magda

Chapter 6

Isolated limb perfusion of soft tissue sarcomas:

A comprehensive review of literature

Seinen JM, Hoekstra HJ

Cancer Treat Rev. 2013 Oct;39(6):569-77

Abstract

Patients with primary irresectable, locally advanced soft tissue sarcomas of the limbs form a challenging group for the treating physician. Multimodality treatment is necessary to guarantee optimal limb salvage and survival rates. Since the introduction of isolated limb perfusion in the late fifties, several treatment regimens have been proposed. Isolated perfusion with melphalan and TNF-α, as part of a multimodality treatment, is regarded as the current best treatment option today. Ongoing studies are investigating potential benefit of other doses, new chemotherapeutic agents and new techniques in perfusion and radiotherapy. This article provides a historical overview of published literature and insight in upcoming treatment techniques.

Introduction

Soft tissue sarcoma (STS) comprise a heterogeneous group of malignancies, accounting for about 1% of all cancers. They may arise in any part of the body, but develop most commonly in the extremities (45%). [1] Because STS typically present as a painless lump without loss of function or influence on the patients general health, there is usually a substantial delay before initial presentation, allowing the tumor to grow to considerable size. In case the tumor is too large for local resection or in close adherence to important structures with resection causing severe impaired limb function, neo-adjuvant therapy could be attempted in order to achieve pre-operative downsizing of the tumor. An induction treatment approach with intra-arterial chemotherapy in combination with radiation has been investigated, with good results in terms of high limb salvage and low local recurrence rates, however, morbidity rates were too high, and the treatment protocol was eventually abandoned. [2,3] Another, well documented, neo-adjuvant treatment possibility is regional limb perfusion (ILP). During the last two decades, several institutions in Europe have utilized the perfusion technique as a safe alternative for amputation. [4] A continuous search for developing and improving the perfusion technique and chemotherapeutic agents has led to numerous publications. This review provides an historical overview of literature, and describes the current status and new applications of isolated perfusion.

Landmarks in the treatment of primary irresectable soft tissue sarcoma

Klopp and colleagues were the pioneers in the field of intra-arterial chemotherapy. In 1950, they explored the benefit of intra-arterial administration of nitrogen mustard for the treatment of various malignancies in the United States. [5] Although a better tumor response in comparison with venous administration was demonstrated, complete eradication was not possible because systemic toxicity precluded maximal effective drug doses. In the late fifties, Chreech, Krementz and Ryan attempted to reduce the systemic toxicity from intra-arterial chemotherapy by introducing a new technique based on the heart–lung machine, utilizing an oxygenated extracorporeal circuit: isolated limb perfusion (ILP). [6] They started using melphalan, which is less neurotoxic, and reported good tumor response in various cancers, mainly in melanomas. [7] The first perfusion in Europe was carried out by Lebrun in Belgium in 1960, and eventually adopted in some 30 cancer centers throughout Europe.

Originally, perfusions were performed under normothermia (37–38 °C). Cavaliere was the first who experimented with hyperthermic ILP and reported enhanced tumor kill with less serious local toxicity. [8] In addition, Wieberdink et al. recommended to calculate melphalan dosage based on limb volume, instead of body weight, to reduce regional toxicity.[9] Further advancements came when the pressure regulated perfusion technique was introduced and leakage monitoring improved. [10-12]

In 1987, Hoekstra et al. reported the ineffectiveness of ILP with melphalan in the treatment of sarcoma. [13] Therefore, other chemotherapeutic agents were explored, but never widely applied in the clinic due to ineffectiveness or severe side effects. [14-19]

A new breakthrough in the history of ILP came in the early nineties, when Lejeune et al. added tumor necrosis factor-α (TNF-) to melphalan (TM–ILP) in the treatment of locally advanced STS of the limbs. [20] TNF-α causes selective destruction of the tumor vasculature and facilitates drug penetration in the tumor due to intratumoral vessel permeability. The addition of TNF-α to the perfusate has led to a 4–5-fold increased uptake of melphalan by the tumor and resulted in an excellent tumor response and limb salvage rates with acceptable local and systemic toxicity. TM–ILP was further explored in a multicentre study in Europe, which confirmed TM–ILP as a safe and effective alternative for amputation in locally advanced STS. [4,21] Although the search for new chemotherapeutic agents has continued in the last decades, no agent has led to better tumor response and local control than the combination of TNF-α and melphalan. A historical overview of literature from isolated limb perfusion in STS is shown in Table 1.

Indications for ILP

ILP is used as an alternative limb sparing treatment for patients with primary, irresectable STS, due to either multifocal disease, large size or close adherence to important structures, and who are planned for amputation. ILP is given with curative intent and aims for the same local control as amputation.

Also, patients with recurrent disease after multimodality treatment have been included in ILP studies with a fair limb salvage rate of 65/100% and limited regional toxicity (Table 1). [22,23] In the many years of experience with perfusion,

other indications have been recognized. High grade STS have a high potential for metastasis, and as much as 30% of patients eventually develop metastasis and die from their disease. In case of systemic progression of disease, there is restraint towards extensive treatment for the primary tumor, due to the possible side effects of treatment and the short life expectancy. Nevertheless, the primary tumor could cause severe functional impairment in the short term leading to considerable reduced quality of life. The first study investigating the role of ILP in the palliative setting was performed in the late nineties, in a small group of patients (*n* = 9) and reported acceptable treatment related morbidity (30%) and high limb salvage (89%), concluding that ILP is a feasible and efficient palliative treatment in disseminated patients. [24] More recently a larger study (*n* = 51), confirmed these findings, concluding that ILP provided limb salvage in nearly 100% of patients with tolerable toxicity (Table 1). [25]

A specific indication for ILP is aggressive fibromatosis, also named desmoid tumor. Classified as cancer, because they can invade locally, but without metastatic potential. Mutilating surgery is therefore not justified. A few studies have described their results for ILP in desmoids patients, however results are limited due to small numbers. [26-28] The largest study (*n* = 12) showed a good tumor overall response (75%) (Table 1). Local control was obtained after 10/12 ILPs and in the other two patients through repeat ILP and systemic chemotherapy, thus leading to an overall local control rate of 100%. [28] Because local toxicity was mild, there seems a fair indication for ILP in symptomatic, irresectable desmoids of the limbs.

Another challenging disease is the Stewart–Treves syndrome, a rare type of sarcoma developing in chronically lymph edematous arms after radical mastectomy, with a multifocal presentation and difficult to eradicate by surgical resection. A small study analyzed 16 ILPs in 10 patients, and showed an 87% overall response rate (complete and partial response), with four patients receiving a second or even third ILP (Table 1). [29] Limb salvage was achieved in eight patients (80%), with a mean follow up duration of 34.8 (3–115) months. In four cases, grade 3 (according to Wieberdink [9]) with edema, blistering and slightly disturbed mobility was observed, and in six cases grade 2 toxicity. Because treatment options are limited in the case of Stewart–Treves syndrome, ILP should be seriously considered in irresectable patients, nonetheless, possible severe side effects should be weighted in treatment decision.

Table 1. Overview results in extremity perfusion for sarcoma.

