Referral patterns, prognostic models and treatment in soft tissue sarcomas

Seinen, Johanna Magda

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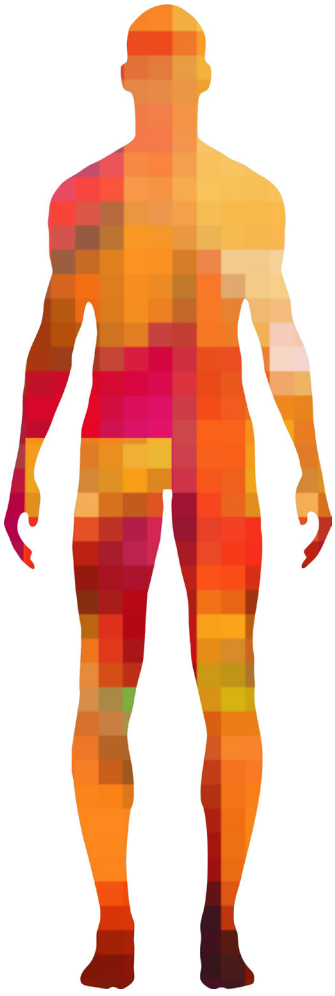

Chapter 1

General introduction

General introduction

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]

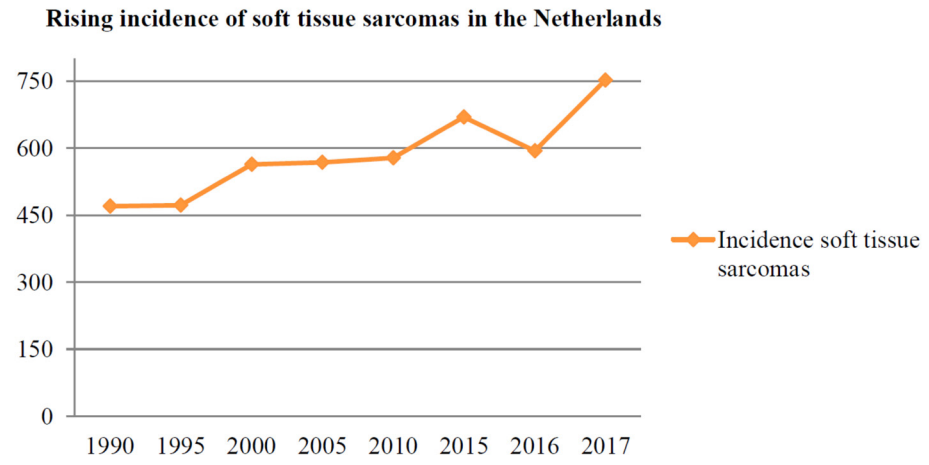

Figure 1. Rising incidence of soft tissue sarcomas in the Netherlands

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.

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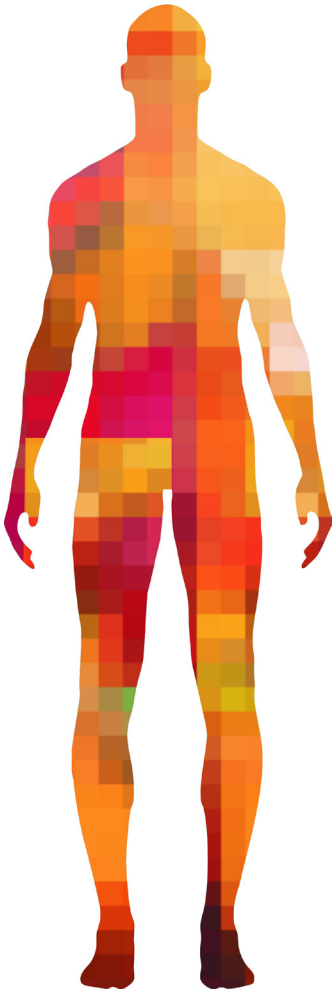
PART I

Diagnosis and referral patterns



Chapter 2

Diagnosis and the referral pattern of soft tissue sarcoma patients

Diagnosis and the referral pattern of soft tissue sarcoma patients

There is a general trend towards centralization of health care. The debate about centralization has been accelerated by studies that show a correlation between volume of surgery and better outcome, which relates particularly to complex oncology health care. [1-3] For sarcoma patients, improved outcome when treated at a high volume hospital has been recognized and recommendations about referral to a specialized sarcoma centre have been promoted worldwide. [4,5]

Soft tissue sarcomas are rare and largely outnumbered by benign soft tissue tumors – e.g. lipomas, fibrous and vascular tumors – by at least 100 to 1 [6], what makes clinical suspicion and recognition of soft tissue sarcomas difficult. This is further complicated by the fact that two-thirds of the tumors are located in the extremities or in the trunk wall and typically present as painless lumps without loss of function or influence on the patients general health. Frequently, patients accidentally observe a mass, or refer to a trauma to the affected area that called their attention to a pre-existing lesion. At diagnosis, the majority of soft tissue sarcomas have reached a size of more than 5 cm [7-10] A soft tissue tumor in the thigh may grow to 10-15 cm in diameter before it becomes apparent and retroperitoneal tumors can grow to 25-30 cm before causing any symptoms. Therefore, any large and/or deep, undefined tumor mass should be evaluated using radiological imaging (contrast enhanced MRI or CT) to assess tumor size, tumor structure, and for tumor staging. An experienced radiologist at the sarcoma centre can differentiate between benign and malignant soft tissue lesions, define the anatomical origin, and in some cases define the nature of the tissue.

For complete diagnosis, histological assessment of the tumor is mandatory by means of biopsy. Because soft tissue sarcomas comprise some 50 subtypes with heterogeneity within, tumors biopsy should be performed at a sarcoma centre to avoid unrepresentative tissue sampling and misdiagnosis. Furthermore, obtained tissue can be stored in tissue banking for future diagnostic and/or research purposes.

Failure to recognize soft tissue sarcomas may lead to shelling out of tumors, so called ‘whoops’ procedures, which have considerable consequences. It may

preclude later staging and excision with proper margins, relevant adjuvant treatment, and as a consequence a high risk of local recurrence. Furthermore, patients managed in a sarcoma centre are intensively followed according to the sarcoma guidelines for early detection of recurrence, which varies from 10-15% locally to over 30% of distant recurrences. [10,11] At the sarcoma centre patients could participate in clinical trials and metastatectomy is increasingly offered in case of single or multiple (lung) metastases. These improvements in multidisciplinary management of soft tissue sarcoma ought to lead to a substantial decrease in morbidity and mortality rates.

There is general agreement that soft tissue sarcoma patients should be referred to a sarcoma centre, and now focus has turned on delay in the diagnosis and treatment of sarcoma patients. [12,13] Due to the subtle presentation and lack of experience, both a patient delay and doctor delay is common, allowing the soft tissue tumor to grow a considerable size, which complicates surgical resection, and increases the risk for development of metastasis. As size is a strong prognostic factor [5, 14] and one of the few that can be influenced, early recognition of sarcomas and prompt referral to a sarcoma centre should be promoted in order to further improve outcome. To ensure adequate referral, simple guidelines are required. Based on epidemiological data showing that 99% of benign soft tissue tumors are superficial and 95% are less than 5 cm in diameter [15], the southern Sweden sarcoma centre in Lund has established simple referral guidelines that recommend referring of all patients with soft tissue tumors larger than 5 cm and all deep-seated tumors, irrespective of size [16]. Depth is defined in relation to the deep fascia, and all tumors below the deep fascia are considered deep-seated tumors. Other countries also included pain or observed tumor growth in the referral guidelines. [17] Although, nationwide guidelines exist for the diagnosis, treatment and follow up of soft tissue sarcoma patients in the Netherlands, and referral to a sarcoma centre is promoted, no official referral guidelines are recorded. [11,12] A recent study conducted at the sarcoma centre in Lund reported a nearly 100% referral rate of patients with sarcoma of the extremities before biopsy or local excision. [4] The successful implementation of referral guidelines is the result of many years of education for medical students and specialists in-training in general surgery and orthopaedics with continuous feedback regarding outcome for patients referred. Nevertheless, the same study did observe a median doctors delay of longer than 1.5 months. Other studies have reported even longer doctors delays of around 6 months. [7,18]

Additionally, the diagnostic work up of soft tissue sarcomas can extend the delay between presentation and treatment when performed inefficient and inadequate. On that account, guidelines for diagnosis and treatment were designed to ensure appropriate pre-operative investigations, accurate staging and evidence based decision making. In the region of the Comprehensive Cancer Centre North-Netherlands (CCCN), the first guidelines for the diagnosis and treatment of patients with STS were developed in February 1983 by a cooperative group for rare tumors. [12] After realization of the first Dutch nationwide accepted guidelines in 1993, the guidelines have been revised several times. Since the latest revision in 2011 (Richtlijn diagnostiek weke delen tumoren (versie 2.0 herziening 2011)) of the Netherlands Comprehensive Cancer Organisation (IKNL), the guidelines recommend to perform conventional X-ray, a MRI scan for sarcomas of the extremities and trunk, and a CT scan for sarcomas of the intra-thoracic and intra-abdominal cavity. Additional imaging like a bone scintigraphy or Positron-emission tomography (PET) scans are not included in the routine diagnostic work-up. For histological diagnosis, a histological core needle biopsy is required. In case of a heterogeneous tumor it is recommended to perform an ultrasound or CT scan guided biopsy.

In conclusion, it is important to acknowledge that centralization *per se* is not sufficient and that delays should be investigated, recognized and addressed. In the next chapter, the referral pattern of a distinct group of soft tissue sarcomas – retroperitoneal sarcomas – is discussed.

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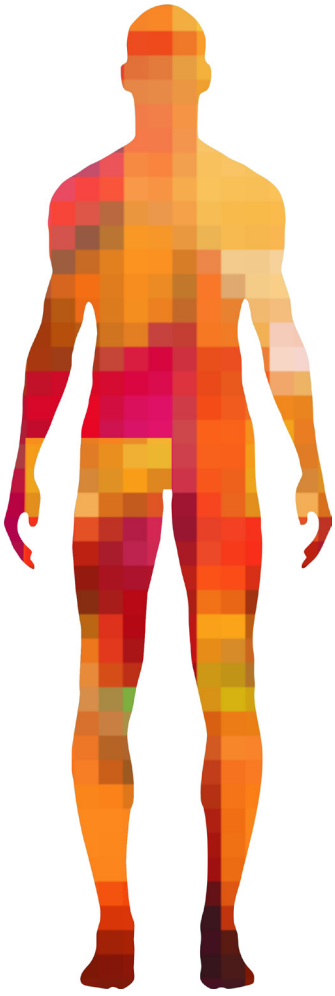

Chapter 3

Delays in the Management of Retroperitoneal Sarcomas

Seinen JM, Almquist M, Styring E, Rydholm A, Nilbert M

Sarcoma. 2010;2010:702573

Abstract

Objectives. Retroperitoneal sarcomas are rare and treatment should optimally be centralized. Despite successful centralization with 90% of the patients referred prior to surgery, delays occur, which led us to assess lead times in a population-based series.

Method. Patients diagnosed with retroperitoneal sarcoma in the southern Sweden health care region 2003–2009 were eligible for the study. Data on referrals and diagnostic investigations were collected from clinical files from primary health care, local hospitals, and from the sarcoma centre. Lead times were divided into patient delays and health care delays caused by primary health care, local hospitals, or procedures at the sarcoma centre.

Results. Complete data were available from 33 patients and demonstrated a median patient delay of 23 days (0–17 months) and median health care delay of 94 days (1–40 months) with delays of median 15 days at the general practitioner, 36 days at local hospitals, and 55 days at the sarcoma centre.

Conclusion. Centralization per se is not sufficient for optimized and efficient management. Our findings suggest that delays can be minimized by direct referral of patients from primary health care to sarcoma centers and indicate that development of coordinated diagnostic packages could shorten delays at the sarcoma centre.

Introduction

Retroperitoneal sarcomas represent 0.1% of all malignancies and are often clinically challenging due to anatomical proximity to vital structures and a considerable risk for local recurrence. [1] The rarity, complex diagnostics, and surgical challenges imply that these tumors should be managed by experienced sarcoma teams. Centralized treatment per se may not be sufficient since delays that may allow tumor progression, complicate surgery, increase the risk of local recurrence, and cause unnecessary worry for patients are experienced at general practitioners and local hospitals as well as at sarcoma centers. [2–6] Delays have been linked to adverse outcome in several tumor types, including breast cancer, colorectal cancer, urothelial cancer, and esophageal cancer. [7–10] Benchmarks for timely management have not been defined in retroperitoneal sarcoma, but large tumor size represents an adverse prognostic factor, which strongly argues for efficient management. Detailed understanding of the causes of delays is needed for optimized management, which led us to identify diagnostic lead times related to the patient, general practitioners, and procedures at local hospitals and at the sarcoma centre in a population-based series of retroperitoneal sarcoma patients.

Materials and methods

Primary, histologically verified retroperitoneal sarcoma was, in the southern Sweden health care region (1.5 million inhabitants), diagnosed in 39 patients between 2003 and 2009. Complete data were available from 33 patients. All relevant medical records from general practitioners, local hospitals and the sarcoma centre were collected. Patient's delay was defined as the time from onset of self-reported symptoms to the first visit to a medical professional, which could be a general practitioner or a specialist. Health care delay was defined as the time from the first visit to the start of treatment, which was in most cases surgery. Hereunder, lead times were specified to occur in primary health care (from the first visit to a general practitioner until referral to a local hospital or sarcoma centre), at local hospitals (from the first visit until the start of treatment or referral to the sarcoma centre) or in the sarcoma centre (from the first visit until start of treatment). Pathology lead time was defined as the time from referral for cytology/biopsy until confirmed malignancy. Radiology lead time was defined as the time from referral

for the first investigation to the result of the final investigation. All lead times were expressed as median times in order to minimize the impact of skewed distributions. According to Swedish health care regulations, the study represents a quality control project, for which ethical permission is not required.

Results

Complete data were available from 33 patients (Table 1). The mean age at diagnosis was 66 (21–87) years, and the study included 17 men. Liposarcoma and leiomyosarcoma were the predominant histopathological subtypes. The majority (*n* = 19) of the tumors were high grade and the mean tumor size was 21 (4–60) cm.

Table 1. Summary of clinicopathologic characteristics

Characteristics	N (%)
Sex (male : female)	17 : 16
Age, mean (range)	66 (21-87)
Tumor size, cm, mean (range)	21 (4-60)
Histopathologic type	
Liposarcoma	13 (40)
Leiomyosarcoma	8 (24)
Spindle cell sarcoma	4 (12)
Inflammatory myofibroblastic sarcoma	1 (3)
GIST	1 (3)
Carcinosarcoma	1 (3)
Atypical solitary fibrous tumor	1 (3)
NOS	4 (12)
Malignancy grade	
Low	9 (27)
Intermediate	1 (3)
High	19 (58)
NOS	4 (12)

GIST: gastrointestinal stromal cell tumor
NOS: not otherwise specified

Median and individual delays are presented in Figures 1 and 2.

The median lead time from onset of self-reported symptoms to the first medical visit was 23 days (0–17 months). Though 15 patients consulted a medical professional within 1 month of onset of symptoms, patient's delay was the predominant in 12/33 cases. The most common symptoms (*n* = 14) were pain or abdominal discomfort whereas 4 tumors were incidentally diagnosed at surgery or radiologic investigations for other causes. The total health care lead time was median 94 days (1–40 months) and consisted of a general practitioner's lead time of median 15 days (0–8 months), a local hospital lead time of 36 days (0–37 months), and a sarcoma centre lead time of 55 days (1–16 months). The longest delays were caused by erroneous primary diagnosis (7, 16, and 40 months) and comorbidity that required complimentary medical procedures prior to surgery (5, 8, and 19 months). Among the 17 patients who consulted a general practitioner, 11 were referred within 1 month of the first visit and 6 were referred directly to the sarcoma centre. From local hospitals, 11/23 patients were referred to the sarcoma centre within 1 month, which implies that half of the patients spent more than a month at this stage. The sarcoma centre lead time of median 55 days represented the longest delay in 12/33 patients.

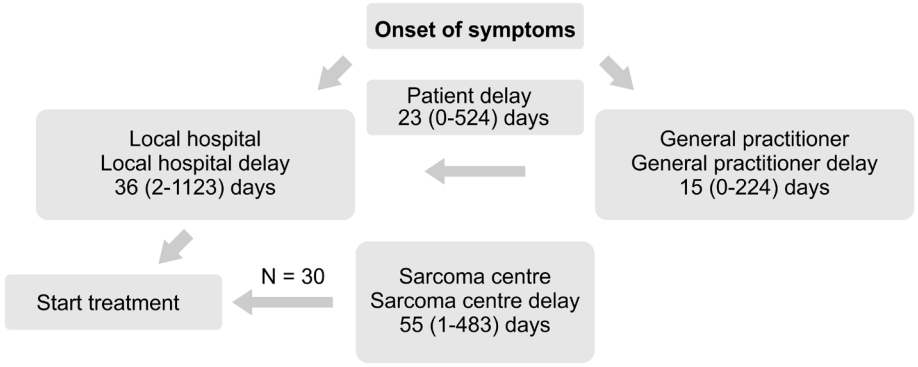

Figure 1. Overview of the different median lead times

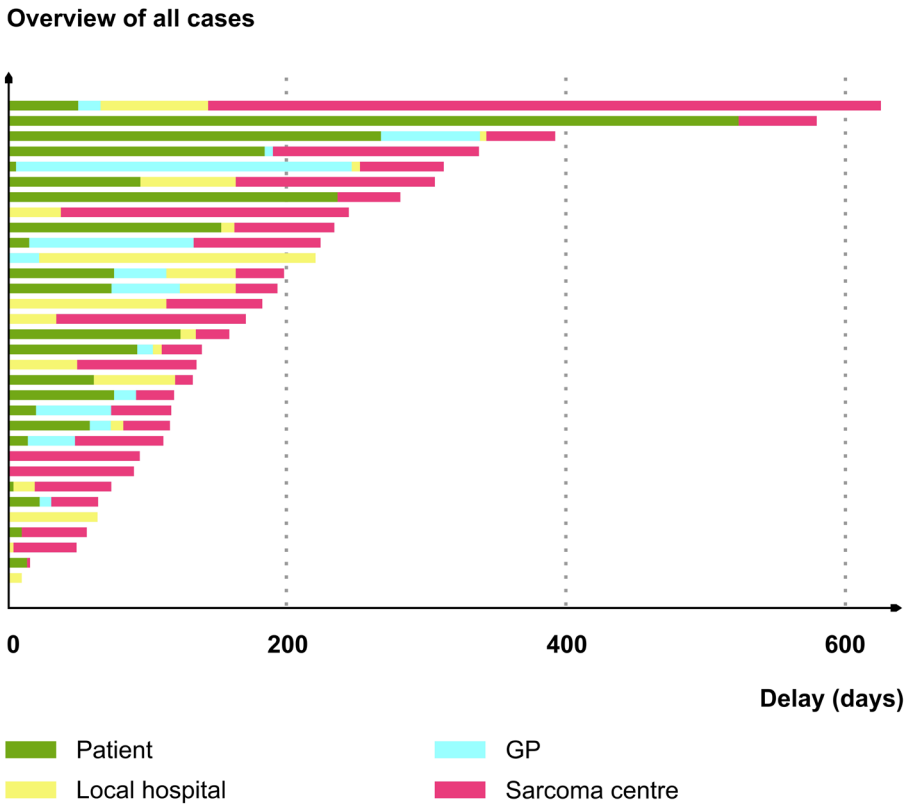

Figure 2. Bar chart demonstrating individual patients' lead times (one outlier with a 3-year local hospital delay was omitted for reasons of illustration).

The diagnostic delays were divided into pathology and radiology lead times (Figure 3). In 25 patients, a fine needle aspiration cytology and/or core needle biopsy was performed, 14 of which were performed at the sarcoma centre. The pathology lead time was median 22 days (0–4 months) with some of the longest delays caused by inconclusive results from cytology/histopathology. Repeated needle biopsies were required in 5 patients, and 11 patients were operated on without a histologically confirmed diagnosis. Radiology lead time was median 36 days (0–8 months) and the investigations included abdominal CT scans in all but one patients, complemented with CT scans of the thorax and renography in most patients. The delay from completed diagnostics to surgery was median 13 (1–57) days.

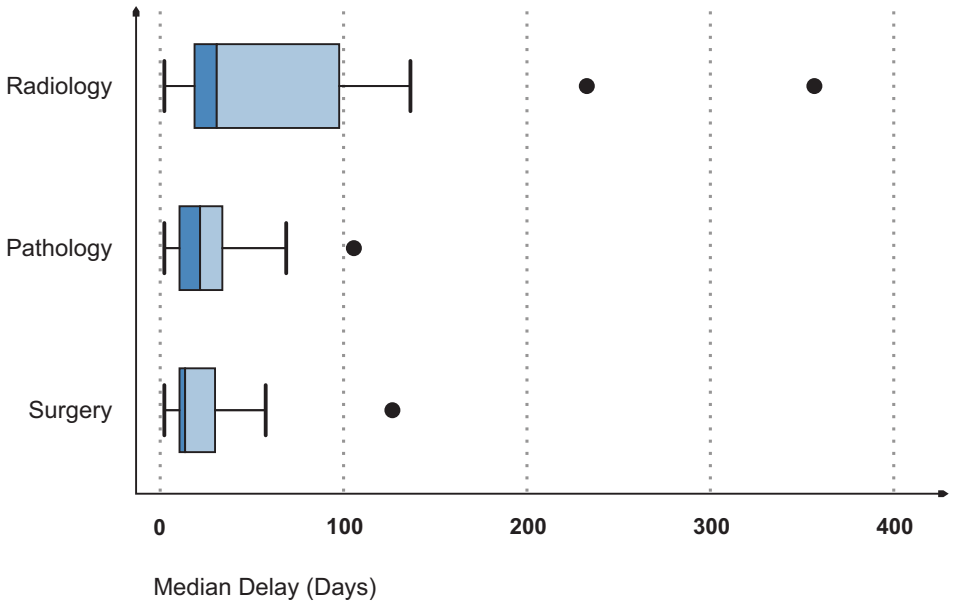

Figure 3. Box-plot demonstrating the radiology, pathology, and surgery lead times at the sarcoma centre. Outliers are marked by •

Management of retroperitoneal sarcomas requires a multidisciplinary approach with contributions from radiologists, pathologists, surgeons, and oncologists. Though primary surgery at a sarcoma centre is beneficial, efficient diagnostics is central. In southern Sweden, centralized treatment has been promoted since a decade with 90% of the patients currently referred to the sarcoma centre before surgery. In order to characterize delays and causes hereof, we assessed lead times in our population-based cohort. The median patient's delay was only 3 weeks, though considerable longer delays occurred in some cases and indeed represented the predominant delay in almost half of the patients (Figure 2). It should, however, be kept in mind that these data are based on self-reported symptoms and thus prone to bias compared to the other lead times, which are based on documented dates of referral. No comparison can be made to published delays for retroperitoneal sarcoma, but in soft-tissue sarcomas, considerable delays have been reported. Brouns et al. reported median patient's delays of 2 months in more than half of the patients and of at least 6 months in 20% of patients [11]. Clark and Thomas reported lead times of median 12 months in referring sarcoma patients from general practitioners [12]. We found a median general practitioners' delay of 16 days, which indeed represents the shortest health care

lead time. Considering the rarity of retroperitoneal sarcomas, these prompt reactions to suspected malignancy are impressive.

Our data demonstrate that the time is lost at the subsequent step for patients that are primarily referred to a local hospital. The median lead time from the local hospital to the sarcoma centre was 5 weeks, and in several cases investigations originally performed at the local hospital were repeated at the sarcoma centre. This observation strongly suggest that patients with suspected retroperitoneal sarcoma should be directly referred to the sarcoma centre in order to avoid unnecessary procedures and reduce lead times.

A series of investigations are typically needed in the diagnostic workup and surgical planning of retroperitoneal sarcoma and treatment decisions are made at multidisciplinary conferences. Against this background, it is not surprising that the sarcoma centre lead time of median 8 weeks was predominant. Additional morphological investigations needed to reach a pathological diagnosis and requests for complimentary imaging were identified as the major causes of delay (Figure 3). Radiology delays were the predominant with median delays exceeding 5 weeks in half of the cases. Separate requests for different examinations rather than coordinated examinations likely contributed to the delays. Due to limited resources at the sarcoma centre, a significant number of radiology investigations were also performed at local hospitals, which contributed to longer lead times, since the results of the investigations were not immediately available to the surgeons at the sarcoma centre. This leads us to suggest that retroperitoneal sarcoma radiology packages could be defined to achieve efficient and coordinated radiologic investigations and hereby reduce lead times. The pathology lead time of median 3 weeks leaves room for improvement. We suggest that cytology specimens from fine needle examinations should be immediately evaluated. Hereby, representative material can be directly ensured and direct resampling ordered when necessary. Finally, the median lead time of 2 weeks from complete diagnostic workup until surgery is considered acceptable against the background of coordinated efforts from oncological surgeons.

Studies that have addressed the diagnostic delays in other less common tumor types; that is, esophageal cancer and cancer of the urinary tract have reached results similar to ours. Esophageal cancer also requires extensive diagnostic work-

up followed by complex surgery when possible. Grotenhuis et al. showed a median hospital delay of 7 weeks from the endoscopy at which a diagnostic biopsy was obtained until surgery and median 2 weeks from the treatment decision at a multidisciplinary conference until surgery [10]. The authors could also demonstrate that rapid management was associated with favorable outcome as regards both morbidity and mortality. Holmäng and Johansson analyzed diagnostic and treatment delays in patients with upper urothelial cancer with a median delay from urography to surgery of 3–8 weeks with considerable differences in delay and tumor stage between different hospitals [9]. They suggest that large tumors lead to more rapid workup and earlier surgery. The rarity and variable clinical course of retroperitoneal sarcoma precludes analysis of outcome, but interestingly, some of the longest doctor's delays occurred in patients with large tumors. We conclude that a substantial number of patients in this population-based retroperitoneal sarcoma cohort experience considerable diagnostic delays. General practitioners' delays were acceptable, local hospital delays should be possible to minimize, and sarcoma center delays could be shortened through improved coordination. Our data point to three possible improvements. Patients with suspected retroperitoneal sarcomas should be directly referred to sarcoma centers to reduce lead times at local hospitals. At the sarcoma centre, radiologic and pathologic investigations should be coordinated, for example, through predefined radiology packages and prioritized evaluation of cytology/pathology specimens. Finally, lead times should be prospectively registered in order to map bottle necks in different systems and evaluate the effect of altered routines for diagnostic workup. Such data would also allow for establishment of clinical diagnostic guidelines and limits for timely care of retroperitoneal sarcoma.

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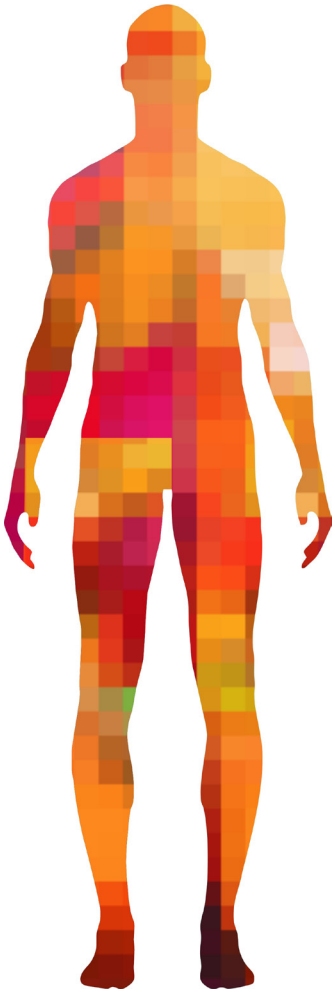
PART II

Prognostic markers and biomarkers



Chapter 4

Prognostic models and the role of biomarkers

Prognostic models and the role of biomarkers

Prognosis means 'foreseeing' and is used in medicine to predict the probable course and outcome of a disease. Especially in the oncology field, prognosis is an important topic and a continuous subject of investigation. Although most studies analyze groups of patients, and the observed outcome cannot be translated directly to the individual patient, these outcomes can be used as a tool to define groups of patients with a low or high risk profile regarding recurrent disease and survival. This distinction between patients with a good and poor outcome is clinically relevant because it supports the decision for treatment, in particular for (neo-) adjuvant treatment. Additional information is needed to generate a better risk profile for the individual patient. Therefore, researchers are looking for new prognostic factors that can estimate the risk on a particular event – e.g. local or distant recurrence and disease specific mortality – over a specific time. Usually a combination of prognostic factors predicts the outcome more precisely and several prognostic factors are therefore used in a prognostic model.

Predicting the prognosis of soft tissue sarcoma patients is complicated due to the heterogeneity of these malignancies, both at the histological and genetic level. Over the last decades, the discovery of novel immunohistochemical markers led to a better distinction between histological subtypes and even the recognition of new subtypes. Today, pathologists can recognize more than fifty different subtypes using immunohistochemical staining. Furthermore, scientific advancements have provided insight into molecular pathways and mechanisms, and showed that histological different soft tissue sarcomas may share the same genetic aberration, thereby introducing another classification based on these genetic alterations. Furthermore, the clinical behavior of the tumors can be related to the histological and genetic specificity, yet similar tumors may have very different clinical behavior.

This chapter describes the classification systems, the different staging and grading systems used in soft tissue sarcomas, prognostic models and new biomarkers.

Classification systems

Histological classification

Soft tissue sarcomas are mesenchymal tumors, predominantly arising from the embryonic mesoderm, but in some cases they arise from the ectoderm, e.g. peripheral nervous sheath tumors. Mesodermal cells give rise to the connective tissues, including pericardium, pleura, blood vessels endothelium, smooth and striated muscle, bone, cartilage, and synovium. Soft tissue sarcomas have been traditionally classified according to the adult mesenchymal tissue they most resemble, though no firm link exists between this tissue and sarcoma origin. For example, there is no evidence that liposarcomas either originate from mature fat, or represent malignant transformation of lipomas. Since 2013 the World Health Organization recognizes since 8 types of soft tissue sarcomas, namely; adipocytic, fibroblastic/myofibroblastic, so-called fibrohistiocytic, smooth muscle, skeletal-muscle, nerve sheat, tumours of uncertain differentiation, as well as a final group of undifferentiated/unclassified sarcomas. [1] At present, the most frequent histological subtypes of the extremities and trunk are leiomyosarcoma, liposarcoma, and undifferentiated pleomorphic sarcoma. [2] Of the abdominal tract, the gastrointestinal stromal tumor (GIST) is the most common sarcoma subtype. [3]

Although most soft tissue sarcomas form only one type of tissue, some of these tumors appear to have the ability to dedifferentiate. Dedifferentiation can be of prognostic value, e.g. myogenic differentiation in pleomorphic sarcomas is reported as an adverse prognostic factor, being associated with more aggressive behaviour and higher metastatic rate. [4] Dedifferentiation and heterogeneity in sarcomas result in a variety of overlapping patterns, making a uniform diagnosis difficult. As a consequence, even experienced sarcoma pathologists frequently disagree as to the cell of origin of an individual tumor, in as many as 28% to 47% of cases. [5-7] Reliable immunohistochemical markers and reproducible genetic changes are therefore greatly contributing to the accurate diagnosis of soft tissue sarcomas.

