Chapter 4

Isolated limb perfusion with TNF and Melphalan for locally advanced soft tissue sarcoma: three time periods at risk for amputation

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Chapter 4

Abstract

Background: The aim of this study was to investigate the long-term limb salvage rate and overall survival after isolated limb perfusion (ILP) with Tumor Necrosis Factor alpha (TNF) and melphalan for locally advanced soft tissue sarcoma (STS).

Methods: From 1991-2003, 73 patients (36 male, 37 female, median age 54 (range 14 – 80) years) years with biopsy proven STS underwent 77 perfusions followed by delayed surgical resection, with or without adjuvant radiation. Limb salvage and overall survival curves were calculated using the Kaplan-Meier method.

Results: A total of 21 amputations (28%) were performed. Overall 1, 5 and 10 years limb salvage was 80.1 ± 4.8, 68.2 ± 6.5% and 60.6 ± 9.2% respectively. Three time episodes were at risk for amputation. The first period was within 1½ year after perfusion mainly due to massive necrosis of the tumor and overlying skin resulting in a soft tissue deficit or recurrent disease (n=17). The second time period was within 5 years with 2 amputations performed for late local recurrence. The third episode occurred ten years after perfusion, 2 amputations performed for critical leg ischemia. Another two patients developed a pathological fracture of the femur due to radiation osteonecrosis. These 4 patients received adjuvant radiotherapy. Overall 1, 5 and 10 years survival was 82.9 ± 9.2%, 58.7 ± 13.1% and 42.5 ± 18.2% respectively.

Conclusions: ILP with TNF and melphalan followed by delayed surgical resection and adjuvant radiation treatment is an effective limb salvage treatment regimen for locally advanced STS. However, we observed late morbidity with 2 amputations performed for critical leg ischemia and 2 pathological fractures of the femur in patients receiving adjuvant radiotherapy.
Amputation after isolated limb perfusion with TNF and melphalan for STS

Introduction
Limb salvage in patients with locally advanced extremity soft tissue sarcomas (STS) continues to be a challenge. Survival in these patients is determined by the development of distant metastases and is not improved with the amputation of the affected limb. Besides amputation, an extensive surgical procedure followed by radiation therapy is a treatment option. Rosenberg et al. showed the same disease free and overall survival as amputation in the early eighties with this treatment regimen. Preoperative therapies to improve limb salvage rates have been propagated. Suit et al. reported already in 1981 on the use of preoperative radiation therapy. Eilber et al. combined preoperative (intra-arterial or systemic) chemotherapy and radiation therapy to improve resectability rates. In a randomized trial O'Sullivan et al. reported a greater risk of wound complications in the preoperative radiotherapy group compared with the postoperative radiotherapy group. The use of brachytherapy may also improve local control and avoid amputation. The current treatment strategy of high grade limb sarcomas is wide local resection with the goal to achieve a R0 resection with a 2 cm margin. In case the margin is less than 2 cm, or a R1 resection (microscopically involved margin), adjuvant radiation therapy with 50-70 Gy is indicated to reduce the risk of local failure. The question whether radiotherapy should be given preoperative or postoperative is still unanswered.

Another strategy for limb salvage in locally advanced extremity STS is to perform an isolated limb perfusion (ILP) with cystostatic agents. Originally developed for the treatment of melanoma of the limb in 1957, the procedure was also applied in the treatment of STS of the limb. In their first experience, Krementz et al. showed an early response rate with melphalan alone of 83%, however complete regression of the tumor was hardly seen. Other perfusions agents in the treatment of limb STS were therefore investigated. Rossi claimed efficacy of doxorubicin, while another study proved that doxorubicin alone was ineffective and combined with melphalan too toxic. Cisplatin showed also to be less effective than melphalan in the limb perfusion setting of sarcomas and carboplatin too neurotoxic.

