Localized extremity soft tissue sarcoma: towards a patient-tailored approach

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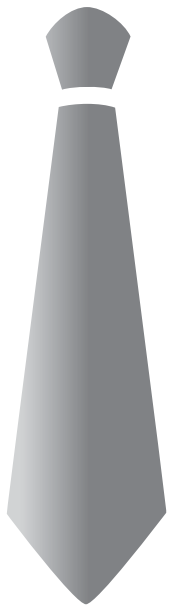

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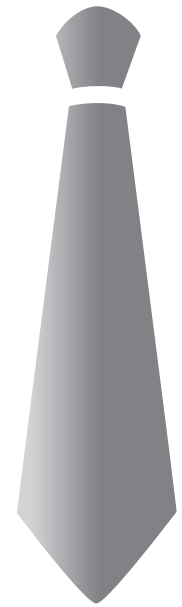

Paranimfen

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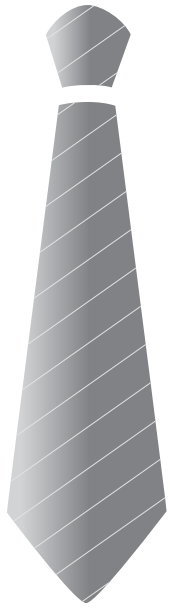
Contents

General introduction & outline of this thesis



General introduction

Soft tissue sarcomas (STS) are relatively rare malignancies accounting for less than 1% of all cancers in adults, resulting in approximately 600-700 new cases in The Netherlands annually.[1] STS form a group of heterogeneous tumors which originate from mesenchymal progenitor cells. These progenitor cells show differentiation into various mesenchymal tissues, e.g. adipose tissue, fibrous tissue and muscle tissue, and over 50 histologic STS subtypes have been described in the latest World Health Organization classification.[2,3] The most common subtypes are pleomorphic undifferentiated sarcoma (including malignant fibrous histiocytoma), leiomyosarcoma, liposarcoma, malignant peripheral nerve sheath tumor and synovial sarcoma, which combined account for approximately three fourths of all STS.[2] STS can occur at any anatomic location, while most commonly (50-60%) they arise in the extremities.[2-4] Other common locations are the head/neck area, trunk and retroperitoneum. The etiology of most STS remains unknown. While, in rare cases STS development has been associated with preceding radiation therapy, immune deficiency, viral infections and genetic and environmental factors.[2]

The incidence of STS rises with increasing patients' age and it shows a slight male predominance.[2-5] The potential of STS to metastasize and thereby to influence patients' survival and prognosis is mainly determined by the tumor grade and the histologic subtype.[2,6,7] Lymfogenic metastases are rare,[2,6] while hematogenic metastases, mainly to the lungs, are relatively common i.e. approximately 50% of all STS patients develop distant metastases during the course of their disease.[8,9] Besides tumor grade and subtype, patients' age and maximum tumor size have been shown to influence the development of distant metastases and (disease-specific) survival. Subsequently, these four parameters have been incorporated into various nomograms to predict patients' outcome.[10,11]

Prior to treatment, a MRI scan followed by a core-needle biopsy of the suspected lesion are performed, and combined they provide essential information needed for the diagnosis and accordingly for adequate treatment of the tumor. Benign soft tissue tumors, mostly lipomas, outnumber STS by 100:1.[2] If a STS is diagnosed, a baseline chest CT scan is made to exclude lung metastases prior to the start of treatment. In extremity myxoid liposarcomas also a staging abdominal CT scan, to exclude abdominal metastases, is currently advised in the latest guidelines of the European Society for Medical Oncology.[12] In case of distant metastases at diagnosis, curative-treatment is no longer feasible in most STS, except in a few chemosensitive subtypes as embryonal rhabdomyosarcoma.[2] However, the role of (neo)adjuvant systemic chemotherapy in the non-metastatic setting in most subtypes remains controversial and is under on-going investigation.[13-15]

Treatment of localized extremity soft tissue sarcomas (ESTS)

Historically the treatment of non-metastatic (localized) ESTS comprised amputation of the affected limb. However, patients who underwent limb-amputation were shown to have similar survival rates when compared with patients who underwent limb-sparing surgery (LSS) combined with external beam radiotherapy (EBRT).[16-19] Accordingly, limb-sparing treatment has become the treatment of choice in localized ESTS since the 1980s. EBRT has been used regularly in addition to LSS to gain local control, and local control rates of 90% can be achieved nowadays.[19-25] The timing of the EBRT has been studied extensively, and no differences in patients' survival were found between preoperatively and postoperatively irradiated patients.[21,26-30] Besides, EBRT might not be essential to obtain local control in some carefully selected patients, i.e. in case of low-grade tumors which are resected with a >1cm resection margin.[31,32] The data available addressing the association between local recurrence development, and subsequently the development of distant metastases and/or the risk for (disease-specific) death are contradictory. Hence, local recurrence development was found to be a predictor for the development of distant metastases and (disease-specific) death in some studies, while this finding was not confirmed in other studies.[24,33-40]

At diagnosis, some ESTS are deemed primarily non-resectable or locally advanced, mainly due to tumor size, proximity to vital structures and/or bony involvement. In these cases, a multimodality treatment-approach consisting of hyperthermic isolated limb perfusion (HILP), surgical resection and in some cases EBRT has been used in over 40 sarcoma centers throughout Europe.[41] Using this multimodality treatment, local tumor control can be achieved resulting in a limb-salvage rate of approximately 80-90% in these patients who would otherwise be considered for limb-amputation.[42-47]

Assessment of treatment efficacy

Over time, the treatment of ESTS improved and changed from limb-amputation into a more limb-sparing approach. This approach is based on a multimodality treatment-setting, e.g. neoadjuvant EBRT, systemic chemotherapy and/or HILP have been used to achieve optimal local control and to prevent limb-amputation, even in locally advanced ESTS.[44,46,48] Neoadjuvant treatment-regimens are used in daily-practice, and as a consequence multiple studies were conducted to establish the changes in these tumors during and following the treatment.

Since the 1990s, fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET-CT) scans have been used to study the changes in metabolic tumor activity induced by HILP in locally advanced ESTS.[49] Furthermore, baseline ^{18}F-FDG PET-CT scans as well as scans following neoadjuvant chemotherapy have been used to predict patients' survival.[50-52] Besides the assessment of the metabolic tumor activity of the tumor prior to and following neoadjuvant treatment, the histologic appearance of the tumor at histopathological examination has been studied. It was shown that the percentage of tumor necrosis following neoadjuvant treatment does not predict patients' survival,[53] as treatment-induced necrosis cannot be distinguished from tumor necrosis already present at diagnosis. Therefore, the percentage of viable tumor cells in pretreated STS might have more predictive value for survival. Recently, the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) published recommendations regarding the histopathological examination of pretreated STS,[54] including a 5-tier STS response score based on the percentage of stainable, possibly viable, tumor cells.

Outline of this thesis

Part I - Treatment of resectable extremity soft tissue sarcoma

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

Part II - Treatment of locally advanced extremity soft tissue sarcoma

This part highlights the treatment of locally advanced ESTS. At first, a new treatment regimen, consisting of neoadjuvant HILP, preoperative radiotherapy and surgery for locally advanced ESTS is described (**chapter 3**). Subsequently, the indications for amputation and the oncological outcome i.e. local control and survival, following limb-amputation in (locally advanced) ESTS are determined in **chapter 4**.

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

This part addresses the metabolic and histopathological tumor responses in pretreated ESTS. **Chapter 5** discusses the use of various volume of interest delineation techniques to study and quantify the changes in metabolic tumor activity using ^{18}F-FDG PET-CT scans during the multimodality neoadjuvant ESTS treatment as described in **chapter 3**.

Chapter 6 evaluates the histopathological tumor response, based on the percentage of stainable tumor cells, of pretreated ESTS using the EORTC-STBSG response score.
Summary and conclusions of this thesis are presented in English and in Dutch (**chapter 7**). Lastly, **chapter 8** provides a view on the future perspectives of ESTS treatment.

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Treatment of resectable extremity soft tissue sarcoma

PART I

Identification of predictors for wound complications following preoperative or postoperative radiotherapy in extremity soft tissue sarcoma

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Eur J Surg Oncol. 2018 Jun;44(6):816-822

Abstract

Introduction
In extremity soft tissue sarcoma (ESTS), external beam radiotherapy (EBRT) has been used in addition to limb-sparing surgery (LSS). This study aims to identify predictors for major wound complication (MWC) development following EBRT and LSS in ESTS.

Methods
This retrospective study includes ESTS patients treated with EBRT and LSS between 2005 and 2017. Two groups were formed; Group I included preoperatively irradiated patients, whereas Group II included patients who underwent postoperative EBRT. Multivariate logistic regression analyses were performed to create a prediction model for MWC development.

Results
One hundred twenty-seven patients were included, 58 patients (45.7%) in Group I and 69 patients (54.3%) in Group II. Some differences in baseline characteristics were found between the groups, e.g. in tumor size and grade, histological subtype and total RT dose. Twenty-three patients (39.7%) in Group I and 14 patients (20.3%) in Group II developed a MWC (p=0.02). Preoperative EBRT was identified as independent predictor for MWC development, OR 2.75 (95%CI 1.21-6.26), p=0.02. Furthermore, a trend towards an increased MWC risk was shown for patients' age (OR 1.02 (0.99-1.04)), delayed wound closure (OR 3.20 (0.64-16.02)) and negative surgical margins (OR 2.26 (0.72-7.11)). The area under the curve (AUC) of the model was 0.68 (0.57-0.79).

Conclusions
This study corroborates the increased MWC risk following preoperative EBRT in ESTS. It remains important to carefully weigh the MWC risk against the expected long-term functional outcome, and to consider the liberal use of primary plastic surgical reconstructions in an individualized multidisciplinary tumor board prior to treatment.

Introduction

Annually, approximately 600-700 patients are diagnosed with a soft tissue sarcoma (STS) in The Netherlands.[1] STS are heterogeneous tumors including multiple histopathologic subtypes. Approximately 50-60% of the STS arise in the extremities.[2,3]
In the past, extremity soft tissue sarcoma (ESTS) treatment traditionally involved limb-amputation. However, comparable disease-free and overall survival rates were shown for patients treated either with amputation or wide local excision and postoperative radiotherapy.[4,5] Therefore, limb-sparing treatment for ESTS has been the treatment of choice.
External beam radiotherapy (EBRT) has been used in addition to limb-sparing surgery (LSS) to gain local control in ESTS patients; a local control rate of 90% can be achieved nowadays.[5-9] However, despite extensive studying no significant differences in local control and survival between patients treated either with preoperative or postoperative EBRT and LSS have been shown to date.[10-15] So, the timing of the EBRT has been subject of debate. Nonetheless, the limb-sparing treatment of ESTS has undergone a gradual transition from postoperative to preoperative EBRT at our institution, mainly based on the data provided by the randomized trial by O'Sullivan et al.[11] The predominant disadvantages of postoperative EBRT may be the larger radiation fields, higher radiation doses and the increased risk for long-term fibrosis.[14] Accordingly, the use of preoperative EBRT has been advocated for two reasons; smaller radiation fields and lower total radiation doses, possibly leading to an improved functional outcome.[16] The predominant disadvantage of preoperative EBRT is the increased risk for postoperative wound complications.[10,11,14,17,18]
The current study aims to identify predictors for the development of postoperative wound complications in ESTS patients following pre- or postoperative EBRT and LSS.

Methods

Patients
The Institutional Review Board approved this retrospective study (case number 2016.676). This study includes ESTS patients over 18 years of age who underwent either pre- or postoperative EBRT and LSS at the University Medical Center Groningen (UMCG) between January 2005 and December 2016. All patients were treated with curative intent. Patients with 'locally advanced' ESTS treated with a combination of hyperthermic isolated limb perfusion, surgical resection and radiotherapy were ex-

cluded.[19,20] Furthermore patients with a medical history of Li-Fraumeni syndrome or neurofibromatosis were excluded. Relevant data were obtained from patient medical records. Patients' age at start of treatment is presented, and the maximum tumor diameter prior to start of treatment was used as tumor size. Tumor location was determined as follows: lower leg including the knee, upper leg including the hip, lower arm including the elbow and upper arm including the shoulder.

Prior to treatment, all STS patients are presented in a multidisciplinary sarcoma tumor board to discuss the appropriate treatment strategy for each patient. Two groups were identified; Group I included patients treated with preoperative EBRT and LSS, whereas Group II included patients treated with postoperative EBRT and LSS. All STS patients treated at the UMCG are referred to and treated by a physiotherapist and a rehabilitation specialist to optimize functional outcome following their treatment.

Radiotherapy

All patients underwent EBRT, either in the pre- or postoperative setting. Three-dimensional conformal radiotherapy (3D-CRT) was delivered with a 6-15 MV linear accelerator after patient-specific immobilization, bolus material was applied along the surgical scar. One patient was treated with intensity modulated radiotherapy (IMRT). For Group I, the diagnostic MRI scan was fused with the radiotherapy planning CT scan to obtain gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV). For Group II, the preoperative MRI scan, planning CT scan, surgical scar and markers (left at the surgical bed during the surgical resection) were used to obtain the clinical target volume (CTV) and planning target volume (PTV).
Delineation of the tumors was performed as described in the review by Haas et al.[14] Although these recommendations were published in 2012, they were already in use before that time. For Group I this meant that the CTV was constructed by expanding the GTV by 4 cm in the longitudinal direction and 1.5 cm in the other directions. Next, the PTV was obtained by expanding the CTV by 1.0 cm in all directions. The total radiation dose in Group I was 50 Gy (25x2 Gy). In case of a positive surgical margin following preoperative EBRT, no postoperative boost was considered, as this does not seem to influence local control rates.[21]

For Group II, the CTV was acquired by expanding the surgical volume by 4 cm in the longitudinal direction and 1.5 cm in all other directions. Next, the PTV was obtained by expanding the CTV by 1.0 cm in all directions. The postoperative EBRT was completed with a 5x2 Gy boost to the tumor bed, resulting in a total postoperative radiation dose of 60 Gy. A boost of 10x2 Gy was applied in case of a R1/R2 resection.

Limb-sparing surgery (LSS)

For Group I, LSS was scheduled to take place six weeks after completion of the EBRT, whereas for Group II the EBRT was planned to start 6-8 weeks after the LSS, provided sufficient wound healing. Plastic surgical reconstructions were performed when indicated, e.g. for primary wound closure or following a wound complication requiring secondary wound closure. The Union for International Cancer Control "R classification" was used to classify the 'quality' of the resection.[22]

All complications, either medical or surgical, occurring within 120 days of LSS were analyzed and scored according to Clavien-Dindo.[23] Furthermore, the occurrence of major wound complications (MWC) was monitored. A MWC was defined as a wound complication requiring any of the following, based on the study by O'Sullivan et al.[11] First, requiring a surgical intervention for wound repair e.g. debridement, abscess drainage and secondary wound closure through plastic surgical flap reconstruction or split skin graft (SSG). Second, requiring non-surgical wound management including: invasive procedure with or without regional anesthesia (e.g. seroma aspiration), readmission for the intravenous administration of antibiotics. Third, requiring persistent deep wound packing (>120 days) or requiring hyperbaric oxygen therapy to obtain wound closure. As hyperbaric oxygen treatment is intensive and generally takes 30-40 daily sessions, these wound complications were included as MWC. Furthermore, these wound complications were scored as a grade IIIa complication.[23]
Typing and grading of all histopathologic specimens, either diagnostic core needle biopsies or specimens following LSS, were performed and defined according to WHO and American Joint Committee on Cancer criteria.[24,25]

Statistical analyses

Discrete variables are presented with frequencies and percentages and continuous variables with medians and interquartile ranges. Mann-Whitney U test was used to compare continuous and ordinal variables. Fisher's exact or chi-square test were used when appropriate to compare nominal variables, p-values <0.05 indicating statistical significance. Multivariate logistic regression analyses was performed to create a prediction model for MWC development. Potential predictors were included in a first multivariate logistic regression model. Backward selection was used, and predictors with a $p<0.2$ were included in the model, 1000x bootstrapping was performed. Odds ratios (OR) and 95% confidence intervals (95% CI) are presented for the model. Subsequently, the area under the curve (AUC) was calculated to determine the predictive value of the final model. SPSS Version 23.0 (IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp) and Stata/SE version 12.0 (StataCorp, Texas, USA) were used for statistical analyses.

Table 1. Patient, tumor and disease characteristics

Characteristic	Group I (n=58)	Group II (n=69)	p-value
Age (years)	58.0 (45.8-68.3)	65.0 (52.0-74.0)	0.066
Gender			0.774
• Female	25 (43.1)	28 (40.6)	
• Male	33 (56.9)	41 (59.4)	
BMI	26.9 (23.6-30.0)	25.6 (23.9-27.8)	0.349
Smoking*			0.502
• No	49 (84.5)	62 (89.9)	
• Yes	8 (13.8)	7 (10.1)	
Diabetes mellitus			0.582
• No	53 (91.4)	61 (88.4)	
• Yes	5 (8.6)	8 (11.6)	
Tumor size (cm)	8.0 (5.8-11.0)	5.0 (3.0-8.0)	<0.001
Tumor grade#			<0.001
• Low	22 (37.9)	8 (11.6)	
• High	35 (60.3)	60 (87.1)	
Tumor location			0.086
• Lower leg	15 (25.9)	15 (21.7)	
• Upper leg	35 (60.3)	31 (44.9)	
• Lower arm	3 (5.2)	9 (13.0)	
• Upper arm	5 (8.6)	14 (20.3)	
Histological subtype			<0.001
• Myxoid liposarcoma	22 (37.9)	4 (5.8)	
• Leiomyosarcoma	5 (8.6)	8 (11.6)	
• Myxofibrosarcoma	17 (29.3)	23 (33.3)	
• Pleomorphic/NOS	8 (13.8)	15 (21.7)	
• Synovial sarcoma	0 (0)	7 (10.1)	
• MPNST	1 (1.7)	3 (4.3)	
• Other	5 (8.6)	9 (13.0)	
Local presentation			<0.001
• First	55 (94.8)	47 (68.1)	
• Recurrent	2 (3.4)	4 (5.8)	
• R2 resection elsewhere	1 (1.7)	18 (26.1)	
Distant presentation			0.500
• M0	58 (100.0)	67 (97.1)	
• M1	0 (0)	2 (2.9)	

*Data presented as: n (%); median (interquartile range). Group I: preoperative EBRT; Group II: postoperative EBRT. *Data for one patient in Group I missing. #Data missing for one patient in both groups.*

Results

A total of 127 patients, 74 male (58.3%) and 53 female (41.7%) with a median age of 62.0 (48.0-73.0) years, were included. Group I included 58 patients (45.7%) and Group II included 69 patients (54.3%). Patients in Group I had larger tumors which were more often of low grade. An unequal distribution of histological subtypes was observed among the groups. Accidental marginal resections performed at referring institutions account for the difference in local tumor presentation. No differences at baseline were found for age, gender, body mass index (BMI), smoking, diabetes mellitus and distant presentation (Table 1). Two patients in Group II were diagnosed with regional disease at presentation. Both were diagnosed with a lymph node metastasis, and were treated with curative intent by a lymph node dissection in addition to the LSS and postoperative EBRT.

The distribution of patients according to the year of treatment differed significantly among the two groups (p<0.001). Between 2005 and 2007, one patient underwent preoperative EBRT while 35 patients underwent postoperative EBRT in this time period. Whereas, 35 patients underwent preoperative EBRT and four patients underwent postoperative EBRT between 2014 and 2016. In Group I, the median time between completion of EBRT and LSS was 7.0 (6.0-9.3) weeks. In Group II the median time between LSS and start of EBRT was 6.0 (5.0-7.0) weeks. Total EBRT dose differed between

Table 2. Treatment-related characteristics

Characteristic	Group I (n=58)	Group II (n=69)	p-value
Year of treatment			<0.001
• 2005-2007	1 (1.7)	35 (50.7)	
• 2008-2010	10 (17.2)	21 (30.4)	
• 2011-2013	12 (20.7)	9 (13.0)	
• 2014-2016	35 (60.3)	4 (5.8)	
Operation time (min)	91.0 (58.0-129.5)	70.0 (48.0-103.0)	0.027
Size resection specimen (cm, diameter)	13.0 (9.0-16.0)	11.5 (7.0-15.8)	0.135
Total EBRT dose* (Gy)	50.0 (50.0-50.0)	60.0 (60.0-70.0)	<0.001
EBRT technique			0.457
• 3D-CRT	57 (98.3)	69 (100)	
• IMRT	1 (1.7)	0 (0)	
Resection quality, tumor margin			0.406
• R0	48 (82.8)	54 (78.3)	
• R1	10 (17.2)	13 (18.8)	
• R2	0	2 (2.9)	
Timing wound closure			0.701
• Direct	54 (93.1)	66 (95.7)	
• Delayed awaiting pathology report	4 (6.9)	3 (4.3)	

Group I and II (p<0.001), and the operation time was longer for patients in Group I, 91.0 (58.0-129.5) vs. 70.0 (48.0-103.0) minutes, p=0.027. No differences considering EBRT technique (3D-CRT vs. IMRT), resection quality, timing or type of wound closure and the use of reconstructive surgery, either primary or secondary, were found. Among the series, a total of seven patients (5.5%) underwent delayed wound closure awaiting the final pathology report. Primary wound closure was achieved in 47 patients (81.0%) and 58 patients (84.1%) in Group I and II respectively. A split skin graft was used for wound closure in five patients (8.6%) in Group I and in eight patients (11.6%) in Group

Table 2. Continued

Characteristic	Group I (n=58)	Group II (n=69)	p-value
Type wound closure			0.386
• Primary	47 (81.0)	58 (84.1)	
• Split skin graft	5 (8.6)	8 (11.6)	
• Vascularized tissue	6 (10.3)	3 (4.3)	
Reconstructive surgery (primary or secondary)			0.059
• No	50 (86.2)	66 (95.7)	
• Yes	8 (13.8)	3 (4.3)	
Timing reconstructive surgery			
• Direct	4	3	
• Secondary awaiting final pathology report	2	0	
• Secondary due to MWC	2	0	
Type reconstructive surgery			
• Free flap	1	0	
• Pedicled flap	7	3	

*Data presented as: n (%); median (interquartile range). Group I: preoperative EBRT; Group II: postoperative EBRT. *All patients in Group I underwent 50 Gy (25x2Gy) EBRT. In Group II: 67 patients (97.1%) underwent 60-70 Gy EBRT. One patient in Group II underwent an hyperfractionated EBRT schedule of 30x1.8 Gy resulting in a total dose of 54 Gy. The second patient developed a local recurrence and distant metastases during the postoperative radiation therapy and the EBRT was aborted after a local palliative dose of 50 Gy. Abbreviations: EBRT=external beam radiotherapy; 3D-CRT=three-dimensional conformal radiotherapy; IMRT=intensity modulated radiotherapy.*

II. Vascularized tissue was used for wound closure in the remaining six patients (10.3%) in Group I and three patients (4.3%) in Group II. However, in Group I an extra two patients ultimately required reconstructive surgery to obtain wound closure due to the development of a MWC (13.8% in total in Group I) (Table 2).

Table 3. Complications for Group I and II according to Clavien-Dindo[23]

	Group I (n=58)	Group II (n=69)	p-value
Total amount of complications	**53**	**42**	
Grade I	**10 (18.9)**	**11 (26.2)**	
Medical	2	2	
• Collapse	1	0	
• Urinary retention	1	2	
Surgical	8	9	
• Seroma	4	6	
• Neuropraxia	2	1	
• Delayed wound healing	1	2	
• Hematoma	1	0	
Grade II	**18 (34.0)**	**14 (33.3)**	
Medical	4	5	
• Atrial fibrillation	2	0	
• Anemia	1	2	
• Pulmonary embolism	1	1	
• Deep venous thrombosis	0	1	
• Urinary tract infection	0	1	
Surgical	14	9	
• Infection needing oral antibiotics	11	7	
• Infection needing intravenous antibiotics	***3***	0	
• Delayed wound healing	0	1	
• Split skin graft loss*		***1***	

Table 3. Continued

	Group I (n=58)	Group II (n=69)	p-value
Total amount of complications	53	42	
Grade IIIa	**9 (17.0)**	**12 (28.6)**	
• Infection	***2***	***4***	
• Seroma	***2***	***5***	
• Wound dehiscence	0	***1***	
• Hematoma	0	***2***	
• Delayed wound healing (hyperbaric O2)	***5***	0	
Grade IIIb	**12 (22.6)**	**5 (11.9)**	
• Infection	***9***	***1***	
• Total flap loss	***1***	0	
• Partial flap necrosis	***1***	0	
• Postoperative bleeding	1	3	
• Compartment syndrome	0	1	
Grade IV	**2 (3.8)**	**0 (0)**	
• Systemic sepsis	1	0	
• Postoperative arterial bleeding	1	0	
Grade V	**2 (3.8)**	**0 (0)**	
• Systemic sepsis	1	0	
• Esophageal ischemia	1	0	
Total patients developing a complication	**34 (58.6)**	**35 (50.7)**	**0.475**
Patients developing a MWC	**23 (39.7)**	**14 (20.3)**	**0.020**

*Data presented as: n (%); Group I: Preoperative EBRT; Group II: Postoperative EBRT. *The split skin graft used for wound closure was lost and removed during an outpatient clinic visit, resulting in delayed wound healing. The complications accounting for the MWCs are indicated in bold italic for both groups.*

Complications

A total of 53 complications in Group I and 42 complications in Group II occurred. Thirty-four patients (58.6%) in Group I and 35 (50.7%) in Group II developed at least one complication (p=0.475). Fifteen patients (25.9%) in Group I and six patients (8.7%) in Group II developed >1 complication. Grade II was the predominant complication grade for both groups. Twenty-three patients (39.7%) in Group I and 14 patients (20.3%) in Group II developed a MWC (p=0.02) (Table 3).

