Soft tissue sarcoma at the turn of the millennium
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Chapter 8

Summary
Soft tissue sarcomas (STS) comprise a relatively heterogenic group of malignant tumors arising in mesenchymal tissues. In 1997, 523 new primary STS were diagnosed in the Netherlands, whereas 219 patients died from this disease that year. In the United States, approximately 8,100 new STS are diagnosed annually, whereas 4,600 patients die annually from their disease. These figures are relatively disappointing when compared to testicular cancer, a malignancy with a similar incidence, but a much lower cancer death rate. In 1997, 415 new primary testicular cancers were diagnosed in the Netherlands, whereas ‘only’ 31 patients died from that disease. In the U.S. these numbers are 6,900 patients and 300 patients, respectively. The unfavourable prognosis of STS is caused mainly by the propensity for metastasis. Moreover, local recurrence rates are relatively high (up to 20%), causing a substantial morbidity. Although STS have been studied quite extensively, several aspects remain unclear. The goal of the present thesis was to get more insight into some of the unsolved aspects of this uncommon malignancy.

The first part of the introduction in Chapter 1 contains general considerations regarding epidemiology, pathogenesis, and prognostic factors in STS. There is a need for population-based studies, as most studies on sarcoma are center-based and may therefore be biased. In recent years, the understanding of the STS biology has improved by advances in cytogenetics and molecular techniques. The increased insight into the interaction between oncogenes, tumor suppressor genes and their regulators may aid in prognostication.

One of the most important prognostic factors is the histopathological tumor (sub)type, which may become indiscernible if prognostic favorable tumor (sub)types are reviewed together with less favorable (sub)types. Therefore, studies that review the various histological (sub)types separately are awaited.

The second part of the introduction deals with guidelines. Guidelines are very meaningful in rare diseases as STS, because the experience in individual hospitals is often limited, whereas treatment often is very complex. In the Netherlands, as in most western countries, STS guidelines have been developed and distributed. Nevertheless, nothing is known about the compliance with these guidelines, although such information seems essential for the development of future guidelines and quality assurance programs.

The last part of the introduction reviews the treatment of STS, which changed dramatically during the second half of the last century. Before the mid-fifties, most STS were excised by local resections or shell-out procedures, resulting in an unacceptable high local failure rate. At the end of the fifties, Bowden, Booher and Stener developed the first limb-saving techniques, which were not widely adopted. After Enneking’s theory of longitudinal STS spread within the compartment, wide en-block resections gained popularity, resulting in low local recurrence rates, but high amputation rates. The studies of Suit and Lindberg and the famous NCI trial formed the base of true multimodality STS treatment.

Unfortunately, the approach of locally advanced STS remained a problem. Morton and Eilber developed a successful multimodality protocol, which was associated with a relatively high acute morbidity rate. Another very successful treatment for these unfavourable tumors has been the hyperthermic isolated limb perfusion (HILP), a technique that was first described in STS in 1977. The major breakthrough came in the early nineties,
when Lejeune added tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) to the HILP regimen, which resulted in a better local response rate and a high limb-salvage rate with an acceptable toxicity.

In recent years, there has been a growing awareness of the potential long-term side effects of cancer treatment protocols. Studies on intensive multimodality therapies used in locally advanced STS should therefore not only report on recurrence rate and short-term morbidity, but also focus on complications and functional outcome in the long-term, as these might interfere with the initial goal of the treatment.

The research questions that formed the basis of this thesis are formulated at the end of the introduction and are dealt with in the following chapters.