Author	Year	Study	Cytostatics	N	CR %
Krementz et al.[79]	1977	Single	M/Act-D/HN2	17	0
Muchmore et al.[80]	1985	Single	M/Act-D/HN2/various	51	6
Stehlin et al.[81]	1984	Single	M/Act-D	65	NS
Lethi et al.[82]	1986	Single	M/Act-D	64	NS
Krementz.[83]	1986	Single	M/Act-D	56	NS
Hoekstra et al.[13]	1987	Single	M	14	NS
Pommier et al.[18]	1988	Single	Cisplatin	17	0
Di Filippo et al.[84]	1988	Single	M/Act-D	55	NS
Klaase et al.[17]	1989	Single	Dox/M	13	7
Kettelhack et al.[85]	1990	Single	M/Act-D	9	NS
Eggermont[86]	1993	Single	TNF/M_IFN	20	55
Hill et al.[45]	1993	Single	TNF/	8	100
Fletcher et al.[90]	1994	Single	Cisplatin	75	NS
Rossi et al.[14]	1994	Single	Dox	23	NS
van Ginkel et al.[16]	1996	Single	Cisplatin	4	NS
Eggermont et al.[21]	1996	Multi	TNF/M_IFN	55	18
Eggermont et al.[4]	1996	Multi	TNF/M_IFN	186	18
Santinami et al.[48]	1996	Single	TNF/M	10	70
Rossi et al.[91]	1996	Single	TNF þ Dox	18	NS
Gutman et al.[51]	1997	Single	TNF/M_IFN	35	37
Olieman et al.[88]	1997	Single	TNF/M	25	40
Olieman et al.[68]	1998	Single	TNF/M (IFN)	34	35
Olieman et al.[24]	1998	Single	TNF/M (IFN)	9	44
Lev-Chelouche et al.[30]	1999	Single	TNF/M (IFN)	5	20
Lev-Chelouche et al.[27]	1999	Single	TNF/M (IFN)	6	33
Lev-Chelouche et al.[87]	1999	Single	TNF/M (IFN)	13	38
Eggermont et al.[92]	1999	Multi	TNF/M_IFN	246	28
Rossi et al.[42]	1999	Single	TNF þ Dox	20	26
Lejeune et al.[56]	2000	Single	TNF/M_IFN	22	18
Daryanani et al.[15]	2000	Single	Carboplatin	4	NS
Lans et al.[29]	2002	Single	TNF/M_IFN	16	56
Noorda et al.[58]	2003	Single	TNF/M_IFN	49	8
van Etten et al.[93]	2003	Single	TNF/M_IFN	29	38
Di Filippo et al.[41]	2003	Single	Dox_TNF	NS	22
Feig et al.[38]	2004	Single	Dox	31	NS
Rossi et al.[39]	2005	Single	TNF/Dox	21	5

PR %	NC %	LS %	LR %	5-year survival %	Remarks
35	65	NS	NS	NS	Historical
12	82	NS	NS	NS	Historical
NS	NS	94	NS	73	Historical
NS	NS	100	11	67	Feasibility EBRT
NS	NS	100	21	65	Historical
NS	NS	100	7	69	Historical
18	82	NS	NS	NS	Cisplatin
NS	NS	78	24	48	Historical
0	93	61	0-24	44-77	Doxorubicin
NS	NS	78	33	66	Historical
40	5	90	NS	NS	TNFα
0	0	64	NS	NS	Low-dose TNFα
NS	NS	NS	7	48-100	Largest cisplatin study
74	26	91	27	48	Doxorubicin
NS	NS	NS	NS	NS	Cisplatin
64	18	84	13	NS	First multicenter study
57	25	82	11	NS	Beromun_registration
20	10	89	NS	NS	None
NS	NS	81	10	NS	None
54	9	85	0/31	NS	None
52	8	NS	NS	NS	Angiographic response
59	6	85	14	60	Feasibility EBRT
33	23	89	22	0	Palliative treatment
80	0	80	NS	NS	Kaposi sarcoma
50	17	100	33	NS	Desmoid
54	8	85	38	NS	Multifocal
47	25	76	NS	NS	Definition irresectability
64	10	84	10	64	None
64	18	77	14	86	None
NS	NS	100	NS	NS	Carboplatin
31	13	80	NS	NS	Lymphangiosarcoma
55	37	57	13	48	None
38	24	76	NS	NS	Elderly patients >75 years of age
55	23	77	7	69	Phase I and II study Dox and Dox þ TNFα
NS	NS	NS	NS	NS	Doxorubicin
57	38	71	19	57	TNFα þ doxorubicin

Table 1. Continued.

Author	Year	Study	Cytostatics	N	CR %
Grunhagen et al.[53]	2005	Single	TNF/M_IFN	240	24
Grunhagen et al.[53]	2005	Single	TNF/M_IFN	48	38
Bonvalot et al.[46]	2005	Single	TNF/M	100	36
Grunhagen et al.[28]	2005	Single	TNF/M_IFN	12	17
Lans et al.[22]	2005	Single	TNF/M_IFN	26	20
Grunhagen et al.[94]	2005	Single	TNF/M_IFN	64	42
Grunhagen et al.[95]	2006	Single	TNF/M_IFN	217	18
Grunhagen et al.[25]	2006	Single	TNF/M_IFN	37	16
Schlag and Tunn[96]	2006	Single	TNF/M_IFN	125	19
Thijssens et al.[64]	2006	Single	TNF/M	39	NS
Thijssens et al.[47]	2006	Single	TNF/M	64	NS
Hayes et al.[44]	2007	Single	TNF/M	18	NS
van Ginkel et al.[57]	2007	Single	TNF/M_IFN	73	25
Hoven-Gondrie et al.[60]	2007	Single	TNF/M_IFN	32	NS
Pennacchioli et al.[97]	2007	Single	M or Dox with or without TNFα	88	32
Cherix et al.[50]	2008	Single	TNF/M	51	25
Hoven-Gondrie et al.[61]	2008	Single	TNF/M	73	NS
Bonvalot et al.[26]	2009	Single	TNF/M	100	19
Di Filippo et al.[98]	2009	Single	TNF_Dox	75	34
Nachmany et al.[55]	2009	Single	TNF/M	42	17
Lasithiotakis et al.[23]	2010	Multi	TNF/M	6	17
Wray et al.[40]	2011	Multi	TNF/M Dox	17 12	6 NS
Grabellus et al.[43]	2011	Single		53	NS
Deroose et al.[49]	2011	Single	TNF/M	208	18
Hoven-Gondrie et al.[54]	2011	Single	TNF/M	102	22
Deroose et al.[69]	2011	Single	TNF/M	122	4
Deroose et al.[89]	2012	Single	TNF/M	29	33
Seinen et al.[99]	2012	Single	TNF/M	72	NS
Seinen et al.[100]	2012	Single	TNF/M	88	17

Abbreviations: Act-D, dactinomycin-D; Dox, doxorubicin; EBRT, external beam radiotherapy; IFN, interferon-g; LR, local recurrence; LS, limb salvage; M, melphalan; Multi, multicenter; NC, no change; HN2, mechlorethamine (nitrogen mustard); NS, not stated; Single, single center; ILP, isolated limb perfusion

PR %	NC %	LS %	LR %	5-year survival %	Remarks
50	26	82	NS	±45	Largest single center
31	29	85	NS	36	Dose reduction
29	35	77	24	NS	Dose reduction
58	25	100	17	NS	Desmoid
50	30	65	27/45	40	Previous irradiated recurrences
45	13	82	45	39	Multifocal/recurrent sarcoma
51	31	75	26	49	Prognostic factor
68	16	92	NS	NS	Palliative treatment
53	28	81	18	NS	None
NS	NS	NS	NS	NS	Quality of life
NS	NS	89	NS	61	Value adjuvant RT
NS	NS	NS	NS	NS	None
69	6	60	NS	70	70% Long-term LS outcome
NS	NS	NS	NS	NS	Vascular morbidity
59	8	83	27	NS	Melphalan or doxo with or without TNFα
41	28	76	35	44	Long-term results
NS	NS	NS	NS	NS	Long-term effects according to LENT-SOMA
39	42	87	14	NS	None
48	18	85	21	62	TNFα and doxorubicin
36	47	?	42	NS	High vs low dose TNFα
50	33	100	NS	NS	Recurrent disease
64	30	41	NS	NS	Phase II trial: comparison of two regimens
NS	NS	NS	NS	NS	
NS	NS	NS	11	NS	Histologic response
53	29	81	30	42	Long-term results largest single center
55	23	77	15	NS	TNFα dose reduction
66	29	89	21	NS	Role of adjuvant RT
38	29	NS	32	52	ILP for distal part limb
NS	NS	NS	NS	NS	Treatment related fractures
55	28	NS	11	NS	Local recurrence after ILP

Kaposi sarcoma, associated with acquired immunodeficiency syndrome, has a wide variety of local treatments, but are only sufficient for localized small tumor burden. Kaposi sarcoma is highly radiosensitive and thus local radiation has been widely used for control, however, recurrences are frequent, and this modality is limited and cannot be used repeatedly. The role of ILP was analyzed in a small group of patients (*n* = 5) and showed a remarkably good overall response rate of 100%, with one patient having a complete response. [30] No surgery was performed. Four patients developed grade 3 toxicity with blisters. Two patients showed progression after 2 months leading to an amputation in one case. Because of a small number of patients and a relative short follow up of 2 years, no strong conclusions can be made, but these finding do suggest that ILP can be considered as palliative treatment in Kaposi sarcoma.

