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Postoperative complications and oncological outcomes after multimodal therapy of localised high risk soft tissue sarcoma

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1 INTRODUCTION

1.1 Definition and epidemiology

Soft tissue sarcomas (STS) are a rare form of malignancies, accounting for less than 1% of all adult malignancies and about 15% of all pediatric malignancies [1]. The incidence rate for STS in Europe is approximately 3.6 per 100 000 [2]. They represent an extremely heterogenous group of malignancies derived from mesenchymal cells or connective tissue and are capable to differentiate into many different cell types. Soft tissue is a nonepithelial extrasceletal tissue (including fat, muscle, nerves, blood vessels and fibrous supporting structures) and derives mostly from embryonic mesoderm with neuroectodermal contribution [3, 4].

STS can occur at any age, with the risk of developing the disease rising with age and with bimodal age distribution with peaks in the fifth and eighth decades [5, 6]. The median age at diagnosis is 65 years. The overall distribution among genders is equal [7]. STS can anatomically occur anywhere in the body where connective tissue is found. The most common anatomical localization is peripheral (49% localized on extremities and 11% on the head and neck) and in about 40% cases truncal (17% thoracic, 9% retroperitoneal, 8% pelvic and 6% abdominal) [6].

1.2 Etiology

Etiology of most STS is still unclear. Several environmental and genetic etiologic factors have been identified. Radiation exposure is known as etiological factor [8]. There is a correlation between radiation therapy and higher risk of subsequent sarcoma, especially angiosarcoma after radiation therapy of breast cancer [9].

Exposure to chemicals (such as polyvinyl chloride, androgenic-anabolic steroids, arsen, dioxins...) is associated with hepatic angiosarcoma [10]. Various host-related factors have been identified, such as host immune suppression and chronic tissue irritation (such as chronic lymphedema or foreign body induced STS). Epstein Barr virus (EBV) associated leiomyosarcoma have been reported especially in the group of immunocompromised patients [11]. Human herpesvirus 8 (HHV8) infection and human immunodeficiency virus (HIV) infection are known risk factors for developing Kaposi sarcoma [10]. Certain genetic syndromes are connected with higher incidence of STS as well, such as neurofibromatosis type 1 (von Recklinghausen's disease) with malignant peripheral nerve sheath tumors (MPNST), Werner syndrome with rare nonepithelial cancers, especially sarcomas. Bloom syndrome and Li-Fraumeni syndrome are associated with increased predisposition for wide range of cancers, including sarcoma [10].

1.3 Symptoms, clinic and diagnosis

Patients usually present with painless, asymptomatic, fast growing mass that often does not limit the function or affect general health [12]. Ultrasound can be used as an effective triage tool for evaluation of soft tissue mass and differentiation between benign and suspicious lesions for patients with clinical suspicion of malignancy [13]. Preferred method for initial radiological diagnostics is magnetic resonance imaging. Furthermore, computed tomography is usually used to assess intra-abdominal STS and for excluding pulmonary metastases in preoperative staging [12]. Even though X-rays are not particularly useful for the diagnosis of STS, they can show a soft tissue calcification and can indicate synovial sarcoma or extraosseous bone-forming sarcoma [14].

Considering the fact that there are no reliable symptoms to differentiate STS from benign tumors, it is necessary to consider biopsy for all soft tissue masses that

grow or persist [15]. Biopsy presents an essential part of the diagnostic pathway for STS. Core needle biopsy, open incision biopsy or excisional biopsy are considered to be the standard approach. Biopsy should be carried out in a way that its pathway and its scar can be removed during definitive surgery [16]. Furthermore, biopsy results shoud be interpreted in conjuction with a radiologist and surgeon [12]. Histopathological reports should include an appropiate description of tumor size, depth in relation to the superficial fascia, tumor margins, as well as histopathological response (if preoperative therapy was carried out) [17].

1.4 Classification, staging and grading

The prognosis of STS is dependant on site, histological grade and size [15]. Currently there are more than 50 histological subtypes of soft tissue sarcoma, defined by the cell type of origin and other molecular and histological characteristics [18]. Histological diagnosis should be assessed according to an update of classification published by World Health Organisation in 2013 [17]. There is an overlap between STS subtypes. However, some histological subtypes have their own biological behaviour and characteristics that can determine the specific treatment [10, 19], such as myxoid liposarcoma. The most common types of soft tissue sarcoma are leiomyosarcoma (21%), NOS (not otherwise specified) sarcoma (20%), liposarcoma (19%) und fibrosarcoma (10%) [7].

There are various staging systems for STS. However, American Joint Committee on Cancer (AJCC) has generally been widely accepted and considered as the standard and is presented in table 1 [19].

Table 1: Adapted from TNM Staging for STS According to the 7th Editions of the American Joint Committee on Cancer Staging Manual

Primary tumor (T)	
TX	Primary tumor can not be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension (T1a: superficial tumor, T1b: deep tumor)
T2	Tumor more than 5 cm in greatest dimension (T2a: superficial tumor, T2b: deep tumor)
Regional lymph nodes (N)	
NX	Regional lymph nodes can not be assessed
N0	No regional lymph node metastasis
N1	Regional lymp node metastasis
Distant metastasis (M)	
MX	Distant metastasis can not be assessed
M0	No distant metastasis
M1	Distant metastasis
Histologic grade (G)	
GX	Grade can not be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated

Stage grouping					
Stage I	T1a, 1b, 2a, 2b	N0	M0	G1	Low grade
Stage II	T1a, 1b, 2a	N0	M0	G2-3	High grade
Stage III	T2b	N0	M0	G2-3	High grade
Stage IV	Any T	N1	M0	Any G	High or low grade
	Any T	N0	M1	Any G	High or low grade

Two most common grading systems for STS are the French Fédération Nationale des Centres de Lutte Contrele Cancer (FNCLCC) system and the United States National Cancer Institute system. Both systems assess different histological features in order to determine the grade of tumor and to select the tumor into the low, intermediate or high grade group [20]. The grading score together with histological features can indicate the aggressiveness and the degree of malignancy of the tumor and predict the clinical course of the disease and the probability of distant metastases, and therefore should be assessed in all STS cases [6, 17]. Grading should not be determined after preoperative treatment, due to therapy related changes in tumor tissues [17].

The FNCLCC grading system is based on three features: tumor necrosis, tumor differentiation and mitotic rate. This classification is presented in table 2. According to FNCLCC grading system, tumors are graded according to summation of each factor's score representing the overall tumor grade (grade 1 - 3). Well-differentiated sarcomas receive a score of 1, whereabout undifferentiated or embryonal-appearing STS receive a score of 3. The United States National Cancer Institute system uses histologic type, mitotic rate, tumor cellularity and pleomorphism to define the grade of the tumor [20, 21].

Table 2: Adapted from French Fédération Nationale des Centres de Lutte Contrele Cancer (FNCLCC) grading system for STS.

Tumor differentiation	
Score 1	Sarcoma closely resembling normal adult mesenchymal tissue
Score 2	Sarcomas for which histologic typing is certain
Score 3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, and synovial sarcomas
Mitotic count	
Score 1	0 - 9 mitoses per 10 HPF (High-power field)
Score 2	10 - 19 mitoses per 10 HPF
Score 3	≥ 20 mitoses per 10 HPF
Tumor necrosis	
Score 0	No necrosis
Score 1	< 50% tumor necrosis
Score 2	≥ 50% tumor necrosis

1.5 Treatment

High risk STS are treated with multimodal therapy, and therefore a multidisciplinary approach is needed (including pathologist, radiologist, radiation oncologist, medical oncologist, surgeon and nuclear medicine specialist). Patients should be treated in sarcoma reference centers [16]. Preferred treatment for high risk STS includes preoperative or postoperative radiation therapy in addition to wide tumor resection, as well as sequential or concomitant chemotherapy and hyperthermia if feasible.

Wide surgical tumor resection represents a cornerstone in multimodal treatment of STS and is the essential component of multimodal treatment for localised STS to achieve local control and potential cure of the tumor [22]. Limb amputation has been replaced with this multimodal approach for most extremity STS [23]. The surgeons objective is a complete resection with maximal perservation of function. Planning of optimal surgical procedure is based on the tumor size and location, involvement of adjacent anatomical structures, response to neoadjuvant therapies and patient preference [14].

After revealing that amputation has equal survival rates compared to limb sparing surgery combined with radiation therapy, the use of radiation therapy in multimodal therapy of STS was introduced and established [14, 24]. The importance of radiation therapy in addition to surgical resection of STS for improvement of LC (local control) rates has been shown in various studies [24, 25]. Furthermore, correlation between local recurrence and decreased OS (overall survival) has been demonstrated [25-27], underlining the importance of radiation therapy in multimodal therapy of STS. However, the timing of radiation therapy to achieve the best survival rates with good functional outcomes and less wound complications has been discussed in various studies.

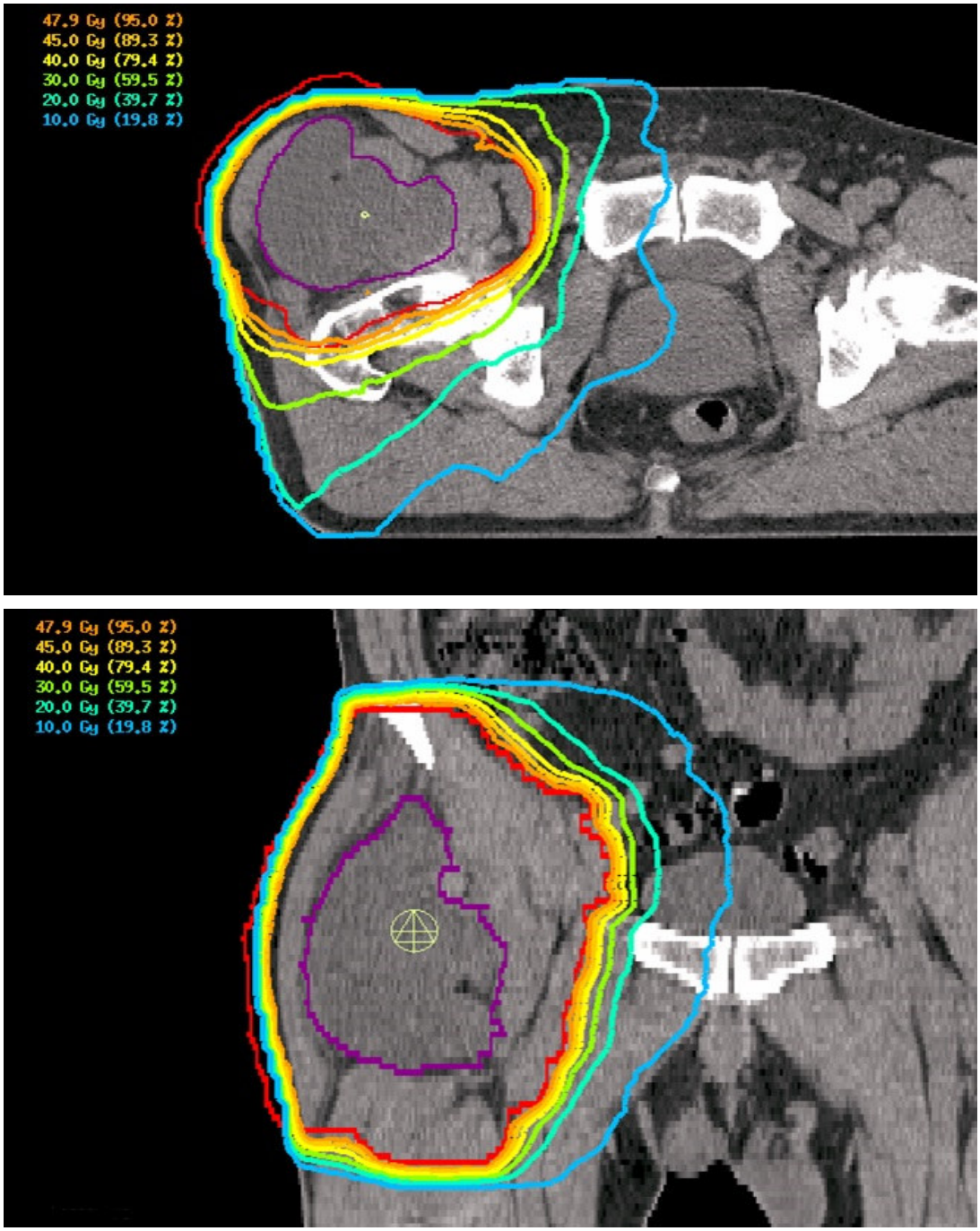

Figure 1: Radiation plan of a 68-years old male patient with myxoid liposarcoma, showing an isodose distribution of radiation therapy plan as well as gross tumor volume (violet) and planning target volume (red). The patient presented initially with an asymptomatic swelling of the lower right proximal extremity. MRI imaging showed a suspicious mass. The diagnosis of a myxoid liposarcoma was confirmed after biopsy. To complete the staging and exclude potential lung metastases, a CT scan of the lungs was performed. The case was presented in the multidisciplinary meeting, which recommended a multimodal preoperative treatment and wide surgical resection. The patient received a preoperative radiation therapy with 50.4 Gy in 28 fractions (1.8 Gy per fraction) with two cycles of concomitant intravenous Ifosfamide chemotherapy and concomitant hyperthermia twice a week (in total 10 treatments). En-Bloc resection was performed 6 weeks after the end of radiation therapy. Treatment was completed without relevant side-effects. Two years after the end of the treatment, no local reccurence and no distant metastasis were demonstrated in extremity-MRI and CT scan of the chest.

1.6 Goal of the study

STS represent an extremely heterogeneous and rare group of malignancies. Therapy for these tumors can be a challenge and treatment planing for each individual patient should be carried out in an interdisciplinary team. Multimodal therapy (including either preoperative or postoperative radiation therapy, as well as concomitant or sequential chemotherapy and concomitant hyperthermia in selected cases) is the standard therapy for high risk STS. As already stated, the use of radiation therapy for STS has been established. However, the adequate timing of radiation therapy is controversial and has been discussed in various studies.

In a study published in 2012 by O`Sullivan et al., a difference regarding the side effect profile was observed between groups of the patients with STS treated with either preoperative or postoperative radiation therapy. Patients were randomized in two groups, one group treated with preoperative radiation therapy and receiving a dose of 50 Gy in 25 fractions and the other group treated with postoperative radiation therapy with 66 Gy in 33 fractions. In general, acute postoperative complications rate was higher in the group of patients treated with preoperative therapy. However, long term complication rate (such as joint stiffness, fibrosis or edema) was higher in the group treated with postoperative radiation therapy. The study demonstrated no difference in survival outcomes for the two patients groups [28]. According to these data, it seems that there is no consensus about the optimal timing of the radiation therapy and a patient-specific decision should be made by a multidisciplinary team [29].

The goal of this study was to assess oncological outcomes and postoperative wound complications of patients with high risk STS treated between 2011 and 2017 at the University Hospital Tübingen. Additionally, patient characteristics and clinical tumor variables that could potentially influence oncological outcomes or postoperative wound complications were assessed. Considering the differences

in oncological outcomes and postoperative wound complications, an analysis of advantages and disadvantages of different timing of radiation therapy (either preoperative or postoperative radiation therapy) in the multimodal treatment of high risk STS was performed.

2 MATERIALS AND METHODS

2.1 Patients and treatment characteristics

This study represents a single institution retrospective analysis. Data of patients with localized soft tissue sarcoma who underwent a curative multimodal therapy were retrospectively collected and analysed. All patients included in the analysis underwent surgical resection and were treated with either adjuvant or neoadjuvant external beam radiation therapy (either intensity-modulated radiation therapy-IMRT or 3D conformal therapy), with or without sequential or concomitant chemotherapy and with or without concomitant hyperthermia.

Included were patients with histologically confirmed STS (excluding gastrointestinal stromal tumor, solitary fibrous tumor, Kaposi's sarcoma), treated between 2011 and 2017 at the University Hospital Tübingen. The study was approved by the local ethics committee (Nr 399/2020BO). Excluded were patients with uterine and head and neck sarcomas, patients younger than 18 years of age and patients with metastatic disease on initial presentation. Patients with no follow up were excluded as well.