The following variables: age, gender, local presentation, histologic subtype, tumor location, tumor size, tumor grade, BMI, smoking, diabetes, operation time, type wound closure, timing wound closure (delayed vs. direct), reconstructive surgery (only including patients for whom vascularized tissue was used for initial wound closure), radiotherapy timing (preoperative vs. postoperative), and tumor margin (R0 vs. R1/R2) were included in the initial model. Multivariate analyses identified preoperative EBRT as predictor for MWC development, OR 2.75 (1.21-6.26), p=0.02. A trend towards an increased MWC risk was found for age OR 1.02 (0.99-1.04), p=0.18, timing of wound closure (delayed vs. direct) OR 3.20 (0.64-16.02), p=0.16 and tumor margins (R0 vs. R1/R2) OR 2.26 (0.72-7.11), p=0.16 (Table 4). The predictive value of this model i.e. the AUC is 0.68 (0.57-0.79) (Figure 1).

Table 4. Final prediction model for the development of a major wound complication

Predictor	OR	95% CI	p-value
Radiotherapy timing			0.02
• Postoperative	1		
• Preoperative	2.75	1.21-6.26	
Age, continuous	1.02	0.99-1.04	0.18
Timing wound closure			0.16
• Direct	1		
• Delayed	3.20	0.64-16.02	
Tumor margins			0.16
• R1/R2	1		
• R0	2.26	0.72-7.11	

Data presented as OR and 95% CI, age in years. Abbreviations: OR=odds ratio; CI=confidence interval.

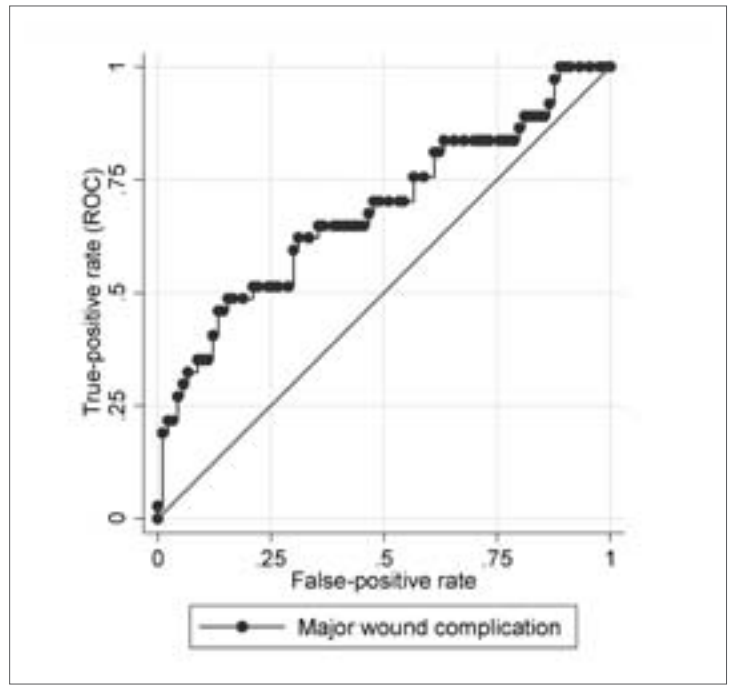

Figure 1. *Receiver operating characteristic (ROC) curve for the development of a major wound complication. Area under the curve is 0.68 (0.57-0.79).*

Discussion

This study shows a significantly increased MWC risk following preoperative EBRT and LSS in ESTS, as nearly 40% of the patients in Group I and 20.3% of the patients in Group II developed a MWC (p=0.02). Multivariate logistic analyses identified preoperative EBRT as significant predictor for MWC development. This finding corroborates earlier reported data.[11,14,17,26] Furthermore, a trend towards an increased MWC risk was shown for elderly patients, patients who underwent an R0 resection and patients who underwent delayed wound closure.

ESTS patients' survival is not influenced by the timing of the EBRT.[11-15] Therefore, the rationale for the timing of EBRT has been based on patient specific variables. These variables comprise expected short- and long-term treatment-induced morbidity e.g. tumor size, tumor depth, radiation dose, timing of the EBRT and also tumor histology i.e. the proven radiosensitivity of myxoid liposarcomas. During preoperative EBRT the tumor volume of some STS increases, however, this increase in volume does not seem to influence local control rates.[27] Several studies, including the randomized trial by O'Sullivan et al., showed significantly more acute wound complications following preoperative EBRT when compared to postoperative EBRT. These studies show that approximately 30-35% of the preoperatively irradiated patients develop a postoperative MWC, compared to approximately 10-20% of patients following postoperative EBRT.[10,11,14,17,18,26] On the contrary, due to the often larger radiation field-size and higher radiation dose, postoperative EBRT is associated with higher risk of fibrosis, joint stiffness and edema during long-term follow-up. The presence of these late complications leads to an impairment in patients' functional outcome.[16]
At our institution a tendency towards the use of preoperative EBRT has taken place during the last years. Hence, in the current study only one of the 36 patients treated between 2005 and 2007 underwent preoperative EBRT, whereas 35 of the 39 patients treated between 2014 and 2016 underwent preoperative EBRT. Preoperative EBRT seems supported by a recent cost-effectiveness analysis, due to more costly postoperative EBRT-induced long-term morbidity.[28] However, there are also data showing that patients' functional outcome is adversely affected by the development of a postoperative MWC.[29,30] Therefore, the cost-effectiveness of preoperative radiotherapy might be questioned.
In myxoid liposarcoma, preoperative EBRT has become standard due to its proven radiosensitivity.[31,32] Accordingly, a radiotherapy dose reduction study in myxoid liposarcoma (NCT02106312) was initiated and first results are awaited. This dose reduction of preoperative EBRT (total dose of 36 Gy) might subsequently result in a decreased MWC risk in this specific histological subtype. Besides dose reduction, preoperative hypofractionated EBRT (5x5 Gy) followed by LSS within one week also seems to be effective in myxoid liposarcoma.[33]

Hypofractionated EBRT has been studied and used more commonly in other cancers, e.g. breast and rectal cancer.[34,35] Data on hypofractionated EBRT in extremity and trunk STS is scarce. A study by Kosela et al. showed that oncological outcome was comparable following 5x5 Gy hypofractionated preoperative EBRT and LSS within one week, when compared with the commonly used 25x2 Gy regimen.[36] Only 7% of the patients in this study required a surgical intervention for the treatment of a wound complication. Furthermore, preoperative hypofractionated EBRT in STS is under ongoing investigation in a phase II trial (NCT02701153), of which the preliminary results were recently presented at the Connective Tissue Oncology Society Annual Meeting, 2017, showing a MWC rate of 17% in these patients.[37]

The current study has some limitations. The small sample size and the retrospective nature of the study harbors the risk of selection bias and missing data. Unfortunately, we were unable to identify and include the patients who were scheduled for LSS and postoperative EBRT, but who failed to undergo the scheduled EBRT. However, we were able to retrieve the patients who were scheduled for preoperative EBRT and LSS who did not undergo LSS. These 8 patients underwent preoperative EBRT, but failed to undergo LSS due to various reasons i.e. local tumor progression during the preoperative EBRT resulting in a non-resectable tumor in one patient, development of distant metastases during EBRT resulting in a palliative setting in five patients and declining health status during EBRT resulting in a situation in which LSS was not feasible in two patients. Although all patients were referred to and treated by a physiotherapist and a rehabilitation specialist, no standardized long-term functional outcome was obtained. Therefore, we were unable to include patients' functional outcome in this study. Moreover, there were some differences in baseline- and treatment characteristics between both groups. Patients in Group I had larger tumors, which might explain the longer operation time, but more importantly this might also partly explain the higher amount of MWCs in Group I. However, neither tumor size nor operation time were identified as independent predictor for MWC development in the current study. Histological subtype differed between the groups, with significantly more low grade tumors in Group I. Since 20 of the myxoid liposarcomas (90.9%) included in Group I were low grade sarcomas, the larger proportion of myxoid liposarcomas in Group I might account for the difference in histological subtype as well as for the difference in tumor grade between the groups. The prediction model for MWC development should be interpreted with caution, the relative small sample size and low amount of events, 37 MWCs in total, influence the predictive value and the AUC for the ROC-curve of the model. However, the model identified preoperative EBRT as significant predictor for MWC development, although some residual confounding might be present. The fact that elderly patients, or patients who underwent delayed wound closure tend to have a higher MWC risk seems reasonable. We cannot explain the association between Ro-resections and the increased MWC risk. Possibly, bias plays a role, where preoperatively irradiated patients have an increased MWC risk but also a higher chance to undergo a Ro-resection[38], but we could not show a difference in margin status in our series.

STS management and outcome can be improved by further centralization of sarcoma treatment.[3,39] The multidisciplinary evaluation of patient- and tumor characteristics, as well as expected short- and long-term treatment-induced morbidity prior to the start of treatment results in an individualized approach.[40] Furthermore this dedicated sarcoma treatment might facilitate a more liberal and consequent use of primary reconstructive surgery which might lower the MWC risk in preoperative irradiated patients.[26,41,42] Hence, in patients who underwent flap reconstruction, preoperative EBRT was not associated with MWC development.[43] Moreover, early involvement of the plastic surgeon might enable the radiation oncologist to spare skin and soft tissue, i.e. consider them as 'organ at risk', which are planned to be used for the plastic surgical reconstruction.

Further studies considering the 'protective' influence of primary reconstructive surgery as well as studies comparing hypofractionated EBRT with conventionally fractionated EBRT are necessary.[44]

Conclusions

This study corroborates the increased MWC risk following preoperative radiotherapy and LSS when compared with postoperative radiotherapy and LSS in ESTS. Therefore, it remains important to carefully weigh the MWC risk against the expected long-term functional outcome, and to consider the liberal use of primary plastic surgical reconstructions in an individualized multidisciplinary tumor board prior to ESTS treatment.

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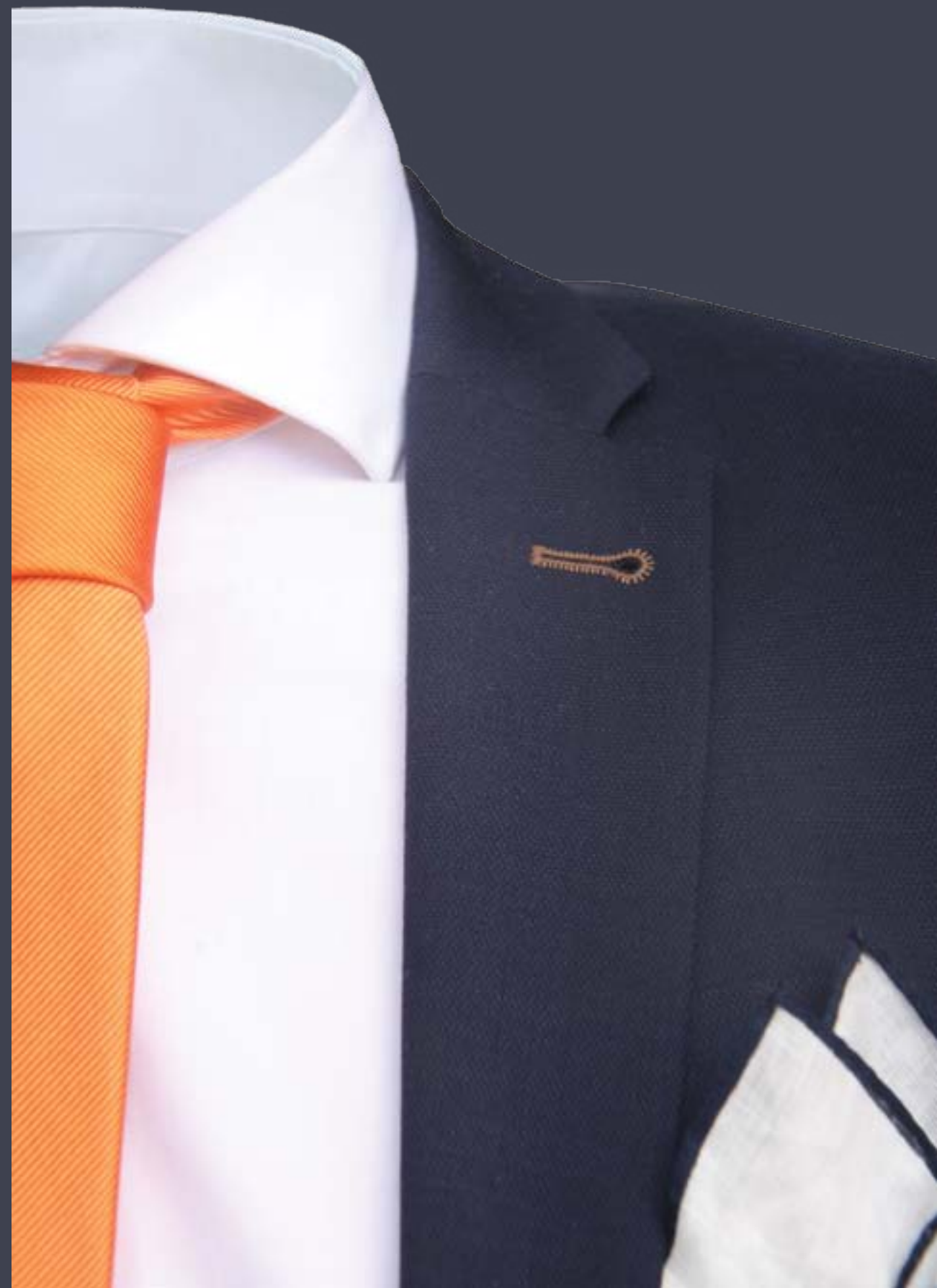
Treatment of locally advanced extremity soft tissue sarcoma

PART III



Hyperthermic isolated limb perfusion, preoperative radiotherapy, and surgery (PRS) a new limb saving treatment strategy for locally advanced sarcomas

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Abstract

Background

This feasibility study presents the results of a new intensive treatment regimen for locally advanced extremity soft tissue sarcomas (ESTS), consisting of hyperthermic isolated limb perfusion (HILP), preoperative external beam radiotherapy (EBRT) and surgical resection.

Methods

From 2011 to 2016, 11 high grade locally advanced ESTS patients underwent this treatment regimen. Preoperative EBRT (12x3 Gy) started <4 weeks following the HILP (TNF-α and melphalan) and the surgical resection was planned to take place <2 weeks following the end of the EBRT.

Results

All patients completed the treatment. After a median follow-up of 32 (23-50) months, the limb was saved in 10 patients (91%), 1 patient (9%) developed a local recurrence, 5 patients (45%) developed distant metastases and 3 patients (27%) died of their disease. During follow-up two patients (18%) developed a pathologic fracture of the treated limb and three patients (27%) developed a major wound complication requiring surgical intervention. The median overall treatment time (OTT) was 56 (49-69) days.

Conclusions

This intensive treatment regimen is feasible and safe in locally advanced ESTS, and it achieves oncological results that are comparable with conventional HILP treatment. In addition, the major wound complication risk is comparable and the OTT is reduced.

Introduction

Annually, approximately 600-700 patients are diagnosed with soft tissue sarcoma (STS) in The Netherlands, making it a relatively rare malignancy which accounts for less than 1% of all cancers in adults.[1]

In patients with extremity soft tissue sarcoma (ESTS), amputation does not improve survival rates.[2] Thus limb salvage treatment has become increasingly important over the years[3] and neoadjuvant treatment regimens have been developed to prevent limb amputation in locally advanced ESTS. In the 1990s, there was renewed interest in hyperthermic isolated limb perfusion (HILP), originally developed by Creech et al. in 1957,[4] for treating locally advanced ESTS.[5-7] Initially, interferon-γ (IFN) and tumor necrosis factor-α (TNF-α) were added to the commonly used melphalan perfusate. However, IFN was soon abandoned due to ineffectiveness.[8,9] The addition of TNF-α however, led to high response rates and limb preservation,[8,9] and eventually to the approval of TNF-α in Europe,[10] resulting in over 40 centers using HILP in the treatment of locally advanced ESTS.[11]

Since 1991, patients with locally advanced ESTS have been treated at the University Medical Center Groningen (UMCG) with neoadjuvant HILP followed by delayed surgical resection, and postoperative external beam radiotherapy (EBRT) when indicated. Hoven-Gondrie et al. described this cohort of 113 patients, of which 63 patients (56%) underwent HILP, surgery, and postoperative EBRT and 50 patients (44%) underwent HILP and surgery alone.[12] This conventional perfusion treatment is extensive, long lasting, and the recovery and waiting time between the different treatment stages is long (six to eight weeks between neoadjuvant HILP and surgical resection and another six to eight weeks between surgical resection and the start of the postoperative EBRT, resulting in an overall median treatment time of 22 (20-24) weeks (including the postoperative EBRT). Due to the postoperative timing of the EBRT, radiation schemes are long and high doses are administered i.e. 30-35x2 Gy. A follow-up study performed at the UMCG showed serious long-term treatment induced morbidity in 63% of patients.[13] Moreover, the long-term morbidity tends to be higher in postoperative irradiated patient as compared with preoperative EBRT in ESTS.[14]

The standard preoperative EBRT dose for ESTS is 50 Gy given in 25 daily fractions of 2 Gy, however, several studies have been conducted combining preoperative hypofractionated EBRT with neoadjuvant chemotherapy.[15]

At the UMCG a new intensive treatment regimen consisting of Perfusion, hypofractionated preoperative Radiotherapy and Surgery (PRS) for locally advanced ESTS was investigated with the ultimate goal to reduce the short- and long-term treatment-induced morbidity and to reduce the overall treatment time (OTT) while achieving comparable oncological outcome. The results of this treatment regimen are presented in this feasibility study.

Materials and methods

Patients

From 2011 to 2016, 11 patients, nine males and two females with a median age of 64 (44-74) years were included in this novel, Institutional Review Board (IRB) approved, treatment regimen (IRB protocol review case-number 2010.299). Patients diagnosed with a primarily non-resectable (locally advanced), non-metastatic, high grade ESTS were included in this study. At the UMCG all sarcoma patients are presented and discussed in a weekly multidisciplinary sarcoma team meeting. Accordingly, patients eligible for HILP treatment were included in the PRS treatment regimen based on a tumor board decision. Data were prospectively collected and retrospectively analyzed. The PRS treatment consisted of neoadjuvant HILP, preoperative hypofractionated EBRT, followed by surgical resection with plastic surgical reconstruction when required. All patients were treated by a rehabilitation specialist and/or physiotherapist prior to, during, and after the treatment course, to optimize the functional treatment outcome. Follow-up ended at death or April 30, 2017. Data concerning demographics, tumor characteristics, comorbidity, hospitalization and follow-up were collected from medical records. The OTT was defined as the time between HILP and surgical resection and was used as marker to estimate the extent of treatment.

Perfusion

The HILP procedure at the UMCG is based on the procedure developed by Creech et al.[4] The operation was performed under general anesthesia. An incision was made, and the major artery and vein of the leg were isolated, collateral vessels ligated, and 3.3 mg heparin per kg bodyweight was given intravenously. The blood flow of the leg was isolated from the systemic circulation by cannulating the main artery and vein and connecting it to an extracorporeal circuit. Subsequently, a tourniquet was applied to minimize leakage of TNF-α (Beromun®, Boehringer-Ingelheim GmbH, Vienna, Austria) and/or melphalan (Alkeran®, GlaxoSmithKline Pharmaceuticals, Research Triangle Park, NC, USA) into the systemic circulation. A precordial scintillation detector and I^{131}-human serum albumin were used to continuously measure the leakage into the systemic circulation.[16,17] The ILP was performed under controlled mild hyperthermia (38.5-40.0˚C). For upper extremity and popliteal perfusions, 1 mg TNF-α was used; while, 2 mg was used for iliac or femoral perfusions. After 15 min of TNF-α perfusion, melphalan (10 mg/L limb volume for upper extremity and popliteal perfusions and 13 mg/L for iliac and femoral perfusions) was added. After another 45 min, the limb was washed with 2 L (for upper extremity and popliteal perfusions) or 6 L (iliac/femoral) of saline. Afterwards, the limb was filled with red blood cell concentrate (1 U). The cannulas were removed, the vessels repaired, and the heparin antagonized with protamine sulphate. To prevent a compartment syndrome, a closed fasciotomy of the anterior compartment of the lower leg was performed.[18,19] The patient was closely observed in the intensive care unit for the first 24 hours following the procedure. The complete perfusion technique and leakage monitoring have been previously described in more detail.[20]

Radiotherapy

To complete the neoadjuvant therapy, patients were treated with preoperative hypofractioned PET-CT guided EBRT, which was planned to start 4 weeks after HILP. Patients underwent an FDG PET-CT in radiation position to delineate the tumor, and to obtain gross tumor and planning target volumes (Figure 1). Intensity modulated radiotherapy was delivered with a linear accelerator in a hypofractionated schedule of 12x3 Gy.

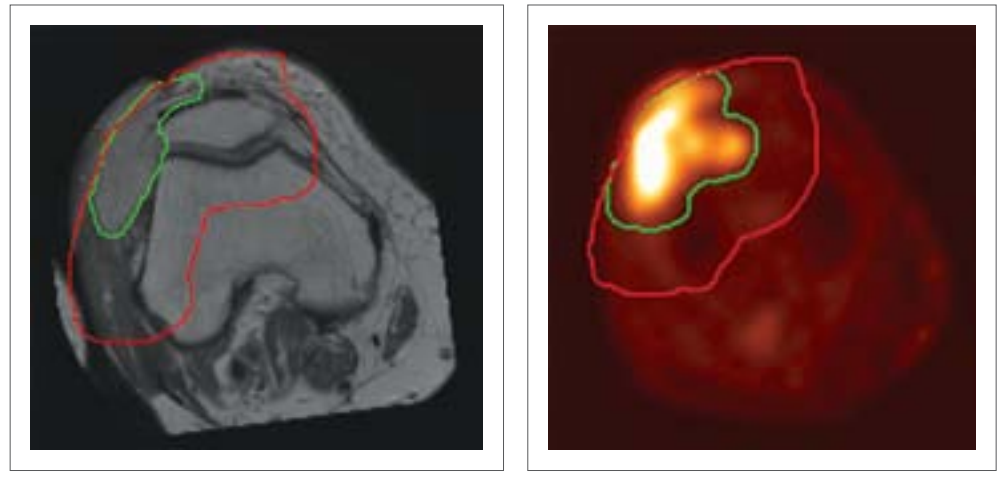

Figure 1. *Delineation of a soft tissue sarcoma of the knee. In green the gross tumor volume and in red the planning target volume. On the left: a MRI scan fused to the radiotherapy planning CT-scan is shown, while on the right the FDG PET-CT scan is used for the delineation.*

Resection

After completion of the preoperative EBRT, the surgical resection was scheduled to take place within 2 weeks. Since only patients with locally advanced ESTS were included, extensive surgical resections were performed. To achieve wound closure, plastic surgical reconstructions were performed when required. Excision was classified as R0 when the resection margins were microscopically free of tumor cells, as R1 when resection margins were involved microscopically, and as R2 when resection margins were macroscopically comprised.[21] Complications that occurred during treatment or within 120 days following the surgical resection were noted and classified according to Clavien-Dindo.[22] Wound complications requiring surgical intervention were defined as major wound complication.

Histopathologic examination

Prior to treatment, a core needle biopsy was performed for histopathologic typing and grading of the tumor.[23,24] All pathologic specimens were re-evaluated in 2017 by a pathologist with expertise in STS. The histopathologic tumor response to neoadjuvant treatment was determined following recently published European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) recommendations.[25] As follows: Grade A, no stainable tumor cells left; Grade B, single stainable tumor cells or small clusters (overall <1% left); Grade C, ≥1% - 10% stainable tumor cells left; Grade D, ≥10% - <50% stainable tumor cells left; and Grade E, ≥50% stainable tumor cells left.

Statistical analysis

All variables were summarized with frequencies and percentages for discrete variables and medians and interquartile ranges (IQRs) for continuous variables; none of the variables were normally distributed. SPSS Version 22.0 (IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp) was used for statistical analyses.

Results

All 11 patients, 9 males (82%) and 2 females (18%) with a median age 64 (44-74) years completed the scheduled PRS treatment regimen and all tumors were resectable following the neoadjuvant HILP and preoperative EBRT (Table 1). All tumors were high grade. Due to vascular involvement, one patient (9.1%) needed a vascular reconstruction following the surgical resection of the tumor remnant. Direct plastic surgical reconstructions were performed in three patients (27%) to obtain wound closure. Histopathologic examination of the resected specimens showed six R0 (55%), four R1 (36%) and one R2 resections (9%). The neoadjuvant treatment-induced tumor responses were: one grade A (9%), one grade B (9%), two grade C (18%), five grade D (45%), and two grade E (18%).

A total of 14 complications (either medical or surgical) occurred in 10 patients following the PRS treatment (Table 2). Three patients (27%) developed a major wound complication (requiring surgical intervention), caused by necrosis or ischemia of the wound or surgical flap reconstruction. In one of these patients a lower limb amputation had to be performed due to ischemia causing an on-going secondary infection of the plastic surgery reconstruction. The median OTT for the PRS patients was 56 (49-69) days.

After a median follow-up of 32 (23-50) months, limb salvage was achieved in 10 patients (91%). One patient (9%) developed a local recurrence, five patients (45%) developed distant metastasis and three patients (27%) died of their disease. At end of follow-up six patients (55%) were alive without evidence of disease and two patients (18%) were alive with disease (Table 3). During follow-up, two pathologic fractures (18%) of the treated limb occurred: a femoral and a tibia compound fracture. The femoral fracture was treated by intramedullary fixation (Figure 2), and the tibia compound fracture was treated conservatively.