Perfusion technique

Isolated perfusion can be performed at three levels of the lower limb; iliac, femoral, or popliteal level, and for the upper limb at two levels; axillary or brachial level (Fig. 1). Isolation of the blood circuit is achieved by ligating the collateral vessels and clamping the major artery and vein after systemical heparinization (Fig. 2).

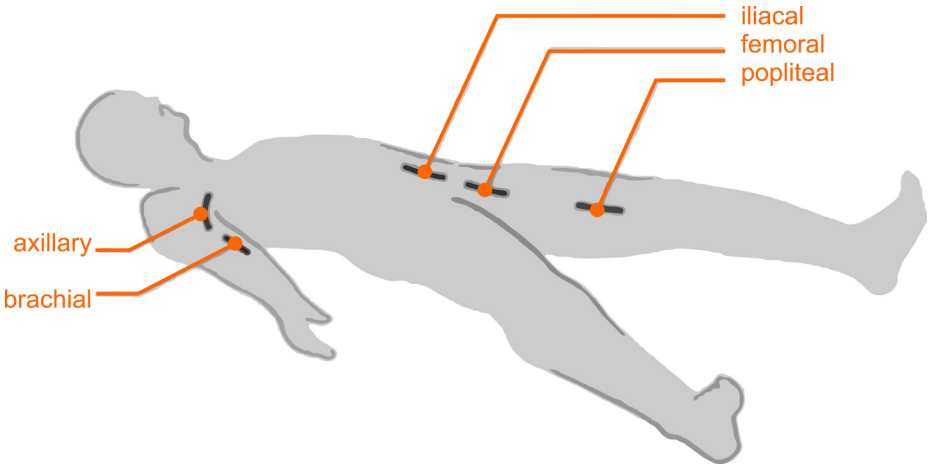

Figure 1. Various perfusion levels of the upper and lower limbs

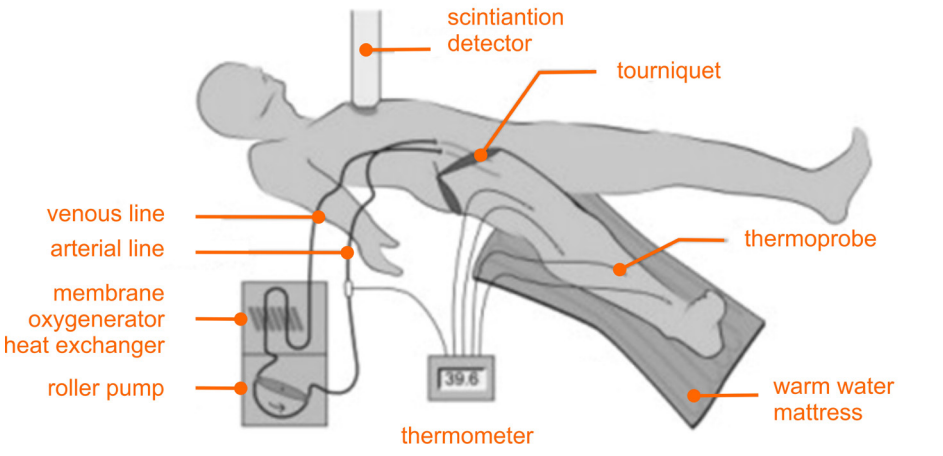

Figure 2. Isolated limb perfusion

With catheters, the main artery and vein are conjoined to the extracorporeal circuit. To prevent leakage through minor vessels in subcutaneous tissue and muscle, an occluding rubber bandage is twisted around the root of the extremity in axillary, iliac and femoral perfusions and an inflating tourniquet is used in popliteal or brachial perfusions. To obtain a good artificial tissue perfusion for adequate tissue oxygenation and effective flow of chemotherapy outside the normal corporeal circuit, regulated perfusion was performed by means of venous clamping and a membrane oxygenator. [10] In general, perfusions are carried out under mild hyperthermic (39–40 °C) circumstances by wrapping the perfused limb in a thermal blanket, continuously monitored with thermistors in subcutaneous tissue and muscle tissue. Despite one comparative study showing no benefit in favor of mild hyperthermia compared to normothermic perfusion [31], both clinical and laboratorial studies reported enhanced anti-tumor activity under hyperthermic condition. [8,32] When the temperature in the subcutaneous tissue of the limb is 38 °C and the pH of the perfusate between 7.2–7.35, cytostatic agents are injected in the perfusion circuit or (slowly) into the arterial line. Based on the fact that TNF-α concentrations remain stable during perfusion but the effect of melphalan is fairly decreased after 30 min, the overall duration of perfusion was shorted from 90 min (30 min TNF perfusion followed by 60 min of melphalan) to 60 min (melphalan is added to the perfusion circuit 15 min after the application of TNF and perfusion is then stopped 45 min later). [32,33]

At the end of the perfusion the extremity is washed out with 3–6 L saline and filled, if indicated, with one unit red blood cell concentrate. Catheters are removed and vessels repaired. A prophylactic closed fasciotomy of the anterior compartment of the lower leg or of the ventral and dorsal compartments of the forearm is performed to prevent a compartment syndrome. [34]

An important part of the perfusion process is the leakage monitoring, which can be recorded through radio-labeled 131-I human serum albumin with a precordial scintillation probe. If leakage exceeds the 2% limit during perfusion, less exposure of the tumor-bearing limb to TNF alpha, increased exposure of the patient systemic circulation to TNF-α, and more systemic side effects can be expected. [12] Leakage of TNF-α into the systemic circuit can even lead to a sepsis-like state that last for approximately 24 h after perfusion. [35]

Perfusion agents

Nitrogen mustard was the first drug used in ILP. Because the resistance of melanomas towards nitrogen mustard, Luck tried melphalan as chemotherapeutic agent in rat melanoma and reported promising results. [36] Chreech and colleagues switched to melphalan in the treatment of melanomas, followed later by STS, and also in combination with other chemotherapeutic agents. [37] Pending the randomized trials with melphalan, other chemotherapeutic agents were explored. Pommier et al. conducted a phase II trial with cisplatin in ILP for STS. [18] Cisplatin is an attractive agent for use in hyperthermic ILP, because it inhibits incorporation of DNA precursors by a mechanism similar to that of alkylating agents. Thirty-five STS patients underwent ILP with cisplatin and in 17 cases response could be measured, showing an overall response rate of only 18%. Almost 10 years later, another small study (n = 4) analyzed the results of cisplatin in ILP for bone and soft tissue sarcomas, however, due to the small number no firm conclusion can be drawn from this study. [16] Cisplatin never got wide application in ILP.

