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Neoadjuvant Treatment of Locally Advanced Soft Tissue Sarcoma of the Limbs: Which Treatment to Choose?

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Key Words. Soft tissue sarcoma • Preoperative therapy • TNF limb perfusion • Radiotherapy • Hyperthermia

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe and weigh the available treatment options for the neoadjuvant therapy of soft tissue sarcoma of the limbs.
2. Discuss the positive effects of preoperative treatment concepts on resection margins.
3. Balance the adverse effects of pretreatment on subsequent operative morbidity.
4. Interpret the weaknesses of currently available study results.

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ABSTRACT

Soft tissue sarcomas (STSs) form a heterogeneous group of malignant neoplasms arising in the mesenchymal connective tissues. They can develop at any anatomic site but 60% occur in the extremities. Initially, treatment of STS relied solely on excision. In the 1970s, Enneking et al. developed the concept of compartmental resection to reduce the local failure rate. Later, Rosenberg et al. demonstrated, in a randomized study, that there was no difference in local tumor control and disease-free survival (DFS) in patients treated with amputation versus limb-saving surgery followed by 50–70 Gy external-beam radiotherapy (EBRT).

A considerable proportion of patients present with locally advanced tumors as a primary or recurrent disease and cannot be resected with adequate clearance margins. These patients are threatened with amputation for complete tumor removal. Improvements in surgical techniques, such as microvascular muscle flaps, allow for the avoidance of limb loss in the majority of cases. However, the use of frozen sections to determine intraoperatively whether clear margins have been achieved is limited by the multiplanarity of resection specimens. Thus, local failure rates are 15%–25%, and preoperative measures to sterilize the invasive margin of sarcomas have been explored. High-dose preoperative EBRT for high-grade STS was developed, and its
combination with intra-arterial or i.v. chemotherapy was reported to be effective. Recently, systemic chemotherapy combined with deep wave hyperthermia was shown to result in a longer DFS time in a large, randomized, phase III study. Treatment concepts differ significantly among centers and are influenced more by availability of technical equipment than by data. It is the aim of this review to elucidate the rationale of different regimens and analyze their potentials as well as weaknesses. *The Oncologist* 2008;13:175–186

**The Aim of Neoadjuvant Treatment**

The aim of preoperative treatment for soft tissue sarcoma (STS) is to “downstage” the sarcoma prior to surgery, resulting in subsequent limb salvage and better local tumor control by making the tumor smaller, less tethered to surrounding tissue, and less viable at its invasion front. In principle, this can be achieved by several different methods (Table 1): systemic chemotherapy [1], external-beam radiotherapy (EBRT) [2], isolated limb perfusion (ILP) [3], the combination of chemotherapy and hyperthermia [4], or chemotherapy combined with radiotherapy [5]. All methods aim at destroying tumor tissue either by targeting its vasculature or by directly affecting tumor cells themselves. The rim of invasion to surrounding tissue characterized by hypervascularity and increased perfusion (contrast media uptake on computed tomography or magnetic resonance imaging [MRI]) (Fig. 1) of the sarcoma should be destroyed, with less tumor cell spillage during subsequent resection [6, 7]. A major disadvantage of conventional chemotherapy is the occurrence of serious systemic side effects and the lack of effective substances beyond doxorubicin and ifosfamide. Recently, hyperthermia has been added to systemic chemotherapy in the neoadjuvant setting and has been proven to add to its value [8]. Isolated limb perfusion (ILP) provides an elegant solution to avoid the issue of systemic side effects by isolating the vasculature of a limb temporarily.

**Hyperthermic ILP: Evolution of a Successful Strategy for STS**

ILP was introduced into clinical practice in the late 1950s by Creech et al. mainly for melanoma patients [9]. Results of early studies for sarcoma were disappointing when ILP was performed with the standard drug melphalan [10] and the same applied for various other cytostatic agents [11, 12]. The lack of efficacy prompted Lejeune and coworkers to investigate the addition of high-dose recombinant human tumor necrosis factor-α (rhTNF-α), which resulted in near complete tumor destruction and prompted a limb-salvage rate of 90% [3]. A multicenter trial led to registration of the drug combination with an overall response rate of 76% and a limb salvage rate of 82% [13]. These data are consistently confirmed by single-center studies and hold true also in adverse situations like sarcoma recurrence in irradiation fields [14] or in patients with multifocal disease [15] (Table 2).

