Soft tissue sarcoma at the turn of the millennium
Nijhuis, Paulus Henricus Antonius

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Chapter 1

Introduction and aim of the thesis
Introduction

Soft tissue sarcomas (STS) can be defined as malignant tumors arising from the non-epithelial extra-skeletal tissue of the body, exclusive of the reticulo-endothelial system and glia. Embryologically, these tumors are derived principally from mesoderm, except some, which derive from the neuroectoderm [1]. The pathogenesis of most STS remains unknown. Genetic factors (neurofibromatosis I and II, retinoblastoma, Li-Fraumeni syndrome, Gardner’s syndrome), environmental factors (exposure to environmental carcinogens as dioxin and some herbicides, and trauma, injury or ionizing radiation in the past), and immunological factors (immunosuppression after transplant surgery) have been identified as etiological factors in STS development [1-11]. As in most other malignancies, it is very unlikely that only one of these various factors is causing the disease; a multifactorial etiology seems obvious.

STS are rare tumors, accounting for approximately 1% of all malignant tumors diagnosed annually (8100 patients in the United States and 422 in the Netherlands) [12,13]. There is a slight male preponderance and the incidence is increasing with age [14,15,16]. As prognosis varies between the different histological types and even between subtypes, an adequate histopathological classification is crucial. The most recent classification of soft tissue tumors is the World Health Organization histological classification (1994), dividing these tumors into 15 categories [17].

Figure 1 presents the distribution of STS according to anatomical site in patients older than 16 years who were treated at the Memorial Sloan-Kettering Cancer Center (MSKCC) from 1982-1990. It should be mentioned that patients with visceral and genitourinary STS were included in that series. Figure 2 shows the distribution according to histopathology in the MSKCC series. In accordance with other reports, the most common histopathological types were liposarcoma (LPS), malignant fibrous histiocytoma (MFH), and leiomyosarcoma [15,18,19,20]. Approximately half of the STS occurred in the extremities (Figure 1), where liposarcoma and MFH were most common [19]. In the retroperitoneum and visceral tissues, however, leiomyosarcoma predominated [19].

![Figure 1](image_url)

*Figure 1.*

Unfortunately, there are only relatively few studies on epidemiological aspects of STS, and most of them are center-based. In the northeastern part of Netherlands, all malignancies, sarcomas included, are registered by the cancer registry of the Comprehensive Cancer Center North-Netherlands (CCCN), which is population-based, thus having a major advantage of avoiding selection bias caused by referral pattern. Collecting and studying data from such a cancer registry may provide more insight into STS epidemiology.

During the last decennia, many prognostic clinical factors have been identified in STS [21-39]. One of the most potent factors determining outcome seems to be the histopathological (sub)type of the tumor, which may become indiscernible if prognostically favorable tumor (sub)types are reviewed together with less favorable (sub)types, as in most reports on STS. Liposarcoma, as a group, has a better prognosis than epithelioid sarcoma [21-28], which in turn has a better prognosis than synovial sarcoma [29]. But even in the group of liposarcomas prognosis largely differs between the various histopathological subtypes [21-24].

Besides histological (sub)type, other prognostic characteristics, as age at presentation, gender, tumor size, anatomical site, tumor depth, surgical margin, tumor grade, tumor necrosis, and vascular invasion have been reported [30-39], and the most important ones have been embedded in the new staging system of the American Joint Committee on Cancer (AJCC) (Table 1) [40]. As liposarcoma is one of the most common STS in which several histopathological subtypes can be distinguished, this tumor is particularly suitable to study prognostic characteristics.

In recent years, the interest in the genetic etiology of malignancies has been increasing rapidly, and significant progress has been made in identifying chromosomal abnormalities in solid tumors. In several STS, characteristic cytogenetic alterations have been found, which often have diagnostic relevance [1,41-45]. As in other solid neoplasms, as well as in some hematological malignancies, it seems likely that some of these alterations have prognostic importance in STS, although, at present, such a relation between (specific) cytogenetic alterations and prognosis and survival in STS could not be demonstrated unequivocally [46,47].
Advances in technology have resulted in an important progress in diagnostic tools in STS. The introduction of the computer tomography scan (CT-scan) caused a major breakthrough in radiodiagnostics because, for the first time, it was possible to visualize the soft tissues directly using X-rays [48]. Notwithstanding its possibilities, this technique also had its shortcomings (the use of X-rays, direct images limited to only two plains, only information on anatomy and not on metabolism). The development of the magnetic resonance imaging (MRI) and the currently available spiral CT-scan overcame the first two shortcomings of the CT-scan [49,50], but still could not cope with the third one. The positron emission tomography scan (PET-scan) and the single photon emission tomography (SPECT) made it possible to study the metabolism of tumors [51,52]. As with all new technology-driven instruments, these challenging techniques can easily be used inappropriately, resulting in significant health-care costs [53]. Therefore, the development of specific diagnostic guidelines is important, especially in rare tumors, as clinical and histopathological presentation widely varies, the experience in individual hospitals is limited, and treatment often is very complex, including many modalities.