In addition, several studies have shown interest in doxorubicin. [14,38-41] In Italy, Rossi and Di Filippo have conducted three trials. [14,41] In the late nineties they analyzed the results of all three trials and reported a complete response in over one-fourth of patients, and an overall limb salvage rate of 92%. [42] The overall grade 4 toxicity was only observed in 2 cases, but the phase II trial showed grade

3/4 toxicity in 22% of patients. [14] The authors conclude that the high toxicity rate is due to a high dose of TNF-α (>1 mg) and high temperature (>41.5 °C), and that the combination of doxorubicin and TNF-α could be safely administered if used in a low doses and under mild hyperthemic circumstances. Feig and colleagues have used doxorubicin in three different doses and in combination with radiation (*n* = 31), and found that at the highest dose level (17.5 mg/m(2)/wk) 30% of patients developed grade 3 toxicity. [38] In a recent study, the high toxicity levels of doxorubicin were confirmed. Wray et al. analyzed 12 patients and observed grade 3 toxicity in 5 patients (42%) and grade 4 toxicity in 7 patients (58%). [40] Even after the dose was lowered, patients developed severe muscle and neurotoxic morbidity. Therefore, doxorubicin has not been included in the standard treatment of ILP for STS.

Similar high local toxicity rates, especially neurotoxic morbidity, were observed for carboplatin, which was tried in three patients with melanoma or STS [15] and was, therefore, not further explored in STS.

Today, the standard regimen for ILP in STS is melphalan and TNF-α. [23,40, 43-50] Between 1993 and 2006, several centers also used interferon-gamma (IFN-γ) in combination with melphalan and TNF-α.[4,51] But because IFN-γ did not seem to add in increasing the limb salvage or survival rate, but did cause morbidity, it was excluded from the regimen. TNF-α (Beromun®, Boehringer Ingelheim International GMbH, Ingelheim am Rhein, Germany) was registered in 1999 by the European Medicine Evaluation Agency (EMEA) for the therapeutic extremity perfusion of locally advanced soft tissue sarcoma and melanoma. In contrast to Europe, Beromun® was not registered by the FDA. [52] Today ILP with melphalan and Beromun® is offered in 36 cancer centers worldwide.

Toxicity ILP with TNF-α and melphalan

Local toxicity is graded according to Wieberdink (Table 2). [9] Within this classification system, the duration of a reaction was not taken into account and the peak of a reaction determined its grading. Because lymphadenectomy in combination with the perfusion may interfere with the classification of a toxic reaction, erythema was considered in such cases more decisive to the grading than edema.

Table 2. Wieberdinks's acute regional toxicity grading system	
Grade 1	No reaction
Grade 2	Slight erythema or edema
Grade 3	Considerable erythema or edema with some blistering: slightly disturbed motility permissible
Grade 4	Extensive epidermolysis or obvious damage to the deep tissues, causing definite functional disturbances: threatening or manifest compartmental syndrome
Grade 5	Reaction that may necessitate amputation

Reviewing previously published studies performing ILP with melphalan and TNF-α, grade 1/2 was observed in all studies, ranging from 24% to 100% (Table 3). [23,40,44,46,49,50] This usually involved erythema and mild edema of the limb. More severe edema and blistering of the skin, or functional impairment (grade 3), was reported in 1–19% of patients. Grade 1–3 is usually visible shortly after ILP and resolves in the majority of patients within weeks or months after treatment. Severe soft tissue damage and neurotoxic morbidity (grade 4) could be detected in only a small number of patients (0–2%) and is in the majority of cases to some degree permanent. In 0–2% of cases soft tissue morbidity necessitated amputation.

Table 3. Local toxicity according to Wieberdink in TM-ILP studies

	N	Grade 1/2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Bonvalot et al.[46]					
TNFα dose:					
0.5mg	25	36	12	0	0
1mg	25	32	8	0	0
2mg	25	24	1	1	0
3/4mg	25	32	1	0	0
Hayes et al.[44][b]	16	-	-	-	2
Cherix et al.[50]	51	90.1	7.8	0	2
Lasithiotakis et al. [23][ab]	6	100	0	0	0
Wray et al.[40]	17	-	-	-	-
Deroose et al.[49]	208	59	19	1.9	0.5

[a] including only recurrent disease
[b] including both melanoma and soft tissue sarcoma

Dose reduction of TNF-α in STS patients

Two major changes in the perfusion technique have been made since the introduction in the fifties. First of all, the duration time was shortened and secondly, the

TNF-α dose has been reduced. The potential advantage of a lower dose of TNF-α includes a lower incidence of systemic adverse events leading to a more simple and safe procedure with a significantly lower cost. An overview of outcomes of clinical dose reduction studies in STS patients is presented in Table 4. Two studies published in 2005 their single centre results. [46,53] Bonvalot et al. conducted a randomized phase II trial (*n* = 100) comparing ILP with melphalan and one of the four assigned doses of TNF-α: 0.5 mg, 1 mg, 2 mg, and 3/4 mg upper/lower limb. At the range of TNFα doses tested, there was no dose effect detected for the objective tumor response. In 13% amputation could not be avoided, but this was not related to TNF-α dose. Although there was no difference in local toxicity, a significant correlation was found for higher TNF-α dose and systemic toxicity. [46] Grunhagen et al. could not confirm the correlation between higher TNF-α dose and systemic toxicity; instead they found a borderline difference of local toxicity in favor of the low TNF-α dose. [53] Furthermore, they concluded that overall response and survival were not affected by dose reduction. A recent study by Hoven-Gondrie et al. confirmed that TNF-α dose does not affect five-year local control rates and (limb)-survival. [54] The study of Nachmany et al. found lower response rates after low-dose ILP which did, however, not translate into higher local recurrence or lower limb salvage rates. [55]

Long term outcome

In the short term, ILP with melphalan and TNF-α enabled limb salvage in 80–86% of patients [56,57] and after 10 years (or longer) following ILP, 61–81% patients could maintain their limb. [49,57] The price of this success are the long-term side effects of the extensive treatment, which are mainly functional side effects, consisting of edema, stiffness, functional impairment, and muscle atrophy. [58,59] More severe morbidity is also observed, sometimes necessitating amputation. Three time periods at risk for amputation have been described; (1) within 1 year after perfusion due to local recurrence or massive necrosis, (2) after 5 years due to late local recurrence, and (3) after 10 years due to critical leg ischemia. [57] Although vascular complications can be severe and prevention is warranted, a routine noninvasive vascular work-up does not seem to add value to normal follow-up. [60] The late effects on normal tissue have been evaluated by means of the LENT–SOMA scoring system (*n* = 32), showing that 63% of patients scored grade 3 on one or more separate items, reflecting severe symptoms with a negative impact on daily activities. [61] A

Table 4. Overview of published clinical dose reduction studies

References	N	Dose TNF (mg)	Median FU (months)	Clin. Resp. (%)
Bonvalot et al.[46]	100		24	
	25	0.5		68
	25	1		56
	25	2		72
	25	3-4		64
Grunhagen et al.[53]	240		NA	
	192	3-4		74
	48	<3-4		69
Bonvalot et al.[26]	100	1	27	79
Nachmany et al.[55]	43			NA
	26	3-4	58[d]	
	17	1	30[d]	
Hoven-Gondrie et al.[54]	102		76[e]	NA
	27	1-2		

TNF, tumor necrosis factor-alpha; FU, follow-up; Clin. Resp., clinical response; Path. Resp., pathological response; CR/PR, complete response/partial response; LS, limb
survival; LR, local recurrence; OS, overall survival; DFS, Disease-free survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; NA, not available.

specific co morbidity of limb sparing treatment with radiotherapy is a bone fracture. [62] Since ILP treatment is often used in case of large tumors, periosteal stripping and radiotherapy are often needed to ensure radical margins and good local control. Therefore patients undergoing ILP are suspected to have a considerable risk in developing a treatment related fracture. Given the high rate of non union, generally more than 50% [63,64], treatment related fractures form a severe hazard to the patient.

In addition, a quality of life study reported that 20% of patients experienced a post traumatic stress syndrome after multimodality treatment with ILP. [65] Therefore, the impact of the extensive treatment with ILP on the functional and psychological level should not be underestimated and patients should be closely monitored to offer prompt medical and psychological help if necessary.