The approval of ILP with rhTNF-α plus melphalan has led to the establishment of over 40 practicing centers in Europe [16]. The situation is different in the U.S. where rhTNF-α is not available because of licensing problems. Furthermore, although the procedure is elegantly simple in concept, in practice it is technically complex and demanding, labor-intensive, and time-consuming, and it requires a multidisciplinary team of physicians, training, and experience.

**The Beneficial Addition of TNF-α to ILP**

TNF-α is a major player in both innate and specific acquired immunity, being secreted by activated macrophages and activated T lymphocytes. In a pilot study conducted by Posner et al. [17], it was observed that TNF-α alone or in combination with interferon (IFN)-γ prompted only minimal or no tumor response. The systemic administration of TNF-α in humans has been abandoned because of life-threatening toxicity [18, 19].

The mode of action of TNF-α–based ILP involves an early effect on the tumor vasculature by increasing endothelium permeability with better penetration of cytostatics to tumor tissue. Selective destruction of the tumor-associated angiogenic vessels occurs as a late effect through perturbation of cell–cell adhesive junctions and inhibition of αvβ3 integrin signaling, followed by death of endothelial cells and tumor vasculature collapse [20]. Recently, electron microscopy studies showed that TNF-α in the setting of ILP selectively increased tumor vascular permeability by targeting vascular endothelial cadherin. This effect led to gaps between endothelial cells, damaging the integrity of the tumor vasculature [21].

This process can be demonstrated by pre- and postperfusion angiography and/or gadolinium-enhanced MRI (Fig. 1) [22]. Magnetic resonance spectroscopy studies have shown that metabolic shutdown of the tumor is virtually complete within 16 hours after perfusion [23, 24]. The selective action of TNF-α on the tumor vasculature was emphasized by the observation that a three- to sixfold higher melphalan uptake was tumor specific, and no greater uptake was noted in normal tissues [25–27]. It is important to men-
tion that tumor remnants after ILP must be resected, otherwise progression of the residual tumor cells will occur. This can be monitored by reappearance of energy-rich phosphates on $^{31}$P-magnetic resonance spectroscopy during long-term follow-up [24].

**Table 1.** Options for preoperative treatment of STS of the extremities

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative radiotherapy</td>
<td>Following the experience of the Canadian randomized study, better in terms of morbidity and field size than postoperative RT; study not powered to demonstrate survival advantage</td>
</tr>
<tr>
<td>Radiochemotherapy</td>
<td>Optimum combination of irradiation and drugs still to be explored; only one study demonstrates better DFS and OS, but not local control, in comparison with historical controls</td>
</tr>
<tr>
<td>Systemic chemotherapy</td>
<td>Not proven to be effective for STS in the neoadjuvant setting</td>
</tr>
<tr>
<td>Systemic chemotherapy plus hyperthermia</td>
<td>Sole prospective phase III study in this field (EORTC 62961) demonstrates significantly longer PFS and OS times irrespective of location if hyperthermia is added to chemotherapy</td>
</tr>
<tr>
<td>Isolated limb perfusion</td>
<td>Convincing data from larger phase II studies only for TNF-α plus melphalan treatment; no randomized comparison available</td>
</tr>
</tbody>
</table>

*Abbreviations: DFS, disease-free survival; EORTC, European Organization for Research and Treatment of Cancer; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; STS, soft tissue sarcoma; TNF, tumor necrosis factor.*

**Figure 1.** Indication for and response to preoperative isolated limb perfusion (ILP) in a high-grade sarcoma (not otherwise specified, grade 3) of the right quadriceps compartment encircling the femur. (A): Pretreatment gadolinium-enhanced magnetic resonance imaging (MRI) scan showing areas of necrosis within the center of the tumor but extensive uptake of contrast media. (B): MRI control 6 weeks after ILP demonstrates complete necrosis of the tumor with a very marginal rim of contrast media uptake. (C): Resection specimen.

**Adverse Effects of ILP with rhTNF-α**

The registered doses of rhTNF-α in the ILP setting are 3 mg for arm perfusions and 4 mg for leg perfusions, combined with 10 mg of melphalan per liter of perfused limb volume. The TNF-α dose exceeds the systemic maximum-tolerated dose of 350 $\mu$g/m² by approximately 5–10×. This is the reason why proper monitoring of leakage to the systemic circulation is necessary. Lower doses of the drug could improve safety and reduce cost. Many centers have adopted a 1- to 2-mg dose of TNF-α, with the conviction that it is as effective as the approved regimen [28, 29]. ILP is performed under mild hyperthermic conditions (38.5–40°C). True hyperthermia (>41°C) is associated with major local toxicity and might lead to amputation as a result of damage to normal tissues [30].

