Timing and Outcomes of Adjuvant Radiotherapy for Soft Tissue Extremity Sarcomas

A Retrospective Analysis of Recurrences and Complications

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Maike van der Hoek

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First reviewer: Univ.-Prof. Dr. med. Eleni Gkika

Second reviewer: Prof. Dr. Dieter Christian Wirtz

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From the Clinic of Radiotherapy and Radiation Oncology

Acting Director: Univ.-Prof. Dr. med. Eleni Gkika

For my parents

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List of abbreviations

3DCRT	3D conformal radiation therapy
adj.	Adjuvant
ASTRO	American Society for Radiation Oncology
BED	Biologically effective dose
CHT	Chemotherapy
CT	Computed tomography
CTV	Clinical target volume
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DpF	Dose per fraction
ESMO	European Society for Medical Oncology
EQD2	Equivalent dose in 2 Gy fractions
Fig.	Figure
G	Grade
GTV	Gross tumour volume
Gy	Gray (unit)
HR	Hazard ratio
IGRT	Image-guided radiation therapy
IMRT	Intensity-modulated radiation therapy
LC	Local control
N	Lymph node involvement within the TNM-classification
M	Metastases within the TNM-classification
MRI	Magnetic resonance imaging
neoadj.	Neoadjuvant
OS	Overall survival
PTV	Planned target volume
R	Resection status
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
STES	Soft-tissue extremity sarcomas

STS	Soft-tissue sarcomas
T	Size of the sarcoma within the TNM-classification
Tab.	Table
V0, V1	Not infiltrating, infiltrating the vascular system
VAC	Vacuum-assisted closure
VMAT	Volumetric-modulated arc therapy
WHO	World Health Organization

1. Introduction

1.1 Epidemiology and aetiology of soft-tissue sarcomas

Sarcomas are very rare mesenchymal tumours that make up a small portion of both adult and paediatric solid malignant tumours. In adults, they account for less than 1 % of all solid malignant tumours and for about 3 % of paediatric solid malignant tumours (Burningham et al., 2012; Dana-Farber Cancer Institute, 2022). The two main groups that are commonly distinguished between are sarcomas originating in bone tissue and soft-tissue sarcomas (STS) with the latter making up about 87.3 % of cases (Burningham et al., 2012). When looking at incidence numbers for the United States for the year 2022, 13,190 people are anticipated to be diagnosed with STS and 5,130 are anticipated to die due to STS (American Cancer Society, 2023). For Europe, the incidence rate of these tumours amounts to about 4 - 5/100.000 per year (Gatta et al., 2017). They primarily affect older adults with the incidence increasing with age and sarcomas becoming more prevalent in the age group of over 50 years old. (Burningham et al., 2012)

The group of STS encompasses about 80 different histological entities, as defined by the World Health Organization (WHO). The most prevalent subtypes among these are leiomyosarcomas and liposarcomas (Gronchi et al., 2021). In general, sarcomas can be found at any site in the body, but are particularly common in the extremities with a rate of 43 % (Deutsche Sarkom-Stiftung, 2020), hence soft-tissue extremity sarcomas (STES) being the focus of this dissertation.

Over the past several decades, various risk factors have been identified for the development of sarcomas, one of the main ones being radiation exposure, often iatrogenic, which patients received in order to treat a different tumour prior to their sarcoma diagnosis. This, along with exposure to chemotherapy (CHT), puts these patients at an increased risk for the development of sarcomas. The risk is further heightened by higher doses of radiation exposure and younger age at the time of exposure. (Virtanen et al., 2006)

Other risk factors consist of viral infections like with Epstein-Barr virus as well as specific genetic mutations and syndromes: Li-Fraumeni syndrome (mutation in the TP53 gene), Neurofibromatosis Type 1 (defects of NF1 gene), Werner's Syndrome (defects in the RECQL2 gene), Tuberous Sclerosis (defect in the TSC1/TSC2 gene) and retinoblastomas

(defects of RB1 gene) are all examples being linked to an increased risk for STS. Chronic lymphoedema, as well as certain chemicals like arsenic, chlorophenol, vinyl chloride and dioxin, were also found to pose risks. (American Cancer Society, 2018; Leitlinienprogramm Onkologie, 2022)

1.2 Diagnostics

Symptoms of STES can include but are not limited to the appearance of a lump or swelling that increases in size over time and can sometimes lead to pain if vital structures like nerves and blood vessels are impacted (Dana-Farber Cancer Institute, 2022). Some primary STES also affect bones in their vicinity during their growth causing them to break and a pathological fracture becoming the presenting problem.