With the addition of Tumor Necrosis Factor alpha (TNF) to the perfusion circuit, Lejeune et al. made a step forward in the treatment of locally advanced extremity soft tissue sarcoma (STS). A large European multi-center study proved the ILP concept in the limb salvage procedures for locally advanced STS with TNF and melphalan. The objective response rate was 75% and a limb salvage rate of 82% was achieved with a minimal treatment related morbidity. Since 1991, patients with locally advanced STS of the limbs, have been treated at
Chapter 4

the University Medical Center Groningen by ILP with TNF, melphalan with or without interferon gamma (IFN) as perfusion agents, followed by delayed surgical excision and postoperative radiation therapy if a marginal resection or non radical resection was performed. Recently we encountered long-term local morbidity and therefore the aim of the present study was to analyze the limb salvage rate and survival in patients with locally advanced STS of the extremities that were treated in our center and to report the late effects of this treatment modality.

Patients and methods

Patient Characteristics

From the time period 1991-2003, 73 patients with soft tissue sarcoma of the extremity underwent 77 perfusions with a combination of TNF and melphalan, with (19) or without IFN (58). Thirty-six males and 37 females, with a median age of 54 (range 14 - 80) years were treated. Tumors were considered unresectable because of size, their multicentricity in the limb, or fixation to the neurovascular bundle and or bone and therefore amputation was the only alternative treatment option. Perfusion was performed at the iliac level in 32 cases (42%), at the popliteal level in 23 cases (30%), at the femoral and axillary level in each 11 cases (14%). There were 60 primary (82%) and 13 recurrent (18%) sarcomas. Sixty two sarcomas were located in the leg (85%) and 11 in the arm (15%). All patients were treated after informed consent was obtained according to the institutional guidelines. Nineteen different histological types of STS were distinguished. The pathological grade of the tumor was scored following the criteria of Coindre et al. as well as the stage of the tumor according to the American Joint Committee on Cancer (AJCC)\textsuperscript{16} (Table 1).\textsuperscript{17} Median tumor size was 16.2 (range 8.3 – 23) cm. In case of multifocal disease, the largest diameter was used.

Perfusion technique

The perfusion technique employed at the University Medical Center Groningen is based on the technique developed by Creech et al.\textsuperscript{18} and described elsewhere.\textsuperscript{19} The major modifications during the last thirty years were the use of modern thermal blankets, improvement in leakage monitoring, the introduction of a membrane oxygenator and heat exchanger, to ensure an
optimal perfusion at 39-40°C. Since an extensive wash out procedure with 6 L of saline is used systemic inflammatory response syndrome (SIRS) is hardly seen. Postoperatively patients can be monitored on the recovery ward instead of the intensive care unit.

Assessment of Tumor Response, tumor remnant and follow-up

Responses were assessed by standardized World Health Organization (WHO) criteria and based on physical examination, and or MRI/CT investigations. Complete response (CR) was defined as the disappearance of all measurable disease in the limb for longer than 4 weeks, partial response (PR) as regression of the tumor size by greater than 50% for longer than 4 weeks, no change (NC) as regression of less than 50% of the tumor in the limb or progression of less than 25% for longer than 4 weeks.

Resection of the tumor remnants was performed between 2 – 15 weeks after perfusion (median 8 weeks). After resection, response was also made on pathological examination. The tumor remnants were measured in three dimensions and the percentage of necrosis estimated in relation to the complete tumor volume. Representative tumor sections were taken, encompassing macroscopically different tumor areas, including necrosis. As a general rule, one section per centimeter largest diameter with a minimum of three was taken. Based on an integration of gross and microscopic findings, a final estimate of the percentages of viable and necrotic or regressive tumor was made.

Excision margins were also evaluated on pathological examination and classified as radical when the resection margins were free of tumor cells (complete resection; R0), or as R1 when resection margins were microscopically involved or as R2 when resection margins were macroscopically positive involved. Postoperative radiotherapy (60 - 70 Gy) was considered indicated in case of <95% necrosis on pathological examination of the tumor or with marginal or microscopically positive resection margins. All patients were followed after perfusion treatment in a standardized protocol. Median follow-up was 27 (range 2 – 138) months.