The incidence of adverse events such as septic shock and hypotension has decreased with increasing experience, standardization of the ILP technique, and technical improvements. Systemic toxicity should be minimal in the absence of drug leakage into the general circulation and can be avoided by adequate measures [31, 32]. Most patients undergoing perfusion with rhTNF-α develop tachycardia, hypotension, and increased cardiac output [33, 34]. There is evidence that leakage from the perfusion circuit to the systemic circulation is responsible for the degree of cardiac alteration. Moderate systemic toxicity, such as fever and chills resulting from the activation of the cytokine cascade, in particular, interleukin (IL)-1 and IL-6, are easily manageable [35].

Postoperatively, edema, erythema, and cutaneous blistering can develop in the perfused limb and are classified according to the scale of Wieberdink et al. [36]. Within 48 hours after ILP, almost all patients develop a grade II or III reaction resolving spontaneously within 2 weeks. However, severe rhabdomyolysis can also be induced by ILP with myoglobinuria and imminent renal failure, representing grade IV–V toxicity. Determination of myoglobin from the perfusate or early postoperatively from the systemic circulation has proven helpful [37]. An increase in intracompartmental pressure during ILP is thought to be linked to neurotoxicity and muscular toxicity, and single centers recommend fasciotomy after ILP for protection [38]. The incidence of vascular complications after ILP is around 2%, and consists mainly of thrombosis at the arteriotomy or venotomy site [39].
THE ROLE OF DIFFERENT DRUGS COMBINED WITH TNF-α DURING ILP

A synergistic effect was expected when adding IFN-γ to TNF-α ILP because induction of TNF-α receptor expression in tumor cells had been observed [40], and toxicity was surprisingly lower when IFN-γ was added [41]. However, results from a randomized phase II trial indicated an only marginal improvement in outcome for the combination [41]. Studies using a combination of doxorubicin and TNF-α gave rather similar response rates to those obtained with TNF-α plus melphalan, but with significantly greater toxicity [42, 43]. Also, the combination of TNF-α with cisplatin turned out to be less effective [44–47] and was associated with dramatic regional toxicity, as with actinomycin D (unpublished data).

Table 2. Principal studies on TNF-α–based ILP for unresectable STS

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>n of patients</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>NC/PD (%)</th>
<th>Limb salvage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pivotal multicenter studies</strong></td>
<td></td>
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</tr>
<tr>
<td>Eggermont et al. (1996) [13]</td>
<td>TNF-α ± IFN-γ + M</td>
<td>195</td>
<td>18a</td>
<td>57a</td>
<td>25a</td>
<td>82</td>
</tr>
<tr>
<td>Eggermont et al. (1999) [83]</td>
<td>TNF-α + M</td>
<td>270</td>
<td>28c</td>
<td>48c</td>
<td>24c</td>
<td>76</td>
</tr>
<tr>
<td><strong>Single-center studies (&gt;20 patients)</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Gutman et al. (1997) [77]</td>
<td>TNF-α ± IFN-γ + M</td>
<td>35</td>
<td>37b</td>
<td>54b</td>
<td>9b</td>
<td>85</td>
</tr>
<tr>
<td>Olieman et al. (1998) [78]</td>
<td>TNF-α + M</td>
<td>34</td>
<td>35b</td>
<td>59b</td>
<td>6b</td>
<td>85</td>
</tr>
<tr>
<td>Rossi et al. (1999) [42]</td>
<td>TNF-α + Dox</td>
<td>20</td>
<td>26c</td>
<td>64b</td>
<td>10b</td>
<td>85</td>
</tr>
<tr>
<td>Lejeune et al. (2000) [79]</td>
<td>TNF-α + M</td>
<td>22</td>
<td>18b</td>
<td>64b</td>
<td>18b</td>
<td>77</td>
</tr>
<tr>
<td>Hohenberger et al. (submitted)</td>
<td>TNF-α + M</td>
<td>55</td>
<td>12</td>
<td>64</td>
<td>24</td>
<td>84</td>
</tr>
<tr>
<td>Noorda et al. (2003) [80]</td>
<td>TNF-α ± IFN-γ + M</td>
<td>49</td>
<td>8b</td>
<td>55b</td>
<td>37b</td>
<td>58</td>
</tr>
<tr>
<td>Gruenhagen et al. (2005) [15]</td>
<td>TNF-α + M</td>
<td>64</td>
<td>42b</td>
<td>45b</td>
<td>13b</td>
<td>82</td>
</tr>
<tr>
<td>Lans et al. (2005) [14]</td>
<td>TNF-α + M</td>
<td>29</td>
<td>20b</td>
<td>50b</td>
<td>30b</td>
<td>65</td>
</tr>
<tr>
<td>Gruenhagen et al. (2006) [81]</td>
<td>TNF-α + M</td>
<td>217</td>
<td>16b</td>
<td>68b</td>
<td>16b</td>
<td>97</td>
</tr>
<tr>
<td>Rossi et al. (2005) [82]</td>
<td>TNF-α + Dox</td>
<td>21</td>
<td>5a</td>
<td>57a</td>
<td>38a</td>
<td>71</td>
</tr>
<tr>
<td>Bonvalot et al. (2005) [29]</td>
<td>TNF-α + M</td>
<td>100</td>
<td>49f</td>
<td>17f</td>
<td>34f</td>
<td>87</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>35f</td>
<td>22f</td>
<td>43f</td>
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</tr>
</tbody>
</table>