Genetic classification

Remarkable gains in the understanding of sarcoma genesis have been attained in the past two decades. First of all, methodologies and laboratory techniques, e.g. reverse transcriptase-polymerase chain reaction (RT-PCR) and fluorescence in-

situ hybridization (FISH), have allowed unraveling of the deregulation pathways and the involved regulating oncoproteins. Hirota and colleagues started the revolution for sarcomas in 1998, when they found that gastrointestinal stromal tumors contain a mutation in a gene called 'c-kit'. [8] This gene encodes for the protein 'KIT' that functions as a receptor, allowing transmission of survival and proliferation signals to cells. Hirota found that this receptor was continuously turned on and in turn caused continuous growth of gastrointestinal stromal tumors.

Secondly, more recent techniques called 'next generation DNA sequencing' allow for more rapid and inexpensive sequencing of both DNA and RNA. Because the costs of sequencing is now less than 1% of the costs ten years ago [9], whole genome analysis has become widely available. The more prevalent identified gene mutations in sarcomas are: p53, retinoblastoma (RB), P13K and isocitrate dehydrogenase (IDH). [10] P53 mutation is found in 15% of all soft tissue sarcomas, but frequently altered in several other malignant tumors, and therefore greatly exploited for targeted therapy. At this moment, most studies analyzing targeted therapy for these four gene mutations mainly preclude pre-clinical studies, although some have advanced to phase II clinical trials, e.g. ridaforolimus targeting P13K and Palbociclib targeting RB. [10]

Based on genetic alterations soft tissue sarcomas can now be broadly divided into two main categories: 1) genetically simple subtypes with specific genetic alterations most often involving formation of a fusion gene, including the SYT-SS18 fusion in synovial sarcoma, the TLS-CHOP fusion in myxoid liposarcoma and PAX3-FKHR in alveolar rhabdomyosarcoma [11,12], and 2) genetically complex subtypes with multiple numerical and structural aberrations, including e.g. undifferentiated pleomorphic sarcomas, leiomyosarcomas and pleomorphic liposarcomas [13].

Prognostic models

There are several prognostic models for soft tissue sarcoma. Similar to other types of malignancies, a staging system is used to provide information about the extension of the disease, based on both clinical and histological parameters. In addition, a grading system is used to describe the level of malignancy of the

sarcoma, based on solely histological parameters. Other prognostic models have been proposed to aid in predicting patient outcome, combining clinical and histological parameters. An example of such a prognostic model is the SIN (Size, vascular Invasion, Necrosis) model, proposed by the Scandinavia Sarcoma Group (SSG), and used throughout Scandinavia. [14]

Staging

There are three staging systems employed for soft tissue sarcomas, including the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) system [15], the Musculoskeletal Tumor Society System [16], and the Memorial Sloan-Kettering system [17]. The most widely used means for classifying the extent of sarcoma is the TNM system of the AJCC /UICC. This TNM based system is based on the size and extent of the primary Tumour (T), the involvement of regional lymph Nodes (N) and the presence of distant Metastasis (M). In 1977, the TNM classification was extended by adding the histological malignancy grade. [18] Later also tumor depth was included, with a distinction between superficial and deep tumors in relation to the fascia. Nowadays the staging of soft tissue sarcomas is based on the size (T1 ≤5cm or T2 >5cm), depth (Ta superficial and Tb deep), the presence or absence of regional lymph node or distant metastasis. These factors are combined with grade. Large series have confirmed size, depth and grade as important prognostic markers. [19,20]

In the 7th edition of the AJCC/UICC staging system, a specific TNM classification for gastrointestinal stromal tumors was introduced [15], which was validated in a prospective study in 2011 [21]. The use of the TNM classification for retroperitoneal sarcomas is less accurate prognostically, since nearly all retroperitoneal sarcomas are larger than 5cm and deep to the superficial fascia, leading to a minimal classification of stage IIB (low grade) or stage III (high grade). In the most recent 8th edition anatomic location is specifically addressed.

Soft tissue sarcomas mainly metastasize through the hematogenous route, and lymph node metastasis is therefore rare. Nevertheless, when present lymph node metastases represent a group of patients with an adverse prognosis with a 5-year overall survival rate of 35% and, therefore, accordingly classified as stage III in the TNM staging system. [22]

Grading

Histological grade is the best prognostic factor in the majority of soft tissue sarcomas. Grade goes back till the late forties when Broder described as first the malignancy grade of soft tissue sarcomas in the subgroup of fibrosarcomas, by means of mitotic activity, number of tumor giant cells and percentage of fibrous stroma. [23] However, it was only until 1977 that Russel and colleagues proposed to integrate histological grade in a prognostic model with the clinical parameters of the TNM classification. [18] Since then, numerous grading systems have been suggested and today a variety of grading systems are used throughout the world with partly different parameters and number of grades. The two most widely applied grading systems are those of the National Cancer Institute (NCI) and of the French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) [24]. The NCI system uses a combination of histological type, cellularity, pleomorphism and mitotic rate. The FNCLCC system is based on a score obtained by evaluating differentiation, mitotic rate and amount of tumor necrosis. Both are three-grade systems. For treatment purposes, the goal of the grade system is to separate patients into a group with a good prognosis (grade 1) and a group with a poor prognosis (grade 3). Therefore, the group with grade 2, corresponding to intermediate malignancy, should be minimized. In a comparative study between the NCI and FNCLCC system, it was demonstrated that both systems highly correlate with prognosis, however, the FNCLCC system had a higher discriminative power to identify patients with high risk. [24] Both staging systems are listed in the latest edition of the World Health Organization classification system of soft tissue tumors. [1]

The College of American Pathologists favors the FNCLCC system, because the NCI system uses parameters – quantification of cellularity and pleomorphism – that are difficult to determine objectively and the FNCLCC may be slightly better in predicting prognosis. [25]

There are limitations to the use of grading parameters. Most of these parameters are subjective and pathologists can disagree on for example the quantification of cellularity, pleomorphism and differentiation. [25] Moreover, a single parameter can not simply be applied to all subtypes, e.g. mitotic count is low in clear cell sarcoma, but this subtype has a high risk of metastasis. [26,27]

SIN prognostic model

The SIN prognostic model was introduced in 1994, and is the result of the collaboration between Scandinavian countries. The SIN system combines size (S), vascular invasion (I) and necrosis (N). In the original description of the system, size was dichotomized at 10 cm, and necrosis was microscopically evaluated and described as present if a focus larger than 4mm was observed. Vascular invasion was dichotomized as present or absent. In 2003, Gustafson et al. revised the SIN system and dichotomized size at 8 cm, which was closer to the median of a population based study. [14] In addition, they found that necrosis, however small, had significant prognostic relevance and re-dichotomized necrosis as present or absent irrespective of extent. [14]

The SIN system is a two-tiered system, dividing patients either into the group with low risk for metastasis (none or only one of the following three factors; tumor size >8 cm, vascular invasion, or microscopic tumor necrosis) or into the group with high risk for metastasis (two or three of these factors). Based on this score, the low and high risk groups differ highly significant.

The reproducibility of the revised SIN model has been assessed in collaboration with pathologists of Bordeaux and Boston. [14] A kappa of 0.77 (good agreement) for inter observer variation in the assessment of overall grading was found. Using the series of Bordeaux, consistent predictions of the five-year metastasis free survival were measured. They concluded that the SIN model offers a reproducible and favorable stratification for patients with low and high risk for metastasis.

Sarcoma biomarkers

Ideally, biomarkers distinguish between different prognostic subsets. Good prognosis groups that encompasses all tumors with very low metastatic potential that may be managed by surgery alone – from the poor prognosis group – which include all tumors with high potential for metastasis and for which (neo-)adjuvant therapy might reduce the risk of metastasis. Many biomarkers have been studied, and the quest to identify new biomarkers is continuously ongoing. This search is influenced by various bias. Sampling errors may cause bias and evaluation risks being performed in non-representative tumor areas. Tumor heterogeneity

has an impact on biomarker scoring. Whole-tumor evaluation may increase reproducibility, but is not an option if neo-adjuvant treatment is used. In addition, the rarity of soft tissue sarcomas and the variety of subtypes implies that study populations are typically restricted in size. Furthermore, to collect a significant number of patients, a long time span is often necessary and may include different treatment strategies that may not be directly comparable. From a statistical point of view, many studies limit their results to univariate analysis. This usual raise the expectation of valuable new biomarkers, but when they are analysed in multivariate analysis including other prognostic markers, their value loses statistical significance. Another important part of the process in evaluating new biomarkers is the reproducibility of the results. A good biomarker should be easy to score, show high reproducibility and should be interpreted according to strict rules.

The future for biomarkers depends not only on the use of prognostic or differential diagnostic marker, but also as predictive markers related to precision medicine. The unraveling of the genetic pathways has given us insight in the tumor growth and tumor sustainability. Elucidating the biology of gene fusions or mutations and their protein products may provide targets for novel therapeutic intervention.

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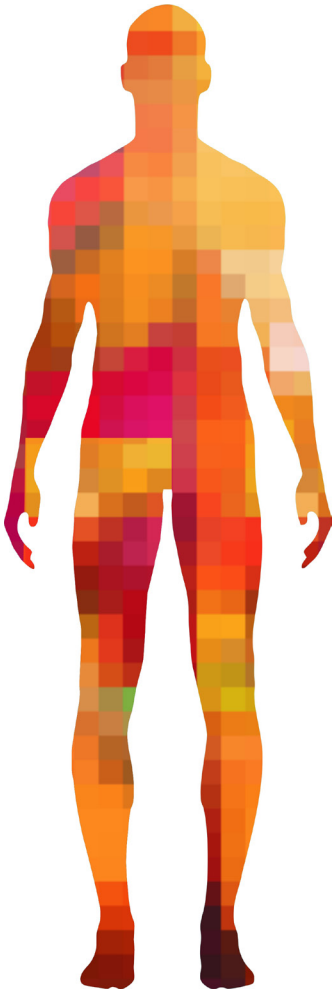

Chapter 5

Prognostic value of proliferation in pleomorphic soft tissue sarcomas:

a new look at an old measure

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Abstract

Objectives. Through proliferation has repeatedly shown a prognostic role in sarcomas, it has not reached clinical application.

Methods. We performed a comprehensive evaluation of the prognostic role of 5 proliferation measures in a large series of soft tissue sarcomas of the extremities and the trunk wall.

Results. One hundred ninety-six primary soft tissue sarcomas of the extremities and the trunk wall were subjected to DNAflow cytometry for quatification of S-phase fraction and to immunohistochemicalevaluation of Ki-67, Top2a, p21, and p27Kip1. In univariate analysis, positive expression of Ki-67 (hazard ratio = 4.5, CI = 1.6-12.1), Top2a (hazard ratio = 2.2, CI = 1.2-3.5) and high S-phase fraction (hazard ratio = 1.8, CI = 1.2-3.7) significantly correlated with risk for metastasis. When combined with currently used prognostic factors, Ki-67, S-phase fraction and Top2a fraction contributed to refined identification of prognostic risk groups.

Conclusion. Proliferation, as assessed by expression of Ki-67 and Top2a and evaluation of S-phase fraction and applied to statistical decision-tree models, provides prognostic information in soft tissue sarcomas of the extremity and trunk wall.
Though proliferation contributes independently to currently applies prognosticators, its role is particularly strong when few other factors are available, which suggests a role in preoperative decision-making related to identification of high-risk individuals who would benefit from neoadjuvant therapy.

Introduction

Soft tissue sarcomas (STS) of the extremities and the trunk wall comprise a heterogeneous group of rare malignant tumors with diverse genetic aberrations, morphological features, and clinical behavior. In STS of the extremity and trunk wall, surgery with wide margin is the cornerstone of therapy, usually combined with radiotherapy, which is considered the standard approach in nearly all high-grade tumors and low-grade ones operated with marginal margin. Still, metastases develop in about one-third of the patients, most of whom will die from their disease.

Several studies have correlated proliferation measures to development of distant metastasis as well as to overall survival in STS. [1-4] However, these findings have not gained clinical applicability, which is explained by small and heterogeneous materials, use of different proliferation measures and uncertainty about the impact of proliferation when additional prognostic markers are considered.

The Ki-67 antigen, also referred to as Ki-67, is present in the nucleus during all active phases of the cell cycle (G1, S, G2, and mitosis) and is strictly associated with proliferative potential. [5] High Ki-67 expression, which has been defined as expression in more than 10–30% of the cells, has been correlated to overall survival in soft tissue sarcoma. [3,6-12] The impact of Ki-67 has, however, been reported to vary according to histologic type, and Ki-67 has in some studies lost its prognostic significance when other prognostic factors, for example, malignancy grade and necrosis, have been taken into account. [7,8,13] Topoisomerase 2 alpha (Top2a) cleaves and re-ligates double-stranded DNA, is essential for cell division and accumulates in cells throughout the cell cycle with peak levels prior to mitosis. Top2a represents a molecular target of anthracyclines and has been broadly studied as a prognostic and predictive marker in a number of tumor types, for example, in breast cancer; still its role in STS remains unclear. [14]

Cyclin-dependent kinase inhibitor 1 (p21) is a member of the KIP family of cyclin-dependent kinase (Cdk) inhibitors, which also includes the cyclin-dependent kinase inhibitor 1B (p27Kip1). p21 and p27Kip1 have dual roles in inducing cell cycle arrest through CDK2 inhibition and act as oncoproteins when located in the cytoplasm. Loss or inactivation of p21 has been reported in solid tumors, and in STS, low levels of p21 have been reported to correlate with low grade. [12,15]

Reduced expression of p27Kip1 has been associated with poor prognosis in epithelial cancers of, for example, the esophagus, the breast, and the prostate, but their role in sarcomas is controversial. [1,4,16-19]

Proliferation, assessed by flow cytometric analysis of S-phase fraction, has also been reported to represent an independent prognostic factor in STS. [2,20,21] The prognostic impact of S-phase has been reported to be equivalent to Ki-67 at low cut-offs with a weaker prognostic effect and discriminative power at higher cut-offs. [21]

The aim of our study was to explore the interactions between clinical variables (size, necrosis, grade and vascular invasion) and proliferation markers (S-phase fraction, Ki-67, Top2a, p21, and p27Kip1) and their impact on prognosis. To analyze how the covariates interact we used the Classification and Regression Tree Analysis (CART) technique, which uses recursive partitioning to generate prognostic subgroups. CART analysis identifies specific combinations of covariates associated with a given risk for metastasis and has been applied in diagnostic and prognostic classification in solid tumors. [22-24]

Materials and methods

Patient and tumor characteristics

The study was approved by the Lund University Ethics Committee. Adult patients (>16 years) with primary, non-metastatic STS of the extremities or the trunk wall who were referred before surgery and from whom paraffin-embedded tumor tissue was available were selected. All patients were treated at the Southern Sweden Sarcoma Centre in Lund between 1980 and 2003 and patient data were identified in the Scandinavian Sarcoma Group registry. The study included three common histologic subtypes during the time period, that is, undifferentiated pleomorphic sarcoma (UPS), pleomorphic leiomyosarcoma and pleomorphic liposarcoma. In total, 203 patients were eligible, 7 of which were excluded due to incomplete data, nonrepresentative paraffin-embedded tumor blocks, or technical issues, which left 196 STS for analysis (Table 1).

Tabel 1 Patient clinicopathological characteristics		
Clinicopathologic characteristics	**Total cohort (n = 196, %)**	**Number with metastasis (n = 70)**
Age at diagnosis, years		
Median (mean)	69 (66)	-
Sex		
Female	86 (44)	-
Male	110 (56)	-
Tumor size		
<5 cm	56 (28)	9
≥5 cm	140 (72)	61
Tumor depth		
Subcutaneous	59 (30)	17
Deep	137 (70)	53
Vascular invasion		
Absent	149 (76)	40
Present	47 (24)	30
Tumor necrosis		
Absent	77 (39)	14
Present	119 (61)	56
Grade		
Low (I-II)	21 (11)	1
High (III-IV)	175 (89)	69
Histology		
UPS	93 (47)	37
Leiomyosarcoma	66 (34)	25
Liposarcoma	37 (19)	8
Local recurrence		
No	144 (74)	45
Yes	52 (26)	25
Postoperative radiotherapy		
No	139 (71)	41
Yes	57 (29)	29
Adjuvant chemotherapy		
No	187 (95)	67
Yes	9 (5)	3

Follow-up included clinical examination and chest radiographs every 3 months for the first 2 years and twice yearly thereafter. No patient was lost to follow-up. The median follow-up for survivors was 6,5 (2-26) years. During follow-up, 52 (26%) patients developed local recurrence, of which 25 also developed metastasis. The metastasis rate was 35%, and occurred most commonly to the lungs with a median time to metastasis of 9 months. The median follow-up for patients free from metastases was 6.4 years, but because of non-proportional hazards

for most prognostic factors, 5-year survival was used for analysis. No patient received preoperative chemotherapy or radiotherapy and all patients underwent primary surgery.

Local treatment was classified as carrying a high risk for local recurrence (marginal surgical margin without postoperative radiotherapy (RT) or intralesional margin irrespective of RT) in 11% of the patients or a low risk for local recurrence (wide margin with or without RT or marginal margin with RT) in 89%. [25] Radiotherapy was given postoperatively to 57 (29%) patients and adjuvant chemotherapy was administered to 9 (5%) patients.

Histopathologic diagnosis was made by a sarcoma pathologist (M.Å.). In total, 93 tumors were classified as UPS, 66 as leiomyosarcoma and 37 as liposarcoma. Tumor characteristics, including localization, size, depth, vascular invasion, and necrosis were obtained from the pathology reports and from the SSG database (Table 1). Necrosis was defined as the presence of amorphous cellular debris, usually associated with a neutrophil polymorphonuclear cell response and was dichotomized as present/absent. Vascular invasion was defined as tumor cells surrounded by an endothelial lining. Tumour cells had to be adherent to the luminal aspect of the vessel wall or, if free-floating, had to be associated with adherent fibrin, red blood cells, or leucocytes. Vascular invasion was classified as present/absent. Depth was defined in relation to the deep fascia and tumor depth was classified as deep/subcutaneous. Malignancy grading was based on a 4-tiered scale used in Scandinavia [26], with grades III-IV corresponding to grade 3 of the three-tiered scale of the Fédération Nationale des Centres de Lutte Contre le Cancer grading system [27] and with 90% being high grade [28]. Compared to a population-based study in STS [29], our cohort was comparable as regards tumor size (8 cm versus 7 cm), grade (89%), depth (70%) and metastasis rate (35%), which implies that our STS series is clinically representative.

Proliferation measures

S-phase fraction from DNA flow cytometric analysis was calculated from frozen or paraffin-embedded archival tissue using a parametric method and the ModFit LT software, as described elsewhere. [30]

Immunohistochemical stains and evaluations

Monoclonal antibodies against Ki-67 (clone M7240), Top2a (clone M7186), p21 (clone M7202), and p27Kip1 (M7203) antibodies from Dako, Glostrup, Denmark) were used for immunohistochemical stains of 4-µm sections.

Heat-induced antigen retrieval was performed prior to staining. Staining was visualized with the EnVision Detection System (Dako, Glostrup, Denmark). A sarcoma pathologist selected one representative tumor block from each tumor. Two observers, who were blinded to the clinical data, assessed all slides. In half of the cases, the 2 observers were A.C. and J.S., and in another half, A.C. and M.J. Evaluations of stained tumor nuclei were based on 5 high-power fields, with an area of 0.28 mm^2, in the region of the tumor slide with the greatest density of staining. The ratio of positive nuclei (independent of intensity was recorded semi quantitatively as <5%, 6%-10%, 11%-20%, 21%-30%, 31%-40%, 41%-50% and >50%. All cases with interobserver discordance (≈10%) in the highest score obtained were re-evaluated simultaneously by the two observers together and a consensual score was attributed. No significant difference in the number of discordant cases was observed between the two pairs of observers.

Statistical analysis

Immunohistochemical expression of the cell cycle markers was evaluated as discrete variables. For each tumor, the highest score in 5 evaluable fields was considered and the immunohistochemical scores were dichotomized at the median into positive and negative. In addition, the clinicopathological variables size, vascular invasion, necrosis, depth, and grade were analyzed as dichotomous variables with predefined cut-off value for size. All analyses were based on the 196 patients for whom all data on proliferation markers, clinicopathological variables, and follow-up were complete. Metastasis-free survival was used as endpoint for all analyses, and metastasis-free survival rates were calculated according to the Kaplan-Meier method.

Pairwise associations between the variables were analyzed using the ϕ coefficient of correlation. The null hypothesis of equal prognostic effect for a given marker in different histotypes and in different treatments, and postoperative treatment was evaluated using a Cox model with a term for the interaction between the variable of interest and the marker.

The log-rank test was used to test for equality of survival curves. Hazard ratios (HRs) with 95% CI are presented as effect measures and were calculated using the Cox proportional hazards model in univariate and multivariate analyses. Proportional hazards assumptions were verified systematically both graphically and using Schoenfeld test. [31]

To further explore the interactions between the significant clinical variables identified in univariate analysis and their impact on risk for metastasis, CART analysis was used. This method uses recursive partitioning to assess the effect of specific variables on the risk of metastasis, thereby generating a tree-structured model. The analysis was performed using a Stata implementation of CART (cart.ado) by Putten. [32] In order to protect against over fitting, we used adjusted P values and defined an upper bound for the P values (P_{stop} = .01) and a minimum number of patients within a group (n_{min} = 10).

All statistical calculations were performed using Stata 11 (StataCorp 2009; Stata Statistical Software: Release 11; StataCorp LP, College Station, TX).

Results

Proliferation measures and their prognostic importance of proliferation
Immunohistochemical expression (Fig. 1) was detected for all proliferation markers with variable expression between the markers and the tumor subtypes (Fig. 2). The median expression was 10% for Ki-67, 20% for Top2a, 5% for p21, and 50% for p27, and the median S-phase fraction was 10%.

Correlations between the proliferation markers were higher (0.27-0.53) for Ki-67-Top2a and Ki-67-S-phase fraction than for Ki-67-p21, Top2-p21, p21-S-phase fraction, and Top2a-S-phase fraction (0.14-0.37) (Table 2). Correlations to prognostic factors were stronger (0.31-0.44) between Ki-67-necrosis as well as Ki-67-grade and Top2a-necrosis than between (0.28-0.29) Top2a-grade and p21-necrosis (Table 2).

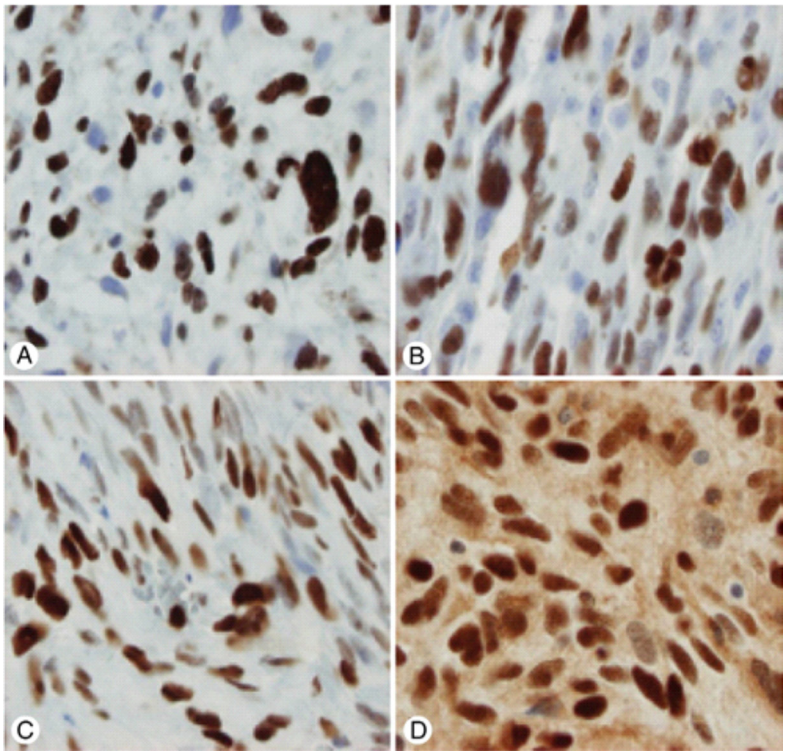

Figure. 1 Representative photographs of immunohistochemical stainings with high expression of Ki-67 (A); Top2a (B); p21 (C); p27Kip1 (D) (all photographs at x40 amplification in Olympus BX45 microscope).

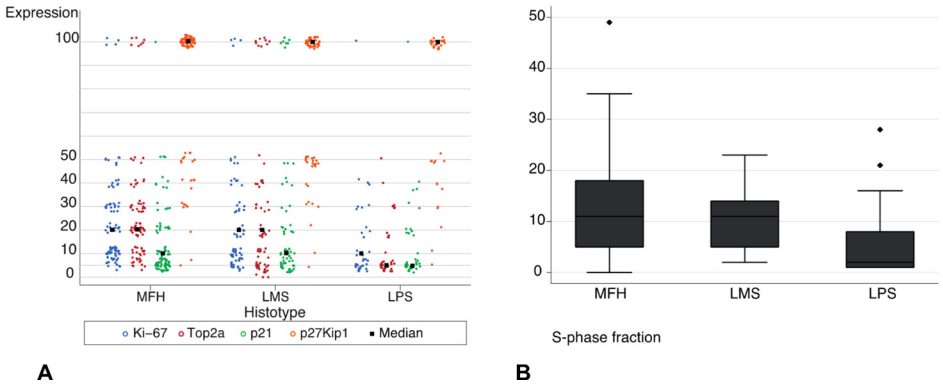

Figure. 2 A, Scatter plot of Ki67, Top2a, p21, and p27Kip expression by histotype (to avoid overplotting, random noise was added to the data). B, Boxplot of S-phase fraction, by histotype.

Table 2. Correlation coefficient (Cramer φ) for proliferation markers and other prognostic factors

Variable	Ki-67	Top2a	p21	S-phase	Size	Depth	Grade	VI	Necrosis
Ki-67									
Top2a	0.53*								
p21	0.27*	0.27*							
S-phase	0.40*	0.37*	0.14*						
Size	0.18*	0.11	0.10	0.007					
Depth	0.03	0.005	0.05	0.09	0.41*				
Grade	0.37*	0.28*	0.13*	0.17*	0.26*	0.04			
Vascular invasion	0.20*	0.10	0.17*	0.06	0.28*	0.05	0.19		
Necrosis	0.44*	0.31*	0.29*	0.26*	0.27*	0.23*	0.41*	0.53*	

Abbreviations: VI, vascular invasion
* Significant correlation

Univariate analysis

Univariate analysis of S-phase fraction and proliferation markers revealed a statistically significant correlation to development of metastases for high S-phase fraction (HR =1.8, CI = 1.2-3.7), high Ki-67 expression (HR = 4.5, CI =1.6-12.1) and high Top2a expression (HR = 2.2, CI = 1.2-3.5), whereas expression of p21 and p27Kip1 did not significantly predict metastasis (Table 3). The findings remained significant after adjustment for type of local treatment (data not shown). Size (<5 cm or ≥5 cm), vascular invasion, necrosis, tumour depth, and malignancy grade also significantly predicted risk of metastasis, whereas histotype did not (Table 3).

Multivariate analysis and CART analysis

Bivariate models were used to test the independent prognostic role of the markers that showed significant correlations in univariate analysis (Supplementary Table 1).

Ki-67 expression independently predicted development of metastases also after adjustment for size or vascular invasion. When size, malignancy grade, necrosis, and vascular invasion were taken into account together, the prognostic ability of Ki-67 expression disappeared, whereas S-phase fraction remained significant after adjustment for size or vascular invasion but not after adjustment for necrosis, grade or the SIN (size, vascular invasion, necrosis) prognostic model used in Scandinavia. Top2a remained significant only after adjustment for size.

Table 3. Univariate analysis (n = 196)			
Variable	**HR**	**95% CI**	***P***
Ki-67 (positive expression)	4.4	1.6 - 12.1	0.004
Top2a (positive expression)	1.9	1.2 - 3.5	0.02
p21 (positive expression)	0.4	0.2 - 0.9	0.18
P27Kip1 (positive expression)	0.9	0.4 - 1.6	0.76
S-phase fraction (positive expression)	2.1	1.2 - 3.7	0.008
Size (≥5cm)	3.7	1.8 - 7.6	<0.001
Vascular invasion (present)	3.5	2.1 - 5.7	<0.001
Necrosis (present)	3.5	2.0 - 6.4	<0.001
Depth (deep)	1.8	1.0 - 3.2	0.04
SIN (high risk[a])	4.0	2.3 - 7.3	<0.001
Grade (high grade)	9.9	1.4 - 71.0	0.02

Abbreviation: CI, confidence interval.
[a]High risk SIN is defined as patients with two or three risk factors among size, vascular invasion, and necrosis

To explore the interactions between the biomarkers evaluated and more established prognostic factors, in metastasis prediction, we performed CART analysis. Herein, the prognostic factors size, vascular invasion, necrosis, depth, histotype, and malignancy grade provided a basis to which the proliferation markers Ki-67, Top2a, and S-phase fraction were added one at a time. Ki-67 and S-phase fraction created branches in the prognostic tree, which implicates an added value to commonly used prognostic markers (Fig. 3).

Vascular invasion was the strongest predictor and thus determined the first branching, where after Ki-67 was the major stratifying factor in the remaining 149 tumors (Fig. 3A). Estimated prediction curves were generated for each group created by the CART analysis (Fig. 3B). Inclusion of S-phase fraction yielded 5 subsets with vascular invasion determining the first split, followed by necrosis, and tumor size. In tumors <5 cm S-phase fraction contributed to the final branching (Fig. 3D). When Top2a was considered only vascular invasion, necrosis and size determined the structure of the tree, generating 4 terminal subsets with different risk for metastasis (Fig. 3C). Therefore, Top2a expression was not a significant prognostic factor in CART analysis including all the other variables.

