Chapter 7

Soft tissue sarcoma: where to go?
**Introduction**

Although surgery is still the keystone in sarcoma treatment, the role for other specialties as radiation oncology, medical oncology, pathology, medical genetics, molecular biology, radiology, nuclear medicine, and epidemiology will continue to increase. Specialists from the various disciplines should cooperate in sarcoma working parties in order to improve treatment results and to stimulate clinical and basic research for future progress in the understanding of this rare tumor. In this chapter, some aspects of future sarcoma treatment are highlighted.

**Specialization and centralization**

Many studies on morbidity and mortality in various surgical procedures have clearly demonstrated a relationship between outcome and case load. Outcome disparity has not only been identified among various institutions, but also among surgeons within one institution [1-3]. Ten years ago, McArdle reported on the impact of variability among surgeons on postoperative morbidity, mortality, and ultimate survival in surgery for colorectal cancer [3]. He concluded that only surgeons with a special interest in colorectal surgery or surgical oncology should undertake such kind of surgery. Later studies confirmed the prognostic importance of surgical subspeciality training in colorectal surgery, but also demonstrated the prognostic importance of case load per surgeon and per institution [4,5]. The independent prognostic importance of the treatment center, the individual surgeon, and patient-volume has also been confirmed in other malignancies [6-9]. At present, considerable effort and resources are spent on large multicenter trials on adjuvant chemo- and/or radiation therapy in the hope to improve cancer survival. In these trials, the type of surgical resection is more and more defined, since there is evidence that outcome is related to the surgery performed, which may be improved by better surgical training and by centralization of difficult surgical procedures. This especially holds true for rare tumors as sarcomas, where the experience of the individual institute is very limited.

The Scandinavian Sarcoma Group has reported on the impact of specialization in STS. In the early eighties, they demonstrated that an adequate resection with associated low local recurrence risk was more often obtained in patients treated in a center compared to those treated at local hospitals [10]. Later, one of their population-based studies clearly showed the benefit for STS patients who were referred to a center before any type of surgery had taken place. Patients referred after surgery or not at all, underwent substantially more operations, whereas their local recurrence rate was higher [11]. However, in a recent study from the Memorial Sloan Kettering Cancer Center, reerection seemed to have no detrimental effect on survival in extremity STS [12]. Moreover, none of the currently available prospective randomized trials supports the hypothesis that better local control enhances survival in sarcoma patients [13-15]. The problem is that the power to detect survival difference in relation to local control is small in the reported randomized trials. A large number of patients will be required to determine whether prevention of local recurrence improves survival [16]. Nevertheless, local control of the primary tumor remains very important for the quality of life of cancer patients.
During the past twenty years, the establishment of a sarcoma working party that has been responsible for the multimodality treatment of sarcomas at the Groningen University Hospital has led to an improvement in local control at various tumor localisations [17]. Nevertheless, specialization should not only focus on sarcoma treatment, but also on diagnosis, especially the histopathological diagnosis, which is often extremely difficult. Histopathological peer review studies have demonstrated that 6-24% of registered soft-tissue and bone sarcomas were considered on review not to be sarcomas, whereas agreement on subtype could be achieved in only 53-75% [18-20]. Experienced pathologists should therefore preferably review histopathological specimens of these rare tumors. Recent progress in immunohistology and molecular biology has improved sarcoma diagnosis. Knowledge of these techniques will become increasingly important because they may serve as aids in the diagnosis and classification of bone and soft tissue tumors, especially in the differential diagnosis of those of confusing nature [21-24]. In order to optimize the use of tumor tissue, it is advisable to submit fresh specimens to the pathologist.

Another argument for specialization in STS is given by the Groningen Sarcoma Group, which reported on the adherence to STS staging guidelines [25]. In a specialized center, compared to non-specialized community hospitals, the case load was higher and the compliance with the guidelines was significantly better. Special attention should be paid to future guideline development, dissemination, and implementation. Centralization of STS treatment in a limited number of hospitals with dedicated multidisciplinary sarcoma working parties appears advisable. In this way, adequate patient volumes can be achieved to ensure a certain threshold of clinical experience, and to enable special fellows, not only in surgical oncology, but also in medical oncology, radiotherapy, and pathology, to get more familiar with various aspects of the multimodality treatment of these rare tumors.

Another important aspect of specialization and centralization of STS treatment and the establishment of a sarcoma working party is the possibility to perform clinical, basic and experimental STS research.

