Referral patterns, prognostic models and treatment in soft tissue sarcomas

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Chapter 1

General introduction

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Soft tissue sarcomas (STS) comprise a heterogeneous group of malignant tumors arising from mesenchymal tissues, which connect, support and surround different structures in the body. Their incidence is relative low but rising, with just over 750 newly diagnosed soft tissue sarcoma patients in 2017 in the Netherlands (Fig. 1). [1] In comparison, the incidence of breast cancer and skin cancer was over 14.000 in the same year. There is a clear peak incidence between 45 and 70 years of age, when more than half of the total soft tissue sarcoma burden develops. The incidence is similar between men and women. [1]

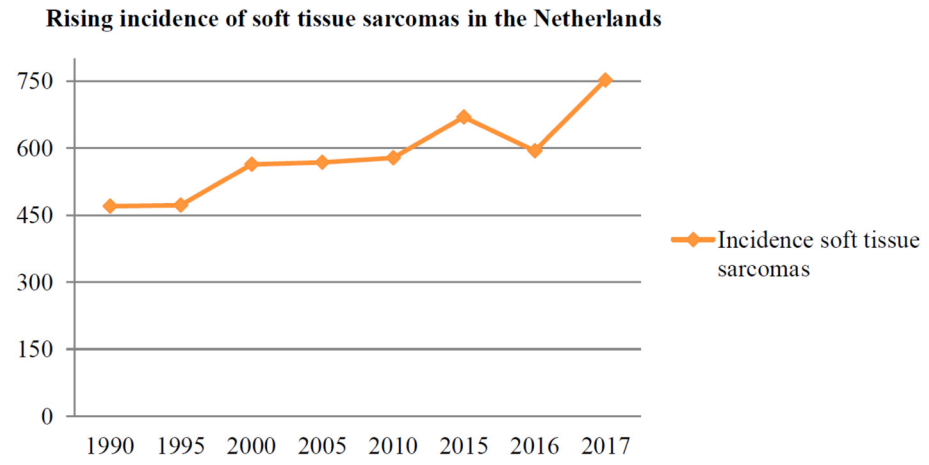

Figure 1. Rising incidence of soft tissue sarcomas in the Netherlands

Due to their infrequency, many physicians, and general practitioners in particular rarely encounter sarcoma patients. Rarity and a typical subtle presentation imply that recognition, diagnosis and treatment of sarcomas is challenging. Due to a high local and distant recurrence rate in high grade soft tissue sarcomas [2], the prognosis is relatively poor with a five year overall survival of 60% [3]. To improve outcome, sarcoma patients should ideally be treated in a sarcoma centre with expertise in surgery, orthopaedics, pathology, radiology, and medical and radiation oncology. [4] On this account, there is a need for simple guidelines and positive feedback to get sarcoma patients referred in time to the sarcoma centre. [5] Chapter 2 describes current consensus and state-of-the art guidelines for the

referral of sarcoma patients. Furthermore, chapter 3 describes more detailed the specific referral pattern of retroperitoneal sarcomas.

In soft tissue sarcoma of the extremity and the trunk wall, surgery with wide margins is the corner stone of therapy. In the eighties, several studies, including a randomized National Cancer Institute (NCI) study, reported a local control rate in STS of the extremities up to 85% with adjuvant radiotherapy, and adjuvant radiotherapy has become the standard of care in cases where a marginal resection has been obtained. [6-11] Systemic chemotherapy is part of routine treatment for most childhood sarcomas, e.g. rhabdomyosarcoma, Ewing sarcoma and osteosarcoma. The effect from adjuvant chemotherapy in adult soft tissue sarcomas remains to be firmly proven. High-risk patients have in most institutions generally been offered chemotherapy with doxorubicin and potentially with ifosfamide added. The STBSG-EORTC group performed in 2014 a pooled analysis of two phase III trials using doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma. Adjuvant chemotherapy was not associated with an improved overall survival for the whole cohort or in subsets of young patients or specific pathologic subgroups of sarcoma. [12] Poor quality of initial surgery was the most important prognostic and predictive factor for the benefit from adjuvant chemotherapy, which is now used in an experimental setting rather than as standard of care. A more recent treatment alternative relates to targeted therapy with e.g. imatinib, trabectedin and pazopanib registered for the histopathologic subtypes GIST, dermatofibrosarcoma protuberans, liposarcoma and leiomyosarcoma and special sarcoma subtypes of advanced metastatic disease. [13] In sarcoma, there is a high unmet need related to prognostic markers that allow identification of high-risk patients. This issue is discussed in chapters 4 and 5, which relates to the existing staging and grading systems and presents new biomarker data.