The standard neoadjuvant chemoradiation protocol used at the University Hospital Tübingen consists of 2 cycles of intravenous ifosfamide (3000 mg/m², first cycle on day 1, second cycle on day 22 of the irradiation), combined with 50.0 or 50.4 Gy irradiation dose in 25 - 28 fractions (1.8 - 2.0 Gy per fraction). According to radiation dose constrains for organs at risk, the total irradiation dose was deescalated to 45.0 Gy in some cases. The standard adjuvant chemoradiation protocol consists of 2 cycles of intravenous ifosfamide (3000 mg/m², first cycle on day 1, second cycle on day 22 of the irradiation), combined with 60.0 - 66.0 Gy irradiation dose in 30 - 33 fractions (2.0 Gy fraction dose). Adjuvant radiation therapy was applied in two phases: initial dose of 50.0 Gy was applied to the clinical target volume (CTV) which included postoperative scar

tissue and postoperative tumor bed (former tumor area) with 3 cm margins. Boost of 10.0 - 16.0 Gy in 2.0 Gy fraction dose was applied only to former tumor area. According to radiation dose constrains for organs at risk, the total irradiation dose was deescalated up to 50.0 Gy in some cases. Radiation therapy was based on a planning CT using individual patient positioning.

A significant number of patients received radio(-chemo)therapy with sequential chemotherapy, which was delivered before or after radiation therapy, using the combination of ifosfamide (3000 mg/m²) and doxorubicin (60 mg/m²) every 22 days for up to 3 - 6 cycles. Sequential chemotherapy for STS at the University Hospital Tübingen is applied according to IAWS-regimen in younger patients with high grade tumors [30]. A significant number of patients received locoregional hyperthermia twice a week during radiation therapy. All patients underwent surgery.

2.2 Data collection

Data were collected retrospectively and abstracted by chart review. Patient characteristics included age and sex. Clinical tumor characteristics included histological type, tumor location, TNM-stage, tumor size, tumor depth to superficial fascia, tumor grading, postoperative surgical margin status and histopathological response status after neoadjuvant therapy. Treatment modalities and characteristics were also assessed, including the date of diagnosis, type of radio(-chemo)therapy (neoadjuvant vs. adjuvant therapy), with or without sequential chemotherapy and with or without concomitant chemotherapy and hyperthermia. The timing, dose and type of radiation (neoadjuvant vs. adjuvant, IMRT vs. 3D conformal therapy) were recorded.

According to the tumor localization, patients were divided into four subgroups:

- Lower extremities (including the groin area)
- Upper extremities (including the axillar area)
- Trunk area (including abdominal, pelvic, thoracic and breast area), retroperitoneum excluded
- Retroperitoneum

Tumor size was measured by the radiological imaging and was defined as the maximal cross-sectional diameter in any plane of the tumor mass or as the sum of maximal diameter if there was more than one tumor mass. Additionally, tumor size was measured in histopathological reports and defined as the maximal cross-sectional diameter. For the purpose of the study and for statistical analysis, we used the tumor size measured by the radiological imaging.

Tumor size was divided into two groups according to American Joint Committee on Cancer staging systems for STS 7th edition [31].

- T1: 5 cm or less
- T2: larger than 5 cm

Tumor depth was defined in relation to the superficial fascia and was divided into two groups:

- Superficial tumors (Ta)
- Deep tumors (Tb)

Histological malignancy grade was performed according to the FNCLCC grading system. Tumors were classified in three malignancy grades based on differentiation, mitotic rate and necrosis [21].

Histopathological reports were evaluated retrospectively. Histopathological report after surgery included the information about surgical margins. They were defined as:

- R0 (negative margin)
- R1 (microscopically positive but macroscopically negative margin)
- R2 (macroscopically positive margin)

Pathology reports also included an evaluation of the histopathological response of the tumor in case of preoperative treatment. For the purpose of analysis, according to pathological response, patients were divided in two subgroups:

- good pathological response (less than 10% vital tumor tissue)
- poor pathological response (10% or more vital tumor tissue) [32].

Overall survival (OS), local control (LC), distant metastasis-free survival (DMFS) and disease-free survival (DFS) were evaluated based on the follow up. OS was defined as the time from the date of diagnosis to the last date of contact or death. A cause of death was not determined. LC and DMFS were defined as the time from the date of diagnosis to date of the last follow up or to date of the diagnosis of local recurrence for LC or distant metastasis for DMFS. DFS was defined as the time from the date of diagnosis to date of the last follow up or to date of the diagnosis of local recurrence or distant metastasis.

Postoperative complications were analysed retrospectively using imaging and clinical follow up and therefore not graded. In a paper published in 2002 (O´Sullivan B et al.), major wound complication was defined as a wound complication that required secondary surgery for wound repair (surgical drainage, debridement and secondary wound closure) or wound management without secondary surgery (for example aspiration of seroma), persistent deep packing (≥ 120 days) or readmission for wound care (for example intravenous antibiotics) [28].

We used this definition to determine major wound complication, but adapted it for the needs of our study. We defined a major wound complication as:

- wound healing disorder that required second surgical procedure (debridement, drainage or secondary wound closure)
- wound infection or abscess with admission of oral or intravenous antibiotic therapy
- postoperative seroma where an invasive procedure was needed (aspiration, drainage or reoperation)
- postoperative hematoma where an invasive procedure was needed (aspiration, drainage or reoperation)
- postoperative fistula

Pathologic fracture was defined as a bone fracture detected in radiological imaging, assumedly as a result of radiation therapy of underlying STS. Bone necrosis was defined as a bone remodeling of the bone structures after radiation therapy of underlying STS and had to be verified in radiological imaging as well.

2.3 Statistical tests

The impact of patient characteristics (sex, age), clinical tumor variables (localization, tumor size, tumor relation to superficial fascia, grading, surgical margins, pathological response), treatment characteristics (neoadjuvant vs. adjuvant therapy, with or without concomitant or sequential chemotherapy and with or without hyperthermia) and major wound complication on OS, LC, DMFS and DFS for the whole patient collective was examined using Kaplan-Meier estimator and compared using the log-rank test. The same analysis was performed for patient groups stratified by the timing of radiation therapy (neoadjuvant vs. adjuvant). Multivariate analyses were carried out by cox regression model.

Influence of therapy modalities and clinical tumor variables on surgical margins and on histopathological response after neoadjuvant therapy was tested using chi-square test. Distribution of patient characteristics and clinical tumor variables in various treatment modalities (stratified by timing and modalities) was tested using chi-square test. The same analysis was performed for the subgroup of patients with retroperitoneal STS compared to non-retroperitoneal STS.

We examined whether major wound complications were related to relevant patient characteristic (sex, age), clinical tumor variables (localization, tumor size, tumor relation to superficial fascia, grading, surgical margins, pathological response) and treatment characteristics (neoadjuvant vs. adjuvant therapy, with or without concomitant or sequential chemotherapy and with or without hyperthermia) using univariate logistic regression and chi-square test. The mean age of patients and the median size of tumor by patients developing a major wound complication were compared using t-test. The impact of prognostic factors for oncological outcomes (tumor size and depth to superficial fascia, localization, surgical margins and pathological response after neoadjuvant therapy) was tested using multivariate analyses.

The mean tumor size was compared between groups of tumor localizations (extremities vs. non-extremities, as well as for retroperitoneum vs. non-retroperitoneum) using t-test.

P value of less than 0.05 was defined as statistically significant. P value less than to 0.1 was defined as a trend to statistical significance.

3 RESULTS

3.1 Patient characteristics and clinical tumor variables

Patient characteristics and clinical tumor variables are presented in table 3 and table 4. A total of 89 patients were included in our analysis, 2 patients were excluded due to missing follow up information, 3 patients were excluded due to progressive disease and resulting inoperability after neoadjuvant radio- or radiochemotherapy. Median follow-up was 2.72 years. The mean age was 59.3 years (range 18 - 87 years). Distribution of sexes was relatively equal, with 56.0% males, followed by female sex with 44.0%. According to the localization of tumor, lower extremity was the most common localization (46.4%), followed by trunk (25.0%), upper extremity (17.9%) and retroperitoneum (10.7%).

The mean tumor size for the entire cohort according to histopathological reports was 11.0 cm (± 7.2 cm). The mean tumor size according to pretherapeutic imaging was 10.2 cm (± 5.9 cm). Comparing the mean pretherapeutic imaging tumor size of extremities (lower and upper extremities) with non-extremities tumor size (trunk and retroperitoneum), our findings show that the mean size of tumors located in extremities was smaller than the mean size of tumors located in the trunk and retroperitoneum, however, without statistical significance (10.2 ± 0.8 cm vs. 12.5 ± 1.7 cm, p = 0.182). Regarding the tumor diameter size, 83.3% of patients had tumors larger than 5 cm in diameter vs. 15.5% of patients with tumors with 5 cm in diameter or less.

Regarding the depth to superficial fascia, majority of patients had deep tumors (84.5%) and only 14.3% of patients had superficial tumors. Most common TNM-staging of the primary tumor was T2b.

Table 3: Patient and tumor characteristics (Total n = 84)

Age (Years)		
Mean	59.34	
Range	18 - 87	
Sex		
Female	37	44.0%
Male	47	56.0%
Localization		
Lower extremities (including the groin area)	39	46.4%
Upper extremities (including the axillar area)	15	17.9%
Trunk (abdominal, pelvic, thoracic and breast area), retroperitoneum excluded	21	25.0%
Retroperitoneum	9	10.7%
Tumor size		
⩽ 5 cm (T1)	13	15.5%
> 5 cm (T2)	70	83.3%
Undetermined	1	1.2%
Tumor depth to superficial fascia		
Superficial (Ta)	12	14.3%
Deep (Tb)	71	84.5%
Undetermined	1	1.2%
Tumor malignancy grade		
Grade I	2	2.4%
Grade II	34	40.5%
Grade III	45	53.6%
Undetermined	3	3.5%
Surgical margin status		
R0	60	71.4%
R1	22	26.2%
R2	2	2.4%

Most common tumor grade was grade III with 53.6%, followed by grade II with 40.5% and grade I with 2.4%. Tumor grading was not determined in the histopathological report for 3.5% patients. Even though most of included patients were diagnosed with high grade STS (grade II and III), two patients with grade I STS were included in the study. One patient with grade I, T1a paravertebral myxofibrosarcoma was treated preoperatively because of its specific localization that wouldn't allow postoperative radiation therapy in the case of R1-resection, due to its paravertebral localization. The second patient was diagnosed with grade I T2b abdominal well-differentiated liposarcoma in biopsy. However, this patient had various strong perfused tumor areas with high suspicion of dedifferentiated liposarcoma in the staging-CT. Assuming a sampling error, the patient was treated with neoadjuvant therapy. Both of these patients were included in our study.

Negative postoperative surgical margins were achieved in the most cases (71.4%). However, 26.2% of patients had R1 and 2.4% of patients had R2 postoperative margins.

According to histopathological reports undifferentiated pleomorphic sarcoma was determined as the most frequent tumor subtype (32.1%). Other common histological subtypes were liposarcoma (20.2%), myxofibrosarcoma (10.7%), leiomyosarcoma (7.1%), synovial sarcoma (5.9%), myxoid liposarcoma (3.6%) and extraskeletal myxoid chondrosarcoma (3.6%). No subgroup analysis considering histological subtypes was performed, due to its high diversity.

Table 4: Histology

Undifferentiated pleomorphic sarcoma	27	32.1%
Liposarcoma	17	20.2%
Myxofibrosarcoma	9	10.7%
Leiomyosarcoma	6	7.1%
Synovial sarcoma	5	5.9%
Myxoid liposarcoma	3	3.6%
Extraskeletal myxoid chondrosarcoma	3	3.6%
Hemangiosarcoma, Angiosarcoma	2	2.4%
Malignant peripheral nerve sheath tumor	2	2.4%
Epithelioid sarcoma	2	2.4%
Spindel cell sarcoma	2	2.4%
Adult rhabdomyosarcoma	1	1.2%
Sclerosing rhabdomyosarcoma	1	1.2%
Spindle cell rhabdomyosarcoma	1	1.2%
Primary extraskeletal chondrosarcoma	1	1.2%
Myxoid leiomyosarcoma	1	1.2%
Mesenchymal chondrosarcoma	1	1.2%
Total (n = 84)		

3.2 Treatment characteristics

Treatment characteristics are presented in table 5. Neoadjuvant treatment was received by 60.7% and adjuvant treatment by 39.3% of patients. IMRT was applied for 32.9% of patients and 3D conformal radiation therapy in 67.1% of patients.

Median preoperative radiotherapy dose was 50.4 Gy (range 45.0 - 56.0 Gy), and median postoperative radiotherapy dose 63.65 Gy (range 50.0 - 66.0 Gy). In the group of patients treated with neoadjuvant therapy, one patient had to abort the therapy at 43.2 Gy because of sepsis. In the group of patients treated with adjuvant therapy, one patient had to abort the therapy at 20.0 Gy because of flap necrosis. Significant number of patients (60.7%) received concomitant chemotherapy parallel to radiation therapy. However, 7 patients received only the first cycle of chemotherapy because of poor tolerance. 39.3% of patients received sequential chemotherapy with median number of cycles of 4 (range 3 - 6). Local or deep hyperthermia was applied in 56.0% of patients with median number of treatments of 10 (range 2 - 15).

Table 5: Therapy characteristics

Neoadjuvant	51	60.7%
Adjuvant	33	39.3%
With concomitant ifosfamide	51	60.7%
Without concomitant ifosfamide	33	39.3%
With concomitant hyperthermia	47	56.0%
Without concomitant hyperthermia	37	44.0%
With sequential chemotherapy	33	39.3%
Without sequential chemotherapy	51	60.7%
Total (n = 84)		

3.3 Oncological outcomes

Median follow-up was 2.72 years. Kaplan-Maier survival curves are presented in figure 2 and figure 3. The 3-year rates for all patients were 89.2% (± 4.3%) for OS, 84.4% (± 5.0%) for LC, 75.1% (± 5.6%) for DMFS and 68.6% (± 6.1%) for DFS.

There was no statistical difference between the groups of patients treated with neoadjuvant and adjuvant therapy for OS (p = 0.379), LC (p = 0.839), DMFS (p = 0.452) and DFS (p = 0.532).

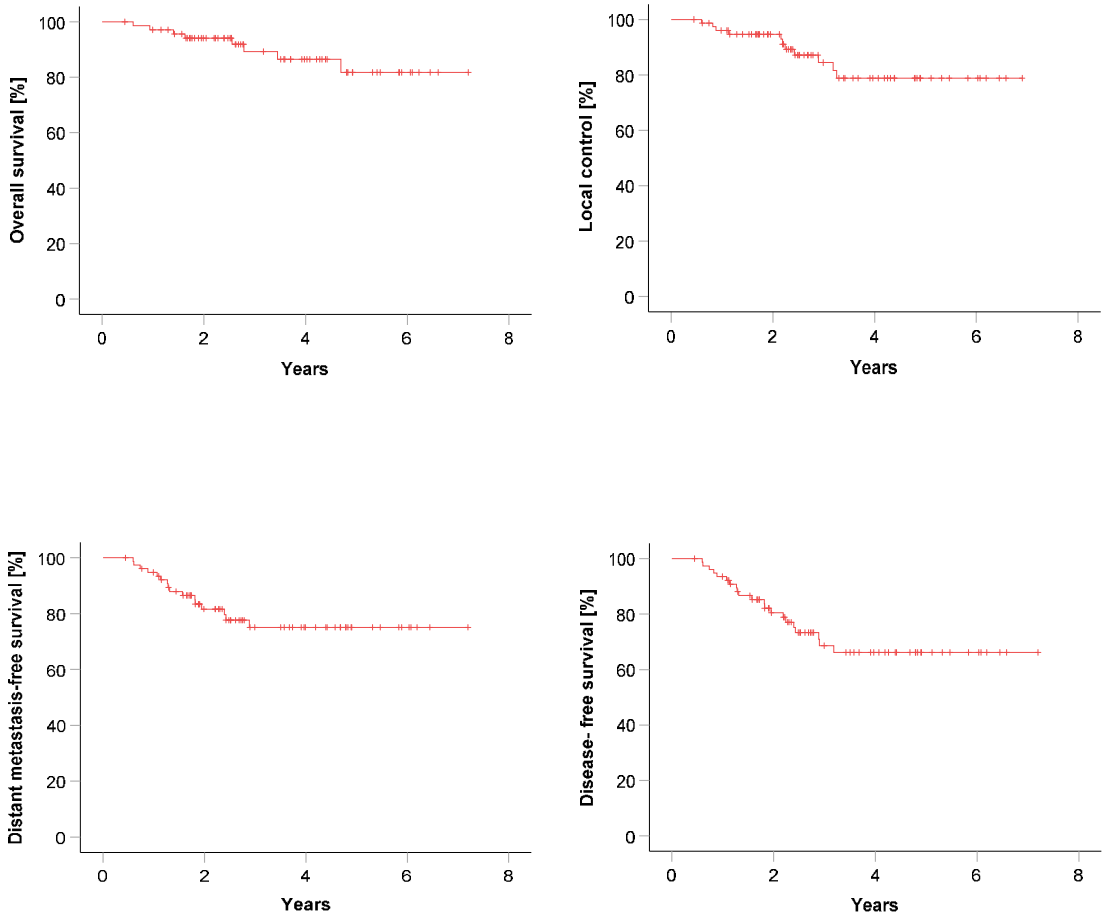

Figure. 2: Kaplan-Meier curves demonstrating overall survival, local control, distant metastasis-free survival and disease-free survival rate.