In February 1983, a cooperative group for rare tumors, consisting of specialists in surgical oncology, medical oncology, radiotherapeutic oncology and pathology from various hospitals in the CCCN-region, recognized this problem and developed regional guide-

<table>
<thead>
<tr>
<th>Table 1. The American Joint Committee on Cancer (AJCC) soft tissue sarcoma staging system.*</th>
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<tbody>
<tr>
<td><strong>Primary Tumor (T)</strong></td>
</tr>
<tr>
<td>TX Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0 No evidence of primary tumor</td>
</tr>
<tr>
<td>T1 Tumor 5 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1a Superficial tumor</td>
</tr>
<tr>
<td>T1b Deep tumor</td>
</tr>
<tr>
<td>T2 Tumor more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T2a Superficial tumor</td>
</tr>
<tr>
<td>T2b Deep tumor</td>
</tr>
<tr>
<td><strong>Regional Lymph Nodes (N)</strong></td>
</tr>
<tr>
<td>NX Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>No No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1 Regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>Distant metastasis (M)</strong></td>
</tr>
<tr>
<td>MX Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>Mo No distant metastasis</td>
</tr>
<tr>
<td>Stage grouping</td>
</tr>
<tr>
<td>Stage IA G1-2, T1a-1b, No, Mo</td>
</tr>
<tr>
<td>Stage IB G1-2, T2a, No, Mo</td>
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<tr>
<td>Stage IIA G1-2, T2b, No, Mo</td>
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<tr>
<td>Stage IIB G3-4, T1a-1b, No, Mo</td>
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<tr>
<td>Stage IIC G3-4, T2a, No, Mo</td>
</tr>
<tr>
<td>Stage III G3-4, T2b, No, Mo</td>
</tr>
<tr>
<td>Stage IV Any G, any T, N1, Mo</td>
</tr>
<tr>
<td>Any G, any T, No, M1</td>
</tr>
</tbody>
</table>

lines for the diagnosis and treatment of soft tissue tumors [54]. A few years later, the Dutch Sarcoma Group initiated national guidelines for STS diagnosis and treatment [55]. Although compliance with such guidelines is important for various reasons (e.g. appropriateness of practice, health-care savings, and better outcome and survival [53,56-58]), and despite an increase in medical practice guideline development and dissemination, compliance with such guidelines has often been surprisingly low. In malignant disorders, reports on the adherence to such guidelines are very limited, whereas in soft tissue tumors, nothing has been published on this item. Nevertheless, such information seems very valuable for future guideline development and introduction.

Treatment of STS has changed dramatically during the second half of the last century. Prior to the 1950s and 1960s, most surgeons dealing with STS performed local resections or shell-out procedures, which were associated with an unacceptable high local recurrence rate of 60-95% [59-63]. In the same period, Bowden and Booher reported limb-saving techniques with a low local recurrence risk [64]. In the same year, 1958, the group of Stener published the same surgical principles and results [65,66]. Both groups might be considered true pioneers in modern STS treatment, because both recognized the infiltrative manner of sarcoma growth, explaining the high local recurrence rate after shell-out procedures. Later, this high local recurrence rate was further explained by Enneking’s theory of sarcoma tumor growth pattern [67]. STS grow in a centrifugal fashion, resulting in the formation of an edematous pseudocapsule of compressed, normal tissue and a reactive zone of proliferating mesenchymal cells and neovascularization. Further tumor growth causes a continuous extent of microscopic tumor pseudopods into this pseudocapsule, where they form microscopic and macroscopic nodules (satellites). Especially in high-grade lesions, such satellites can also be found in surrounding ‘normal’ tissue, far beyond the pseudocapsule (skip metastases). In extremities, where most of the STS are located, the tumor extends longitudinally, within the compartment, bounded by fibrous barriers (muscle fascia and aponeurosis, deep fascia and intermuscular septae). Crossing these barriers is a late phenomenon, and is associated with high-grade lesions [67,68].