Statistical Analysis

Survival and limb salvage curves were calculated according to the Kaplan-Meier method and Log-rank test. Values of P ≤ 0.05 were considered to be statistically significant. Graph Pad Prism® version 2.0 for Windows statistical software was used.
Chapter 4

Results

Tumor response

A clinical complete response was observed after 19 ILP’s (25%), a PR after 53 ILP’s (69%) and NC after 5 ILP’s (6%) local progression was never observed. Resection of the remnant tumor was performed in 68 patients (93%). The pathological response is illustrated in Figure 1. After 17 ILP’s (23%) no viable tumor cells were found on pathological examination. In 29 ILP’s (37%) 90% or more necrosis was found on pathological examination. Adding both groups together a good response to ILP was found in 60% of the patients. In 17 ILP’s (22%) an intermediate response was found on pathological examination (necrosis 50-80%). After 8 ILP’s (10%) less than 20% of necrosis or no necrosis was found on pathological examination. In 5 patients (7%) tumor response was not assessed because of progression of distant metastases in 4 patients and a local recurrence in one patient that necessitated a second perfusion resulting in 90% necrosis of the tumor. No correlation could be demonstrated between grade and percent necrosis of the tumor after perfusion (Pearson’s correlation). Post operative radiotherapy (total dose 60-70 Gy, 25 x 2 Gy daily and 10-20 Gy boost) was given in 37 patients with microscopically involved or marginally free resection margins. Radiation therapy started within 5-6 weeks after tumor resection. Radiation treatment was delivered through a multiple-field technique with CT treatment planning on a linear accelerator, 6-15 MV.

Amputations and limb salvage

A total of 21 amputations (28%) were performed. Table 2 presents the time interval between ILP and amputation and the rationale for amputation. Overall 1, 5 and 10 years limb salvage was 80.1 ± 4.8, 68.2 ± 6.5% and 60.6 ± 9.2% respectively (Figure 2). When analyzing the limb salvage curve, a distinction in 3 time episodes was observed at risk for amputation. The first period was observed within the first one and a half year after perfusion (17 patients) due to a perfusion induced massive necrosis of the tumor and overlying skin resulting in a soft tissue deficit (6 patients), tumor recurrence after perfusion (5 patients), wound complications after ILP followed by radiotherapy (2 patients), a microscopically involved resection margin with the rejection of the patient for adjuvant radiotherapy of the foot (2 patients), one patient with an insufficient clinical response and in one patient an arterial trombosis occurred with no
vascular reconstruction possibilities 2 months after resection of a local recurrence in the groin. The second time period was within 5 years after ILP, with 2 amputations performed for late local recurrent disease (37 and 58 months after perfusion). The third episode occurred around ten years after perfusion. Amputation was performed for critical leg ischemia with neuropathy due to treatment induced atherosclerosis of the remaining tibial artery which was not suitable for arterial reconstruction (110 and 125 months after perfusion). An example of the clinical appearance of patient no 21 is shown in Figure 3. In this patient a popliteal ILP was performed at the age of 18 years for a chondrosarcoma. After marginal resection this patient received 66 Gy adjuvant radiotherapy. Ten years after ILP an amputation was performed because of critical leg ischemia. No recurrent disease was found on pathological examination of the amputated specimen. Another two patients developed a pathological fracture of the femur due to radiation induced osteonecrosis (78 and 129 months after perfusion). All of these 4 patients with late post ILP complications received high dose post-perfusion radiotherapy (60 - 70 Gy).

**Systemic metastases and survival**

Twelve patients presented with distant metastases at time of ILP (16% stage IV AJCC), 50% of these patients had lung metastases whereas remarkably the other halve had lymph node metastases. Eleven of these patients died of disease after a median period of 9 (range 2 - 54) months), one patient is alive with no evidence of disease after 11 months. During follow-up 25 patients (36%) developed distant metastases at a median interval of 9 (range 2 - 100) months. A significant difference (P < .001) was observed between patients with no distant metastases at the time of ILP (mets -) compared with patients with metastases at the time of ILP (mets +) (Fig. 4). Overall 1, 5 and 10 year’s survival for all patients was 82.9 ± 9.2%, 58.7 ± 13.1% and 42.5 ± 18.2% respectively (Figure 4).