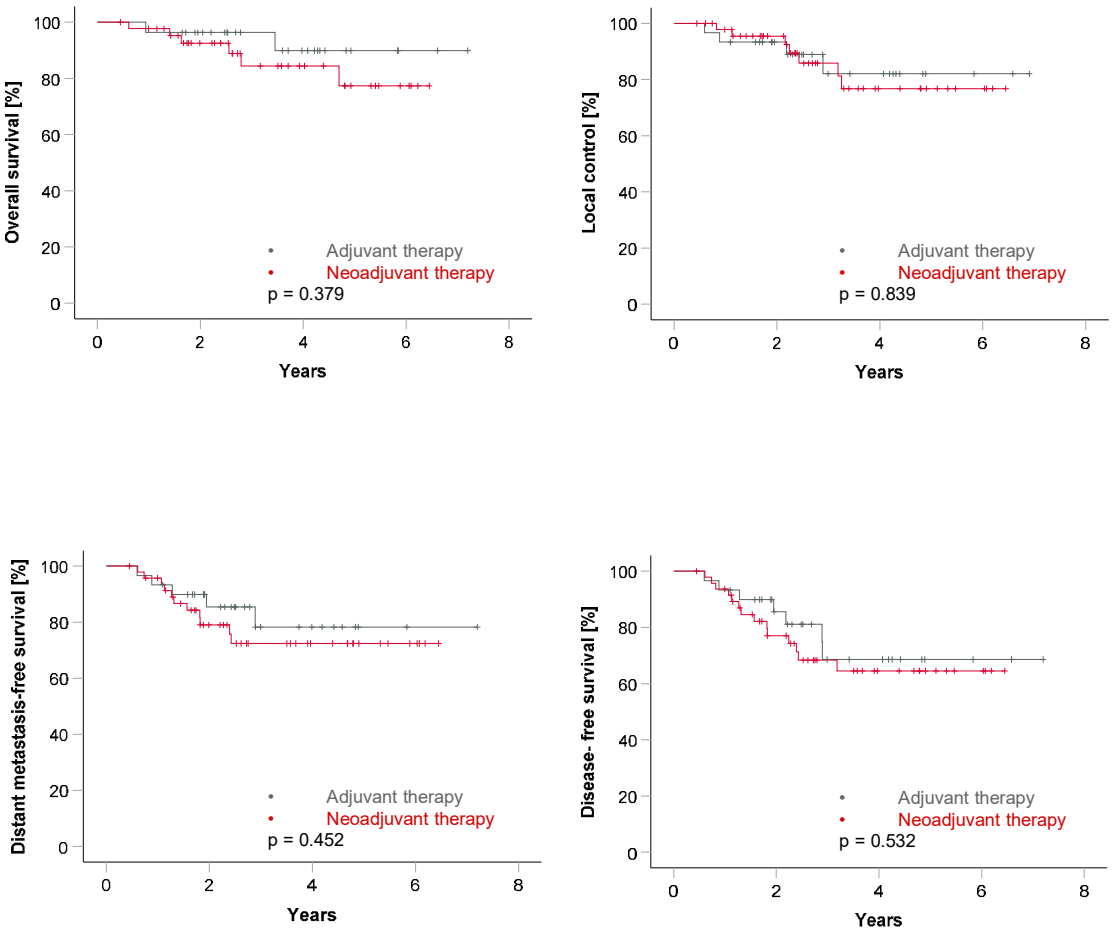

Figure 3: Kaplan-Meier curves demonstrating overall survival, local control, distant metastasis-free survival and disease-free survival rate stratified by the treatment characteristics (neoadjuvant vs. adjuvant therapy). There was no statistical significance between the two groups.

The impact of concomitant chemotherapy, concomitant hyperthermia and sequential chemotherapy on oncological outcomes for the whole patient collective was analysed. No statistically significant correlation was observed between sequential chemotherapy and OS (p = 0.562), LC (0.850), DFS (p = 0.924) or DMFS (p = 0.756); between concomitant chemotherapy and OS (p = 0.086), LC (0.794), DFS (p = 0.254) or DMFS (p = 0.083); and between concomitant hyperthermia and OS (p = 0.530), LC (p = 0.588), DFS (p = 0.568) or DMFS (p = 0.599). Notably, a trend to statistical significance between concomitant chemotherapy and worse OS (p = 0.086) and DMFS (p = 0.083) was

observed. However, using multivariate analysis it was not shown to be of any independent prognostic importance.

Influence of concomitant chemotherapy on OS and DMFS stratified by the timing of treatment (neoadjuvant vs. adjuvant) was analysed. In the subgroup of patients treated with neoadjuvant therapy, better DMFS rates for patients treated without concomitant chemotherapy were demonstrated ($p = 0.037$). In this specific subgroup of patients, no distant metastases were observed during follow up. There was no statistically significant difference for OS between patients treated with neoadjuvant therapy with or without concomitant chemotherapy ($p = 0.102$). Furthermore, no deaths were observed during follow up in the group of patients treated with neoadjuvant therapy without concomitant chemotherapy. In the subgroup of patients treated with adjuvant therapy, no difference for OS ($p = 0.781$) and DMFS ($p = 0.897$) was observed between patients treated with or without concomitant chemotherapy.

Patients that received concomitant chemotherapy had higher rate of tumors larger than 5 cm ($p = 0.012$) and higher proportion of patients with retroperitoneal STS with trend to statistical significance ($p = 0.067$).

Differences of patient and tumor characteristics in subgroups of patients treated with neoadjuvant and adjuvant therapy were analysed. Our findings show that patients with tumors larger than 5 cm in its size were more often treated with neoadjuvant therapy ($p = 0.013$). No statistical significance regarding sex ($p = 0.510$), age ($p = 0.182$), localization ($p = 0.967$), tumor depth to superficial fascia ($p = 0.128$) and tumor grading ($p = 0.223$) was found.

The difference in treatment modalities in the subgroups of patients treated with neoadjuvant and adjuvant therapy was analysed. Patients treated with

neoadjuvant therapy received more often concomitant chemotherapy ($p = 0.001$) and hyperthermia ($p < 0.001$), as well as sequential chemotherapy ($p < 0.001$).

Comparing postoperative surgical margins and treatment modalities, our analysis showed that patients treated with neoadjuvant therapy more often had negative postoperative surgical margins ($p = 0.035$).

We investigated the factors which might explain the higher rate of negative surgical margins in the group of patients treated with neoadjuvant radiation therapy. Our analysis showed that concomitant chemotherapy was also associated with higher rate of negative surgical margins in this group of patients ($p = 0.047$). Furthermore, a trend to statistical significance was found between concomitant hyperthermia and negative postoperative surgical margins ($p = 0.075$). No significant correlation was found between sequential chemotherapy and negative surgical margins by patients treated with neoadjuvant radiation therapy ($p = 0.728$). We observed a trend to statistical significance for correlation between good pathological response after neoadjuvant therapy with negative postoperative surgical margins ($p = 0.066$).

Analysing the entire patient collective, we observed no impact of positive postoperative surgical margins on DMFS ($p = 0.677$) or DFS ($p = 0.170$). However, patients with positive surgical margins (either microscopically or macroscopically) had reduced OS ($p = 0.034$) and LC rates ($p = 0.020$).

Considering tumor localization, significantly higher proportion of resections with positive surgical margins was observed in the group of retroperitoneal STS compared to non-retroperitoneal STS ($p = 0.007$). Positive surgical margins were detected in 28.6% of the total patients collective. Regarding its localization,

positive surgical margins were observed in 66.6% of retroperitoneal STS, 28.6% of truncal STS, 23.1% of lower extremity STS and 20.0% of upper extremity STS.

Using log-rank test, we compared the impact of negative surgical margins on oncological outcomes in the subgroups of patients treated either with neoadjuvant or adjuvant therapy. This analysis showed that for patients treated with neoadjuvant therapy, positive surgical margins had no negative impact on OS ($p = 0.252$), LC ($p = 0.223$), DFS ($p = 0.502$) or DMFS ($p = 0.517$).

In the group of patients treated with adjuvant therapy, positive postoperative surgical margins had negative impact on OS ($p = 0.018$) and LC ($p = 0.038$), but no impact on DMFS ($p = 0.696$) or DFS ($p = 0.100$) in univariate analyses. Even though positive postoperative margins showed no statistically significant impact on DFS for patients treated with adjuvant therapy ($p = 0.100$), our analysis showed discrepancy in 3-year DFS rates for patients with negative surgical margins (83.5 ± 8.7%) vs. DFS rate for patients with positive surgical margins (25.3 ± 2.1%). Using multivariate analyses, we found a correlation between positive surgical margins and worse LC with trend to statistical significance ($p = 0.070$). No influence as independent prognostic factor was demonstrated for OS in multivariate analyses.

Impact of clinical tumor characteristics (tumor size and tumor depth to superficial fascia) on oncological outcomes (OS, LC, DFS and DMFS) is presented in figure 4 and figure 5.

There was no statistically significant difference in oncological outcomes for patient groups stratified by the tumor size. However, in the group of patients with tumors smaller than 5 cm in the size, there were no distant metastases observed, resulting in a trend to statistical significance regarding DMFS ($p = 0.070$) in

univariate analyses, but with no significance in multivariate analyses as independent prognostic factor.

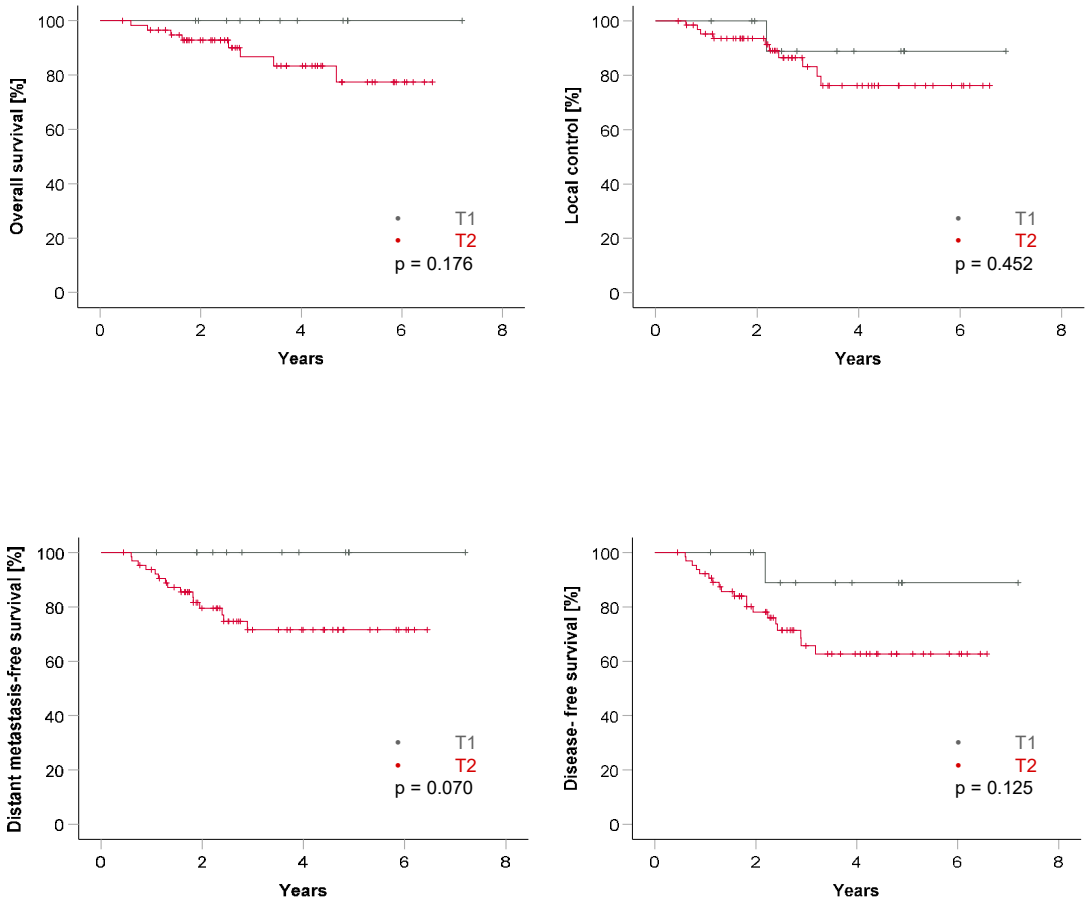

Figure 4: Kaplan-Meier survival curves stratified by the size of tumor (T1 ≤ 5 cm; T2 > 5 cm). No difference in survival curves was observed. However, there is a trend to statistical significance considering distant metastasis-free survival. In the group of patients with small tumors (< 5 cm), there were no distant metastases and no deaths during the follow up observed.

Considering the depth of the tumor to the superficial fascia, better outcome for superficial tumors for DFS (p = 0.034) was observed in univariate analyses. A trend to statistical significance was observed for DMFS (p = 0.079). During the follow up, no local recurrences or distant metastasis were observed in the group of patients with superficial tumors, resulting in statistical significance for DFS.

Tumor depth to superficial fascia was not shown as independent prognostic factor in multivariate analysis.

Considering the size of the tumor and tumor depth in relation to superficial fascia, no statistical difference for OS was observed. However, in the group of patients with tumors smaller than 5 cm in size, no deaths during the follow up were observed.

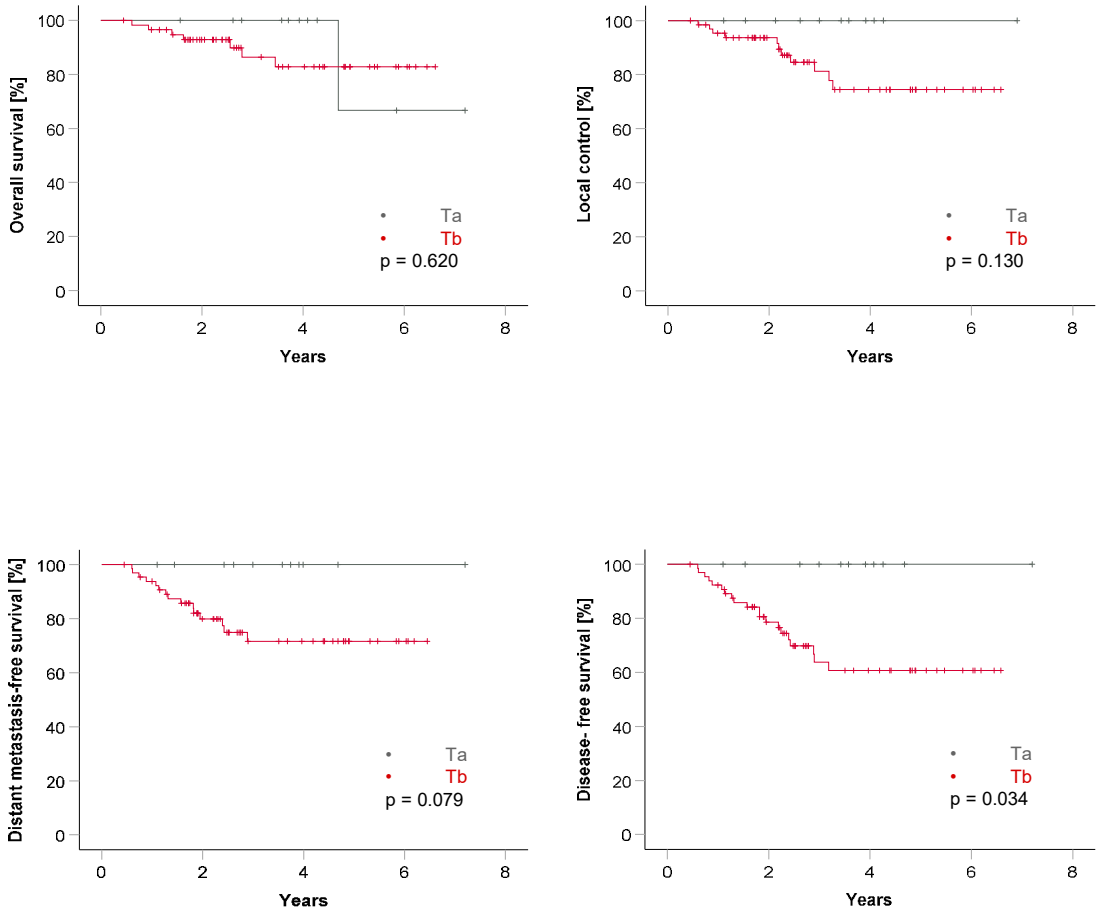

Figure 5: Kaplan-Meier survival curves stratified by the depth of the tumor from the superficial fascia (Ta = superficial; Tb = deep). Patients with superficial tumors had significantly better disease-free survival rates. For the distant metastasis-free survival, there was a trend to statistical significance. In the group of the patients with superficial tumors there were no local recurrences or distant metastasis during the follow up, resulting in significant difference in disease free survival.