Objective clinical response rate by World Health Organization criteria.

CR, complete remission; Dox, doxorubicin; IFN, interferon; M, melphalan; NC, no change; PD, progressive disease; PR, partial remission; TNF, tumor necrosis factor.

DOES PREOPERATIVE ILP IMPROVE FUNCTIONAL OUTCOME?

In a large, single-institution study (Hohenberger P, Herrmann A, Kettelhack C et al., submitted manuscript), the long-term disease-specific survival rate, local recurrence rate, functional outcome, and disability were evaluated in 63 patients who underwent hyperthermic ILP with TNF-α and melphalan followed by resection for mainly stage IIIB STS. Four months, 1 year, and 3 years postoperatively, the patient’s limb function and disability were evaluated and classified by means of the rating scale of the Musculoskeletal Tumor Society (MSTS) and the Toronto Extremity Salvage Score (TESS) as well as the Reintegration to Normal Living index [48]. The functional outcome according to the MSTS scale was 23.8 points of a maximum of 30 and the
median TESS was 81.3%. Improvement in function and adaptation to daily life routine were documented by an increasing TESS over time. A functional outcome analysis showed that the level of impairment induced was moderate and of minor influence on handicap levels. Sixty-nine percent of the patients who were employed or going to school were able to continue in these endeavors.

IS THERE A SURVIVAL BENEFIT FROM PREOPERATIVE ILP?

An aggressive surgical approach after TNF-α ILP results in excellent long-term local control rates in high-grade STS. There are no prospective data available for comparison with surgery alone with respect to survival time. The problems with limb-saving therapy may initially override the aspect of overall survival, and the incidence of distant metastasis is not well reported in the ILP series available. These locally advanced tumors with extracompartmental growth and/or infiltration to neurovascular bundles usually represent grade 3 lesions with a high incidence of distant metastasis [49]. The treatment is considered to act locoregionally only, and few patients who had TNF-α ILP were eligible to participate in the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) 62931 phase III study evaluating the value of intensive adjuvant systemic chemotherapy postoperatively.

COMBINING REGIONAL NEOADJUVANT TREATMENT MODALITIES

Eilber et al. [50] studied the combination of intra-arterial or i.v. doxorubicin with 17.5–30 Gy of preoperative EBRT, showing a complete response rate of 49% and a limb salvage rate of 98% for high-grade extremity STS without significant treatment-related morbidity. The most recent report on this protocol used in upper extremity sarcoma found a 96% local control rate in 53 patients and the achievement of limb salvage in all patients [51, 52]. Flap reconstructions were required in 43% of the patients, yielding an overall complication rate of 11%.