The rarity of STES proves a challenge in accurately and promptly diagnosing the sarcoma on the basis of such symptoms alone which is why it has been proven that sarcomas should, if possible, be diagnosed and treated at high-volume treatment centres (defined as treating at least ten sarcomas per year). This is due to the higher level of experience and expertise available at these centres which has been shown to result in improved survival rates (Abarca et al., 2018) (see below). If the initial diagnosis happens to be made at a low-volume hospital patients are mostly referred as stated above.

For superficial tumours, ultrasound can be utilised as the initial imaging modality, but in order to confirm a diagnosis of malignancy, cross-sectional imaging should be requested with contrasted magnetic resonance imaging (MRI) being the imaging modality of choice. Alternatively, a computed tomography scan (CT) can lead to the diagnosis. Ideally, the resolution should be at least 0,5 mm x 0,5 mm with a slice thickness of 3 mm - 5 mm according to current guidelines and T1-weighted as well as T2-weighted and diffusion-weighted images are required. (Leitlinienprogramm Onkologie, 2022) This imaging is also crucial when planning possible resections, as preoperative imaging is required to plan surgical steps. The tissue composition of the STES affects the appearance on the abovementioned imaging modalities, depending on which histological subtype of STS is affecting the patient. It is imperative that these imaging studies be reviewed by an experienced radiologist to obtain an accurate diagnosis. However, it should be noted that histological certainty cannot be achieved solely from a CT or MRI scan.

Consequently, imaging should be accompanied by a biopsy and, subsequently, a pathological analysis. This biopsy should be carried out as a punch or incision biopsy and is relatively low-risk compared to an open biopsy. To minimise the risk of sarcoma cells contaminating the surrounding tissue, it is essential that the biopsy access pathway be removed during the sarcoma resection procedure. In the case of the tumour being smaller than three centimetres and there is a possibility that a definite resection with negative margins can be achieved immediately, an excision biopsy may be considered. (Leitlinienprogramm Onkologie, 2022) In some cases, where the sarcoma is found during a routine operation or is resected prior to obtaining a pathological diagnosis, tissue is sent to a pathology lab after the initial operation. Due to the diverse nature of the group of sarcomas, it is not uncommon for the tissue to be sent to a secondary laboratory for confirmatory testing. Sarcomas are sorted by their histological type defined by the WHO (newest edition: Soft Tissue and Bone Tumours, 5th edition, 2020) and put into three different categories: grade (G) 1 (well-differentiated), G2 (intermediate) and G3 (poorly-differentiated). In some studies, G2 and G3 both get sorted into a “high-grade” group. With tumour differentiation, mitotic count and necrosis rate the sarcoma can be sorted into the Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) rating. It is also possible to define the type of sarcoma by certain characteristic genetic abnormalities, for example, the MDM2/CDK4 amplification for atypical and highly-differentiated liposarcomas. (Leitlinienprogramm Onkologie, 2022)

In conclusion, the diagnostic foundation for determining appropriate treatment options for sarcomas includes radiologic imaging and the results of the biopsy as analysed by a pathology report.

1.3 Therapy of soft-tissue extremity sarcomas

The complexity of the treatment necessitates interdisciplinary collaboration among various medical specialities, which should be readily available at the selected hospital. The following medical specialities must collaborate to form an effective team: orthopaedic surgery, oncology, pathology, radiology, radiation oncology, rehabilitation and psychiatry (Siegel et al., 2015). Patients’ cases should be discussed in interdisciplinary conferences in order to be able to provide the best treatment plans and support. Patients’ due informed consent for the therapy regime is needed.