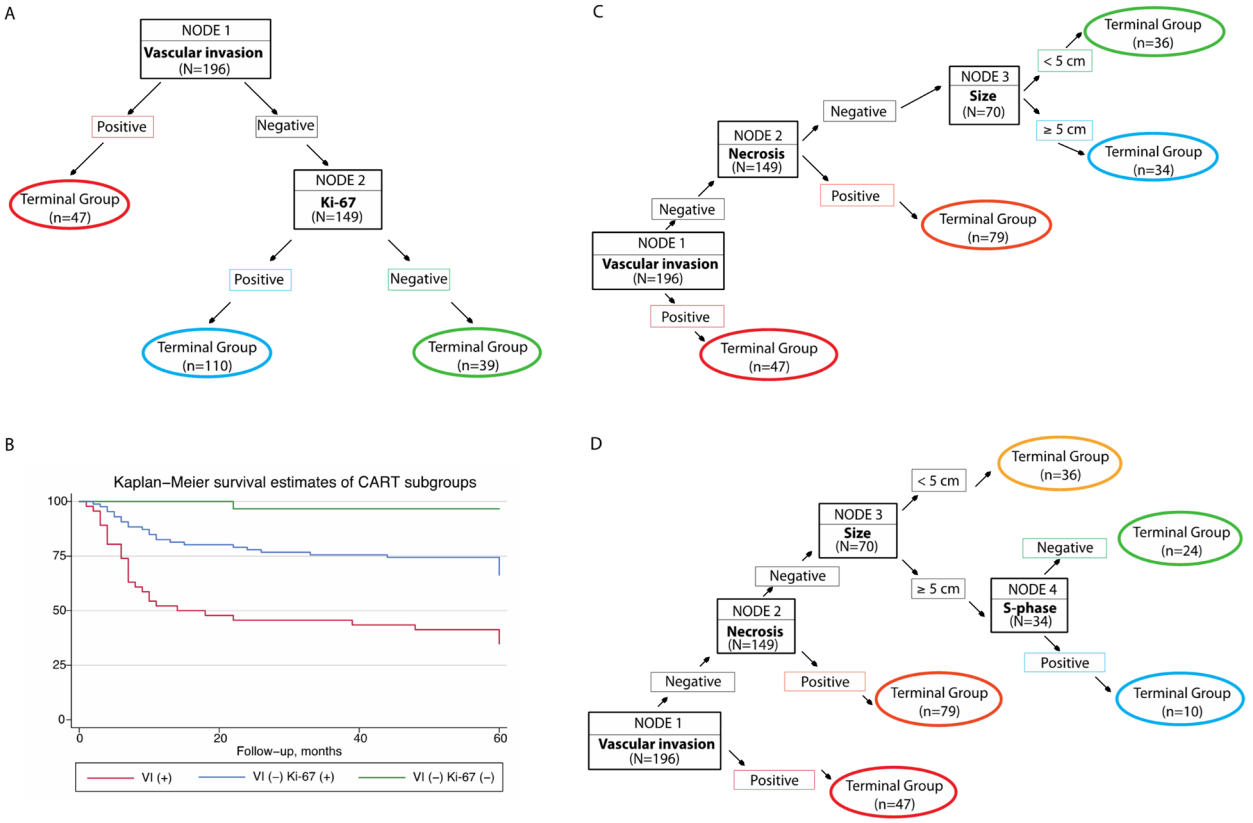

Figure. 3 Default classification tree generated in the presence of vascular invasion, size, deep, necrosis, histotype, grade, and Ki-67 (A), Top2a (C) and S-phase fraction (D). Squares represent non-terminal groups and ellipses terminal subgroups, in which the number of patients is also indicated (n). For the tree issued with Ki-67, Kaplan-Meier survival estimates, according to the generated risk groups are presented (B).

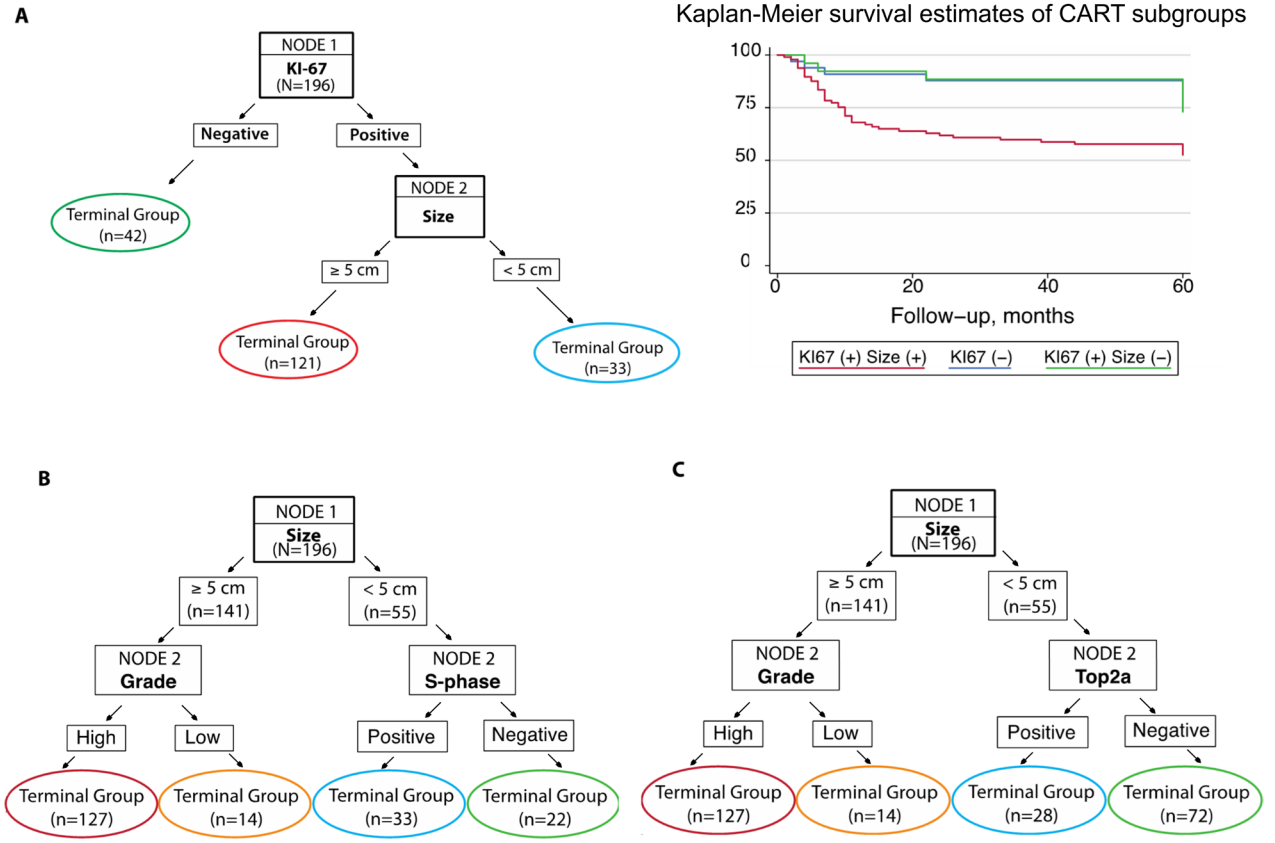

Figure. 4 Classification tree generated considering size, histotype, grade, and Ki-67 (A), S-phase fraction (B) and Top2a (C). Kaplan-Meier survival estimates of the CART subgroups are also presented for Ki-67 (A). Squares represent non-terminal groups and ellipses terminal subgroups, in which the number of patients is also indicated (n).

In the preoperative setting, limited prognostic information is available and generally includes size, histotype, and grade. In order to reflect the prognostic value in this setting, we added Ki-67, Top2a, and S-phase fraction to these factors one at the time (Fig. 4). In the presence of tumor size, histotype did not provide significant prognostic information, whereas high expression of Ki-67, Top2a, S-phase, and grade did. Ki-67 was the strongest prognostic factor (Fig. 4A) splitting the patients in two groups, where after size further divided the subset with high Ki-67 expression. This partition resulted in three subsets with different metastasis rates (Fig. 4A). In the presence of Top2a or S-phase fraction, size was the strongest prognostic factor. Hereafter, Top2a and S-phase fraction were the most important in small tumors, whereas grade determined risk in large tumors (Fig. 4B and C).

Discussion

We determined the prognostic strength of 5 major proliferation markers in a large STS cohort including common subtypes, that is, leiomyosarcoma, pleomorphic liposarcoma and UPS. Positive correlations were identified for several proliferation markers and prognostic markers with the strongest correlations for Ki-67-Top2a, Ki-67-S-phase, and Ki-67-necrosis (Table 2). This supports observations on correlations between Ki-67 and S-phase fraction, mitotic rate, grade, and necrosis. [7,10,11,27,33] The prognostic impact of the proliferation markers did in univariate analysis identify S-phase, Top2a, and Ki-67 as prognostic markers. The prognostic significance of histotype in STS is controversial. [6,9,34-36] Among pleomorphic sarcomas, myogenic differentiation has also been reported as an adverse prognostic factor [37], but in our data set, we could not find a significant interaction between Ki-67 and histotype (data not shown), therefore suggesting that proliferation could be a useful prognostic factor in pleomorphic sarcomas as a group.

Proliferation markers have not reached clinical application in STS, which largely depends on failure to integrate these markers into currently used prognostic systems, and to distinguish their contribution from that of other prognostic factors, for example, age, tumor size, depth, histologic type, malignancy grade, and necrosis.

There is therefore a need to integrate different markers and to determine their impact in specific subgroups. CART analysis visualizes interaction between survival covariates and allows identification of groups with similar prognosis and has

been applied in diagnostic and prognostic classification in several solid tumor types. [22-24]

Vascular invasion was a major prognostic predictor in pleomorphic STS, but in two thirds of the tumors without vascular invasion, CART analysis identified Ki-67 expression as a major prognostic determinant (Fig. 3) and demonstrated that S-phase fraction contributed to prognostic stratification, following vascular invasion and necrosis in large STS.

Increasing use of preoperative therapy motivates development of factors that can be determined in diagnostic biopsies, which excludes most of the currently applied markers, for example, vascular invasion and necrosis that need to be evaluated in surgical specimens. We therefore sought to address a prognostic model only taking into account factors proliferation markers in conjunction with preoperatively available clinicopathological markers, that is, tumor size, histotype and grade.

Herein, Ki-67 was a major prognostic factor (Fig. 4A). These findings suggest that clinical prognostic classification could consider as high risk only tumors with positive Ki-67 expression and large size. Albeit not included in the initial node, both Top2a and S-phase fraction could contribute to establish risk groups by dividing the small size tumors into two groups (Fig. 4B, 4C), hereby suggesting that in complement to size, Ki-67 should be considered for preoperative prognostication. In conclusion, proliferation markers are independent prognostic factors in pleomorphic STS. In particular, assessment of Ki-67 expression and S-phase fraction combined with currently used prognostic factors contributes

Proliferation in pleomorphic soft tissue sarcoma to refined risk stratification that may allow preoperative application for refined selection of high-risk patients for neoadjuvant therapies.

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Supplementary data

Table 1: Patient clinicopathological characteristics

Clinicopathologic characteristics	Total cohort (N=196, %)	Number with metastasis (n=70)
Age at diagnosis, years		
Median (Mean)	69 (66)	-
Sex		
Female	86 (44)	-
Male	110 (56)	-
Tumor size		
< 5 cm	56 (28)	9
≥ 5 cm	141 (72)	61
Tumor depth		
Subcutaneous	59 (30)	17
Deep	137 (70)	53
Vascular invasion		
Absent	149 (76)	40
Present	47 (24)	30
Tumor necrosis		
Absent	77 (39)	14
Present	119 (61)	56
Grade		
Low (I-II)	21 (11)	1
High (III-IV)	175 (89)	69
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UPS	93 (47)	37
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Local recurrence		
No	144 (74)	45
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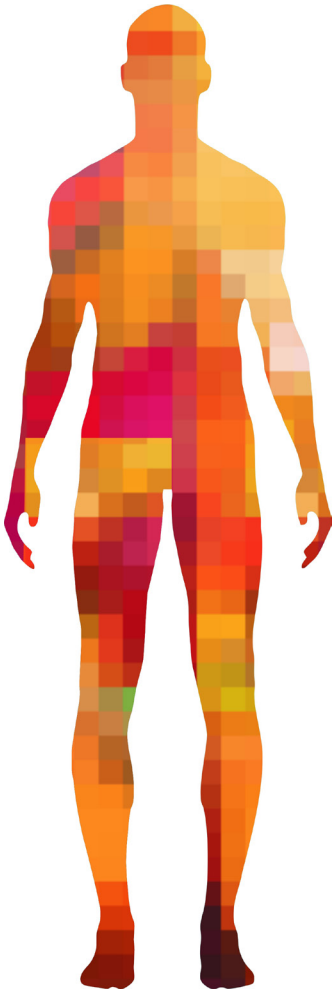
Postoperative radiotherapy		
No	139 (71)	41
Yes	57 (29)	29
Adjuvant chemotherapy		
No	187 (95)	67
Yes	9 (5)	3

HR: Hazard ratio; CI, confidence interval
*High risk SIN defined as patients with two or three risk factors among size, vascular invasion and necrosis

PART III

Isolated limb perfusion



Chapter 6

Isolated limb perfusion of soft tissue sarcomas:

A comprehensive review of literature

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Cancer Treat Rev. 2013 Oct;39(6):569-77

Abstract

Patients with primary irresectable, locally advanced soft tissue sarcomas of the limbs form a challenging group for the treating physician. Multimodality treatment is necessary to guarantee optimal limb salvage and survival rates. Since the introduction of isolated limb perfusion in the late fifties, several treatment regimens have been proposed. Isolated perfusion with melphalan and TNF-α, as part of a multimodality treatment, is regarded as the current best treatment option today. Ongoing studies are investigating potential benefit of other doses, new chemotherapeutic agents and new techniques in perfusion and radiotherapy. This article provides a historical overview of published literature and insight in upcoming treatment techniques.

Introduction

Soft tissue sarcoma (STS) comprise a heterogeneous group of malignancies, accounting for about 1% of all cancers. They may arise in any part of the body, but develop most commonly in the extremities (45%). [1] Because STS typically present as a painless lump without loss of function or influence on the patients general health, there is usually a substantial delay before initial presentation, allowing the tumor to grow to considerable size. In case the tumor is too large for local resection or in close adherence to important structures with resection causing severe impaired limb function, neo-adjuvant therapy could be attempted in order to achieve pre-operative downsizing of the tumor. An induction treatment approach with intra-arterial chemotherapy in combination with radiation has been investigated, with good results in terms of high limb salvage and low local recurrence rates, however, morbidity rates were too high, and the treatment protocol was eventually abandoned. [2,3] Another, well documented, neo-adjuvant treatment possibility is regional limb perfusion (ILP). During the last two decades, several institutions in Europe have utilized the perfusion technique as a safe alternative for amputation. [4] A continuous search for developing and improving the perfusion technique and chemotherapeutic agents has led to numerous publications. This review provides an historical overview of literature, and describes the current status and new applications of isolated perfusion.

Landmarks in the treatment of primary irresectable soft tissue sarcoma

Klopp and colleagues were the pioneers in the field of intra-arterial chemotherapy. In 1950, they explored the benefit of intra-arterial administration of nitrogen mustard for the treatment of various malignancies in the United States. [5] Although a better tumor response in comparison with venous administration was demonstrated, complete eradication was not possible because systemic toxicity precluded maximal effective drug doses. In the late fifties, Chreech, Krementz and Ryan attempted to reduce the systemic toxicity from intra-arterial chemotherapy by introducing a new technique based on the heart–lung machine, utilizing an oxygenated extracorporeal circuit: isolated limb perfusion (ILP). [6] They started using melphalan, which is less neurotoxic, and reported good tumor response in various cancers, mainly in melanomas. [7] The first perfusion in Europe was carried out by Lebrun in Belgium in 1960, and eventually adopted in some 30 cancer centers throughout Europe.

Originally, perfusions were performed under normothermia (37–38 °C). Cavaliere was the first who experimented with hyperthermic ILP and reported enhanced tumor kill with less serious local toxicity. [8] In addition, Wieberdink et al. recommended to calculate melphalan dosage based on limb volume, instead of body weight, to reduce regional toxicity.[9] Further advancements came when the pressure regulated perfusion technique was introduced and leakage monitoring improved. [10-12]

In 1987, Hoekstra et al. reported the ineffectiveness of ILP with melphalan in the treatment of sarcoma. [13] Therefore, other chemotherapeutic agents were explored, but never widely applied in the clinic due to ineffectiveness or severe side effects. [14-19]

A new breakthrough in the history of ILP came in the early nineties, when Lejeune et al. added tumor necrosis factor-α (TNF-) to melphalan (TM–ILP) in the treatment of locally advanced STS of the limbs. [20] TNF-α causes selective destruction of the tumor vasculature and facilitates drug penetration in the tumor due to intratumoral vessel permeability. The addition of TNF-α to the perfusate has led to a 4–5-fold increased uptake of melphalan by the tumor and resulted in an excellent tumor response and limb salvage rates with acceptable local and systemic toxicity. TM–ILP was further explored in a multicentre study in Europe, which confirmed TM–ILP as a safe and effective alternative for amputation in locally advanced STS. [4,21] Although the search for new chemotherapeutic agents has continued in the last decades, no agent has led to better tumor response and local control than the combination of TNF-α and melphalan. A historical overview of literature from isolated limb perfusion in STS is shown in Table 1.

Indications for ILP

ILP is used as an alternative limb sparing treatment for patients with primary, irresectable STS, due to either multifocal disease, large size or close adherence to important structures, and who are planned for amputation. ILP is given with curative intent and aims for the same local control as amputation.

Also, patients with recurrent disease after multimodality treatment have been included in ILP studies with a fair limb salvage rate of 65/100% and limited regional toxicity (Table 1). [22,23] In the many years of experience with perfusion,

other indications have been recognized. High grade STS have a high potential for metastasis, and as much as 30% of patients eventually develop metastasis and die from their disease. In case of systemic progression of disease, there is restraint towards extensive treatment for the primary tumor, due to the possible side effects of treatment and the short life expectancy. Nevertheless, the primary tumor could cause severe functional impairment in the short term leading to considerable reduced quality of life. The first study investigating the role of ILP in the palliative setting was performed in the late nineties, in a small group of patients (*n* = 9) and reported acceptable treatment related morbidity (30%) and high limb salvage (89%), concluding that ILP is a feasible and efficient palliative treatment in disseminated patients. [24] More recently a larger study (*n* = 51), confirmed these findings, concluding that ILP provided limb salvage in nearly 100% of patients with tolerable toxicity (Table 1). [25]

A specific indication for ILP is aggressive fibromatosis, also named desmoid tumor. Classified as cancer, because they can invade locally, but without metastatic potential. Mutilating surgery is therefore not justified. A few studies have described their results for ILP in desmoids patients, however results are limited due to small numbers. [26-28] The largest study (*n* = 12) showed a good tumor overall response (75%) (Table 1). Local control was obtained after 10/12 ILPs and in the other two patients through repeat ILP and systemic chemotherapy, thus leading to an overall local control rate of 100%. [28] Because local toxicity was mild, there seems a fair indication for ILP in symptomatic, irresectable desmoids of the limbs.

Another challenging disease is the Stewart–Treves syndrome, a rare type of sarcoma developing in chronically lymph edematous arms after radical mastectomy, with a multifocal presentation and difficult to eradicate by surgical resection. A small study analyzed 16 ILPs in 10 patients, and showed an 87% overall response rate (complete and partial response), with four patients receiving a second or even third ILP (Table 1). [29] Limb salvage was achieved in eight patients (80%), with a mean follow up duration of 34.8 (3–115) months. In four cases, grade 3 (according to Wieberdink [9]) with edema, blistering and slightly disturbed mobility was observed, and in six cases grade 2 toxicity. Because treatment options are limited in the case of Stewart–Treves syndrome, ILP should be seriously considered in irresectable patients, nonetheless, possible severe side effects should be weighted in treatment decision.

Table 1. Overview results in extremity perfusion for sarcoma.

Author	Year	Study	Cytostatics	N	CR %
Krementz et al.[79]	1977	Single	M/Act-D/HN2	17	0
Muchmore et al.[80]	1985	Single	M/Act-D/HN2/various	51	6
Stehlin et al.[81]	1984	Single	M/Act-D	65	NS
Lethi et al.[82]	1986	Single	M/Act-D	64	NS
Krementz.[83]	1986	Single	M/Act-D	56	NS
Hoekstra et al.[13]	1987	Single	M	14	NS
Pommier et al.[18]	1988	Single	Cisplatin	17	0
Di Filippo et al.[84]	1988	Single	M/Act-D	55	NS
Klaase et al.[17]	1989	Single	Dox/M	13	7
Kettelhack et al.[85]	1990	Single	M/Act-D	9	NS
Eggermont[86]	1993	Single	TNF/M_IFN	20	55
Hill et al.[45]	1993	Single	TNF/	8	100
Fletcher et al.[90]	1994	Single	Cisplatin	75	NS
Rossi et al.[14]	1994	Single	Dox	23	NS
van Ginkel et al.[16]	1996	Single	Cisplatin	4	NS
Eggermont et al.[21]	1996	Multi	TNF/M_IFN	55	18
Eggermont et al.[4]	1996	Multi	TNF/M_IFN	186	18
Santinami et al.[48]	1996	Single	TNF/M	10	70
Rossi et al.[91]	1996	Single	TNF þ Dox	18	NS
Gutman et al.[51]	1997	Single	TNF/M_IFN	35	37
Olieman et al.[88]	1997	Single	TNF/M	25	40
Olieman et al.[68]	1998	Single	TNF/M (IFN)	34	35
Olieman et al.[24]	1998	Single	TNF/M (IFN)	9	44
Lev-Chelouche et al.[30]	1999	Single	TNF/M (IFN)	5	20
Lev-Chelouche et al.[27]	1999	Single	TNF/M (IFN)	6	33
Lev-Chelouche et al.[87]	1999	Single	TNF/M (IFN)	13	38
Eggermont et al.[92]	1999	Multi	TNF/M_IFN	246	28
Rossi et al.[42]	1999	Single	TNF þ Dox	20	26
Lejeune et al.[56]	2000	Single	TNF/M_IFN	22	18
Daryanani et al.[15]	2000	Single	Carboplatin	4	NS
Lans et al.[29]	2002	Single	TNF/M_IFN	16	56
Noorda et al.[58]	2003	Single	TNF/M_IFN	49	8
van Etten et al.[93]	2003	Single	TNF/M_IFN	29	38
Di Filippo et al.[41]	2003	Single	Dox_TNF	NS	22
Feig et al.[38]	2004	Single	Dox	31	NS
Rossi et al.[39]	2005	Single	TNF/Dox	21	5

PR %	NC %	LS %	LR %	5-year survival %	Remarks
35	65	NS	NS	NS	Historical
12	82	NS	NS	NS	Historical
NS	NS	94	NS	73	Historical
NS	NS	100	11	67	Feasibility EBRT
NS	NS	100	21	65	Historical
NS	NS	100	7	69	Historical
18	82	NS	NS	NS	Cisplatin
NS	NS	78	24	48	Historical
0	93	61	0-24	44-77	Doxorubicin
NS	NS	78	33	66	Historical
40	5	90	NS	NS	TNFα
0	0	64	NS	NS	Low-dose TNFα
NS	NS	NS	7	48-100	Largest cisplatin study
74	26	91	27	48	Doxorubicin
NS	NS	NS	NS	NS	Cisplatin
64	18	84	13	NS	First multicenter study
57	25	82	11	NS	Beromun_registration
20	10	89	NS	NS	None
NS	NS	81	10	NS	None
54	9	85	0/31	NS	None
52	8	NS	NS	NS	Angiographic response
59	6	85	14	60	Feasibility EBRT
33	23	89	22	0	Palliative treatment
80	0	80	NS	NS	Kaposi sarcoma
50	17	100	33	NS	Desmoid
54	8	85	38	NS	Multifocal
47	25	76	NS	NS	Definition irresectability
64	10	84	10	64	None
64	18	77	14	86	None
NS	NS	100	NS	NS	Carboplatin
31	13	80	NS	NS	Lymphangiosarcoma
55	37	57	13	48	None
38	24	76	NS	NS	Elderly patients >75 years of age
55	23	77	7	69	Phase I and II study Dox and Dox þ TNFα
NS	NS	NS	NS	NS	Doxorubicin
57	38	71	19	57	TNFα þ doxorubicin

Table 1. Continued.

Author	Year	Study	Cytostatics	N	CR %
Grunhagen et al.[53]	2005	Single	TNF/M_IFN	240	24
Grunhagen et al.[53]	2005	Single	TNF/M_IFN	48	38
Bonvalot et al.[46]	2005	Single	TNF/M	100	36
Grunhagen et al.[28]	2005	Single	TNF/M_IFN	12	17
Lans et al.[22]	2005	Single	TNF/M_IFN	26	20
Grunhagen et al.[94]	2005	Single	TNF/M_IFN	64	42
Grunhagen et al.[95]	2006	Single	TNF/M_IFN	217	18
Grunhagen et al.[25]	2006	Single	TNF/M_IFN	37	16
Schlag and Tunn[96]	2006	Single	TNF/M_IFN	125	19
Thijssens et al.[64]	2006	Single	TNF/M	39	NS
Thijssens et al.[47]	2006	Single	TNF/M	64	NS
Hayes et al.[44]	2007	Single	TNF/M	18	NS
van Ginkel et al.[57]	2007	Single	TNF/M_IFN	73	25
Hoven-Gondrie et al.[60]	2007	Single	TNF/M_IFN	32	NS
Pennacchioli et al.[97]	2007	Single	M or Dox with or without TNFα	88	32
Cherix et al.[50]	2008	Single	TNF/M	51	25
Hoven-Gondrie et al.[61]	2008	Single	TNF/M	73	NS
Bonvalot et al.[26]	2009	Single	TNF/M	100	19
Di Filippo et al.[98]	2009	Single	TNF_Dox	75	34
Nachmany et al.[55]	2009	Single	TNF/M	42	17
Lasithiotakis et al.[23]	2010	Multi	TNF/M	6	17
Wray et al.[40]	2011	Multi	TNF/M Dox	17 12	6 NS
Grabellus et al.[43]	2011	Single		53	NS
Deroose et al.[49]	2011	Single	TNF/M	208	18
Hoven-Gondrie et al.[54]	2011	Single	TNF/M	102	22
Deroose et al.[69]	2011	Single	TNF/M	122	4
Deroose et al.[89]	2012	Single	TNF/M	29	33
Seinen et al.[99]	2012	Single	TNF/M	72	NS
Seinen et al.[100]	2012	Single	TNF/M	88	17

Abbreviations: Act-D, dactinomycin-D; Dox, doxorubicin; EBRT, external beam radiotherapy; IFN, interferon-g; LR, local recurrence; LS, limb salvage; M, melphalan; Multi, multicenter; NC, no change; HN2, mechlorethamine (nitrogen mustard); NS, not stated; Single, single center; ILP, isolated limb perfusion

PR %	NC %	LS %	LR %	5-year survival %	Remarks
50	26	82	NS	±45	Largest single center
31	29	85	NS	36	Dose reduction
29	35	77	24	NS	Dose reduction
58	25	100	17	NS	Desmoid
50	30	65	27/45	40	Previous irradiated recurrences
45	13	82	45	39	Multifocal/recurrent sarcoma
51	31	75	26	49	Prognostic factor
68	16	92	NS	NS	Palliative treatment
53	28	81	18	NS	None
NS	NS	NS	NS	NS	Quality of life
NS	NS	89	NS	61	Value adjuvant RT
NS	NS	NS	NS	NS	None
69	6	60	NS	70	70% Long-term LS outcome
NS	NS	NS	NS	NS	Vascular morbidity
59	8	83	27	NS	Melphalan or doxo with or without TNFα
41	28	76	35	44	Long-term results
NS	NS	NS	NS	NS	Long-term effects according to LENT-SOMA
39	42	87	14	NS	None
48	18	85	21	62	TNFα and doxorubicin
36	47	?	42	NS	High vs low dose TNFα
50	33	100	NS	NS	Recurrent disease
64	30	41	NS	NS	Phase II trial: comparison of two regimens
NS	NS	NS	NS	NS	
NS	NS	NS	11	NS	Histologic response
53	29	81	30	42	Long-term results largest single center
55	23	77	15	NS	TNFα dose reduction
66	29	89	21	NS	Role of adjuvant RT
38	29	NS	32	52	ILP for distal part limb
NS	NS	NS	NS	NS	Treatment related fractures
55	28	NS	11	NS	Local recurrence after ILP

Kaposi sarcoma, associated with acquired immunodeficiency syndrome, has a wide variety of local treatments, but are only sufficient for localized small tumor burden. Kaposi sarcoma is highly radiosensitive and thus local radiation has been widely used for control, however, recurrences are frequent, and this modality is limited and cannot be used repeatedly. The role of ILP was analyzed in a small group of patients (*n* = 5) and showed a remarkably good overall response rate of 100%, with one patient having a complete response. [30] No surgery was performed. Four patients developed grade 3 toxicity with blisters. Two patients showed progression after 2 months leading to an amputation in one case. Because of a small number of patients and a relative short follow up of 2 years, no strong conclusions can be made, but these finding do suggest that ILP can be considered as palliative treatment in Kaposi sarcoma.

Perfusion technique

Isolated perfusion can be performed at three levels of the lower limb; iliac, femoral, or popliteal level, and for the upper limb at two levels; axillary or brachial level (Fig. 1). Isolation of the blood circuit is achieved by ligating the collateral vessels and clamping the major artery and vein after systemical heparinization (Fig. 2).