Discussion

The current study shows that the combination of neoadjuvant HILP and preoperative EBRT is feasible in locally advanced ESTS. Over the past decades the limb saving treatment for locally advanced ESTS has evolved greatly, and new treatment strategies in ESTS treatment have been developed with the goal to improve outcome and/or to decrease morbidity. First, the addition of postoperative EBRT to HILP and delayed surgical resection resulted in a significant improvement in local control without increasing morbidity in ESTS patients.[26,27] Moreover, a follow-up study showed that dose reduction and a shorter HILP duration was safe and effective for patient outcome, as the 5-year local control rates and (limb) survival were not compromised.[28]

HILP followed by delayed surgical resection and postoperative EBRT when indicated is commonly used and accepted throughout Europe to achieve local tumor control and limb salvage in locally advanced ESTS.[11] This results in a limb salvage rate of approximately 80-90% in patients who would otherwise be considered for amputation.[8,9,12,29-32] A systematic review by Bhangu et al.[29] reported a limb salvage rate of 81%,

Table 1. Patient and tumor characteristics

Patient	Gender	Age	Histopathologic findings	Location	Tumor size
1	M	32	Synovial sarcoma	Upper leg	6
2	F	41	Synovial sarcoma	Lower leg	4
3	F	74	Pleomorphic undifferentiated sarcoma	Upper leg	10
4	M	54	Pleomorphic undifferentiated sarcoma	Upper leg	17
5	M	63	Pleomorphic undifferentiated sarcoma	Lower leg	9
6	M	71	Myxofibrosarcoma	Upper leg	5
7	M	44	Myxofibrosarcoma	Upper leg	17
8	M	74	Pleomorphic undifferentiated sarcoma	Knee	7
9	M	64	Leiomyosarcoma	Knee	6
10	M	75	Pleomorphic undifferentiated sarcoma	Lower leg	8
11	M	67	Leiomyosarcoma	Knee	6

Age at start of treatment (years). Tumor size; maximum diameter (cm) at preoperative MRI-scan.

local recurrence rate of 27%, distant failure rate of 40% and a median 5-year disease specific survival ranging from 47-56% following HILP for ESTS.[29]

The oncological outcome for patients following the PRS treatment regimen i.e. limb salvage rate of 91%, local recurrence rate of 9%, distant failure rate of 45% and disease-specific survival of 73% seems to be comparable with the oncological outcome as reported in the literature.[8,9,12,29-32]
The subtle higher limb salvage rate in the current study might be due to the relatively short follow-up. This might also account for the lower local recurrence rate and higher disease specific survival rate in the current study. However, the difference in local recurrence rate might also be caused by the consequent use of preoperative EBRT in the current series. Postoperative EBRT following HILP and delayed surgical resection was shown to improve the local tumor control in locally advanced ESTS, whereas the timing of EBRT does not seem to influence the oncological outcome in resectable ESTS.[33-36] The distant failure rate in the current series (45%) seems similar to the 40% previously reported.[29] However, due to the small sample size and relative short follow-up, the current results should be interpreted with some caution and they need further confirmation in larger patient-cohorts.

Table 2. Complications following PRS treatment

Total amount of complications	PRS (n=11) n=14	Complication grade according to Clavien-Dindo[22] I-IIIb
Medical	3 (21%)	
• Urinary tract infection	1	II
• Urinary retention	2	I
Surgical	11 (79%)	
• Seroma	2	I
• Rash following melphalan administration	1	I
• Wound infection needing intravenous antibiotics	1	II
• Deep venous thrombosis	1	II
• Cellulitis needing intravenous antibiotics	3	II
• Wound infection	1	IIIb
• Partial flap loss	2	IIIb
Patients developing a complication	**10 (91%)**	
Patients developing a major wound complication	**3 (27%)**	

Major wound complication: wound complication occurring during treatment or <120 days of surgical resection requiring surgical intervention. Abbreviation: PRS=perfusion, preoperative radiotherapy and surgery.

The major wound complication risk found in the current study seems to be comparable with earlier reported data, which showed that 26% of patients required re-operation, re-intervention or deep wound packing due to a wound complication, after surgical resection following isolated limb perfusion.[31] The subtle higher percentage in the current study might be related to the intensified and shortened treatment course, whereas the administration of EBRT in the preoperative setting in the PRS treatment regimen might also play a role.[33]

Table 3. Treatment results and oncological outcome

Patient	Histopathologic response Grade*	R-status#	Local recurrence	Distant metastases	Status
1	C	R0	No	No	Alive without disease
2	D	R0	No	Yes	Died of disease
3	D	R0	No	No	Alive without disease
4	D	R1	No	Yes	Died of disease
5	A	R0	Yes	Yes	Died of disease
6	E	R1	No	No	Alive without disease
7	D	R0	No	Yes	Alive with disease
8	B	R0	No	No	Alive without disease
9	D	R1	No	Yes	Alive with disease
10	E	R1	No	No	Alive without disease
11	C	R2	No	No	Alive without disease

**Histopathologic response Grade A, no stainable tumor cells left; Grade B, single stainable tumor cells or small clusters (overall <1% left); Grade C, ≥1% - 10% stainable tumor cells left; Grade D, ≥10% - <50% stainable tumor cells left; and Grade E, ≥50% stainable tumor cells left.[25] #R-status.[21]*

Due to tumor heterogeneity in STS, tumor necrosis present prior to the start of treatment cannot be distinguished from tumor necrosis induced by neoadjuvant treatment, possibly leading to an overestimation of the effect of neoadjuvant treatment. Therefore, the effectiveness of neoadjuvant treatment, based on tumor necrosis, reported in previous studies, including UMCG HILP series, might be questioned and tumor necrosis should not be used when making treatment decisions.[25,37] Moreover, the tumor response can differ throughout these heterogeneous tumors while the tumor response at the closest surgical margin might have the most predictive value for local recurrence. In 2016, this led to a proposal for the standardization of the histopathologic examination of STS by the EORTC-STBSG. This protocol included a STS response score in which the tumor response to neoadjuvant treatment is estimated according to the proportion of stainable tumor cells.[25] A recent study did not find an association between the STS response score and survival following preoperative EBRT and

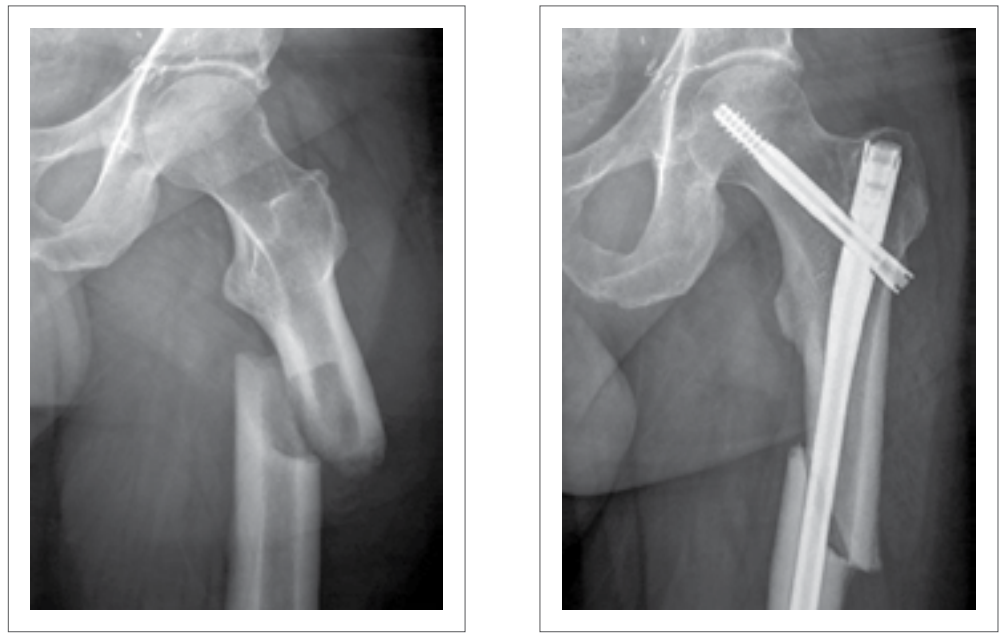

Figure 2. *Pathologic femoral fracture treated by intramedullary fixation.*

surgical resection.[38] However, further studies considering local control and survival are necessary.

Postoperative EBRT in ESTS is characterized by long treatment times and high doses of radiotherapy resulting in increased long-term morbidity when compared with preoperative EBRT.[14,15,33,35] Furthermore, the conventional HILP treatment is extensive, long lasting and includes long waiting periods between the different treatment stages (i.e. 6-8 weeks between the HILP and surgical resection, and another 6-8 weeks between the surgical resection and the start of postoperative EBRT). Despite the higher major wound complication risk incorporated with preoperative EBRT, a tendency towards the use of preoperative EBRT seems to have originated in the treatment of resectable ESTS.
As mentioned, the standard preoperative EBRT dose in ESTS treatment is 50 Gy in 25 daily fractions of 2 Gy nowadays.[15] In the past various preoperative hypofractionated EBRT regimens, 10x3.5 Gy, 10x3 Gy, 5x3.5 Gy and 8x3.5 Gy, combined with neoadjuvant chemotherapy have been conducted and resulted in acceptable local control rates.[39-43] Recently, the oncological outcome in resectable ESTS and trunk STS following 5x5 Gy hypofractionated preoperative EBRT was found to be comparable with the onco-

logical outcome following the commonly used 25x2 Gy regimen. Furthermore, only 7% of the patients in the 5x5 Gy study developed a wound complication requiring a surgical intervention.[44] Dose reduction and hypofractionation in localized myxoid liposarcomas is under ongoing investigation and the first results of the DOREMY-study (NCT02106312) are awaited. These new hypofractionated preoperative EBRT schemes might lead to a further reduction in wound complication risk.
In summary, the results of the current study indicate that combining HILP and preoperative hypofractionated EBRT as neoadjuvant treatment is feasible and might further improve the treatment of patients with locally advanced ESTS without increasing the risk of local failure.

Conclusion

This study demonstrates that the intensive PRS treatment regimen is feasible and safe in locally advanced ESTS. The PRS treatment which combines neoadjuvant HILP and preoperative EBRT, achieves oncological results that are comparable with oncological outcome from earlier reported data. In addition, the major wound complication risk is comparable and the overall treatment time is reduced.

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Amputations for extremity soft tissue sarcoma in an era of limb salvage treatment: local control and survival

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Abstract

Background
Despite multimodality limb salvage treatment (LST) for locally advanced extremity soft tissue sarcoma (ESTS), some patients still need an amputation. Indications for amputation and oncological outcome for these patients are described

Methods
Between 1996 and 2016, all patients who underwent an amputation for ESTS were included. Patients who underwent an amputation as primary or as non-primary treatment formed Group I and II, respectively.

Results
Thirty-nine patients were included, 16 in Group I (41%) and 23 in Group II (59%). Tumor size or local recurrence which could not be treated with LST were the two main reasons for amputation. Local recurrence free survival (LRFS) (p=0.396), distant metastases free survival (DMFS) (p=0.965), disease-specific survival (DSS) (p=0.745) and overall survival (OS) (p=0.718) were comparable for both groups. Ten-year LRFS was 90.0% vs. 83.7%; DMFS was 31.0% vs. 42.2%; DSS was 52.2% vs. 44.1%; and OS was 44.2% vs. 41.6%, for group I and II respectively.

Conclusions
Oncological outcome seems to be comparable between patients who underwent a primary or a non-primary amputation for ESTS. With the on-going possibilities concerning prosthesis and rehabilitation programs, it remains important to decide in a multidisciplinary sarcoma team meeting which treatment suits best for each individual patient.

Introduction

Soft tissue sarcomas (STS) are rare, malignant tumors with an incidence of 12 310 new cases in the United States and 729 in the Netherlands in 2016, resulting in 4 990/300 STS related deaths in the United States and in the Netherlands in 2016.[1-3] STS form a heterogeneous group of tumors including more than 50 different histologic subtypes. The most common subtypes are pleomorphic undifferentiated sarcoma (including malignant fibrous histiocytoma), liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor, which account for a total of 76% of all STS.[4] STS can occur at any anatomic location but most often arise in the limbs (60–70%).[5-7] Despite complete resection, with or without (neo)adjuvant treatment, STS are known for their potential to recur locally and/or to cause distant metastases, mainly to the lungs. The available data considering the improvement of survival following (neo)adjuvant systemic chemotherapy are inconsistent and under on-going investigation.[8-10] Amputation does not increase the survival rate of patients with extremity soft tissue sarcoma (ESTS) when compared with limb salvage surgery combined with (postoperative) radiotherapy. So, limb salvage treatment (LST) has been the treatment of choice since the early 1980s.[11-13] The comparable survival of patients treated with either amputation or LST is caused by the similar effect of systemic chemotherapy in case of metastatic disease. Future identification of new systemic chemotherapy regimens might lead to an improvement of survival in these patients.

Despite attempts to salvage the affected limb, some patients still require an amputation of the affected limb, even after successful hyperthermic isolated limb perfusion (HILP) or preoperative radiation therapy.[14-16] Several patient-related factors (age, comorbidity) and tumor-related factors (tumor size, grade, proximity to vital structures) play a role in the decision to perform an amputation.[5,6,14,17]
This study describes the indications and oncological outcome for patients who underwent an amputation for ESTS at the University Medical Center Groningen (UMCG) between 1996 and 2016.

Patients and methods

Patients
The Institutional Review Board (IRB) approved data collection by review of patient medical records (IRB case number 2016.675). All patients who underwent an amputa-

tion for ESTS at the UMCG between January 1996 and January 2016, were included in this study. Patients were divided into two groups: those who underwent a primary amputation (Group I) and those who underwent an amputation as non-primary treatment for ESTS (Group II).
At the UMCG, all sarcoma patients are discussed in a multidisciplinary sarcoma team meeting prior to the start of treatment. This study retrospectively assessed all patients who underwent an amputation in the treatment of their ESTS. Including primary amputations, non-primary amputations, palliative amputations and amputations performed for non-oncologic factors necessitating amputation during follow-up.
To give insight in the indications for amputation among ESTS patients, the main reason/or most attributable reason for amputation was formulated for each patient in this series. Amputation levels were preoperatively discussed in the multidisciplinary sarcoma team meeting and all patients were referred to a rehabilitation specialist for evaluation of the appropriate level of amputation.
Data concerning demographics, tumor characteristics, patient treatment history, and hospitalization were collected from medical records. Demographic data included sex and age at diagnosis, type of amputation, and oncological outcome. (follow-up ended at death or April 30, 2017). The tumor characteristics obtained from patient medical records included tumor size, tumor location, and histological subtype.

Methods

Indications for amputation and data on each treatment modality (surgical and non-surgical) were collected. Oncological outcome was measured by local recurrence free survival (LRFS) and distant metastases free survival (DMFS) after amputation. Furthermore, disease-specific survival (DSS) and overall survival (OS) were calculated from diagnosis till end of follow-up.

Statistical analysis

Variables were summarized with frequencies and percentages for discrete variables and medians and interquartile ranges (IQRs) for continuous variables; none of the variables were normally distributed. The Mann–Whitney U test was used to compare demographics and clinical variables. Oncological outcome was calculated using the Kaplan–Meier method and Log-rank test. P values <0.05 were considered to indicate statistical significance. SPSS Version 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) and GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com) were used for statistical analysis.

Results

Patients and tumors

Patient demographics and tumor characteristics are presented in Table 1. A total of 39 patients, median age 58.0 (52.0–69.0) years, 24 women (61.5%) and 15 (38.5%) men, were included in the study. A total of 16 patients (41%) underwent a primary amputation (Group I), and 23 patients (59%) underwent amputation as non-primary treatment (Group II).
The overall median tumor diameter at diagnosis was 8.7 (4.7–13.0) cm, for Group I, 11.5 (8.5–15.5) cm, and Group II, 6.1 (4.0–10.0) cm, (p=0.008). The most common tumor location was the upper leg (37.5%) for Group I, and the lower leg (34.8%) for Group II. A variety of histologic subtypes were seen, including pleomorphic undifferentiated sarcoma, liposarcoma (either myxoid, dedifferentiated, or pleomorphic), and synovial sarcoma (Table 1).

Amputations

There were 19 transfemoral amputations (48.7%), four transtibial amputations (10.3%), four transhumeral amputations (10.3%), two transradial amputations (5.1%), two interscapulothoracic amputations (5.1%), three Syme's amputations (7.7%), three hip disarticulations (7.7%), one shoulder disarticulation (2.6%), and one partial hand amputation (2.6%) among the series. The median time between the primary diagnosis and the amputation was 17.0 (9.0–94.0) weeks, Group I, 8.5 (3.0–12.8) weeks, and Group II, 80.0 (17.0–184.0) weeks (p<0.001). The technique of the various amputations and amputation levels is well described by Malawer and Sugarbaker.[18]

As mentioned, the indications for amputation were discussed in the multidisciplinary sarcoma team meeting and the main reason/or most attributable reason for amputation was formulated to be able to classify the patients according to the indication for amputation. The treatment chosen for each individual patient depends on several patient and tumor characteristics. In Group I, a primary amputation was performed due to the non-resectability of the tumor caused by large tumor size in 8 patients (50%), in these patients it was estimated that the extent of surgical resection necessary would have resulted in a non-functional limb. Therefore, a primary amputation was performed instead. In four patients (25%) an amputation was necessary due to bony involvement, these patients had (large) tumors with involvement of the bone in which no other treatment option was feasible. In two patients (12.5%) the involvement of the neurovascular bundle was the main reason for amputation. In the remaining

Table 1. Patient demographics and tumor characteristics

	Total series (n=39)	Group I (n=16)	Group II (n=23)	p-value
Male gender	15 (38.5)	7 (44.0)	8 (35.0)	0.740
Age at diagnosis (years)	58.0 (52.0-69.0)	57 (52.3-67.5)	59 (41.0-70.0)	0.943
Tumor size (cm)	8.7 (4.7-13.0)	11.5 (8.2-15.5)	6.1 (4.0-10.0)	0.008
Histological subtype				
• Liposarcoma	5 (12.8)	3 (18.8)	2 (8.7)	
• MPNST	1 (2.6)	0 (0)	1 (4.3)	
• Myxofibrosarcoma	3 (7.7)	1 (6.3)	2 (8.7)	
• Synovial sarcoma	7 (17.9)	3 (18.8)	4 (17.4)	
• Rabdomyosarcoma	2 (5.1)	1 (6.3)	1 (4.3)	
• Angiosarcoma	1 (2.6)	1 (6.3)	0 (0)	
• Pleomorphic undifferentiated sarcoma	10 (25.6)	5 (31.3)	5 (21.4)	
• Radiation induced sarcoma	2 (5.1)	2 (12.5)	0 (0)	
• Other	8 (20.5)	0 (0)	8 (34.8)	
Tumor location				
• Upper leg	8 (20.5)	6 (37.5)	2 (8.7)	
• Knee	5 (12.8)	1 (6.3)	4 (17.4)	
• Lower leg	11 (28.2)	3 (18.8)	8 (34.8)	
• Foot	5 (12.8)	2 (12.5)	3 (13.0)	
• Upper arm	3 (7.7)	3 (18.8)	0 (0)	
• Lower arm	6 (15.4)	1 (6.3)	5 (21.7)	
• Hand	1 (2.6)	0 (0)	1 (4.3)	

Table 1. Continued

	Total series (n=39)	Group I (n=16)	Group II (n=23)	p-value
Type of amputation				
• Transfemoral	19 (48.7)	6 (37.5)	13 (56.5)	
• Transtibial	4 (10.3)	2 (12.5)	2 (8.7)	
• Transhumeral	4 (10.3)	1 (6.3)	3 (13.0)	
• Transradial	2 (5.1)	0 (0)	2 (8.7)	
• Interscapulothoracic	2 (5.1)	2 (12.5)	0 (0)	
• Syme's	3 (7.7)	1 (6.3)	2 (8.7)	
• Hip disarticulation	3 (7.7)	3 (18.8)	0 (0)	
• Shoulder disarticulation	1 (2.6)	1 (6.3)	0 (0)	
• Partial hand	1 (2.6)	0 (0)	1 (4.3)	

Data presented as n (%); median (IQR); Group I: Amputation as primary treatment; Group II: Amputation as non-primary treatment. Abbreviations: IQR=Inter Quartile Range; MPNST=Malignant Peripheral Nerve Sheath Tumor.

two patients (12.5%) limb salvage was not possible due to abscess formation within the tumor and secondary local infection, leading to an unsuited local environment for LST. The first patient suffered from a locally advanced STS of the upper leg. After the diagnostic biopsy the patient developed a tumor perforation through the skin and a secondary infection with abscess formation within the tumor. This infection deteriorated despite the administration of antibiotics. This local environment made the intended HILP irresponsible and a primary amputation was performed instead. The second patient had been suffering from a swollen and painful foot during an entire year prior to the presentation in our center. The patient had refused to seek medical help during that year. A soft tissue mass was diagnosed which was accompanied by a large abscess of the entire foot. The abscess was drained and a core-needle biopsy of the soft tissue mass was performed simultaneously. Histopathologic examination of the biopsy showed a synovial sarcoma. Due to the abscess formation his entire foot was destructed and a primary amputation was performed. Figure 1 shows four MR-images for non-resectable ESTS necessitating primary amputation.

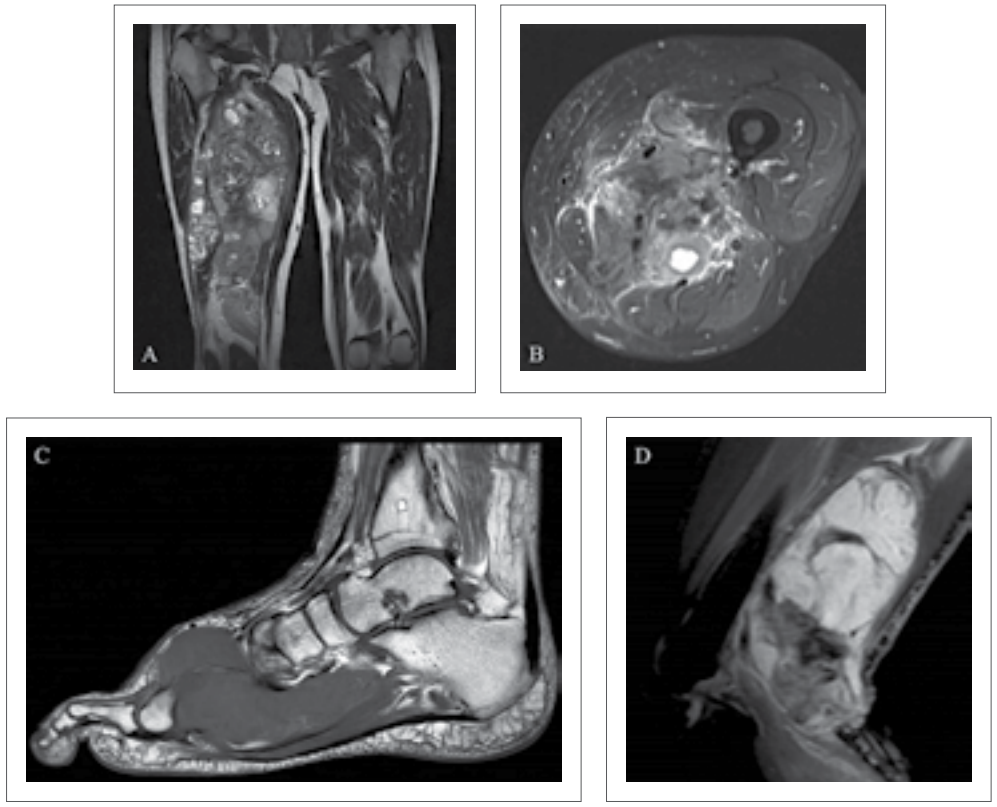

Figure 1. *MR-images showing four examples for non-resectable ESTS necessitating primary amputation.*
A *Coronal image of a large ESTS of the right upper leg without involvement of the femur or the neurovascular structures.*
B *Transversal image of an ESTS of the left upper leg with involvement of the neurovascular structures.*
C *Sagittal image of an ESTS of the right foot with bony involvement.*
D *Sagittal image of an ESTS of the left upper leg with skin perforation, abscess formation and secondary infection within the tumor (femur in black in this setting).*

In Group I, one patient (6.3%) received 50 Gy preoperative external beam radiotherapy (EBRT) to facilitate a Syme's amputation of the foot. Since the preoperative EBRT was given to ensure adequate margins for the primarily intended amputation, this patient was included in Group I.
The 23 patients in Group II underwent several treatment modalities preceding the non-primary amputations. Fifteen patients (65.2%) underwent more than one treatment modality preceding the amputation, and a total of 58 treatments, median 2 (1-4) treatments per patient were performed in Group II, as follows: 35 surgical resections, 12 HILPs, two regimes of chemotherapy and nine EBRT regimes.
In Group II, the indication to perform an amputation was a local recurrence, which could not be treated with LST in 12 patients (52.2%). Other indications to perform an amputation were: tumor progression and/or no tumor response to LST in four patients (17.4%), microscopically compromised margins after LST in three patients (13.0%), and ischemia and/or secondary infection of the treated limb in four patients (17.4%)(Table 2).

A local recurrence which could not be treated with LST differs from tumor progression and/or no tumor response to LST. Hence, the patients who underwent an amputation because of a local recurrence which could not be treated with LST initially underwent successful LST. During follow-up they developed a local recurrence in which LST was not possible and therefore a non-primary amputation was performed. Whereas patients who suffered from tumor progression and/or no tumor response to limb salvage treatment underwent an attempt for LST. This attempt for LST failed and the patients suffered from tumor progression during LST or their tumor did not respond to the LST. In these patients the unsuccessful attempt for LST necessitated a non-primary amputation.
Non-oncologic factors as ischemia and/or secondary infection of the treated limb necessitated a non-primary amputation during follow-up in four patients (17.4%). However, non-oncologic factors as intolerable pain, patient dissatisfaction with functional status or patients' preference for amputation after initial LST were not found among the series.