Role of radiotherapy

Rosenberg was the first to prove the value of adjuvant radiotherapy in limb-saving sarcoma surgery [66], showing in a long term follow up study that it decreased the probability of local recurrence without influencing overall survival. [67] The latter study also mentioned that in selected patients (not clearly specified, but patients

Path Resp. (CR/PR) (%)	LS (%)	LR (%)	OS (%)	DFS (%)	LRFS (%)	DMFS (%)
		27[a]	82[a]	49[a]	NA	NA
43	88					
62	80					
67	88					
64	92					
NA	NA	NA	47[b]	NA	59[b]	50[b]
NA	85	NA	36[b]	NA	44[b]	45[b]
58	87	18[c]	89[c]	NA	NA	67[c]
			NA	NA	NA	NA
65	76	38				
31	53	46				
76[f]	77	15	56[g]	NA	85[b]	52[b]
59[f]	85	4	57[g]	NA	96[b]	36[b]

a Two-year rates.
b Five-year rates.
c Three-year rates.
d Mean FU.
e Only for patients alive after FU.
f In case of no resection clinical response was used.
g Five-year disease-specific survival (DSS) was used.

with widely negative resection margins did not develop local recurrence in their study population) with low risk for recurrence, radiotherapy could be avoided due to important lifetime risk for complications. [67] Two studies from the same centre in The Netherlands (*n* = 15/64) analyzed the role of adjuvant radiotherapy after ILP and delayed surgical resection and showed a significant decrease in local recurrences after performing adjuvant radiotherapy. [47,68] One of these studies (*n* = 64) considered surgical margins and showed that in the R0 group, patients with radiotherapy had a better local control rate (100%) than the patients without radiotherapy (55%) ($p = 0.0003$), concluding that radiotherapy should be considered even if R0 resection is achieved. [47] This in contrast to the results of another centre in The Netherlands showing no benefit for adjuvant radiotherapy in local control for patients undergoing successful ILP (induction of >50% necrosis) and R0 resection (*n* = 28), because this group did not develop any local recurrences. [69] Important to mention is that these concerned solely the patients with primary, unifocal tumors. So, although there is generally agreement that adjuvant radiotherapy is beneficial in case of ILP and resection with R1 margins, no final conclusion can be made about the role of adjuvant radiotherapy after ILP and delayed resection with RO margins.

In the middle of the 1990s a new radiation approach began to emerge, using a larger number of incident beams, known as intensity-modulated radiotherapy (IMRT). In combination with the use of the CT scan, which allows a three-dimensional image of the tumor and surrounding tissue, IMRT has made it possible to reduce the radiation doses without compromising target coverage. A few studies have published their first, successful results with this technique in the treatment of STS patients. [70-72] Roberge et al. reviewed pathological response in histological specimens following pre-operative IMRT and found significant responses in term of necrosis and fibrosis; nevertheless, there was minimal early volumetric response to radiation, especially for high-grade tumors. [71] If pre-operative radiotherapy could have a role in combination with ILP to improve limb salvage rate and local recurrence free survival is not yet discussed in literature and makes an interesting topic for further studies. The University Medical Centre in Groningen, The Netherlands has, therefore, recently started a prospective trial to investigate a new treatment schedule with ILP, pre-operative radiation and delayed surgical resection.

The newest advancement in radiation planning is functional image-guided radiation therapy (IGRT). This dual modality technique fuses the images of the CT scan and the positron emission tomography (PET) scan, thereby producing functional and anatomical data. The advantages are that the CT scan provides an anatomical context and allows for correction of PET emission data errors, e.g. photon attenuation, while the PET scan can identify areas of disease that are not apparent on CT images alone. [73] Current studies have to evaluate the role of this radiation planning technique in the pre- and post-operative setting in the treatment of sarcomas.

Isolated limb infusion

Although results after ILP are satisfactory, the technique involves a complex and invasive surgical procedure with a substantial risk of complications. Therefore, a new, minimally invasive procedure for administering regional chemotherapy called isolated limb infusion (ILI) has been developed at the Sydney Melanoma Unit. [74] Essentially, ILI is a nonoxygenated, low-flow ILP performed via percutaneously inserted catheters. For melanomas, large studies with melphalan and actinomycin D have observed similar response rates (both overall response and complete response) compared with conventional ILP. [75,76] So far, only

limited publications exist for the use of ILI treatment in STS. [77,78] Moncrieff et al. analyzed 21 patients undergoing ILI with various chemotherapeutic agents (melphalan, actinomycin D, mitomycin C, doxorubicin and cisplatin), showing a 90% overall response rate, and 14% of patients developing grade 4 toxicity. [78] Hagazy et al. analyzed 40 patients undergoing ILI with doxorubicin and pre-operative radiotherapy and found a tumor response of 80%, with no grade 4 toxicity, but in 30% of patients grade 2 or 3 morbidity. [77]

The first results of IFI in STS appear encouraging in terms of response rate, albeit these studies concern small study populations and different chemotherapy schedules, and only one study with long term follow up. Therefore, long term results should be awaited.

Conclusion

Isolated limb perfusion for soft tissue sarcoma patients with primary irresectable tumors is a successful alternative for amputation, providing limb salvage in the long term for over two-third of patients. The majority of patients experiences to some degree local toxicity, which usually subsides within weeks or months. A small group of patients develops severe local morbidity which necessitates intervention, but rarely requires amputation. The most frequent reasons for amputation are extensive necrosis, local recurrence and long term vascular morbidity. In one fifth of patients, multimodality treatment with perfusion causes considerable psychological effects, comparable with a post traumatic stress syndrome. Early recognition and prompt interference of these patients is warranted. To reduce treatment related morbidity, better insight in drug efficacy is needed, as well as development of new effective chemotherapeutic agents.

The perfusion technique is highly specialized, requiring experienced professionals and appropriate facilitated institutions, and therefore limited available in a few cancer centers. Isolated limb infusion, which is a less invasive and complicated technique, is a promising new technique with good tumor response rates. The long term effects of this technique should be awaited.