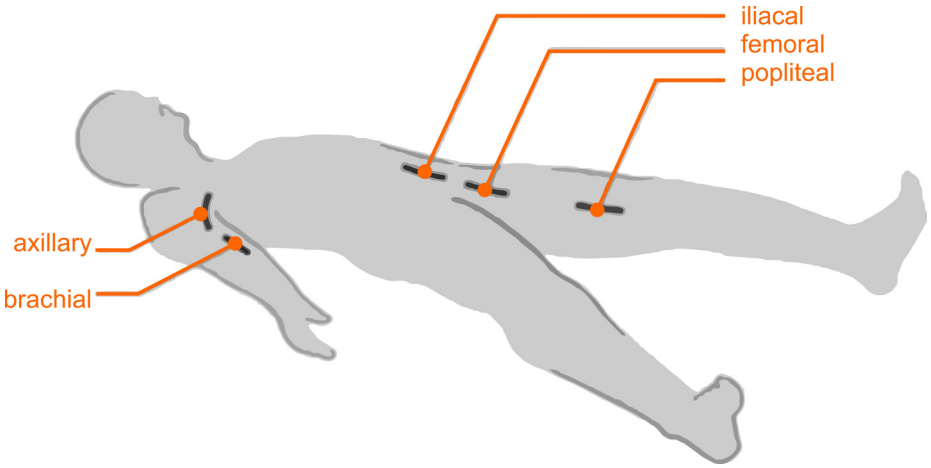

Figure 1. Various perfusion levels of the upper and lower limbs

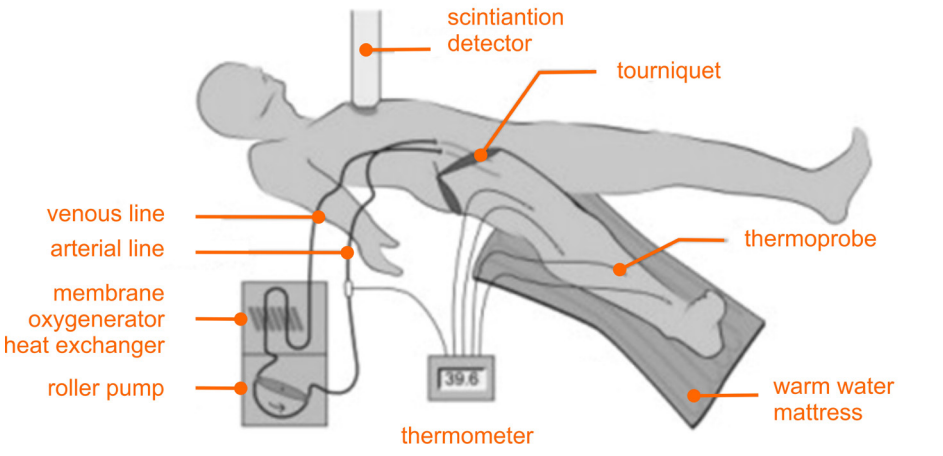

Figure 2. Isolated limb perfusion

With catheters, the main artery and vein are conjoined to the extracorporeal circuit. To prevent leakage through minor vessels in subcutaneous tissue and muscle, an occluding rubber bandage is twisted around the root of the extremity in axillary, iliac and femoral perfusions and an inflating tourniquet is used in popliteal or brachial perfusions. To obtain a good artificial tissue perfusion for adequate tissue oxygenation and effective flow of chemotherapy outside the normal corporeal circuit, regulated perfusion was performed by means of venous clamping and a membrane oxygenator. [10] In general, perfusions are carried out under mild hyperthermic (39–40 °C) circumstances by wrapping the perfused limb in a thermal blanket, continuously monitored with thermistors in subcutaneous tissue and muscle tissue. Despite one comparative study showing no benefit in favor of mild hyperthermia compared to normothermic perfusion [31], both clinical and laboratorial studies reported enhanced anti-tumor activity under hyperthermic condition. [8,32] When the temperature in the subcutaneous tissue of the limb is 38 °C and the pH of the perfusate between 7.2–7.35, cytostatic agents are injected in the perfusion circuit or (slowly) into the arterial line. Based on the fact that TNF-α concentrations remain stable during perfusion but the effect of melphalan is fairly decreased after 30 min, the overall duration of perfusion was shorted from 90 min (30 min TNF perfusion followed by 60 min of melphalan) to 60 min (melphalan is added to the perfusion circuit 15 min after the application of TNF and perfusion is then stopped 45 min later). [32,33]

At the end of the perfusion the extremity is washed out with 3–6 L saline and filled, if indicated, with one unit red blood cell concentrate. Catheters are removed and vessels repaired. A prophylactic closed fasciotomy of the anterior compartment of the lower leg or of the ventral and dorsal compartments of the forearm is performed to prevent a compartment syndrome. [34]

An important part of the perfusion process is the leakage monitoring, which can be recorded through radio-labeled 131-I human serum albumin with a precordial scintillation probe. If leakage exceeds the 2% limit during perfusion, less exposure of the tumor-bearing limb to TNF alpha, increased exposure of the patient systemic circulation to TNF-α, and more systemic side effects can be expected. [12] Leakage of TNF-α into the systemic circuit can even lead to a sepsis-like state that last for approximately 24 h after perfusion. [35]

Perfusion agents

Nitrogen mustard was the first drug used in ILP. Because the resistance of melanomas towards nitrogen mustard, Luck tried melphalan as chemotherapeutic agent in rat melanoma and reported promising results. [36] Chreech and colleagues switched to melphalan in the treatment of melanomas, followed later by STS, and also in combination with other chemotherapeutic agents. [37] Pending the randomized trials with melphalan, other chemotherapeutic agents were explored. Pommier et al. conducted a phase II trial with cisplatin in ILP for STS. [18] Cisplatin is an attractive agent for use in hyperthermic ILP, because it inhibits incorporation of DNA precursors by a mechanism similar to that of alkylating agents. Thirty-five STS patients underwent ILP with cisplatin and in 17 cases response could be measured, showing an overall response rate of only 18%. Almost 10 years later, another small study (n = 4) analyzed the results of cisplatin in ILP for bone and soft tissue sarcomas, however, due to the small number no firm conclusion can be drawn from this study. [16] Cisplatin never got wide application in ILP.

In addition, several studies have shown interest in doxorubicin. [14,38-41] In Italy, Rossi and Di Filippo have conducted three trials. [14,41] In the late nineties they analyzed the results of all three trials and reported a complete response in over one-fourth of patients, and an overall limb salvage rate of 92%. [42] The overall grade 4 toxicity was only observed in 2 cases, but the phase II trial showed grade

3/4 toxicity in 22% of patients. [14] The authors conclude that the high toxicity rate is due to a high dose of TNF-α (>1 mg) and high temperature (>41.5 °C), and that the combination of doxorubicin and TNF-α could be safely administered if used in a low doses and under mild hyperthemic circumstances. Feig and colleagues have used doxorubicin in three different doses and in combination with radiation (*n* = 31), and found that at the highest dose level (17.5 mg/m(2)/wk) 30% of patients developed grade 3 toxicity. [38] In a recent study, the high toxicity levels of doxorubicin were confirmed. Wray et al. analyzed 12 patients and observed grade 3 toxicity in 5 patients (42%) and grade 4 toxicity in 7 patients (58%). [40] Even after the dose was lowered, patients developed severe muscle and neurotoxic morbidity. Therefore, doxorubicin has not been included in the standard treatment of ILP for STS.

Similar high local toxicity rates, especially neurotoxic morbidity, were observed for carboplatin, which was tried in three patients with melanoma or STS [15] and was, therefore, not further explored in STS.

Today, the standard regimen for ILP in STS is melphalan and TNF-α. [23,40, 43-50] Between 1993 and 2006, several centers also used interferon-gamma (IFN-γ) in combination with melphalan and TNF-α.[4,51] But because IFN-γ did not seem to add in increasing the limb salvage or survival rate, but did cause morbidity, it was excluded from the regimen. TNF-α (Beromun®, Boehringer Ingelheim International GMbH, Ingelheim am Rhein, Germany) was registered in 1999 by the European Medicine Evaluation Agency (EMEA) for the therapeutic extremity perfusion of locally advanced soft tissue sarcoma and melanoma. In contrast to Europe, Beromun® was not registered by the FDA. [52] Today ILP with melphalan and Beromun® is offered in 36 cancer centers worldwide.

Toxicity ILP with TNF-α and melphalan

Local toxicity is graded according to Wieberdink (Table 2). [9] Within this classification system, the duration of a reaction was not taken into account and the peak of a reaction determined its grading. Because lymphadenectomy in combination with the perfusion may interfere with the classification of a toxic reaction, erythema was considered in such cases more decisive to the grading than edema.

Table 2. Wieberdinks's acute regional toxicity grading system	
Grade 1	No reaction
Grade 2	Slight erythema or edema
Grade 3	Considerable erythema or edema with some blistering: slightly disturbed motility permissible
Grade 4	Extensive epidermolysis or obvious damage to the deep tissues, causing definite functional disturbances: threatening or manifest compartmental syndrome
Grade 5	Reaction that may necessitate amputation

Reviewing previously published studies performing ILP with melphalan and TNF-α, grade 1/2 was observed in all studies, ranging from 24% to 100% (Table 3). [23,40,44,46,49,50] This usually involved erythema and mild edema of the limb. More severe edema and blistering of the skin, or functional impairment (grade 3), was reported in 1–19% of patients. Grade 1–3 is usually visible shortly after ILP and resolves in the majority of patients within weeks or months after treatment. Severe soft tissue damage and neurotoxic morbidity (grade 4) could be detected in only a small number of patients (0–2%) and is in the majority of cases to some degree permanent. In 0–2% of cases soft tissue morbidity necessitated amputation.

Table 3. Local toxicity according to Wieberdink in TM-ILP studies

	N	Grade 1/2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Bonvalot et al.[46]					
TNFα dose:					
0.5mg	25	36	12	0	0
1mg	25	32	8	0	0
2mg	25	24	1	1	0
3/4mg	25	32	1	0	0
Hayes et al.[44][b]	16	-	-	-	2
Cherix et al.[50]	51	90.1	7.8	0	2
Lasithiotakis et al. [23][ab]	6	100	0	0	0
Wray et al.[40]	17	-	-	-	-
Deroose et al.[49]	208	59	19	1.9	0.5

[a] including only recurrent disease
[b] including both melanoma and soft tissue sarcoma

Dose reduction of TNF-α in STS patients

Two major changes in the perfusion technique have been made since the introduction in the fifties. First of all, the duration time was shortened and secondly, the

TNF-α dose has been reduced. The potential advantage of a lower dose of TNF-α includes a lower incidence of systemic adverse events leading to a more simple and safe procedure with a significantly lower cost. An overview of outcomes of clinical dose reduction studies in STS patients is presented in Table 4. Two studies published in 2005 their single centre results. [46,53] Bonvalot et al. conducted a randomized phase II trial (*n* = 100) comparing ILP with melphalan and one of the four assigned doses of TNF-α: 0.5 mg, 1 mg, 2 mg, and 3/4 mg upper/lower limb. At the range of TNFα doses tested, there was no dose effect detected for the objective tumor response. In 13% amputation could not be avoided, but this was not related to TNF-α dose. Although there was no difference in local toxicity, a significant correlation was found for higher TNF-α dose and systemic toxicity. [46] Grunhagen et al. could not confirm the correlation between higher TNF-α dose and systemic toxicity; instead they found a borderline difference of local toxicity in favor of the low TNF-α dose. [53] Furthermore, they concluded that overall response and survival were not affected by dose reduction. A recent study by Hoven-Gondrie et al. confirmed that TNF-α dose does not affect five-year local control rates and (limb)-survival. [54] The study of Nachmany et al. found lower response rates after low-dose ILP which did, however, not translate into higher local recurrence or lower limb salvage rates. [55]

Long term outcome

In the short term, ILP with melphalan and TNF-α enabled limb salvage in 80–86% of patients [56,57] and after 10 years (or longer) following ILP, 61–81% patients could maintain their limb. [49,57] The price of this success are the long-term side effects of the extensive treatment, which are mainly functional side effects, consisting of edema, stiffness, functional impairment, and muscle atrophy. [58,59] More severe morbidity is also observed, sometimes necessitating amputation. Three time periods at risk for amputation have been described; (1) within 1 year after perfusion due to local recurrence or massive necrosis, (2) after 5 years due to late local recurrence, and (3) after 10 years due to critical leg ischemia. [57] Although vascular complications can be severe and prevention is warranted, a routine noninvasive vascular work-up does not seem to add value to normal follow-up. [60] The late effects on normal tissue have been evaluated by means of the LENT–SOMA scoring system (*n* = 32), showing that 63% of patients scored grade 3 on one or more separate items, reflecting severe symptoms with a negative impact on daily activities. [61] A

Table 4. Overview of published clinical dose reduction studies

References	N	Dose TNF (mg)	Median FU (months)	Clin. Resp. (%)
Bonvalot et al.[46]	100		24	
	25	0.5		68
	25	1		56
	25	2		72
	25	3-4		64
Grunhagen et al.[53]	240		NA	
	192	3-4		74
	48	<3-4		69
Bonvalot et al.[26]	100	1	27	79
Nachmany et al.[55]	43			NA
	26	3-4	58[d]	
	17	1	30[d]	
Hoven-Gondrie et al.[54]	102		76[e]	NA
	27	1-2		

TNF, tumor necrosis factor-alpha; FU, follow-up; Clin. Resp., clinical response; Path. Resp., pathological response; CR/PR, complete response/partial response; LS, limb
survival; LR, local recurrence; OS, overall survival; DFS, Disease-free survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; NA, not available.

specific co morbidity of limb sparing treatment with radiotherapy is a bone fracture. [62] Since ILP treatment is often used in case of large tumors, periosteal stripping and radiotherapy are often needed to ensure radical margins and good local control. Therefore patients undergoing ILP are suspected to have a considerable risk in developing a treatment related fracture. Given the high rate of non union, generally more than 50% [63,64], treatment related fractures form a severe hazard to the patient.

In addition, a quality of life study reported that 20% of patients experienced a post traumatic stress syndrome after multimodality treatment with ILP. [65] Therefore, the impact of the extensive treatment with ILP on the functional and psychological level should not be underestimated and patients should be closely monitored to offer prompt medical and psychological help if necessary.

Role of radiotherapy

Rosenberg was the first to prove the value of adjuvant radiotherapy in limb-saving sarcoma surgery [66], showing in a long term follow up study that it decreased the probability of local recurrence without influencing overall survival. [67] The latter study also mentioned that in selected patients (not clearly specified, but patients

Path Resp. (CR/PR) (%)	LS (%)	LR (%)	OS (%)	DFS (%)	LRFS (%)	DMFS (%)
		27[a]	82[a]	49[a]	NA	NA
43	88					
62	80					
67	88					
64	92					
NA	NA	NA	47[b]	NA	59[b]	50[b]
NA	85	NA	36[b]	NA	44[b]	45[b]
58	87	18[c]	89[c]	NA	NA	67[c]
			NA	NA	NA	NA
65	76	38				
31	53	46				
76[f]	77	15	56[g]	NA	85[b]	52[b]
59[f]	85	4	57[g]	NA	96[b]	36[b]

a Two-year rates.
b Five-year rates.
c Three-year rates.
d Mean FU.
e Only for patients alive after FU.
f In case of no resection clinical response was used.
g Five-year disease-specific survival (DSS) was used.

with widely negative resection margins did not develop local recurrence in their study population) with low risk for recurrence, radiotherapy could be avoided due to important lifetime risk for complications. [67] Two studies from the same centre in The Netherlands (*n* = 15/64) analyzed the role of adjuvant radiotherapy after ILP and delayed surgical resection and showed a significant decrease in local recurrences after performing adjuvant radiotherapy. [47,68] One of these studies (*n* = 64) considered surgical margins and showed that in the R0 group, patients with radiotherapy had a better local control rate (100%) than the patients without radiotherapy (55%) ($p = 0.0003$), concluding that radiotherapy should be considered even if R0 resection is achieved. [47] This in contrast to the results of another centre in The Netherlands showing no benefit for adjuvant radiotherapy in local control for patients undergoing successful ILP (induction of >50% necrosis) and R0 resection (*n* = 28), because this group did not develop any local recurrences. [69] Important to mention is that these concerned solely the patients with primary, unifocal tumors. So, although there is generally agreement that adjuvant radiotherapy is beneficial in case of ILP and resection with R1 margins, no final conclusion can be made about the role of adjuvant radiotherapy after ILP and delayed resection with RO margins.

In the middle of the 1990s a new radiation approach began to emerge, using a larger number of incident beams, known as intensity-modulated radiotherapy (IMRT). In combination with the use of the CT scan, which allows a three-dimensional image of the tumor and surrounding tissue, IMRT has made it possible to reduce the radiation doses without compromising target coverage. A few studies have published their first, successful results with this technique in the treatment of STS patients. [70-72] Roberge et al. reviewed pathological response in histological specimens following pre-operative IMRT and found significant responses in term of necrosis and fibrosis; nevertheless, there was minimal early volumetric response to radiation, especially for high-grade tumors. [71] If pre-operative radiotherapy could have a role in combination with ILP to improve limb salvage rate and local recurrence free survival is not yet discussed in literature and makes an interesting topic for further studies. The University Medical Centre in Groningen, The Netherlands has, therefore, recently started a prospective trial to investigate a new treatment schedule with ILP, pre-operative radiation and delayed surgical resection.

The newest advancement in radiation planning is functional image-guided radiation therapy (IGRT). This dual modality technique fuses the images of the CT scan and the positron emission tomography (PET) scan, thereby producing functional and anatomical data. The advantages are that the CT scan provides an anatomical context and allows for correction of PET emission data errors, e.g. photon attenuation, while the PET scan can identify areas of disease that are not apparent on CT images alone. [73] Current studies have to evaluate the role of this radiation planning technique in the pre- and post-operative setting in the treatment of sarcomas.

Isolated limb infusion

Although results after ILP are satisfactory, the technique involves a complex and invasive surgical procedure with a substantial risk of complications. Therefore, a new, minimally invasive procedure for administering regional chemotherapy called isolated limb infusion (ILI) has been developed at the Sydney Melanoma Unit. [74] Essentially, ILI is a nonoxygenated, low-flow ILP performed via percutaneously inserted catheters. For melanomas, large studies with melphalan and actinomycin D have observed similar response rates (both overall response and complete response) compared with conventional ILP. [75,76] So far, only

limited publications exist for the use of ILI treatment in STS. [77,78] Moncrieff et al. analyzed 21 patients undergoing ILI with various chemotherapeutic agents (melphalan, actinomycin D, mitomycin C, doxorubicin and cisplatin), showing a 90% overall response rate, and 14% of patients developing grade 4 toxicity. [78] Hagazy et al. analyzed 40 patients undergoing ILI with doxorubicin and pre-operative radiotherapy and found a tumor response of 80%, with no grade 4 toxicity, but in 30% of patients grade 2 or 3 morbidity. [77]

The first results of IFI in STS appear encouraging in terms of response rate, albeit these studies concern small study populations and different chemotherapy schedules, and only one study with long term follow up. Therefore, long term results should be awaited.

Conclusion

Isolated limb perfusion for soft tissue sarcoma patients with primary irresectable tumors is a successful alternative for amputation, providing limb salvage in the long term for over two-third of patients. The majority of patients experiences to some degree local toxicity, which usually subsides within weeks or months. A small group of patients develops severe local morbidity which necessitates intervention, but rarely requires amputation. The most frequent reasons for amputation are extensive necrosis, local recurrence and long term vascular morbidity. In one fifth of patients, multimodality treatment with perfusion causes considerable psychological effects, comparable with a post traumatic stress syndrome. Early recognition and prompt interference of these patients is warranted. To reduce treatment related morbidity, better insight in drug efficacy is needed, as well as development of new effective chemotherapeutic agents.

The perfusion technique is highly specialized, requiring experienced professionals and appropriate facilitated institutions, and therefore limited available in a few cancer centers. Isolated limb infusion, which is a less invasive and complicated technique, is a promising new technique with good tumor response rates. The long term effects of this technique should be awaited.

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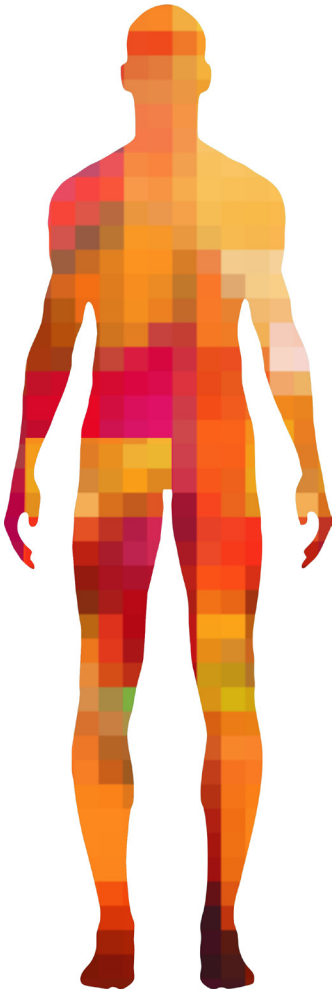

Chapter 7

Fractures after multimodality treatment of soft tissue sarcomas with isolated limb perfusion and radiation; likely to occur and hard to heal

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Abstract

Objectives. Treatment associated fractures (TAFs) are known severe side effects after surgery and radiotherapy for soft tissue sarcoma (STS). There is no literature about TAF after multimodality treatment with isolated limb perfusion (ILP) for locally advanced STS. This study aimed to analyze predictive factors, treatment and outcome for TAF after multimodality treatment with ILP.

Method. Out of 126 consecutive patients undergoing ILP after 1991 till now, 25 patients were excluded due to no surgery or direct amputation at initial surgery. Therefore, 101 patients were at risk and 12 developed a TAF (12%).

Results. The majority of tumors was located at the upper leg and knee (N=60), and 11 patients developed a TAF (18%) after median 28 (5-237) months. Twenty-five tumors were located at the lower leg, and 1 patient developed a TAF after 12 months (4%). No patients with a tumor at the upper extremities (N=16) developed a TAF. Ten out of 12 patients with a fracture received adjuvant RT with a dose of 50 Gy, and a median boost dose of 18 (10-20) Gy. Predictive factors were periosteal stripping, age over 65 years at time of treatment and tumor size after ILP ≥ 10cm. Multivariate analysis showed periosteal stripping and tumor size after ILP ≥ 10cm as significant predictive factors.

The majority of the fractures were treated with intramedullary nailing. Only one of 12 patients without radiotherapy reached bone union (8%). The median survival after developing TAF was 18 (1-195) months.

Conclusion. The overall risk of TAF after multimodality treatment with ILP was relatively high with 15% at ten years. The incidence of TAF for patients with tumors located at the thigh and knee after resection with periosteal stripping and radiotherapy was even >50%. The treatment of these fractures is challenging due to the high non-union rate, requiring an extensive orthopedic oncological TAF experience.

Introduction

Since (neo-)adjuvant radiotherapy has become the standard of care in case of marginal resection margins in the treatment of soft tissue sarcoma (STS), local control rates have improved up to 80-95%. [1-5] However, due to the more frequent use of radiotherapy, the incidence of treatment related complications such as fractures has increased as well; the reported incidence ranging from 1.2 – 9%, with most fractures occurring in the femoral bone. [1, 6-10]

Radiation is believed to attribute to impaired proliferation of normal functioning osteoblasts, as well as prohibiting neo-angiogenesis in fracture healing. [11, 12] In addition, periosteal stripping has previously been reported as risk factor for fracture [7, 9, 13], which is due to the fact that disruption of the periosteum leads to a significant decrease in cortical bone perfusion. [14, 15] Although numerous studies have looked at the incidence and predictive factors of treatment associated fractures (TAF) in STS patients undergoing surgery and adjuvant radiotherapy, not much is known about the incidence and issues in STS patients with primary irresectable tumors undergoing isolated limb perfusion (ILP), delayed surgery and adjuvant radiotherapy. Due to the large size of these primarily irresectable tumors, close proximity to the bone and marginal resection margins, which often necessitates periosteal stripping and radiotherapy to ensure clear margins and good local control, there is an accumulation of risk factors for the development of treatment associated fractures (TAF). These fractures have a high non union rate and are a major cause of patient morbidity. The management of TAF is controversial. [16-18] Furthermore, there are even authors suggesting prophylactic intramedullary nail stabilization.[16-19]

The aim of this study was to look at the incidence and predictive factors of TAF in STS patients undergoing isolated limb perfusion (ILP), delayed surgery and adjuvant radiotherapy, with special regard to their local treatment and outcome. To compare incidence, predictive factors, treatment and outcome, a review of current literature was performed.

Patients and methods

The Institutional Review Board approved this retrospective study (case number 201800233).

The prospectively collected database of 126 consecutive patients undergoing ILP and delayed surgery from 1991 till now was studied. The reason for multimodality treatment with ILP was no feasible primary surgery due to large tumor size and/or close adherence to vascular or nerve structures as previously described.[20]

The median follow up after diagnosis was 64 (5-233) months, and for the survivors the median follow up was 106 (8-233) months. Seven patients were lost to follow up, one after 2 years, the other six patients after 5 years or longer.

Patient records were reviewed to corroborate the information in the database, especially with regard to the size of the tumor, evidence of bone involvement by the tumor, radiation dose, and radiation fields. The operation and histology report were used to determine whether periosteum was removed as part of the specimen.

Fracture Analysis

A treatment related fracture was considered when the following criteria were met: 1) minimal or no trauma, and 2) located at the site of the original sarcoma. A delayed union was considered to occur if there were no radiographic signs of healing at 6 months postoperatively but subsequent healing did occur with or without further surgical intervention. A nonunion was present if union had not occurred at last follow up or death, minimal one year after occurrence.

Isolated Limb Perfusion

The ILP technique has been described previously. [21, 22] After 59 ILPs, perfusion duration was shortened from 90 to 60 min, and after 75 ILPs a reduced dose of TNF was used without affecting the local treatment.[21] Currently, in axillary and popliteal perfusions 1 mg TNFα (Beromun®, Boehringer-Ingelheim GmbH, Vienna, Austria) and in iliac and femoral perfusions 2 mg TNFα is used. The dose of Melphalan (Alkeran®, GlaxoSmithKline Pharmaceuticals, Research Triangle Park, NC, USA) used in ILP is based on limb volume: 10 mg/L for lower limb

perfusions and 13 mg/L for upper limb perfusions. In the first 21 ILPs, performed between 1991 and 1993, Interferon-γ (IFN-γ) was added to the schedule.

Surgery

Surgery was performed 6-8 weeks after ILP. There were no compartment resections performed as suggested by Enneking. [22] The goal was to perform a wide local R0 resection and to avoid a R2 resection. Major nerves or vessels were only resected to overcome a R2 resection, while a R1 resection was accepted. For sarcomas fixed to the bone, the periostium was stripped to ensure an R1 resection.

Radiotherapy

Postoperative external beam radiotherapy was considered indicated in case of <95% tumor necrosis with marginal resection margins, microscopically or macroscopically involved resection margins. Radiotherapy was administered in a schedule of 50 Gy with fractions of 2 Gy daily, 5 times a week, started within 6-8 weeks after surgery. In case of R0 resection, an additional boost dose of 10 Gy was administered to the tumor bed and in case of R1 resection a boost dose of 20 Gy was delivered.

From 2011 we changed the multimodality treatment scheme into ILP, pre-operative RT using 12 times 3 Gy and surgery within 2-4 weeks, with the aim to reduce overall treatment time. A total of 11 patients underwent this scheme.

Chemotherapy

Postoperative chemotherapy was given within European Organization for the Research and Treatment of Cancer trials (EORTC 62061 and 62931) before the start of radiotherapy, or outside a trial in the palliative setting, in case of distant metastases.

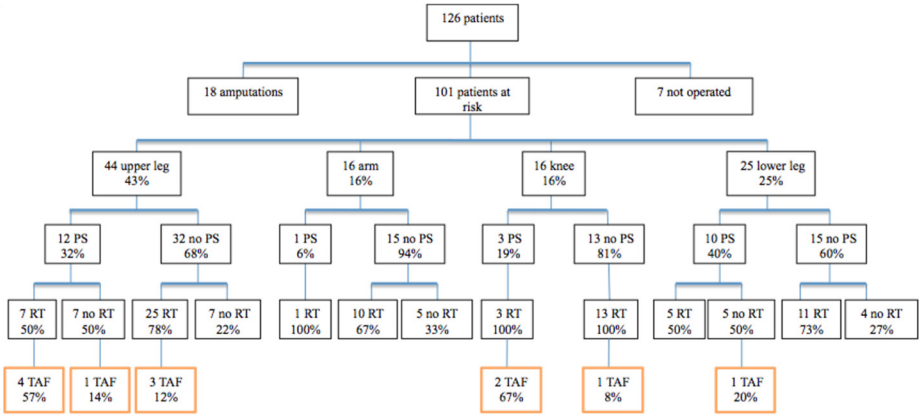
Statistical analysis

The risk of fracture was determined by Kaplan Meier survivorship, because the length of follow up varied, and fractures occurred at variable times. Fractures were considered to be events. Patients were censored at the last follow up or at death. If patients required subsequent amputation for local recurrence, then the patients were censored at the time of amputation. Univariate analysis on cate-

gorical factors was performed with the log rank test. Cox multiple regression with forward, stepwise, conditional analysis was used to identify independent predictors of fracture. All analyses were performed using IBM SPSS statistical software version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

Results

Reviewing all 126 consecutive patients, 7 patients were excluded because they underwent no surgery after ILP, and another 18 patients were excluded because they underwent amputation at initial surgery (Figure 1). Therefore, 101 patients were identified at risk for a TAF (80%).



Abbreviations: LSS = limb saving surgery, PS = periosteal stripping, RT = Radiotherapy, TAF = treatment associated fractures

Figure 1. Overview of patients developing a treatment associated fracture

Eighteen patients underwent chemotherapy, 12 because of metastasis and 6 as part of the EORTC trial. Fourty-four patients died during the study period (44%). Twelve patients (12%) developed a TAF, after median follow up of 29 (4-236) months. One patient developed a femoral fracture after twenty years at the age of 68 years, due to standing up from a chair; she was treated with radiotherapy to a dose of 70 Gy. Patient and tumor characteristics are presented in Table 1.