In Chapter 2, we describe epidemiological aspects of STS, based on the cancer registry of the Comprehensive Cancer Center North-Netherlands (CCCN). The aim of the study was to gain insight into true epidemiological aspects of STS, and to provide data for the development of future STS clinical trials. Four hundred and fifty-six primary STS (Kaposi, urogenital and gastrointestinal STS excluded) that were registered from 1989-1995 by the cancer registry of the CCCN were analyzed. The age-adjusted incidence of STS was 3.6/100,000/year. At initial diagnosis, most patients (n=225) were aged between 50-74 years (49%), whereas 118 patients (26%) were 25-49 years, 53 patients (12%) were younger than 25 years, and 60 patients (13%) were 75 years or older. Most STS were located in the extremities (45%), especially the lower limb and hip region (29%). The most common histological tumor types were malignant fibrous histiocytoma (MFH) and liposarcoma (both 18%), followed by leiomyosarcoma (15%), dermatofibrosarcoma (14%), fibrosarcoma (7%), and rhabdomyosarcoma (5%). The incidence of the histological types was age-dependent. Most of the head/neck STS were T1-tumors, whereas all retroperitoneal STS were T2-tumors. Notwithstanding the existence of staging guidelines in the CCCN region, presence or absence of lymph node involvement was not recorded in 210 patients (57%). Twelve of 158 patients with a documented N-stage (8%) had lymph node metastases at initial presentation. However, using a ‘best-case-scenario’, in which all unknown N-stages are to be considered as node-negative, the overall incidence of nodal involvement would be 3%. The M-stage was not recorded in 129 patients (35%). At presentation, 34 of 239 patients (14%) with documented M-stage had distant metastases. Using the ‘best-case-scenario’, the overall incidence of distant metastatic disease would be 9%. Five patients (1%) had both lymph node and distant metastases at presentation. Although lymph node involvement was not related to tumor size, distant metastases were significantly related to T-stage. Distant metastases were encountered in 21% of retroperitoneal STS, in 14% of lower limb and hip STS, but were absent in head/neck STS.

Most obvious differences in treatment were found between children and adolescents (≤20 years) and patients above 70 years. In contrast to localized disease, where we could not demonstrate any treatment difference, treatment in (regional and/or distant) metastatic disease was different between both groups. Less than 50% of the older patients with metastatic disease were treated and only 20% received some form of chemotherapy, in contrast to the younger patients, who were all treated with, at least, chemotherapy. As nearly half of the patients are older than 65 years at initial presentation, and roughly 10%
are children and adolescents, only 40% of all adult patients presenting with a STS may be eligible for clinical trials investigating the value of (neo) adjuvant chemotherapy in adult STS. Therefore, either new STS trials should be developed especially for the elderly, or future trials should not contain upper age limits. Instead, inclusion of older people should be dependent on other criteria, as WHO performance scale or absence of certain co-morbidity.

In Chapter 3, we analyze the long-term results of a very intensive multimodality treatment protocol used in locally advanced STS of the extremities. The treatment protocol implied continuous intraarterial doxorubicin for three consecutive days (20 mg/m²), followed by preoperative radiotherapy (10 x 3.5 Gy) and tumor resection, with or without postoperative external beam radiotherapy (EBRT). This treatment scheme was adopted at the Groningen University Hospital in the early eighties. Although the acute morbidity of this intensive protocol was well known, hardly anything was known about late complications. In an era, where there is a growing awareness of potential long-term side effects in cancer survivors, it is necessary to gain more insight into this aspect of cancer treatment. We therefore analyzed 11 patients with locally advanced STS who were treated between 1983 and 1987 according to the above mentioned multimodality scheme. Three patients suffered a severe acute local skin necrosis after intraarterial doxorubicin (27%), which deteriorated in two of them after preoperative radiotherapy. Limb-salvage was possible in ten patients (91%). After a median follow-up of 84 (range 3-136) months, six patients died (55%), five from metastatic disease and one from a non-disease-related cerebral hemorrhage. Five patients were still alive after a median follow-up of 120 (range 110-136) months. Three of them developed disabling functional limitations of the affected extremity. In two patients, limitations were caused by severe long-term complications: a complete neuropathy of the sciatic nerve five years after treatment and a spontaneous fracture of the affected femur 91 months after therapy with no healing tendency since. The third patient developed a very severe fibrosis of the affected limb, resulting in an invalidating limb function. Potential contributing factors to these problems in the long-term were discussed: 1) interaction between doxorubicin and radiotherapy, 2) hypofractionated radiation schemes, and 3) addition of postoperative EBRT, leading to a high biological effective radiation dose. Although the Groningen Sarcoma Working Party abandoned this treatment regimen after the introduction of hyperthermic isolated limb perfusion (HILP) with TNF-α and melphalan, this study demonstrates once more the need for long-term follow-up surveys in order to discover potential side effects that might eventually interfere with the primary treatment goal.