References

1. Nijhuis PH, Schaapveld M, Otter R, Molenaar WM, van der Graaf WT, Hoekstra HJ. Epidemiological aspects of soft tissue sarcomas (STS)-consequences for the design of clinical STS trials. Eur J Cancer 1999;35:1705–10.
2. Eilber FC, Rosen G, Eckardt J, Forscher C, Nelson SD, Selch M, et al. Treatment- induced pathologic necrosis: a predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. J Clin Oncol 2001;19:3203–9.
3. Nijhuis PH, Pras E, Sleijfer DT, Molenaar WM, Koops HS, Hoekstra HJ. Long- term results of preoperative intra-arterial doxorubicin combined with neoadjuvant radiotherapy, followed by extensive surgical resection for locally advanced soft tissue sarcomas of the extremities. Radiother Oncol 1999;51:15–9.
4. Eggermont AM, Schraffordt Koops H, Klausner JM, Kroon BB, Schlag PM, Lienard D, et al. Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas. The cumulative multicenter European experience. Ann Surg 1996;224:756–64. discussion 764–765.
5. Klopp CT, Alford TC, Bateman J, Berry GN, Winship T. Fractionated intra- arterial cancer; chemotherapy with methyl bis amine hydrochloride; a preliminary report. Ann Surg 1950;132:811–32.
6. Creech Jr O, Krementz ET, Ryan RF, Winblad JN. Chemotherapy of cancer: regional perfusion utilizing an extracorporeal circuit. Ann Surg 1958;148:616–32.
7. Krementz ET, Creech Jr O, Ryan RF, Reemtsma K. An appraisal of cancer chemotherapy by regional perfusion. Ann Surg 1962;156:417–28.
8. Cavaliere R, Ciocatto EC, Giovanella BC, Heidelberger C, Johnson RO, Margottini M, et al. Selective heat sensitivity of cancer cells. Biochemical and clinical study. Cancer 1967;20:1351–81.
9. Wieberdink J, Benckhuysen C, Braat RP, van Slooten EA, Olthuis GA. Dosimetry in isolation perfusion of the limbs by assessment of perfused tissue volume and grading of toxic tissue reactions. Eur J Cancer Clin Oncol 1982;18:905–10.
10. Fontijne WP, Mook PH, Koops HS, Oldhoff J, Wildevuur CR. Improved tissue perfusion during pressure regulated hyperthermic regional isolated perfusion. A clinical study. Cancer 1985;55:1455–61.
11. Daryanani D, Komdeur R, Ter Veen J, Nijhuis PH, Piers DA, Hoekstra HJ. Continuous leakage measurement during hyperthermic isolated limb perfusion. Ann Surg Oncol 2001;8:566–72.
12. van Ginkel RJ, Limburg PC, Piers DA, Koops HS, Hoekstra HJ. Value of continuous leakage monitoring with radioactive iodine-131-labeled human serum albumin during hyperthermic isolated limb perfusion with tumor necrosis factor-alpha and melphalan. Ann Surg Oncol 2002;9:355–63.
13. Hoekstra HJ, Schraffordt Koops H, Molenaar WM, Oldhoff J. Results of isolated regional perfusion in the treatment of malignant soft tissue tumors of the extremities. Cancer 1987;60:1703–7.
14. Rossi CR, Vecchiato A, Foletto M, Nitti D, Ninfo V, Fornasiero A, et al. Phase II study on neoadjuvant hyperthermic-antiblastic perfusion with doxorubicin in patients with intermediate or high grade limb sarcomas. Cancer 1994;73:2140–6.
15. Daryanani D, de Vries EG, Guchelaar HJ, van Weerden TW, Hoekstra HJ. Hyperthermic isolated regional perfusion of the limb with carboplatin. Eur J Surg Oncol 2000;26:792–7.
16. van Ginkel RJ, Schraffordt Koops H, de Vries EG, Molenaar WM, Uges DR, Hoekstra HJ. Hyperthermic isolated limb perfusion with cisplatin in four patients with sarcomas of soft tissue and bone. Eur J Surg Oncol 1996;22:528–31.
17. Klaase JM, Kroon BB, Benckhuijsen C, van Geel AN, Albus-Lutter CE, Wieberdink J. Results of regional isolation perfusion with cytostatics in patients with soft tissue tumors of the extremities. Cancer 1989;64:616–21.
18. Pommier RF, Moseley HS, Cohen J, Huang CS, Townsend R, Fletcher WS. Pharmacokinetics, toxicity, and short-term results of cisplatin hyperthermic isolated limb perfusion for soft-tissue sarcoma and melanoma of the extremities. Am J Surg 1988;155:667–71.

19. Seynhaeve AL, de Wilt JH, van Tiel ST, Eggermont AM, ten Hagen TL. Isolated limb perfusion with actinomycin D and TNF-alpha results in improved tumour response in soft-tissue sarcoma-bearing rats but is accompanied by severe local toxicity. Br J Cancer 2002;86:1174–9.
20. Lienard D, Ewalenko P, Delmotte JJ, Renard N, Lejeune FJ. High-dose recombinant tumor necrosis factor alpha in combination with interferon gamma and melphalan in isolation perfusion of the limbs for melanoma and sarcoma. J Clin Oncol 1992;10:52–60.
21. Eggermont AM, Schraffordt Koops H, Lienard D, Kroon BB, van Geel AN, Hoekstra HJ, et al. Isolated limb perfusion with high-dose tumor necrosis factor-alpha in combination with interferon-gamma and melphalan for nonresectable extremity soft tissue sarcomas: a multicenter trial. J Clin Oncol 1996;14:2653–65.
22. Lans TE, Grunhagen DJ, de Wilt JH, van Geel AN, Eggermont AM. Isolated limb perfusions with tumor necrosis factor and melphalan for locally recurrent soft tissue sarcoma in previously irradiated limbs. Ann Surg Oncol 2005;12:406–11.
23. Lasithiotakis K, Economou G, Gogas H, Ioannou C, Perisynakis K, Filis D, et al. Hyperthermic isolated limb perfusion for recurrent melanomas and soft tissue sarcomas: feasibility and reproducibility in a multi-institutional Hellenic collaborative study. Oncol Rep 2010;23:1077–83.
24. Olieman AF, van Ginkel RJ, Molenaar WM, Schraffordt Koops H, Hoekstra HJ. Hyperthermic isolated limb perfusion with tumour necrosis factor-alpha and melphalan as palliative limb-saving treatment in patients with locally advanced soft-tissue sarcomas of the extremities with regional or distant metastases. Is it worthwhile? Arch Orthop Trauma Surg 1998;118:70–4.
25. Grunhagen DJ, de Wilt JH, Graveland WJ, van Geel AN, Eggermont AM. The palliative value of tumor necrosis factor alpha-based isolated limb perfusion in patients with metastatic sarcoma and melanoma. Cancer 2006;106:156–62.
26. Bonvalot S, Rimareix F, Causeret S, Le Pechoux C, Boulet B, Terrier P, et al. Hyperthermic isolated limb perfusion in locally advanced soft tissue sarcoma and progressive desmoid-type fibromatosis with TNF 1 mg and melphalan (T1-M HILP) is safe and efficient. Ann Surg Oncol 2009;16:3350–7.
27. Lev-Chelouche D, Abu-Abeid S, Nakache R, Issakov J, Kollander Y, Merimsky O, et al. Limb desmoid tumors: a possible role for isolated limb perfusion with tumor necrosis factor-alpha and melphalan. Surgery 1999;126:963–7.
28. Grunhagen DJ, de Wilt JH, Verhoef C, van Geel AN, Eggermont AM. TNF-based isolated limb perfusion in unresectable extremity desmoid tumours. Eur J Surg Oncol 2005;31:912–6.
29. Lans TE, de Wilt JH, van Geel AN, Eggermont AM. Isolated limb perfusion with tumor necrosis factor and melphalan for nonresectable Stewart–Treves lymphangiosarcoma. Ann Surg Oncol 2002;9:1004–9.
30. Lev-Chelouche D, Abu-Abeid S, Merimsky O, Isakov J, Kollander Y, Meller I, et al. Isolated limb perfusion with high-dose tumor necrosis factor alpha and melphalan for Kaposi sarcoma. Arch Surg 1999;134:177–80.
31. Klaase JM, Kroon BB, Eggermont AM, van Geel AN, Schraffordt Koops H, Oldhoff J, et al. A retrospective comparative study evaluating the results of mild hyperthermic versus controlled normothermic perfusion for recurrent melanoma of the extremities. Eur J Cancer 1995;31A:58–63.
32. de Wilt JH, Manusama ER, van Tiel ST, van Ijken MG, ten Hagen TL, Eggermont AM. Prerequisites for effective isolated limb perfusion using tumour necrosis factor alpha and melphalan in rats. Br J Cancer 1999;80:161–6.
33. Eggermont AM, de Wilt JH, ten Hagen TL. Current uses of isolated limb perfusion in the clinic and a model system for new strategies. Lancet Oncol 2003;4:429–37. 34. Schraffordt Koops H. Prevention of neural and muscular lesions during hyperthermic regional perfusion. Surg Gynecol Obstet 1972;135:401–3.
35. Zwaveling JH, Maring JK, Clarke FL, van Ginkel RJ, Limburg PC, Hoekstra HJ, et al. High plasma tumor necrosis factor (TNF)-alpha concentrations and a sepsis-like syndrome in patients undergoing hyperthermic isolated limb perfusion with recombinant TNF-alpha, interferon-gamma, and melphalan. Crit Care Med 1996;24:765–70.
36. Luck JM. Action of p-[di(2-chloroethyl)]-amino-l-phenylalanine on Harding– Passey mouse melanoma. Science 1956;123:984–5.