Patients that present with locally advanced, primarily irresectable, primary or recurrent soft tissue sarcomas of the extremities may benefit from treatment options in the form of hyperthermic isolated limb perfusion (HILP), e.g. the regional delivery of chemotherapy treatment. This technique can be offered as either neo-adjuvant therapy followed by surgery and/or radiation treatment or as definitive palliative treatment. In 1996, the results of the first multicentre trial of HILP with Tumor Necrosis Factor alpha (TNFαHIL) with Melphalan as induction therapy showed a limb salvage rate of 84%, with acceptable systemic and regional toxicity profiles. [14]

HILP is nowadays used as a safe treatment alternative for locally advanced sarcomas of the limb. Severe short-term and long-term side effects exist. Within a year after perfusion massive necrosis of the tumor and overlying skin can develop that in all cases leads to an amputation of the limb. Late side effects that may appear ten years after therapy include critical limb ischemia with a risk of amputation. [15] Chapter 6 is a description of the history of isolated limb perfusion and reports the challenges and long-term complications of the HILP treatment. In addition, multimodality treatment with perfusion, surgery and radiotherapy alters the blood supply of – and changes the load to – the bones, which eventually can lead to treatment-induced fractures, that cause a significantly impaired functional ability. Chapter 7 comprises the incidence, risk factors and possible treatment for treatment-induced fractures.

A severe late side effect of treatment is an angiosarcoma. Within this group of patients, women who develop an angiosarcoma after breast-conserving treatment with radiation for breast cancer form a distinct group. Along with the increasing incidence of breast cancer, and the replacement of mastectomy by breast-conserving treatment with radiation, the incidence and the clinical presentation of secondary angiosarcomas have changed. [16] Given the vascular nature of angiosarcoma, it is tempting to assume that these tumors should be the ideal targets for vascular endothelial growth factor (VEGF) inhibitors. The French Sarcoma Group has investigated the multi-tyrosine kinase inhibitor sorafenib and reported a limited antitumor activity in angiosarcoma. Until now, targeted drugs are experimental and used in clinical trials and no standard (neo-)adjuvant therapy is currently available for clinical practice. Since local control by means of surgery is difficult due to their multifocal appearance, patients with angiosarcoma of the breast have a known poor prognosis. Chapter 9 reports the outcome for angiosarcoma patients treated with surgery.

Not all soft tissue sarcomas are highly malignant with a poor prognosis. A special subtype in the classification of soft tissue sarcomas with a more benign character is desmoid type fibromatosis. This tumor infiltrates locally, but rarely metastasizes. [2] Therefore, the overall survival rate is nearly 100% and patients rarely die due to their disease. For this reason, extensive mutilating surgery as first approach is debated. Instead, non radical surgery is compensated by using adjuvant radiotherapy to lower the risk of local recurrence. In the nineties,

some institutions began to offer patients treatment with solely radiation therapy, with reasonable good results for local control. [17] Nevertheless, as described previously, radiation therapy has side effects in the short and long term. These side effects of treatment, in combination with the benign features of desmoid type fibromatosis, has led physicians believe that observation could be a good alternative treatment. The low incidence of just 3% of STS [18], has limited the possibility for randomized trials and studies with large populations, therefore, meaningful conclusions about the most appropriate treatment approach remains difficult. Chapter 11 shows the results of a systematic review about four different treatment strategies, i.e surgery alone, surgery and radiotherapy, radiotherapy alone and observation, for desmoid type fibromatosis and their outcome.

The last chapter in this thesis refers to future perspectives in sarcoma treatment. As different aspects in sarcoma treatment have been addressed throughout this thesis, new ideas and recently started studies will be discussed.