Based on these new insights, en-block resections of the entire compartment containing the tumor or amputations were recommended, resulting not only in a drop of local recurrence rate to 5-30%, but also in a high amputation rate of 40-50% [60,61,68-70]. Although these so-called ‘compartment resections’ were widely adopted, the division of surgical oncology of the Groningen University Hospital performed only wide local resections followed by external beam radiotherapy (EBRT) or amputation of the affected limb.

Modern STS management started at the end of the seventies and the beginning of the eighties. Suit and Lindberg were the first to demonstrate the importance of adjuvant radiotherapy in STS therapy [71,72]. Their results formed the basis of the famous National Cancer Institute (NCI) trial by Steven Rosenberg et al., a study that became one of the cornerstones in today’s state of the art STS treatment [70]. For the first time, a prospective randomized study showed that adequately performed local resection followed by high dose radiotherapy formed a reliable limb-saving treatment, comparable to amputation with regard to local recurrence, disease-free and overall survival rates.
Unfortunately, the optimal treatment for locally advanced extremity sarcomas remained an unsolved problem. One of the most promising approaches at that time was a multimodality therapy, consisting of preoperative (intraarterial) chemotherapy, immediately followed by EBRT, and surgical resection. This technique was initiated by Morton and Eilber [73], and later further developed by Eilber and co-workers at the UCLA School of Medicine [74,75]. The sequence of the various therapies was based on the premise that preoperative treatment of micrometastases at the periphery of the tumor with intact blood supply would enable the surgeon to perform a local surgical procedure. In three sequential trials, Eilber et al. showed a high limb salvage rate of 95%, with a low local recurrence rate of approximately 10% [75]. In the early eighties, this treatment strategy was adopted by the Groningen Sarcoma Working Party, which added postoperative EBRT to the treatment protocol in case of a marginal resection or involvement of the surgical margin [76]. The multimodality treatment, as initiated by Morton and Eilber, has been associated with a substantial short-term morbidity, especially wound complications [75]. Although there has been a growing awareness of potential long-term side-effects of intensified (multimodality) cancer treatment protocols, only very few reports have dealt with the long-term complications and functional outcome after this intensive STS treatment [75,77-79].

Another way to decrease the number of amputations in locally advanced extremity STS has been hyperthermic isolated limb perfusion (HILP) with cytostatics agents. Several drugs have been used (melphalan, the standard drug for HILP in melanoma, doxorubicin, cisplatinum, and other agents), without improvement of local control or disease-free survival when compared to the other therapies, as intravenous or intraarterial adriamycin in combination with neoadjuvant radiotherapy followed by local resection [75,80-83]. It was not until the early nineties, that significant progress was made by the addition of tumor necrosis factor-alpha (TNF-\(\alpha\)) to melphalan in HILP for locally advanced extremity STS [84]. This resulted in a high response rate and high limb salvage rates with an acceptable toxicity level [85]. In the early nineties, the Groningen Sarcoma Working Party changed the treatment of locally advanced extremity STS in HILP with TNF-\(\alpha\), melphalan, with or without interferon-gamma (IFN-\(\gamma\)), with good results [85]. In 1998, this sarcoma group published the results of a study on adjuvant EBRT (60-70 Gy) after HILP with melphalan, TNF-\(\alpha\), and IFN-\(\gamma\) and delayed tumor resection of locally advanced extremity STS with histopathological viable tumor after resection [86]. It was demonstrated that this was feasible and that the addition of EBRT increased local tumor control without increasing treatment morbidity. Recently, Ham et al. highlighted several aspects of modern surgical sarcoma treatment at the Groningen University Hospital [87].

Since the mid eighties, the cancer registry of the CCCN has registered all STS in the CCCN-region, and the Groningen Sarcoma Working Party discusses all sarcomas referred to the Groningen University Hospital. In recent years, many aspects of these tumors have been studied and reported by this sarcoma group, resulting in several theses [88-90]. Still a variety of questions remain unanswered. The goal of the present thesis is to get more insight into several aspects of this uncommon malignancy.
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Aim of the thesis

1. To provide more insight into epidemiological aspects of STS, based on a population-based survey.

2. To study the impact of the histopathological heterogeneity on prognosis in one of the most common STS, liposarcoma.

3. To evaluate the necessity of long-term follow-up, especially in case of intensive, multimodality treatment protocols, in order to determine long-term effects, which might interfere with the primary goal of such therapies.

4. To investigate the adherence to (diagnostic) STS guidelines, and to evaluate the role of centralization in the diagnostic management of these rare tumors.

5. To look into the (near) future of STS treatment, and to evaluate the prognostic importance of cytogenetic changes in these tumors.

References


Chapter 1

Introduction and aim of the thesis