Over the years, a multi-modal therapeutic approach has been established and investigated, incorporating surgery, chemotherapy (CHT), and radiotherapy (RT). This has resulted in significant advancements in the treatment of sarcomas and an improvement in patient survival outcomes.

1.3.1 Surgery

One of the crucial components of therapy is the complete surgical removal of the sarcoma (classified as a so-called R0 resection). This is vital in order to decrease the recurrence rate and enhance OS (Dickinson et al., 2006; Gronchi et al., 2007; Novais et al., 2010; Trovik et al., 2000; Vraa et al., 2001). Thus, meticulous preoperative planning and imaging are imperative for effective preparation. When sarcoma treatment was being developed, a lot of patients underwent complete limb amputation in order to ensure complete sarcoma removal. Rosenberg et al. studied this in 1982 and found that this was not necessary, but could be avoided with a wide resection and subsequent irradiation therapy (Rosenberg et al., 1982). This resulted in fewer complications, better limb functionality and a higher quality of life after treatment had concluded. Since then, it has been repeatedly emphasised that limb-sparing, but complete (R0-rated) resections play a critical role in achieving successful treatment outcomes, including a reduction in the frequency of recurrences (Dickinson et al., 2006; Gronchi et al., 2007; Jebsen, 2013; Novais et al., 2010; Vraa et al., 2001). Amputation can still be necessary in cases where the sarcoma has already infiltrated nerves and blood vessels or when a life-threatening situation presents itself, but nowadays, limb-sparing approaches remain the standard. A comprehensive compartment resection may be required, involving the removal of a complete anatomical compartment defined as surrounded by one aponeurosis (Leitlinienprogramm Onkologie, 2022).

If the tumour is ≤ 3 cm or is superficial in nature, a primary R0 resection should be aimed for. In instances where this is not feasible, a second operation is necessary in order to guarantee complete tumour removal and with that mitigate the risk of local recurrences. Infiltrated bone or vessels should be removed as well. If the patient underwent a previous biopsy, tumour cells could have been displaced within the biopsy canal so that the resection should be inclusive of the biopsy site. Ideally, the wound should be closed in a manner that minimises tension in order to ensure quick healing and allow for the

subsequent application of adjuvant irradiation therapy. When tension-free closure is not possible, vacuum-assisted closure (VAC) can be employed to ensure proper wound healing. (Leitlinienprogramm Onkologie, 2022)

1.3.2 Chemotherapy

For sarcomas bigger than 5 cm and G2- and G3-rated sarcomas preoperative CHT is generally advised which should include an anthracycline-based regime (Leitlinienprogramm Onkologie, 2022). The goal is to reduce the original tumour mass as well as eradicate tumour cells that are too small to be seen on imaging and therefore could result in a successive R1-resection. Since sarcomas are a group composed of so many different histological entities, their chemosensitivity has also been the subject of studies. In one study by Gronchi et al. in 2017 (Gronchi et al., 2017), a preoperative “histotype-tailored chemotherapy regimen” failed to provide a significant benefit and was inferior to the standard chemotherapy regimen including epirubicin and ifosfamide. The benefit of that standard regimen was interpreted as being due to the preoperative nature of CHT that provided the actual benefit.

For the same group of high-risk sarcomas, adjuvant CHT may also be offered to the patient. While some studies have demonstrated a significant benefit from an anthracycline-based postoperative regimen (Pervaiz, 2008; Sarcoma Meta- analysis Collaboration (SMAC), 2000), however, in other studies, the same effect could not be clearly shown. As a result, adjuvant CHT is considered to be an optional treatment meant for high-risk sarcomas, according to the German sarcoma treatment guidelines (Leitlinienprogramm Onkologie, 2022).