Follow-up

Median follow-up (time from diagnosis to end of follow-up) was 41.0 (16.0–155.0) months; Group I, 33.5 (11.5–79.8) months and Group II, 56.0 (16.0–176.0) months (p=0.207). No significant differences in LRFS (p=0.396), DMFS (p=0.965), DSS (p=0.745) and OS (p=0.718) were found between both Groups (Figure 2). Ten-year LRFS was 90.0% vs. 83.7%; DMFS was 31.0% vs. 42.2%; DSS was 52.2% vs. 44.1%; and OS was 44.2% vs. 41.6%, for group I and II respectively.

In Group I, one patient (6.3%) developed a local recurrence and eight patients (50.0%) developed distant metastasis during follow-up. Six patients received palliative treatment for metastatic disease (one patient palliative EBRT and five patients palliative systemic treatment). For Group I, the median time of detection of a local recurrence or distant metastases was 13.0 (13.0-13.0) and 4.5 (1.3-17.0) months, respectively.

Table 2. Treatment characteristics and indications for amputation

	Total series (n=39)	Group I (n=16)	Group II (n=23)	p-value
Time between diagnosis and amputation	17.0 (9.0-94.0)	8.5 (3.0-12.8)	80.0 (17.0-184.0)	<0.001
Distant metastases, present prior to amputation	4 (10.3)	0 (0.0)	4 (17.4)	
Local recurrence, present prior to amputation	14 (35.9)	0 (0.0)	14 (60.7)	
Local resection prior to amputation	19 (48.7)	0 (0.0)	19 (82.6)	
Neoadjuvant radiation therapy	9 (23.1)	1 (6.3)	8 (34.8)	
Neoadjuvant chemotherapy	2 (5.1)	0 (0.0)	2 (8.7)	
Hyperthermic isolated limb perfusion	11 (28.2)	0 (0.0)	11 (47.8)	
Adjuvant radiation therapy, after amputation	2 (5.1)	1 (6.3)	1 (4.3)	
Adjuvant chemotherapy, after amputation	2 (5.1)	1 (6.3)	1 (4.3)	
Palliative radiation therapy*	7 (18.4)	1 (6.7)	6 (26.1)	
Palliative chemotherapy*	7 (17.9)	5 (31.3)	2 (8.7)	
Total amount of treatments prior to amputation	59	1	58	

Table 2. Continued

	Total series (n=39)	Group I (n=16)	Group II (n=23)	p-value
Indications for primary amputation				
• Tumor size		8 (50)		
• Involvement of neurovascular structures		2 (12.5)		
• Involvement of bone		4 (25.0)		
• Abscess formation making LST irresponsible		2 (12.5)		
Indications for non-primary amputation				
• Local recurrence in which LST was not possible			12 (52.2)	
• Tumor progression and/or no tumor response to LST			4 (17.4)	
• Microscopically comprised margins after LST			3 (13.0)	
• Ischemia and/or secondary infection after LST			4 (17.4)	

*Data presented as n (%); median (IQR); time in weeks. Group I: Amputation as primary treatment; Group II: Amputation as non-primary treatment. Abbreviations: IQR=Inter Quartile Range; LST=Limb salvage treatment. *In Group I, One patient with widespread metastases was lost to follow-up, so information regarding potential palliative treatment is missing.*

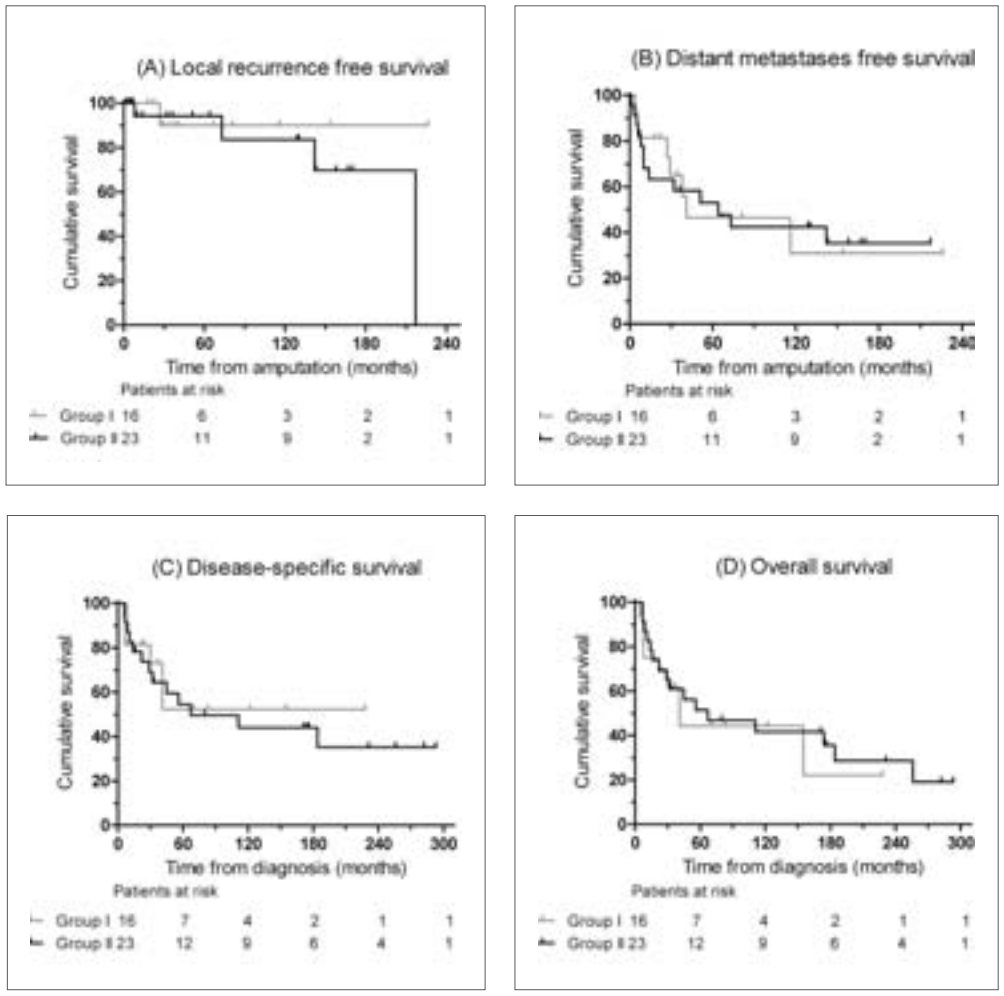

Figure 2. *Kaplan-Meier plots showing no significant differences for:* **A** *Local recurrence free survival (p=0.396) and* **B** *Distant metastases free survival (p=0.965) after amputation;* **C** *Disease-specific survival (p=0.745) and* **D** *Overall survival (p=0.718) after diagnosis.*

In Group II, four patients (17.4%) were diagnosed with distant metastases prior to the amputation, and a total of 13 patients (56.5%) developed distant metastases during follow-up after amputation. Four patients (17.4%) in Group II developed a local recurrence after amputation, of whom three were simultaneously diagnosed with distant disease. Six patients (26.1%) in Group II received palliative EBRT for metastatic disease, and a further two patients (8.7%) received palliative systemic therapy. For Group II, the median time of detection of a local recurrence or distant metastases was 18.5 (3.0-59.5) and 6.0 (2.0-24.0) months, respectively. Among the series, one patient with widespread metastases was lost to follow-up. Table 3 presents the follow-up characteristics of the time-period after diagnosis and after amputation.

As mentioned, in Group II four patients (17.4%) were diagnosed with distant metastases prior to amputation. However, not all four patients underwent a palliative amputation. Two patients had a inguinal lymph none-metastasis accompanying their primary tumor which were treated with curative-intent by a groin lymph node dissection in addition to the local LST. Both of these patients underwent a non-primary amputation during follow-up. The third patient had a local recurrence in his upper leg and the staging chest CT-scan showed lung metastases. After careful consideration and discussion in the multidisciplinary sarcoma team meeting the complaints of the local recurrence justified the amputation. The fourth patient was diagnosed with a large sarcoma of the upper leg. After initial surgical resection a local recurrence occurred and an intra-abdominal metastasis was diagnosed simultaneously. Regrettably, the initial surgical resection comprised the blood supply of the leg which resulted in ischemia and a secondary infection of the leg necessitating the non-primary amputation.
Currently, seven patients (43.8%) are alive in Group I, five with no evidence of disease and two with evidence of disease. In Group II, seven patients (30.4%) are still alive, six with no evidence of disease and one with evidence of disease.

Discussion

Nowadays, (neo)-adjuvant treatment protocols (EBRT, HILP and/or chemotherapy) and surgery have made it possible to achieve a limb salvage rate of approximately 80-90% for ESTS.[13,19-23] However, in some cases a primary amputation is warranted for various reasons.
This study describes two groups of high risk ESTS patients in whom an amputation was performed. Group I describes the characteristics of patients who underwent a primary amputation and Group II describes the patients in whom an attempt for LST was followed by a non-primary amputation during follow-up. The non-primary amputation followed after a median of 80.0 (17.0–184.0) weeks from diagnosis, and a median of 2 (1-4) treatments per patient.

Table 3. Follow-up after diagnosis and after amputation

	Total series (n=39)	Group I (n=16)	Group II (n=23)	p-value
Follow-up after diagnosis				
Time between diagnosis and end of follow-up	41.0 (16.0-155.0)	33.5 (11.5-79.8)	56.0 (16.0-176.0)	0.207
Survival, patients alive at end of follow-up	14 (35.9)	7 (43.8)	7 (30.4)	
Follow-up after amputation				
Local recurrence, developed after amputation	5 (12.8)	1 (6.3)	4 (17.4)	
Median time of detection	13.0 (4.0-50.0)	13.0 (13.0-13.0)	18.5 (3.0-59.5)	
Histological subtype				
• Liposarcoma	1 (20.0)	0 (0)	1 (25.0)	
• MPNST	1 (20.0)	0 (0)	1 (25.0)	
• Radiation induced sarcoma	1 (20.0)	1 (100.0)	0 (0)	
• Other	2 (40.0)	0 (0)	2 (50.0)	
Treatment of local recurrence				
• Curative re-resection + radiation therapy	1 (20.0)	0 (0)	1 (25.0)	
• Curative re-amputation	2 (40.0)	0 (0)	2 (50.0)	
• Palliative radiation therapy	1 (20.0)	1 (100)	0 (0)	
• Palliative comfort care	1 (20.0)	0 (0)	1 (25.0)	
Distant metastasis, developed after amputation	21 (53.8)	8 (50.0)	13 (56.5)	
Median time of detection	6.0 (2.0-18.5)	4.5 (1.3-17.0)	6.0 (2.0-24.0)	
Histological subtype				
• Liposarcoma	3 (14.3)	1 (12.5)	2 (15.4)	
• Myxofibrosarcoma	3 (14.3)	1 (12.5)	2 (15.4)	
• Synovial sarcoma	2 (9.5)	1 (12.5)	1 (7.7)	
• Rabdomyosarcoma	2 (9.5)	1 (12.5)	1 (7.7)	
• Pleomorphic undifferentiated sarcoma	5 (23.8)	2 (25.0)	3 (23.1)	
• Radiation induced sarcoma	2 (9.5)	2 (25.0)	0 (0)	
• Other	4 (19.0)	0 (0)	4 (30.8)	

Data presented as n (%); median (IQR); time in months. Group I: Amputation as primary treatment; Group II: Amputation as non-primary treatment. Abbreviations: IQR=Inter quartile range; MPNST=Malignant Peripheral Nerve Sheath Tumor.

The predominant indications for amputation in Group I, were tumor size and involvement of bone and/or neurovascular structures. In these patients, an attempt for LST would have led to a non-functional limb. In Group II, the predominant indication for amputation was failure of the local/regional treatment, resulting in a local recurrence in which LST was no longer possible. The indications for primary and for non-primary amputation are consistent with earlier published data.[6,14,17,24,25]

In a study by Stojadinovic et al., 1178 patients with localized primary STS of the extremity were identified and treated with limb salvage surgery.[25] Of these patients, 204 (17%) developed local recurrence, of whom 18 were treated with a (non-primary) amputation whereas the remaining patients underwent another limb salvage surgery. Thirty-four of this latter group were selected for a matched-pair analysis to compare outcomes. Amputation was associated with an improvement in local control of disease (94% vs. 74%; p=0.04), but no significant difference in disease-free, disease-specific, or overall survival was found between the two groups.[25]

In the current series it was shown that patients who underwent an attempt at LST, that ultimately resulted in a non-primary amputation, seem to have comparable oncological outcome when compared with patients who underwent a primary amputation. The DSS and OS rates might be lower than OS rates for STS in general (10-year survival of approximately 55%).[26] However, it has to be taken into account that the patients in the UMCG series had initial ESTS with a poor prognosis, due to tumor size and/or histology.

In Group II, prior to a non-primary amputation, 10 patients underwent a surgical resection as initial treatment of their ESTS. Seven of these 10 patients underwent their initial surgical resection at an outside institution (i.e. accidental marginal resection). Although oncological outcome following an accidental marginal resection may be similar, these patients require wider resections.[27,28] In the current series, all seven patients underwent a re-resection at our center and none of these patients had to undergo an amputation due to inadequate initial treatment. Most of these patients developed a local recurrence necessitating amputation during follow-up.

In the current study, only one patient in Group I developed a local recurrence, in contrast to four local recurrences (17.4%) in Group II. Three patients out of these latter four were simultaneously diagnosed with distant metastases, so the clinical significance of these 'local failures' is questionable, e.g. expression of metastatic disease. Furthermore, the LRFS and DMFS were found to be comparable between the two Groups.

Among the series, four patients (10.3%) were diagnosed with distant disease prior to the amputation. As mentioned, two of these patients were treated with curative-intent while the other two patients underwent a palliative amputation. The median OS

following amputation was 5.5 months for these four patients and 1 month following the two palliative amputations performed. This poor median OS following palliative amputation seems to be comparable with the 6 months median OS recently reported by Smith et al.[29]

The current study shows that patients who underwent a non-primary amputation underwent 58 treatment modalities (median two treatments per patient) preceding the amputation. Although this figure of median two treatments modalities prior to the amputation in the 23 patients in Group II seems low, a previous study has shown that the psychological impact of regional tumor treatment (HILP in this study) is large, resulting in post-traumatic stress syndrome in 20% of patients.[30] In contrast, other studies did not show differences in quality of life and functional outcome when comparing amputation with LST in the treatment of ESTS.[31,32] Another study shows that 80% of the patients who underwent a non-primary amputation did not regret undergoing the initial attempt at LST.[33]

In the last decades, many options for prosthesis parts have entered the market, including improved socket designs, technological advances such as microprocessor-equipped prosthesis components (ankle and knee), and a wider choice in foot selection. A better prosthetic rehabilitation program also offers patients a better quality of life. Since the 1990s, osseointegration (Swedish) techniques, to ensure a stable fixation of the titanium implant into the bony tissue of the amputation stump, have evolved to become more standardized, too.[34,35] With this technique, the human–prosthesis interface has been optimized, gait optimization has been achieved, and functional outcome has been improved. With the development of evidence-based guidelines, the amputee patient can have a standardized protocol for a rehabilitation program, which in the end leads to a better functional result.[36-38] Considering the implications of ablative surgery, there are no data available comparing patients' self-sufficiency after an upper vs. lower limb amputation is performed. However, it seems logical that lower limb amputations have a smaller impact on one's daily routine than upper limb amputations do. Due to the fact that the upper limb harbors much more subtle tactile functions and fine motor skills as the lower limb, prosthetic options after an upper limb amputation are less and the implications on the patients' life are substantial. The finding that primary amputations were performed for larger and more proximally located ESTS might be caused by the fact that these tumors are diagnosed in a later stadium due to a naturally larger limb-circumference, i.e. limb volume, of the proximal limbs. Accordingly, ESTS of the distal limbs might be diagnosed earlier leading to more LST options since these tumors might be less extensive at time of diagnosis. Still, the development of a local recurrence or failure of the LST might result in a non-primary amputation for some of these distal ESTS.

This study has some limitations, the retrospective character of this study encompasses the risk of retrospective selection bias. However, this study includes all patients who underwent an amputation in the treatment of their ESTS, patients in Group I all had tumors necessitating a primary amputation. Whereas, patients in Group II had tumors in which an initial (or several) attempt for LST was considered to be possible. Furthermore, it was chosen to exclude tumor grade from this manuscript, since almost one-third of data considering tumor grades was missing. Due to the retrospective nature of this study it was impossible to retrieve the tumor grade for these 12 patients. Whereas, the remaining 27 patients all suffered from a high grade (grade 2 or 3) ESTS.

In summary, patients with ESTS for whom an amputation is indicated have a worse prognosis than patients with STS in general. However, patients who underwent a primary or a non-primary amputation for ESTS seem to have comparable oncological outcomes. Given this comparable oncological outcome, the need is urgent on behalf of the patient for amputation levels to be chosen adequately and for optimal rehabilitation to be provided by surgeons and rehabilitation specialists.[39,40]

Conclusion

The timing of amputation does not seem to affect the oncological outcome of ESTS patients. Therefore LST remains the treatment of choice, even for locally advanced ESTS. Attempts to achieve local control with LST in patients with ESTS can result in multiple intensive treatments per patient. However, the time between diagnosis and amputation was significantly longer for Group II when compared with Group I (80.0 (17.0–184.0 vs. 8.5 (3.0–12.8) weeks, $p<0.001$). Despite all efforts, some patients will need a non-primary amputation because of a local recurrence, failure of LST or LST-related complications. On-going possibilities are being realized in prosthesis and rehabilitation programs, therefore it remains important to decide in a multidisciplinary fashion which treatment suits best for each individual patient.

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Metabolic and histopathological tumor responses in pretreated extremity soft tissue sarcoma

PART III

Volume of interest delineation techniques for ^{18}F-FDG PET-CT scans during neoadjuvant extremity soft tissue sarcoma treatment in adults: a feasibility study

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Abstract

Background

This study explores various volume of interest (VOI) delineation techniques for fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography ([18]F-FDG PET-CT) scans during neoadjuvant extremity soft tissue sarcoma (ESTS) treatment.

Results

During neoadjuvant treatment, hyperthermic isolated limb perfusion (HILP) and preoperative external beam radiotherapy (EBRT), 11 patients underwent three [18]F-FDG PET-CT scans. The first scan was made prior to the HILP, the second after the HILP but prior to the start of the EBRT and the third prior to surgical resection. An automatically drawn VOI_{auto}, a manually drawn VOI_{man}, and two gradient-based semi-automatically drawn VOIs (VOI_{grad} and VOI_{grad+}) were obtained. Maximum standardized uptake value (SUVmax), SUVpeak, SUVmean, metabolically active tumor-volume (MATV) and total lesion glycolysis (TLG) were calculated from each VOI. The correlation and level of agreement between VOI delineation techniques was explored. Lastly, the changes in metabolic tumor activity were related to the histopathologic response. The strongest correlation and an acceptable level of agreement was found between the VOI_{man} and the VOI_{grad+} delineation techniques. A decline (VOI_{man}) in SUVmax, SUVpeak, SUVmean, TLG and MATV (all $p<0.05$) was found between the three scans. A >75% decline in TLG between scan 1 and scan 3 possibly identifies histopathologic response.

Conclusions

The VOI_{grad+} delineation technique was identified as most reliable considering reproducibility when compared with the other VOI delineation techniques during the multimodality neoadjuvant treatment of locally advanced ESTS. A significant decline in metabolic tumor activity during the treatment was found. TLG deserves further exploration as predictor for histopathologic response after multimodality ESTS treatment.

Background

Soft tissue sarcomas (STS) are relatively rare malignancies, accounting for less than 1% of all cancers in adults. The number of patients presenting with STS each year is 600-700 in the Netherlands, leading to approximately 300 STS related deaths annually.[1,2] Roughly 50-60% of the STS arise in the extremities.[3,4] At presentation, some of these extremity soft tissue sarcomas (ESTS) are considered non-resectable or 'locally advanced'. Since the 1990s neoadjuvant hyperthermic isolated limb perfusion (HILP) has been used in Europe to prevent limb amputation in these patients,[5] resulting in a limb salvage rate of 80-90% in locally advanced ESTS nowadays.[6-9] HILP is used in all types of adult locally advanced ESTS. It allows to administer regional chemotherapy in high doses, as the affected limb is isolated from the systemic circulation during the procedure. Neoadjuvant systemic chemotherapy in ESTS is currently under ongoing investigation, as the data available considering patients' oncological outcome are inconsistent.[10-12]

Fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography ([18]F-FDG PET-CT) scans have been used to evaluate tumor changes following HILP in locally advanced ESTS since the mid-1990s.[13] Pretreatment maximum standardized uptake value (SUVmax), metabolically active tumor-volume (MATV) and total lesion glycolysis (TLG) were identified as significant predictors for overall survival in STS in a recent meta-analysis.[14] Furthermore, post-treatment SUVmax was shown to be promising in monitoring treatment response. However, the identification of this latter parameter was solely based on two articles included in this meta-analysis. The first only included rhabdomyosarcomas, which is a chemosensitive sarcoma, and the second only included chest wall sarcomas.[14-16]

The SUVmax of a lesion depends solely on the highest measured [18]F-FDG uptake in one voxel, thereby making the measured SUVmax susceptible for noise.[17] Furthermore, the question remains whether this one measurement is representative for large, heterogeneous tumors, as STS. In contrast, the SUVmax is the most robust parameter when comparing various software delineation programs, delineation methods and observers.[18] The outcome of MATV and TLG parameters are much more dependent of the method of tumor delineation and the software program used for these analyses. We hypothesized that the use of peak standardized uptake value (SUVpeak) and mean standardized uptake value (SUVmean) in addition to SUVmax, TLG and MATV might

result in a more reliable prediction of tumor changes induced by neoadjuvant treatment.

To the best of our knowledge the use of various VOI delineation techniques has not yet been explored in, and during the neoadjuvant treatment of STS. Furthermore, in this patient population no sequential analysis of multiple ^{18}F-FDG PET-CT scans has been performed previously. In this feasibility study, consecutive ^{18}F-FDG PET-CT scans per patient were used to investigate the use of four VOI delineation techniques because variations in VOI will directly affect the measured SUVmean, MATV and TLG and could thus affect the performance of the PET assessments. Furthermore, we explored the changes in metabolic tumor activity (SUVmax, SUVpeak, SUVmean, MATV and TLG) to neoadjuvant HILP and preoperative EBRT during the treatment course of locally advanced ESTS. Lastly, the relationship between changes in metabolic tumor activity and histopathologic response was explored.

Materials and methods

This study has been approved by the Institutional Review Board (IRB) and the need for written informed consent was waived (IRB case number 2016.984). From 2011 to 2017, 11 patients with a median age of 64 (IQR 44-74; range 32-74) years were treated according to a novel treatment regimen consisting of neoadjuvant HILP, preoperative hypofractionated EBRT, followed by surgical resection of the tumor. All patients were diagnosed with a locally advanced, non-metastatic, high grade ESTS (Table 1). Patients eligible for HILP treatment were included in this novel treatment regimen based on a tumor board decision. Inclusion and exclusion criteria, as well as treatment details have been described in more detail elsewhere.[19] Patients were scheduled for three ^{18}F-FDG PET-CT scans. The first scan was made prior to the start of neoadjuvant treatment (baseline), the second after the HILP, but prior to the start of the preoperative EBRT and was additionally used for EBRT delineation. The third scan was made after completion of the neoadjuvant treatment (HILP and EBRT), but prior to surgical resection. Figure 1 illustrates the change in ^{18}F-FDG uptake during the treatment course for one of the patients.