With respect to the extent of surgery after TNF-α ILP, a limited (conservative) surgical approach has been combined with adjuvant EBRT of 60–70 Gy. In 73 patients, 58% received radiotherapy (EBRT+ group) and 42% did not (EBRT− group). A significantly better local control rate was observed in the EBRT+ group than in the EBRT− group (p < .0001). In the EBRT− group, an R1 or R2 resection resulted in earlier relapse of local disease than with R0 resections (p = .047) [53]. According to an earlier report, the morbidity of this treatment was high and wound healing was markedly delayed, with soft-tissue necrosis and infection necessitating amputation in two patients. Radiation-induced fibrosis and limb edema affected the majority of patients in the EBRT+ group. A further complication was neuropathy, causing severely disabling motor deficits, limb contractures, and arterial occlusion [54]. Adjuvant EBRT reduces the risk for local recurrence after resection in STS patients treated with TNF-α ILP. It is indicated only when resection margins are microscopically positive in a tumor with major areas of viable cancer tissue left after ILP.

THE CONCEPT OF PREOPERATIVE RADIOTHERAPY

Historically, treatment of STS consisted of a combination of surgical resection oriented at the compartments the tumor arose in [55] and subsequent irradiation with the belief that radiotherapy destroys what the surgeon had left unintentionally [56]. In the 1980s, the idea of high-dose preoperative irradiation of STS was introduced into clinical studies [2, 57], and the results obtained were judged to be superior to those obtained with postoperative radiotherapy, particularly for larger lesions and tumors of higher grade. Like ILP, the idea behind preoperative radiotherapy is to downstage the tumor prior to surgery and to ease surgical excision with healthy margins, therefore allowing limb salvage [58]. Neoadjuvant radiotherapy has proven value in improving survival in cancer of the rectum [59]. However, its role in STS of the extremities is not fully established, despite almost 30 years of experience.

WHY IRRADIATE PREOPERATIVELY?

Advantages of preoperative radiotherapy for STS were outlined by Bujko, Pisters, and colleagues [2, 60, 61]. They include a short interval between radiotherapy and surgery, more conservative surgery because of tumor downstaging, and a lower likelihood of intraoperative tumor cell spillage into the surgical bed because of virtually complete tumor cell inactivity during surgery. It has long been proven that preoperative irradiation results in a smaller treatment volume than with postoperative irradiation: field size, 241 cm² versus 391 cm² (p < .001) [62]. Furthermore, treatment planning is easier because the gross tumor volume is readily definable [61]. The postoperative irradiation field must include all surgically handled tissues, including the drain sites, contributing to a larger irradiation field. This was confirmed recently in a Canadian randomized trial of pre- versus postoperative irradiation [63]. Another important argument for preoperative irradiation is that there is no delay between treatment components resulting from compromised wound healing postoperatively. This effect is particularly important in cases of early local aggressive recurrence after surgical excision but before irradiation [2].
WHY NOT IRRADIATE PREOPERATIVELY?
Despite the above-mentioned advantages of preoperative irradiation, there are, of course, disadvantages (Table 3). In general, wound morbidity is an important factor when excising STS, because large tissue volumes are removed. Additionally, it has been documented that wound morbidity is higher after preoperative radiotherapy. Collagen production by fibroblasts is significantly reduced after irradiation [64]. The wound-complication rate after preoperative irradiation and subsequent surgery was 37% in a series of 203 patients reported by Bujko et al. [60] Secondary surgery to control wound morbidity was necessary in 16% of the patients, and six patients ultimately required amputation. Almost a decade later, another series reported a wound-complication rate of sarcoma resection after EBRT of 44%, with 23% of the patients requiring secondary surgery [65]. In the Canadian randomized study, the wound-complication rate was 35% in patients after preoperative radiotherapy, compared with 17% in the postoperative group [63]. Preoperative EBRT brings about a high wound-complication rate not only in STS of the extremities, but also in other regions of the body, for example, in the head and neck, with a 20% wound-complication rate [66]. And as preoperative irradiation irreversibly destroys tumor tissues, it prevents (or makes difficult) a full pathological analysis [2] (Fig. 2).

DOES A HIGHER COMPLICATION RATE NEGATE THE USEFULNESS OF PREOPERATIVE IRRADIATION?
There are many factors that can contribute to the wound-healing rate that were not specifically addressed in the previous studies: type of wound closure, local anatomy of the tumor site, timing of EBRT [63]. Surgeons tend to use non-primary closure (i.e., with the incorporation of the vascularized tissue graft) of the wound after excision of a sarcoma of the extremity that was preoperatively irradiated. This might bias outcome in regard to wound healing. Therefore, neoadjuvant irradiation might be preferable over the postoperative approach in regions adjacent to the lung, joints, and nerve plexus or in the upper extremities [63].