1.3.3 Radiotherapy and its timing

The focus of this dissertation shall remain on the irradiation management of sarcomas, which is thoroughly described in the following. Radiotherapy is a critical component of modern STES treatment, particularly for high-grade (G2 and G3) sarcomas and if an R0 resection was not feasible (Leitlinienprogramm Onkologie, 2022) in order to mitigate the risk of future local recurrences. It is not generally used for G1-graded or R0-resected sarcomas. Although the benefits of radiotherapy have been proven and it is generally recommended by German (Leitlinienprogramm Onkologie, 2022), European (by ESMO

(European Society for Medical Oncology) (Gronchi et al., 2021) and American guidelines (by ASTRO (American Society for Radiation Oncology)) (Salerno et al., 2021), RT being an essential component of treatment is still vastly underused (Bagaria et al., 2014), providing the need for further studies.

As stated above, RT has been proven to provide a significant benefit, especially when it comes to reducing the risk of recurrences and, in turn, improving survival (Delaney et al., 2007; Yang et al., 1998; Zagars et al., 2003). This benefit remains proven true even though sarcomas are said to only be moderately irradiation sensitive, which is not dependent on their malignancy though (Leitlinienprogramm Onkologie, 2022). The alpha/beta ratio is used to reflect this concept. A higher alpha/beta ratio indicates a more radio-sensitive tumour, whereas a lower alpha/beta ratio implies greater benefits from fractionated RT. For sarcomas, the alpha/beta ratio is generally considered to be 4, which is regarded as low, although the heterogeneity of sarcomas should be taken into consideration. This number is largely based on studies of rhabdomyosarcomas and liposarcomas (van Leeuwen et al., 2018; Soyfer et al., 2013; Yang et al., 2021).

There are ongoing discussions about the timing and whether to apply RT in a neoadjuvant (neoadj.) or adjuvant (adj.) setting. Despite this question of adequate timing, both modalities have a significant benefit on the overall survival (OS) (Ramey et al., 2018). Neoadj. RT is highly effective with high rates of necrosis (> 90 % of tumour volume) being able to be induced which correlates with a high rate of local control (LC) (MacDermed et al., 2010). O'Sullivan et al. (2002) were able to demonstrate that with lower doses in preoperative RT compared to postoperative RT the outcome was not inferior, but, instead, resulted in fewer adverse effects. Another reason for this may be the tumour volume, which, preoperatively, is better to define due to preoperatively unchanged anatomy. Additionally, the irradiation volume does not need to include a whole surgery field as is the case with adj. RT. On the other hand, RT induces tissue damage that might be difficult for surgeons to navigate later on. Other studies were able to find a significant benefit of preoperative RT in reference to OS, metastatic-free survival and the possibility of complete R0-resections (Gingrich et al., 2017; Sampath et al., 2010).

Generally, resection is recommended three to eight weeks after the end of neoadj. RT in order to give irradiation-damaged tissue time to heal (Leitlinienprogramm Onkologie, 2022). This neoadj. therapy is the standard in the United States today and is clearly

recommended (“strong recommendation, moderate evidence”) by the ASTRO guidelines which cite similar effects but less permanent adverse events with neoadj. RT (Salerno et al., 2021) (see below) that Davis et al. described (Davis et al., 2005).
At the same time, postoperative RT three to six weeks after surgery still remains prevalent in Europe (Hoefkens et al., 2016) (2016), although neoadj. RT is described to be on the rise (Gronchi et al., 2021). The German guidelines recommend RT in general, while not clearly favouring one option over the other, although stating that there might be a benefit to the survival of neoadj. RT based on O’Sullivan et al.’s findings (Leitlinienprogramm Onkologie, 2022; O’Sullivan et al., 2002). The aforementioned studies suggest a trend towards the preoperative irradiation approach, however, a clear resolution to the question of timing proven in realistic clinical settings remains to be found.
Nevertheless and even if the patient already underwent neoadj. RT, postoperative RT remains recommended for high-risk patient groups, as it provides benefits for high-grade sarcomas or positive resection margins in order to reduce the risk of recurrences.
An intraoperative boost is not standard in the treatment of sarcomas but can be made use of in the case of a probable non-complete resection, meaning R1- or R2-classified (Leitlinienprogramm Onkologie, 2022).