The impact of postoperative histopathologic response after neoadjuvant therapy on oncological outcomes (OS, LC, DFS and DMFS) is presented in figure 6. We observed a statistically significant correlation between good pathologic response and LC (p = 0.004) and DMFS (p = 0.012), resulting in a statistically significant difference for DFS (p = 0.001) and leading to better OS (p = 0.042). Furthermore, in multivariate analyses, good pathological response was the only independent prognostic factor for good OS (p = 0.020), DFS (p = 0.012) and DMFS (p = 0.030), but not shown as independent prognostic factor for LC.

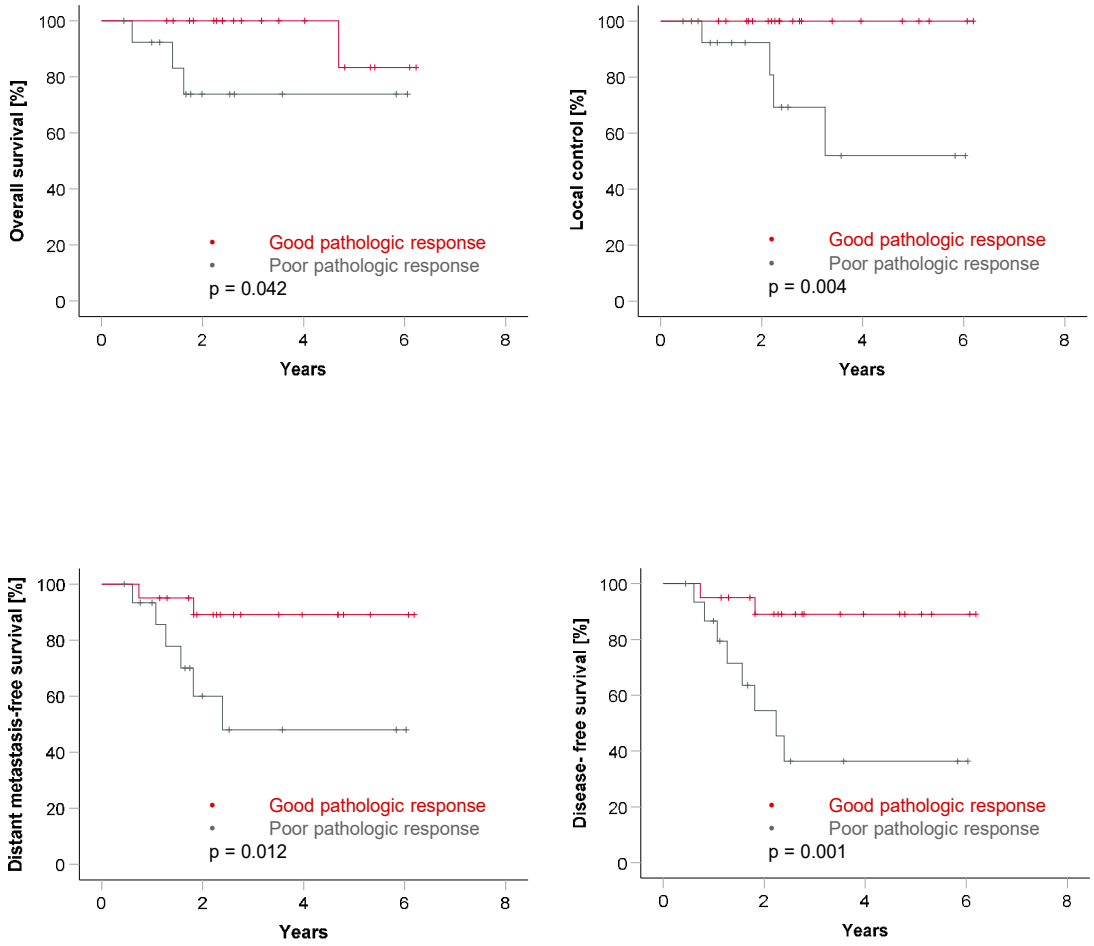

Figure 6: Kaplan-Meier survival curves stratified by the pathologic response after neoadjuvant therapy (n = 51); (Good pathologic response = less than 10% vital tumor tissue; poor pathologic response = 10 - 100% vital tumor tissue). Patients with good pathologic response had better oncological outcomes concerning local control, distant metastasis-free survival und disease-free survival, leading to better overall survival.

These findings indicate that from all examined patient characteristics and tumor features, good pathologic response might be the strongest predictive factor for oncological outcomes for the group of patients treated with preoperative radio(-chemo)therapy. In the group of patients with good pathologic response, no local recurrences were observed during the follow up. Treatment modalities and tumor characteristics were correlated with pathological response. We found no correlation between concomitant chemotherapy ($p = 0.964$), concomitant hyperthermia ($p = 0.964$), tumor grading ($p = 0.262$), tumor size ($p = 0.816$) and tumor depth to superficial fascia ($p = 0.748$) with pathological response. However, patients treated with sequential chemotherapy in addition to neoadjuvant or adjuvant therapy had statistically significant better pathological response ($p = 0.034$). Considering the tumor localization, we observed a trend to statistical significance for good pathological response for tumors located in upper and lower extremities or trunk (including abdomen) compared with retroperitoneum ($p = 0.066$). In the group of retroperitoneal STS, no tumor showed good pathological response.

Oncological outcomes for retroperitoneal STS were compared with non-retroperitoneal STS (including trunk, lower and upper extremities). The results are presented in figure 7. This comparison showed poor oncological outcomes for patients with tumors located in retroperitoneum. With statistical significance, retroperitoneal localization was connected with worse OS ($p = 0.017$), LC ($p = 0.002$) and DFS ($p = 0.034$) in univariate analyses. For DMFS, there was no statistically significant difference between retroperitoneal and non-retroperitoneal STS. In multivariate analyses however, retroperitoneal localization was not shown as an independent prognostic factor for poor oncological outcomes.

Correlation of patients and tumor characteristics and treatment modalities with retroperitoneal tumor localization was assessed. No statistical differences in patient characteristic (sex, age) and therapy modalities connected with retroperitoneal STS were found. Comparing tumor characteristics, positive

postoperative surgical margins were with statistical significance more often found after resection of retroperitoneal STS (p = 0.007) compared to non-retroperitoneal STS. Regarding tumor size, no statistically significant difference was found between retroperitoneal and non-retroperitoneal STS. However, all retroperitoneal STS in this study were larger than 5 cm in its size. Mean tumor size was compared using T-test resulting in 12.6 cm (± 2.9 cm) for retroperitoneal STS and 9.9 cm (± 0.7 cm) for non-retroperitoneal STS (p = 0.389).

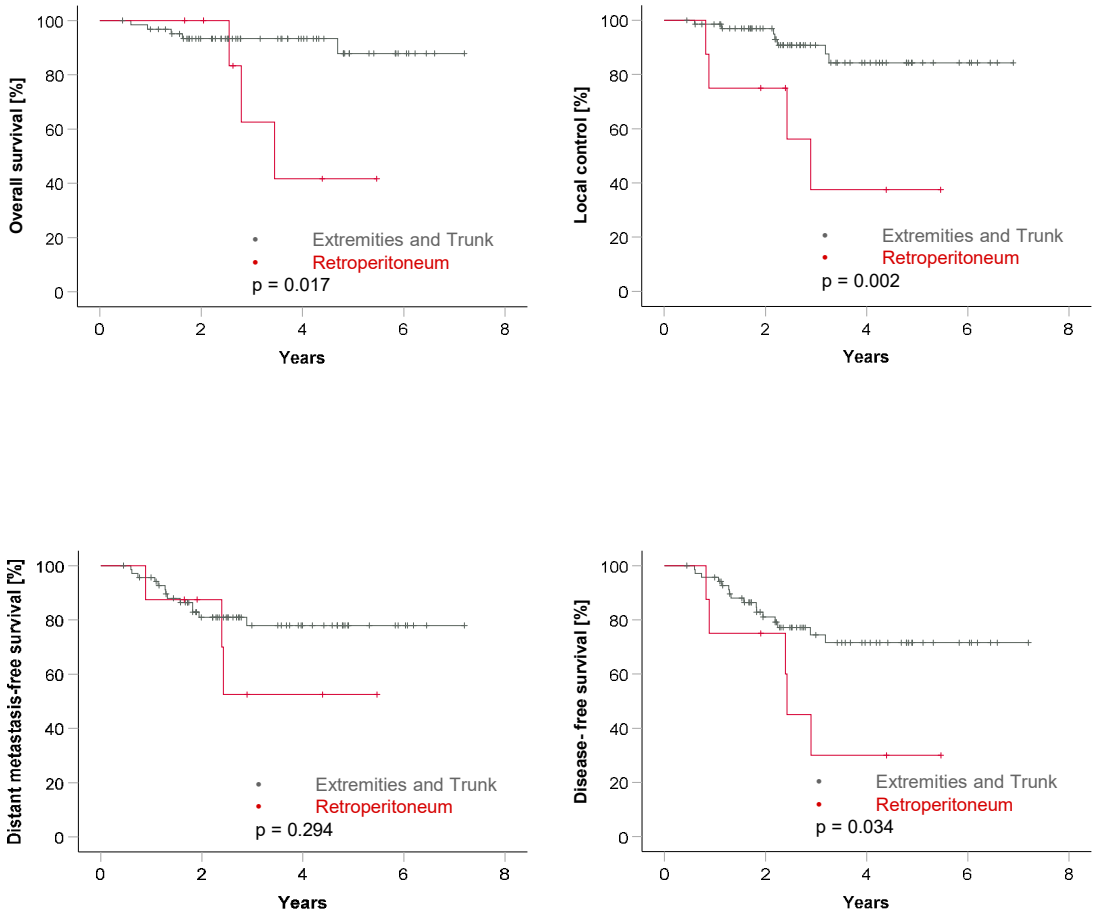

Figure 7: Kaplan-Meier survival curves stratified by localization of the tumor (extremities and trunk vs. retroperitoneum). Patients with retroperitoneal soft tissue sarcoma had worse overall survival, local control and disease-free survival rates. There was no significant difference between the two groups for distant metastasis-free survival.

3.4 Wound complications and risk factors

Out of 84 patients, the overall rate of major wound complications was 29.8% (n = 25). Major wound complications are presented in table 6. There were 14.3% (n = 12) of the patients that developed a postoperative wound healing disorder that required a second surgery. Wound infection that required oral or intravenous antibiotic therapy was observed in 16.7% of the patients (n = 14). Abscesses were seen in 5.9% (n = 5) of the patients and postoperative fistula in 7.2% (n = 6) of the patients. Postoperative seroma and hematoma with the need for an invasive procedure (aspiration, drainage or reoperation) were observed in 9.5% (n = 8) and 3.6% (n = 3) of the patients.

Table 6: Major wound complications

	No complications	Complications
Major wound complication	59	25 (29.8%)
• Wound healing disorder	72	12 (14.3%)
• Wound infection	70	14 (16.7%)
• Abscess	79	5 (5.9%)
• Postoperative seroma	76	8 (9.5%)
• Postoperative hematoma	81	3 (3.6%)
• Fistula	78	6 (7.2%)
Total (n = 84)		

Using log-rank test, a correlation between major wound complications and oncological outcomes (OS, LC, DMFS and DFS) was tested. No correlation was found between major wound complications and LC ($p = 0.373$), DMFS ($p = 0.956$) and DFS ($p = 0.817$). Statistically significant reduced OS-rate was found in univariate analyses for patients that developed major wound complication ($p = 0.015$). However, this was not confirmed in multivariate analysis as an independent prognostic factor. Stratified by the timing of radiation therapy, no impact was found in the group of patients treated with neoadjuvant therapy ($p = 0.360$), but only in the group of patients treated with adjuvant therapy ($p = 0.001$). However, in this specific group of patients, none of patients ($n = 2$) died due to postoperative complication.

We analysed if reduced OS by patients with major wound complications was connected with tumor localization. With statistical significance, non-extremity STS with major wound complication had worse OS, compared with extremity-STS ($p = 0.050$). Furthermore, comparing retroperitoneal with non-retroperitoneal-STS, no decrease of OS rate was demonstrated for retroperitoneal STS with major wound complication ($p = 0.151$). However, our analysis showed discrepancy in 5-year OS rates by patients with major wound complication and non-retroperitoneal localization (86.2 ± 9.1%) vs. retroperitoneal localization with major wound complication (25.0 ± 2.2%).

We examined whether major wound complications were related to other relevant patient characteristic, clinical tumor variables and treatment characteristics. No correlation was found between age ($p = 0.256$) or sex ($p = 0.333$) and major wound complications in general. Statistically significant correlation was found between age > 65 years and higher rate of postoperative hematoma ($p = 0.016$). Using T-test, mean age of patients that developed major wound complication (58.2 ± 1.9 years) was compared to the age of those that had no complications (61.8 ± 2.4 years) also with no statistical significance ($p = 0.249$).

There was no statistically significant correlation between the tumor size and tumor depth to superficial fascia to major wound complication in general ($p = 0.956$ and $p = 0.272$). Median tumor size was compared between patients that developed a major wound complication (9.6 ± 0.9 cm) and patients that did not develop any sort of major wound complication (10.5 ± 0.9 cm) resulting in no statistical significance ($p = 0.493$).

Analyzing complications per localization of tumor, our findings show that 64% ($n = 16$) of major wound complications occurred in the lower extremity, 4% ($n = 1$) in upper extremity, 12% ($n = 3$) in trunk and 20% ($n = 5$) in retroperitoneum. Lower extremity represents 46.4% of all tumor localizations, resulting in statistical significance for major wound complication for this localization ($p = 0.036$). Furthermore, lower extremity was identified as a risk factor for developing a postoperative seroma ($p = 0.016$) and wound healing disorder ($p = 0.006$).

Retroperitoneal localization was identified as a risk factor for major wound complications in general. From all patients with retroperitoneal STS, 55.5% of them developed at least one major wound complication, resulting in a trend for statistical significance for this localization ($p = 0.073$). Patients with retroperitoneal STS had a significantly higher risk of developing postoperative abscess ($p < 0.001$). For developing a fistula, there was a trend to significance observed ($p = 0.069$). No statistical significance was determined for correlation of retroperitoneal location of STS and wound healing complication that required second surgical intervention ($p = 0.762$), wound infection ($p = 0.162$), postoperative seroma ($p = 0.874$) and hematoma ($p = 0.202$). The impact of retroperitoneal localization on major wound complication is presented in figure 8.