^{18}F-FDG PET-CT

The ^{18}F-FDG PET-CT scans were performed using a hybrid PET-CT scanner (Siemens Biograph mCT). Patients fasted at least six hours prior to scanning, and fasting glucose levels were checked at time of injection, none of the patients suffered from diabetes

Table 1. Patient and tumor characteristics

Patient No.	Gender	Age (years)	Histopathologic findings	Tumor location	Tumor size (cm)
1	M	32	Synovial sarcoma	Upper leg	6
2	F	41	Synovial sarcoma	Lower leg	4
3	F	74	Pleomorphic undifferentiated sarcoma	Upper leg	10
4	M	54	Pleomorphic undifferentiated sarcoma	Upper leg	17
5	M	63	Pleomorphic undifferentiated sarcoma	Lower leg	9
6	M	71	Myxofibrosarcoma	Upper leg	5
7	M	44	Myxofibrosarcoma	Upper leg	17
8	M	74	Pleomorphic undifferentiated sarcoma	Knee	7
9	M	64	Leiomyosarcoma	Knee	6
10	M	75	Pleomorphic undifferentiated sarcoma	Lower leg	8
11	M	67	Leiomyosarcoma	Knee	6

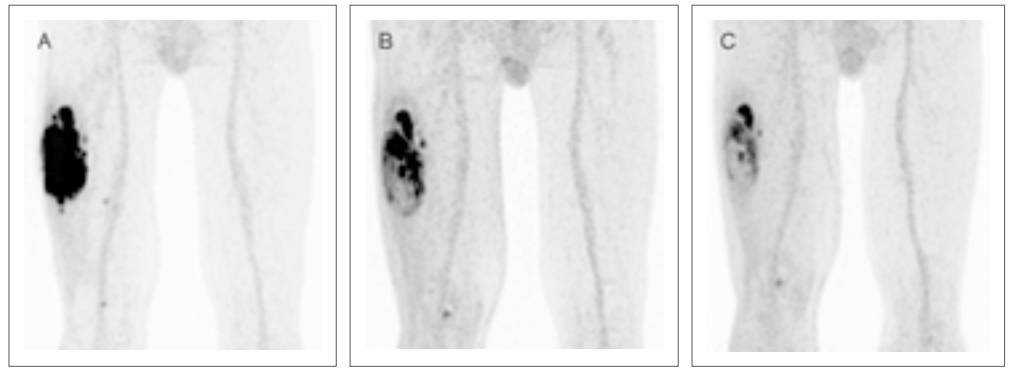


Figure 1. *Coronal ^{18}F-FDG PET-CT images showing the heterogeneous ^{18}F-FDG uptake throughout the tumor for one of the patients during the treatment course.*
A *scan 1 (baseline)*
B *scan 2 (after HILP)*
C *scan 3 (after EBRT)*

mellitus. ^{18}F-FDG (3 MBq/kg) was injected and the PET-CT scan was started one hour afterwards. Patients were scanned in supine position and images of the affected limb were acquired in 3D mode, in 2 to 5 bed positions, 1-3 minutes/bed position based on the patient's body weight. A preceding low dose CT scan was performed and used for attenuation and scatter correction. All images were reconstructed using an EARL compliant protocol, from 2011 to 2014 the images were reconstructed using the following reconstruction: 3i_24s; image size 400; filter: Gaussian; FWHM 5.0mm, and from 2014 to 2017 the images were reconstructed with the following reconstruction parameters: 3i_21s; image size 256; filter: Gaussian; FWHM 6.5mm; quality ref mAS 30. All scans were acquired according to European Association of Nuclear Medicine guidelines (version 1.0/2.0).[20,21]

Image analyses

Scans were imported into Accurate (in-house developed analysis software, as previously used by Frings and Kramer et al.[22,23], and recently described by Boellaard.[24] Scans were reviewed and analyzed by one researcher. To explore the effect of various delineation techniques on the measurement of the metabolic parameters, the volume of interest (VOI) of each tumor was drawn in four different ways: (1) an automatically drawn VOI_{auto} (using 50% of the SUVpeak contour, corrected for local background,[22] (2) a manually drawn VOI_{man} (visually following tumor contours), (3) a semi-automatic drawn VOI_{grad} (a contour that is located at the maximum PET image intensity gradient near the boundary of the tumor). Because of tumor heterogeneity, necrotic tumor parts (mostly tumor centers) were not included in this third VOI. Therefore a fourth VOI was derived from the VOI_{grad}, in which all necrotic tumor parts were manually filled and included, resulting in the fourth VOI_{grad+} (Figure 2).
Five metabolic parameters: SUVmax (voxel with the highest SUV value), SUVpeak (using a 1mL sphere), SUVmean, TLG (SUVmean x MATV) and MATV, all based on lean body mass, as recommended by Boellaard et al.[21], were derived for the four VOI delineation techniques.

Due to tumor necrosis in most tumors, either treatment-induced or due to tumor heterogeneity, only the VOI_{man} comprised the entire tumor (including necrosis). Therefore, the VOI_{man} was chosen as reference measurement, and the other VOI techniques were compared with the VOI_{man}. We selected VOI_{man} as reference VOI for pragmatic reasons (as the VOI_{man} encompasses the entire tumor), not suggesting that this approach is best. Correlation analyses, Bland-Altman analyses and patient ranking were performed to compare correlation and level of agreement between the VOI delineation techniques. Bland-Altman analyses[25] and patient ranking are described in more detail in the Supplemental Methods. Changes in metabolic tumor activity during neoadjuvant treatment were measured using the five metabolic parameters obtained from the reference VOI_{man} and were related to histopathologic responses. Histopathologic tumor responses were established in accordance with the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) STS response score.[19] Grade A representing no stainable tumor cells; Grade B, single stainable tumor cells or small clusters (overall below 1% of the whole specimen); Grade C, ≥1%-<10% stainable tumor cells; Grade D, ≥10%-<50% stainable tumor cells; and Grade E, ≥50% stainable tumor cells.[26]
Histopathologic responders had tumor remnants which showed <10% stainable cells, combining response grades A, B and C. Non-responders had ≥10% stainable cells in their tumor remnant, Grade D or E. Lastly, the relationship between changes in metabolic tumor activity and histopathologic responses was explored.

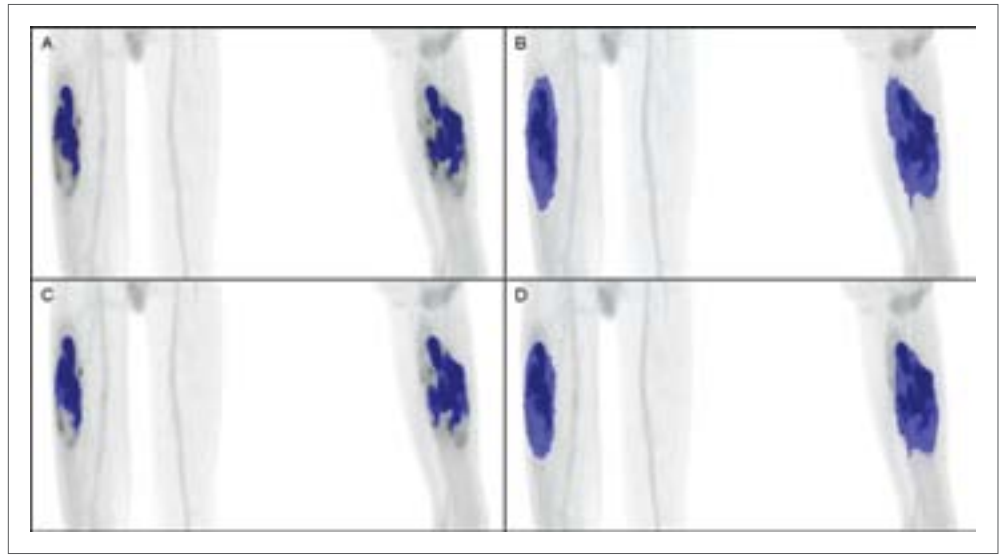


Figure 2. *An example illustrating the differences in tumor delineation between the four VOI delineation techniques, for patient 4 scan 2.*

A VOI_{auto} **C** VOI_{grad}
B VOI_{man} **D** VOI_{grad+}

Statistical analysis

Discrete variables were summarized with frequencies and percentages, and continuous variables with medians and interquartile ranges (IQRs); none of the variables were

normally distributed. Fisher's exact and Mann-Whitney U test were used to compare variables. Wilcoxon signed rank and Friedman's test were used to compare the measurements between the three scans. Correlation coefficients were calculated, and tested using Spearman's test. The level of agreement between VOI techniques was determined by Bland-Altman analyses.[25] A p-value <0.05 indicated statistical significance. Microsoft Excel (2010) was used to create the Bland-Altman plots. SPSS version 23.0 (IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp) and GraphPad Prism version 5.04 (GraphPad Software for Windows, San Diego California USA) were used for statistical analyses.

Results

Thirty-two ^{18}F-FDG PET-CT scans were acquired. The third PET-CT scan of patient 10 could not be performed due to scheduling difficulties. For patient 1, in scan 3 it was not possible to draw a VOI_{auto}, since the tumor showed an almost complete metabolic response at this treatment stage and it did not meet the margin thresholds to complete the VOI_{auto}. Since it was possible to define the other three types of VOIs, this scan was included in the analyses and a value of zero was given to the metabolic parameters for the VOI_{auto}. The median time between the HILP and scan 2 was 21 (18-21) days, whereas the time between the end of EBRT and scan 3 was 3 (1-3) days.

Correlation, level of agreement and ranking of patients between VOIs

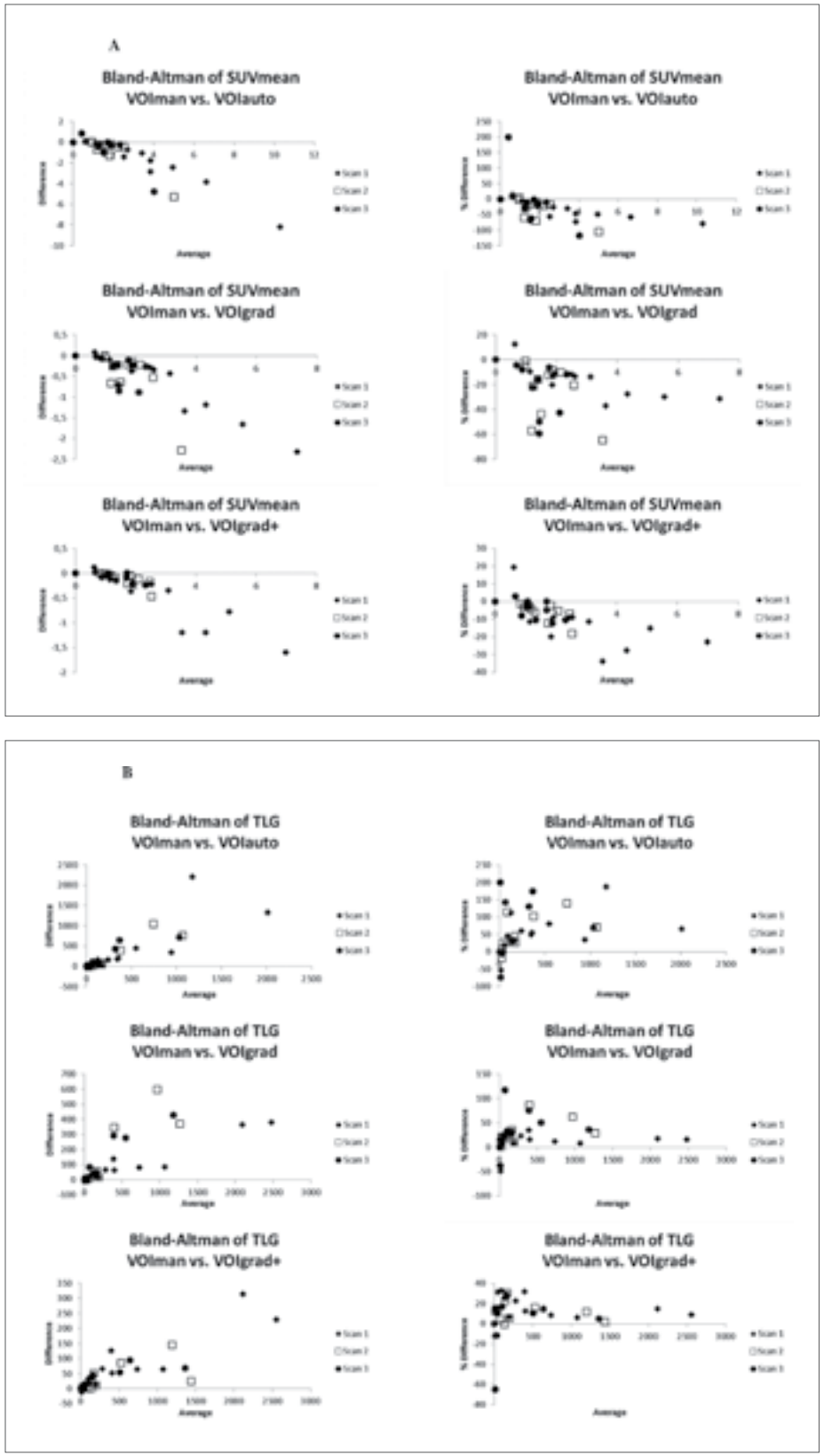
The correlation between VOIs for all scans and all metabolic parameters was strongest between the VOI_{man} and the VOI_{grad+}, as indicated in bold in Table 2. The Bland-Altman plots showed an acceptable level of agreement between the VOI_{man} and the VOI_{grad+} (Supplemental Figure 1).

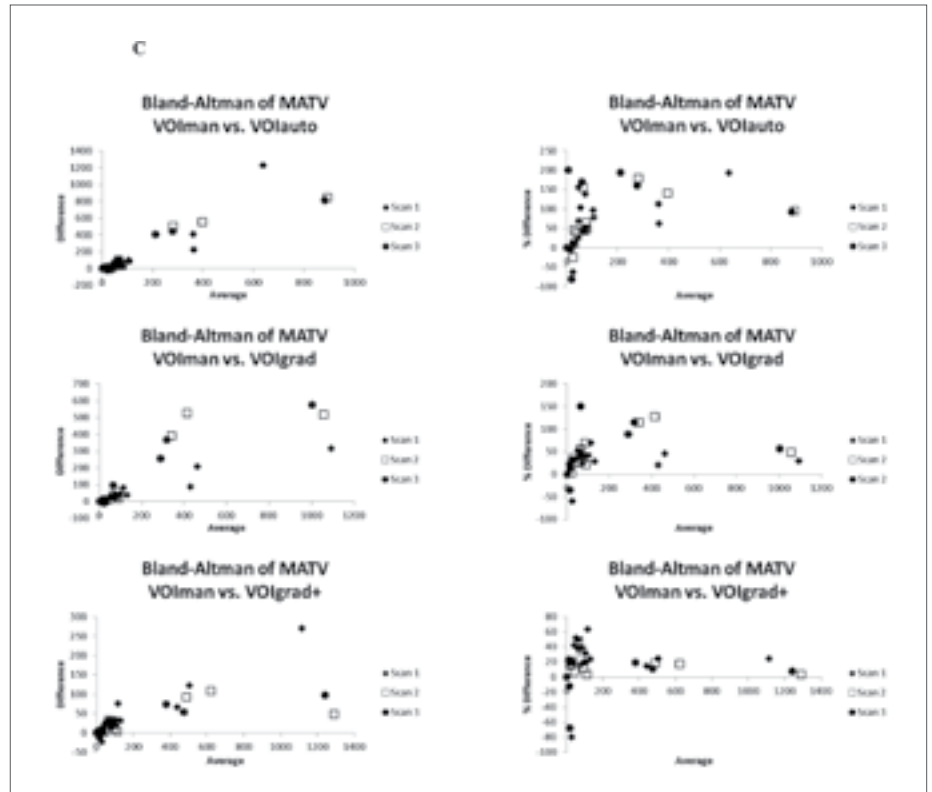
No larger difference than 1 place in ranking for SUVmean and TLG for the serial ^{18}F-FDG PET-CT scans was found when comparing the VOI_{man} and the VOI_{grad+} delineation techniques, for the MATV no larger difference than 2 places in ranking was found. A relative large difference of 4 or more in ranking between VOI delineation techniques is indicated in bold in Supplemental Table 1. Among others this was found for the MATV at scan 1 of patient 7 with considerable necrotic tumor parts. The measured MATV was found to be highest when using the $VOI_{man, grad and grad+}$ techniques. However when the VOI_{auto} technique was used it was only ranked a 9th place due to exclusion of tumor necrosis.

Table 2. Spearman's correlation between the VOI_{man} and $VOI_{auto/grad/grad+}$ for the serial ^{18}F-FDG PET-CT scans

Parameter	Scan 1		Scan 2		Scan 3	
	Correlation coefficient	p-value	Correlation coefficient	p-value	Correlation coefficient	p-value
SUVmax						
• $VOI_{man-auto}$	1.000	NA	1.000	NA	0.988	<0.001
• $VOI_{man-grad}$	1.000	NA	1.000	NA	1.000	NA
• $VOI_{man-grad+}$	**1.000**	**NA**	**1.000**	**NA**	**1.000**	**NA**
SUVpeak						
• $VOI_{man-auto}$	1.000	NA	1.000	NA	0.988	<0.001
• $VOI_{man-grad}$	1.000	NA	1.000	NA	1.000	NA
• $VOI_{man-grad+}$	**1.000**	**NA**	**1.000**	**NA**	**1.000**	**NA**
SUVmean						
• $VOI_{man-auto}$	0.964	<0.001	0.836	0.001	0.564	0.090
• $VOI_{man-grad}$	0.991	<0.001	0.882	<0.001	0.758	0.011
• $VOI_{man-grad+}$	**0.991**	**<0.001**	**0.982**	**<0.001**	**0.988**	**<0.001**
TLG						
• $VOI_{man-auto}$	0.845	0.001	0.982	<0.001	0.842	0.002
• $VOI_{man-grad}$	0.991	<0.001	1.000	NA	0.976	<0.001
• $VOI_{man-grad+}$	**0.991**	**<0.001**	**0.991**	**<0.001**	**0.988**	**<0.001**
MATV						
• $VOI_{man-auto}$	0.309	0.355	0.555	0.077	0.430	0.214
• $VOI_{man-grad}$	0.955	<0.001	0.973	<0.001	0.806	0.005
• $VOI_{man-grad+}$	**0.936**	**<0.001**	**1.000**	**NA**	**0.964**	**<0.001**

Spearman's test for correlations was used to calculate significance. The strongest correlation for the three PET scans was found between the VOI_{man} and the VOI_{grad+}, as indicated in bold. Abbreviations: VOI=volume of interest; VOI_{man}=manually drawn VOI; VOI_{auto}=automatically drawn VOI; VOI_{grad}=VOI based on the gradient between voxels; VOI_{grad+}=VOI_{grad} + necrosis; ^{18}F-FDG PET-CT=Fluorine-18-fluoro-deoxyglucose positron emission tomography with computed tomography; SUVmax=maximum standardized uptake value; SUVpeak=peak standardized uptake value; SUVmean=mean standardized uptake value; TLG=total lesion glycolysis; MATV=metabolically active tumor-volume; IQR=inter quartile range; NA=not applicable.





Supplemental Figure 1. *Bland-Altman plots showing the level of agreement between the VOI_{man} and the $VOI_{auto/grad/grad+}$ for the serial ^{18}F-FDG PET-CT scans for:* **A** *SUVmean;* **B** *total lesion glycolysis (TLG);* **C** *metabolically active tumor-volume (MATV).*

Metabolic tumor activity

During neoadjuvant treatment all five metabolic parameters for the reference VOI_{man} declined between scans 1-3 (all $p<0.05$, Figure 3, Table 3).

This decline was further explored by calculating the absolute and the percentage difference between the three serial scans. The percentage difference was obtained by dividing the difference between scans by the measured value of the first scan. A significant decline in SUVmax, SUVpeak and SUVmean was found between scan 1 vs. scan 2, as well as between scan 1 vs. scan 3. However, no significant decline in SUVmax, SUVpeak and SUVmean was found between scan 2 vs. scan 3. The decline in TLG was significant between all serial scans. A significant decline in MATV was found between scan 2 vs. scan 3. The decline in metabolic tumor activity for all parameters except MATV was largest between scan 1 vs. 2, whereas the decline in MATV was largest between scan 2 vs. 3 (Figure 4, Table 4).

Supplemental table 1. Ranking of patients for SUVmean, TLG and MATV according to the four VOI delineation techniques

Patient No.	SUVmean scan 1				SUVmean scan 2				SUVmean scan 3			
	VOI man	VOI auto	VOI grad	VOI grad+	VOI man	VOI auto	VOI grad	VOI grad+	VOI man	VOI auto	VOI grad	VOI grad+
1	10	10	10	10	10	10	10	10	9	10	9	9
2	11	11	11	11	9	11	11	9	10	9	10	10
3	7	8	7	7	11	7	7	11	**7**	**3**	**6**	**7**
4	2	2	2	2	1	1	1	2	4	1	1	3
5	6	4	6	6	**6**	**8**	**8**	**4**	5	8	7	5
6	9	9	8	8	5	6	5	6	2	4	3	2
7	8	7	9	9	8	9	9	8	6	7	8	6
8	1	1	1	1	7	4	6	7	**8**	**5**	**4**	**8**
9	4	5	4	4	2	2	2	1	1	2	2	1
10	5	6	5	5	3	3	3	3	N/A	N/A	N/A	N/A
11	3	3	3	3	4	5	4	5	3	6	5	4
Patient No.	**TLG scan 1**				**TLG scan 2**				**TLG scan 3**			
	VOI man	VOI auto	VOI grad	VOI grad+	VOI man	VOI auto	VOI grad	VOI grad+	VOI man	VOI auto	VOI grad	VOI grad+
1	10	10	10	10	10	10	10	10	9	10	10	10
2	11	11	11	11	11	11	11	11	10	9	9	9
3	3	2	3	3	3	3	3	3	3	4	3	3
4	1	1	1	1	2	2	2	2	2	5	2	2
5	8	9	8	8	9	9	9	9	7	6	6	7
6	9	8	9	9	6	6	6	7	5	3	5	5
7	**2**	**7**	**2**	**2**	1	1	1	1	1	1	1	1
8	4	3	4	4	7	8	7	6	6	8	7	6
9	5	5	6	6	5	4	5	5	4	2	4	4
10	6	4	5	5	4	5	4	4	N/A	N/A	N/A	N/A
11	7	6	7	7	8	7	8	8	8	7	8	8

Supplemental table 1. Continued

Patient No.	MATV scan 1				MATV scan 2				MATV scan 3			
	VOI man	VOI auto	VOI grad	VOI grad+	VOI man	VOI auto	VOI grad	VOI grad+	VOI man	VOI auto	VOI grad	VOI grad+
1	**10**	**5**	**10**	**11**	10	9	10	10	9	10	10	10
2	**11**	**6**	**11**	**9**	11	8	11	11	**10**	**5**	**7**	**8**
3	3	1	2	3	2	2	2	2	2	3	3	2
4	2	2	3	2	**3**	**7**	**3**	**3**	**3**	**9**	**2**	**3**
5	**8**	**11**	**7**	**7**	9	10	9	9	7	6	6	7
6	9	7	9	10	6	3	5	6	5	2	4	5
7	**1**	**9**	**1**	**1**	1	1	1	1	1	1	1	1
8	**6**	**10**	**5**	**5**	**4**	**11**	**6**	**4**	**4**	**8**	**8**	**4**
9	4	4	6	6	7	4	7	7	6	4	5	6
10	5	3	4	4	5	5	4	5	N/A	N/A	N/A	N/A
11	7	8	8	8	8	6	8	8	8	7	9	9

Rank 1 is given for the highest value, and rank 11 for the lowest value calculated for SUVmean, TLG and MATV for all scans. In bold: a difference of four or more between the highest and lowest rank. Abbreviations: VOI=volume of interest; VOI_{man}=manually drawn VOI; VOI_{auto}=automatically drawn VOI; VOI_{grad}=VOI based on the gradient between voxels; VOI_{grad+}=VOI_{grad} + necrosis; SUVmean=mean standardized uptake value; TLG=total lesion glycolysis; MATV=metabolically active tumor-volume; NA=not applicable.

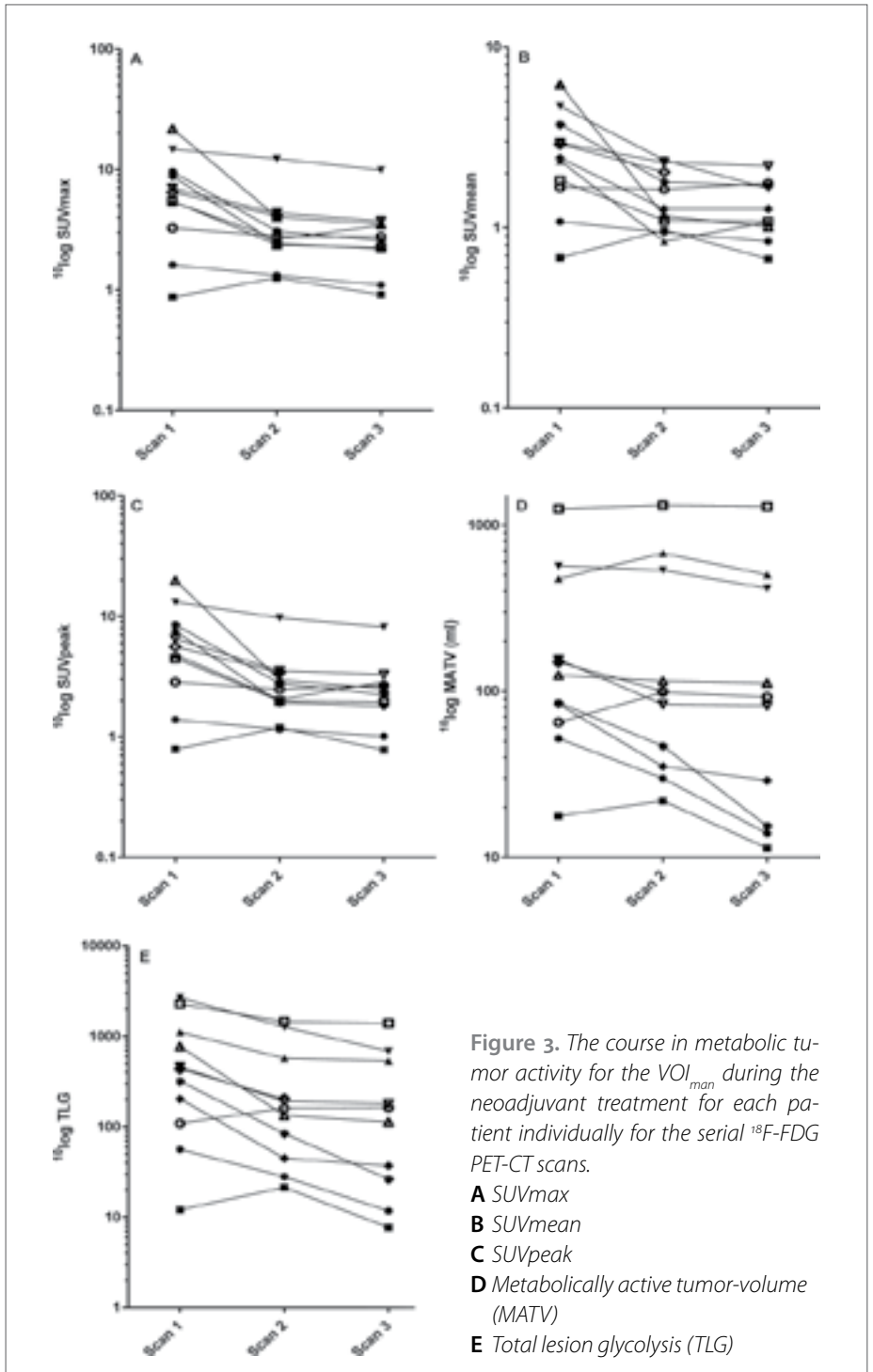


Figure 3. *The course in metabolic tumor activity for the VOI_{man} during the neoadjuvant treatment for each patient individually for the serial ^{18}F-FDG PET-CT scans.*
A *SUVmax*
B *SUVmean*
C *SUVpeak*
D *Metabolically active tumor-volume (MATV)*
E *Total lesion glycolysis (TLG)*

Table 3. Metabolic tumor activity for the VOI_{man} for the serial ^{18}F-FDG PET-CT scans

Parameter	Scan 1	Scan 2	Scan 3	p-value
SUVmax	6.5 (3.3-9.5)	2.8 (2.4-4.1)	2.7 (1.9-3.6)	0.002
SUVpeak	5.6 (2.8-8.5)	2.5 (1.9-3.4)	2.4 (1.6-3.0)	0.001
SUVmean	2.4 (1.7-3.7)	1.3 (1.0-2.0)	1.2 (1.0-1.7)	0.006
TLG	434.8 (108.6-1112.8)	159.9 (44.7-570.9)	137.5 (22.6-572.6)	0.003
MATV (ml)	124.4 (64.8-474.2)	98.3 (35.2-534.2)	87.1 (15.1-437.7)	0.025

Data presented as median (IQR). Abbreviations: VOI=volume of interest; VOI_{man}=manually drawn VOI; ^{18}F-FDG PET-CT=Fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography; SUVmax=maximum standardized uptake value; SUVpeak=peak standardized uptake value; SUVmean=mean standardized uptake value; TLG=total lesion glycolysis; MATV=metabolically active tumor-volume; IQR=inter quartile range.