**Discussion**

The results of an European multi-center trial performed in the nineties, lead to the approval of using TNF for ILP in patients with locally advanced extremity sarcomas by the European Medicine Evaluation Agency. Currently ILP with TNF is available in more than 30 Centers and in 2002, 350 so called TNF-perfusions were performed. As one of the first centers that participated in the TNF ILP experience and practice for over a decade we recently
encountered long-term treatment related morbidity necessitating amputation of the perfused limb 10 years after treatment. For this reason we analyzed our results of ILP with TNF and melphalan and describe our results in the present study.

We observed an overall response rate of 82% which is in the range of the 63 - 91% response rates reported in the literature.\textsuperscript{15,23-25} Although a suggestion has been made for a relation between the grade of a sarcoma and the response to TNF ILP we could not demonstrate a correlation between grade and the percent necrosis after ILP with TNF. This is in concordance with the results of the Amsterdam group.\textsuperscript{23} Various reports have shown that a limb salvage rate of 81-86% can be achieved in patients with locally advanced limb sarcoma.\textsuperscript{15,23-25} An independent review committee reconsidered the unresectability criteria of all enrolled patients in the European study. Eighty percent of the patients in this study met indeed the criteria for unresectability and survival curves based on a match control study with cases of the Scandinavian Soft Tissue Sarcoma Databank showed that TNF ILP had no negative effect on survival.\textsuperscript{26}

We used the Kaplan-Meier method to calculate limb salvage as this method adjust for censored observations, i.e. patients who were alive and well at the time of last contact or patients who have died of distant metastases but with preserved limb function. Using this method we calculated a 1 year limb salvage rate of 80% with amputations performed mainly because of post perfusion related complications or early local recurrence in the first year after ILP. A second curve in limb salvage was observed within 5 years after TNF ILP in two patients with late local recurrences. A third bent in the limb salvage curve was observed around ten years after ILP. This was a new observation in two patients that presented with critical leg ischemia with ulceration and continuous pain. Besides ILP with TNF and melphalan, both patients received adjuvant radiotherapy (66 and 70 Gy) after marginal tumor resection.

What seems to be the cause of this late morbidity? Analysis of the functional and long-term morbidity in 97 patients with stage I melanoma treated with ILP with melphalan as the sole perfusion agent in our own center, showed after a median follow up of 36 (range 12-76) months, no patients with critical leg ischemia.\textsuperscript{27} The Rotterdam and Amsterdam perfusion group reported a long-term morbidity consisting of muscle atrophy or fibrosis in 11% of the patients after ILP with melphalan, however cases of critical leg ischemia are not described.\textsuperscript{28} The fact that in our series no muscle atrophy or fibrosis was found might be explained by the
Amputation after isolated limb perfusion with TNF and melphalan for STS

fact that we always perform a lateral fasciotomy after ILP to prevent a compartment syndrome. With a literature search for late morbidity after ILP with TNF and melphalan, no studies could be retrieved.

The clinical importance of late morbidity after radiotherapy has evolved since the publication of Eifel et al. who retrospectively reviewed the medical records of 1784 FIGO stage IB patients receiving primary radiotherapy at the MD Anderson Cancer Center between 1960 and 1989.29 She showed that after 5 years, there was a small but continuous risk of experiencing major complications of radiotherapy, i.e. urinary, rectal and small bowel complications, all the way to 20 years of follow-up. Johansson et al. described a high occurrence of severe neuropathy closely linked to the development of fibrosis around the nerve trunks, after aggressive postoperative telecobalt therapy received in 1963-1965 in a group of 71 breast cancer patients that were initially treated with modified radical mastectomy.30 Radiotherapy damage to the vascular system was demonstrated by Hopewell in an experimental setting, arteries of the hamster cheek pouch, showed localized constrictions after irradiation.31 These constrictions were caused by clones of endothelial cells and may be the predominant factor influencing the degeneration of the capillary bed after radiotherapy.32 Evidence of this occlusive effect of vessels by proliferating endothelial cells after radiation have also been reported by other investigators.33

Another argument to subscribe the observed late morbidity, at least in part, to the radiotherapy is the fact that another two patients receiving adjuvant radiotherapy after ILP with TNF and melphalan, developed a pathological fracture of the femur (78 and 129 months after ILP with TNF and melphalan). Radiotherapy induced osteonecrosis is a well known phenomenon after radiotherapy. Lin et al. described 12 fractures of the femur after surgery and irradiation for STS of the thigh. Treatment of these fractures was difficult and demanding with only 4 bony unions after a mean follow-up of 37 months.34 When we add up the evidence of developing fibrosis after ILP with melphalan and the development of fibrosis after radiotherapy, the combination of the two regiments could explain the observed late morbidity rate in the present series.