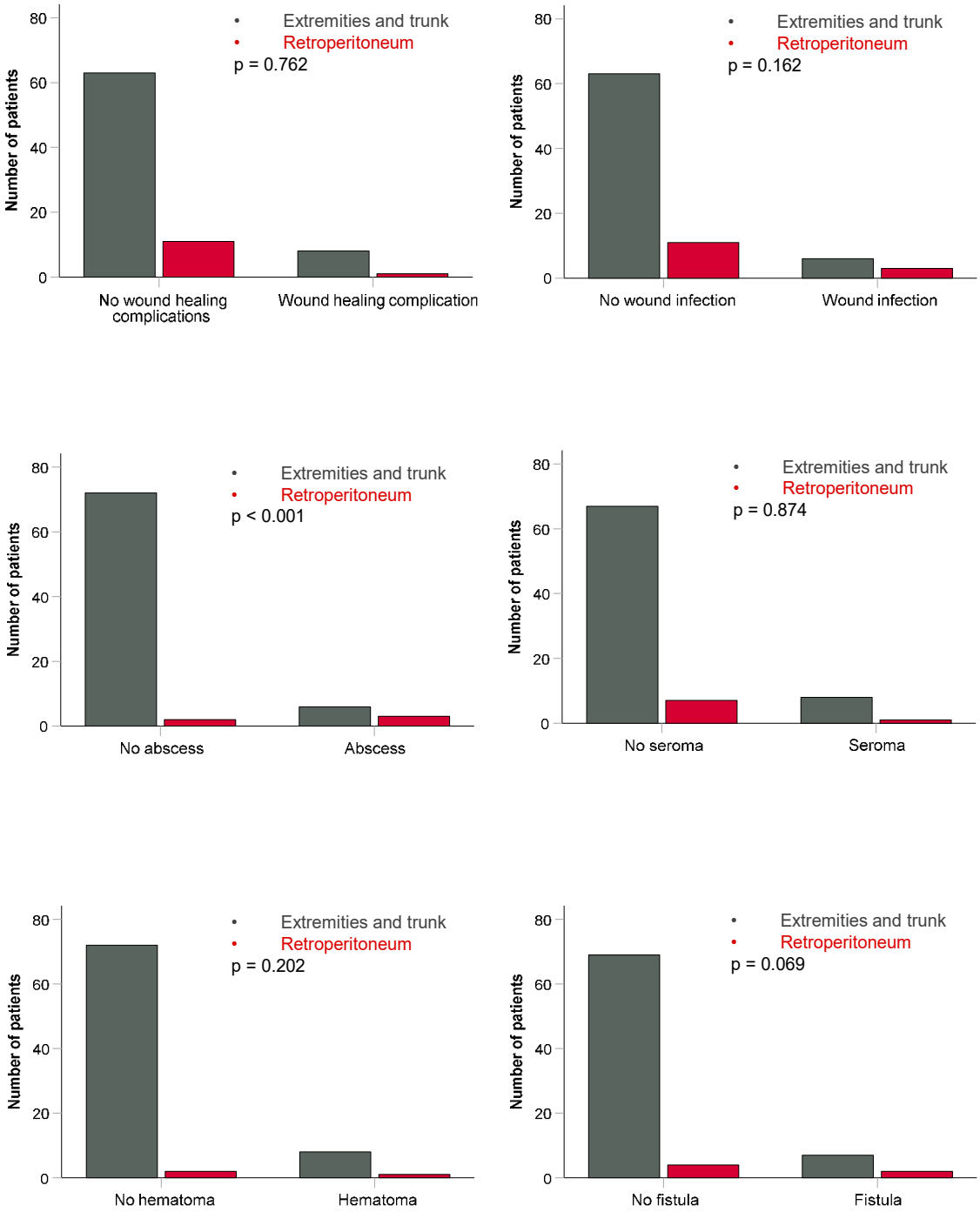

Figure 8: Bar graphs comparing the correlation of the localisation of tumor (extremities and trunk vs. retroperitoneum) with postoperative complications. With statistical significance, retroperitoneal localisation was identified as a risk factor for postoperative abscess. There was no significant difference between two groups for wound healing complication, wound infection, postoperative hematoma and seroma. However, a trend to statistical significance was observed for postoperative fistulas.

The impact of treatment characteristics (neoadjuvant therapy vs. adjuvant therapy) on major wound complication was tested and is presented in figure 9. This study demonstrated a higher number of patients with major wound complications in the group treated with neoadjuvant therapy compared to adjuvant therapy (35.3% vs. 21.2%). However, no statistical significance was demonstrated (p = 0.168).

This study showed that neoadjuvant therapy is associated with higher rate of wound infection (23.5% vs. 6.1%, p = 0.041). A trend to statistical significance for wound healing complications (19.6% vs. 6.1%, p = 0.092) was observed in the group of patients treated with neoadjuvant therapy. No significant correlation was found for abscess (7.8% vs. 3.0%, p = 0.379), postoperative seroma (11.8% vs. 6.1%, p = 0.407), postoperative hematoma (5.9% vs. 0.0%, p = 0.162) and fistula (9.8% vs. 3.0%, p = 0.244). In table 7 and figure 9, we demonstrated the distribution of major wound complications stratified by treatment modalities (neoadjuvant vs. adjuvant therapy).

Table 7: Major wound complications stratified by the timing of the treatment (neoadjuvant vs. adjuvant therapy)

	Neoadjuvant therapy	Adjuvant therapy
Patients with MWC	18 (35.3%)	7 (21.2%)
Total number of MWCs	40	8
• Wound healing complication	10 (19.6%)	2 (6.1%)
• Wound infection	12 (23.5%)	2 (6.1%)
• Abscess	4 (7.8%)	1 (3.0%)
• Postoperative seroma	6 (11.8%)	2 (6.1%)
• Postoperative hematoma	3 (5.9%)	0 (0.0 %)
• Fistula	5 (9.8%)	1 (3.0%)
Total patients (n = 84)	n = 51	n = 33

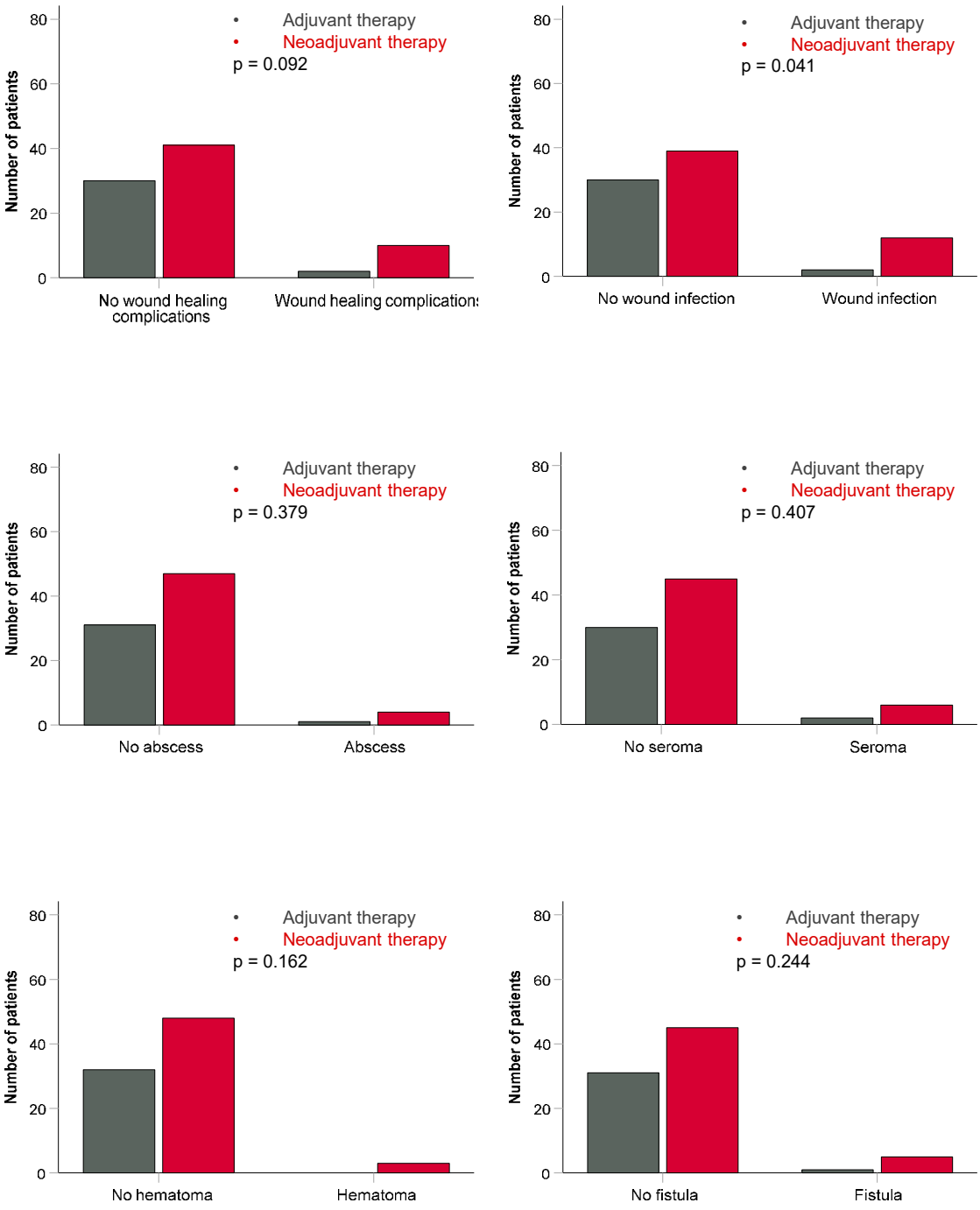

Figure 9: Bar graphs comparing the correlation of neoadjuvant and adjuvant therapy with postoperative complications. With statistical significance, neoadjuvant therapy was identified as a risk factor for developing a wound infection, with trend to significance for developing a wound healing complication. No significant association was found for abscess, fistula, postoperative hematoma and seroma.

The impact of different therapy modalities on major wound complications was analysed using chi-square test (neoadjuvant or adjuvant radiation therapy with or without concomitant chemotherapy, concomitant hyperthermia or sequential chemotherapy). Analysing these factors, no statistically significant impact on major wound complications was observed. In the whole patients collective, no influence of concomitant chemotherapy ($p = 0.688$), concomitant hyperthermia ($p = 0.995$) or sequential chemotherapy ($p = 0.373$) on major wound healing complications in general was demonstrated. Also, no statistically significant correlation was found between those additional therapy modalities and any of major wound complications: wound healing complication, wound infection, abscess, postoperative seroma, hematoma or fistula (data not shown).

Overall rate of pathological fractures in the entire cohort was 4.8% (n = 4/ 84) and 5.5% (n = 3/ 54) in the subgroup of extremity STS. 75% of pathological fractures (n =3) were localized in upper (n = 1) or lower extremity (n = 2). One pathological fracture was localized in the lumbar spine. Neoadjuvant and adjuvant therapy were both associated with 2 pathological fractures. Overall rate of bone necrosis in the entire cohort was 4.8% (n = 4/ 84) and 5.5% (n = 3/ 54) in the subgroup of extremity STS. We tested the correlation between treatment characteristics and bone necrosis and pathological fracture in the subgroup of patients with soft tissue sarcoma located in upper and lower extremities. Our findings suggest that sequential chemotherapy is connected with pathological fracture with statistical significance ($p = 0.042$) and with bone necrosis with trend to statistical significance ($p = 0.053$). The impact of sequential chemotherapy on pathological fracture and bone necrosis is presented in figure 10. Patients that received concomitant hyperthermia or concomitant chemotherapy did not have higher rates of pathological fracture ($p = 0.767$, $p = 0.165$) or bone necrosis ($p = 0.808$, $p = 0.180$) of extremities.

Analysing the whole patient collective, patients treated with additional concomitant chemotherapy did not have statistically significant higher rates of

pathological fracture (p = 0.104) or bone necrosis (p = 0.570). However, all of the patients that developed a pathological fracture (n = 4) received concomitant chemotherapy. A statistically significant correlation was found between bone necrosis and pathological fracture (p < 0.001). Using chi-square test, we investigated if there is a correlation between patient characteristics (age and sex) or clinical tumor characteristics (tumor size, depth to superficial fascia, tumor grading) and bone necrosis or pathological fracture. No significant correlation was found (data not shown).

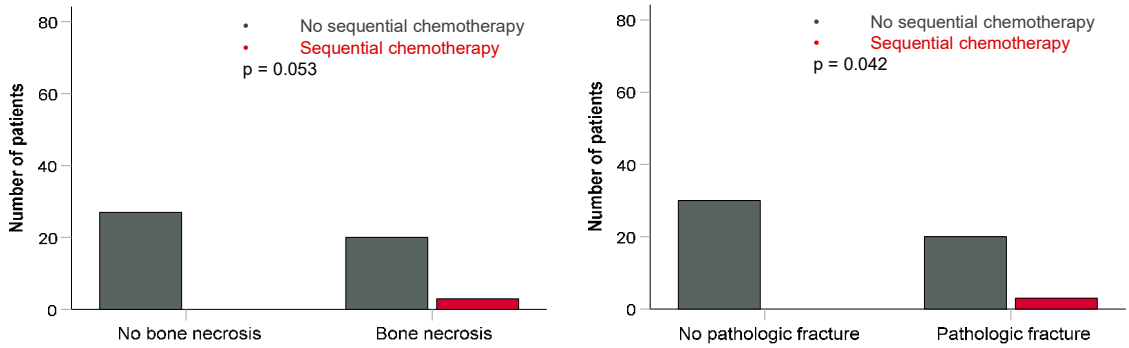

Figure 10: Bar graphs comparing the correlation of sequential chemotherapy with bone necrosis and pathologic fracture. Patients which received sequential chemotherapy had a higher rate of bone necrosis with trend to statistical significance (p= 0.053). With statistical significance, sequential chemotherapy was identified as a risk factor for developing a pathological fracture (p= 0.042).

The influence of preexisting diabetes (diabetes mellitus type 1 or type 2) on major wound complication is presented in figure 11. Our findings show a strong connection between preexisting diabetes and major wound complication in general (p < 0.001). Additional analysis showed a correlation with wound infection (p = 0.001), abscess (p = 0.031) and fistula (p = 0.001). A trend to statistical significance was observed for wound healing complication that needed a second operation for patients with preexisting diabetes (p = 0.088). We found no significant correlation between diabetes and postoperative seroma (p = 0.176) and hematoma (p = 0.202).

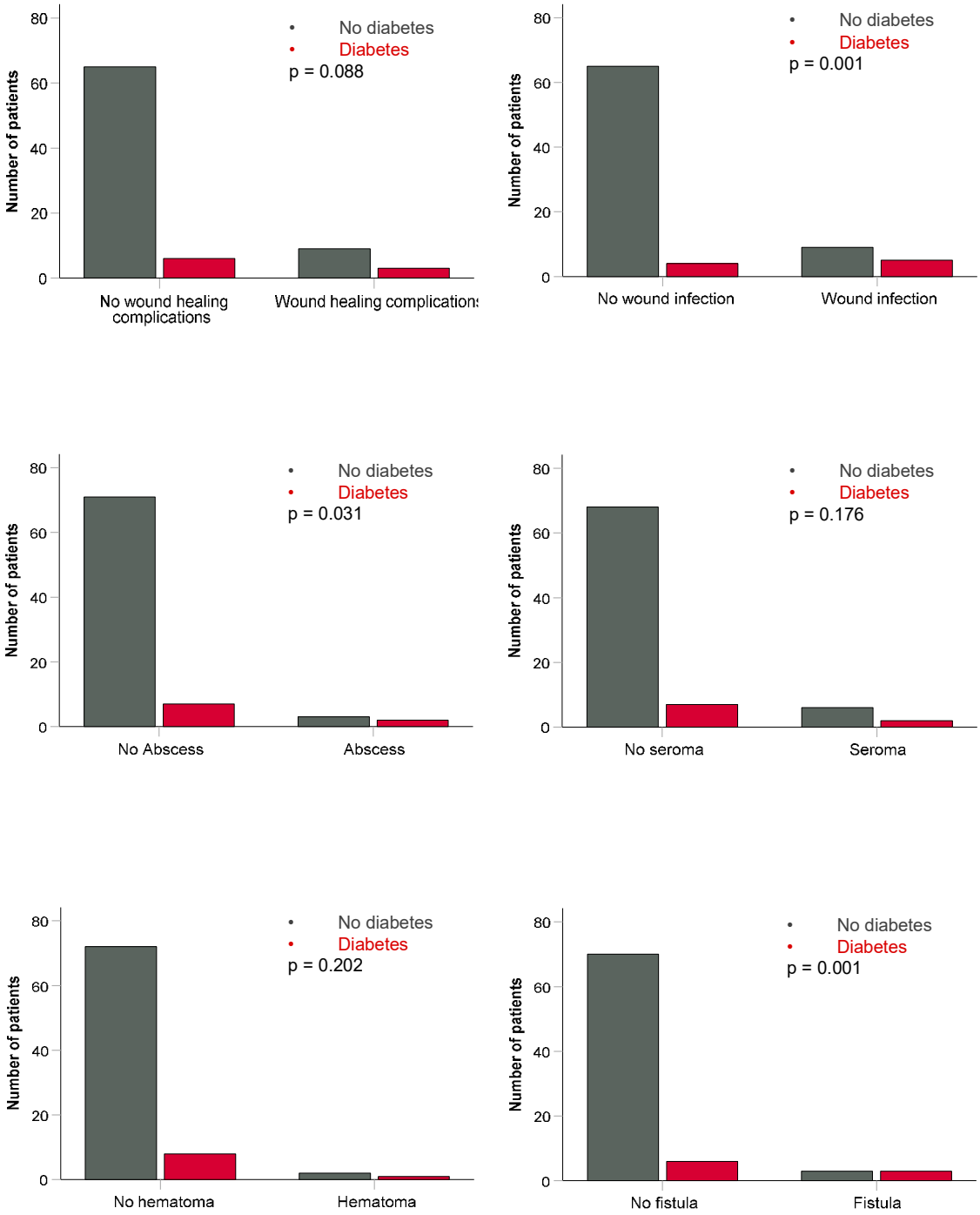

Fig. 11: Bar graphs comparing the correlation of diabetes with postoperative complications. Preexisting diabetes was significantly associated with wound infection, abscess and postoperative fistula, with trend to statistical significance for wound healing complications. No significant association was found for the postoperative hematoma and seroma.