IS THERE SURVIVAL BENEFIT FROM PREOPERATIVE IRRADIATION?
Nonrandomized studies that directly compared preoperative with postoperative irradiation showed no statistically significant difference in survival [2, 67]. O’Sullivan et al. [63] have shown a slightly, but statistically significant, better overall survival rate in STS of the extremities irradiated preoperatively. The difference became visible only after 2.5 years of follow-up. At 36 months after treatment, the overall survival rate was around 90% in the preoperative group versus 75% in the postoperative group [63]. Therefore, longer follow-up from the Toronto study group is awaited. It will probably show a difference in the overall 5-year survival rates, confirming the superiority of preoperative EBRT. Unfortunately, that study was not powered for this analysis, because the wound-complication rate was chosen as the primary endpoint for sample size calculation.

DOES PREOPERATIVE IRRADIATION DECREASE FUNCTIONAL OUTCOME?
In general, functional outcomes of combined surgery and neoadjuvant irradiation for STS are not inferior to those of surgery and adjuvant irradiation. Davis et al. [68] observed a slightly, but statistically significant, lower functional outcome at 6 weeks after surgery measured by the MSTS scale and the TESS for preoperative versus postoperative irradiation. However, this was the only time point during a 2-year observation period when a difference could be observed [68]. The difference at 6 weeks could be attributed to the wound morbidity rate, which was twice as high in the preoperative group. At later time points most wound problems had been managed and the influence of healing problems had no further impact on the functional result.

A follow-up study from Toronto confirmed the superiority of preoperative irradiation for STS over postoperative radiotherapy. There was less extensive fibrosis at a 2-year follow-up in patients who received EBRT prior to surgery than in patients who received postoperative irradiation. The less extensive fibrosis was significantly related to better MSTS scale and TESS functional scores. Forty-eight percent of patients in the postoperative arm and 31.5% in the preoperative arm had grade ≥ 2 fibrosis (p = .07). The radiation field size was predictive of greater rates of fibrosis (p = .002) and joint stiffness (p = .006) [69].

EBRT 3–6 weeks prior to surgery with a field size extending 5 cm above and below the most proximal and the most distal point of the tissue at risk could be considered standard treatment. A total dose of 50 Gy delivered in 25-Gy fractions seems adequate. Postoperatively, in those patients in whom pathological examination shows tumor cell at the resection margins, the field 2 cm around the tumor bed could be irradiated with another 16–25 Gy [63, 70].

DOES THE USE OF “SENSITIZING” CHEMOTHERAPY AND RADIOTHERAPY CAUSE BENEFICIAL EFFECTS?
Anticancer drugs such as doxorubicin and ifosfamide are viewed as having radiosensitizing effects [71, 72]. Theoretically, this effect might allow for a decrease in the radiation dose without compromising the induction of tumor necrosis or could be used to enhance cell death at an identical irradiation dose. Because patients with locally advanced, high
grade sarcomas are at high risk for metastatic spread, combining radiation and chemotherapy could also provide initial systemic treatment of undetected distant disease.

One of the first studies in this vein reported the use of low-dose doxorubicin (12 mg/m² per day) administered in parallel with EBRT (150 or 200 cGy/day) for 5 days with cycles repeated every 2–3 weeks. The partial response rate was 56% in 115 patients, with another 11% of complete remissions. Chemoradiation was well tolerated and no case of grade 3 or 4 leukopenia occurred [73]. Several small-scale studies of doxorubicin-based chemotherapy concurrent with radiation showed promising results. Later, Cormier et al. [71] reported on the safety and applicability of neoadjuvant chemoradiation of 50.4 Gy together with ifosfamide at a median dose per cycle of 10 g/m². The use of increasing doses of doxorubicin from 12.5 to 20 mg/m² per week during 5 weeks concurrent with radiotherapy was reported to be safe and prompted an R0 or R1 resection in 26 of 27 patients. In that study, 50% of the patients had ≥90% tumor necrosis, including two patients with pathological complete remission (pCR) [72]. However, 23% of the patients developed major wound complications.