Although, in general, biological behaviour and prognosis of liposarcomas (LPS) are more favourable compared to most other STS, prognosis can widely vary depending on tumor characteristics, especially histological (sub)type and tumor grade. The study, presented in Chapter 4, aimed to get more insight into epidemiological aspects of LPS, to evaluate treatment results and to determine prognostic factors for local recurrence, metastasis, disease-free and disease-specific survival. All consecutive, completely resected AJCC stage I-III LPS, treated at the Groningen University Hospital from 1977-2000, were analyzed (n=69). The legs and retroperitoneum
were the most common tumor sites (n=38 and n=11, respectively), followed by trunk (n=6), arms (n=5), head/neck (n=5), and buttock (n=4). Twenty-five patients received adjuvant radiotherapy (36%), three patients were treated by resection and chemotherapy (4%), and nine patients were treated by all three modalities (13%). In 53 patients (77%), surgical margins were microscopically free (R0-resection), whereas in the other 16 patients margins were microscopically involved (R1-resection). The most common histological subtypes were myxoid LPS (n=34; 49%) and well-differentiated LPS (n=26; 38%), followed by dedifferentiated LPS (n=6; 9%), and pleomorphic LPS (n=3; 4%). After a median follow-up of 71 (range 5-231) months, the overall local recurrence and metastasis rate at five years after diagnosis were 27% and 16%, respectively. It was concluded that liposarcoma is a quite heterogeneous disease, and that its outcome is determined to a significant degree by histological subtype, grade, size, stage, depth, and type of resection. Compared to other STS, LPS had a relatively mild biological behavior, with the exception of very large, deeply located, dedifferentiated and/or grade II-III LPS. Retroperitoneal localization was an additional negative prognostic factor for local recurrence. However, in contrast to some reports in the literature, we were not (yet) able to demonstrate a significant influence of retroperitoneal localization on survival.

As the diagnostic management of STS is essential for definitive treatment, adherence to diagnostic guidelines seems important. Chapter 5 reports on the appropriateness of the diagnostic management of STS in the CCCN-region, according to these guidelines. All primary STS (n=351), registered by the CCCN from January 1989-January 1996, were analyzed with regard to adherence to the diagnostic guidelines. Urogenital, gastrointestinal STS, and Kaposi sarcomas were excluded. In the specialized center (Groningen University Hospital), 69% of patients were younger than 60 years, whereas in the eighteen district hospitals, 63% of patients were 60 years or older. With increase of age, referral to the center declined in a linear fashion. For all guidelines, adherence was significantly better in the center. In district hospitals, case load had no significant influence on compliance with the guidelines, except for the management of STS ≥3 cm. In district hospitals, where less than 15 patients were treated in the 7-years period, significantly more often an inadequate or even no biopsy procedure was performed prior to resection. As correct diagnosis, staging and treatment has been shown to be important in the management of many tumors, it was concluded that STS should be concentrated in a limited number of hospitals that collaborate with (the) specialized center(s).

Ways to improve development, dissemination, implementation, and evaluation of guidelines are discussed. Ideally, future guidelines should be developed by those who are to use them, should be disseminated by enthusiastic educational programs, and should be implemented by a quality control program with patient-specific feedback. Furthermore, special attention should be paid to the older patients, as they were significantly more often not referred to a specialized center for treatment.