37. Krementz ET, Carter RD, Sutherland CM, Muchmore JH, Ryan RF, Creech Jr O. Regional chemotherapy for melanoma. A 35-year experience. Ann Surg 1994;220:520–34. discussion 534–535.
38. Feig B, Ross M, Hunt K. A prospective evaluation of isolated limb perfusion with doxorubicin in patients with unresectable extremity sarcomas. Ann Surg Oncol 2004;11:S80.
39. Rossi CR, Mocellin S, Pilati P, Foletto M, Campana L, Quintieri L, et al. Hyperthermic isolated perfusion with low-dose tumor necrosis factor alpha and doxorubicin for the treatment of limb-threatening soft tissue sarcomas. Ann Surg Oncol 2005;12:398–405.
40. Wray CJ, Benjamin RS, Hunt KK, Cormier JN, Ross MI, Feig BW. Isolated limb perfusion for unresectable extremity sarcoma: results of 2 single-institution phase 2 trials. Cancer 2011;117:3235–41.
41. Di Filippo F, Garinei R, Anza M, Cavaliere F, Giannarelli D, Cagol PP, et al. Doxorubicin in isolation limb perfusion in the treatment of advanced limb soft tissue sarcoma. J Exp Clin Cancer Res 2003;22:81–7.
42. Rossi CR, Foletto M, Di Filippo F, Vaglini M, Anza' M, Azzarelli A, et al. Soft tissue limb sarcomas: Italian clinical trials with hyperthermic antiblastic perfusion. Cancer 1999;86:1742–9.
43. Grabellus F, Kraft C, Sheu-Grabellus SY, Bauer S, Podleska LE, Lauenstein TC, et al. Tumor vascularization and histopathologic regression of soft tissue sarcomas treated with isolated limb perfusion with TNF-alpha and melphalan. J Surg Oncol 2011;103:371–9.
44. Hayes AJ, Neuhaus SJ, Clark MA, Thomas JM. Isolated limb perfusion with melphalan and tumor necrosis factor alpha for advanced melanoma and soft- tissue sarcoma. Ann Surg Oncol 2007;14:230–8.
45. Hill S, Fawcett WJ, Sheldon J, Soni N, Williams T, Thomas JM. Low-dose tumour necrosis factor alpha and melphalan in hyperthermic isolated limb perfusion. Br J Surg 1993;80:995–7.
46. Bonvalot S, Laplanche A, Lejeune F, Stoeckle E, Le Pechoux C, Vanel D, et al. Limb salvage with isolated perfusion for soft tissue sarcoma: could less TNF- alpha be better? Ann Oncol 2005;16:1061–8.
47. Thijssens KM, van Ginkel RJ, Pras E, Suurmeijer AJ, Hoekstra HJ. Isolated limb perfusion with tumor necrosis factor alpha and melphalan for locally advanced soft tissue sarcoma: the value of adjuvant radiotherapy. Ann Surg Oncol 2006;13:518–24.
48. Santinami M, Deraco M, Azzarelli A, Cascinelli F, Chiti A, Costagli V, et al. Treatment of recurrent sarcoma of the extremities by isolated limb perfusion using tumor necrosis factor alpha and melphalan. Tumori 1996;82:579–84.
49. Deroose JP, Eggermont AM, van Geel AN, Burger JW, den Bakker MA, de Wilt JH, et al. Long-term results of tumor necrosis factor alpha- and melphalan- based isolated limb perfusion in locally advanced extremity soft tissue sarcomas. J Clin Oncol 2011;29:4036–44.
50. Cherix S, Speiser M, Matter M, Raffoul W, Lienard D, Theumann N, et al. 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. J Surg Oncol 2008;98:148–55.
51. Gutman M, Inbar M, Lev-Shlush D, Abu-Abid S, Mozes M, Chaitchik S, et al. High dose tumor necrosis factor-alpha and melphalan administered via isolated limb perfusion for advanced limb soft tissue sarcoma results in a >90% response rate and limb preservation. Cancer 1997;79:1129–37. http://www.ema.europa.eu.
52. Grunhagen DJ, de Wilt JH, van Geel AN, Graveland WJ, Verhoef C, Eggermont AM. TNF dose reduction in isolated limb perfusion. Eur J Surg Oncol 2005;31:1011–9.
53. Hoven-Gondrie ML, Bastiaannet E, van Ginkel RJ, Suurmeijer AJ, Hoekstra HJ. TNF dose reduction and shortening of duration of isolated limb perfusion for locally advanced soft tissue sarcoma of the extremities is safe and effective in terms of long-term patient outcome. J Surg Oncol 2011;103:648–55.
54. Nachmany I, Subhi A, Meller I, Gutman M, Lahat G, Merimsky O, et al. Efficacy of high vs low dose TNF-isolated limb perfusion for locally advanced soft tissue sarcoma. Eur J Surg Oncol 2009;35:209–14.

55. Lejeune FJ, Pujol N, Lienard D, Mosimann F, Raffoul W, Genton A, et al. Limb salvage by neoadjuvant isolated perfusion with TNFalpha and melphalan for non-resectable soft tissue sarcoma of the extremities. Eur J Surg Oncol 2000;26:669–78.
56. van Ginkel RJ, Thijssens KM, Pras E, van der Graaf WT, Suurmeijer AJ, Hoekstra HJ. Isolated limb perfusion with tumor necrosis factor alpha and melphalan for locally advanced soft tissue sarcoma: three time periods at risk for amputation. Ann Surg Oncol 2007;14:1499–506.
57. Noorda EM, Vrouenraets BC, Nieweg OE, van Coevorden F, van Slooten GW, Kroon BB. Isolated limb perfusion with tumor necrosis factor-alpha and melphalan for patients with unresectable soft tissue sarcoma of the extremities. Cancer 2003;98:1483–90.
58. Olieman AF, Schraffordt Koops H, Geertzen JH, Kingma H, Hoekstra HJ, Oldhoff J. Functional morbidity of hyperthermic isolated regional perfusion of the extremities. Ann Surg Oncol 1994;1:382–8.
59. Hoven-Gondrie ML, Thijssens KM, Van den Dungen JJ, Loonstra J, van Ginkel RJ, Hoekstra HJ. Long-term locoregional vascular morbidity after isolated limb perfusion and external-beam radiotherapy for soft tissue sarcoma of the extremity. Ann Surg Oncol 2007;14:2105–12.
60. Hoven-Gondrie ML, Thijssens KM, Geertzen JH, Pras E, van Ginkel RJ, Hoekstra HJ. Isolated limb perfusion and external beam radiotherapy for soft tissue sarcomas of the extremity: long-term effects on normal tissue according to the LENT–SOMA scoring system. Ann Surg Oncol 2008;15:1502–10.
61. Lin PP, Schupak KD, Boland PJ, Brennan MF, Healey JH. Pathologic femoral fracture after periosteal excision and radiation for the treatment of soft tissue sarcoma. Cancer 1998;15–82(12):2356–65.
62. Helmstedter CS, Goebel M, Zlotecki R, Scarborough MT. Pathologic fractures after surgery and radiation for soft tissue tumors. Clin Orthop Relat Res 2001;389:165–72.
63. Lin PP, Schupak KD, Boland PJ, Brennan MF, Healey JH. Pathologic femoral fracture after periosteal excision and radiation for the treatment of soft tissue sarcoma. Cancer 1998;82:2356–65.
64. Thijssens KM, Hoekstra-Weebers JE, van Ginkel RJ, Hoekstra HJ. Quality of life after hyperthermic isolated limb perfusion for locally advanced extremity soft tissue sarcoma. Ann Surg Oncol 2006;13:864–71.
65. Rosenberg SA, Tepper J, Glatstein E, Costa J, Baker A, Brennan M, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 1982;196:305–15.
66. Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998;16:197–203.
67. Olieman AF, Pras E, van Ginkel RJ, Molenaar WM, Schraffordt Koops H, Hoekstra HJ. Feasibility and efficacy of external beam radiotherapy after hyperthermic isolated limb perfusion with TNF-alpha and melphalan for limb- saving treatment in locally advanced extremity soft-tissue sarcoma. Int J Radiat Oncol Biol Phys 1998;40:807–14.
68. Deroose JP, Burger JW, van Geel AN, den Bakker MA, de Jong JS, Eggermont AM, et al. Radiotherapy for soft tissue sarcomas after isolated limb perfusion and surgical resection: essential for local control in all patients? Ann Surg Oncol 2011;18:321–7.
70. Hong L, Alektiar KM, Hunt M, Venkatraman E, Leibel SA. Intensity-modulated radiotherapy for soft tissue sarcoma of the thigh. Int J Radiat Oncol Biol Phys 2004;59:752–9.
71. Roberge D, Skamene T, Nahal A, Turcotte RE, Powell T, Freeman C. Radiological and pathological response following pre-operative radiotherapy for soft-tissue sarcoma. Radiother Oncol 2010;97:404–7.
72. Stewart AJ, Lee YK, Saran FH. Comparison of conventional radiotherapy and intensity-modulated radiotherapy for post-operative radiotherapy for primary extremity soft tissue sarcoma. Radiother Oncol 2009;93:125–30.
73. Zaidi H, Vees H, Wissmeyer M. Molecular PET/CT imaging-guided radiation therapy treatment planning. Acad Radiol 2009;16(9):1108–33.
74. Thompson JF, Kam PC. Isolated limb infusion for melanoma: a simple but effective alternative to