Histopathologic response

Histopathologic response to neoadjuvant treatment varied among the 11 patients, as follows: one grade A (9.1%), one grade B (9.1%), two grade C (18.2%) (totaling to four histopathologic responders (36.4%)), five grade D (45.5%), and two grade E (18.2%) (totaling to 7 non-responders (64.4%)). The histopathologic responders seem to be identifiable by a decline in TLG of >75% between scan 1 and 3 calculated using the VOI_{man} (Table 5).

To further explore the identification of the histopathologic responders, the difference and percentage difference in TLG between scan 1 and 3 for the four VOI delineation techniques was calculated (Supplemental Table 2). A calculated decline in TLG of >75% using the $VOI_{grad/grad+}$, identified the same histopathologic responders as the VOI_{man}. The VOI_{auto} however failed to identify patient 5 as histopathologic responder. Furthermore, a >75% decline in TLG was also found with the VOI_{auto} and VOI_{grad} in patients 3 and 4, and with the VOI_{grad+} in patient 4.

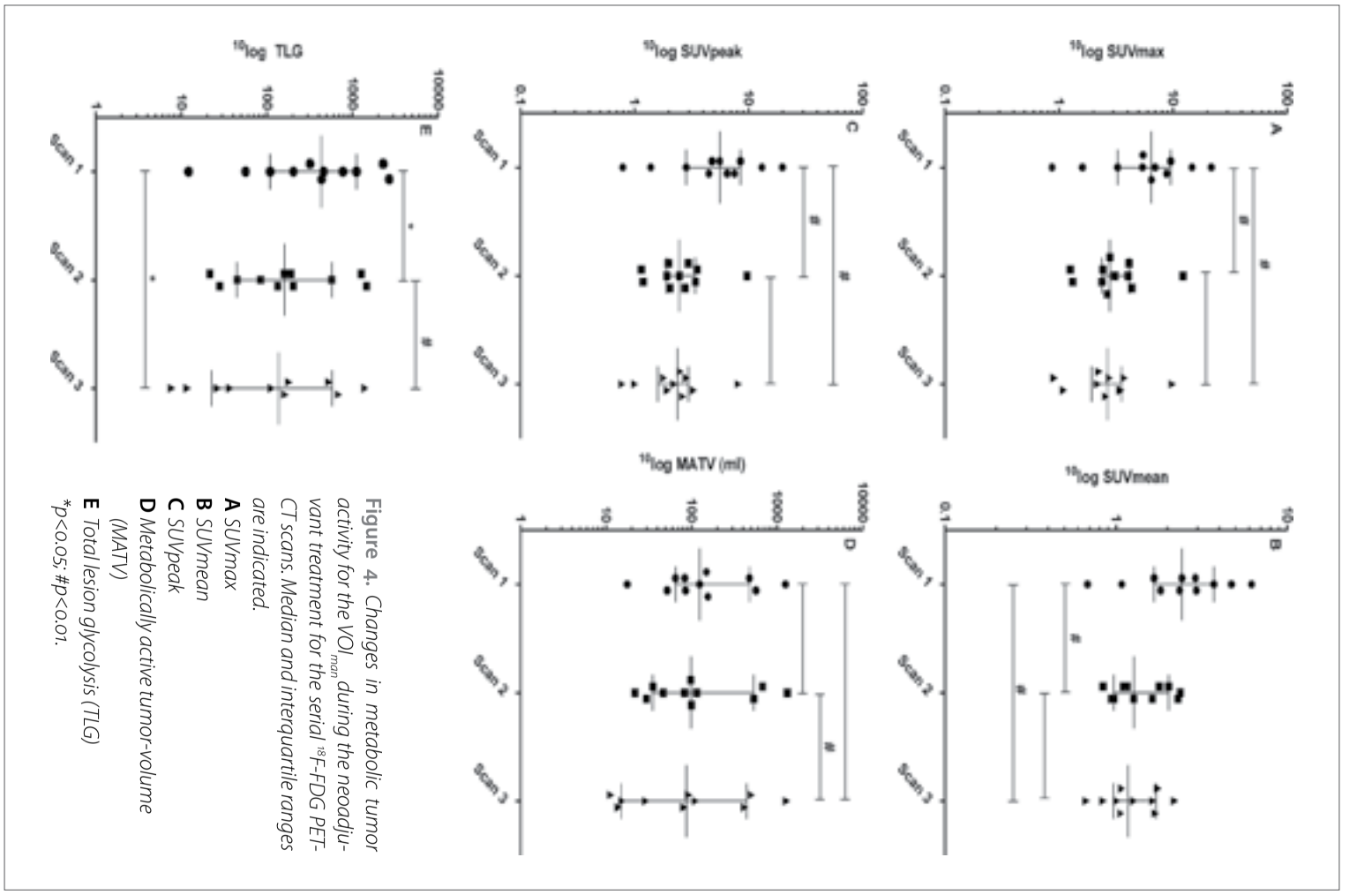


Figure 4. *Changes in metabolic tumor activity for the VOI_{man} during the neoadjuvant treatment for the serial ^{18}F-FDG PET-CT scans. Median and interquartile ranges are indicated.*

A *SUVmax*

B *SUVmean*

C *SUVpeak*

D *Metabolically active tumor-volume (MATV)*

E *Total lesion glycolysis (TLG)*

**p<0.05; #p<0.01.*

Table 4. Changes in metabolic tumor activity for the VOI_{man} during the neoadjuvant treatment between the serial ^{18}F-FDG PET-CT scans

Parameter	Scan 1 vs. 2		Scan 2 vs. 3		Scan 1 vs. 3	
	Δ	Δ %	Δ	Δ %	Δ	Δ %
SUVmax	-2.6 (-6.4 to -0.5)#	-37.7 (-67.7 to -16.4)	-0.3 (-0.5 to -0.1)	-13.6 (-17.5 to -4.7)	-3.2 (-6.7 to -0.5)#	-41.6 (-73.5 to -27.7)
SUVpeak	-2.8 (-5.6 to -0.4)#	-45.8 (-67.4 to -17.3)	-0.2 (-0.5 to 0.0)	-9.3 (-16.8 to 0.4)	-2.9 (-5.9 to -0.3)#	-45.1 (-74.4 to -21.9)
SUVmean	-0.9 (-1.9 to -0.1)#	-39.3 (-52.0 to -13.2)	-0.1 (-0.2 to 0.0)	-4.6 (-17.2 to 2.3)	-1.0 (-2.3 to -0.2)#	-44.1 (-57.2 to -17.0)
TLG	-233.6 (-637.9 to -28.0)*	-52.6 (-73.6 to -36.3)	-18.4 (-57.0 to -10.6)#	-16.3 (-59.7 to -5.5)	-285.0 (-714.7 to -34.4)*	-67.5 (-82.6 to -38.2)
MATV (ml)	-22.1 (-48.2 to 33.5)	-7.5 (-44.9 to 23.5)	-13.2 (-53.0 to -5.3)#	-19.8 (-49.4 to -2.7)	-25.4 (-70.6 to 27.6)	-31.2 (-67.2 to 3.8)

*Data presented as median (IQR). Abbreviations: VOI=volume of interest; VOI_{man}=manually drawn VOI; ^{18}F-FDG PET-CT=Fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography; SUVmax=maximum standardized uptake value; SUVpeak=peak standardized uptake value; SUVmean=mean standardized uptake value; TLG=total lesion glycolysis; MATV=metabolically active tumor-volume; IQR=inter quartile range. *=p<0.05; #=p<0.01.*

Table 5. Changes in metabolic tumor activity for the VOI_{man} during the neoadjuvant treatment between ^{18}F-FDG PET-CT scan 1 and 3, combined with the corresponding histopathologic tumor response for each patient

Patient No.	Scan 1 vs. 3 SUVmax		Scan 1 vs. 3 SUVpeak		Scan 1 vs. 3 SUVmean		Scan 1 vs. 3 TLG		Scan 1 vs. 3 MATV (ml)		EORTC-STBSG response Grade[26]
	Δ	Δ %	Δ	Δ %	Δ	Δ %	Δ	Δ %	Δ	Δ %	
1	-0.5	-32.0	-0.4	-27.0	-0.2	-22.4	-44.4	**-79.2**	-38.0	-73.1	***C***
2	0.1	5.2	-0.0	-1.7	0.0	-0.7	-4.4	-36.3	-6.4	-35.8	D
3	-2.0	-36.6	-2.0	-40.7	-1.3	-54.6	-578.1	-51.9	27.9	5.9	D
4	-4.8	-32.7	-4.9	-37.6	-3.1	-65.1	-1986.4	-74.3	-150.4	-26.5	D
5	-6.6	-75.0	-5.7	-76.2	-1.2	-47.6	-165.7	**-81.8**	-54.4	-65.2	***A***
6	-0.5	-15.0	-0.2	-6.4	0.1	5.0	53.8	49.5	27.5	42.4	E
7	-3.2	-59.0	-2.5	-56.5	-0.7	-40.6	-883.9	-38.8	38.6	3.1	D
8	-18.2	-83.8	-17.3	-87.3	-5.2	-83.7	-658.4	**-85.4**	-12.8	-10.3	***B***
9	-3.2	-46.5	-3.2	-49.5	-0.8	-25.5	-278.7	-60.7	-73.5	-47.3	D
10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	E
11	-7.0	-73.1	-6.3	-73.8	-2.0	-54.4	-291.3	**-91.7**	-69.6	-81.9	***C***

Histopathologic responders are indicated in bold italic. A percentage difference of >75% in TLG seemed to identify the histopathologic responders, these values are indicated in bold. Abbreviations: ^{18}F-FDG PET-CT=Fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography; SUVmax=maximum standardized uptake value; SUVpeak=peak standardized uptake value; SUVmean=mean standardized uptake value; TLG=total lesion glycolysis; MATV=metabolically active tumor-volume; EORTC-STBSG=European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group.

Supplemental Table 2. Changes in TLG according to the four VOI delineation techniques between ^{18}F-FDG PET-CT scan 1 and scan 3, combined with the corresponding histopathologic tumor response for each patient

Patient No.	VOI_{man} TLG		VOI_{auto} TLG		VOI_{grad} TLG		VOI_{grad+} TLG		EORTC-STBSG response Grade[26]
	Δ	Δ %	Δ	Δ %	Δ	Δ %	Δ	Δ %	
1	-44.4	**-79.2**	-47.3	**-100.0**	-33.5	**-77.0**	-30.8	**-75.4**	***C***
2	-4.4	-36.3	-4.1	-20.0	-8.7	-43.7	-8.3	-35.7	D
3	-578.1	-51.9	-665.8	**-85.6**	-786.3	**-76.5**	-568.7	-54.2	D
4	-1986.4	-74.3	-1308.0	**-96.7**	-1886.6	**-82.3**	-1852.9	**-75.8**	D
5	-165.7	**-81.8**	-19.5	-34.6	-153.6	**-83.0**	-156.3	**-82.4**	***A***
6	53.8	49.5	47.4	69.3	45.7	58.9	46.5	59.7	E
7	-883.9	-38.8	601.1	795.2	-947.1	-49.5	-639.3	-32.5	D
8	-658.4	**-85.4**	-312.5	**-94.4**	-660.7	**-95.7**	-612.9	**-86.6**	***B***
9	-278.7	-60.7	-129.6	-49.9	-193.0	-59.8	-198.7	-59.7	D
10	NA	NA	NA	NA	NA	NA	NA	NA	E
11	-291.3	**-91.7**	-142.2	**-83.7**	-228.0	**-90.2**	-223.5	**-88.4**	***C***

Histopathologic responders are indicated in bold italic. All TLG values indicating a percentage differences of >75% are indicated in bold. Abbreviations: ^{18}F-FDG PET-CT=Fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography; VOI_{man}=manually drawn VOI; VOI_{auto}=automatically drawn VOI; VOI_{grad}=VOI based on the gradient between voxels; VOI_{grad+}=VOI_{grad} + necrosis; TLG=total lesion glycolysis; EORTC-STBSG=European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group.

Discussion

This study studying four VOI delineation techniques in three consecutive ^{18}F-FDG PET-CT scans per patient demonstrates a significant decline in metabolic tumor activity (VOI_{man}) during the neoadjuvant treatment, consisting of HILP and preoperative EBRT, of locally advanced ESTS. The decline in SUVmax, SUVpeak, SUVmean and TLG between scan 1 vs. 2 implies that the HILP accounts for the largest effect on metabolic tumor activity. The MATV seems to be affected most by the EBRT, given the significant decline found between scan 2 vs. 3.

In search of a uniform and reproducible way to calculate changes in metabolic tumor activity in these upfront highly heterogeneous tumors, the use of four different VOI delineation techniques was studied. The VOI_{man} (defined as reference VOI) is the only delineation technique in which the entire tumor is encompassed independently of the amount of necrosis present in the tumor. Therefore the VOI_{man} delineation technique seems to be most reliable when used for calculating the metabolic tumor activity. However, the VOI_{man} delineation technique is time-consuming, making it unfit for implementation into daily practice. A high correlation, acceptable level of agreement and comparable ranking was found between the VOI_{man} and the VOI_{grad+} delineation techniques. The differences in ranking between the four VOI delineation techniques are best explained by the high amount of necrosis present in these tumors, as tumor necrosis did not meet the margin thresholds of the VOI_{auto} and VOI_{grad}. To obtain the VOI_{grad+}, the necrosis was manually included and therefore the ranking of patients was comparable to the ranking according to the VOI_{man}.
Thus, the VOI_{grad+} delineation technique seems to be a reliable and reproducible technique for the delineation of heterogeneous tumors as ESTS. Further studies including larger patient-cohorts in various solid tumor types are necessary for the validation and reproducibility of the various VOI delineation techniques. This study, however, demonstrates that the applied VOI delineation technique is important to consider because we found that assessment of response based on metabolic parameters derived from different VOIs may differ across subjects.
The metabolic tumor changes during neoadjuvant treatment between scan 1 vs. scan 3 were analyzed and compared with the corresponding histopathologic tumor response. Out of the five metabolic parameters tested, TLG seemed to identify the histopathologic responders most reliably (>75% decrease in TLG between scan 1 and scan 3) when using the VOI_{man} delineation technique. Using the 75% decrease in TLG as a cut-off value was derived empirically from the data, used as example, and to obtain pilot data for using and comparing these techniques. When compared with the VOI_{man} delineation technique, the VOI_{grad+} technique identified the same histopathologic responders with only one additional patient. It seems that these two delineation techniques most reliably identify histopathologic responders, because they include tumor necrosis. The difference in performance of the VOI_{man} and VOI_{grad+} delineation techniques in identifying histopathologic responders is very subtle. However, the VOI_{grad+} delineation technique was found to be easier in use and is considerably less time-consuming than the VOI_{man} technique, making it more suitable for implementation into daily practice. The VOI delineation techniques and the TLG cut-off value need confirmation in larger patient-cohorts.

During the last years, the predictive value of ^{18}F-FDG PET-CT scans in staging and monitoring treatment response during neoadjuvant treatment has been established for various solid tumors (including metastatic colorectal cancer and non-small cell lung cancer. [23,27-29] Therefore, further ESTS studies in which metabolic tumor activity, e.g. >75% decrease in TLG with VOI_{man} and/or VOI_{grad+}, is explored as predictor for monitoring therapy response, for histopathologic findings and for oncological outcome are warranted. The identification of reproducible and reliable VOI delineation techniques, as well as the identification of robust PET parameters for the interpretation of changes in metabolic tumor activity is relevant because this will enable clinicians to shorten delineation time, and to compare results between observers, patients and centers for ESTS and for other solid tumor types.

This study has some limitations, such as the retrospective character and the small patient population of the study. Only 11 patients were included, however, all patients but one underwent all three ^{18}F-FDG PET-CT scans and therefore it was possible to establish the changes in metabolic tumor activity during the neoadjuvant treatment in all patients. Possibly the interpretation of the third PET scan is biased by local inflammatory changes following the EBRT. These inflammatory changes might partly explain the significantly more pronounced decrease in metabolic tumor activity following the HILP then following the EBRT, as found in the current series. Despite this potential bias due to radiation-induced local inflammatory changes a decrease in metabolic tumor activity between scan 1 and 3 was found, which theoretically might have been larger without these changes. For the purpose of this study, all data considering the metabolic tumor activity were obtained from an additional analyses of the ^{18}F-FDG PET-CT scans, since these data are not used in routine patient care. Interestingly, the EORTC-STBSG response score [26] could be used to explore the relationship between changes in metabolic tumor activity and histopathologic response. However, the prognostic value of the STS response score according to the proportion of stainable tumor cells needs further validation.[30]

Conclusions

This study identified the VOI_{grad+} delineation technique as most reliable considering reproducibility when compared with the other delineation techniques during the multimodality neoadjuvant treatment of locally advanced ESTS. Moreover, the VOI_{grad+} delineation technique was considerably less time-consuming to perform when compared to the VOI_{man} technique, potentially resulting in easier implementation in clinical practice. A significant decline in metabolic tumor activity during the treatment was found. The decrease in metabolic tumor activity was significantly more pronounced after HILP than after preoperative radiotherapy. TLG seems promising, but warrants further confirmation, as predictor for histopathologic response in ESTS. Further studies in larger ESTS patient-cohorts in which the investigated metabolic parameters and VOI delineation techniques are confirmed and validated as predictors for monitoring treatment response, for histopathologic response and for oncological outcome are warranted, as this will result in an increase in the clinical applicability of metabolic tumor activity assessments in longitudinal sarcoma ^{18}F-FDG PET-CT studies.

Supplemental methods

Bland-Altman analyses

Bland-Altman analyses were performed to determine the level of agreement between volume of interest (VOI) delineation techniques. Bland-Altman plots were created to compare the reference VOI_{man} with the other three VOI delineation techniques. Plots comparing the difference vs. the average as well as the percentage difference vs. the average between the VOI_{man} and the three other VOI delineation techniques were created. The percentage difference was obtained by dividing the difference between the measured values by the average of these values. This was performed for SUVmean, TLG and MATV, and not for SUVmax and SUVpeak, since the measured values for these latter parameters were identical for all scans, independently of the VOI delineation technique that was used.

Ranking of patients

Patients were ranked according to the SUVmean, TLG and MATV for each scan. SUVmax and SUVpeak were not included, for the same reason as stated above. The highest value was given rank 1 and the lowest value was given rank 11. Using this ranking method, the VOI delineation techniques were compared. A difference in ranking of four or more between the highest and lowest rank was indicated in bold.

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Histopathological tumor response following neoadjuvant hyperthermic isolated limb perfusion in extremity soft tissue sarcomas: evaluation of the EORTC-STBSG response score

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Abstract

Introduction
This study aims to evaluate the applicability and prognostic value of the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) histopathological response score in extremity soft tissue sarcoma (ESTS) patients treated with neoadjuvant hyperthermic isolated limb perfusion (HILP) and delayed surgical resection.

Methods
Patients treated between 1991 and 2016 were included. The histopathological tumor response was established in accordance with the EORTC-STBSG response score. The distribution of patients was assorted according to the 5-tier histopathological response score for tumor grade, histological subtype and HILP regimen. Predictors for local recurrence free survival (LRFS) and overall survival (OS) were identified through Kaplan-Meier and Cox regression analyses.

Results
Ninety-one patients were included and their resection specimens were reanalyzed. Which resulted in 11 Grade A (12.1%), ten Grade B (11.0%), 15 Grade C (16.5%), 22 Grade D (24.2%) and 33 Grade E (36.3%) responses found among the series. The histopathological response was significantly influenced by the HILP regimen used, p=0.033. Median follow-up was 65.0 (18.0-157.0) months. The histopathological response was not associated with LRFS nor OS. Resection margins, HILP regimen and adjuvant radiotherapy were associated with LRFS. Patients' age, tumor grade, tumor size and histological subtype were predictors for OS.

Conclusions
The EORTC-STBSG response score is applicable for determining the histopathological response to neoadjuvant ESTS treatment. However, this response does not seem to predict LRFS nor OS in locally advanced ESTS.

Introduction

Soft tissue sarcomas (STS) are relatively rare and heterogeneous tumors, including over 50 histopathological subtypes.[1] Approximately 50-60% of the STS arise in the extremities.[2] In the Netherlands, 600-700 patients are diagnosed with a STS leading to 300 STS related deaths annually.[3,4]
Extremity soft tissue sarcomas (ESTS) patients' survival is mainly determined by metastatic potential, whereas local tumor treatment is of lesser importance. Consequently, local tumor treatment has evolved from amputation to limb salvage surgery combined with radiotherapy.[5,6] At presentation, some ESTS are considered to be locally advanced. Since the overall survival of ESTS patients is not increased by amputation of the affected limb,[5] neoadjuvant hyperthermic isolated limb perfusion (HILP), followed by surgical resection, has been used to prevent amputation in locally advanced ESTS in over 40 centers throughout Europe,[7,8] resulting in a limb salvage rate of 80-90%.[9-12]

Apart from neoadjuvant HILP, preoperative radiotherapy has been used in ESTS for decades. More recently, neoadjuvant chemotherapy has been tested in clinical trials in high-risk, but localized STS.[13,14] To evaluate the histopathological response to these neoadjuvant treatment strategies, a standardized approach for the pathological examination of pretreated sarcomas was proposed by the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) in 2016.[15] This protocol includes a 5-tier response score based on the percentage of stainable, potentially viable tumor cells, clearly different from earlier methods in which the percentage of tumor necrosis was scored to determine the tumor response. Notably, thus far, data from the literature did not prove that the amount of tumor necrosis is prognostic in pretreated STS.[15,16] As tumor necrosis can be present in some STSs at diagnosis, it seems trustworthy to use the percentage of stainable cells in determining the histopathological response to neoadjuvant treatment. Recently, the first study applying the EORTC-STBSG response score found that it has no prognostic value with respect to recurrence free- and overall survival in a cohort of 100 extremity and trunk STS patients treated with radiotherapy prior to surgical resection.[17]
This single tertiary sarcoma-center study aims to assess the applicability and the prognostic value of the EORTC-STBSG response score in locally advanced ESTS patients treated with neoadjuvant HILP followed by surgical resection of the residual tumor.

Patients and methods

Patients

The Institutional Review Board approved this study (case-number 2017.319). All consecutive patients over 18-years of age, with primary or recurrent, localized ESTS treated with neoadjuvant HILP followed by surgical resection, after 6-8 weeks, at the University Medical Center Groningen (UMCG) between 1991 and 2016 were analyzed. None of the patients were treated with neoadjuvant chemotherapy. Patients' characteristics were obtained through medical record review. Patients for whom the required biopsy/tumor specimen was not available or not suitable for reanalyzes were excluded from the cohort.

Hyperthermic isolated limb perfusion

The HILP technique used, is based on the technique developed by Creech et al.[18] and has previously been described in more detail.[19] Under general anesthesia the major artery and vein of the affected limb were isolated and cannulated, thereby, isolating the blood flow of the limb from the systemic circulation. The cannulas were connected to an extracorporeal circuit. Subsequently, a tourniquet was applied to minimize leakage of the cytostatic agents into the systemic circulation. At the beginning, the perfusate consisted of interferon-γ (IFN-γ), tumor-necrosis factor-α (TNF-α) (Beromun®, Boehringer-Ingelheim GmbH, Vienna, Austria) and melphalan (Alkeran®, GlaxoSmith-Kline Pharmaceuticals, Research Triangle Park, NC, USA). IFN-γ was soon abandoned, due to its ineffectiveness.[7,9] Potential leakage of the cytostatic agents into the systemic circulation was continuously monitored by a precordial scintillation detector and I^{131}-human serum albumin.[20,21] To perform the perfusion under controlled mild hyperthermia (38.5-40.0˚C), the limb was externally heated. Due to improvements in the HILP treatment, not all patients in this series were treated according the same HILP regimen. IFN-γ was abandoned, the TNF-α dose was reduced and the perfusion time was shortened.[11] Until 2001 the perfusion duration was 90 min whereas from 2001 till now the duration was 60 min. The 90 min regimen was divided in 30 min of TNF-α perfusion, followed by 60 min of melphalan perfusion. The 60 min regimen, started with 15 min of TNF-α perfusion, then the melphalan was added and after another 45 min the perfusion was ended. Nowadays, 2 mg TNF-α is used for femoral and iliac perfusions. Whereas 1 mg TNF-α is used for upper extremity and popliteal perfusions. These TNF-α doses are lower than the formerly used 3-4 mg TNF-α.[11] The melphalan dose was based on the limb volume, 10 mg/L for upper extremity and popliteal perfusions, and 13 mg/L for iliac and femoral perfusions. Following the perfusion, the limb was flushed with saline, 2 L for upper extremity and popliteal perfusions, and 6 L for iliac and femoral perfusions. Following the flushing of the limb, the limb was filled with 1U red blood cell concentrate. Afterwards, the cannulas were removed, the vessels repaired and the heparin antagonized with protamine sulphate. A closed fasciotomy of the anterior compartment of the lower leg was performed to prevent a compartment syndrome.[22,23] The first 24 hours following the procedure, the patient was closely observed in the medium care or intensive care unit.