Prognostic factors: old and new

During the last decades, many prognostic factors have been identified, and the most relevant ones have been incorporated into various staging systems. Of these, the revised American Joint Committee on Cancer (AJCC) staging system is the most widely used (Table 1). The AJCC STS staging system relies upon histological grade, tumor size, depth, as well as the presence of nodal or distant metastasis [26], all classical parameters with proven value as prognosticators [27-30]. One of the major limitations of the present AJCC staging system is that it does not take into account the anatomical site, which is an important determinant of outcome. Patients with retroperitoneal and visceral sarcomas have a worse overall prognosis compared to patients with extremity STS [27,31-33].

In addition to the tumor characteristics embedded in the AJCC system, several other parameters have been identified as prognostic factors [27-29]. Among these, the specific histological (sub)type of the STS is considered secondary in importance to the histological grade. STS as fibrosarcoma, leiomyosarcomas and malignant peripheral nerve sheath tumors have a poorer outcome, whereas liposarcomas tend to do better [27,31]. Other negative
prognostic factors are local recurrence [11,27], microscopically positive margins [27,29], tumor necrosis [11,34,35], and vascular invasion [11,36,37]. Age over 50 years [27] and male sex [28] have been identified as unfavourable prognostic factors in some series, whereas other series could not confirm this [27,29,38]. Although the AJCC staging system allows for the identification of high-risk patients at presentation, i.e. patients with large (> 5 cm), high-grade, deep lesions, one should realize that, with the current clinicopathological factors, clinicians can at best identify (non-metastasized) patients with up to 50% risk of distant failure, i.e. the patient with a G3T2b lesion [39]. Therefore, future studies will have to focus on the identification of new prognostic indicators that might facilitate the identification of the highest-risk subset of patients. Recent research into angiogenesis, molecular biology, and cytogenetics has revealed some new prognostic factors. High intratumoral microvessel density [40], high S-phase fraction [41-43], and a high expression of proliferation markers (proliferating cell nucleolar antigen, Ki-67, nucleolar organizer regions) [44-48] have been associated with a poor survival. However, as results have not been unequivocal, the use of these parameters as clinical indicators of prognosis remains controversial, and prospective long-term observational studies in a large number of patients will be required to establish the clinical impact of these factors. Although the value of DNA ploidy as a prognostic indicator is well established in many other cancers, its prognostic relevance in STS remains unclear and controversial [37,49-51]. In recent years, more specific chromosome and gene

Table 1. The American Joint Committee on Cancer (AJCC) soft tissue sarcoma staging system.*

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Histopathologic grade</th>
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<tbody>
<tr>
<td>TX Primary tumor cannot be assessed</td>
<td>GX Grade cannot be assessed</td>
</tr>
<tr>
<td>T0 No evidence of primary tumor</td>
<td>G1 Well differentiated</td>
</tr>
<tr>
<td>T1 Tumor 5 cm or less in greatest dimension</td>
<td>G2 Moderately differentiated</td>
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<tr>
<td>T1a superficial tumor</td>
<td>G3 Poorly differentiated</td>
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<tr>
<td>T1b deep tumor</td>
<td>G4 Undifferentiated</td>
</tr>
<tr>
<td>T2 Tumor more than 5 cm in greatest dimension</td>
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<tr>
<td>T2a superficial tumor</td>
<td></td>
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<tr>
<td>T2b deep tumor</td>
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<tr>
<td>Regional Lymph Nodes (N)</td>
<td></td>
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<tr>
<td>NX Regional lymph nodes cannot be assessed</td>
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</tr>
<tr>
<td>No No regional lymph node metastasis</td>
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<tr>
<td>N1 Regional lymph node metastasis</td>
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<tr>
<td>Distant metastasis (M)</td>
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<tr>
<td>MX Distant metastasis cannot be assessed</td>
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<td>Mo No distant metastasis</td>
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abnormalities have been associated with prognosis. Mutation or functional inactivation of the \textit{p53} tumor suppressor gene has been reported in several STS types \cite{30,52-54}. Functional inactivation of both the wild type and mutant \textit{p53} protein can be achieved by amplification of the \textit{murine double minute 2 (MDM2)} gene. The presence of \textit{p53} gene mutations and/or \textit{MDM2} amplification seems to be associated with adverse outcome \cite{52,55,56}. Nevertheless, more thorough evaluation is needed. Another tumor suppressor gene often altered in STS is the \textit{retinoblastoma gene (RB1)}. Absence of expression of this gene has been associated with poor outcome \cite{57}, but results have been contradictory \cite{58}. The role of oncogenes in initiation or progression of STS seems rather limited, with a possible exception of the \textit{myc} oncogene. A correlation between expression/amplification of this gene with higher tumor grade and poorer survival has been reported in STS \cite{59-61}. Although new cellular and molecular prognostic factors have been identified, there is presently no consensus how these factors should be incorporated into clinical practice. Once more, the need for centralization, further consensus development and multicenter collaboration seems obvious because of the rarity of these tumors.