1.3.3.1 Technique

There are two prevalent and recommended techniques for treating STES with RT: intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) with the latter being a specialised delivery method of IMRT (Herman et al., 2013). IMRT is a technique of external beam RT that was developed in the early 2000s. It is based on a 3D model of the sarcoma, that was determined in so-called planning CTs or MRIs resulting in a predefined target volume (gross tumour volume (GTV)). This enables radiation beams from multiple angles to be focused on the target volume and not on healthy surrounding tissue. IMRT enables the subdivision of each beam into smaller units, referred to as beamlets, which allows for the definition of individual intensity levels, enabling the delivery of varying radiation intensities to specific regions of the tumour. Subsequently, other healthy tissue surrounding the sarcoma can be spared more successfully resulting in high “target conformity”. By defining dose limits for surrounding tissues, one can accurately prescribe a certain amount of the radiation dose to the tumour,

surrounding margins and adjacent tissue and organs. (Taylor and Powell, 2004) This is made possible by moving so-called multi-leaf collimators, which shape the beams to their desired field and intensity. Static modes of delivery include the “sliding window technique” with which the multi-leaf collimators continuously move to create an irradiation pattern and the “stop-and-shoot” method that stops the collimators at different positions to deliver irradiation (Herman et al., 2013).

Since 2007, VMAT has been utilised as well, which constitutes a dynamic IMRT delivery method in which the gantry is rotated continuously around the patient at 360° while applying continuous irradiation. Radiation beams can be constantly manipulated individually in their intensity by multi-leaf collimators constantly in motion. The rotation speed, the aperture and the dose rate are all able to be controlled so as to achieve high conformity in less time than IMRT. (Teoh et al., 2011)

Both methods, VMAT and static IMRT, are able to spare healthy surrounding tissue effectively, minimising the likelihood of adverse events. This is supported by the immobilisation of the patient in order to ensure accurate and reproducible positioning.

Generally, different types of irradiation fields are distinguished from one another, which are graphically illustrated in Figure (Fig.) 1: Shown are the gross tumour volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV). The GTV encompasses the macroscopic sarcoma volume as can be seen in the preoperative imaging. From that, the CTV gets calculated to account for microscopic tumour cell spread. For sarcomas, this is recommended to be the perimeter of the GTV plus 1.5 cm in the radial direction, meaning perpendicular to the direction of the surrounding muscle, and 3 cm (CTV1) in the longitudinal direction, including oedema surrounding the sarcoma, as well as the biopsy canal or the surgical field and scar. For a dose increase as described below, the latter gets reduced to 2 cm (CTV2). Despite the immobilisation of the patient, a security margin is added in order to allow for inaccuracies due to movement and beam alignment. This normally includes the CTV with an extra margin of 5 - 10 mm, although this relies on regular guidance by imaging. (Leitlinienprogramm Onkologie, 2022; Salerno et al., 2021)

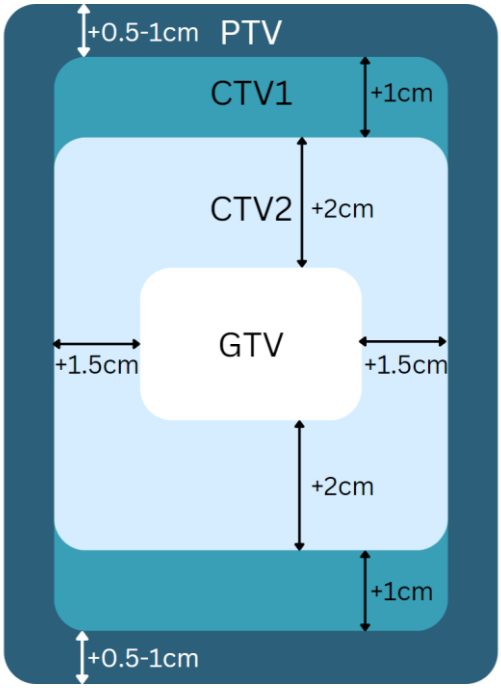


Fig. 1: Graphic illustration of the irradiation volumes with margins (Leitlinienprogramm Onkologie, 2022; Wang et al., 2015). GTV = gross tumour volume, CTV = clinical target volume, PTV = planning target volume.