Table 1. Patient and tumor characteristics			
Clinicopathologic characteristic	**Group**	**Patients at risk with TAF (n = 12)**	**Patients at risk without TAF (n = 89)**
Age at start treatment, years	Median (range)	48 (22-77)	56 (15-84)
Sex	Male	7	52
	Female	5	37
Tumor size, cm (after ILP)*	0 – 10	3	55
	≥ 10	9	34
Grade	High	10	75
	Low	2	14
Unifocal disease	Yes	8	74
	No	2	13
Primary disease	Yes	10	80
	No	2	9
Location	Arm	0	16
	Upper leg	8	36
	Knee	3	13
	Lower leg	1	24
Histological subtype	Undifferentiated pleomorphic sarcoma	3	13
	Myxoid liposarcoma	1	12
	Other	8	64
Local recurrence	Yes	1	10
	No	11	79
Radiotherapy	Yes	10	66
	No	2	23
Periosteal stripping	Yes	8	18
	No	4	70
Adjuvant Chemotherapy	Yes	2	20
	No	10	69

Abbreviations: TAF = treatment associated fracture, ILP = isolated limb perfusion
*from 4 patients tumor size not known

The majority of tumors were located at the upper leg (n=44), of which 12 patients underwent periosteal stripping, 32 received adjuvant radiotherapy and 7 patients underwent both periosteal stripping and adjuvant radiotherapy (Figure 1). Patients undergoing both periosteal stripping and radiotherapy had the highest fracture risk, respectively 57% of patients with tumors located at the upper

leg, and 67% located at the knee. Two of these patients with tumors at the upper leg received RT twice for a primary tumor as well as for a local recurrence, with overlapping radiation field. One patient with a tumor of the thigh developed a TAF without receiving adjuvant radiation, but after periosteal stripping and resection of the anterior lateral muscle group.

Of the remaining patients at risk for TAF, 25 had a tumor located at the lower leg, and 1 developed a TAF after receiving periosteal stripping. None of the patients with tumors located at the arm developed a TAF.

Risk factors for fractures

The risk of fracture for the total cohort of 101 patients at 5 and 10 years was 12% and 15% respectively. Univariate analysis showed three risk factors with statistically significance for the development of TAF (Table 2): periosteal stripping (p = 0.002), age ≥ 65 years at start of treatment (p = 0.002) and tumor size ≥ 10 cm after ILP (p = 0.003). Continuing with multivariate analysis, tumor size ≥ 10 cm after ILP (p = 0.013) and periosteal stripping (p = 0.018) remained independent significant negative predictive factors of TAF.

Ten out of twelve patients with a fracture received adjuvant RT, which consisted of a complete radiation schedule of 50 Gy, with a median boost dose of 18 (10-20) Gy. All fractures developed in the booster area. Nevertheless, RT was not a risk factor for development of fractures at ten years (p = 0.755).

Treatment and outcome

Seven out of ten patients with a femoral fracture were initial treated with intramedullary nailing, two patients were treated with plate fixation and one with a cast (Table 3).

Table 2. Univariate analysis: Risk factors and development of treatment related fractures (at five and ten years)

Clinicopathologic characteristic	Group	Kaplan Meier risk of TAF at 5 years (%)	Kaplan Meier risk of TAF at 10 years (%)	*P* – value
Periosteal stripping	Yes	27	36	
	No	5	7	0.002
Age at start treatment, years	< 65	8	13	
	≥ 65	17	17	0.002
Tumor size, cm (after ILP)	< 10	3	3	
	≥ 10	21	33	0.003
Sex	Male	10	19	
	Female	11	11	NS
Radiation	Yes	10	15	
	No	13	13	NS
Radiation dose booster (Gy)	Yes	9	14	
	No	14	14	NS
Grade	High	12	17	
	Low	6	6	NS
Unifocal disease	Yes	11	16	
	No	8	8	NS
Primary disease	Yes	11	16	
	No	9	9	NS
Location	Upper leg	17	28	
	Lower leg	5	5	
	Knee	12	12	
	Arm	0	0	NS
Chemotherapy	Yes	12	12	
	No	10	15	NS

Abbreviations: TAF = treatment associated fracture, ILP = isolated limb perfusion, UPS = undifferentiated pleomorphic sarcoma, NS = not significant

Table 3. Treatment and outcome for patients with treatment associated fractures

P	Time to TAF (months)	Age at diagnosis (years)	Location	Treatment	Follow up
No adjuvant radiotherapy					
1	36	22	Femur	Plate fixation	No re-operation
2	12	51	Tibia	Amputation	No re-operation
Adjuvant radiotherapy					
3	224	63	Distal femur	Intramedullary nail	LISS-plate (insufficient stabilization)
4	95	65	Femur	Intramedullary nail	No re-operation
5	237	68	Femur	Plate fixation	New DCS plate after taking out LISS plate due to pseudoathrosis and breaking plate
6	67	50	Femur	Intramedullary nail	- Intramedullary fixation (broken nail) - Intramedullary fixation (broken nail) - Resection prox. femur and reconstruction with a prosthesis (broken nail)
7	5	64	Femur	Intramedullary nail	Additional screws (broken nail)
8	5	72	Distal femur	Cast	Intramedullary fixation
9	6	72	Femur	Intramedullary nail	No re-operation
10	28	77	Femur	Intramedullary nail	No re-operation
11	28	47	Femur	Intramedullary nail	No re-operation
12	7	65	Tibial plateau	No operation	No operation

Abbreviations: P = patient, TAF = treatment associated fracture, DFN = distal femural nail, LISS = less invasive stabilization system, n.a. = not applicable, NED = no evidence of disease, DOD = death of disease, AWD = Alive with disease

One patient (nr 2 in Table 3) with a tibia fracture had a concurrent non healing post radiation wound which necessitated an amputation. Only one patient out of the eleven patients undergoing limb salvage treatment reached consolidation of the bone after one year. In the follow up, four patients needed re-operation due to insufficient stabilization or broken intramedullary nails. One patient had three broken nails and received eventually a reconstruction with a tumor endoprosthesis (Figure 2). In one patient a conservative treatment with a cast was unsuccessful and eventually intramedullary nailing was performed. To evaluate the mobility after treatment we reviewed the patient charts. Most patients had impaired mobility, and needed support from crutches. Three patients have reasonable mobility without support. One patient has moderate mobility due to pseudoarthrosis as consequence of the internal fixation, but refused tumor prosthesis.

Union	Mobility	Overall survival after TAF (months)	Status
Yes, delayed	Normal	195	NED
n.a.	n.a.	10	DOD
No	> 1h walking without pain, normal function	8	NED
No	Max 10m, due to pain (athrosis)	126	NED
No	Mobile with walker	56	NED
No No	No mobility problems due to prosthesis, some functional limitations due to resection of muscles	110	NED
n.a.			
No	Max 50m with crutches	13	DOD
No	Mobile with crutches	19	DOD
No	n.a. (early death)	1	DOD
No	Mobile with crutches	10	NED
No	Mobile with crutches	24	AWD
No	Mobile with crutches	16	AWD

The median survival after TAF was 18 (1-195) months, with four patients dying due to lung metastases within 1.5 years. Of the remaining eight patients, six are free of disease and two are alive with metastasis.

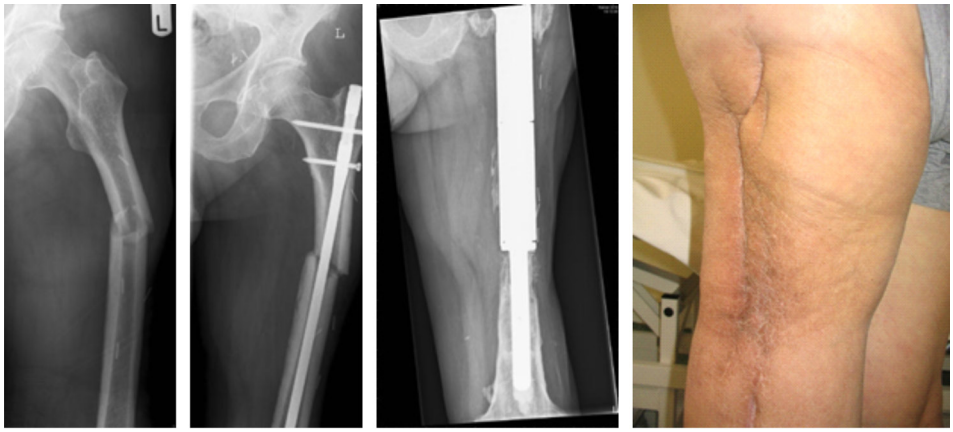
Review of literature

We performed a review of the literature and searched for studies about treatment associated fractures after surgery and radiotherapy for soft tissue sarcomas (Table 4). [6, 8-10, 13, 23, 24] None of these studies included ILP. The incidence of TAF varied from 1.2 – 9%. Two studies performed multivariate analysis and reported a high radiation dose (≥ 60 Gy), periosteal stripping, gender and age (> 55 years) as independent prognostic factors. All studies reported a low percentage of <50% (delayed) bone union.

Table 4. Review of literature: incidence, treatment and outcome			
Study	**Time to fracture (years)**	**Incidence of TAF (%)**	**Univariate: Risk factors**
Lin et al. 1998* [9]	2 (mean)	9/205 (4.4)	Periosteal stripping Tumor location (anterior) Gender (Female) Chemotherapy Age (≥50years) Radiation type (external)
Helmstedter et al. 2001 [13]	3.4 (mean)	20/285 (7)	Periosteal stripping Tumor location (anterior)
Holt et al. 2005** [8]	3.4 (median)	27/364 (7.4)	High dose (≥60 Gy) Gender (female) Age (> 55 years)
Cannon et al. 2006** [6]	5.2 (median)	5/412 (1.2)	Periosteal stripping Femur circumference in RT field (100%)
Kim et al. 2010 [23]	3.5 (mean)	39/1045 (3.7)	-
Blaes et al. 2010* [10]	13 (median)	8/89 (9)	Periosteal stripping Femur circumference in RT field (100%) Tumor location (anterior)
Bishop et al. 2016* [24]	40 (median)	12/596 (2)	Periosteal stripping Femur circumference in RT field (100%) Perioperative bone exposure Perioperative chemotherapy
Seinen et al. 2017 *Current series*	29 (median)	12/101 (12)	Periosteal stripping Age (>65 years) Tumor size (>10cm)

*Tumor located at femur, **Tumor located at lower extremity
Abbreviations: TAF = treatment associated fracture, RT = radiotherapy, IM – intra medullar, ORIF = open reduction and internal fixation

Multivariate: Risk factors	Treatment	Outcome
Periosteal stripping	7 unknown 1 primary endoprosthetic replacement 1 primary amputation	3 delayed union 4 non union
-	10 nails (IM, other) 1 prosthesis 7 casts 2 immobilization	4 delayed union 9 non union 5 union
High dose (≥60 Gy) Gender (female) Age (> 55 years)	-	-
-	-	-
-	30 ORIF 6 prosthetic replacement	19 non union 11 union
-	-	3 delayed union 2 non union 3 union
-	-	-
Periosteal stripping Tumor size (>10cm)	2 plate fixation 7 Intramedullary nail 1 amputation 2 conservative	10 non union 1 delayed union (1 amputation)



A B C D

Figure 2. Patient with a TAF of the thigh (nr 5 of Table 3). Femoral fracture (A), Intramedullary nailing (B), Tumor prosthesis (C), Follow up result (D)

Discussion

The extensive combined modality treatment for locally advanced soft tissue sarcoma patients has provided an alternative for amputation, with 80-86% long term limb salvage with good functional outcome and overall survival.[25] The local recurrence rate in the current study population undergoing limb salvage surgery (n=101) was only 11%, in spite of large tumor sizes. The distant metastases rate was 46%. The incidence of metastasis in patients treated for locally advanced STS is 36 – 43% [26, 27, 28] and most of these patients eventually die due to their disease. Nevertheless, this extensive treatment can cause severe long term morbidity, e.g. TAF, which results in impaired functional outcome.

A unique series of TAF is described after ILP, surgery, periosteal stripping and/or radiotherapy, with an overall risk of TAF at ten years of 15%. The incidence of TAF was high (12%). When only patients with tumors of the thigh were considered, the incidence was even as high as 22%. But the highest incidence was found in patients with tumors located at the thigh and knee who underwent both periosteal stripping and radiotherapy (>50%). Compared with previous reported incidences of 1.2 – 9% [6, 8-10, 13, 23, 24] of studies analyzing patients undergoing only surgery and radiotherapy, the incidence of a pathological fracture is substantially higher after multimodality treatment including ILP. Which is at least partially ex-

plained by the treatment indication of ILP for large tumors, precipitating extensive resection of muscles, high risk of periosteal stripping and larger radiation fields. In addition, TNF alpha and Melphalan have effect on osteoclast activity, thereby possibly contributing to the higher risk of TAF. Melphalan modifies the bone microenvironment by stimulating the formation of osteoclasts. [29] TNF alpha is a cytokine involved in the regulation of osteoclast activity, promoting bone resorption via a primary effect on osteoblasts. [30]

Moreover, patients undergoing multimodality treatment with ILP seem to develop TAF in a shorter follow up time (median 2.7 years) compared with patients not undergoing ILP (mean 2 – 3.5 years, median 3.4 –13 years). [6, 8-10, 13, 23, 24] Another large study analyzing outcome after ILP did not report TAF's, which could be due to a shorter follow up (29 vs 64 months) and other primary end points of the study. [27]

In accordance with previously published studies we found periosteal stripping and age ≥ 65 years as predictive factors of TAF. [6, 8-10, 13] The amount of stripping could not be measured quantitatively. The significant association between size and fracture could implicate that the amount of stripping may have been therefore, roughly proportional to the size of the tumor.

Tumor size ≥ 10 cm and periosteal stripping were the only independent significant predictive factors in multivariate analysis in this study, of which tumor size has previously not been reported as predictive factor. This is not surprising since the patients in this study were undergoing ILP due to their irresectable nature, which is mostly due to their large tumor size. Two reasons could underlie the association between size and fracture risk, first of all, the radiation field is based on the tumor size and resection area, and secondly, a large tumor is more likely to have close adherence to the bone which necessitate periosteal stripping. Other factors such as tumor location (anterior), female gender and femur circumference in RT field have previously been suggested as negative predictive factors for TAF. [6, 8-10, 13, 23, 24] Female gender has been related to increased risk fracture due to concurrent diminished bone mineral density after menopause. In this study the age of the women with fractures was relative low (median 57 years) compared to men (median 72 years), which could explain why no difference for gender was found.

In this study, radiotherapy was not a significant predictive factor at ten years for fracture. Separate analysis were performed regarding; pre- vs postoperative RT, booster (70 Gy) vs no booster (60 Gy) and tumor location, however this did not affect outcome (data not shown). However, there is epidemiological evidence that links radiation to pathological fractures. [6-10, 13] Also, there are histological observations of decreased osteocyte number, suppressed osteoblastic activity, and diminished vascularity in tissue of patients who underwent radiotherapy. [11, 12] Moreover, irradiated bone shows diminished angiogenic response to injury due to abnormal vascularity. [11, 12] A possible explanation is that two patients developed TAF's without radiotherapy, comprising 17% of the total number of patients with TAF's.

Most likely, it is the combination of several factors that induce vulnerability of the bone. Diminished muscle mass, which results from surgical excision also plays a role by increasing and changing the loading forces on bone and exacerbate fatigue damage, which was the likely mechanism behind the fracture of one patient in this study who did not receive radiotherapy.

Most of the factors that increase the risk of TAF are impossible to eliminate. But new developments of radiation techniques, e.g. intensity-modulated radiation therapy (IMRT) and proton radiation therapy, might achieve minimizing the dose to the surrounding normal soft tissue while maintaining adequate coverage of the target volume [31], thereby lowering the total dose to the bone. In addition, new treatment schedules with pre-operative radiotherapy, which allows smaller radiation fields and lower doses, could also lower the risk for TAF. The long term results of these treatments have to be awaited.

Moreover, sarcoma specialists now rise the question if radiotherapy should have a standard role in the multimodality setting, since Deroose et al have shown that good response to ILP (>50% tumor necrosis) followed by R0 resection have low risk of recurrence and radiotherapy does not add further benefit. [32,33]

Continuing in the perspective of pre-operative RT, direct reconstruction with plastic surgery could reduce late radiation effects, such as fibrosis. This procedure is of major interest in cases of exposed functional structures, such as tendons or

joints where fibrosis and edema can compromise functional restrictions, thereby changing weight load and adding to a higher risk fracture. [34, 35]

One of the few preventive measures for osteoradionecrosis is hyperbaric oxygen therapy, of which the positive effect has mainly been analyzed at the location of the jaw. [36] The basic principle of this technique is that it induces neovascularization and reduces fibrosis in radiated hypoxic tissues. Also part of the patients benefit of this technique in case of soft tissue wound healing problems. If this treatment could also help to induce union for TAF after multimodality treatment in soft tissue sarcomas, is not yet analyzed.

The diagnosis of TAF can sometimes be made on plain radiographs, however additional imaging with magnetic resonance imaging can be helpful to detect early stress fracture or even a possible recurrent disease. [37,38] The additional value of a biopsy is arguable because of the high probability of osteonecrosis and the low diagnostic efficacy. [16]

Treatment of patients with TAF after extensive therapy with ILP, delayed surgery – especially including periosteal stripping – and RT is challenging. Given the high rate of non union, generally > 50% [9, 10, 13, 23], and the often long time before consolidation is reached, surgical treatment is indicated in the majority of cases. Yet, these patients are highly sensitive for infection and wound healing problems. [10, 21, 28] Therefore, fractures of the long bones should preferably be treated with minimal surgery like intramedullary (IM) nailing. It is important for the treating physician to realize that this type of fracture is not a normal fracture. The tendency to heal is extremely low and repetitive nailing in case of refracture or non union is contraindicated. The fixation should not be removed at a later date because the likelyhood of refracture is high. The advantages of IM nailing is a small incision, and a long nail can support the total area of osteonecrosis. The disadvantage is that TAF's have a high risk of non – or delayed – union, and the IM nail has to bear the load forever. [39] There is heavily impaired bone healing and one cannot rely on normal fracture healing concepts. Indeed, three patients in this study needed revision surgery after IM nailing due to broken nails or insufficient stabilization. To enhance rapid union of bone, hyperthrophy of the bone and less resorption of cortical bone, a vascularized bone graft is sometimes used [40], however, this does imply a larger incision with an increased risk of infection

and wound healing problems. The quality of the host vessels can be impaired due to ILP, RT and progressed age. Therefore, we would not recommend to use supplemental bone grafting in case of union failure after IM nailing. An alternative is plate fixation, but this involves a wider incision in an irradiated area with poor healing properties and a higher risk of fracture outside the plate.

Not much is known about the difference in outcome between prosthetic replacement and less invasive surgery. A retrospective study of Kim et al. analyzed the difference in outcome for patients undergoing open reduction and internal fixation (ORIF) and prosthetic replacement. [23] For the ORIF technique they used both plates and IM nailing. They found that patients undergoing ORIF had significantly more complications and needed more revision surgery. If this was mainly true for the patients undergoing plate fixation or IM nailing is not clear from the article. Since the infection rate is generally high and prosthetic replacement involves an extensive challenging surgery due to a fibrotic surgical area after previous treatment, we recommend to save prosthetic replacement for those long survivors that require revision surgery due to insufficient stabilization, broken material or in case of painful non union. The exposure should preferably be done via a different approach leaving the radiated skin intact.

In this series, only one patient with TAF underwent amputation, the other patients underwent in most cases invasive treatment with plate fixation or intramedullary nailing. Resulting in some cases in reasonable functional outcome and in other cases in impaired functional outcome with the need of walking aids. Nevertheless, these patients did not wish for amputation and prosthesis.

Conclusion

Over one out of ten patients treated with ILP, surgery and radiotherapy for primarily irresectable soft tissue sarcomas of the limb developed a TAF. Patients with tumors located at the thigh or knee, undergoing both radiotherapy and periosteal stripping, have the highest risk, more than half developed a TAF. TAF is a pathological fracture with a union rate as low as 8%. Treatment of TAF's is challenging and should be performed in dedicated sarcoma centers.

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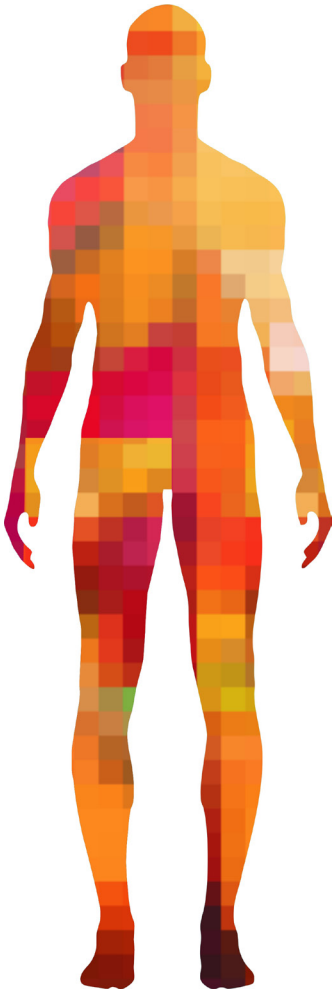
PART IV

Angiosarcoma



Chapter 8

Angiosarcoma

Angiosarcoma

The term angiosarcoma applies to a range of malignant endothelial vascular neoplasms, mimicking the morphologic and functional features of normal endothelium, which can affect a variety of sites. Soft tissue angiosarcoma consists for the majority out of cutaneous tumors, and less than one quarter present as deep soft tissue tumor. [1] Angiosarcomas usually occur in adulthood, with a peak incidence in the seventh decade. The tumor is very uncommon and has a low prevalence worldwide. Several conditions are associated with the development of angiosarcomas, including neurofibromatosis (NF1) [2,3], adjacent to synthetic vascular grafts [4] and following radiation therapy.

Among angiosarcomas, the location at the breast forms a special subgroup. Two main groups are described: primary angiosarcomas and secondary angiosarcomas of the breast. Primary angiosarcomas account for less than 1% of all breast malignancies [5] and their peak incidence is in the third and fourth decade of life. Secondary angiosarcomas are further defined into two subgroups: angiosarcomas following longstanding lymphedema, known as Stewart Treves syndrome, and angiosarcomas following radiation therapy. Stewart Treves syndrome can develop in the lymph edematous arm as a consequence of breast cancer treatment with axillary nodal dissection and was firstly described by Stewart and Treves in 1948. [6] Since the treatment for early stage breast cancer has changed to a more conservative approach with lumpectomy and adjuvant radiation, less cases of Stewart Treves have been observed and more angiosarcomas in the radiated field. Patients treated for breast cancer with radiation have a five fold higher risk for angiosarcoma than patients not receiving radiation. [7] The clinical presentation differs between these two subgroups; angiosarcomas following radiation develop earlier and have shorter symptom duration than the Stewart Treves tumors. [8] Radiation associated angiosarcomas of the breast will be further described in the next chapter.

A systematic review published in 2012, reported all literature about radiation associated sarcoma since 1970. [9] Focusing on the radiation associated sarcoma of the breast, the incidence is particularly low considering the long time span of the studies. The radiation dose to the breast as part of the conservative breast cancer treatment was median 53Gy. Previous studies have shown a dose related

risk of radiation induced sarcomas, starting upon as much as 14Gy. [10,11] The age at the time of diagnosis of radiation associated sarcoma was median 68 years, and the latency period between the treatment of breast cancer and the diagnosis of radiation induced sarcoma was median 9 years. The relative long latency period at which radiation associated sarcoma of the breast develop implies a long follow up in the hospital or at least a good self examination by the patient.

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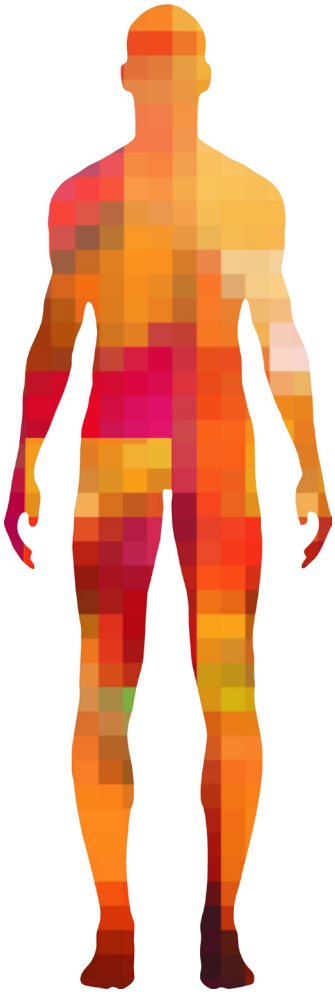

Chapter 9

Radiation-Associated Angiosarcoma After Breast Cancer:

High Recurrence Rate and Poor Survival

Despite Surgical Treatment with R0 Resection

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Abstract

Objective. Secondary angiosarcoma of the breast is a rare but severe long-term complication of breast cancer treated with breast-conserving surgery and radiotherapy. We characterized a population-based cohort of patients with secondary angiosarcomas from two tertiary hospitals to investigate this complication with respect to surgical treatment and outcome.

Methods. We identified 35 patients with a history of radiation for breast cancer that developed angiosarcoma in the irradiated field from 1990 to 2009. Of these, 31 underwent surgery and were included for analysis.

Results. Angiosarcoma developed after median 7 years (range 3–25 years). R0 resection was obtained in 23 of 31 patients after primary treatment. Local recurrence developed in 19 patients after median 6 months (range 1–89 months). Regional and distant metastases occurred in 13 patients after median 17 months (range 2–50 months); nine which also had local recurrence. Patients whose local recurrence could be operated on had a better survival after treatment than those who were not considered for surgical treatment, median 34 months (range 6–84 months) compared with 6 months (range 5–24 months). The median disease-free survival and disease-specific survival was 16 and 37 months, respectively.

Conclusions. Despite R0 resection, two-thirds of the patients developed a local recurrence. Survival among those with local recurrence was better if the patient could be treated with surgery. Overall, the prognosis was dismal and median DSS was just over 3 years.

Introduction

Breast-conserving treatment (BCT) with radiotherapy has replaced mastectomy as the standard care for early-stage breast cancer in the last few decades. [1] Radiotherapy is usually administered at a maximum of 50 Gy to the operated area, in some cases with an extra booster of 10–20 Gy to the tumor bed. The incidence of breast cancer is increasing; currently, it affects one in ten women in the western world. Accordingly, more secondary angiosarcomas have been reported, with a cumulative incidence of 0.9 per 1,000 breast cancer cases over 15 years. [2] The development of secondary angiosarcoma has been linked to radiotherapy and lymphedema. [3-5]

Secondary angiosarcomas after BCT have an observed median latency period of ~4–8 years. [6-10] Because of their rarity and seemingly harmless presentation, frequently comprising painless and bruise like skin lesions, both patients and doctors often neglect the initial symptoms and diagnosis is delayed. Patients often have localized, but multifocally growing, disease that is confined to the breast at diagnosis. Surgery is the mainstay of treatment and is usually performed with local resection or mastectomy. The risk of local recurrence and metastasis is high. [9] There have been several studies of (neo-) adjuvant chemotherapy, but the effects remain unclear. [9,11,12]

The poor outcome of secondary angiosarcoma is well known, albeit mainly through numerous case reports. [8,13,14] Few have looked at the surgical treatment and outcome. [15] We have performed a 2-center retrospective study to characterize the disease with respect to treatment and outcome in a population-based cohort undergoing surgery with curative intent.

Methods

Cohort

We identified all female patients with histopathologically diagnosed angiosarcoma of the breast in the northern Dutch Health Care Region (1.8 million inhabitants) and the southern Swedish Health Care Region (1.7 million inhabitants). The northern Dutch part of the nationwide network and registry of histopathology

and cytopathology in the Netherlands (PALGA) (since 1971) and the southern Swedish part of the national Swedish Cancer Registry (since 1958), and, in addition, the pathology registry (since 1960) were used to identify all cases within the populations. Patients with breast cancer diagnosed prior to angiosarcoma were selected (n = 50). Prerequisites used for this study were those proposed by Cahan et al.[16] and modified by Arlen et al. [17]: (1) a sarcoma arising within the field of previous radiotherapy, (2) differing histology between the secondary sarcoma and primary tumor, and (3) at least a 3-year latency period between radiation therapy and development of the sarcoma. Under these criteria, 35 cases were identified from 1990 to 2009. Surgery with curative intent was performed on 31 patients. Data regarding the radiotherapy dose, type of surgery for the angiosarcoma, local recurrence, metastatic disease, and death were obtained from hospital and primary care records.

Patient Characteristics

The median age of patients at the time of breast cancer diagnosis was 59 years (range 42–77 years). As part of breast cancer therapy, radiotherapy was administered at a median dose of 50 Gy (range 45–70 Gy). Nearly one-third of the patients received an extra radiation boost to the tumor bed, resulting in a total dose of 66–70 Gy.

Outcome Measures

The endpoints of this study were disease-free survival (DFS), disease-specific survival (DSS), time to local recurrence, and time to distant metastasis. DFS was defined as the time from start of treatment to local recurrence, distant metastasis, or last follow-up. DSS was defined as time from diagnosis of secondary angiosarcoma to death due to angiosarcoma or last follow-up. Time to local recurrence was defined as the time from treatment to radiological or pathological confirmation of local recurrence. Time to distant metastasis was defined as the time from treatment of the secondary angiosarcoma to radiological or pathological confirmation of metastasis. In the text, surgical margins were defined as R1 (microscopically intralesional) or R0 (microscopically free margin).The data are presented as median and range, unless stated otherwise.

Statistical Analysis

The DFS and DSS were calculated according to the Kaplan–Meier method. All analyses were performed using SPSS software version 18 (released September 9, 2010; SPSS, Chicago, IL).

Results

Angiosarcoma Characteristics

In 13 of 35 patients, angiosarcoma presented as a blue or red discoloration of the skin; in 14 patients, it started with a tumor, and in eight patients, both discoloration and tumor were present. The tumors had a median size of 4 cm (range 1–15 cm), with a multifocal appearance. The median time from the administration of radiotherapy to the development of angiosarcoma was 7 years (range 3–25 years), and the median age of the patients when the angiosarcoma was diagnosed was 67 years (range 47–89 years). Of the 35 patients, 31 underwent surgery with curative intent and were included in the survival analysis. The four patients who did not undergo surgery had metastatic or locally advanced disease (Fig. 1).