**“TRUE” SYSTEMIC CHEMOTHERAPY COMBINED WITH IRRADIATION**

In an effort to devise a chemotherapy regimen that would be accepted as a sole systemic treatment, DeLaney et al. [74] developed the MAID protocol consisting of doxorubicin, ifosfamide, dacarbazine, and mesna. They administered three cycles together with 44 Gy of EBRT prior to STS resection. The most recent report on 48 patients treated in 1989–1999 found the outcome to be superior to that of historical controls in freedom from distant metastases (p = .0016), disease-free survival time (p = .0002) and overall survival time (p = .0003), whereas the advantage in terms of the local control rate was not significant. Wound complications occurred in 58%. Late complications included myelodysplasia and pathological fracture, with no standardized results on functional outcome available.

The Radiation Therapy Oncology Group conducted a prospective, phase II trial to evaluate the MAID regimen in a multi-institutional setting in 66 patients with high-grade extremity sarcoma of at least 8 cm in diameter [75]. Patients received three cycles of neoadjuvant MAID chemotherapy, interdigitated preoperative radiation therapy (44 Gy admin-

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**Table 3. Arguments for and against preoperative versus postoperative radiotherapy for soft tissue sarcoma of the extremities**

<table>
<thead>
<tr>
<th>Preoperative irradiation</th>
<th>Postoperative irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arguments in favor of</td>
<td></td>
</tr>
<tr>
<td>Lower dose (50 Gy)</td>
<td>Lower wound-complication risk (17%)</td>
</tr>
<tr>
<td>Smaller field size (easily definable tumor volume)</td>
<td>Tumor cells for pathology easily available</td>
</tr>
<tr>
<td>Less fibrosis and edema</td>
<td></td>
</tr>
<tr>
<td>Better functionality (TESS and MSTS scale score)</td>
<td></td>
</tr>
<tr>
<td>No delay because of extended wound-healing time</td>
<td></td>
</tr>
<tr>
<td>Arguments against</td>
<td></td>
</tr>
<tr>
<td>Higher wound-complication risk (35%)</td>
<td>Higher dose (60–66 Gy)</td>
</tr>
<tr>
<td>Destruction of tumor cells for pathology</td>
<td>Larger field size (tumor volume plus operation field difficult to define)</td>
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<td></td>
<td>More fibrosis and edema</td>
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<td></td>
<td>Worse functionality (TESS and MSTS scale score)</td>
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<td></td>
<td>Possible delay because of extended wound-healing time</td>
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</table>

Abbreviations: MSTS, Musculoskeletal Tumor Society; TESS, Toronto Extremity Salvage Score.
istered in split courses), and another three cycles of MAID postoperatively. Seventy-nine percent of patients completed the preoperative protocol and 59% completed all planned treatment. Three patients (5%) experienced lethal toxicities (myelodysplasia and infection). Another 83% of the patients experienced grade 4 toxicities. Sixty-one patients underwent surgery and 58 of these were R0 resections, of which five were amputations. The estimated 3-year locoregional failure rate was 17.6% if amputation is considered a failure, and 10.1% if not. Estimated 3-year disease-free, distant disease-free, and overall survival rates were 56.6%, 64.5%, and 75.1%, respectively. The authors concluded that the substantial toxicity of the trial precluded its unmodified use outside clinical trials.

A retrospective survey from Germany summarized the results of 23 patients having been treated with accelerated split-course radiation (1.6 Gy twice daily, total dose range 50–69 Gy) with concomitant chemotherapy consisting mainly of doxorubicin and ifosfamide but also using regimens adopted from Ewing’s sarcoma treatment. Grade 3 or 4 neutropenia was seen after 46% of cycles of chemotherapy, with one patient dying from septicemia. Effective tumor downstaging was documented in four of 22 patients who underwent resection (pCR in three patients). The abstract reported delayed wound healing in one of the 22 patients; however, four patients lost the limb as a result of other side effects. After a median follow-up duration of 26 months, the overall, disease-free, and distant metastasis-free survival rates were 83%, 64%, and 68%, with a local control rate of 94% [76]. If the high morbidity rates and toxicity of combination chemotherapy plus EBRT are taken into account, this treatment option definitely requires further investigation in a prospectively controlled setting.

**NEOADJUVANT SYSTEMIC CHEMOTHERAPY ALONE**

There is only one prospective, randomized study evaluating the use of neoadjuvant systemic chemotherapy, the EORTC STBSG 62871 trial. Patients with high-risk STS, defined as a tumor ≥8 cm, a grade II–III tumor <8 cm, or a grade II–III locally recurrent tumor, were randomized to either surgery alone or three cycles of 3-weekly doxorubicin (50 mg/m²) and ifosfamide (5 g/m²) before surgery. The drug schedule was found to be feasible and did not compromise subsequent treatment; however, it failed to demonstrate any benefit in terms of the overall or progression-free survival duration. The trial was closed after completion of phase II, because accrual was too slow to justify expanding the study into the scheduled phase III study. At a median follow-up time of 7.3 years, the 5-year disease-free survival rate was 52% for the no-chemotherapy arm and 56% for the chemotherapy arm ($p = .3548$). The 5-year overall survival rates for the two arms were 64% and 65%, respectively [1].