These recommendations are based on the RTOG-trials: when those security margins for RT were used and also reduced depending on sarcoma size (≥ 8 cm: CTV + 3 cm longitudinal, + 1.5 cm radial; < 8 cm: CTV + 2 cm longitudinal, + 1 cm radial), Wang et al. experienced good local control with all recurrences occurring within the 95 % isodose. Also, this resulted in fewer late adverse events which indicated the benefit and safety of those close margins (Wang et al., 2015).

1.3.3.2 Dose

For neoadj. RT, 50 Gray (Gy) in 25 fractions, meaning 2 Gy per fraction (dose per fraction, DpF) within a time frame of five weeks is generally recommended. For postoperative RT, it is either the same amount of irradiation or 50.4 Gy in 28 fractions (1.8 Gy DpF). If following an adj. RT regime, an additional 10 to 16 Gy can be added to the clinical target volume (CTV2) depending on the resection margins meaning the total dose comes to lie between 60 - 66 Gy. (Leitlinienprogramm Onkologie, 2022; Salerno et al., 2021) Noticeably, postoperative doses are higher than preoperative doses, which the various adverse effects (discussed below) have been attributed to. These elevated doses are

based on the finding that local control was improved by postoperative irradiation doses exceeding 64 Gy compared to doses of less than 64 Gy (Delaney et al., 2007; Zagars et al., 2003).

When considering the manner in which to fractionate the radiation dose, there are hypofractionated and hyperfractionated methods available. For hypofractionation, this is considered to be the case if single doses consist of more than 2.2 Gy according to Roohani et al. (2022). When applying 5 x 5 Gy doses preoperatively resulting in 25 Gy of total irradiation, some phase-II trials discussed in Roohani et al.'s literature review found similar local control rates with no increase in the rate of adverse events described below. As stated above, the alpha/beta ratio of sarcomas is considered to be 4, which means that they prove to be highly susceptible to higher single doses. Additionally, this hypofractionated irradiation modality leads to a shorter treatment time which could increase treatment compliance and also means that more patients can be treated in the same amount of time. However, phase-III studies are necessary to further establish these findings and put them into perspective. (Roohani et al., 2022) For adjuvant therapy, a hypofractionated approach seems to work as well, showing good local control with a short treatment time (Soyfer et al., 2013).

1.3.3.3 Adverse events related to radiotherapy

Due to the particular anatomy that comes with treating sarcomas of the extremities and the high irradiation doses mentioned above, particularly for adj. RT, it is important to address the potential side effects.

Prevalent are irritations and damage to the particular area of skin that received radiation, for example, radiation dermatitis with erythema (29.1 %), skin induration (46.8 %) desquamation (6.3 %) and even skin necrosis. Sometimes, the skin will suffer from hyperpigmentation after radiation (17.7 %). Further possible side effects are limb oedema (63.3 %) resulting in swelling and tenderness of the affected area, pain (43.0 %) and neuropathy (17.7 % sensory, 7.6 % motor), as well as general side effects like nausea (8.9 %) and fatigue (27.8 %). Incidences are given in parentheses according to the above-named 2015 trial by Wang et al. (2015) in which the reduced security margins were successfully tested.