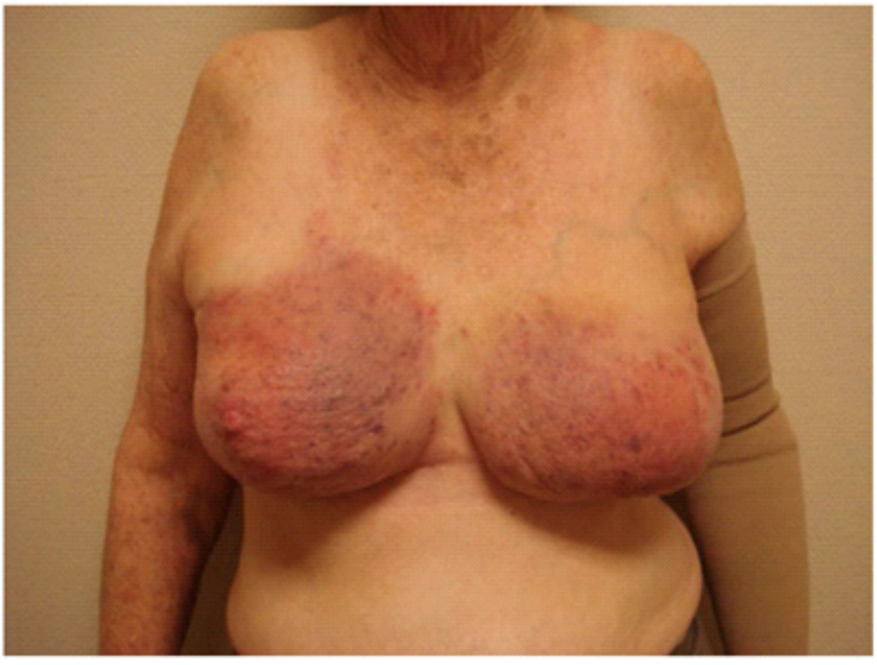

Figure 1. Patient with extensive angiosarcoma in both breasts

Primary Treatment

The main surgical approaches used for resection of the primary tumor of the secondary angiosarcoma were local excision of the tumor (*n* = 7) (either due to previous mastectomy as part of breast cancer treatment or the local excision was performed outside our tertiary hospitals) and mastectomy (*n* = 24) (Table 1). In all cases operated on at the two tertiary centers, the aim was a minimum macroscopic margin of 2 cm. An R0 resection was achieved in 23 patients after primary treatment, seven patients were operated on twice for primary tumor. A total of 16 cases required reconstruction at treatment for the primary tumor, and the choice of reconstruction was tailored to the size of the defect. In 13 cases a split-thickness skin graft was used, in 1 case reconstruction with a pedicled flap of the latissimus dorsi and in 2 cases a combination of both techniques were used for reconstruction.

In addition to surgical treatment for the primary tumor, one patient received neo-adjuvant chemotherapy (adriamycin 6 cycles) and one patient received adjuvant radiotherapy (50.4 Gy) after intralesional surgery.

In our series, mastectomy achieved R0 margins at higher rates than local resection (14 of 24 compared with 2 of 7). In addition, in three patients excision of all irradiated tissue was performed based on the radiotherapy field film, achieving R0 resection in 2 cases.

Local Recurrence

After a median of 6 months (range 1–89 months), 19 patients developed a local recurrence. Of these, 14 had an initial R0 resection. In patients with local recurrence, 11 patients underwent surgery, which resulted in R0 resection in ten patients. Adjuvant radiotherapy was administered to one patient and adjuvant chemotherapy to one. Of the eight patients not undergoing surgery, one received radiotherapy and one both radiotherapy and chemotherapy (Table 2). The reason for not performing surgery in five of eight patients was concurrent metastasis, of whom four patients received chemotherapy. In the remaining three cases, extensive local disease was the reason not to perform surgery in 2 cases and in 1 case the reason was unknown. Patients who underwent surgery for local recurrence survived a median of 34 months (range 6–84 months) after surgery, compared with 6 months (5–24 months) for those who did not.

Table 1. Treatment and outcome for primary angiosarcoma disease

P	Primary operation	Reconstruction	Margins	(neo-)adjuvant treatment	Local recurrence	Metastasis
1	Mastectomy	STSG	R0	No	Yes	No
2	Mastectomy	STSG	R0[a]	No	Yes	No
3	Mastectomy	STSG	R0	No	No	Yes
4	Mastectomy	No	R0	No	No	No
5	Mastectomy	No	R0	No	No	No
6	Mastectomy	STSG	R0[a]	No	Yes	Yes
7	Mastectomy	No	R0	No	No	Yes
8	Mastectomy	STSG	R0	No	Yes	No
9	Mastectomy	No	R0	No	Yes	No
10	Local excision	No	R0[a]	No	Yes	No
11	Mastectomy	No	R0	No	No	No
12	Mastectomy	STSG	R0	No	Yes	Yes
13	Mastectomy	No	R0[a]	Radiotherapy	Yes	No
14	Local excision	STSG	R0	No	No	No
15	Mastectomy	Muscle flap	R2	Chemotherapy	Yes	Yes
16	Local excision	No	R0[a]	No	No	No
17	Mastectomy	STSG	R2	No	Yes	Yes
18	Mastectomy	No	R2	No	Yes	No
19	Local excision	STSG	R2	No	No	Yes
20	Local excision	No	R0	No	Yes	No
21	Mastectomy	STSG	R1	No	Yes	No
22	Mastectomy	No	R0	No	Yes	Yes
23	Mastectomy	No	R2	No	Yes	Yes
24	Mastectomy	No	R0	No	Yes	No
25	Mastectomy	STSG	R0	No	No	Yes
26	Mastectomy	STSG	R2	No	Yes	Yes
27	Mastectomy	STSG	R0	No	Yes	Yes
28	Mastectomy	No	R0	No	No	No
29	Mastectomy	Muscle flap + STSG	R0[a]	No	No	No
30	Local excision	No	R2	No	Yes	Yes
31	Local excision	Muscle flap + STSG	R0[a]	No	No	No

STSG : split thickness skin graft
[a]After two surgeries for the primary tumor

Table 2. Treatment and outcome for local recurrence and metastasis			
N	**Initial margin primary tumor**	**Time from treatment to LR (months)**	**Treatment for LR**
Local recurrence			
1	R0	5	Local excision
2	R0	2	Local excision
3	R0	89	Local excision
4	R0	40	Local excision
5	R0	18	Local excision
6	R0	5	Local excision
7	R0	4	Mastectomy
8	R0	22	Resection based on RT film; ifosfamid, doxorubicin (6 cycles)
9	R0	1	None
10	R0	86	None
Metastasis			
1	R0	-	-
2	R0	-	-
3	R0	-	-
4	R0	-	-
Local recurrence + metastasis			
1	R0	6	-
2	R0	8	Local excision
3	R1	2	None
4	R1	12	None
5	R0	2	Local excision + RT 30Gy
6	R1	2	-
7	R1	2	RT, dose unknown
8	R0	18	None
9	R0	12	Local excision

LR local recurrence, RT radiotherapy
[a]Recurrence: first appearing (local recurrence or distant metastasis)

	Time from treatment to metastasis (months)	Treatment for metastasis	Survival after recurrence[a] (months)
	-	-	14
	-	-	34
	-	-	63
	-	-	20
	-	-	49
	-	-	6
	-	-	57
	-	-	84
	-	-	1
	-	-	2
	17 (vertebrae)	RT 20Gy	20
	2 (lung)	RT 41Gy	16
	24 (axillary)	Resection	29
	50 (cerebral, abdominal)	None	3
	23 (lung)	None	18
	18 (vertebrae)	RT 8Gy	16
	2 (contralateral breast)	Adriamycin (6 cycles); paclitaxel, bevacizumab (5cycles), cyclofosfamid	24
	8 axillary	Resection, RT (dose unknown); adriamycin (5 cycles); fluorouracil, farmorubicin, cyclofosfamid (4 cycles)	14
	6 (thoracic wall into lungs)	Cisplatin	9
	2 (contralateral breast, sacrum)	None	1
	2 (cerebral, abdominal)	Cisplatin	5
	17 (axillary, lung)	Resection + RT 45Gy; doxorubicin + isofosfamid (1 cycle); gemzar, taxotere	8
	41 (axillary)	Resection + RT 50Gy; doxorubicin + ifosfamid	55

Metastatic Disease

There were nine patients who developed distant metastatic disease, and four patients developed regional metastatic disease after a median of 17 months (range 2–50 months). Of these patients nine also had a local recurrence. In the four patients with regional metastatic disease, resection of metastasis to lymph nodes was performed, which led to 1 case of R0 resection, 2 cases of R1 resection, and 1 case with unknown margins. Patients with regional metastasis who underwent surgery survived a median of 20 months (range 8–29 months) after surgery, compared with 5 months (range 1–24 months) for those with distant metastasis who did not undergo surgery. Of the 13 patients with metastases, six patients received chemotherapy and six patients underwent radiotherapy (Table 2).

Survival

With a median follow-up of 27 months (range 1–151 months), 21 of 31 patients died; 17 of the deaths were due to angiosarcoma, three due to other diseases, and one patient died of unknown cause. There were ten patients still alive at last follow-up. Of these patients, nine had no evidence of disease after a median follow-up of 53 months (range 10–108 months). The remaining patient had local disease after 7 years. Of the patients with metastasis, one patient was still alive 2.5 years after surgery for regional metastasis. The three patients who underwent excision of all irradiated tissue, based on the radiation field films, with R0 margins were alive after 2, 2.5, and 9 years with no evidence of disease. For the total population, the median DFS and DSS was 16 and 37 months, respectively (Fig. 2a, b).

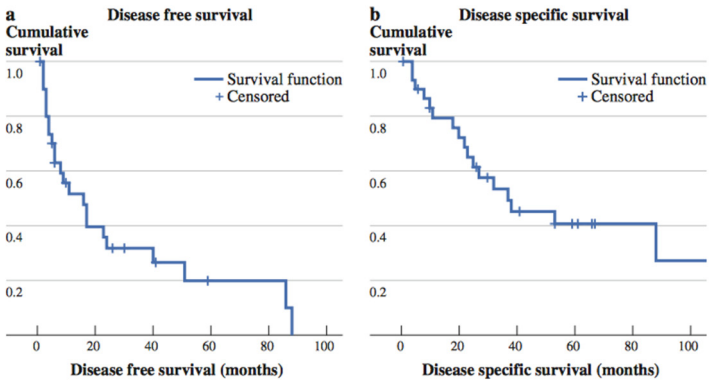

Figure 2. a DFS in months, b DSS in months. a There were patients alive without disease, these are among the censored cases

Discussion

Although secondary angiosarcomas of the breast have an approximate incidence of only 0.9 per 1,000 breast cancer cases [2], they are important because this disease has a very poor prognosis and is related to a previous medical treatment. In this study, two-thirds of the patients with secondary angiosarcoma presented with the typical blue/red discoloration of the skin, sometimes in combination with palpable tumor. The lesions can be single or multiple nodules, and papules or vesicles. One-third of the patients presented solely with a tumor; therefore, suspicion of secondary angiosarcoma should not rest only upon discoloration of the skin. In any patients with discoloration that does not disappear or tumor development within the radiation field, a needle or open biopsy should be performed. Mammography and/or MRI play only a limited role in diagnostics, but MRI may be slightly better at detecting an angiosarcoma. [18,19] Since the first case of secondary angiosarcoma of the breast was described in 1987, the prognosis has remained poor, with a median survival of 1–3 years. [5] In our population-based study, we found similar median survivals of 16 and 37 months for DFS and DSS, respectively. Only two of our 35 identified patients presented with metastatic angiosarcoma, both died of the disease within 6 months.

Compared with previously reported population-based studies (Fodor et al. 2006, *n* = 8; Hodgson et al. 2007, *n* = 31; and Marchal et al. 1999, *n* = 9) [6,19,20], our cohort had similar median ages at the time of diagnosis of breast cancer (mean 60 years) and secondary angiosarcoma (mean 68 years). To the best of our knowledge, this is the equal largest study (*n* = 31) published for secondary angiosarcoma developing in the irradiated field, but the largest study focusing on surgical treatment and outcome.

Most secondary angiosarcomas present as localized disease without metastasis. Nevertheless, they are difficult to control and often recur locally. [9] In our series, mastectomy achieved R0 margins at higher rates than local resection. In addition, three patients had mastectomy with resection of all irradiated tissue as primary treatment, R0 margins achieved in 2 cases and are alive after 2–9 years without evidence of disease.

Of the 31 patients who underwent surgery, the primary treatment resulted in R0 resections in 23 patients. Despite this, nearly two-thirds of these patients developed a local recurrence. We believe this to be due to the multifocal growth of angiosarcoma and tumor tissue left behind, even if the surgical margins are considered free. In this study, 11 of 19 patients with a local recurrence were considered eligible for surgery. The five patients with metastasis and three patients with locally extensive disease were not considered suitable for surgical treatment. The patients selected for surgery for local recurrence survived longer than those who did not. This difference we believe is due to different stages of tumor, and hence surgery has not necessarily made the difference. However, we conclude that local recurrence per se should not disqualify from aiming at surgery with curative intent.

In addition, four patients with lymph node metastases underwent surgery. Of these, two patients were without evidence of disease at the last follow-up, more than 2 years after surgery. The other two patients died of tumor after 8 and 14 months because of their angiosarcoma.

In other types of soft tissue sarcoma, adjuvant radiotherapy is frequently applied to improve local control. However, since secondary angiosarcomas develop within a field of radiation, usually the surrounding tissue has already received the maximum dose of radiation. In spite of this, one patient was treated with radiotherapy and initially responded well to therapy. After a few months, however, the disease progressed rapidly. A small single-center study (n = 14) that looked at hyperfractionated and accelerated radiotherapy (HART), with or without surgical resection, found a 64 % 5-year progression-free survival. [9] Other studies reported a good response to (neo-) adjuvant treatment with paclitaxel in some patients. [12,21,22] Interpretation of these results is hampered by the limited number of cases and the heterogeneity of the study populations. Therapies targeting angiogenesis through the vascular endothelial growth factor (VEGF) pathway and VEGF receptors (VEGFR) (e.g., sunitinib, sorafenib, and bevacizumab) have been promising in some patients with angiosarcoma; however, they clearly do not benefit a majority of patients. [23]

Another important field of study concerns the dose, extent, and duration of radiotherapy as part of breast-conserving therapy. Studies comparing hypofractionated and conventional fractionation of radiotherapy for breast cancer have been conducted, as have studies investigating radiotherapy for a quadrant of the breast instead of the entire breast. [24,30] If changes in the dose, extent, and duration of radiotherapy are implemented, the risk of developing secondary angiosarcoma will have to be monitored closely.

In conclusion, the only chance of curative treatment for secondary angiosarcoma is extensive surgery, preferably with resection of all irradiated tissue performed. The rarity of the disease, its complex behavior, and the need for extensive surgery indicates that these tumors should be managed at a tertiary sarcoma center. Despite free margins, two-thirds of the patients in our study developed a local recurrence. Surgical intervention in a selected group improved survival for patients with local recurrence. However, the median DSS was still only 3 years.

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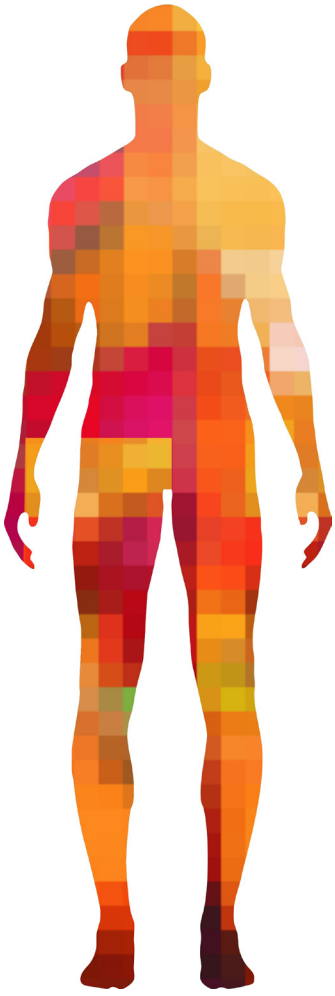
PART V

Desmoid type fibromatosis



Chapter 10

Desmoid type fibromatosis

Desmoid type fibromatosis

Desmoid type fibromatosis (DF) is part of a group of disorders characterized by excessive proliferation of spindle-shaped mesenchymal cells, e.g. Dupuytren's and Peyronie's diseases [1]. Deep DF is even more rare than superficial DF. Its hallmark is infiltrative growth without the potential to metastasize and the inability to dedifferentiate into a high grade malignancy in case of recurrence. Therefore DF is considered to be an intermediate tumor according to the World Health Organization. [1]

Pediatric and adult DF have an equal incidence between genders, but the peak incidence is at 30 years of age and is more common in women. The overall incidence of DF is low and only makes up for 0.03% of all types of cancer. [2] There are several distinctive patient groups in which the prevalence of DF is transcending the prevalence in the normal population; pregnant women, post surgery patients, and patients with Gardner disease (familial colorectal polyposis) or familial adenomatous polyposis (FAP). The latter genetic syndromes known to be autosomal dominantly inherited with mutations located in the adenomatous polyposis coli (APC) gene on chromosome 5q21–22. [3-5] APC in turn helps to regulate the β-catenin, which has a key role in wound healing and fibroproliferative disorders. [6] Patients with FAP have a nearly 100% chance of developing a colorectal malignancy, therefore, most patients are offered a preventive proctocolectomy. As a consequence, more patients survive and the incidence of DF has increased within this group. The prevalence of DF in this group is 7-12%, with a lifetime risk of about 20%. [7] The other associated conditions as pregnancy and trauma suggest that there are also endocrine and physical factors underlying the pathogenesis of DF.

Because DF is a heterogeneous tumor with a variety of locations, it has an unpredictable clinical course. For clinical utility DF is usually classified according to anatomical location - intra-abdominal, abdominal wall and extra abdominal. The clinical presentation is like other soft tissue sarcomas usually with a painless mass that grows insidiously. Sometimes they cause neurological symptoms and, when located at the extremities, they can cause decreased functional mobility. Intra-abdominal fibromatosis is often asymptomatic, but can lead to gastro intestinal bleeding or acute abdomen secondary to bowel perforation.

Differential diagnosis of DF is: scar tissue, proliferative myositis, nodular fasciitis, other types of fibromatosis and other types of soft tissue sarcomas. The preferred imaging is magnetic resonance imaging (MRI), except for intra abdominal DF, in which computomography (CT) scan is more valuable. But final diagnosis is based on histology.

The treatment for DF has evolved over time and an aggressive first approach is now debated. In the beginning of the 21th century imatinib was reported as an active agent against DF. [8] Later also pazopanib [9] and sorafenib [10] have been found active against AF. However, none of these targeted therapies are standardized first line therapy. And ongoing studies are trying to validate earlier findings. [11,12]

Another type of treatment is antihormonal treatment. The rationale behind the use of antihormonal therapy, mainly tamoxifen, is based on observations of the natural history of the disease. Higher incidences of desmoids during and after pregnancy and reports of spontaneous tumor regression after menopause, form the basis for antihormonal therapy. However, although several studies have shown that almost all DF express nuclear estrogen receptor-β, only a small subset of patients respond to antihormonal therapy.

In 2003, a systematic review about the pharmalogical treatment was published (anti estrogen therapy n = 37, other hormonal treatment n = 31, anti inflammatory therapy n = 29, interferon therapy n = 9, chemotherapy n = 148) showing that systemic treatment is affective against DF.[4] The rational behind an endocrine approach is logic regarding the role of cyclooxygenase-2 (COX-2), fibroblast derived growth factor and the receptor for hyaluronan-mediated motility (Rham) in the pathogenesis of DF. [6] Yet, the included studies that were analyzing the effects of non cytotoxic treatment were consisting for a large part out of case reports.

None of the abovementioned systematic or targeted therapy is standard, and as an alternative to invasive treatment with surgery a new approach towards DF has been investigated; a wait-and-see policy. The next chapter reviewed literature about standard surgery, radiotherapy and the new conservative approach.

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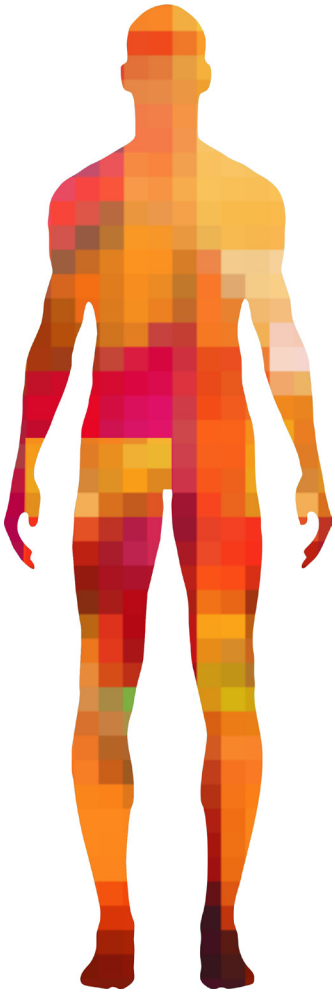

Chapter 11

Four different treatment strategies in desmoid type fibromatosis:

A systematic review

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Abstract

Background. The treatment approach for desmoid type fibromatosis is changing. Although surgery is the mainstay in common practice, recent literature is reporting a more conservative approach. We compared the local control rate for surgery, surgery with radiotherapy, radiotherapy alone and a wait and see policy in a systematic review.

Methods. A comprehensive search of the databases PubMed/Medline, Embase and Cochrane, of the medical literature published in 1999 till March 2017 was performed by two reviewers, including articles about extra abdominal desmoid type fibromatosis without the genetical variants. A total of 671 studies were assessed for eligibility, and 37 studies were included for analysis, representing 2780 patients.

Results. The local control rates for surgery alone, surgery and radiotherapy, radiotherapy alone and observation were 75%, 78%, 85% and 78%, respectively. For patients with recurrent disease observation had a better local control rate than surgery alone (p = 0.001). In the observation group, stabilization of the tumor was seen in median 14 (range 12-35) months. The time to local recurrence in the treatment group was median 17 (range, 11-52) months.

Conclusion. A watchful conservative first line approach with just observation and closely monitoring, by means of physical examination and MRI, appears to be justified in a subgroup of patients without clinical symptoms and no possible health hazards if the tumor would progress.

Introduction

Although desmoid type fibromatosis (DF) is histological classified as a low grade soft tissue sarcoma it can clinically lead to severe morbidity, functional impairment and even death when located at anatomical critical sites. The treatment approach has changed over time: surgery remained the mainstay in the treatment of DF, but other treatment modalities were explored. Due to the infiltrative pattern and the lack of a pseudocapsule, clear margins are difficult to obtain, necessitating repeated operations and causing severe cosmetic and functional morbidity. Moreover, surgery itself can evoke recurrent disease as trauma is a known predictive factor in the development of DF. [1] In the nineties, adjuvant radiotherapy was successfully applied to improve local control. [2] Radiotherapy alone was performed in selected cases, usually in patients with unresectable tumors, leading in some cases to local control or even regression. [3, 4] Systemic treatment has been reported as an effective treatment in some studies, albeit the number of patients in these studies was low and optimal drug doses and treatment duration remain unclear. [5] More recently, a wait-and-see policy has been advocated because DF has the potential to regress spontaneously. [6]

Since DF has a low mortality and usually occurs in young patients, treatment morbidity in the short and long term is an important factor in the treatment decision. Due to the low incidence of DF, studies usually concern small number of patients, therefore we aimed to analyze outcome for different treatment strategies in a systematic review.

Material and Method

A comprehensive computer-aided search of the databases PubMed/Medline, Embase and Cochrane, of medical literature published after 1998, was conducted in March 2017 using the search term in Pubmed/Medline was: '(desmoid[All Fields] OR aggressive fibromatosis[All Fields]) AND surgery[All Fields] AND English[Language] NOT case report[All Fields] Not polyposis[Title Word] NOT pediatric[All Fields]' (in which surgery was replaced by 'radiotherapy' and 'wait and see'). The search term in Embase was: ''desmoid tumor'/exp AND surgery AND [english]/lim AND [1-1-1999]/sd NOT [01-3-2017]/sd NOT 'case report'/exp NOT

polyposis' (in which surgery was replaced by 'radiotherapy' and 'wait and see'). The search term in Cochrane: 'Desmoid'. We augmented our computerised literature search by manually reviewing the reference lists of identified studies and relevant reviews. Two reviewers (JMS/MGN) independently selected studies for possible inclusion in the review by checking titles. Criteria for inclusion were: clinical studies evaluating one of the four treatment strategies in desmoid tumors/aggressive fibromatosis: 1) surgery alone, 2) surgery with adjuvant radiotherapy, 3) radiotherapy alone and 4) wait-and-see policy. Criteria for exclusion were: studies about case reports, reviews and editorials. Furthermore, we excluded all articles that studied solely children, Gardner syndrome or familial polyposis coli as subjects, because paediatric patients have a high recurrence rate and often have a different treatment strategy, and because DF in Gardner syndrome can be considered a different category due to the genetic linkage. The articles related to one anatomic region were also excluded because certain anatomic regions have their own specific biological tumor behaviour [7].

The final decision regarding inclusion was based on the full article. Two reviewers (JMS/MGN) independently assessed the eligibility of the studies. If there was any disagreement between the readers, a consensus was reached by discussion.

In the surgical group, recurrent disease is described as recurrent disease after complete resection. In the radiotherapy and observation group, recurrent disease would be described after complete regression, and progressive disease after partial regression or stabilization of disease.

Statistical methods

The Fisher exact test was used to assess the significance of differences between local control rates of the different treatment modalities. Local control was defined as no recurrence or no progression of disease. The 2-sided p value was used and was considered significant if $p < 0.05$. This data is available in the supplementary table 1. The Fisher exact test is considered appropriate for independent observations; all articles describing the same study populations were excluded.

Since the treatment modalities solely radiotherapy and observation do not include surgical margins, no comparison was made within this subgroup (Supplementary table 1). In addition, no statistical analysis of comparison was made in case the number of patients was very small.

Results

Literature search and data description

Using the search strategy, 671 studies were listed, of which 85 met the inclusion criteria based on the abstract. Finally, after reading the full text, 37 studies were included in the analysis (Fig 1). [1, 6-41]

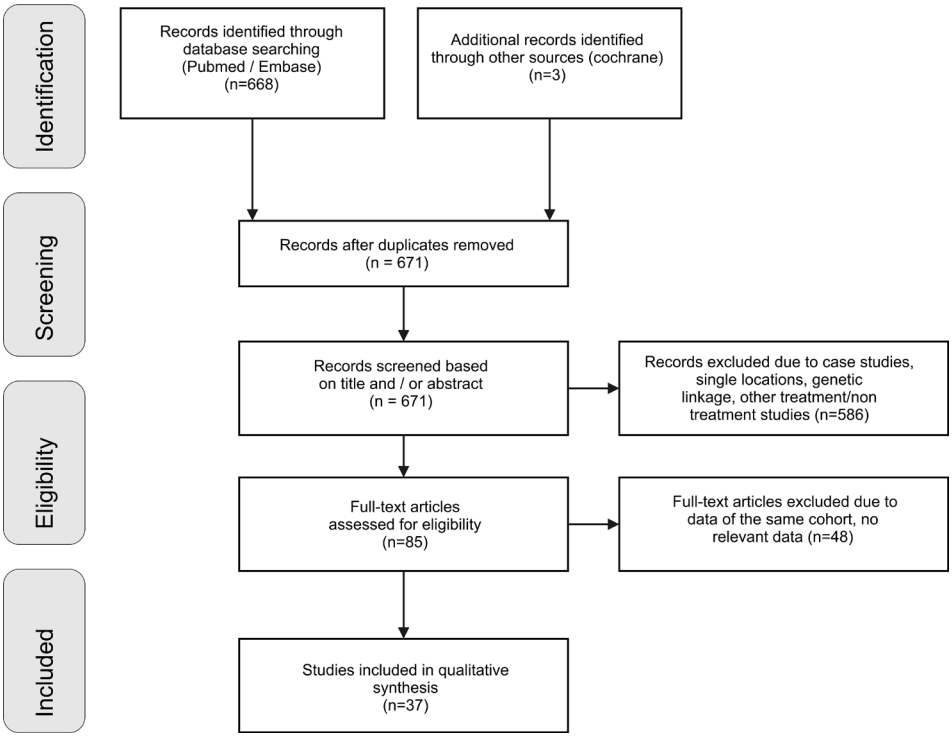


Figure 1. Flow diagram literature search

Table 1. Overview of the number of patients, radiation dose, and follow-up for each article included in the systematic review

Author	primary/ recurrence (%/%)	Tumor location (%)
Bonvalot S[7]	100 (primary)	abd/chest wall (42), LE (23), UE (7), HN (14), trunk (14)
Stoeckle E[8]	65/35	-
El-Haddad[9]	48/52	E (52), trunk (39), HN (9)
Husain Z[10]	-	LE (20), UE (40), buttock (10), Trunk (20), HN (10)
Huang K[11]	75/25	abd wall (50), LE (18), trunk (11), HN (18), UE (3)
Ballo MT[12]	45/55	abd wall (10), HN (10), trunk (44), buttock (5), UE (18), LE (13)
Gronchi A[13]	63/27	abd wall (22), trunk (50), LE (12), UE (8), HN (8)
Duggal A[14]	71/29	UE (34), LE (20), trunk (31), abd wall (3), buttock (12)
Gluck I[15]	76/24	trunk (57), E (13), HN (20), abd/pelvis (10)
Jelinek JA[16]	-	abd (17), E (83)
Park HC[17]	-	E (36), HN (16), trunk (32), buttocks (16)
Lev D[18]	74/26	UE (14), LE (16), abd wall (16), trunk (27), intra abd (14), retroperitoneal (6), HN (7)
Phillips SR[19]	73/27	abd wall (21), HN (4), trunk (42), UE (9), LE (17) buttock (7)
Mankin HJ[20]	-	UE (7), LE (48), trunk (34), abd wall/pelvis (11)
Dalen BP[21]	-	abd wall (24), UE (22), LE (22), trunk (31), HN (1)
Zlotecki RA[22]	42/58	UE (42), LE (35), trunk (7), abd (11), HN (5)
Barbier O[23]	42/58	UE (31), LE (58), buttock (11)
Baumert BG[24]	60/40	
Fiore M[6]	65/35	E (33), trunk (17), HN (4), abd wall (40), intra abd (7)
Merchant NB[25]	100 (primary)	E (49), trunk (23), abd wall (20), HN(8)
Nakayama T[26]	82/18	abd wall (18), UE (9), HN (18), LE (46), trunk (9)
Pajaras B[27]	90/10	abd wall (45), intra abd (15), UE (15), HN (10), LE (10), trunk (5)
Pignatti G[28]	42/58	UE (30), LE (60), trunk (8), other (2)
Schulz-Ertner D[29]	43/57	HN (8), UE (25), LE (29), abd wall (10), intra abd (10), trunk (18)
Sharma V[30]	88/12	E (45), HN (14), Trunk (14), abd (27)
Shido Y[31]	-	trunk (30), UE (13), LE + buttock (57)
Sorensen A[32]	-	abd(30), extra abd (70)
Guney Y[33]	-	UE (29), LE (29), HN (14), buttock (14), trunk (14)
Rudiger HA[34]	59/41	UE (31), LE (43), trunk (26)

Surgery	Surgery + RT	RT	Observation	Radiation dose (range) Gy		Median FU (months)
67	13	-	-	50 (4-60)	S + RT	76
92	7	-	-	50 (20-60)	S + RT	123
6	41	4	3	50.4 (45-60)	S + RT	88
-	10	-	-	50.7 (44-62)	S + RT	48
106	25	-	-	(45-55)	S + RT	102
122	46	21	-	60 55	S + RT RT	113
172	40	-	-	57 (45-65)	S + RT	135
27	8	-	-	50 (10-64)	S + RT	68*
54	28	13	-	56 (50-68) 50 (50-59)	S + RT RT	
19	35	-	-	54	S + RT [a]	38
-	21	3	-	48 (40-59)	S + RT, RT	39*
94	35	9	-	(50-56)	S + RT, RT	69
73	-	2	18	(30-72)	S + RT, RT	63
185	39	-	-	-		31
29	-	1	-	-		-
-	65 [c]		-	54 (50-56)	S + RT, RT	72
-	-	-	26	-		16*
42	68		-	59 (3-74)	S + RT	72
-	-	-	83	-		33
74	31	-	-	(45-65)	S+RT [b]	49
2	-	9	-	-		56
17	2	-	-	50 (50)	S + RT	35
63	17	0	1	(35-66)	S + RT	134*
-	26	2	-	48 (36-60)	RT [b]	46
15	15	4	8	60 (9-70) 50 (40-50)	S + RT RT	-
30	-	-	-	-		89
44	28	-	-	-		96
-	4	3	-	51 (50-62) 50 (40-50)	S + RT RT	16
-	17	17	-	50 (24-60)	S + RT	51*

Table 1. Continued

Author	primary/ recurrence (%/%)	Tumor location (%)
Chew C[35]	36/64	UE (43), LE (40), HN (17)
Kriz[36]	48/52	E (54) trunk (38) abd wall (8)
Zeng[1]	67/33	abd wall (27) intra abd (11) trunk (18) E (14) HN (25) buttock (4)
Prodinger[37]		UE (49) LE (51)
Shin[38]	74/26	trunk/HN (41) E (59)
Sri ram[39]		UE (10) HN (23) trunk (18) buttock (14) LE (35)
Keus[40]	61/39	UE (32) LE (32) HN (2) trunk (23) abd wall (11)
Ergen[41]	20/80	UE (20) LE (45) trunk (20) intra abd (10) HN (5)

RT = Radiotherapy, S = Surgery, FAP = Familial Adenomatous Polyposis FU: Follow-Up
E = extremity, LE = lower extremity, UE = upper extremity, HN = head and neck, abd = abdominal

The total amount of patients studied for surgery was 1670, for surgery and adjuvant radiotherapy 815, for radiotherapy alone 155 and for observation 140 (Table 1). The median radiation dose for the surgery and adjuvant radiotherapy group was 54 (3-74) Gy, and for the radiotherapy alone group 50 (30-72) Gy. The median follow up was 63 (16-150) months.