\textbf{Treatment of STS in the new millennium}

As in most solid tumors, surgery will remain the most important modality to cure patients with a primary STS. Minimal invasive techniques and attention for functional outcome dominate modern surgery, not only in surgical oncology (for example breast conservative surgery and sentinel lymph node biopsy in breast cancer), but also in gastrointestinal surgery (various laparoscopic approaches), vascular surgery (endovascular aneurysm repair), and orthopedic surgery (minimal invasive percutaneous plate osteosynthesis and less invasive stabilization system). In STS, the prospective trial from the National Cancer Institute, comparing amputation to wide excision and postoperative radiotherapy (both with adjuvant chemotherapy), was very important for the development of multimodality, limb-saving treatment \cite{13}. The conclusions of this trial were supported by other randomized trials of less or more aggressive local treatment of STS \cite{62-65}. Nowadays, limb-sparing surgery is possible in roughly 90\% of patients with extremity STS \cite{27,66,67}.

Treatment of locally advanced extremity STS remains a challenging problem. As amputation does not influence survival \cite{13}, limb-saving techniques have been developed. Nevertheless, amputation of the limb still might be a good treatment, especially in sarcomas invading joints, bones, or neurovascular structures, although involvement of major nerves is not an indication per se for ablative surgery \cite{68}.

In the seventies, Morton and Eilber developed the multimodality therapy of preoperative intraarterial chemotherapy (doxorubicin), followed by external beam radiotherapy (EBRT) and surgical resection \cite{69-71}. This treatment has been applied to patients with intermediate and high-grade extremity STS. In the early days, when patients were treated with preoperative intraarterial doxorubicin, immediately followed by ten fractions of 3.5 Gy EBRT and surgical resection, treatment related morbidity was very high (35\%). However, local recurrence and amputation rates were low, 9\% and 5\% respectively. To decrease morbidity, the total radiation dose was lowered to 17.5 (5 x 3.5) Gy, which indeed reduced treatment-related complications, but also significantly increased local failure rate to 15\%.
An intermediate radiation dose of 28 (8 x 3.5) Gy appeared to achieve an excellent local control rate of 91%, and an acceptable complication rate, with only 6% requiring reoperation. In addition, there was no difference between intraarterial and intravenous administration routes of doxorubicin [71]. Notwithstanding these good results, which even seem to increase by the addition of ifosfamide to the regimen, long-term treatment-related complications can result in disabling limb function [72]. Although the intraarterial chemotherapy, with or without stop flow occlusion has some theoretical advantages (‘first pass’ effect and/or decreased drug extraction), to date there is no indication for intraarterial chemotherapy in the treatment of STS of the extremities [73].