It also has to be noticed, that radiation treatment can lead to secondary cancers as described above in the aetiology of sarcomas.
O'Sullivan et al. (2002) found that preoperative RT leads to more wound complications with surgery compared to adj. RT (35 % vs. 17 %). This included secondary operations or invasive procedures for wound care, readmission due to wound complications or deep packing of the wound for more than 120 days. Hence, limb functionality after six weeks was better in the adj. RT group, which obviously has a positive impact on the patient's quality of life. For example, Götzl et al. (2019) reported that quality of life was significantly worse after neoadj. RT after major complications occurred in 28 % compared to not having undergone RT. It has to be kept in mind though, that RT is used for more high-risk tumours which could be a major confounder.
When looking at late radiation toxicity a couple of years later though, the group that had received preoperative radiotherapy compared more beneficially: morbidities studied were subcutaneous fibrosis, joint stiffness and oedema at the 2-year mark after having gone through RT. Results showed a trend that these morbidities were worse with adj. RT. (Davis et al., 2005) Given the permanency of these morbidities associated with adj. RT, which is more pronounced than the acute wound complications that accompany neoadj. RT, the utilisation of postoperative RT has witnessed a decrease. Consequently, neoadj. RT has emerged as the method of choice and is also recommended by the American guidelines.
In order to prevent adverse effects, high target conformity has been strived for which has been made possible with techniques like IMRT (and VMAT) described above, which multiple studies have shown (Folkert et al., 2014; O'Sullivan et al., 2013). Also, the reduced security margins in Wang et al. (2015)'s study decreased late toxicity endpoints like more severe subcutaneous tissue fibrosis, joint stiffness and oedema: Wang et al. found a rate of 10.5 % compared to 37 % from Davis et al. (2005)'s study.

1.3.5 Other therapy options: immunotherapy and targeted therapies

There are also other therapy modalities of subordinate importance, for example, regional deep hyperthermia in which the malignant tissue gets heated up to 40 - 43 °C by electromagnetic waves. This is normally combined within a neoadj. CHT and can improve therapy response, local control and even overall survival. It is only a feasible course of action to consider for high-risk sarcomas, though.

Isolated limb perfusion is a very technically advanced method making use of Melphalan and Tasonermin which is a recombinant human necrosis factor α-1a. In order to be able to achieve isolated extremity perfusion, the vascular system has to be surgically isolated in order to prevent leakage of the chemotherapeutics into other anatomical regions of the body. Due to its toxicity, this approach is exclusively recommended for extremity tumours that would warrant limb amputation. (Leitlinienprogramm Onkologie, 2022) Similarly to regional deep hyperthermia this approach is not a standard method and may not even be available at the chosen medical treatment facility.

1.2 Mortality rates, prognostic factors and recurrence rates

Improved diagnostics and treatment modalities have led to a decline in mortality rates, resulting in 5-year survival rates of approximately 70 % for STES. However, such survival rates are contingent upon the treatment facility, as it could be shown that high-volume treatment centres tend to achieve higher survival rates compared to low-volume treatment centres: In their study, Abarca et al. (2018) defined high-volume centres as those that treat ten or more sarcomas per year. These institutions exhibited a 5-year survival quota of 72.7 %. It is worth noting that this study excluded metastatic disease (M1) as well as underage patients. In studies that included M1-sarcomas, survival rates dropped considerably to around 50 % (Soydemir et al., 2020) and such rates tend to vary widely depending on the therapeutic regimen employed.

Prognostic factors for survival are overwhelmingly rooted in the histological tumour differentiation and timing of discovery with a higher histological grading and the presence of recurrences or metastases resulting in worse outcomes. Older patients also presented with worse outcomes. When looking at treatment choices that can be made in order to increase survival, wide surgical resection and the application of irradiation as well as high irradiation doses were found to be beneficial to patients. (Cai et al., 2013; Gatta et al., 2017; Jebsen et al., 2008; Soydemir et al., 2020) Due to recurrences being one of the predictors of worse survival, an effort has been made in order to decrease the recurrence rate and increase disease-free survival (DFS) (defined by the absence of recurrences or death). As stated above, one of the most important factors in preventing recurrences, especially local ones, is a complete R0-classified resection which lowers the risk of a local recurrence drastically (Pisters et al., 1996). When only looking at positive R1-classified

margins the rate of local recurrences was found to be between 15 % and 35 % for STES and able to be reduced by radiotherapy with doses > 64 Gy. (Delaney et al., 2007; Leitlinienprogramm Onkologie, 2022) Most recurrences appear within two years laying the base for the implementation of regular follow-up visits for patients (Eilber et al., 2005).