4 DISCUSSION

4.1 Role of radiation therapy in multimodal treatment of soft tissue sarcoma

Treatment of high risk localized STS is based on multimodal concepts (including radiation therapy and chemotherapy or hyperthermia in select cases) and wide surgical excision. All of the patients included in our study with STS located in extremities, were operated using limb-sparing resection, which represents a standard treatment for most cases of extremity-STS. The first prospective randomized study that demonstrated that external beam radiation therapy in addition to limb-sparing resection of extremities STS is equieffective to limb amputation concerning OS rates, was published in 1982 by Rosenberg SA et al. [24]. Since then, external beam radiation therapy in addition to wide surgical excision has been established as a standard treatment for high risk STS. The role of external beam radiation therapy in addition to wide surgical excision of STS has been analysed in a systematic review and meta-analysis published in 2018 by Albertsmeier M et al., resulting in better LC for STS of all localizations, as well as better OS for retroperitoneal STS treated with additional external beam radiation therapy compared with the group of patients treated with surgical resection only. Regarding OS of non-retroperitoneal STS, no difference between two groups was observed in this meta-analysis [25]. Better OS rate for patients with retroperitoneal STS treated with additional perioperative radiation therapy compared to patients treated with surgical resection alone was observed in another large propensity-matched study [33], underlining the importance of radiation therapy in multimodal therapy of retroperitoneal STS. However, a prospective randomized study published by Bonvalot S et al. failed to demonstrate the benefit of preoperative radiation therapy for retroperitoneal STS. Possible methodological limitation that might have influenced the results of this study is involving a relatively high proportion of low grade STS (32.7%, n= 87). Furthermore, this study failed to show benefit of preoperative radiation therapy for high risk STS. Thus, no concomitant or sequential chemotherapy or

hyperthermia was given, which might have underestimated the importance of multimodal treatment for high-risk STS. 75.5% of patients in this study had retroperitoneal liposarcoma, and in this particular subgroup, an additional analysis has shown a 10% absolute benefit for abdominal recurrence-free survival (with statistical significance). Considering a relatively low morbidity associated with radiotherapy, this study might indicate a benefit of preoperative radiation therapy for this particular subgroup of STS [34].

Another randomized prospective study compared oncological outcomes (LC and OS) of extremity STS stratified by tumor grading. This study showed the improvement of LC-rates and no improvement of OS-rates in the group of patients treated with adjuvant radiation therapy (compared to patients treated with surgical resection only) for both high and low grade tumors [35]. On the contrary to these findings, some studies demonstrated statistically significant improvement for OS for the group of extremity STS that received adjuvant radiation therapy compared with the group of the patients treated with limb-sparing surgical resection only [36]. This improvement of OS targets especially high grade STS with tumor size larger than 5 cm in its diameter [26, 36].

It seems that the data about the impact of radiation therapy on the improvement of OS rates for STS are discrepant. The reason why most studies failed to clearly demonstrate the improvement of OS rate might be due to a small number of patients in the most of the studies, as well as salvage options for extremity tumors (such as limb amputation for isolated local recurrences) [37]. However, the role of extern beam radiation therapy in addition to surgical resection of STS for improvement of LC has been proven in various studies [24, 25]. Further studies also indicate a correlation of local recurrence and decreased OS [26, 27, 38]. A study published in 2003 by Eilber FC et al. investigated the effect of local recurrence on OS. This study showed that local recurrence was the most significant independent factor associated with decreased survival for high-grade extremity STS [38]. Similar findings were observed in the study published in 2001

by Trovik SC et al., which showed an association of local recurrence and increased risk of distant metastasis [39]. These findings underline the importance of external beam radiation therapy in the treatment of STS, not only for the improvement of LC rates, but also for eventual improvement of OS rates.

4.2 Oncological outcomes and influence of the timing of radiation therapy

In our study, using a single-institutional retrospective database, oncological outcomes and postoperative complications of patients with STS were analysed. All patients included in our study underwent surgical resection and were treated with additional radiotherapy, either neoadjuvant or adjuvant. Overall, good oncological outcomes were observed, with 3-year rates of 89.2% (± 4.3%) for OS, 84.4% (± 5.0%) for LC, 75.1% (± 5.6%) for DMFS and 68.6% (± 6.1%) for DFS. Comparing oncological outcomes (OS, LC, DMFS and DFS) stratified by treatment modalities (neoadjuvant vs. adjuvant radiation therapy), no statistical significance between those two patient groups was observed.

Similar findings were confirmed by an update of randomized controlled trial published in 2002 by O'Sullivan B et al., that failed to show improved oncological outcomes (OS and LC) for patients with extremity STS treated with neoadjuvant therapy, compared to patients treated with adjuvant therapy in addition to surgical resection. In this study, patients were stratified by tumor size (≤ 10 cm and > 10 cm). Risk factors between two groups were relatively equally distributed (tumor size, tumor grade, resection margins). However, in the group of patients treated with neoadjuvant therapy, there was a higher percentage of patients with deep tumors (59%), compared to the group of patients treated with adjuvant therapy (49%) [28].

Various further retrospective studies investigated the differences in oncological outcomes for patients with STS treated with either neoadjuvant or adjuvant radiation therapy [25, 28, 33, 40-43]. Comparing the impact of timing of radiation therapy, most of the studies demonstrated no difference for OS rates between the groups of patients treated with neoadjuvant therapy compared to adjuvant therapy [40, 42, 43]. Considering the DMFS rates, similar findings were observed in both studies [40, 42], which leads to the conclusion, that the timing of radiation therapy has no impact on the risk for metastatic spread of the tumor. The risk for metastatic spread of the tumor might rather be determined by the biological tumor characteristics [40]. Additionally, no statistically significant differences in LC rates were observed between the groups of the patients treated with neoadjuvant or adjuvant therapy for extremities STS in general [40, 42]. However, it seems that neoadjuvant therapy might be superior to adjuvant therapy in achieving LC for large tumors [44]. Furthermore, a large retrospective study published in 2016 by Nussbaum DP et al. investigated the influence of the timing of the radiation therapy on oncological outcomes for retroperitoneal STS. Again, clear benefit on LC and OS rates were observed for both, neoadjuvant and adjuvant radiation therapy compared to the group of patients treated with surgical resection only. The mortality for many patients with retroperitoneal STS seems to be connected to local recurrence [33, 45] and it seems that neoadjuvant radiation therapy improves the chance for negative surgical margins [46], which translates to better LC rates of retroperitoneal STS in the group of the patients treated with neoadjuvant therapy [33, 46]. However, the impact of the timing of radiation therapy on OS rates for retroperitoneal STS remains unclear [46]. Furthermore, adjuvant radiation therapy for retroperitoneal STS is often hard or impossible to achieve, due to limitations for organs of risk.

The impact of timing of radiation therapy on oncological outcomes was summarized in a large systematic review and meta-analysis published in 2018 by Albertsmeier M et al. In this study, a trend for better OS was observed, favoring neoadjuvant therapy over adjuvant therapy for non-retroperitoneal STS. However, no statistical significance was reached. For retroperitoneal STS, OS

rate was significantly higher in the group of patients treated with neoadjuvant therapy. Concerning LC, for the group of patients with retroperitoneal STS, significantly better LC was achieved with neoadjuvant therapy. In the group of non-retroperitoneal STS, a positive effect of neoadjuvant therapy on LC was found in the two largest studies included in the meta-analysis [25]. Comparing these finding with the results of an update of a randomized controlled trial published by O'Sullivan B et al, that found no OS and LC benefit for patients with extremities STS treated with neoadjuvant therapy [28], the impact of the timing of radiation therapy on oncological outcomes of non-retroperitoneal STS remains relatively unclear. In conclusion, considering the timing of radiation therapy (neoadjuvant vs. adjuvant), oncological outcomes of our study are comparable to findings of the most of the published studies.

Nevertheless, factors which could possibly affect these results and may affect oncological outcomes were investigated. Our study showed that patients treated with neoadjuvant therapy, more often received more aggressive multimodal therapy. Patients treated with neoadjuvant therapy were with statistical significance more often treated with concomitant or sequential chemotherapy and concomitant hyperthermia, compared to the group of the patients treated with adjuvant therapy. Furthermore, the group of patients treated with neoadjuvant therapy had unfavorable distribution of risk factors, such as significantly higher number of tumors larger than 5 cm in its diameter. Thus, our data might suggest that neoadjuvant treatment might be beneficial, as patients with unfavorable prognostic factors do not have an inferior outcome.

4.3 The role of chemotherapy and hyperthermia in multimodal treatment of soft tissue sarcoma

The role of chemotherapy in addition to radiation therapy and surgical resection of STS has been controversial. Different chemotherapy regimes and timings have been analysed [47-53], showing discrepant results. In a randomized phase II study published in 2001, no statistically significant improvement of OS was demonstrated for patients treated with neoadjuvant chemotherapy (doxorubicin/ ifosfamide) in addition to surgical resection for high risk STS [48]. Influence of concomitant chemotherapy (epirubicine/ ifosfamide) in addition to adjuvant radiotherapy for high risk STS failed to demonstrate a benefit regarding LC, DMFS and OS for patients treated with adjuvant radiochemotherapy compared to patients treated with only adjuvant radiotherapy in addition to surgical resection [49]. However, methodological limitations, such as retrospective design and relatively small number of patients involved in this study, might explain the failure of improvement of oncological outcomes for patients treated with additional chemotherapy [49]. On the contrary to these findings, a large retrospective study published in 2017 by Mahmoud O et al. investigated the role of concomitant or sequential chemotherapy in addition to radiotherapy and surgical resection for large (≥ 8 cm) high grade STS of extremity and trunk. This study showed a 12% improvement of 5-year survival for patients treated with combined multimodal therapy (chemotherapy and radiation therapy regardless of its sequence, in addition to surgical resection) over the group of patients treated only with chemotherapy or radiation therapy and surgical resection, which indicates that adjunctive modalities in combination might increase overall survival [50]. A systematic meta-analysis published by Pervaiz N et al. in 2008 showed an improvement of oncological outcomes (OS, LC, DFS and DMFS) in the group of patients treated with additional adjuvant doxorubicin/ ifosfamide chemotherapy [51]. These findings were supported by further studies which demonstrated an improvement of OS and DMFS rates for patients with high grade STS treated with adjuvant chemotherapy [52, 53]. However, a meta-analysis published in 2014 by Le Cesne et al., demonstrated a benefitial effect of neoadjuvant chemotherapy

for relapse-free survival, but not for OS. This effect was shown especially for marginally resected STS [54]. The role of concomitant hyperthermia in localized resectable STS has been established. Excellent local control was observed after neoadjuvant thermoradiotherapy of high-grade STS [55]. Additionally, a randomized phase 3 study observed an improvement of DFS and OS rate for patients treated with locoregional hyperthermia concomitantly to chemotherapy +/- sequential radiotherapy, compared to the group of patients treated with neoadjuvant chemotherapy +/- sequential radiotherapy [56]. Another study showed an improvement of DFS rate for patients with high grade STS treated with hyperthermia and/ or chemotherapy in addition to neoadjuvant radiation therapy compared to patients treated with neoadjuvant radiation therapy only [57].

In our study, even though the patients treated with neoadjuvant therapy were with statistical significance treated with more aggressive therapy, compared to the group of patients receiving adjuvant therapy, no improvement of oncological outcomes in that group of patients was observed. Patients treated with neoadjuvant therapy received more often concomitant chemotherapy ($p = 0.001$) and hyperthermia ($p < 0.001$), as well as sequential chemotherapy ($p < 0.001$). Furthermore, patients treated with sequential chemotherapy, concomitant chemotherapy or concomitant hyperthermia in addition to radiation therapy, had no improvement of oncological outcomes in our study. In the group of patients treated with concomitant chemotherapy, a trend to worse OS ($p = 0.086$) and DMFS ($p = 0.083$) was observed. Stratified with the timing of the radiation therapy, this effect was seen only in the group of patients treated with neoadjuvant therapy, and might be explained due to unfavorable distribution of risk factors in the group of patients treated with additional chemotherapy and with neoadjuvant therapy. Thus, no distant metastases or deaths were observed in the subgroup of patients treated with neoadjuvant therapy and without concomitant chemotherapy.

4.4 Tumor characteristics and oncological outcomes, prognostic factors

To explain the lack of improvement of oncological outcomes in the group of patients treated with neoadjuvant therapy and to detect a potential bias, the distribution of risk factors (tumor size, tumor depth to superficial fascia, tumor grading and postoperative surgical margins) was investigated. Comparing clinical tumor characteristics in these two patient groups, the study showed that patients treated with neoadjuvant therapy, with statistical significance had a higher rate of tumors larger than 5 cm in its size ($p = 0.013$), which can be identified as a risk factor which put the group of patients treated with neoadjuvant therapy to higher risk for poor oncological outcomes. These findings might explain comparable oncological outcomes between neoadjuvant and adjuvant treated patients, regardless statistically higher rate of additional concomitant or sequential chemotherapy and concomitant hyperthermia in the group of patients treated with neoadjuvant therapy. Furthermore, methodological limitations of this study as well as retrospective study design might be considered a bias regarding these findings. Patients were not randomized regarding its treatment modalities and timing of radiation therapy, but the decision was rather made in the multidisciplinary meeting, whereupon patients with risk factors (such as high grade, tumor size > 5 cm as well as deep seated tumors) were more often treated with neoadjuvant therapy and multimodal regimes. Regarding age, sex, depth to superficial fascia, tumor grading and localization, no statistically significant difference in the distribution of these factors between the groups of patients treated with neoadjuvant vs. adjuvant therapy was observed. The distribution of histological subtypes of STS and their impact on survival curves was not tested, due to its high heterogeneity.

Furthermore, using univariate analyses we observed a trend to statistical significance for poor OS and DMFS rates by patients treated with concomitant chemotherapy in addition to radiation therapy, which is discrepant to findings of a systematic meta-analysis published by Pervaiz N et al. in 2008 [51]. However,

patients treated with concomitant chemotherapy had statistically significant higher rate of tumors larger than 5 cm in its diameter and also a higher proportion of retroperitoneal STS with trend to statistical significance. These tumor characteristics are known risk factors and might have put the group of patients treated with concomitant chemotherapy to higher risk for poorer oncologic outcomes. Furthermore, higher rate of tumors larger than 5 cm in its size ($p = 0.013$) in the group of patients treated with neoadjuvant therapy, and the fact that patients treated with concomitant chemotherapy had higher rate of tumors larger than 5 cm ($p = 0.012$), might be a possible explanation for worse DMFS rate in the group of patients treated with neoadjuvant therapy and concomitant chemotherapy. In addition, retrospective study design might be considered to be a bias regarding these findings.

Impact of tumor size on oncological outcomes of STS has been investigated in various studies [53, 58-62]. In a large retrospective study published in 1995 by Pisters WTP et al., tumor size larger than 5 cm, as well as subfascial tumor localization were detected as independent prognostic factors for poor oncological outcomes regarding DMFS and disease specific survival. No impact of these factors on LC was observed [59]. Similar findings were observed in another retrospective study, which identified tumor size and depth to superficial fascia as predictors for poor oncological outcomes considering OS and DMFS [53]. These two factors are included in TNM staging for STS, due to its prognostic importance for STS. On the contrary, there are some hints, that depth to superficial fascia is not an independent prognostic factor, but rather a poor prognostic factor if combined with high grade and size larger than 5 cm [61]. Various studies investigated the impact of tumor size and tumor depth to superficial fascia on LC and found no impact as well [53, 58-60, 62]. These findings are concordant to the findings of our study.

In our study, considering tumor size and depth to superficial fascia, using univariate analyses, we observed worse oncological outcomes for patients with

large tumors (>5 cm), as well as for deep seated tumors. DFS rate was statistically significant worse in the group of patients with deep seated tumors (p = 0.034). Worse DMFS rates with trend for statistical significance were observed for patients with tumors larger than 5 cm (p = 0.070), as well as for deep seated tumors (p = 0.079). In the group of patients with tumors smaller than 5 cm, no distant metastases and no deaths were observed. Furthermore, no local recurrences or distant metastases were observed in the group of patients with epifascial tumors. These effects did not influence OS, which in our study was not statistically significant better for patients with small tumors (<5 cm) or superficial tumors. Possible explanation for relatively equal OS rates by these groups of patients might be a methodological limitation of the study, such as relatively small sample size considering high heterogeneity of STS, as well as retrospective study design. In addition, STS smaller than 5 cm are relatively often treated with surgical resection only, and therefore the number of such tumors in our study is limited.