Another technique, used in locally advanced STS of the extremities, is the hyperthermic isolated limb perfusion (HILP). In 1958, Creech and co-workers pioneered the use of regional isolated perfusion for melanoma of the limb, using an extracorporal circulation system [74]. The addition of hyperthermia, based on studies of Cavaliere and Stehlin, yielded the technique of hyperthermic isolated limb perfusion as a new and important therapy in the management of (advanced) extremity tumors [75,76]. Krementz was one of the first to report on the results of this limb-saving treatment modality in locally advanced extremity sarcomas [77]. In STS, melphalan, the standard drug for HILP in melanoma, has been studied most extensively, although other agents (doxorubicin, cisplatin, etc) have also been applied [78-80]. At the end of the eighties, it looked like HILP would not achieve a major breakthrough in the treatment of locally advanced extremity sarcomas as results were disappointing and not better than other limb-salvaging protocols [71,81,82]. In the early nineties, however, much progress was made by studies from Lejeune and co-workers, who added tumor necrosis factor- alpha (TNF-α) and interferon- gamma (IFN-γ) to the HILP regimen with melphalan, resulting in higher local response rates, with high limb-salvage rates and acceptable toxicity [83]. Recently, Eggermont published the results of 55 patients with primarily irresectable STS of the extremities, who were perfused in four European centers [84]. Notwithstanding the rather unfavorable group of patients in the latter study, with 24% multifocal primary or multiple recurrent STS, and a median tumor size of 18 cm, treatment response was very good. The complete and partial response rates were 36% and 51%, respectively. After a median follow-up of 27 months, limb salvage with good function was achieved in 84% of the patients [84]. Data from eight European centers showed more or less the same results [85]. Clinical and pathological tumor response and limb salvage rates in patients who received additional IFN-γ was virtually identical to those observed in patients treated with HILP with TNF-α and melphalan only. However, systemic toxicity was higher in the IFN group [85]. In 1998, Olieman demonstrated that in locally advanced extremity STS, adjuvant EBRT was feasible after HILP and surgical resection. This treatment resulted in a better local tumor control without increased treatment morbidity [86]. However, long-term results have to be awaited. The future HILP-TNF-α research has to be directed towards dose-reduction studies. Results from these studies are pending, and may have further impact on the applicability of TNF-α for other malignancies. Unfortunately, there will still be STS, especially in the extremities, which remain irresectable, because patients are no candidates for HILP. Such tumors might be treated by high dose EBRT only. In a series of Tepper, EBRT alone could achieve local control in 44% of patients for radiation doses greater than 64 Gy, in contrast to only 15% for lower
doses [87]. Local control rate was better for tumors of 5 cm or less (88%), than for tumors of 5-10 cm (53%), or greater than 10 cm (30%). As most (unresectable) STS of the extremities are large at presentation [86,88], very low local control rates may be expected from EBRT only.

Other radiation techniques, as brachytherapy and intraoperative radiotherapy (IORT), have been applied as a radiation boost technique in sarcoma treatment. These modalities are attractive, because they involve a much smaller treatment volume than conventional methods and because they can be combined with the surgical procedure, whereas conventional EBRT can only be started after wound healing. In 1996, Pisters and Brennan from MSKCC published the long-term results of a randomized trial on adjuvant radiation therapy in STS [14]. Brachytherapy significantly improved the local control rate in high-grade lesions. In low-grade STS, however, adjuvant brachytherapy did not improve local control, which was in contrast to the findings of a randomized prospective trial on adjuvant EBRT from the National Cancer Institute, demonstrating also a significant decrease in local recurrence rate in low-grade STS treated with adjuvant EBRT [15]. Improvement in local control in both the brachytherapy and adjuvant EBRT trial was not associated with a decrease in the rate of distant metastases or an improved disease-specific survival [14,15]. The experience in IORT for STS is still very limited. This appealing technique has been applied especially in retroperitoneal STS [89-92], with only a few reports on extremity STS [93-95]. All of these studies demonstrated the feasibility of this method in combination with surgical resection and adjuvant low-dose EBRT (≤ 40 Gy). In extremity STS, good local control rates have been reported with IORT and low-dose postoperative EBRT [95]. The only prospective, randomized trial, comparing 20 Gy IORT in combination with low-dose postoperative EBRT (35-40 Gy) with postoperative high-dose EBRT (50-55 Gy) in retroperitoneal STS, demonstrated a significantly lower local recurrence rate in the IORT group, with fewer complications of disabling radiation-related enteritis, but with more radiation-related peripheral neuropathy. However, again, enhanced local control did not translate into prolonged survival [91].

In extremity STS, presently available data suggest similar local control rates for preoperative chemoradiation, pre-operative radiotherapy only, and postoperative radiotherapy [96-101]. In large, high-grade lesions, brachytherapy (and perhaps IORT) may be superior to conventional EBRT, whereas the opposite seems to be true for large low-grade tumors. For the future, not much progress in local control of STS is expected. However, relatively new radiotherapy modalities, as three-dimensional conformal radiotherapy, inverse radiotherapy planning, and intensity modulated radiation therapy, seem to provide several advantages over conventional radiotherapy with regard to treatment-related morbidity [102-104].