Overall survival for all patients showed a steadily decline with a ten year percentage of 42%. Even after 110 and 120 months patients die of distant metastases. Sixteen percent of the patients had metastases at the time of ILP. A significant difference in survival was observed comparing these patients with pulmonary or lymphphe node metastases with patients lacking metastases at time of ILP. Five- year overall survival of 59% in this series is higher than the
reported 5 year survival of 48% in the Amsterdam experience and the reported 32% of Lejeune et al.\textsuperscript{23,24} This in an unexpected observation since selection criteria for ILP with TNF between the institutes are comparable.

Patients with high-grade tumors and diameters greater than 5 centimeter have a great tendency to metastasize. These patients could theoretically benefit from neo-adjuvant chemotherapy. A quantitative meta-analysis of data from 14 trials of doxorubicin-based adjuvant chemotherapy showed indeed a benefit from systemic adjuvant chemotherapy of 6% for local relapse-free interval, however there was no overall survival benefit at 10 years.\textsuperscript{35} Delaney et al. developed a regimen of preoperative chemotherapy consisting of mesna, adriamycin, ifosfamide, and dacarbazine (MAID) interdigitated with radiotherapy followed by resection and postoperative chemotherapy with or without radiotherapy to improve outcome in patients with high grade extremity STS. Compared with a historical group of control patients, outcome in the MAID group was superior.\textsuperscript{36} In an update of 64 patients 5 required amputation because of disease, 3 had unresectable disease and 1 patient refused surgery. Estimated three-year survival and local-regional control were 75.1% and 79.3%, respectively. These results are comparable with the results of the present study.\textsuperscript{37} However, systemic therapy is associated with systemic toxic effects in contrast with the mild systemic side effects observed after ILP with TNF and melphalan.

Since 1992 we have not changed the indication for TNF perfusion. Patients who were candidates for amputation of the involved limb, based on the preoperative MRI, were offered an ILP with TNF and melphalan with the ultimate goal to preserve the limb with a locally advanced soft tissue sarcoma. After ILP patients received a delayed surgical resection and adjuvant radiation therapy in those patients with marginal or microscopically positive resection margins. This treatment resulted in a high limb salvage rate in patients with locally advanced STS, however late morbidity can occur especially when adjuvant postoperative radiotherapy is applied. Therefore continuous follow-up of these patients is warranted.
Table 1 Histological grade of the tumors according to Coindre et al.\textsuperscript{17} and stage of the tumors according to AJCC.\textsuperscript{16}

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>II</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>III</td>
<td>40</td>
<td>54</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>50</td>
<td>69</td>
</tr>
<tr>
<td>IV</td>
<td>12</td>
<td>16</td>
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Table 2  Amputations performed in 21 patients sorted on interval duration.