isolated limb perfusion. J Surg Oncol 2004;88:1–3.
75. Lindner P, Doubrovsky A, Kam PC, Thompson JF. Prognostic factors after isolated limb infusion with cytotoxic agents for melanoma. Ann Surg Oncol 2002;9:127–36.
76. Kroon HM, Moncrieff M, Kam PC, Thompson JF. Outcomes following isolated limb infusion for melanoma. A 14-year experience. Ann Surg Oncol 2008;15:3003–13.
77. Hegazy MA, Kotb SZ, Sakr H, El Dosoky E, Amer T, Hegazi RA, et al. Preoperative isolated limb infusion of Doxorubicin and external irradiation for limb-threatening soft tissue sarcomas. Ann Surg Oncol 2007;14:568–76.
78. Moncrieff MD, Kroon HM, Kam PC, Stalley PD, Scolyer RA, Thompson JF. Isolated limb infusion for advanced soft tissue sarcoma of the extremity. Ann Surg Oncol 2008;15:2749–56.
79. Krementz ET, Carter RD, Sutherland CM, Hutton I. Chemotherapy of sarcomas of the limbs by regional perfusion. Ann Surg 1977;185(5):555–64.
80. Muchmore JH, Carter RD, Krementz ET. Regional perfusion for malignant melanoma and soft tissue sarcoma: a review. Cancer Invest 1985;3:129–43.
81. Stehlin JS, Giovanella BC, Gutierrez AE, et al. 15years' experience with hyperthermic perfusion for treatment of soft tissue sarcoma and malignantmelanoma of the extremities. Front Radiat Ther Oncol 1984;18:1977–82.
82. Lehti PM, Moseley HS, Janoff K, et al. Improved survival for soft tissue sarcoma of the extremities by regional hyperthermic perfusion, local excision and radiation therapy. Surg Gynecol Obstet 1986;162:149–52.
83. Krementz ET. Lucy Wortham James lecture. Regional perfusion. Current sophistication, what next? Cancer 1986;57:416–32.
84. Di Filippo F, Calabrò AM, Cavallari A, et al. The role of hyperthermic perfusion as a first step in the treatment of soft tissue sarcoma of the extremities. World J Surg 1988;12:332–9.
85. Kettelhack C, Kraus T, Hupp T, et al. Hyperthermic limb perfusion for malignant melanoma and soft tissue sarcoma. Eur J Surg Oncol 1990;16:370–5. 86.
86. Eggermont AM. Treatment of irresectable soft tissue sarcomas of the limbs by isolation perfusion with high dose TNF-a in combination with c-interferon and melphalan. In: Fiers W, Buurman WA, editors. Tumor necrosis factor: molecular and cellular biology and clinical relevance. Basel (Switzerland): Karger Publishers; 1993. p. 239–43.
87. Lev-Chelouche D, Abu-Abeid S, Kollander Y, Meller I, Isakov J, Merimsky O et al. Multifocal soft tissue sarcoma: limb salvage following hyperthermic isolated limb perfusion with high-dose tumor necrosis factor and melphalan. J Surg Oncol 1999;70:185–9.
88. Olieman AF, van Ginkel RJ, Hoekstra HJ, Mooyaart EL, Molenaar WM, Schraffordt Koops H. Angiographic response of locally advanced soft-tissue sarcoma following hyperthermic isolated limb perfusion with tumor necrosis factor. Ann Surg Oncol 1997;4:64–9.
89. Deroose JP, van Geel AN, Burger JW, Eggermont AM, Verhoef C. Isolated limb perfusion with TNF-alpha and melphalan for distal parts of the limb in soft tissue sarcoma patients. J Surg Oncol 2012;105:563–9.
90. Fletcher WS, Pommier RF, Woltering EA, et al. Pharmacokinetics and results of dose escalation in cisplatin hyperthermic isolation limb perfusion. Ann Surg Oncol 1994;1:236–43.
91. Rossi CR, Foletto M, Alessio S, et al. Limb-sparing treatment for soft tissue sarcomas: influence of prognostic factors. J Surg Oncol 1996;63:3–8.
92. Eggermont AM, Schraffordt Koops H, Klausner JM, et al. Limb salvage by isolated perfusion with tumor necrosis factor alpha and melphalan for locally advanced extremity soft tissue sarcomas: result of 270 perfusions in 247 patients. J Clin Oncol; Proc Am Soc Clin Oncol 1999;11:497.
93. van Etten B, van Geel AN, de Wilt JH, et al. Fifty tumor necrosis factor-based isolated limb perfusions for limb salvage in patients older than 75 years with limb-threatening soft tissue sarcomas and other extremity tumors. Ann Surg Oncol 2003;10:32–7.
94. Grunhagen DJ, Brunstein F, Graveland WJ, et al. Isolated limb perfusion with tumor necrosis factor and melphalan prevents amputation in patients with multiple sarcomas in arm or leg. Ann Surg Oncol 2005;12:473–9.

95. Grunhagen DJ, de Wilt JH, Graveland WJ, et al. Outcome and prognostic factor analysis of 217 consecutive isolated limb perfusions with tumor necrosis factor-alpha and melphalan for limb threatening soft tissue sarcoma. Cancer 2006;106:1776–84.
96. Schlag PM, Tunn PU. Isolated limb perfusion with tumor necrosis factor-alpha and melphalan. Dtsch Arztebl 2007;104:2268–73.
97. Pennacchioli E, Deraco M, Mariani L, et al. Advanced extremity soft tissue sarcoma: prognostic effect of isolated limb perfusion in a series of 88 patients treated at a single institution. Ann Surg Oncol 2007;14:553–9.
98. Di Filippo F, Giacomini P, Rossi CR, Santinami M, Garinei R, Anzà M. Hyperthermic isolated perfusion with tumor necrosis factor-alpha and doxorubicin for the treatment of limb-threatening soft tissue sarcoma: the experience of the Italian Society of Integrated Locoregional Treatment in Oncology (SITILO). In Vivo 2009;23:363–7.
99. Seinen JM, Jutte PC, van Ginkel RJ, Pras E, Hoekstra HJ. Treatment associated fractures after multimodality treatment with isolated limb perfusion of soft tissue sarcomas; what to do? submitted for publication.
100. Seinen JM, van Ginkel RJ, Hoekstra HJ. How to deal with local limb failure after limb sparing treatment with isolated perfusion with TNFa and melphalan and delayed surgery for soft tissue sarcoma patients? submitted for publication.