These findings lead to conclusion, that the role of neoadjuvant radiation therapy in our study might be underestimated, as the tumor size might be the factor that could put the group of patients treated with neoadjuvant therapy to higher risk for poorer oncologic outcomes, as the large tumor size can predict higher rates of distant metastasis, which leads to worse survival rates.

We found no significant impact of tumor grading on oncological outcomes in our study. This might be explained by a small number of patients with low grade tumors included in our study (n = 2), as the patients with low grade tumors are usually treated with surgical resection only. However, the impact of high tumor grading on oncological outcomes has been investigated in many studies and is established as a poor prognostic factor for distant recurrence [53, 59, 61], as well as for poor OS [60].

Furthermore, retroperitoneal localization of STS in our study was significantly correlated with poor oncological outcomes considering OS (p = 0.017), LC (p = 0.002) and DFS (p = 0.034) in univariate analyses. No significance in DMFS rate was observed between patients with retroperitoneal and non-retroperitoneal STS. Further analysis of tumor characteristics comparing retroperitoneal to non-retroperitoneal STS demonstrated a higher rate of positive postoperative surgical margins (p = 0.007). Median size of retroperitoneal STS was larger compared with non-retroperitoneal STS (12.6 cm ± 2.9 cm vs. 9.9 cm ± 0.7 cm; p = 0.389), with no statistical significance, possibly due to small number of patients with retroperitoneal STS in the entire patient collective and large standard errors. All patients with retroperitoneal STS had tumors larger than 5 cm in its diameter. These risk factors put the group of retroperitoneal STS to a higher risk for poor oncological outcome. Distribution of histological subtypes in the group of retroperitoneal STS in our study was relatively homogeneous, consisting of 75% dedifferentiated liposarcoma. These findings were compared with further studies that investigated oncological outcomes in patients with retroperitoneal dedifferentiated liposarcoma [63, 64]. One study demonstrated a high rate of local recurrences (80%), and relatively small rate of distant recurrences (19%). However, the majority of patients involved in the study were treated with surgical resection only, without multimodal therapy, and therefore the results are not directly comparable with our study [64]. Another study published in 2016 by Gronchi A et al. reported 8-year OS rate of 43.9%. Most of the deaths were caused by local recurrence, local recurrence rate was over 40% at 8 years, whereas the distant metastasis risk was less than 20% and therefore comparable with the previous study [63]. These findings lead to the conclusion, that a significant reduction of OS and DFS of retroperitoneal STS in our study is mainly connected to relatively high rate of local recurrences in this particular subgroup. Further studies have identified inadequate surgical resection as a main reason of high local recurrence rate of retroperitoneal STS, and therefore underlined the importance of R0 resection for retroperitoneal STS for improvement of LC, as well as OS [45, 65, 66]. However, that approach seems to be difficult to achieve, due to large tumor size of retroperitoneal STS, as well as complicated anatomy with

inability to obtain a wide surgical resection [65]. Findings of those studies are concordant to the results of our study. Relatively unfavorable tumor characteristics of retroperitoneal STS considering its size and high proportion of positive postoperative surgical margins might result in worse LC which translates to reduced OS and DFS rates. In conclusion, additional preoperative radiation therapy might be a reasonable strategy to improve local control.

4.5 **Surgical margins and oncological outcomes**

Various studies investigated the impact of surgical margins on oncological outcomes. The importance of negative surgical margins to achieve good LC not only for retroperitoneal STS, but also in the therapy of STS in general, has been established in various studies [23, 53, 59, 60, 65-67]. However, its impact on OS and DMFS remains relatively unclear. Further studies investigated an impact of LC on OS and DMFS [23, 38, 68-71]. It seems that local recurrence is a poor prognostic factor and translates to higher rate of distant recurrences [69, 71] and to reduced OS rates [23, 38, 68, 69, 71]. Additional studies investigated a correlation between inadequate surgical margins and distant recurrence and found no direct correlation [23, 70]. However, one study demonstrated a very strong correlation between positive surgical margins and local recurrence, which was further associated with higher incidence of distant recurrences [70]. Stojadinovic A et al. published a large retrospective study of 2084 localized STS and found a strong correlation between positive surgical margins and not only worse LC, but also worse DMFS and OS rates [67].

Similar findings were observed in our study. Analysing the entire patient cohort, reduced OS ($p = 0.034$) and LC ($p = 0.020$) rates were found in patients with positive surgical margins in univariate analyses. In multivariate analyses, positive surgical margins seem to be the only independent prognostic factor for poor LC

with trend to statistical significance (p = 0.070), but is not shown as an independent prognostic factor for OS. No correlation between positive surgical margins and DMFS and DFS rate was observed, which leads to the conclusion, that negative surgical margins are associated with poor LC rates, which might translate to reduced OS rate in that group of patients. Especially high rates of positive surgical margins were seen in the group of retroperitoneal STS (66.6%), resulting in statistical significance compared to non-retroperitoneal STS (p = 0.007). This might be considered as a risk factor which might reflect worse LC and OS rate for the whole patient collective.

However, analyzing the subgroups of patients with positive surgical margins treated with either neoadjuvant or adjuvant therapy, we found no correlation of positive surgical margins and oncological outcomes in the group of patients treated with neoadjuvant therapy (OS p = 0.252; LC p = 0.223; DFS p = 0.502 or DMFS p = 0.517). It seems that positive surgical margins in our patient collective correlates with poor OS (p = 0.018) and LC (p = 0.038) rates only in the group of patients treated with adjuvant therapy. Regarding DMFS (p = 0.696) and DFS (p = 0.100) rates, no statistically significant correlation was observed for patients treated with adjuvant therapy. However, additional analysis demonstrated a discrepancy in 3-year DFS rates by patients with negative surgical margins (83.5 ± 8.7%) compared to DFS rate by patients with positive surgical margins (25.3 ± 2.1%). This disproportion in DFS rates was not significant due to relatively small proportion of patients in this subgroup analysis.

Additionally, our analysis demonstrated that patients treated with neoadjuvant therapy more often had negative postoperative surgical margins (p = 0.035), which also might be a selection bias, as the patients that have only a relative indication for radiation therapy and are operated with R1-resection, tend to be treated with adjuvant therapy. These findings are concordant to data of other studies that found statistically significant higher rate of negative surgical margins by patients treated with neoadjuvant therapy for extremities STS [29, 72] and

retroperitoneal STS [73]. While analyzing treatment modalities, we observed that patients treated with neoadjuvant radiation therapy had more often negative surgical margins if they were treated with additional concomitant chemotherapy ($p = 0.047$). Furthermore, a trend to statistical significance was found between concomitant hyperthermia and negative surgical margins in the group of patients treated with neoadjuvant radiation therapy ($p = 0.075$).

These findings underline the importance of adequate surgical resection as a cornerstone of the multimodal therapy of STS. Furthermore, our findings suggest, that an aggressive neoadjuvant multimodal treatment (with concomitant chemotherapy and hyperthermia) might improve the chances of adequate surgical resection. This approach seems especially important for retroperitoneal STS, STS with complicated anatomy and inability to obtain a wide surgical resection, as well as for large tumors, where surgical resection with negative margins is unlikely. Neoadjuvant (multimodal) therapy might be recommendable in these situations, especially considering that R1-resection does not seem to have an impact on LC after neoadjuvant therapy. Furthermore, a high dose of postoperative radiation therapy for retroperitoneal STS is often limited, due to constraints of organs at risk.

4.6 **Pathological response after neoadjuvant therapy**

Histopathological response after neoadjuvant chemotherapy has been established as an independent prognostic factor in the treatment of osteosarcoma and Ewing`s sarcoma [74, 75]. Many studies investigated the role and meaning of pathological response as a prognostic factor after neoadjuvant therapy of STS [22, 23, 76-79]. Various studies demonstrated a correlation between good pathological response after neoadjuvant radiochemotherapy [22, 23, 79] or neoadjuvant chemotherapy [76] and better oncological outcomes

regarding OS [22, 23], LC [22], DMFS [23, 79] and DFS [76]. In contrast to these findings, other studies found no correlation between histopathological response and oncological outcomes [77, 78]. However, both of these studies analysed patients treated with neoadjuvant chemotherapy, without radiation therapy. This approach might have underestimated the importance of radiation therapy in achieving good histopathologic response rates.

In our study, we defined a good pathological response as less than 10% vital tumor tissue. This strategy is in line with various studies investigating the impact of pathological response after neoadjuvant therapy. We demonstrated a correlation between good pathological response and LC (p= 0.004) and DMFS (p= 0.012), resulting in a statistically significant difference for DFS (p= 0.001) and leading to a better OS (p= 0.042) in univariate analyses. Furthermore, good pathological response seems to be the only independent prognostic factor for better OS (p = 0.020), DFS (p = 0.012) and DMFS (p = 0.030) in multivariate analyses, but has no significance as independent prognostic factor for LC. In the group of patients with good pathological response, no local recurrences were observed, which underlines the importance of good pathological response as a prognostic factor for good oncological outcomes.

In the group of retroperitoneal STS, no tumors showed good pathological response after neoadjuvant therapy. This finding might be considered as an additional factor which might influence poor oncological outcomes for patients with retroperitoneal STS. Regarding treatment modalities, concomitant hyperthermia and chemotherapy seem to have no impact on pathological response. However, a correlation between sequential chemotherapy and good pathological response was demonstrated (p = 0.034), which might indicate a correlation between aggressive regimes of neoadjuvant therapy with high percentage of good pathological responses [80]. Another possible explanation might be, that the time between the start of therapy and surgical resection in patients treated with sequential chemotherapy is much longer. This assumption

might be supported by a large study published in 2017 by Macchia G et al. that compared correlation of pathological response after neoadjuvant chemoradiotherapy and time to surgery of patients with rectal cancer. This study confirmed the correlation of lengthening the interval between chemoradiotherapy and surgical resection with improvement of pathological response [81]. However, this study investigated rectal cancer, and therefore is not directly comparable with our patient population.

4.7 Postoperative complications

We analysed postoperative complications after multimodal treatment of STS for the whole cohort. In total, 25 patients had at least one major wound complication (29.8%), which is similar to rates in other published studies that investigated postoperative complications after both, neoadjuvant and adjuvant therapy (in total between 21.2% and 28.7%) [28, 82-85]. Comparing the timing of the treatment, we observed a higher rate of major wound complications in the group of patients treated with neoadjuvant therapy (35.3%), compared to the patients treated with adjuvant therapy (21.2%), however without statistical significance ($p = 0.168$). A higher rate of wound infections ($p = 0.041$) and wound healing complications ($p = 0.092$) was observed in the group of patients treated with neoadjuvant therapy. However, it seems that the timing of therapy had no impact on postoperative hematoma and seroma, abscess and fistula. This topic will be analysed in more detail in chapter 5.8.

The rates of postoperative complications are relatively consistent throughout literature. Rat-model experimental studies demonstrated a correlation between radiation and doxorubicin-chemotherapy and wound healing inhibition, presumably by reduction of collagen synthesis [86, 87]. Various clinical studies analysed acute postoperative complications after multimodal treatment of STS

[28, 43, 82-85, 88-91]. Treatment modalities varied among the studies. Some studies analysed postoperative complications after neoadjuvant therapy only [88-91] and reported a wide range of postoperative complications (ranging from 13.5% to 35.0%). Further studies investigated postoperative complications after both, neoadjuvant and adjuvant therapy, and reported a total rate of postoperative complications between 21.2% and 28.7% [28, 82-85]. All of these studies demonstrated statistically significant higher rate of postoperative complications in the group of patients treated with neoadjuvant therapy (between 23.8% and 39.7%) [28, 43, 82-85]. The rate of postoperative complications in patients treated with adjuvant therapy were lower (between 8% and 23.1%) [28, 43, 82-85].

Our study demonstrated a higher rate of major wound complications in the group of patients treated with neoadjuvant therapy as well, but without statistical significance (35.3% vs. 21.2%, p = 0.168). Factors which might explain this lack of statistical significance and relatively high total rate of major wound complications in our study were analysed. Various differences in definitions of acute postoperative complication or major wound complication were identified. Many studies based and adopted their definition of major wound complications or acute postoperative complications on the definition of O´Sullivan et al. which was introduced in 2002 [28, 82, 84, 85, 90]. However, various differences were identified, such as exclusion of postoperative seroma treated with needle aspiration [90] or wound infections treated with intravenous antibiotics alone [84]. On the contrary to that, in our retrospective analysis, we included wound infections treated with either oral or intravenous antibiotic, as well as postoperative hematoma or seroma treated with either needle aspiration, or drainage or re-operation. Furthermore, most of the studies did not include retroperitoneal STS in their analysis [28, 43, 82, 84, 85, 88-91]. Considering a relatively high rate of major wound complications for retroperitoneal STS in our study (55%), this might be identified as a factor which additionally explains the higher rate of major wound complications in our patient cohort. To the best of my knowledge, there are no published studies that analysed major wound complications after multimodal therapy of retroperitoneal STS only.

Regardless of relatively high rate of postoperative complications or major wound complications, their impact on oncological outcomes remains relatively unclear. These complications tend to be non-progressive with time [28] and are usually manageable with pharmacological or surgical intervention [82]. A study published in 2017 by Broecker SJ et al. demonstrated a reduced disease specific survival rate in the group of patients that developed a postoperative complication. However, this study included only 47% of patients treated with perioperative therapy (either radiotherapy or chemotherapy or combination of both) and is therefore not directly comparable with our study [92]. On the contrary to these findings, a further study found no correlation between postoperative infection and oncological outcomes (OS, LC, DMFS) for extremities STS. Similar to the findings of the study published by Broecker SJ et al. in 2017, using univariate analyses we observed a reduced OS rate in the group of patients that developed a major wound complication in general ($p = 0.015$), which was not confirmed in multivariate analysis as an independent prognostic factor. Stratified by the timing of radiation therapy, no impact was found in the group of patients treated with neoadjuvant therapy ($p = 0.360$), but only in the group of patients treated with adjuvant therapy ($p = 0.001$). However, in this specific group of patients, none of patients ($n = 2$) died due to postoperative complication. In conclusion, we assume there is no direct correlation of major wound complication and OS. It might be rather explained by unfavorable distribution of risk factors in patients with major wound complications, such as higher number of retroperitoneal STS ($p = 0.073$).

Patients that developed major wound complications had worse OS in the subgroup of non-extremity STS compared to extremity-STS ($p = 0.050$). No statistical significance for OS was demonstrated for the subgroup of retroperitoneal STS that developed major wound complication, compared to non-retroperitoneal STS. However, discrepancy in 5-year OS rates by patients with major wound complication and non-retroperitoneal localization ($86.2 \pm 9.1\%$) vs. retroperitoneal localization with major wound complication ($25.0 \pm 2.2\%$) was

shown. This lack of statistical significance might be explained by relatively small number of patients with retroperitoneal STS in the whole patient collective (n = 9/ 84; 10.7%). Worse OS rates for patients with primary retroperitoneal sarcoma and with severe postoperative complications have been reported in the literature [93].

Due to the retrospective study design and its limitations, late toxicity after multimodal treatment of STS was not analysed, with the exception of pathological fractures, which occurred rarely (4.8%). This result was comparable with published data [82, 94-99]. This topic will be analysed more detailed in chapter 5.9. Furthermore, various studies investigated the correlation of radiation therapy and late toxicity. Late or chronic radiation-related complications include subcutaneous tissue fibrosis, edema, joint stiffness, neurological injury, and bone changes including osteitis, bone necrosis and pathological fracture [82, 100]. Postoperative radiation therapy is connected with higher rate of late radiation toxicity compared to preoperative radiation therapy [42, 100]. Possible explanation for this difference in late toxicity rates might be smaller radiation volumes and lower radiation doses required for preoperative radiation therapy [101, 102].

In conclusion, a higher rate of postoperative complications was demonstrated in the group of patients treated with neoadjuvant therapy, but it seems that there is no impact of these complications on survival rates in the group of patients treated with neoadjuvant therapy ($p = 0.360$). Keeping these findings in mind, and considering a higher rate of late radiation toxicity in the literature following postoperative radiation therapy, it seems generally recommendable to use preoperative therapy over postoperative therapy, especially for retroperitoneal, abdominal and pelvine STS (where a high postoperative radiation dose is hardly applicable), as well as for borderline resectable STS, where downsizing of tumor size might be eventually achieved using preoperative therapy. However, optimal treatment for STS in general is hard to recommend and this decision should be

made in a multidisciplinary meeting, considering various patient characteristics and clinical tumor characteristics.