<table>
<thead>
<tr>
<th>N</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Interval (months)</th>
<th>Rationale for amputation</th>
<th>Current status</th>
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<tbody>
<tr>
<td>1</td>
<td>PUS</td>
<td>60</td>
<td>0</td>
<td>Postperfusion necrosis(^{38})</td>
<td>NED 120 months</td>
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<tr>
<td>2</td>
<td>Angiosarcoma</td>
<td>74</td>
<td>1</td>
<td>Local recurrence</td>
<td>DOD 11 months</td>
</tr>
<tr>
<td>3</td>
<td>Fibrosarcoma</td>
<td>76</td>
<td>1</td>
<td>Postperfusion necrosis</td>
<td>NED 2 months</td>
</tr>
<tr>
<td>4</td>
<td>PUS</td>
<td>67</td>
<td>2</td>
<td>Postperfusion necrosis</td>
<td>DOD 9 months</td>
</tr>
<tr>
<td>5</td>
<td>Epithelioid sarcoma</td>
<td>21</td>
<td>2</td>
<td>Postperfusion necrosis</td>
<td>DOD 54 months</td>
</tr>
<tr>
<td>6</td>
<td>Leiomyosarcoma</td>
<td>17</td>
<td>2</td>
<td>Insufficient clinical response</td>
<td>DOD 7 months</td>
</tr>
<tr>
<td>7</td>
<td>Liposarcoma</td>
<td>60</td>
<td>2</td>
<td>R1 resection, RT not possible</td>
<td>AWD 10 months</td>
</tr>
<tr>
<td>8</td>
<td>PNET</td>
<td>62</td>
<td>3</td>
<td>Local recurrence</td>
<td>DOD 17 months</td>
</tr>
<tr>
<td>9</td>
<td>Synovial sarcoma</td>
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<td>3</td>
<td>Postperfusion necrosis</td>
<td>DOD 50 months</td>
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<td>63</td>
<td>3</td>
<td>Postperfusion necrosis</td>
<td>NED 72 months</td>
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<td>11</td>
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<td>80</td>
<td>4</td>
<td>Local recurrence</td>
<td>DOD 10 months</td>
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<tr>
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<td>65</td>
<td>4</td>
<td>R1 resection, RT not possible</td>
<td>NED 6 months</td>
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<tr>
<td>13</td>
<td>Epithelioid sarcoma</td>
<td>22</td>
<td>6</td>
<td>Local recurrence *</td>
<td>DOD 39 months</td>
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<td>14</td>
<td>Haemangiopericytoma</td>
<td>50</td>
<td>8</td>
<td>Wound complications after ILP with radiotherapy *</td>
<td>AWD 65 months</td>
</tr>
<tr>
<td>15</td>
<td>PUS</td>
<td>71</td>
<td>12</td>
<td>Wound complications after ILP with radiotherapy *</td>
<td>NED 14 months</td>
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<tr>
<td>16</td>
<td>PUS</td>
<td>61</td>
<td>15</td>
<td>Arterial occlusion</td>
<td>AWD 17 months</td>
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<td>42</td>
<td>18</td>
<td>Local recurrence</td>
<td>NED 20 months</td>
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<tr>
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<td>Liposarcoma</td>
<td>53</td>
<td>37</td>
<td>Local recurrence</td>
<td>DOD 110 months</td>
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<tr>
<td>19</td>
<td>Liposarcoma</td>
<td>39</td>
<td>58</td>
<td>Local recurrence</td>
<td>DOD 120 months</td>
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<tr>
<td>20</td>
<td>PNET</td>
<td>56</td>
<td>110</td>
<td>Critical leg ischemia</td>
<td>NED 118 months</td>
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<tr>
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<td>Chondrosarcoma</td>
<td>18</td>
<td>125</td>
<td>Critical leg ischemia</td>
<td>NED 134 months</td>
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</table>

NED = no evidence of disease; AWD = alive with disease; DOD = death of disease; PUS = pleomorphic undifferentiated sarcoma; PNET = malignant peripheral nerve sheath tumor; R1 resection = microscopically involved resection margin; RT = radiotherapy; * patients with a second TNF melphalan ILP
Figure 1 Percentage of necrosis estimated on pathological examination of the resected tumor remnant in relation to the number of patients.

Figure 2 Limb salvage curve in patients with locally advanced soft tissue sarcoma treated with TNF and melphalan isolated limb perfusion.
**Figure 3** Clinical appearance of the lower leg of patient no 21 (Table 3) before amputation for critical leg ischaemia.

**Figure 4** Overall survival in patients with locally advanced soft tissue sarcoma treated with ILP, TNF and melphalan. A significant difference was observed between patients with no distant metastases at the time of ILP (mets -) compared with patients with metastases at the time of ILP (mets +).
Amputation after isolated limb perfusion with TNF and melphalan for STS

References


Chapter 4


Amputation after isolated limb perfusion with TNF and melphalan for STS

Chapter 4