References

1. Cijfers over kanker. http://www.cijfersoverkanker.nl
2. Weiss SW, Goldblum JR, Enzinger FM. (2013) Enzinger and Weiss's soft tissue tumors (4th edition). Philadelphia : Mosby Elsevier.
3. Hoekstra Hj, Thijssens K, van Ginkel RJ. Role of surgery as primary treatment and as intervention in the multidisciplinary treatment of soft tissue sarcoma. Ann Oncol. 2004;15 Suppl 4:iv181-6.
4. Rydholm A. Improving the management of soft tissue sarcoma. Diagnosis and treatment should be given in specialist centres. BMJ. 1998 Jul 11;317(7151):93-4.
5. Styring E, Billing V, Hartman L, Nilbert M et al. Simple guidelines for efficient referral of soft-tissue sarcomas: a population-based evaluation of adherence to guidelines and referral patterns. J Bone Joint Surg Am. 2012 Jul 18;94(14):1291-6.
6. Singer S, Demetri GD, Baldini EH, Fletcher CD. Management of soft-tissue sarcomas: an overview and update. Lancet Oncol. 2000 Oct;1:75-85.
7. Ham SJ, van der Graaf WT, Pras E, Molenaar WM et al. Soft tissue sarcoma of the extremities. A multimodality diagnostic and therapeutic approach. Cancer Treat Rev. 1998 Dec;24(6):373-91.
8. Suit HD, Mankin HJ, Wood WC, Proppe KH et al. Preoperative, intraoperative, and postoperative radiation in the treatment of primary soft tissue sarcoma. Cancer. 1985 Jun 1;55(11):2659-67.
9. Lindberg RD, Martin RG, Romsdahl MM, Barkley HT Jr. Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. Cancer. 1981 May 15;47(10):2391-7.
10. Fein DA, Lee WR, Lanciano RM, Corn BW et al. Management of extremity soft tissue sarcomas with limb-sparing surgery and postoperative irradiation: do total dose, overall treatment time, and the surgery-radiotherapy interval impact on local control? Int J Radiat Oncol Biol Phys. 1995 Jul 15;32(4):969-76.
11. Rosenberg SA, Tepper J, Glatstein E, Costa J et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg. 1982 Sep;196(3):305-15.
12. Le Cesne A, Ouali M, Leahy MG, Santoro A et al. Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials. Ann Oncol. 2014 Dec;25(12):2425-32.
13. van der Graaf WT, Blay JY, Chawla SP, Kim DW et al. EORTC Soft Tissue and Bone Sarcoma Group; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012 May 19;379(9829):1879-86.
14. Eggermont AM, Schraffordt Koops H, Liénard D, Kroon BB, van Geel AN et al. Isolated limb perfusion with high-dose tumor necrosis factor-alpha in combination with interferon-gamma and melphalan for nonresectable extremity soft tissue sarcomas: a multicenter trial. J Clin Oncol. 1996 Oct;14(10):2653-65.
15. van Ginkel RJ, Thijssens KM, Pras E, van der Graaf WT et al. Isolated Limb Perfusion with tumor necrosis factor alpha and melphalan for locally advanced soft tissue sarcoma: three time periods at risk for amputation. Ann Surg Oncol. 2007 Apr;14(4):1499-506.
16. Yap J, Chuba PJ, Thomas R, Aref A et al. Sarcoma as a second malignancy after treatment for breast cancer. Int J Radiat Oncol Biol Phys.2002 Apr 1;52(5):1231-7.
17. Nuyttens JJ, Rust PF, Thomas CR,Jr, Turrisi AT,3rd. Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors: A comparative review of 22 articles. Cancer 2000: 88:1517-1523.
18. Plukker JT, van Oort I, Vermey A, Molenaar I, Hoekstra HJ, Panders AK, Dolsma WV, Koops HS. Aggressive fibromatosis (non-familial desmoid tumour): therapeutic problems and the role of adjuvant radiotherapy. Br J Surg. 1995 Apr;82(4):510-4.

PART I

Diagnosis and referral patterns