4.8 Prognostic factors for major wound complications

The impact of patient and tumor characteristics, as well as therapy modalities on postoperative complications in general, wound healing complications, wound infection, abscess, postoperative hematoma and seroma and fistula were analysed.

No correlation was found between age ($p = 0.256$) or sex ($p = 0.333$) and major wound complication. A statistically significant correlation was found between age > 65 years and postoperative hematoma ($p = 0.016$). These findings are supported by further studies, which have not found a correlation between sex and age and postoperative complications in patients with STS [83-85]. In contrast to these findings, increased age has been described as one of major risk factors for impaired wound healing in general. Some studies described a delay in wound healing connected with increased age, but no influence on the quality of healing [103, 104]. A systematic review and meta-analysis published by Slump J. et al. in 2018 analysed the impact of patient age on postoperative wound complications after resection of STS. This meta-analysis reported discrepant results among published studies [105]. A further study describes the clinical impact of age-related changes in acute wound healing as rather small and relates a poor healing in chronic wounds as more related to comorbidities rather than age alone [106].

Furthermore, no correlation was found between tumor size and depth to superficial fascia and postoperative complications in general. Due to a small number of low grade STS, no impact of grading on postoperative complications

was observed. Various studies investigated the impact of tumor characteristics on postoperative complications and demonstrated discrepant findings. These studies used various cutoff points of tumor size, which makes them hard to compare [28, 83, 84, 88, 107]. All of these studies included extremities STS [28, 83, 84, 88, 107], but also truncal STS [83, 84, 88] and head STS [84]. A retrospective study published in 2014 by Moore J. et al. demonstrated a linear relation between tumor diameter and major wound complications as well as 5.4% increase in the wound complication rate for each additional centimeter of tumor size [84]. These findings were supported by further studies, demonstrating a higher rate of major wound complications after treatment of tumors larger than 10 cm in diameter [28, 88]. On the contrary to these findings, additional studies found no correlation between tumor size and postoperative wound complications [83, 107]. Further studies demonstrated however a correlation between resection volume and wound healing complications [108] and between duration of the operation and wound complications [109], which might indicate the correlation of postoperative complications with deep seated and large tumors in these studies.

Tumors located in lower extremities had significantly higher rate of major wound complications in general ($p = 0.036$). Lower extremity was identified as a risk factor for developing a postoperative seroma ($p = 0.016$) and wound healing complication ($p = 0.006$), but had no impact on wound infection, postoperative hematoma, abscess and fistula. Furthermore, retroperitoneal localization was associated with higher rate of major wound complications, with trend to statistical significance ($p = 0.073$). This localization was associated with higher rates of abscess ($p < 0.001$), as well as with postoperative fistula with trend to statistical significance ($p = 0.069$), but had no impact on postoperative hematoma and seroma, delayed wound healing and wound infection. Most of the published studies that investigated risk factors for postoperative wound complications excluded retroperitoneal STS and therefore are not directly comparable with our study. However, many studies identified lower extremity sarcomas as a risk factor for postoperative complications in general [28, 83, 91, 110, 111]. The large meta-analysis and systematic review published in 2019 by Slump J. et al. identified

tumor location in the lower extremity as the strongest tumor-related predictor for wound complications [105].

Additional chemotherapy (either concomitant or sequential) or concomitant hyperthermia had no impact on major wound complications in our study. These findings are concordant with the results of published studies, demonstrating no correlation of neoadjuvant [112], adjuvant [113] or any chemotherapy [84] on major wound complications. In a study published in 1999 by Prosnitz et al., oncological outcomes and wound complications were evaluated for patients with STS treated with neoadjuvant radiation therapy and hyperthermia with curative intent. In this study, 38% of patients developed major wound complications, which is comparable to results of our study, where 35.3% of patients treated with neoadjuvant therapy developed major wound complications [55].

One of the most important causes of impaired wound healing is diabetes mellitus. Studies of the immune cells necessary for wound healing, as well as studies of injured tissue implicate a correlation of diabetes mellitus and delayed response to injury and impaired functioning of immune cells [114]. Furthermore, diabetes mellitus causes a prolonged inflammatory phase in the cascade of wound healing, due to delayed macrophage introduction and diminished leukocyte migration which causes prolonged healing of infections in diabetic patients [115]. A large meta-analysis and a systematic review published in 2015 by Martin ET. et al. demonstrated a strong correlation between diabetes and risk of surgical site infection [116]. The effect of preexisting diabetes (either diabetes mellitus type 1 or type 2) on major wound complication was investigated in our study. Strong correlation between preexisting diabetes and major wound complication in general was observed ($p < 0.001$). Additional analysis demonstrated a correlation with wound infection ($p = 0.001$), abscess ($p = 0.031$) and fistula ($p = 0.001$). A trend to statistictical significance was observed for wound healing complication that needed a second operation for patients with preexisting diabetes ($p = 0.088$). No impact of preexisting diabetes on postoperative hematoma or seroma was

observed. Various published studies are concordant with these data, demonstrating a correlation of diabetes and major wound complications after resection of STS [84, 88].

4.9 Pathological fracture and osteonecrosis

Correlation between treatment characteristics and bone necrosis and pathological fracture in the subgroup of the patients with soft tissue sarcoma located in upper and lower extremities was investigated. Univariate analyses showed a significant correlation between sequential chemotherapy and pathological fracture ($p = 0.042$), as well as a trend to statistical significance for bone necrosis ($p = 0.053$). Concomitant hyperthermia or chemotherapy were not associated with higher rates of pathological fracture or bone necrosis of extremities. However, all of the patients that developed a pathological fracture ($n = 4$) received concomitant chemotherapy, which might indicate the role of chemotherapy as a risk factor for pathological fracture. Due to limited number of patients in the study, as well as very small number of patients that developed a pathological fracture, subgroup analyses were not performed.

Limited published data about this topic identified various prognostic factors for pathological fractures after radiation therapy of STS. Reported fracture rates vary between 1.2% and 6.4% [82, 94-99], which is concordant to our rate of 4.8%. Female sex [95, 97, 98], periostal stripping [82, 96, 98, 117], age [40, 97], high dose radiation therapy [97], chemotherapy [98, 117], circumferential exposure of bone to radiation therapy [82, 117], tumor size [95], positive tumor margins and anterior compartment involvement of lower extremity [96] were identified as risk factors. In contrast to these findings, another retrospective study found no correlation between radiation dose, adjuvant chemotherapy, patient age or gender and pathological fracture. However, this study included only 5 patients

with pathological fracture, and therefore the analysis of risk factors is quite limited [82]. We found no correlation between age and sex, tumor size, depth to superficial fascia or tumor grading to bone necrosis or pathological fracture. However, it seems that there is no clear consensus about risk factors for pathological fracture. Relatively small number of patients in most of the studies that investigated this topic might explain discrepant findings between these studies. Overall, low fracture rates point towards sufficient sparing of bones with currently used dose constraints for extremity-STS radiation therapy.

5 CONCLUSION

The role of radiation therapy in multimodal therapy for high risk STS has been established. However, the impact of timing of radiation therapy and its influence on oncological outcomes is controversial and has been discussed in various studies. In our study, no statistically significant difference in oncological outcomes between patients treated with either neoadjuvant or adjuvant therapy was demonstrated. Patients treated with neoadjuvant therapy were treated with more aggressive therapy, as more patients in this subgroup received either concomitant or sequential chemotherapy or concomitant hyperthermia. Nevertheless, this patient subgroup had similar oncological outcomes to the subgroup of patients treated with adjuvant therapy. However, patients treated with neoadjuvant therapy had unfavorable distribution of risk factors, which might have put this subgroup of patients to the risk for poor oncological outcomes and might explain similar oncological outcomes for the two groups of patients.

As expected, higher rate of major wound complications was observed in the subgroup of patients treated with neoadjuvant therapy, however with no statistical significance and with imbalanced risk factors. Regardless of relatively high rate of major wound complications in the group of patients treated with neoadjuvant therapy, it seems that there is no direct impact on oncological outcomes for this specific subgroup of patients. These complications seem to be non-progressive with time and are usually manageable. Considering a higher rate of late radiation toxicity after adjuvant radiotherapy in the literature, it seems generally recommendable to use neoadjuvant therapy, especially for retroperitoneal, abdominal or pelvic STS, where the application of high dose of adjuvant radiation therapy is limited, due to dose limitations in organs at risk. Thus, the final decision about optimal treatment should be carried out in the multidisciplinary meeting, considering various patient characteristics and clinical tumor characteristics.

6 SUMMARY

In a single institution retrospective study, oncological outcomes and major wound complications for patients with localized STS treated with multimodal therapy were analysed.

No statistically significant difference in oncological outcomes for patients treated with either neoadjuvant or adjuvant therapy was observed. However, regarding the distribution of risk factors, it seems that patients treated with neoadjuvant therapy have a higher risk for poor oncological outcomes, considering statistically significant higher rate of tumors larger than 5 cm. Prognostic factors for oncological outcomes were analysed. Using univariate analyses, worse oncological outcomes were observed for patients with large and deep tumors, as well as retroperitoneal STS. Positive surgical margins were connected with worse LC which led to worse OS rate. However, stratified by the timing of radiation therapy, an impact of positive surgical margins was demonstrated only for patients treated with adjuvant therapy. Furthermore, good pathological response after neoadjuvant therapy was identified as the only independent factor for better OS, DFS and DMFS in multivariate analysis.

Higher rate of major wound complications was demonstrated in the group of patients treated with neoadjuvant therapy, with no statistical significance. Risk factors for major wound complications were analysed. Higher rate of major wound complications, especially postoperative seroma and wound healing complication were observed for STS in lower extremity. Furthermore, retroperitoneal STS were connected with higher rates of abscess and fistula. Diabetes was identified as one of the most important risk factors for major wound complications in general, but is limited to infection-related complications in a subgroup analyses. Regardless relatively high rate of major wound complications in the group of

patients treated with neoadjuvant therapy, they had no impact of oncological outcomes in his subgroup.

Due to methodological limitations and retrospective design, late toxicity was not analysed, except pathological fracture and osteonecrosis. All of the patients developing pathological fracture were treated with additional chemotherapy. Furthermore, statistically significant higher rate of pathological fractures was found in the group of patients treated with sequential chemotherapy, underlining the role of chemotherapy as a risk factor for developing a pathological fracture.

In conclusion, considering oncological outcomes, distribution of major wound complications and its influence on oncological outcomes, it seems generally recommendable to use neoadjuvant therapy for high risk STS. This recommendation is especially applicable to retroperitoneal, pelvic and abdominal STS, where a high dose of postoperative radiation therapy is often limited, due to dose limitations in organs at risk. However, final decision about the optimal treatment should be carried out after considering various patients characteristics and clinical tumor characteristics.

7 ZUSAMMENFASSUNG

In einer retrospektiven Einzelinstitutstudie wurden onkologische Ergebnisse und schwerwiegende Wundkomplikationen bei Patienten mit lokalisiertem Weichteilsarkom analysiert, die mit multimodaler Therapie behandelt wurden.

Für Patienten, die entweder mit einer neoadjuvanten oder einer adjuvanten Therapie behandelt wurden, zeigte sich kein statistisch signifikanter Unterschied in den onkologischen Ergebnissen. In Bezug auf die Verteilung der Risikofaktoren scheint es jedoch, dass Patienten, die mit einer neoadjuvanten Therapie behandelt wurden, ein höheres Risiko für schlechte onkologische Ergebnisse hatten, wenn man die statistisch signifikant höhere Rate von Tumoren über 5 cm berücksichtigt. Prognostische Faktoren für onkologische Ergebnisse wurden analysiert. Eine univariate Analyse zeigte schlechtere onkologische Ergebnisse bei Patienten mit großen und tief sitzenden Tumoren sowie retroperitonealem Weichteilsarkom. Positive Resektionsränder waren mit einer schlechteren LC verbunden, was zu einer schlechteren OS-Rate führte. Stratifiziert nach Strahlentherapiemodalität wurde jedoch nur bei Patienten, die mit einer adjuvanten Therapie behandelt wurden, ein Einfluss positiver Resektionsränder nachgewiesen. Darüber hinaus wurde in der multivariaten Analyse ein gutes pathologisches Ansprechen nach neoadjuvanter Therapie als einziger unabhängiger Faktor für ein besseres OS, DFS und DMFS identifiziert.

Höhere Raten schwerer Wundkomplikationen wurden in der Gruppe der neoadjuvant behandelten Patienten nachgewiesen (ohne statistische Signifikanz). Risikofaktoren für schwerwiegende Wundkomplikationen wurden analysiert. Höhere Raten schwerer Wundkomplikationen wurden bei Weichteilsarkomen in der unteren Extremität beobachtet (insbesondere postoperative Serome und Wundheilungskomplikationen). Eine höhere Abszess- und Fistelrate wurde bei retroperitonealen Weichteilsarkomen nachgewiesen. Diabetes wurde als einer der wichtigsten Risikofaktoren für schwerwiegende

Wundkomplikationen identifiziert (jedoch nur für infektassoziierte Komplikationen). Trotz relativ hoher Raten schwerer Wundkomplikationen in der Gruppe der mit neoadjuvanter Therapie behandelten Patienten, zeigte sich kein Einfluss der schweren Wundkomplikationen auf die onkologischen Ergebnisse für diese Gruppe.

Aufgrund methodischer Einschränkungen und des retrospektiven Designs wurden Spättoxizitäten mit Ausnahme von pathologischen Frakturen und Osteonekrose nicht analysiert. Alle Patienten, bei denen eine pathologische Fraktur auftrat, wurden mit einer zusätzlichen Chemotherapie behandelt. Darüber hinaus wurde in der Gruppe der mit sequentieller Chemotherapie behandelten Patienten eine statistisch signifikant höhere Rate an pathologischen Frakturen festgestellt, was die Rolle der Chemotherapie als Risikofaktor für die Entwicklung einer pathologischen Fraktur möglich macht.

In Anbetracht der onkologischen Ergebnisse, der Verteilung der wichtigsten Wundkomplikationen und ihres Einflusses auf die onkologischen Ergebnisse, erscheint es im Allgemeinen empfehlenswert, eine neoadjuvante Therapie bei Hochrisiko Weichteilsarkoma anzustreben. Diese Empfehlung gilt insbesondere für retroperitoneale, pelvine und abdominale Weichteilsarkome, bei denen eine hohe Dosis der postoperativen Strahlentherapie aufgrund von Einschränkungen der gefährdeten Organe häufig begrenzt ist. Die endgültige Entscheidung über die optimale Behandlung sollte jedoch unter Berücksichtigung verschiedener Patientenmerkmale und klinischer Tumoreigenschaften interdisziplinär getroffen werden.

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9 DECLARATION OF OWN WORK AND CONTRIBUTION

I declare that this thesis has been composed by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. The study was carried out in the Clinic for Radiation Oncology at the University Hospital Tübingen under the supervision of PD Dr. med. F. Eckert.

The study was designed in collaboration with PD Dr. med. F. Eckert. The data presented in this thesis were collected and evaluated by own work. Statistical analysis was carried out by me, according to the instructions of PD Dr. med. F. Eckert. All sections of the paper that use quotes or describe an argument or concept developed by another author have been referenced.

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Vlatko Potkrajcic

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11 ABBREVIATIONS

- AJCC: American Joint Committee on Cancer
- cm: Centimeter
- CT: Computed tomography
- DFS: Disease-free survival
- DMFS: Distant metastasis-free survival
- FNCLCC: French Fédération Nationale des Centres de Lutte Contrele Cancer
- G: Histological grade
- Gy: Gray
- HPF: High-power field
- IMRT: Intensity-modulated radiation therapy
- LC: Local control
- M: Distant metastasis
- mg: Milligram
- MRI: Magnetic resonance imaging
- MWC: Major wound complication
- N: Regional lymph nodes
- OS: Overall survival
- %: Percent
- R0: Negative surgical margins
- R1: Microscopically positive but macroscopically negative surgical margins
- R2: Macroscopically positive surgical margins
- STS: Soft tissue sarcoma
- T: Primary tumor
- T1: Tumor 1
- T2: Tumor 2
- Ta: Tumor a
- Tb: Tumor b

- TNM: Tumor, node, metastasis
- Vs: Versus

12 LIST OF TABLES

13 LIST OF FIGURES