Methods

Prior to treatment, core-needle biopsies were performed for typing and grading of the tumors according to 'American Joint Committee on Cancer' and 'World Health Organization (WHO)' criteria.[1,24] Tumor margins were classified according to the 'Union for International Cancer Control' R classification[25] i.e. R0 for microscopically free tumor margins, R1 for microscopically compromised margins and R2 for macroscopically compromised margins. As previously reported, the histopathological examination of STSs, including the determination of the percentage tumor necrosis of the resection specimens has been standardized at the UMCG since 1991.[10,11,26] In 2017, all resection specimens were re-analyzed by a pathologist with special interest and expertise in STS, who was blinded for clinical outcome, to classify the histopathological tumor response in accordance with the 5-tier, stainable tumor cell based, EORTC-STBSG response score; Grade A, no stainable tumor cells; Grade B, single stainable tumor cells or small clusters (overall below 1% of the whole specimen); Grade C, ≥1%-<10% stainable tumor cells; Grade D, ≥10%-<50% stainable tumor cells; Grade E, ≥50% stainable tumor cells.[15]

The influence of tumor grade, histological subtype and HILP regimen on the histopathological response was investigated by assorting patients' distribution for these parameters according to the five response grades. Histopathological responders were defined as having <10% stainable tumors cells, combining response grade A, B and C. The remaining patients were considered histopathological non-responders with response grade D or E. Uni- and multivariate survival analyses were performed to identify associations between patient, tumor and treatment characteristics and 10-year local recurrence free survival (LRFS) or 10-year overall survival (OS).

Statistical analyses

Data are presented as frequencies and percentages for discrete variables and median and inter quartile ranges (IQR) for continuous variables. None of the variables were normally distributed. The Mann-Whitney U and Kruskal-Wallis test were used to compare patients' distribution for tumor grade, histological subtype and HILP regimen according to their corresponding response scores. A p-value <0.05 was considered to indicate statistical significance. Oncological outcome was defined as time from date of HILP to event, either local recurrence or death. The Kaplan-Meier method and log-rank test were used for univariate survival analyses. Cox-regression was used to perform multivariate survival analyses. All potential predictors were included in a first multivariate cox-regression model. Backward selection was used, and predictors with a p<0.1 were included in the final model. Hazard ratios (HR) and 95% confidence intervals (CI) are presented. SPSS version 23.0 (IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp) was used.

Results

Ninety-one patients, 48 male (52.7%), with a median age of 58.0 (44.0-65.0) years were included. Median tumor size was 9.0 (6.0-13.0) cm. Nearly 90% of the tumors were high grade and 83.5 % of the tumors were located in the lower extremity. Eighty-one patients (89.0%) were treated for primary disease, the remaining 10 patients (11.0%) for recurrent disease. The predominant histological subtype was pleomorphic undifferentiated sarcoma not otherwise specified (Table 1). Not all patients underwent the same HILP regimen; 41 patients (45.1%) underwent the long and high dose HILP regimen, 12 patients (13.2%) underwent the short but high dose HILP regimen, 38 patients (41.8%) underwent the, now commonly accepted, short and low dose HILP regimen and 13 patients (14.3%) underwent a limb perfusion during the years that IFN-γ was included in the perfusate. Sixty patients (65.9%) underwent postoperative external beam radiotherapy (EBRT) following the HILP and surgical resection. Seventy patients (76.9%) underwent a Ro resection. The previously reported histopathological tumor responses were no change (NC), <50% necrosis, in 25 patients (27.5%); partial response (PR), 50-99% necrosis, in 50 patients (54.9%); and complete response (CR), 100% necrosis in 16 patients (17.6%). All 91 resection specimens were reanalyzed, and classified according to the EORTC response score. Eleven patients had no stainable tumor cells left in the resection specimen, Grade A (12.1%). Ten patients had <1% stainable tumor cells, Grade B (11.0%). Fifteen patients had ≥1%-<10% stainable tumor cells, Grade C (16.5%). Twenty-two patients had ≥10%-<50% stainable tumor cells, Grade D (24.2%) and

Table 1. Patient and tumor characteristics

Characteristic	Total n=91 (%)
Age, years (IQR)	58.0 (44.0-65.0)
Gender	
• Male	48 (52.7)
• Female	43 (47.3)
Tumor size, cm (IQR)	9.0 (6.0-13.0)
Tumor grade	
• High	80 (87.9)
• Low	11 (12.1)
Tumor location	
• Lower extremity	76 (83.5)
• Upper extremity	15 (16.5)
Histological subtype	
• Pleomorphic undifferentiated/NOS	25 (27.5)
• Myxofibrosarcoma	14 (15.4)
• Myxoid liposarcoma	14 (15.4)
• Synovial sarcoma	11 (12.1)
• Leiomyosarcoma	9 (9.9)
• MPNST	3 (3.3)
• Pleomorphic rhabdomyosarcoma	3 (3.3)
• Pleomorphic liposarcoma	3 (3.3)
• Other	9 (9.9)
Local presentation	
• Primary	81 (89.0)
• Recurrent	10 (11.0)

Data presented as n (%) or median (IQR). Abbreviations: IQR=interquartile range; NOS=not otherwise specified; MPNST=malignant peripheral nerve sheath tumor.

Table 2. Treatment and tumor response characteristics

Characteristic	Total n=91 (%)
HILP type	
• Iliac	36 (39.6)
• Femoral	13 (14.3)
• Popliteal	27 (29.7)
• Axillar	12 (13.2)
• Brachial	3 (3.3)
HILP drugs	
• IFN-γ/TNF-α/Melphalan	13 (14.3)
• TNF-α/Melphalan	78 (85.7)
HILP regimen	
• Long (90 min) and high dose TNF-α	41 (45.1)
• Short (60 min) and high dose TNF-α	12 (13.2)
• Short (60min) and low dose TNF-α	38 (41.8)
Resection quality	
• R0	70 (76.9)
• R1	18 (19.8)
• R2	3 (3.3)
Adjuvant EBRT	
• No	31 (34.1)
• Yes	60 (65.9)
Tumor necrosis, historical	
• NC; <50%	25 (27.5)
• PR; 50-99%	50 (54.9)
• CR; 100%	16 (17.6)
EORTC STS response score	
• Grade A	11 (12.1)
• Grade B	10 (11.0)
• Grade C	15 (16.5)
• Grade D	22 (24.2)
• Grade E	33 (36.3)
Histopathological responder	
• No	55 (60.4)
• Yes	36 (39.6)

Data presented as n (%). Abbreviations: HILP=hyperthermic isolated limb perfusion; IFN-γ=interferon-γ; TNF-α=tumor necrosis factor-α; EBRT=external beam radiotherapy; NC=no change; PR=partial response; CR=complete response. EORTC STS response score: Grade A, no stainable tumor cells; Grade B, single stainable tumor cells or small clusters (overall below 1% of the whole specimen); Grade C, ≥1%-<10% stainable tumor cells; Grade D, ≥10%-<50% stainable tumor cells; Grade E, ≥50% stainable tumor cells.[15]
Histopathological responders having <10% stainable tumor cells.

33 patients had ≥50% stainable tumor cells, Grade E (36.3%). Resulting in 36 responders (39.6%) and 55 non-responders (60.4%) (Table 2).
Table 3 presents patients' distribution for tumor grade, histological subtype and HILP regimen according to the five histopathological response grades. No significant differences in distribution were found for tumor grade and histological subtype among the EORTC grades, p=0.104 and 0.111 respectively. A significant difference in distribution among the response grades was found for the various HILP regimens, p=0.033.

Follow-up

Median follow-up was 65.0 (18.0-157.0) months for the entire cohort. Ten patients (11.0%) developed a local recurrence and 47 patients (51.6%) developed distant metastases. Ultimately, 43 patients (47.3%) died of disease and 8 patients (8.8%) died of other causes. At end of follow-up 40 patients (44.0%) were alive. Of which 36 patients (90.0%) had no evidence of disease, while 4 patients (10%) were alive with disease.
Univariate survival analyses displayed a significant influence of the HILP regimen, resection quality and adjuvant EBRT on 10-year LRFS. Showing a worse 10-year LRFS for patients treated with the short + high dose TNF-α HILP regimen, as well as for patients with compromised resection margins. Furthermore, postoperative irradiated patients

Table 3. Tumor response following neoadjuvant HILP according to tumor grade, histological subtype and HILP regimen

Characteristic	Total n=91	EORTC Grade					p-value
		Grade A (n=11)	Grade B (n=10)	Grade C (n=15)	Grade D (n=22)	Grade E (n=33)	
Tumor grade							0.104*
• High	80 (87.9)	9 (91.8)	8 (80.0)	12 (80.0)	20 (90.9)	31 (93.9)	
• Low	11 (12.1)	2 (18.2)	2 (20.0)	3 (20.0)	2 (9.1)	2 (6.1)	
Histological subtype							0.111#
• Pleomorphic undifferentiated/NOS	25 (27.5)	6 (54.5)	3 (30.0)	3 (20.0)	5 (22.7)	8 (24.2)	
• Myxofibrosarcoma	14 (15.4)	-	1 (10.0)	1 (6.7)	4 (18.2)	8 (24.2)	
• Myxoid liposarcoma	14 (15.4)	1 (9.1)	2 (20.0)	4 (26.7)	5 (22.7)	2 (6.1)	
• Synovial sarcoma	11 (12.1)	-	2 (20.0)	1 (6.7)	3 (13.6)	5 (15.2)	
• Leiomyosarcoma	9 (9.9)	2 (18.2)	1 (10.0)	3 (20.0)	1 (4.5)	2 (6.1)	
• MPNST	3 (3.3)	-	-	2 (13.3)	-	1 (3.0)	
• Pleomorphic rhabdomyosarcoma	3 (3.3)	1 (9.1)	-	-	-	2 (6.1)	
• Pleomorphic liposarcoma	3 (3.3)	-	-	-	-	3 (9.1)	
• Other	9 (9.9)	1 (9.1)	1 (10.0)	1 (6.7)	4 (18.2)	2 (6.1)	
HILP regimen							0.033#
• Long (90 min) and high dose TNF-α	41 (45.1)	8 (72.7)	6 (60.0)	6 (40.0)	9 (40.9)	12 (36.4)	
• Short (60 min) and high dose TNF-α	12 (13.2)	-	3 (30.0)	3 (20.0)	4 (18.2)	2 (6.1)	
• Short (60min) and low dose TNF-α	38 (41.8)	3 (27.3)	1 (10.0)	6 (40.0)	9 (40.9)	19 (57.6)	

*Data presented as n (%). Abbreviations: EORTC=European Organization for Research and Treatment of Cancer; NOS=not otherwise specified; MPNST=malignant peripheral nerve sheath tumor; HILP=hyperthermic isolated limb perfusion; TNF-α=tumor-necrosis factor-α. *Mann-Whitney U test. #Kruskal-Wallis test.*

had a 10-year LRFS of 89.5% compared to 65.2% for patients who did not undergo adjuvant EBRT, p=0.004. No significant association between the histopathological tumor response and 10-year LRFS was found. Due to the limited amount of local recurrences, no multivariate analyses for LRFS was performed. Patients' age at start of treatment, tumor grade, histological subtype and adjuvant EBRT were significantly associated with 10-year OS in univariate analyses (Table 4). Multivariate cox-regression analyses identified patients' age 1.04 (1.01-1.06), p=0.003; tumor size 1.09 (1.03-1.15), p=0.001; high tumor grade 4.52 (1.12-18.23), p=0.034; and histological subtype, p=0.011 to be predictors for 10-year OS (Table 5). Leiomyosarcoma and MPNST were associated with a significantly worse 10-year OS.

Discussion

This study shows that the EORTC-STBSG response score can be applied to determine the histopathological tumor response following neoadjuvant HILP and delayed surgical resection in locally advanced ESTS. A significant difference in the percentage stainable tumor cells was found for the various HILP regimens used during the study period. However, no association between the histopathological tumor response, i.e. tumor necrosis or stainable tumor cells, and LRFS or OS was found.

STS are heterogeneous tumors and the neoadjuvant treatment-induced tumor changes can differ throughout the tumor. Furthermore, STS tend to have a necrotic tumor center at presentation due to rapid tumor growth. At histopathological examination after resection it is impossible to determine the cause of necrosis (pre-existent or treatment-induced). Earlier studies showed that the percentage of tumor necrosis following neoadjuvant treatment is not prognostic for oncological outcome in ESTS.[15,16] Therefore the EORTC response score may have greater potential for the determination of the therapy effect compared to the determination of the percentage tumor necrosis. However, as our results show, the EORTC response score does not seem to influence the LRFS or OS.

In bone sarcomas, especially osteosarcomas, the use of tumor necrosis and later the proportion of vital tumor cells has been established, and was found to be prognostic.[27-29] Subsequently, histopathological responders, <10% vital tumor cells, and non-responders in osteosarcomas were identified by the WHO.[1] The standardized protocol for the pathological examination of pretreated STS as proposed by the EORTC-STBSG includes a 5-tier STS response score to interpret the efficacy of the various neoadjuvant treatment strategies used in STS nowadays.[15]

Table 4. Univariate analyses of the association between patient, tumor and treatment characteristics and 10-year LRFS and OS

Characteristic	n	10-year LRFS (%)	10-year LRFS p-value	10-year OS (%)	10-year OS p-value
All patients	91	81.6	NA	45.7	NA
Age, years			0.507		0.003
• <45	23	83.7		73.7	
• 45-54	17	68.6		45.4	
• 55-65	30	91.6		43.3	
• ≥ 65	21	79.0		15.9	
Gender			0.178		0.733
• Male	48	90.9		43.8	
• Female	43	73.0		48.2	
Tumor size (cm; 4 missing)			0.944		0.442
• <5	16	79.1		50.0	
• ≥ 5	71	82.8		44.5	
Tumor grade			0.529		0.050
• High	80	80.9		42.3	
• Low	11	85.7		71.6	
Tumor location			0.154		0.617
• Lower extremity	76	85.0		46.9	
• Upper extremity	15	60.9		40.0	
Histological subtype			0.829		0.011
• Pleomorphic undifferentiated/NOS	25	84.3		32.0	
• Myxofibrosarcoma	14	80.2		42.9	
• Myxoid liposarcoma	14	88.9		71.4	
• Synovial sarcoma	11	83.3		72.7	
• Leiomyosarcoma	9	43.8		22.2	
• MPNST	3	NA*		0.0	
• Pleomorphic rhabdomyosarcoma	3	NA*		66.7	
• Pleomorphic liposarcoma	3	NA*		33.3	
• Other	9	80.0		53.3	
Local presentation			0.116		0.477
• Primary	81	84.7		43.9	
• Recurrent	10	63.5		60.0	
HILP type			0.320		0.085
• Iliac	36	72.7		41.3	
• Femoral	13	NA*		44.9	
• Popliteal	27	92.0		55.6	
• Axillar	12	60.2		50.0	
• Brachial	3	NA*		0.0	

Table 4. Continued

Characteristic	n	10-year LRFS (%)	10-year LRFS p-value	10-year OS (%)	10-year OS p-value
HILP drugs			0.653		0.903
• IFN-γ/TNF-α/Melphalan	13	76.4		46.2	
• TNF-α/Melphalan	78	82.7		45.6	
HILP regimen			0.008		0.634
• Long (90min) + high dose TNF- α	41	84.2		41.5	
• Short (60 min) + high dose TNF-α	12	48.9		50.0	
• Short (60min) + low dose TNF-α	38	97.2		49.3	
Resection quality			0.006		0.704
• R0	70	88.0		45.5	
• R1	18	59.9		50.0	
• R2	3	66.7		33.3	
Adjuvant EBRT			0.004		0.047
• No	31	65.2		34.9	
• Yes	60	89.5		51.5	
Tumor necrosis, historical			0.931		0.928
• NC; <50% necrosis	25	81.7		50.9	
• PR; 50-99% necrosis	50	84.2		44.0	
• CR; 100% necrosis	16	76.2		43.8	
EORTC STS response score			0.514		0.260
• Grade A	11	85.7		45.5	
• Grade B	10	83.3		60.0	
• Grade C	15	NA*		26.7	
• Grade D	22	81.8		58.7	
• Grade E	33	72.6		42.4	
Histopathological responder			0.156		0.729
• No	55	77.5		48.8	
• Yes	36	87.8		41.7	

*Data presented as actuarial survival percentages, log-rank test was used for comparison of characteristics. *Not applicable, all cases were censored. Abbreviations: LRFS=local recurrence free survival; OS=overall survival; NA=not applicable; HILP=hyperthermic isolated limb perfusion; IFN-γ=interferon-γ; TNF-α=tumor-necrosis factor-α ; NOS=not otherwise specified; MPNST=malignant peripheral nerve sheath tumor; NC=no change; PR=partial response; CR=complete response; EORTC=European Organization for Research and Treatment of Cancer; STS=soft tissue sarcoma.*

Table 5. Multivariate cox-regression analyses of the association between patient, tumor and treatment characteristics and 10-year OS

Characteristic	Overall survival	
	HR (95% CI)	p-value
Age, years	1.04 (1.01-1.06)	0.003
Tumor size (cm)	1.09 (1.03-1.15)	0.001
Tumor grade		0.034
• Low	1	
• High	4.52 (1.12-18.23)	
Histological subtype		0.011
• Myxoid liposarcoma	1	
• Leiomyosarcoma	5.86 (1.47-23.34)	
• Myxofibrosarcoma	1.52 (0.36-6.39)	
• Synovial sarcoma	1.54 (0.29-8.23)	
• MPNST	10.66 (1.92-59.37)	
• Pleomorphic undifferentiated/NOS	2.76 (0.71-10.69)	
• Pleomorphic rhabdomyosarcoma	0.65 (0.06-6.63)	
• Pleomorphic liposarcoma	0.75 (0.11-5.05)	
• Other	1.25 (0.26-6.08)	

Abbreviations: OS=overall survival; HR=hazard ratio; CI=confidence interval; NOS=not otherwise specified.

The current study could not establish an association between this STS response score and LRFS or OS. Subsequently patients were divided into two groups, being histopathological responders and non-responders to create larger groups for statistical analyses. The cut-off value used was based on the cut-off value currently used to determine response to chemotherapy for osteosarcomas. Histopathological responders were defined as having residual tumors containing <10% stainable tumor cells. However, as Table 4 shows being a histopathological responder did not influence 10-year LRFS nor OS.

The first study applying the EORTC-STBSG response score, showed no prognostic value considering recurrence free- and overall survival in a cohort of 100 extremity and trunk STS patients treated with radiotherapy prior to surgical resection of the residual tumor.[17] Till date, there is no data addressing the prognostic value of the EORTC response score following chemotherapy in STS. As the use of (neo)adjuvant chemotherapy is controversial and under ongoing investigation in localized STS,[14] it might be of interest to include the EORTC-STBSG response score as parameter in current and future studies, especially since the histopathological tumor response of the primary tumor might provide additional information regarding the chemosensitivity of potential metastases developing during follow-up in these patients.
The current study has some limitations. The retrospective nature affects data collection and selection of patients. Not all patients in this cohort underwent the same HILP regimen. Over time IFN-γ was abandoned due to its ineffectiveness, the TNF-α dose was lowered and the perfusion duration was shortened. These improvements in HILP treatment were found to be safe and effective in terms of long-term patient outcome.[7,9,11] However, as established in the current series these changes in HILP regimen significantly influence the histopathological response when classified according to the EORTC-STBSG score.

The current study shows an univariate association between the various HILP regimens, resection margins and adjuvant EBRT, and 10-year LRFS. The significant effect of the HILP regimen on LRFS was unexpected, and seems to be explained by a worse LRFS for patients who underwent the short and high dose regimen. We cannot fully explain this worse LRFS for these patients. However, this regimen is no longer in use as the shorter and reduced dose regimen was shown to be oncologically safe in 2011.[11] In corroboration with earlier studies, we found that the 10-year OS is predicted by patients' age, tumor size, tumor grade and histological subtype through multivariate analyses in the current series.[1,30-33] However, there are studies showing that local recurrence development is a predictor for distant metastases and (disease-specific) death as well.[34-36] Due to small sample size and low event rate i.e. local recurrence rate, we were not able to perform multivariate analyses for LRFS. Besides, nearly 66% of the patients in this cohort received postoperative EBRT following the HILP and surgical resection, and although the adjuvant EBRT does not influence the histopathological response, it is well-accepted that postoperative EBRT following HILP and surgical resection lowers the local recurrence risk.[26] Since postoperative EBRT lowers the local recurrence risk, the tumor margin combined with the tumor response at the closest surgical margin might be of prognostic value for local recurrence development. Studies addressing the influence of the histopathological response at the closest

surgical margin combined with the role of postoperative EBRT in these cases are necessary.

In conclusion, we corroborated earlier studies, showing that the histopathological tumor response, scored by the relative amount of tumor necrosis or stainable tumor cells, has no prognostic value considering LRFS and OS in pretreated STS. Therefore, the histopathological response should not be used in making treatment decisions at this point. Nevertheless, it is important to standardize the pathological examination of pretreated STS and to conform to the use of the EORTC-STBSG response score. In pretreated STS the use of stainable tumor cells seems rational and trustworthy, and further prospective research considering its prognostic value for oncological outcome is warranted.

Conclusions

In STS management, the proposed standardization of histopathological examination of pretreated STS by the EORTC-STBSG is a step forwards. However, in our series the histopathological response (either stainable tumor cells or tumor necrosis) of these tumors does not seem to have prognostic value considering LRFS and OS and therefore it should not be used in making treatment decisions at this point. Further prospective studies addressing the prognostic value of the histopathological response, preferably including vital tumor cells, in pretreated STS are necessary.

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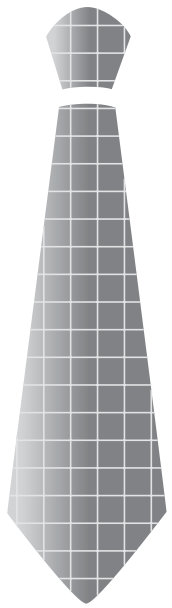
Summary and conclusions
Samenvatting en conclusies



Summary & conclusions

Part I - Treatment of resectable extremity soft tissue sarcoma

As limb-amputation was shown not to improve survival rates, surgical resection of the tumor has become the mainstay of extremity soft tissue sarcoma (ESTS) treatment since the randomized trials by Rosenberg et al. in the 1980s.[1] Accordingly, the treatment of ESTS has evolved from limb-amputation to a more conservative multimodality approach.[2,3] This enables clinicians to prevent limb-amputation in >90% of the patients nowadays.[4-7] External beam radiotherapy (EBRT) is used commonly in addition to surgical resection to gain local tumor control. In 2002, the randomized controlled trial by O'Sullivan et al. showed a significant increase in major wound complications (MWC) following preoperative EBRT, when compared with postoperative EBRT in addition to surgical resection.[3] However, as postoperative EBRT involves higher radiation doses and larger radiation fields it is associated with an increased risk for the development of fibrosis, possibly leading to a detrimental long-term functional outcome.[8] **Chapter 2** aimed to identify predictors for MWC development following EBRT and surgical resection in ESTS treatment. In preoperative irradiated patients a MWC rate of 39.7% was found, whereas 20.3% of the postoperatively irradiated patients developed a MWC in our series. Subsequently, preoperative EBRT was identified as significant predictor for MWC development, while a trend towards an increased MWC risk was found for patients' age, timing of wound closure and tumor margins. Besides, a shift in the distribution of patients treated with preoperative or postoperative EBRT in addition to surgical resection was shown. Hence, out of the 36 patients treated between 2005 and 2007 one patient underwent preoperative EBRT, whereas 35 out of the 39 patients treated between 2014-2016 underwent preoperative EBRT.

Part II - Treatment of locally advanced extremity soft tissue sarcoma

The treatment of locally advanced, or primarily non-resectable, ESTS is particularly challenging. The involvement of neurovascular structures, bony involvement or large tumor size, involving multiple compartments, necessitate an extensive treatment regimen to facilitate limb salvage treatment in these locally advanced ESTS.[9-11] Hyperthermic isolated limb perfusion (HILP) with melphalan and tumor necrosis factor-α (TNF-α) followed by surgical resection of the tumor and postoperative EBRT in selected cases is used throughout Europe to prevent limb-amputation in patients who would otherwise be considered for ablative surgery.[12] Traditionally HILP was followed by surgical resection of the tumor (after 6-8 weeks) and if indicated, postoperative EBRT starting 6-8 weeks following the surgical resection was administered.[10] **Chap-**

ter 3 presents a shorter but intensive treatment regimen for locally advanced ESTS, consisting of HILP, preoperative EBRT and surgical resection of the tumor remnant. This intensified treatment was found to be feasible and safe in locally advanced ESTS, while the oncological outcome was found to be similar to the traditionally used regimen. As highlighted in **chapter 4**, limb-salvage treatment is not or no longer feasible for some patients. In these cases, limb-amputation is the only remaining treatment option to obtain local tumor control. Non-resectability of the tumor caused by large tumor size was found to be the main indication for a primary amputation, whereas a local recurrence which could not be treated with a limb salvage treatment option was the predominant indication to perform a non-primary amputation. Furthermore, we showed in **chapter 4** that while the time between diagnosis and amputation differs significantly for primary and non-primary amputated patients, their oncological outcome seems to be comparable.