Treatment results

The median age was 34 years. DF is more common among women than men, ratio 2:1.

Analysing the amount of patients with local control in relation to the total amount of patients per treatment group, the median local control rates for surgery alone, surgery and radiotherapy, radiotherapy alone and observation were 75%, 78%, 85% and 78%, respectively.

The role of surgical margins

Within the surgical group radical resections (36%) were as common as marginal resections (35%), intralesional resections were less common (11%).

Surgery	Surgery + RT	RT	Observation	Radiation dose (range) Gy		Median FU (months)
-	40	1	1	-		150
-	37	15	-	50-60 55-65	S + RT RT	44
184	39	-	-	38-66	S + RT	54
10	17	-	-	50-60	S + RT	65
95	24	-	-	38-70	S + RT	82*
48	19	5	-			48
-	-	44	-	56	RT	60
-	18	2	-	60 (40-64)	S + RT	77.5

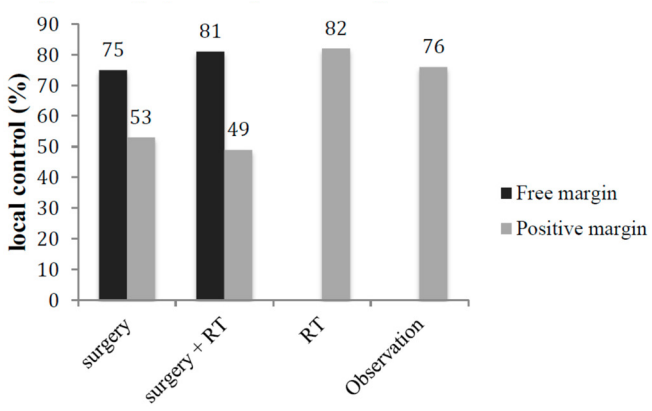
[a] 5 patients received intra operative radiotherapy
[b] Some patients received brachytherapy
[c] Number of patients receiving S+RT and RT alone
[*] Mean follow up

As expected, local recurrence was more common after surgery with positive margins compared to negative margins (Fig 2A, Supplementary Table 1). Adjuvant radiotherapy after positive margins did not improve the local control rate (p = 0.549).[7-9, 11, 12, 14, 15, 17-19, 21, 24, 26, 28, 30-33, 35]

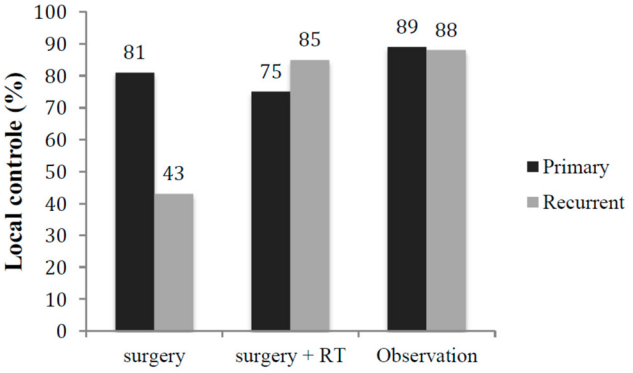
Between the treatment groups radiotherapy and observation, irrespective of surgical margins, no significant difference existed in terms of local control (p = 0.355).

The role of tumor status

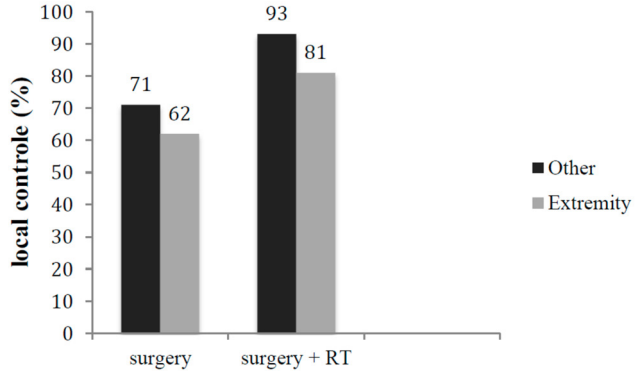
Patients with recurrent disease had less local recurrences after being treated with adjuvant radiotherapy compared to surgery alone (p < 0.001) (Fig 2B). [8, 10, 14, 17, 20, 22, 31, 32] Moreover, patients who were being observed had a better local control rate than patients treated with surgery alone (p = 0.001). [8, 14, 20, 23, 26, 31]



A. Surgical margin; free vs positive margin



B. Tumor status; primary vs recurrent disease



C. Location; Other vs extremity

Figures 2 A-C Local controle rate stratisfied per subgroup

Similar results were seen when the observation group was compared to the total surgical group with or without adjuvant radiotherapy, although this did not reach statistical significance (p = 0.063). [8, 10, 14, 17, 20, 22, 23, 26, 31, 32] For radiotherapy alone the numbers were too small to perform statistical analysis.

The role of tumor location and size

Even though the percentage of patients with local control was higher in the group of patients treated with adjuvant radiotherapy for both tumors located at the extremities and other locations, this did not reach statistical significance (p = 0.481 and p = 0.755, respectively) (Fig 2C). [10, 14, 17, 21, 22, 26, 32] Regarding the radiotherapy alone and the observation group numbers were too small to analyse.

For analyzing tumor size, we used the recurrence free survival instead of actual number of patients since more articles noted local control rate this way. Tumors over 5cm[13, 26], had a worse recurrence free survival than smaller tumors, irrespective of treatment. In the observation group no difference in five years recurrence free survival was observed for tumor size[11] (Table 2).

Table 2. Recurrence free survival of the different treatment modalities with respect to tumor size.

	Surgery		**Surgery + Radiotherapy**		**Radiotherapy**		**Observation**	
	5RFS	10RFS	5RFS	10RFS	5RFS	10RFS	5RFS	10RFS
<5cm	94	60, 94	-	84	-	100	44, 52	-
≥5cm	72	63, 66	-	69	-	68	60, 52	-

RFS = Recurrence free survival

Time to recurrence or stabilization of disease

The median time to local recurrence including all treatment groups as noted in 15 articles was 17 (range, 11-52) months. Two articles noted a mean recurrence time of 16 and 20 months.

For the observational treatment group, three studies described the median time to stabilization of the tumor, which was 14 (range, 12-35) months. The median time to tumor growth in this treatment group was 32 (range, 14-38) months.

Multivariate analysis:
A multivariate analysis was performed in eight studies. Prognostic factors predicting a negative outcome were large size (>4 or 5 cm), tumor location (limb, other locations than abdominal wall), positive surgical margins, deep seated tumors, age (<30 years), surgical treatment without adjuvant radiotherapy, recurrent disease and extracompartmentally situated tumors.

Complications and deaths due to treatment
In nine studies 14 patients were described who died of treatment or disease related causes, which is <1% of all treated patients. Since most articles did not describe the actual cause of death, it is not certain if any patient died due to the tumor itself.

Figure 3 describes the complications related to treatment. Soft tissue defects ranged from light dermatitis, most commonly caused by radiotherapy, to severe skin necrosis (in one case necessitating admittance to the intensive care). Severe treatment related complications were described in four patients who developed a secondary sarcoma (fibrosarcoma, angiosarcomas, MPNST) in the radiation field.

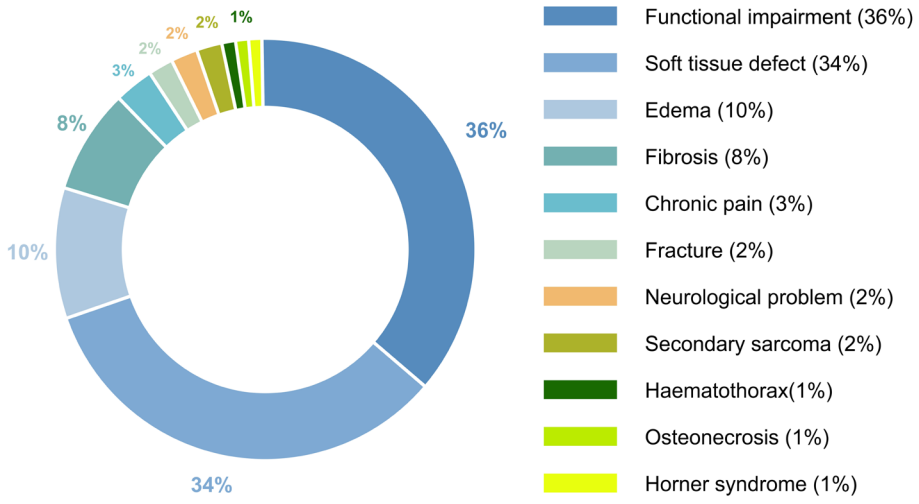


Figure 3. Treatment related complications in percentage

Discussion

In this systematic analysis we looked at the outcome of patients treated with surgery with four different treatment strategies with regard to local recurrence rates. Irrespective of treatment modality, the local control rate was good, with over 75% local control in each treatment group. This finding is in concordance with recently published data.[42]

Adjuvant radiotherapy is in many cases used to lower the risk of local recurrence in case of positive margins. In this review, contrary to previous findings of Nuyttens et al[2] and Janssen et al[42], no significant advantage for adjuvant radiotherapy was observed regarding local control[7, 8, 10, 11, 14, 17, 19, 24, 26, 28, 31, 32, 35]. There is however, a strong effect for adjuvant radiotherapy in recurrent disease, comparatively to the results of Janssen et al[42]. An international survey in Europe showed that recurrences after radiation tend to develop most commonly at the field border or in areas receiving less than 50Gy[24]. This implies wide field margins and high radiation doses in order to achieve a better local control rate. Although the radiation dose in this analysis varied, most institutions used ≥50Gy.

Recently the EORTC carried out a multicenter prospective phase 2 trial to determine the tumor response in patients with inoperable desmoid type fibromatosis using 56Gy radiotherapy. Keus et al. reported a good local control rate of 82%. [40] In the majority of cases this meant partial regression (36%) or stabilized disease (41%), only in a few cases complete regression (14%) of the tumor was observed. Interestingly, even after three years response was observed on MRI. Despite this good result, eventually 23% developed local progression, even after initial response. In two patients treatment could not be continued due to extensive toxic effect of radiation. The complication rate in Nuyttens et al.[2] was reported in over one fifth of patients, and in Keus et al.[40] around one third. Only a small percentage (5%) developed severe skin toxic effects of grade 3/4.[40] The link between the radiation dose and the risk of local progression/recurrence is debated, but some argue a better local control rate at high doses of 56 Gy[21]. However, the incidence of complications increased parallel with the dose given. Although the majority of complications is not severe and reversible, some severe complications including fractures and secondary sarcomas occurred, which were also

observed in this review. More common complications were functional impairment and soft tissue defects (70% of all complications), of which the latter was in most cases reversible. The overall death rate is very low, with less than 1% of patients dying either due to the disease or treatment complications.

Around ten years ago the first reports about a wait and see policy were published. Due to the fact that data are usually small due to a relatively low incidence of DF, concerning 3% of all soft tissue sarcomas[43], this analysis pooled data to determine whether or not conservative treatment reaches acceptable local control rates compared to surgical treatment. The majority of patients in this analysis were still treated with surgery (surgical treatment n = 2485 vs. non surgical treatment n = 295), with about one sixth of institutions describing radiotherapy alone and/or observation.

In most institutions a selection is performed for patient undergoing more conservative therapy. In case of radiotherapy alone, patients usually had large tumors, or tumors in close adherence to important structures that limited radical surgery. [12, 15, 18, 30] Patients considered for observation usually had a tumor, that in case of growth, was still eligible for surgery and had no major clinical symptoms. [6, 7, 19, 23] Only one study used a routinely first line conservative approach for all patients presenting to the institution[6] with a relatively good local control rate of 65%. Of the patients with primary disease, 35% had progressive disease, and in 32% of these patients surgical treatment was finally necessary. Interestingly, the progression free survival rate of patients with primary tumors was 47% and with local recurrence 54%. Stabilization of the tumor arose after a median time of >1 year after observation, and a local recurrence or progression occurred after a median time of <3 years, which means that patients should be regularly observed within the first five years. If sudden progression does develop, treatment should be re-evaluated.

Surprisingly, the treatment groups of radiotherapy alone and observation had a relative similar local control rate as the surgery group. One reason could be that surgery itself is a stimulant for tumor growth. Interestingly, the radiotherapy alone group did not have better local control rates than the observation group ($p = 0.355$). It should be noted that there is a selection bias favouring the observation group, due to the selection of tumors with a less aggressive pattern. In addition,

the follow up of the two largest studies using primary observation was mean 16 months and median 33 months, while the follow up of the largest studies with radiotherapy only was median 56 months.

For primary tumors the local control rate did not seem to be influenced by the choice of treatment. The opposite is true for recurrent disease, in which adjuvant radiotherapy has a definite advantage over surgery alone ($p = 0.001$). This could be explained by the more aggressive nature of recurrent disease.

Based on this systematic review no preference of treatment could be indicated based on tumor location (extremity vs other locations), although outcome of patients with tumors located at the extremities was worse. Especially patients with large tumors located at the extremities have a worse local outcome, regardless of the surgical margins.[13]

Patients with a tumor size larger than 5cm had a worse local outcome, independent of the type of treatment except for the observation group.

In addition to the variables mentioned in the previous section, other studies that performed multivariate analysis showed that deep seated tumors, age (<30 years) and extracompartmentally situated tumors were negative predicting markers of local outcome. Similar predicting markers were also found in other soft tissue sarcomas.[35, 44, 45]

It is important to note that pooling of the data led to large sample sizes, however, when analyzing the subgroups, the sample sizes diminished due to lack of reported data items. In addition, selection and reporting bias occurred due to the retrospective design of most included studies.

Meta-analyses of the trial results were considered, but were deemed not feasible because the heterogeneity of the patients, tumor characteristics and interventions, were too great to allow for pooling of data.

Conclusion

With consideration of previously mentioned weaknesses of this study and careful interpretation of the results, a watchful waiting approach as a first line option could be justified, in addition with closely monitoring by means of physical examination and MRI during at least five years of follow up, in a subgroup of patients without clinical symptoms and no possible health hazards if the tumor would progress, and taking into account that a considerable group of patients eventually does need surgical treatment. More data is needed to confirm a conservative approach as a safe treatment for DF, especially in smaller patient subgroups.

In case of recurrent disease, adjuvant radiotherapy with a dose ≥ 50Gy has a definitive advantage over surgery alone. A multidisciplinary sarcoma team should finally make the decision with respect to the treatment options.

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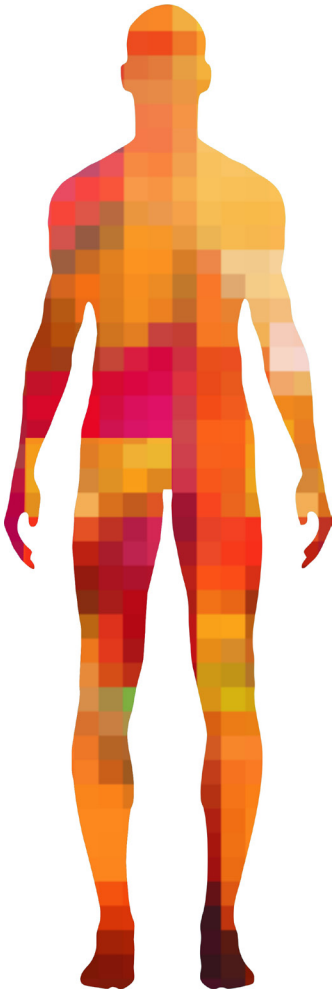
Supplementary data

Supplementary table 1. Local control rate of the different treatment modalities with respect to surgical margins, tumor status at presentation and tumor location

	Surgery		Surgery + Radiotherapy		
	No (a/b)	**%**	**No (a/b)**	**%**	**P value[c]**
Free margins	171/229	75	25/31	81	0.820
Positive margins	126/238	53	48/98	49	0.549
Primary	150/185	81	36/48	75	0.419
Recurrent	34/80	43	83/98	85	0.000
Other	15/21	71	38/41	93	0.755
Extremity	16/26	62	71/88	81	0.481

a no of patients with local control
b total amount of patients
[c] P value in comparison with surgery alone
[d] P value in comparison with surgery with and without radiotherapy
[e] P value in comparison with radiotherapy alone
nv: not valid

	Radiotherapy			Observation				
	No (a/b)	%	P value[c]	No (a/b)	%	P value[c]	P value[d]	P value[e]
	46/56	82	nv	112/148	76	nv	nv	0.355
	-	-	nv	17/19	89	0.536	0.545	nv
				15/17	88	0.001	0.063	nv
	-	-	nv	-	100	nv	nv	nv
	-	-	nv	-	50	nv	nv	nv



Chapter 12

Future perspectives

Tumorgenesis and targeted therapy

The future of soft tissue sarcoma treatment relies in the increasing knowledge of sarcoma tumorgenesis. In the last few decades, advancement in technology has given us the opportunity to improve our understanding why cells start to grow uncontrollably. Different pathways and signaling factors that contribute to the development have been revealed. [1-3] Another important insight that has had a major impact on clinical practice is the discovery of new distinctive sarcoma subtypes based on genetic differences. Ten years ago, the classification of sarcoma subtypes existed out of 50 different soft tissue sarcomas [4], based on morphological characteristics, nowadays we know that there are additional subtypes, most of which have specific biologic behaviors and responsiveness or resistance to therapy, leading to an explicit need of individualized therapy.

A booming topic in sarcoma treatment is targeted therapy. Probably, one of the more famous discoveries was the c-kit mutation in gastrointestinal stromal tumors, and the spectacular responsiveness of these tumors to imatinib. [5, 6] Till than, only systemic chemotherapy was available, e.g. doxorubicin and paclitaxel, which were limited effective in only some sarcoma subtypes. The finding of targeted therapy like imatinib, which was really effective and at the same time less toxic on non-cancer cells, gave rise to an exploding start of innovative molecular science. Other pathways, leading to either loss of tumor suppression, e.g. p53 mutation, or tumor progress, e.g. up regulation of vascular endothelial growth factor (VEGF) regulating tumor angiogenesis, have been reported. [7, 8] This led to the identification of new targeted drugs such as pazopanib, which targets VEGF receptors, thereby inhibiting angiogenesis in for example leiomyosarcoma [9] and trabectedin in myxoid liposarcoma [10]. Some of these drugs have now also been approved in clinical setting. Although, these findings are helpful and promising in improving sarcoma treatment, it has to be noted that in terms of disease free and overall survival the results are sometimes limited to only a few months extra. [9] Therefore, new drugs have to be critically assessed, taking into consideration the real profit for patient survival, quality of life, and also taking financial costs into account.

Furthermore, as is the case with systemic chemotherapy, resistance also develops for targeted therapies and may be caused by secondary genetic alterations.

Resistance to imatinib in patients with GIST for example has become a new problem; therefore, the EORTC is currently performing phase II trials investigating cabozantinib in patients with metastatic disease and regorafenib as first line treatment. [11]

In collaboration with colleagues in Sweden the genetic differences and possible targeting pathways in angiosarcomas were explored, which are a particular difficult to treat subtype of sarcoma. Angiosarcomas can either develop as a primary tumor or secondary to earlier treatment, like radiotherapy, and are morphologically indistinguishable. A total of 26 primary and 29 secondary angiosarcomas were studied in this collaboration using whole genome analysis and validated with immunohistochemistry. [12] Although several years ago whole genome sequencing was costly and took years to give results, today, the technology is more efficient, and genome sequencing is executed in days and is financially more appealing for to be used in clinical practice. The asset of whole genome analysis is that previously unknown genes may be identified as contributing to sarcoma development. The above mentioned study showed that in total 103 genes were significantly deregulated between primary and secondary angiosarcomas. Secondary angiosarcomas showed upregulation of *MYC, KIT* and *RET* and downregulation of *CDKN2C*. Functional annotation analysis identified multiple target genes in the receptor protein tyrosine kinase pathway. This implies possibilities for diagnostic application and a mechanistic basis for therapeutic evaluation of RET-kinase-inhibitors. For future studies it would be relevant to investigate possible angiosarcoma treatment strategies.

Another challenge in precision medicine is the identification of markers predictive of response. Since treatment of sarcomas is associated with short and long term side effects, an optimized risk measure is central. This motivates sarcoma specialists to identify grading systems and prognostic models based on tumor characteristics using immunohistochemistry technique, leading to the well known grading systems proposed by the French Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) and the National Cancer Institute (NCI). Now that genetic profiling helped us defining distinctive tumor characteristics, it seems obvious that these will be incorporated in prognostic models to define patient categories benefiting from therapy. [13] And in addition to help predict patient survival. [3]

Improving quality of life of sarcoma patients and organization of health care

Sarcoma patients are willing to endure heavy treatment regimens in order to survive. Nevertheless, quality of life for cancer patients is becoming a more important topic in clinical practice discussing the different treatment options. Some side affects are under exposed, and sometimes due to their rare incidence a challenge to treat. Despite an usually thorough follow up after treatment, in which side effects are recognized and treated by the individual doctor, not much of this information is shared among them. Recording treatment related effects, its treatment and publishing the results are necessary to improve their treatment.

In the case of locally advanced soft tissue sarcoma of the extremities, in which surgery alone is not sufficient and a treatment schedule of hyperthermic isolated limb perfusion (HILP), surgery and usually in addition radiotherapy is given, patients are subjected to an exhausting long treatment schedule of several months. To improve this treatment schedule the University Medical Centre Groningen initiated several years ago a more efficient treatment schedule, starting with HILP, a short course of radiotherapy (12x3GY), shortly followed by surgical resection (IRB protocol review case-number 2010/299). The whole treatment time lasted no longer than 6 weeks. [14] These patients are now studied to compare outcome, in terms of disease free and overall survival and side effects, to patients treated with the more extensive schedule. This is an on going study, but intermediate analysis after ten patients has shown the same treatment outcome till now.

Another important subject in this analysis is how the different treatment modalities affect the tumor. After each modality an FDG-PET scan is performed and tumor necrosis is measured. In this way the additive value of high dose chemotherapy in the HILP setting and preoperative radiotherapy on diminishing tumor activity can be studied in a non-invasive manner and compared with the final pathology of the resected specimen.

Furthermore, final tumor response will be measured in the specimen after surgery. Recently, the EORTC-STBSG proposed a new classification to evaluate the histopathological tumor response. Instead of measuring tumor necrosis, vital

tumor cells are scored and related to treatment response. This proposal has to be validated, as is currently done by joined effort of the surgical and pathological department at the UMCG.

Organization of health care of sarcoma patients deserves also attention. Due to its rare entity, patients and physicians can cause delay in treatment, which eventually can lead to decreased chances of survival. In order to see where these problems arise, it is necessary to look into the time schedules of referrals. Analyzing published research about this problem, it is clear that this is a worldwide problem, and confined to several types of sarcomas. Recognizing the problem is a good first start, however, now we need to continue solving the problem by educating doctors about sarcomas, and determine clear referral requirements. In Sweden it has been spread throughout the country that all soft tissue tumors larger than 5cm or deep seated should be referred to a sarcoma centre before treatment is started [15]. This has not led to an overwhelming offer of patients with tumors to surgeons at sarcoma centres [16], but did lead till less 'whoops' procedures.

At the sarcoma centre itself, further improvement of efficient health care is equally important.

In 2012 a treatment model for sarcoma care in the Dutch medical society was developed by the Department of Surgical Oncology in close collaboration with the other team members of the UMCG Sarcoma working party. [17] The essence of this model was based on specialty transcending care. In the University Hospital in Groningen, sarcoma patients are treated by a sarcoma team consisting out of professionals with expertise in each necessary field; medical oncology, nuclear medicine, orthopaedic surgery, pathology, pediatric oncology, radiation oncology, radiology and surgery. Their aspiration of improving health care is limited by the fact that hospitals work with department-regulated care, in which surgery for example, is managed by a different team of people as is radiation oncology. It was proposed to make the sarcoma team in the lead and make the sarcoma team responsible for the delivered sarcoma care, the cost of diagnostic and treatment and the overall quality of care. In order to improve care efficiency, a template was made for referral of patients to the sarcoma centre and sarcoma meetings (Fig .1).

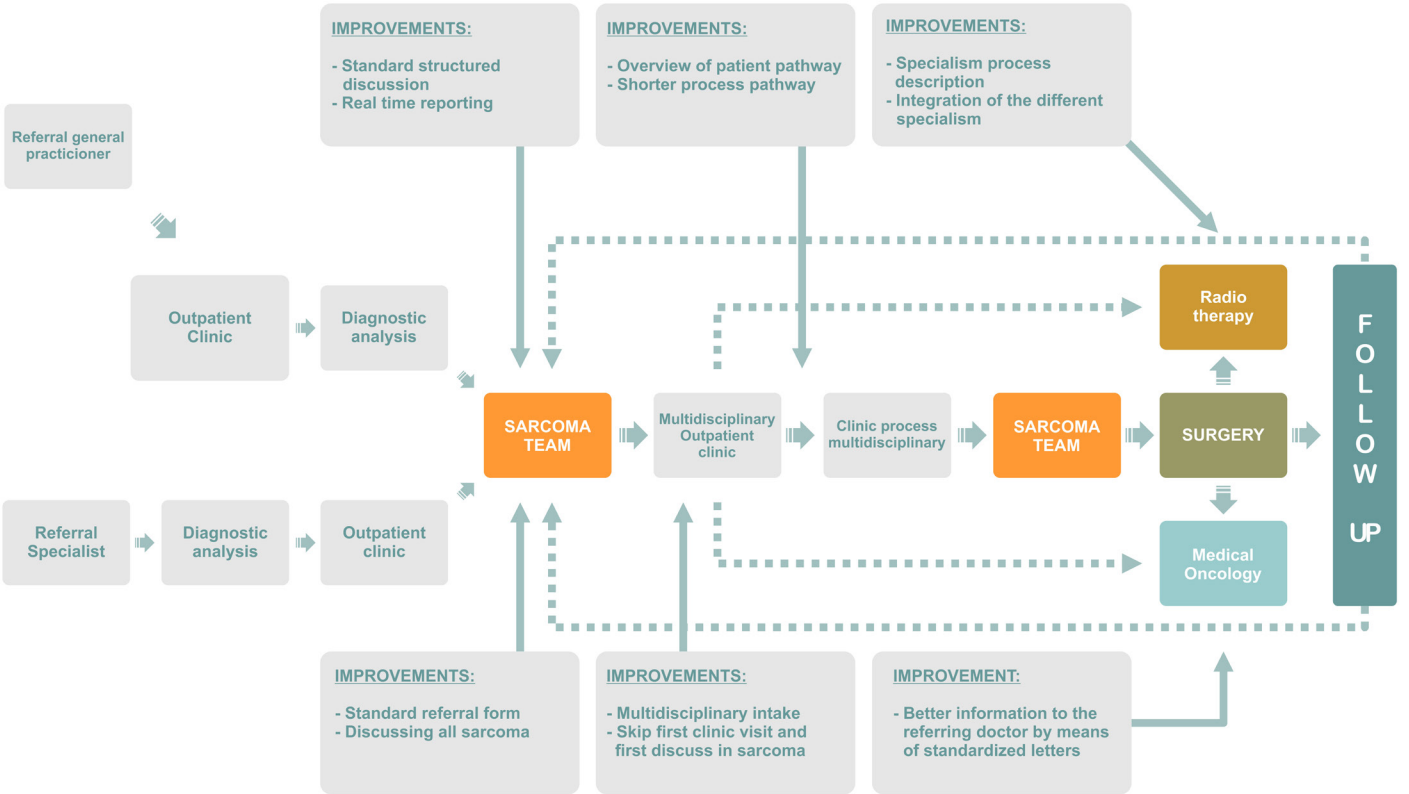


Figure 1. Flow diagram showing referrals and clinical process

Furthermore, to evaluate team efforts to improve sarcoma care, key performance indicators e.g. treatment outcome, patient and doctor satisfaction, were compiled, which in addition will enable the team to show results publically. Giving the professional the responsibility and autonomy for health care will not only improve quality of care but will also be cost effectively. Future research of the implementation of 'Resultaat Verantwoordelijke Eenheid' ('Result Responsible Unit') will determine whether or not this is the case.