**PREOPERATIVE SYSTEMIC CHEMOTHERAPY PLUS HYPERTERMIA**

Most recently, the results of a prospective, randomized, neoadjuvant study combining systemic chemotherapy and deep-wave hypertermia (EORTC/European Society for Hypertermic Oncology 62961) were presented [4]. Positioning of the patient into an electromagnetic ring-antenna system allows for the establishment a defined field of regional hypertermia heating the area of the sarcoma to 42.5°C. Maintaining this temperature over 90 minutes results in significant changes in tumor blood flow and inter-
strial fluid pressure (Figs. 3 and 4) [6]. After successful conduct of a phase II study [77], the phase III trial took nearly 8 years to complete [8]. Eligible patients included 341 patients with ≥5 cm, grade II–III, deep and extracompartamental STS who were randomly assigned to receive four cycles of systemic chemotherapy (etoposide, ifosfamide, doxorubicin [EIAI]) alone or combined with deep-wave hyperthermia (RHT) (EIA+RHT) administered every 3 weeks both prior to and after tumor resection. Patients with primary as well as recurrent sarcoma were allowed to enter the study, which was carried out mainly in two German centers (Munich and Berlin).

The overall response rate (complete remission plus partial remission) was significantly higher for the EIA+RHT group (28.7%) than for the EIA alone group (12.6%; p = .002). The primary endpoint of the study was local progression-free survival (LPFS). The median LPFS duration was 45.3 months for EIA+RHT and 23.7 months for EIA (log-rank p = .015; hazard ratio [HR], 0.66; p = .01). The results were consistent for extremity, trunk, and retroperitoneal sarcomas. Astonishingly, if the nature of the underlying disease is taken into account, the rate of distant metastasis developing post-treatment is low, also resulting in an advantage in terms of survival for the combination therapy. After a median follow-up time of 25 months, patients who received EIA+RHT had a longer superior disease-free survival time than patients treated with EIA alone (31.7 months versus 16.2 months; p = .003; HR, 0.65) [8].

Thus, tumor response to neoadjuvant treatment, disease-free survival, and LPFS seem to be boosted by adding hyperthermia, which did not yield greater toxicity. At present, this study is the only one in the setting of neoadjuvant STS therapy with adequate statistical power.

**IS NEOADJUVANT THERAPY WORTH THE EFFORT?**

There is still debate on whether limb amputation is superior to limb-sparing treatment modalities in locally advanced sarcoma with respect to the question of whether or not the functional result outweighs the necessity of adding sophisticated therapy. Using our own data and the data from Toronto assessing functional long-term outcome after TNF-α ILP or preoperative radiotherapy, the question can clearly be answered with “yes.” It can be demonstrated that both strategies provide wide margins of clearance with excellent long-term local control. Functional outcome clearly justifies the extended effort underlined by the fact that the vast majority of patients were able to complete professional training and/or were limited only to a very minor extent in their daily activities.

**CONCLUSION**

The different approaches to preoperative therapy of locally advanced STS described in this review all require experienced multidisciplinary treatment teams. Each center advocates its own strategy by reporting encouraging results and confirming the feasibility of the therapy. However, direct comparison of any of the available treatment options is lacking, particularly with regard to long-term results (i.e., survival benefit, local and distant recurrence rate). Radiotherapy alone is the more easily applicable therapy, whereas TNF-α ILP requires the highest logistic effort. The advantage of combined radiochemotherapy is that, for systemic effects, chemotherapy is adequately dosed; however, this comes at the cost of the highest toxicity rates. Hyperthermia has no value as a treatment of its own, but it was found to improve the effects of systemic chemotherapy, which again, in itself, has not been proven to be beneficial in the neoadjuvant setting. To clarify these issues, an adequately powered, multicenter, properly designed, randomized trial is required. Relevant endpoints are locoregional progression-free survival, overall survival, and functional outcome.

**AUTHOR CONTRIBUTIONS**

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