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

The more routine use of neoadjuvant treatment modalities i.e. HILP, preoperative EBRT and neoadjuvant systemic chemotherapy in localized ESTS has consequently led to more research focusing on the assessment of neoadjuvant treatment-efficacy. Since the 1990s, fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET-CT) scans have been used to assess and quantify the changes in metabolic tumor activity, commonly expressed as maximum standardized uptake value (SUVmax) and SUVmean.[13] In **chapter 5** we present the use of various volume of interest (VOI) delineation techniques for the quantification of the metabolic tumor activity of locally advanced ESTS during neoadjuvant multimodality treatment, consisting of neoadjuvant HILP, preoperative EBRT and surgical resection. In addition to the commonly used SUVmax and SUVmean, SUVpeak, total lesion glycolysis (TLG) and metabolically-active tumor volume (MATV) were obtained for all scans. Considering the VOI delineation techniques, the VOI_{grad+} delineation technique was shown to be most reliable considering reproducibility when compared with the three other delineation techniques. A significant decline in metabolic tumor activity during this treatment was found, this decline was most pronounced following the HILP. TLG was shown to be promising as predictor for histopathological response in pretreated ESTS, however, it warrants further confirmation in larger patient-cohorts. The histopathological response of pretreated ESTS was further studied in **chapter 6**. The percentage tumor necrosis has been used commonly to express the extent of the histopathological tumor response following neoadjuvant treatment. However, the percentage tumor necrosis at histopathological examination in pretreated ESTS is not prognostic for oncological outcome.[14] Possibly, because the amount of treatment-induced necrosis cannot be distinguished from tumor necrosis already present, due to tumor heterogeneity, prior to treatment.[15] **Chapter 6** establishes that the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group response score[15] is applicable for the determination of the histopathological tumor response in pretreated ESTS. However, it seems that neither local recurrence free survival nor overall survival are predicted by this stainable, possibly viable, tumor cell based response score.

In conclusion, the preceding chapters of this thesis address various aspects and advancements in the treatment of, locally advanced, localized ESTS. Insights in the ongoing and future research in the treatment of, locally advanced, localized ESTS will be addressed in the following chapter; **Chapter 8** – Future perspectives.

Samenvatting en conclusies

Deel I - Behandeling van het resectabele weke delen sarcoom van de extremiteiten

Nadat Rosenberg en collega's in de jaren 80 aantoonden dat de overleving van patiënten met een weke delen sarcoom van de extremiteiten niet verbeterde door een amputatie van het aangedane ledemaat, is de chirurgische resectie van de tumor de hoeksteen van de behandeling geworden.[1] Hierdoor is door de jaren heen, de behandeling van het weke delen sarcoom van de extremiteiten geëvolueerd van een amputatie bij het merendeel van de patiënten tot een multimodale behandeling gericht op het behouden van het aangedane ledemaat.[2,3] Tegenwoordig kan dan ook bij >90% van deze patiënten een amputatie voorkomen worden.[4-7] Om lokale tumorcontrole te verkrijgen, wordt in aanvulling op de chirurgische resectie van de tumor vaak radiotherapie (RT) toegepast. In 2002 toonde de gerandomiseerde studie van O'Sullivan en collega's een significante toename van het aantal patiënten met een ernstige wondcomplicatie na het gebruik van preoperatieve RT in vergelijking met patiënten die postoperatieve RT ondergingen in aanvulling op de chirurgische resectie van de tumor.[3] In vergelijking met preoperatieve RT, wordt postoperatieve RT gekenmerkt door hogere stralingsdoses en grotere bestralingsvelden. Hierdoor is postoperatieve RT geassocieerd met een toegenomen risico op het ontwikkelen van fibrose op de lange termijn, welke mogelijk leidt tot een verslechtering van de functionele uitkomst voor de patiënt.[8] **Hoofdstuk 2** heeft als doel om voorspellers voor het ontwikkelen van een ernstige wondcomplicatie na RT en chirurgische resectie van een weke delen sarcoom van de extremiteit te identificeren. Van de preoperatief bestraalde patiënten in ons cohort ontwikkelde 39,7% een ernstige wondcomplicatie, terwijl 20,3% van de postoperatief bestraalde patiënten een ernstige wondcomplicatie ontwikkelden. Het gebruik van preoperatieve RT werd dan ook geïdentificeerd als significante voorspeller voor het ontwikkelen van een ernstige wondcomplicatie. Daarnaast werd een trend voor het ontwikkelen van een ernstige wondcomplicatie gevonden voor de timing van het sluiten van de wond, de resectiemarges en het toenemen van de leeftijd van de patiënt. Verder werd er een verschuiving in de verdeling van pre- en postoperatief bestraalde patiënten gevonden. Tussen 2005 en 2007 onderging namelijk één van de 36 behandelde patiënten preoperatieve RT, terwijl tussen 2014 en 2016 35 van de 39 behandelde patiënten preoperatieve RT ondergingen.

Deel II - Behandeling van het 'lokaal uitgebreid' weke delen sarcoom van de extremiteiten

De behandeling van het 'lokaal uitgebreid', of het primair niet-resectabele, weke delen sarcoom van de extremiteiten vormt een uitdaging. De betrokkenheid van neurovasculaire structuren, botten, maar ook tumorgrootte en de betrokkenheid van meerdere compartimenten maken een uitgebreide tumorbehandeling noodzakelijk om zo een amputatie te voorkomen.[9-11] In Europa wordt hypertherme geïsoleerde ledemaatperfusie, met melfalan en tumor necrosis factor-α (TNF-α), gevolgd door chirurgische resectie van de tumor en voor sommige geselecteerde patiënten postoperatieve RT gebruikt, om een amputatie te voorkomen in het geval van een lokaal uitgebreid weke delen sarcoom van de extremiteiten.[12] Van oudsher werd de ledemaatperfusie gevolgd door een chirurgische resectie van de tumor (na 6-8 weken) en op indicatie werd dit gevolgd door postoperatieve RT. De RT startte dan ongeveer 6-8 weken na de resectie van de tumor.[10] **Hoofdstuk 3** beschrijft een kortere maar meer intensieve behandelstrategie voor de behandeling van het lokaal uitgebreide weke delen sarcoom van de extremiteiten. Deze behandeling bestaat uit: hypertherme geïsoleerde ledemaatperfusie, preoperatieve RT en chirurgische resectie van de tumor rest. Deze geïntensiveerde behandeling blijkt haalbaar en veilig te zijn, terwijl de oncologische uitkomsten van deze patiënten vergelijkbaar zijn met die van de patiënten die de conventionele behandeling ondergingen. Zoals **hoofdstuk 4** beschrijft, is het voor sommige patiënten niet, of niet meer, mogelijk om een ledemaatsparende behandeling te ondergaan. In deze gevallen is een amputatie de enige behandelmogelijkheid die overblijft om de lokale tumor onder controle te krijgen. Tumorgrootte was de belangrijkste indicatie voor het uitvoeren van een primaire amputatie, terwijl een lokaal recidief waarbij geen ledemaatsparende opties meer mogelijk waren, de voornaamste reden was om een niet-primaire amputatie uit te voeren. Bovendien toont **hoofdstuk 4** aan dat, hoewel de tijd tussen diagnose en amputatie significant verschillend is voor patiënten die een primaire dan wel een niet-primaire amputatie ondergaan, hun oncologische uitkomsten wel vergelijkbaar lijken te zijn.

Deel III - Metabole en histopathologische tumor respons van voorbehandelde weke delen sarcomen van de extremiteiten

De toename in het routinematig gebruik van neoadjuvante behandelmodaliteiten, als hypertherme geïsoleerde ledemaatperfusie, preoperatieve RT en neoadjuvante systemische chemotherapie in het gelokaliseerde weke delen sarcoom van de extremiteiten heeft ertoe geleid dat meer onderzoek gefocust is op het vaststellen van de effectiviteit van deze neoadjuvante behandelingen. Sinds de jaren 90 worden fluor-18-fluordeoxyglucose positron emissie tomografie met computer tomografie (^{18}F-FDG PET-CT) scans gebruikt om de verandering in metabole tumor activiteit vast te stellen en te kwantificeren. Hierbij wordt de metabole tumoractiviteit vaak uitgedrukt als de maximale standardized uptake value (SUVmax) en de gemiddelde standardized uptake value (SUVmean).[13] In **hoofdstuk 5** presenteren we het gebruik van verschillende volume of interest (VOI) delineatietechnieken voor het kwantificeren van de metabole tumoractiviteit van het lokaal uitgebreid weke delen sarcoom van de extremiteiten gedurende de multimodale neoadjuvante behandeling. Deze behandeling bestaat uit hypertherme geïsoleerde ledemaatperfusie, preoperatieve RT en chirurgische resectie van de tumor. Naast de algemeen gebruikte SUVmax en SUVmean, werden voor alle scans ook de SUVpeak, de totale glycolyse en het metabool-actieve tumor volume (MATV) vastgesteld. Met betrekking tot de reproduceerbaarheid, blijkt de VOI_{grad+} delineatie techniek het meest betrouwbaar te zijn in vergelijking met de drie andere delineatietechnieken. Gedurende deze behandeling is een significante afname in metabole tumoractiviteit gevonden, welke het meest uitgesproken lijkt te zijn in de periode na de ledemaatperfusie. Verder lijkt de totale glycolyse veelbelovend te zijn als voorspeller van de histopathologische tumorrespons in voorbehandelde weke delen sarcomen van de extremiteiten. Echter, verder onderzoek in grotere patiëntcohorten is noodzakelijk om deze uitkomsten te bevestigen. De histopathologische tumor respons van voorbehandelde weke delen sarcomen van de extremiteiten is nader onderzocht in **hoofdstuk 6**. Het percentage tumornecrose wordt van oudsher vaak gebruikt om de histopathologische tumorrespons op de neoadjuvante behandeling vast te stellen. Echter, het percentage tumornecrose welke bij histopathologisch onderzoek wordt vastgesteld blijkt niet voorspellend te zijn voor de oncologische uitkomst van de patiënt.[14] Mogelijk wordt dit veroorzaakt doordat de hoeveelheid tumornecrose die door de behandeling geïnduceerd is niet kan worden onderscheiden van de necrose die door de heterogeniteit van de tumor al aanwezig was voor de start van de behandeling.[15] **Hoofdstuk 6** laat zien dat de histopathologische response score van de 'European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group'[15] gebruikt kan worden om de tumor respons vast te stellen in voorbehandelde weke delen sarcomen van de extremiteiten.

Echter, het lijkt dat noch de lokaal recidief vrije overleving noch de totale overleving van deze patiënten voorspeld kan worden met behulp van deze op kleurbare, mogelijk vitale, tumorcellen gebaseerde respons score.

In conclusie, de voorgaande hoofdstukken van dit proefschrift behandelen verschillende aspecten en vorderingen in de behandeling van het (lokaal uitgebreide) gelokaliseerde weke delen sarcoom van de extremiteiten. Verschillende inzichten in het voortdurende en toekomstige onderzoek naar de behandeling van het (lokaal uitgebreide) gelokaliseerde weke delen sarcoom van de extremiteiten zullen nader worden beschreven in het volgende hoofdstuk: **Hoofdstuk 8** – Future perspectives.

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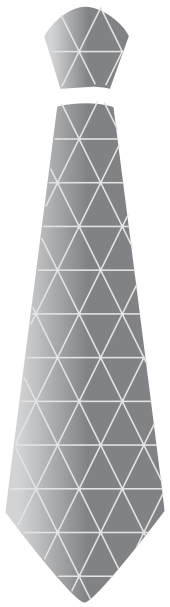
Future perspectives



Future perspectives

Radiotherapy in extremity soft tissue sarcoma

Surgical resection of the tumor combined with external beam radiotherapy (EBRT) is standard of care in most localized resectable extremity soft tissue sarcomas (ESTS) nowadays. EBRT is essential in most patients to obtain sufficient local tumor control, and can be administered either in the pre- or in the postoperative setting. The preoperative timing of EBRT is a known risk factor for the development of a major wound complication following surgical resection of the tumor remnant. Whereas postoperative EBRT induces more long-term fibrosis, edema and joint stiffness due to the larger radiation fields and higher doses, resulting in a detrimental functional outcome for these patients.[1] Several advances in EBRT regimens and techniques in the treatment of ESTS are under current and ongoing investigation with the ultimate goal to achieve optimal oncological results while reducing treatment-induced short- and long-term morbidity.

Although data regarding hypofractionation of preoperative EBRT in ESTS is scarce, recent results seem to be promising. A 5x5 Gy hypofractionated preoperative EBRT regimen followed by surgical resection of the tumor within one week was found to be oncologically safe, while only 7% of these patients required a surgical intervention for the treatment of a wound complication in this series.[2] Furthermore, the preliminary results of an ongoing phase II trial (NCT02701153) on preoperative hypofractionated EBRT were recently presented at the Connective Tissue Oncology Society Annual Meeting, showing a 17% major wound complication rate in the patients treated.[3] These wound complications rates seem to be lower than the 30-35% major wound complication rate following conventional fractionated (25x2 Gy) preoperative EBRT.[4-8] Therefore these new fractionation regimens might provide a useful alternative for the conventional EBRT treatment schemes.

Long-term morbidity resulting in a deteriorated functional outcome seems to be more pronounced in postoperative irradiated patients, although, the development of a major wound complication also is associated with an impairment of functional outcome.[9,10] To reduce the long-term treatment-induced morbidity following postoperative EBRT, a randomized controlled trial was initiated in which patients are randomized into; Arm A, 25x2 Gy preoperative intensity modulated radiation therapy (IMRT), or Arm B, 25x2 Gy postoperative IMRT followed by a 8x2 Gy boost in case of positive surgical margins (NCT02565498). The conventionally used postoperative dose of 60-70 Gy

is thus lowered to 50 Gy in this trial, which might contribute to a reduction of the EBRT induced long-term morbidity.

EBRT techniques are subject to advancements as well. The above mentioned randomized trial compares the use of pre- and postoperative IMRT. Considering the oncological outcome, IMRT was shown to be associated with a significantly reduced local recurrence risk when compared with the commonly used three-dimensional conformal radiotherapy (3D-CRT).[11] Moreover, a phase II study tended to show a reduced wound complication risk following preoperative IMRT in comparison with 3D-CRT, as IMRT enables the radiation oncologist to deliver adequate radiation doses to the tumor volume, while it allows a dose reduction in tissues surrounding the tumor.[12,13] This reduced wound complication risk following IMRT needs further validation in larger prospective trials. Besides the technical advancements in photon-based EBRT, proton beam radiotherapy (PBT) is used more commonly in soft tissue sarcoma (STS).[14] In some cases PBT might be advantageous over photon-based EBRT owing to the unique energy absorption profile. The energy of the protons is delivered to a narrow range at the depth of the tumor, this peak in energy deposition is also known as the Bragg Peak. Beyond, or distally from the Bragg Peak, almost no energy is delivered, which allows for a significant reduction of the radiation dose delivered to the normal tissues surrounding the tumor.[14,15] The selection of patients that might benefit from PBT over the commonly used photon-based EBRT is challenging and in the Netherlands a model-based approach has been developed, which was adopted by the Dutch Health Council.[15] PBT is currently under ongoing investigation (NCT01561495) for ESTS, but its role might be limited as 3D-CRT and IMRT techniques seem to be sufficient for adequate radiotherapy planning and treatment in most ESTS patients, while PBT seems to be beneficial in paediatric and retroperitoneal sarcomas.[14]

Plastic surgical reconstructions and wound management

Plastic surgical reconstructions have been used to obtain wound closure following extensive surgical resections in ESTS. In preoperatively irradiated patients, flap reconstructions permit the transposition from healthy tissue to the previously irradiated surgical area which results in an alteration in the risk for the development of a major wound complication.[16] Although direct plastic surgical reconstructions may complicate the surgical procedure, they also seem to lower the major wound complication risk in preoperatively irradiated patients.[8,17] Hence, in patients who underwent direct reconstructive surgery, the preoperative radiotherapy was not associated with major wound complication development.[18] Further studies considering the appropriate patient selection for plastic surgical reconstructions, as well as studies investigating the 'protective' influence of direct flap reconstructions are necessary.

Besides the advancements in EBRT techniques and plastic surgical reconstructions, several improvements in the postoperative wound care are currently under investigation to minimize the risk for the development of a major wound complication. The use of postoperative hyperbaric oxygen therapy (HBOT) is currently under investigation in a randomized trial (NCT03144206). This trial divides preoperatively irradiated patients into two groups. Patients in group I undergo the administration of HBOT directly following the surgical resection of the tumor, while patients in group II do not. HBOT comprises an intensive treatment commonly consisting of 20-40 daily sessions, during which the patient breathes 100% oxygen in a pressurized (2-3 atmosphere absolute pressure (ATA)) chamber. During this treatment the partial pressure of oxygen in the patients' blood and accordingly in the damaged tissues is extremely increased, thereby it was shown to be beneficial for patients with ischemic wounds and late radiation-induced tissue injuries.[19-21] Secondly, negative pressure wound therapy (NPWT) is investigated in preoperatively irradiated lower ESTS patients (NCT02638298). Patients are randomized into the use of NPWT or not. Accordingly, following the surgical resection of the tumor and closure of the wounds, NPWT is applied for half of the patients, while the other half of patients undergo traditional wound management with dry gauzes. NPWT provides gentle suction on the wound, and its influence on the development of postoperative wound complications is investigated.

High risk localized extremity soft tissue sarcoma

Patients' oncological outcome following extremity soft tissue sarcoma treatment is mainly determined by the tumors potential to metastasize distantly, mainly to the lungs. Accordingly, several studies investigating the influence of (neo)adjuvant chemotherapy in high risk localized, non-metastatic, ESTS have been conducted during the last years.[22-24] The data available is somewhat inconsistent and conflicting, making the implementation of standardized (neo)adjuvant chemotherapy in localized ESTS troublesome.[25] An improvement in oncological outcome was found for a subgroup of localized ESTS patients treated with (neo)adjuvant chemotherapy, but further research is needed to correctly identify those patients who might benefit from the treatment.[26]

Locally advanced extremity soft tissue sarcoma

The treatment of locally advanced ESTS is particularly demanding and multiple regional chemotherapy, i.e. hyperthermic isolated limb perfusion or isolated limb infusion, based regimens have been used to obtain limb-salvage to date. As recently presented in a large systematic review various chemotherapy agents, regimens and

techniques are used throughout the world for the treatment of locally advanced ESTS.[27] The treatment of this rare subgroup of patients is especially hard to standardize, necessitating the need for the further centralization of sarcoma treatment in order to effectuate a patient-tailored treatment approach based on the counsel of a multidisciplinary sarcoma tumor board.

Amputation in extremity soft tissue sarcoma

Nowadays, limb-salvage can be achieved in most ESTS patients, even in those patients with locally advanced tumors. However, when limb-salvage treatment fails, amputation of the affected limb is the only treatment-option that remains.[28-30] The level of amputation is mainly determined by the extensiveness of the tumor. However, also patients' functional outcome following the amputation should be considered. The involvement of a rehabilitation specialist at an early stage in the amputation decision-process facilitates the determination of adequate amputation levels, a discussion regarding potential prosthesis use in the future and a patient-tailored postoperative rehabilitation program which all will improve the patients' functional outcome following the amputation.

Limb-amputation in the metastatic setting should be reserved for patients suffering from severe symptoms of the local tumor, as survival following palliative amputation is generally poor, i.e. <8 months.[28,29]

Histology based treatment

Approximately 50 histologic STS subtypes are identified in the latest World Health Organization classification[31], and therefore a histology based treatment seems to have a large potential for these patients. For instance, the proven radiosensitivity of myxoid liposarcomas led to the standardization of preoperative EBRT in these patients.[32,33] Besides, a preoperative hypofractionated, 5x5 Gy, EBRT regimen followed by surgical resection of the tumor within one week was found to be effective in myxoid liposarcomas of the extremities.[34] As a result of this, a radiotherapy dose reduction study in myxoid liposarcomas was initiated (DOREMY-study, NCT02106312) and first results are awaited. The dose reduction of preoperative EBRT, to a total dose of 36 Gy, in these tumors must be proven to be oncologically safe, and alongside, this dose reduction might result in a decreased major wound complication risk in this specific subtype.

As mentioned above, neoadjuvant chemotherapy is currently under ongoing investigation for high risk localized ESTS. In the metastatic setting the chemotherapy is patient-tailored and among others based on the histologic subtype. Subsequently a study was conducted randomizing high risk localized ESTS patients into a standardized neoadjuvant chemotherapy regimen (control arm) or into a histotype-tailored regimen. Surprisingly, no survival benefit for the histotype-tailored regimen was shown.[35] Further studies regarding the sensitivity to (neo)adjuvant chemotherapy regimens for specific histologic subtypes are warranted.[36]

Metabolic and histopathological responses in pretreated extremity soft tissue sarcoma

The evaluation of treatment efficacy through the measurement of treatment responses will take a larger part in the contemporary treatment of ESTS, as the use of neoadjuvant treatment regimens i.e. chemotherapy, hyperthermic isolated limb perfusion and/or radiotherapy is rising. This response evaluation either prior to surgical resection of the tumor through imaging modalities or following the surgical resection through the histopathological evaluation of resection specimens needs to be standardized and validated.

The validation of parameters to evaluate the metabolic tumor activity on fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET-CT) scans needs to be accompanied by the validation of volume of interest (VOI) delineation techniques. The VOI used directly affects the values measured for the various parameters. The search for an robust and easy to implement VOI delineation technique for these heterogeneous tumors accompanied by the identification of the most predictive PET derived parameter within this VOI is needed. Alongside these advancements in PET imaging, also progression in magnetic resonance imaging (MRI) are expected. A recent feasibility study in 11 lower ESTS patients who underwent preoperative chemoradiotherapy showed that it might be possible to predict histopathological response using dynamic contrast-enhanced MRI.[37]

The standardization of the histopathological examination of pretreated STS by the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG), including a 5-tier response score[38] is a step forwards. However, further research needs to demonstrate the predictive value of this response score. Several studies including high risk localized ESTS patients whom are treated with neoadjuvant chemotherapy are currently ongoing. Hopefully, the results of the histopathological examination of these tumors will provide more insight in the response of these localized tumors including the relevance of the response induced by the neoadjuvant treatment. Hence, a good or excellent histopathological tumor response in a high risk localized tumor might result in a prolonged overall survival as micro metastases, not yet visible on the staging CT-chest scan, are treated as well. In contrast, a poor histopathological response of the primary tumor might be a reason to intensify the local treatment or to choose an alternative chemotherapy regimen in case of development of distant metastases during follow-up.

After the validation of both metabolic and histopathological responses in pretreated ESTS, it might be possible to alter the standardized treatment regimen into a patient-tailored approach based on treatment efficacy as measured at the response evaluation.

Centralization of ESTS treatment

The treatment of ESTS has changed significantly over the past decades, from ablative surgery in the mid-1980s to a multimodality limb-saving approach including, radiotherapy, hyperthermic isolated limb perfusion, neoadjuvant chemotherapy and extensive surgical resections combined with plastic surgical reconstructions. These advancements in ESTS treatment have complicated the decision making process and subsequently differences in treatment approaches and outcome have originated between high-volume and low-volume (<10 resections annually) hospitals.[39,40] A recently published study showed less positive surgical margins and even an improvement in overall survival for STS patients treated in high-volume hospitals. Furthermore, adherence to clinical practice guidelines was found to be associated with an increase in progression-free and overall survival.[41]

In the future, further centralization of ESTS treatment will facilitate an evidence based patient-tailored treatment following discussion in a multidisciplinary tumor board. Consequently, this will contribute to a further improvement in the treatment and outcome of STS patients. Besides, further centralization of daily sarcoma care strengthens the opportunities to conduct further prospective research and to reduce treatment costs.[42] In the Netherlands the treatment of STS patients can be further centralized into five specialized sarcoma-centers enabling clinicians to provide optimal sarcoma-care.[39]

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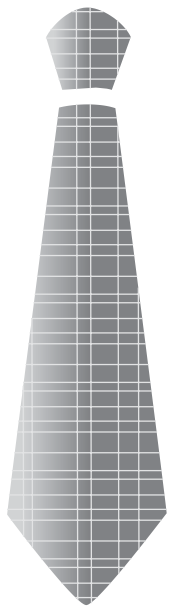
Curriculum Vitae
Dankwoord



Curriculum Vitae

Marc Stevenson werd geboren op 25 januari 1991. Als oudste zoon van Jan Stevenson en Ineke Brouwer en broer van Evelien, groeide hij op in Roden. Zijn middelbare schooltijd bracht hij door op het Augustinus College te Groningen en in 2009 behaalde hij zijn VWO diploma.

In september 2009 begon hij aan de studie Geneeskunde aan de Rijksuniversiteit van Groningen. In de zomer van 2015 rondde hij zijn semi-arts stage bij de Chirurgie af, en daarmee behaalde hij zijn arts-examen. In aansluiting hierop, begon hij in september 2015 als ANIOS op de afdeling Chirurgie van het Universitair Medisch Centrum Groningen, waar hij gedurende een jaar werkzaam was.
In september 2016 startte Marc zijn promotietraject bij de afdeling Chirurgische Oncologie van het Universitair Medisch Centrum Groningen, onder begeleiding van prof. dr. H.J. Hoekstra, prof. dr. A.J.H. Suurmeijer en dr. L.B. Been.

Marc startte in september 2018 met zijn opleiding tot chirurg. Het eerste jaar van zijn opleiding vindt plaats in het Universitair Medisch Centrum Groningen (Opleiders dr. R.J. van Ginkel en prof. dr. J.M. Klaase). Vervolgens zal hij zijn opleiding voortzetten in het Deventer Ziekenhuis (Opleider dr. B.H.P. Elsman).

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Marc