A contributing aspect in the previously mentioned model is that professional autonomy leads to better job satisfaction for the professional. [18] In the last years worldwide, and more recently here in the Netherlands, 'fit to perform' became an important issue among medical professionals. It appeared that burn out or distressed feelings are high among medical trainees and professionals. [19-21] Moreover, there is a relationship between burn out and medical errors [21]. Therefore, it is not only in the interest of the medical professional but also from a point of view of patient safety, that medical professionals are enabled to be fit to perform. Many years, studies have focused on eliminating stressful factors, like diminishing working hours. However, more recent studies have linked improving work engagement with better job satisfaction, reporting professional autonomy as an important aspect. [22]
In concordance with previous findings the future should be with the medical professionals in the lead.

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APPENDIX

Samenvatting

Weke delen sarcomen zijn relatief zeldzaam en de diagnose werd in Nederland in 2017 meer dan 700 keer gesteld. [1] Ter vergelijking wordt de diagnose van goedaardige weke delen zwellingen ongeveer 100 keer vaker gesteld. [2] Op basis van nieuwe technologieën, met name op het gebied van genetica, is de classificatie van weke delen sarcomen onderhevig aan veranderingen. Op dit moment worden meer dan 50 verschillende subtypen erkend.

Weke delen sarcomen geven aspecifieke klachten en vaak zelfs alleen een voelbare zwelling zonder pijn. Dit maakt het op tijd herkennen zeer lastig en leidt het regelmatig, zowel bij patiënt en/of dokter, tot een vertraging in het stellen van de uiteindelijke diagnose sarcoom. Aangezien de tijd tot het stellen van de diagnose en het inzetten van behandeling de prognose kan beïnvloeden is het belangrijk dat er geen vertraging optreedt in het stellen van de juiste diagnose. Net zo belangrijk is, dat patiënten ofwel behandeld worden in een van de vijf sarcoom centra in Nederland, dan wel consultatie plaatsvindt met betrekking tot de diagnose en voorgestelde behandeling. Dit om zogenaamde 'whoops' procedures, waarbij pas achteraf de diagnose sarcoom wordt gesteld, te voorkomen. Daarom wordt in Zweden gepleit tot het verwijzen van alle patiënten met diep gelegen tumoren of tumoren groter dan 5 cm in de weke delen naar sarcoom centra. Dit heeft ertoe geleid dat bijna 100% van de patiënten met weke delen sarcoom uiteindelijk werd verwezen naar een sarcoomcentrum, waarvan driekwart voor het verrichten van een biopt. [3] De richtlijn zal overigens niet leiden tot een overmaat aan verwijzingen van patiënten met goedaardige zwellingen, aangezien 1 op de 4 patiënten daadwerkelijk de diagnose sarcoom kreeg. [3]

In Nederland bestaan er geen officiële richtlijnen voor het verwijzen, maar wordt wel geadviseerd om patiënten met vergelijkbare tumorkenmerken te bespreken in een multidisciplinair overleg en te bespreken met een van de vijf sarcoom centra.

Een speciale groep binnen de weke delen sarcomen zijn retroperitoneale tumoren. Deze tumoren, zoals laaggradige liposarcomen, kunnen wel zo groot worden als 20 cm voordat patiënten hier klachten van ervaren. In hoofdstuk 3 wordt beschreven dat meer dan 90% van de patiënten met retroperitoneale tumoren

wordt verwezen naar een sarcoom centrum voordat behandeling is gestart. De gemiddelde vertraging door de dokter bij het stellen van de diagnose was aanzienlijk, namelijk 3 maanden. Het grootste deel hiervan werd veroorzaakt door het diagnostisch proces in het (perifere) ziekenhuis en het sarcoomcentrum, en niet zozeer bij de huisarts. Een mogelijke verbetering is om huisartsen beter te informeren over sarcomen, het bestaan van sarcoom centra en het direct kunnen door verwijzen naar sarcoom centra. Daarnaast kan het sarcoom centrum zelf het diagnostisch proces beter stroomlijnen zodat vertraging wordt voorkomen. Recent heeft het sarcoom team van het Universitair Medisch Centrum Groningen daadwerkelijk een voorstel gedaan voor een nieuw behandelmodel om de sarcoomzorg meer efficiënt en kosten effectief te maken. [4]

Voor de meeste weke delen sarcomen geldt nog steeds dat chirurgie de voornaamste behandeling is. In de jaren ’80, heeft o.a. een gerandomiseerde studie van de NCI aangetoond dat de lokale controle tot 85% verbeterd kon worden met aanvullende radiotherapie. [5-10] Radiotherapie is sindsdien standaard behandeling geworden na krappe of R1/R2 resecties. In tegenstelling tot radiotherapie heeft (neo)adjuvante chemotherapie geen invloed gehad op de ziektevrije en algehele overleving. [11-12] Een uitzondering zijn enkele weke delen tumoren die wel gevoelig zijn voor chemotherapie zoals de vaak bij kinderen voorkomende Ewing sarcomen, rhabdomyosarcomen en extraskeletaal osteosarcomen.

Er bestaan verschillende prognostische modellen, die patiënten indelen in laag of hoog risico voor recidief ziekte. De bekendste zijn die van de National Cancer Institute (NCI) en de French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC). Het NCI model gebruikt histologisch subtype, pleomorfisme en mitose aantal. Het FNCLCC model is gebaseerd op de score van differentiatie, mitose aantal en hoeveelheid tumor necrose. In hoofdstuk 5 wordt de rol van proliferatie beschreven als prognostische marker. Hiervoor is gebruik gemaakt van immunohistochemische beoordeling van Ki-67, Top2a, p21, en p27Kip1. Het voordeel van proliferatie is dat het bepaald kan worden op een histologisch biopt, zodat het gebruikt kan worden in het pre-operatieve beslissingsproces voor het geven van neo-adjuvante chemotherapie voor lokaal uitgebreide weke delen tumoren. Niettemin is een histologisch biopt altijd beperkt door een kleine hoeveelheid weefsel uit een tumor, die mogelijk gebieden kent van necrose en dedifferentiatie.

In de laatste jaren worden genetische ‘pathways’ ontrafeld, wat heeft geleid tot ‘targeted therapy’, waarvan enkele medicijnen inmiddels zijn goedgekeurd voor de kliniek, zoals imatinib, trabectedin en pazopanib. [13]

Voor patiënten met lokaal uitgebreide, primair niet te opereren, primaire of secundaire weke delen sarcomen van de extremiteiten bestaat een alternatieve vorm van behandeling in Europa in de vorm van geïsoleerde ledemaat perfusie onder hyperthermie. Deze techniek kan worden aangeboden in de vorm van neoadjuvante therapie gevolgd door in opzet curatieve operatie of als een primair palliatieve behandeling. In geval van een niet operabel sarcoom van een ledemaat, met of zonder afstandsmetastasen, kan met behulp van een hypertherme geïsoleerde ledemaat perfusie met TNFa en melphalan bij ongeveer 90% van de patiënten de ledemaat behouden blijven met acceptabel percentage bijwerkingen. [14-15]

In 1996 werden de resultaten van de eerste multicenter trial met perfusie met Tumor Necrosis Factor alpha (TNFαHIL) en Melphalan gepubliceerd, dat een ledemaat sparende overleving liet zien van 84%. [16] Desondanks kan ernstige necrose van de huid op korte termijn, en ernstige ischemie op de lange termijn, leiden tot amputatie. [17] Bovendien kan deze behandeling tezamen met opereren en adjuvante bestraling de kans op pathologische fracturen sterk doen toenemen met een 10jaars risico van 15%, welke de kwaliteit van leven sterk beïnvloedt. (Hoofdstuk 7)

Hoofdstuk 6 omvat een historische beschrijving van de geïsoleerde perfusie behandeling en de uitdagende korte en lange termijn complicaties.

Bij vrouwen met borstkanker die in het verleden een mamma amputatie ondergingen en een okselklierdissectie en bestraling van de oksel en eventueel thoraxwand, werd sporadisch een zeer bijzonder sarcoom gediagnosticeerd in een arm met lymfoedeem, het Steward-Treves syndroom. Een sarcoom waarvoor een amputatie van de aangedane ledemaat vaak niet was te voorkomen, totdat de geïsoleerde ledemaat perfusie met TNFa en melphalan beschikbaar kwam. [18] Daarnaast wordt in toenemende mate het angiosarcoom van de borst gediagnosticeerd bij vrouwen die een borstsparende behandeling hebben ondergaan voor borstkanker. [19] Het is eveneens een zeer zeldzaam sarcoom. In 2014

werd aangetoond dat secundaire angiosarcomen zich anders ontwikkelen dan primaire angiosarcomen doordat zij andere genetische 'pathways' volgen, zoals de toegenomen regulatie van MYC, KIT en RET en de verminderde regulatie van CDKN2C. Het herkennen van deze 'pathways' geeft de mogelijkheid om diagnostisch te differentiëren tussen beide groepen, en kan tegelijkertijd dienen als basis voor therapeutische evaluatie van RET-kinase remmers. [20]

Gezien de vasculaire aard van de tumor, is het aannemelijk om aan te nemen dat deze tumoren goed reageren op 'targeted therapy' met VEGF remmers. De Franse sarcomen groep heeft sorafenib als potentiele medicatie onderzocht en beschreef een matige antitumor activiteit. Tot nu toe wordt medicamenteuze therapie gezien als experimentele behandeling en dus alleen gebruikt in klinische trials. Chirurgie is tot nu toe de enige mogelijkheid tot curatie. In hoofdstuk 9 wordt beschreven dat R0 resectie alleen mogelijk is indien zeer radicaal wordt geopereerd en dan nog in ongeveer driekwart van de patiënten haalbaar is. Ondanks radicale resectie ontwikkelde meer dan de helft van de patiënten een lokaal recidief binnen aanzienlijke tijd (mediaan 6 maanden). [21] Van de patiënten met recidief had de groep die in aanmerking kwam voor re-resectie een betere overleving dan de groep die niet in aanmerking kwam voor operatie. Helaas was de mediane overleving niet veel meer dan drie jaar.

Niet alle weke delen sarcomen hebben een slechte prognose. Een speciale subtype binnen de weke delen sarcomen vormen de desmoide type fibromatose tumoren. Deze tumoren kunnen lokaal wel invaderend groeien, maar metastaseren niet. De overleving is daarom nagenoeg 100% en patiënten komen zeldzaam te overlijden aan hun ziekte. Vanwege deze goede prognose zijn mutilerende operaties als eerste stap binnen curatieve setting niet wenselijk. Om deze reden wordt aanvullende radiotherapie gegeven voor extra lokale controle bij marginale resecties. In 2013 heeft de EORTC in een fase 2 trial het effect van alleen radiotherapie met 56Gy op inoperabele tumoren gepubliceerd, waarbij een goede lokale controle van 82% wordt beschreven. [22] Slechts in een klein aantal werd daadwerkelijk complete regressie bereikt (14%). Ondanks dit goede resultaat ontwikkelde uiteindelijk 23% lokale progressie.

Niettemin induceert radiotherapie ook korte en lange termijn morbiditeit zodat ook andere behandelingen worden overwogen. De laatste jaren is een trend

waarneembaar waarbij een afwachtende houding wordt aangenomen waarbij het gedrag van de tumor wordt geobserveerd. Het gaat hier vaak om een subgroep van tumoren die geen klachten geven en bij groei niet direct inoperabel worden zodat chirurgie nog wel achter de hand kan worden gehouden. Vanwege de lage incidentie van desmoid type fibromatose, die slechts 3% van het totaal aantal weke delen sarcomen beslaat, zijn de gerapporteerde aantallen in studies meestal klein. Daarom wordt in hoofdstuk 11 een systematische analyse van vier verschillende behandelstrategieën gedurende de afgelopen decennia, namelijk opereren, opereren en radiotherapie, radiotherapie alleen en observatie, beschreven.

Conclusie

De diagnose en de behandeling van weke delen sarcomen is over het algemeen complex en daarbij onderhevig aan verandering door continu nieuwe inzichten. Mede door de lage incidentie is het daarom niet haalbaar voor de meeste specialisten om de literatuur bij te houden en de meest recente, vaak gecombineerde behandelopties toe te passen. Het consulteren, c.q. verwijzen naar een sarcoom centrum is daarom noodzakelijk, hetzij voor het stellen van de juiste diagnose en/of uitvoeren van de behandeling. Van een sarcoom centrum wordt een laagdrempelige consultatie of verwijzing, met een efficiënt diagnostisch traject en een goede monitoring van behandeling en terugkoppeling naar verwijzers verwacht.

De verbetering van de prognose van weke delen sarcomen patiënten lijkt voort te komen uit de toegenomen kennis over het ontstaan van een sarcoom en de genetische ‘pathways’ die daarbij ontrafeld worden en de daarbij behorende mogelijke ‘target therapies’. Desalniettemin, moet rekening gehouden worden met de bijwerkingen en hoge kosten van deze therapieën en moet een juiste selectie kunnen worden gemaakt van tumoren die waarschijnlijk goed zullen reageren.

Ten slotte kan de samenwerking tussen de (sarcoom) centra, nationaal en internationaal, leiden tot onderlinge kennisverwerving, en het behandelen van grotere, gedefinieerde patiënten groepen binnen goed gedocumenteerde onderzoeken.

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Summary

Soft tissue sarcomas are relatively rare, and the incidence of newly diagnosed patients in the Netherlands in 2017 was over 700 patients. [1] In comparison, the incidence of benign soft tissue lesions was around 100 times more. [2] Based on new technologies, especially in the area of genetics, the classification of soft tissue sarcomas is subjected to major changes. At this moment over 50 different subtypes are recognized.

Soft tissue sarcomas give rise to non-specific complaints and often only to a painless palpable mass. This makes the detection of these tumours difficult and leads regularly to both patient and doctors delay in anticipation of the correct diagnosis. Since these delays to the start of treatment influence prognosis, it is important to try to shorten these delays. Equally important is that patients are either treated in one of the five sarcoma centres in the Netherlands, or consultation is sought beforehand regarding diagnosis and proposed treatment. This is to prevent so-called 'whoops' procedures, in which the diagnosis of sarcoma is made after surgical resection. For this reason, there is in Sweden a plea for the referral of all patients with deep seated tumours or tumours larger than 5 cm to sarcoma centres. As a result, almost 100% of patients with soft tissue sarcomas were eventually referred to a sarcoma centre, three-quarters of which were referred even before performing biopsy. [3] Moreover, the guideline will not lead to an excess of referrals of patients with benign tumours, since 1 in 4 patients actually got the diagnosis of sarcoma. [3]

In the Netherlands, no official referral guideline exist, but it is generally advised to discuss patients with similar tumour characteristics in a multidisciplinary setting and consult dedicated sarcoma specialists at one of the five sarcoma centres.

A special group within the soft tissue sarcomas are retroperitoneal tumours. These tumours, such as low-grade liposarcomas, can be as large as 20 cm before patients experience symptoms. Chapter 3 describes that more than 90% of patients with retroperitoneal tumours are referred to a sarcoma centre before treatment is started. However, the average doctor delay till diagnosis was substantial, namely 3 months. The most notable cause of this delay was induced by the diagnostic process at the referring hospital and sarcoma centre, less due

to the general practitioner. A possible improvement is to better educate general practitioners about sarcomas, the existence of sarcoma centres, and the possibility to directly refer to sarcoma centres. In addition, the sarcoma centre itself can improve the diagnostic process to shorten delays. Recently, the sarcoma team of the University Medical Centre Groningen actually made a proposal for a new treatment model to make sarcoma care more efficient and cost effective. [4]

Still today, surgery remains the mainstay in soft tissue sarcoma treatment. In the eighties, among other studies, a randomized trial of the National Cancer Institute (NCI) has demonstrated that local control could be improved till 85% using adjuvant radiotherapy. [5-10] Thereafter, radiotherapy has become standard therapy after marginal (R1) or incomplete (R2) surgical excision. In contrary to radiotherapy, (neo-)adjuvant chemotherapy did not influence disease free or overall survival. [11-12] Exceptions to this rule are some soft tissue sarcomas frequently diagnosed in children, e.g. Ewing sarcomas, rhabdomyosarcomas and extra skeletal osteosarcomas.

Different prognostic models are used to divide patients into low or high risk groups for recurrence of disease. The best known models are the one of the NCI and the French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC). The NCI model uses histological subtype, pleomorpism and mitotic count. The FNCLCC model is based on tumour differentiation, mitotic count and percentage of tumour necrosis. Chapter 5 describes the role of proliferation as prognostic marker. Proliferation was based on immunohistochemical determination of Ki-67, Top2a, p21, and p27Kip1. The advantage of proliferation is that it can be used in biopsies; permitting pre-operative decision-making whether or not neo adjuvant chemotherapy could have benefit in locally advanced soft tissue sarcomas. Nevertheless, a histological biopsy is always limited by small amount of tissue from a tumour that may have areas of necrosis and dedifferentiation.

In the last decade genetic pathways have been discovered that have led to targeted therapy, of which several drugs recently have been approved for clinical use, e.g. imatinib, trabectedin en pazopanib. [13]

For patients with locally advanced, primary non-operable, primary or secondary soft tissue sarcomas of the extremities there exists an alternative form of

treatment in Europe, namely hyperthermic isolated limb perfusion (H-ILP). This technique can be offered in the form of neo-adjuvant therapy followed by an intentionally curative operation, or as a primary palliative treatment. In the case of a primary non-operable sarcoma of the extremities, with or without distant metastases, perfusion with TNFa and melphalan can contribute to limb salvation with an acceptable percentage of side effects in approximately 90% of patients. [14-15]

In 1996 the results of a multi centre trial with H-ILP with Tumor Necrosis Factor alpha (TNFαHIL) en Melphalan were published, showing a limb salvage rate of 84%. [16] Nonetheless, severe necrosis in the short term and severe ischemic reaction in the long term can lead to amputation. [17] Moreover, H-ILP in combination with surgical treatment and radiotherapy increases the risk of pathological fractures, with an overall 10years risk of 15%, which substantially influence quality of life. (Chapter 7)

Chapter 6 outlines an historical description of the H-ILP treatment including challenging short and long-term complications.

In women who have suffered breast cancer and treated with breast amputation and additional axillary lymph node dissection, and/or radiotherapy of the axilla and possibly also the thoracic wall, rarely a special sarcoma has been diagnosed in an arm with oedema, the Steward-Treves syndrome. This type of lymphangiosarcoma was usually treated with amputation, until H-ILP came available. [18] Additionally, there is an increasing incidence of angiosarcoma of the breast following radiation after breast sparing surgery. [19]. Nevertheless, its occurrence is sporadic. In 2014, it was reported that secondary angiosarcomas develop differently than primary angiosarcomas because they follow different genetic pathways, such as the upregulation of MYC, KIT and RET and the down regulated CDKN2C. The recognition of these pathways gives rise to the possibility of diagnostic differentiating between both tumours, and at the same time as a base for therapeutic evaluation of RET-kinase inhibitors. [20]

Given the vascular nature of the tumour, it is likely to assume that these tumours respond well to targeted therapy with VEGF inhibitors. The French sarcoma group studied sorafenib as a potential drug and described moderate antitumor activity. Up to now, drug therapy has been seen as experimental treatment and

thus only used in clinical trials. Surgery is the only possibility to cure the disease so far. Chapter 9 describes that R0 resection is only possible if very radical surgery is performed and in about three-quarters of the patients this is still feasible. Despite radical resection, more than half of the patients developed a local recurrence within a considerable time (median 6 months). [21] Of the patients with relapse, the group eligible for re-resection had a better survival than the group that did not qualify for surgery. Unfortunately, the median survival was not much more than three years.

Not all soft tissue sarcomas have a poor prognosis. A special subtype within the soft tissue sarcomas is desmoid type fibromatosis. These tumours are locally invasive, but do not metastasize. Survival is therefore almost 100%, and patients die rarely due to their disease. Consequently, mutilating operations as a first step within a curative setting are not desirable. For this reason, additional radiotherapy is given for additional local control in marginal resections. In 2013, the EORTC published the effect of radiotherapy alone with 56Gy on inoperable tumours in a phase 2 trial, describing a good local control of 82%. [22] Only in a small number, complete regression was actually achieved (14%). Despite this good result, 23% eventually developed local progress.

Nevertheless, radiotherapy also induces short and long-term morbidity so that other treatments are also considered. In recent years, a trend has been observed in which a wait-and-see attitude is embraced by means of regular check-ups including radiological imaging of the tumour. This is often a subgroup of tumours that do not cause any symptoms and are not immediately inoperable in the event of growth so that surgery can still be kept as an alternative. Due to the low incidence of desmoid type fibromatosis, which accounts for only 3% of the total number of soft tissue sarcomas, the reported numbers in studies are usually small. Therefore, Chapter 11 describes a systematic analysis of four different treatment strategies during the past decades, namely surgery, surgery and radiotherapy, radiotherapy alone and observation.

Conclusion

Diagnosis and treatment of soft tissue sarcomas is generally complex and subjected to change through continuous new insights. Furthermore, due to their low incidence it is not feasible for most specialists to keep up with literature and to apply the most recent, often multimodality, treatment options. Consultation, or referring to a sarcoma centre, is therefore necessary, either for making the correct diagnosis and/or performing the treatment. To promote this, a low-threshold consultation or referral, with an efficient diagnostic process and a good monitoring of treatment and feedback to referrers, is expected from a sarcoma centre.

The improvement of prognosis of soft tissue sarcoma patients is based on increasing knowledge about the development of a sarcoma and the genetic pathways that are unravelled and the associated possible target therapies. Nonetheless, the side effects and high costs of these therapies must be taken into account and proper selection should be made of tumours that are likely to respond well.

Finally, cooperation between the (sarcoma) centres, nationally and internationally, can lead to mutual knowledge acquisition, and the treatment of larger, defined patient groups within well-documented studies.

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Curriculum Vitae

Jojanneke Seinen was born on 4th of March, 1985. After graduating from secondary school she started studying Medicine at the University of Groningen in 2003. Before entering the internships in the fourth year she went for four months to Ruiru in Kenya, to work as a volunteer in an orphanage and school. This experience started the interest in education, and later on in her career she participated in several educational boards and committees.

From the beginning of the study she had the wish of becoming a surgeon. So in the last year of the study, in 2009, she decided to do her final internships at the surgical oncology department at the University Medical Centre Groningen and at the general surgical department at the Martini Hospital in Groningen. Here grew the interest in soft tissue sarcomas. It was a logical choice to continue with this subject for the final thesis of the study.

In anticipation of starting the thesis she searched in Pubmed for literature, and found many interesting articles from the research group in Lund, Sweden. Therefore, she wrote an email to professor Mef Nilbert in Lund and asked if it was possible to participate in scientific studies in their laboratory. She asked professor Harald Hoekstra to be her mentor in the Netherlands. And there, the idea for a PhD project became real. She worked in the laboratory in Lund from 2009 till 2010 guided by dr. Ana Carneiro, which she combined with clinical practice in Skånes Universitetssjukhus guided by professor Anders Rydholm, dr. Fredrik Vult von Steyern and dr. Emelie Styring. Continuing the collaboration with Lund, she extended her research at the University Medical Centre in Groningen in 2010. Together with professor Albert Suurmeijer, both clinical and laboratory analysis were executed.

In 2012 she continued with her ambition of becoming a surgeon and worked as a resident at the surgical department at the Martini Hospital in Groningen for one year. In 2013 she was accepted as a surgical trainee and started working as a surgical resident at the hospital Medisch Spectrum Twente, Enschede. In 2016 she continued her residency at the University Medical Centre Groningen. In the last two years of the trainee she will specialize in gastrointestinal and oncology surgery, with a special interest in endocrinology.

PhD Portfolio

PhD candidate	Jojanneke Seinen
PhD supervisors	Prof. dr. H.J. Hoekstra, Prof. dr. M. Nilbert, Prof. dr. A.J.H. Suurmeijer

Participation (inter)national congresses

2018	European Society of Endocrine Surgeons, Amsterdam, the Netherlands
2013-2018	Surgeons annual congress, Veldhoven, the Netherlands
2012	Society for Surgical Oncology (SSO), Orlando, Florida, United States
2011	Connective Tissue Oncology Society (CTOS), Chicago, United States
2011	Scandinavian Sarcoma Group (SSG), Malmo, Sweden
2011	SSO, San Antonio Texas, United States
2010	European Musculo-Skeletal Oncology Society (EMSOS), Birmingham, England
2010	CTOS, Paris, France
2009	CTOS, Miami, United States

Oral presentations

2015	Seinen JM, Mastboom WJB. Hurthle Cell carcinoma of the thyroid. *Najaarsvergadering Heelkunde*
2011	Seinen JM, Jönsson M, Bendahl PO, Baldetorp B, Rambech E, Åkerman M, Rydholm A, Nilbert M, Carneiro A. Prognostic value of proliferation markers in soft tissue sarcomas: a new look at an old measure. *SSG, Malmo, Sweden.*
2011	Seinen JM, Styring E, Vult von Steyern F, Rydholm A, Suurmeijer AJH, Hoekstra HJ. Postradiation angiosarcoma after breast cancer; high recurrence rate and poor survival despite free surgical margins. *SSG, Malmo, Sweden.*

2011 Seinen JM, Pras E, Hoekstra HJ. Study protocol isolated limb Perfusion followed by preoperative Radiotherapy, Surgery in the limb salvage treatment of locally advanced soft tissue sarcomas of the extremities. *Department of Radiology, University Medical Centre Groningen.*

2010 Seinen JM, Almquist M, Styring E, Rydholm A, Nilbert M. Delays in the management of retroperitoneal sarcomas. *EMSOS, Birmingham, England.*

2010 Seinen JM, Almquist M, Styring E, Rydholm A, Nilbert M. Delays in the management of retroperitoneal sarcomas. *Department of Surgery, Lund, Sweden.*

Poster presentations

2012 Seinen JM, Jutte PC, van Ginkel RJ, Pras E, Hoekstra HJ. Treatment associated fractures after multimodality treatment with isolated limb perfusion of soft tissue sarcomas; what to do? *SSO, Orlando, Florida, United States.*

2011 Seinen JM, van Ginkel RJ, Hoekstra HJ. Treatment options and outcome for patients developing local recurrence after isolated perfusion and delayed surgical resection. *CTOS, Chicago,Illinois,United States.*

2011 Seinen JM, Styring E, Verstappen V, Vult von Steyern F, Nilbert M, Suurmeijer AJH, Hoekstra HJ. Postradiation angiosarcoma after breast cancer; high recurrence rate and poor survival despite optimal surgical intervention. *SSO, San Antonio, Texas, United States.*

2010 Seinen JM, Carneiro A, Jonsson M, Bendahl PO, Baldetorp B, Rambech E, Rydholm A, Nilbert M. Prognostic importance of proliferation markers in soft tissue sarcomas. *CTOS, Paris, France.*

Awards

2011 Nomination Professor Chris Gips award for best thesis

2010 Best thesis in Medicine at the University Groningen

Clinical experience

2017 – 2018	Surgical resident, surgical oncology, University Medical Centre Groningen. Supervisor: dr. Robert van Ginkel
2016 – 2017	Surgical resident, general surgery, University Medical Centre Groningen. Supervisor: dr. Robert van Ginkel
2013 – 2016	Surgical resident, general surgery, Medical Spectrum Twente, Enschede Supervisor: prof. dr. Joost Klaase
2012 – 2013	Resident general surgery, Martini Hospital Groningen. Supervisor: dr. Peter Baas
2009 – 2010	Department of Orthopedic Surgery, Emergency room, Lund University Hospital, Sweden. Supervisors: prof. dr. Anders Rydholm, dr. Fredrik Vult von Steyern Associate professor, dr. Emelie Styring
2008 – 2009	Internship general surgery (14 weeks), Martini Hospital Groningen. Supervisor: dr. Gerard Glade Internship surgical oncology (6 weeks), University Medical Centre Groningen. Supervisor: prof. dr. Harald Hoekstra

Other

2017 – 2018	Member central board of education, University Medical Centre Groningen, the Netherlands Committee of activities for surgical residents, University Medical Centre Groningen, the Netherlands
2015 – 2016	Member Education Committee, Surgery region north, the Netherlands
2013 – 2016	Member Board of Residents Medical Spectrum Twente, Enschede, the Netherlands
2011 – 2012	Member of Professor Chris Gips Foundation Creating and coordinating the website of the sarcoma team, University Medical Centre Groningen, the Netherlands
2010	Volunteer Organizing Committee Karnaval Lund, Sweden
2009 – 2010	Member Theater Committee in Lund, Sweden
2008	Member Board of Education Ziekenhuisgroep Twente, Almelo, the Netherlands
2006	Volunteer orphanage, Ruiru, Kenia
2005	Volunteer institute for physical and mentally disabled people, Bedum, the Netherlands.

List of publications

1. Seinen JM, Almquist M, Styring E, Rydholm A, Nilbert M. Delays in the Management of Retroperitoneal Sarcomas. Sarcoma 2010;2010:702573
2. Seinen JM, Jönsson M, Bendahl PO, Baldetorp B, Rambech E, Åkerman M, Rydholm A, Nilbert M, Carneiro A. Prognostic value of proliferation in pleomorphic soft tissue sarcomas: a new look at an old measure. Human Pathology 2012 Dec;43(12):2247-54
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9. Seinen JM, Niebling NG, Bastiaannet E, Pras B, Hoekstra HJ. Four different treatment strategies in aggressive fibromatosis: A systematic review. Accepted Clinical and Translational Radiation Oncology
10. Seinen JM, Jutte PC, Been LB, Pras E, Hoekstra HJ. Fractures after multimodality treatment of soft tissue sarcomas with isolated limb perfusion and radiation; likely to occur and hard to heal. Eur J Surg Oncol. 2018. Apr 24. (Epub ahead of print)

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