Localized extremity soft tissue sarcoma: towards a patient-tailored approach
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General introduction & outline of this thesis
General introduction

Soft tissue sarcomas (STS) are relatively rare malignancies accounting for less than 1% of all cancers in adults, resulting in approximately 600-700 new cases per year in The Netherlands annually. STS form a group of heterogeneous tumors which originate from mesenchymal progenitor cells. These progenitor cells show differentiation into various mesenchymal tissues, e.g. adipose tissue, fibrous tissue and muscle tissue, and over 50 histologic STS subtypes have been described in the latest World Health Organization classification. The most common subtypes are pleomorphic undifferentiated sarcoma (including malignant fibrous histiocytoma), leiomyosarcoma, liposarcoma, malignant peripheral nerve sheath tumor and synovial sarcoma, which combined account for approximately three fourths of all STS. STS can occur at any anatomic location, while most commonly (50-60%) they arise in the extremities. Other common locations are the head/neck area, trunk and retroperitoneum. The etiology of most STS remains unknown. While, in rare cases STS development has been associated with preceding radiation therapy, immune deficiency, viral infections and genetic and environmental factors.

The incidence of STS rises with increasing patients’ age and it shows a slight male predominance. The potential of STS to metastasize and thereby to influence patients’ survival and prognosis is mainly determined by the tumor grade and the histologic subtype. Lymphogenic metastases are rare, while hematogenic metastases, mainly to the lungs, are relatively common i.e. approximately 50% of all STS patients develop distant metastases during the course of their disease. Besides tumor grade and subtype, patients’ age and maximum tumor size have been shown to influence the development of distant metastases and (disease-specific) survival. Subsequently, these four parameters have been incorporated into various nomograms to predict patients’ outcome.

Prior to treatment, a MRI scan followed by a core-needle biopsy of the suspected lesion are performed, and combined they provide essential information needed for the diagnosis and accordingly for adequate treatment of the tumor. Benign soft tissue tumors, mostly lipomas, outnumber STS by 100:1. If a STS is diagnosed, a baseline chest CT scan is made to exclude lung metastases prior to the start of treatment. In extremity myxoid liposarcomas also a staging abdominal CT scan, to exclude abdominal metastases, is currently advised in the latest guidelines of the European Society for Medical Oncology. In case of distant metastases at diagnosis, curative-treatment is no longer feasible in most STS, except in a few chemosensitive subtypes as embryonal rhabdomyosarcoma. However, the role of (neo)adjuvant systemic chemotherapy in the non-metastatic setting in most subtypes remains controversial and is under on-going investigation.
Treatment of localized extremity soft tissue sarcomas (ESTS)

Historically the treatment of non-metastatic (localized) ESTS comprised amputation of the affected limb. However, patients who underwent limb-amputation were shown to have similar survival rates when compared with patients who underwent limb-sparing surgery (LSS) combined with external beam radiotherapy (EBRT). Accordingly, limb-sparing treatment has become the treatment of choice in localized ESTS since the 1980s. EBRT has been used regularly in addition to LSS to gain local control, and local control rates of 90% can be achieved nowadays. The timing of the EBRT has been studied extensively, and no differences in patients' survival were found between preoperatively and postoperatively irradiated patients. EBRT might not be essential to obtain local control in some carefully selected patients, i.e. in case of low-grade tumors which are resected with a >1cm resection margin. The data available addressing the association between local recurrence development, and subsequently the development of distant metastases and/or the risk for (disease-specific) death are contradictory. Hence, local recurrence development was found to be a predictor for the development of distant metastases and (disease-specific) death in some studies, while this finding was not confirmed in other studies.

Assessment of treatment efficacy

Over time, the treatment of ESTS improved and changed from limb-amputation into a more limb-sparing approach. This approach is based on a multimodality treatment-setting, e.g. neoadjuvant EBRT, systemic chemotherapy and/or HILP have been used to achieve optimal local control and to prevent limb-amputation, even in locally advanced ESTS. Neoadjuvant treatment-regimens are used in daily-practice, and as a consequence multiple studies were conducted to establish the changes in these tumors during and following the treatment. Since the 1990s, fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography ("18F-FDG PET-CT) scans have been used to study the changes in metabolic tumor activity induced by HILP in locally advanced ESTS. Furthermore, baseline "18F-FDG PET-CT scans as well as scans following neoadjuvant chemotherapy have been used to predict patient's survival. Besides the assessment of the metabolic tumor activity of the tumor prior to and following neoadjuvant treatment, the histologic appearance of the tumor at histopathological examination has been studied. It was shown that the percentage of tumor necrosis following neoadjuvant treatment does not predict patients' survival, as treatment-induced necrosis cannot be distinguished from tumor necrosis already present at diagnosis. Therefore, the percentage of viable tumor cells in pretreated STS might have more predictive value for survival. Recently, the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) published recommendations regarding the histopathological examination of pretreated STS, including a 5-tier STS response score based on the percentage of stainable, possibly viable, tumor cells.

Outline of this thesis

Part I - Treatment of resectable extremity soft tissue sarcoma

In resectable ESTS, wide surgical resection of the tumor is the mainstay of treatment. In addition, (neo)adjuvant EBRT is commonly used to achieve local tumor control. However, EBRT use harbors an increased wound complication risk, especially in the preoperative setting. Chapter 2 aims to identify predictors for wound complications following radiotherapy and surgical resection in ESTS treatment.

Part II - Treatment of locally advanced extremity soft tissue sarcoma

This part highlights the treatment of locally advanced ESTS. At first, a new treatment regimen, consisting of neoadjuvant HILP, preoperative radiotherapy and surgery for locally advanced ESTS is described. Subsequently, the indications for amputation and the oncological outcome i.e. local control and survival, following limb-amputation in (locally advanced) ESTS are determined in chapter 4.

Part III - Metabolic and histopathological tumor responses in pretreated extremity soft tissue sarcoma

This part addresses the metabolic and histopathological tumor responses in pretreated ESTS. Chapter 5 discusses the use of various volume of interest delineation techniques to study and quantify the changes in metabolic tumor activity using "18F-FDG PET-CT scans during the multimodality neoadjuvant ESTS treatment as described in chapter 3. Chapter 6 evaluates the histopathological tumor response, based on the percentage of stainable tumor cells, of pretreated ESTS using the EORTC-STBSG response score. Summary and conclusions of this thesis are presented in English and in Dutch (chapter 7). Lastly, chapter 8 provides a view on the future perspectives of ESTS treatment.
References


Treatment of resectable extremity soft tissue sarcoma

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