The aim of the study presented in Chapter 6 was to determine the prognostic significance of cytogenetic changes in soft tissue sarcomas, using a computer-assisted cytogenetic analysis. From 1984-1993, 38 primary STS (88%) and 5 local recurrent STS (12%) were karyotyped successfully. None of these STS was previously treated by chemo- and/or radiotherapy. Liposarcoma was the most frequent STS (47%), followed by synovial
sarcoma (12%), and MFH (9%). After a median follow-up of 55 months, 20 patients had no evidence of disease (47%), 6 were alive with recurrent disease (14%), and 17 patients had died, 16 of which from their disease. At multivariate analysis, chromosomal gain at the long arm of chromosome 1 (1q) and chromosomal loss at the short arm of chromosome 4 (4p) were statistically significant negative prognostic factors regarding survival (Relative Risk (RR) 39 and 6, respectively). Regarding metastasis-free survival, the only significant negative prognostic factor was chromosomal loss at the short arm of chromosome 18 (18p), with a relative risk of 8. Furthermore, there was a strong association between loss in 18p and gain in 1q in patients with the shortest survival.

This study provides indications for a correlation between cytogenetic changes and metastasis and prognosis in STS. Some of the findings confirm earlier reports, whereas others are novel in STS and need to be confirmed in additional studies. The computer-assisted approach used in this study, is valuable in the analysis of large groups of complex karyotypes in order to detect common chromosomal alterations. The strong association between alterations in the long arm of chromosome 1 and the short arm of chromosome 18 in non-survivors is very challenging and may have prognostic value in STS.

In Chapter 7, we look into the near future of STS treatment and discuss some important issues as centralization and specialization, new prognostic factors, and developments that might be interesting for future STS treatment.

In many malignancies, the independent prognostic importance of the treatment institution, the individual surgeon, and case load has been confirmed. At present, when considerable effort and resources are spent on large multicenter trials on adjuvant chemo- and/or radiation therapy in the hope to improve cancer survival marginally, there is growing evidence that outcome could be increased much more by improvements in surgery. Such improvements may be accomplished by better surgical training and by centralization of difficult surgical procedures and multidisciplinary treatment protocols. This especially holds true for rare tumors as sarcomas where the experience of the individual institutions and surgeons is very limited.

With the current clinicopathological prognostic factors, clinicians can identify at best patients with approximately a 50% risk of distant failure (G3T2b). Therefore, future studies should focus on the identification of new prognostic indicators that might facilitate the identification of a higher-risk subset of patients. Recent research into angiogenesis, molecular biology, and cytogenetics has revealed some new prognostic factors as high intratumoral microvessel density, high S-phase fraction, overexpression of proliferation markers as Ki-67, DNA aneuploidy, mutation or functional inactivation of the \( p53 \) tumor suppressor gene, \( MDM2 \) gene amplification, loss of expression of the \( RB1 \) gene, and amplification of \( myc \) oncogene. At present, there is no consensus how these factors should be incorporated into clinical practice. Thorough future studies are necessary before routine clinical use of these cellular and molecular markers.

The last part of this chapter deals with STS treatment in the new millennium, and starts with a historical overview of the development of modern multimodality treatment.

In radiotherapy, relatively new techniques, as brachytherapy, intraoperative radiotherapy, three-dimensional conformal radiotherapy, inverse radiotherapy planning, and intensity
modulated radiation therapy, might be valuable to shorten treatment time, to save surrounding normal tissues, and/or to enable further dose-escalation. The role of adjuvant systemic chemotherapy is very limited in STS. Combination modalities involving chemotherapy, immunotherapy, biological response modifiers, and modulators of multidrug resistance might improve the efficacy.

At last, differentiation therapy is described as a new and very appealing approach that may become an alternative or addition to conventional anti-tumor therapy. This treatment that is based on the theory of reprogramming malignant cells to stabilize or even convert them into normal tissue, has been studied especially in liposarcoma. The first positive results have recently been published.

Many of these new techniques are very appealing, and, although in some of them results from experimental and clinical pilot studies are very encouraging, the way to routine clinical use is still very long. To improve treatment results and to stimulate research, centralization and specialization seems important, especially in rare tumors as STS. In order to develop new treatment strategies, STS should preferably be treated in trials only and sarcoma working parties should be encouraged to collaborate more.