In STS treatment, the role of adjuvant systemic chemotherapy remains quite controversial. The most effective single agents in STS are doxorubicin (adriamycin), dacarbazine (DTIC) and ifosfamide [105-109]. Although dose intensification and combination with growth factor support can further increase response rates [110-112], the role of such intensive high-dose combination chemotherapy remains controversial and side effects are not negligible [113,114], whereas randomized trials have not shown conclusively whether adjuvant chemotherapy benefits adult patients with localized STS. At present, the meta-
analysis from the Sarcoma Meta-Analysis Collaboration (SMAC) is the most reliable, up-to-date analysis of the effect of doxorubicin-based chemotherapy in localized resectable STS [115]. Overall, this review suggested that adjuvant doxorubicin-based chemotherapy could lengthen the time alive without recurrence, with a trend towards improved survival. There was a 27% risk reduction in the risk of local failure, with an absolute benefit of 6% at 10 years (81% vs 75%; P=0.016). With regard to distant relapse-free survival, a risk reduction of 30% was reported with an absolute benefit of 10% at 10 years (70% vs 60%; P=0.0003). The overall recurrence-free survival at 10 years improved with 10% (55% vs 45%; P=0.0001). However, with regard to the overall survival, the absolute benefit at 10 years was only 4% (54% vs 50%; P=0.19). Subgroup analysis demonstrated the clearest evidence of a treatment effect on survival in patients with extremity STS, where an absolute benefit of 7% at 10 years was reported (P=0.029).

From this and other reviews on adjuvant chemotherapy in STS, it is clear that future randomized trials should be larger than those from the past, because modest improvements are probably the best that can be expected. This will not be possible without entry of STS patients into sarcoma trials, and large-scale collaboration between research groups. New active systemic agents with limited toxicity are needed. However, most new drugs that have recently been tested in phase II trials have shown discouraging response rates [116-121].

Other potential ways to improve the efficacy of systemic therapy may be combination modalities involving chemotherapy, immunotherapy, biologic response modifiers, and modulators of multidrug resistance [122-124].

An intriguing new approach is the differentiation therapy, which has been proposed as an alternative to conventional anti-tumor therapy because many tumor cells retain some ability to differentiate through induction by chemical agents [125]. As differentiation status is predictive of clinical outcome in many STS, modulation of differentiation may favor clinical behavior. In rhabdomyosarcoma cells, exposure to low concentrations of actinomycin D and exposure to GR-891, a novel 5-fluorouracil acyclonucleoside prodrug, led to a terminal process of myogenetic differentiation [126-129]. Tontonoz demonstrated that human liposarcoma cells could be induced to undergo terminal differentiation by treatment with troglitazone, a ligand for the peroxisome proliferator-activated receptor-gamma (PPAR-γ) nuclear receptor [130]. Demetri demonstrated in three patients with intermediate to high-grade liposarcomas in vivo troglitazone-induced histological and biochemical differentiation, with a marked reduction in Ki-67 expression [131]. Clinical trials investigating this new technique are currently underway in the MDACC and the Dana Farber Cancer Institute [130,131]. The differentiation treatment has the potential of changing the outcome of intermediate and high-grade liposarcomas, which may be important especially in the retroperitoneum.

Another example of a new alternative treatment strategy is the treatment of unresectable or metastatic gastrointestinal stromal tumors with specific inhibitors of the constitutively active mutant c-kit tyrosine kinase that is expressed in most gastrointestinal stromal tumors in which it may play a central part in the pathogenesis [132-134].
Conclusion

The Sarcoma Working Party of the Groningen University Hospital and Faculty of Medicine, as well as the Comprehensive Cancer Center North-Netherlands facilitate clinical treatment of STS patients and basic STS research. During the last decade, the major breakthrough in STS was the introduction of TNF-α in HILP for primarily unresectable STS of the extremities, increasing the limb-salvage rate to a maximum, without increasing treatment-related morbidity or reducing (disease-free) survival.

New techniques have been developed, and some are very appealing. Although results from experimental and clinical pilot studies have been encouraging, the way to routine clinical use is still very long. To stimulate research and to improve treatment results, centralization and specialization seems important, especially in rare tumors as STS. To answer urgent questions, e.g. the survival benefit of adjuvant chemotherapy, STS should be treated only in trials and sarcoma working parties should be encouraged to collaborate. Only then, we will be able to dissolve the fog around many aspects of this intriguing tumor, so that we can enter this new millennium with the conviction that the future for STS treatment looks bright.

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