1.5 Scope of this thesis

Given the established significance of an R0 resection and subsequent radiation therapy in managing STS discussed above, particularly in terms of reducing the likelihood of recurrences, this thesis will aim to explore the outcomes of irradiation therapy in real-world clinical settings and provide insights into the practical implementation of especially postoperative RT. As the past decade has seen an increase in research efforts aimed at understanding the efficacy of these treatment options for STES, it has become imperative to explore how this research has affected the practical clinical context.

Within the scope of this dissertation, we intend to investigate the following outcomes: overall disease outcome, meaning overall survival, recurrences and local control. Most importantly, the timing of postoperative RT and the above-mentioned adverse effects associated with this treatment modality are also key areas of interest. Specifically, we aim to evaluate the impact of postoperative RT timing on the above-mentioned outcomes, as well as the occurrence and severity of treatment-related adverse effects.

Additionally, wound complications that occurred in this patient collective are to be accessed as well. Another key objective of this study is to identify prognostic factors that can predict the disease-specific outcomes and side effects or complications associated with RT and surgery. Among the factors to be examined is the total irradiation dose of adjuvant RT.

This is an essential step in evaluating the efficacy of adj. RT, as well as establish the optimal timing of this treatment option. By examining the impact of postoperative irradiation therapy itself and its timing on patient prognosis and therapy, these findings may inform future treatment strategies and ultimately enhance the quality of care for patients. Additionally, through the identification of patient populations at increased risk of adverse effects, treatment plans may be optimised in order to improve patient outcomes and minimise potential harm.

2. Materials and methods

Given the practical clinical relevance of this research, parts of it have been published in Koeksal et al. (2022) which is used to identify this research in tables that appear within the results below. Tables and figures already used within the abovementioned paper are adequately marked and cited.

2.1 Patient data and data acquisition

This study was designed as a retrospective cohort study. To determine the sample size required to achieve a statistically significant result showing correlation, a moderate coefficient of correlation of 0.5 was chosen, along with a significance level alpha of 0.05 and a desired power of 0.9. This analysis yielded a necessary sample size of 38 patients, which was deemed feasible.

From November 2021 onwards until February 2nd the next year, patient data from the University Hospital of Bonn was acquired and accessed. To be eligible for this study, patients must have received treatment or undergone diagnostic procedures at this hospital within the last ten years meaning after November 2011. Sources for the data were the clinical information system ORBIS (version 08043901.03000.DACHL; DH Healthcare GmbH, Bonn, Germany), the radiology information systems MEDOS (version 9.3; NEXUS AG, Donaueschingen, Germany), the oncology information system ARIA (version 15.05.56.01; Varian Medical Systems, Inc., CA, USA) and the German Centre for Cancer Registry. The latter was only used to acquire accurate death dates. All data was treated confidentially and patients' identities were anonymised through the use of assigned numbers after initial data acquisition. Additionally, duplicates were identified and excluded once data acquisition was complete.

As graphically displayed in Figure 2, after finding 580 patients that matched the search for “sarcoma” (581 including one duplicate), it was decided to narrow down the patient collective to patients that were diagnosed with soft-tissue sarcomas (STS) (289) and more specifically, a STES which affected 106 patients. Patients with STS of the head and neck, trunk or abdomen were excluded. Since the focus of this dissertation shall be RT and its toxicities, the patient selection flow chart has been designed to represent just that: a

subgroup of 40 patients that underwent postoperative RT was formed out of 46 that had received RT, either in a neoadj., definite or adj. manner.

Patients with sarcomas of other locations for example head and neck, trunk or abdomen and sarcomas primarily occurring in the skin or bones were not included in the analyses and excluded from this study which is also demonstrated in the following graphic.

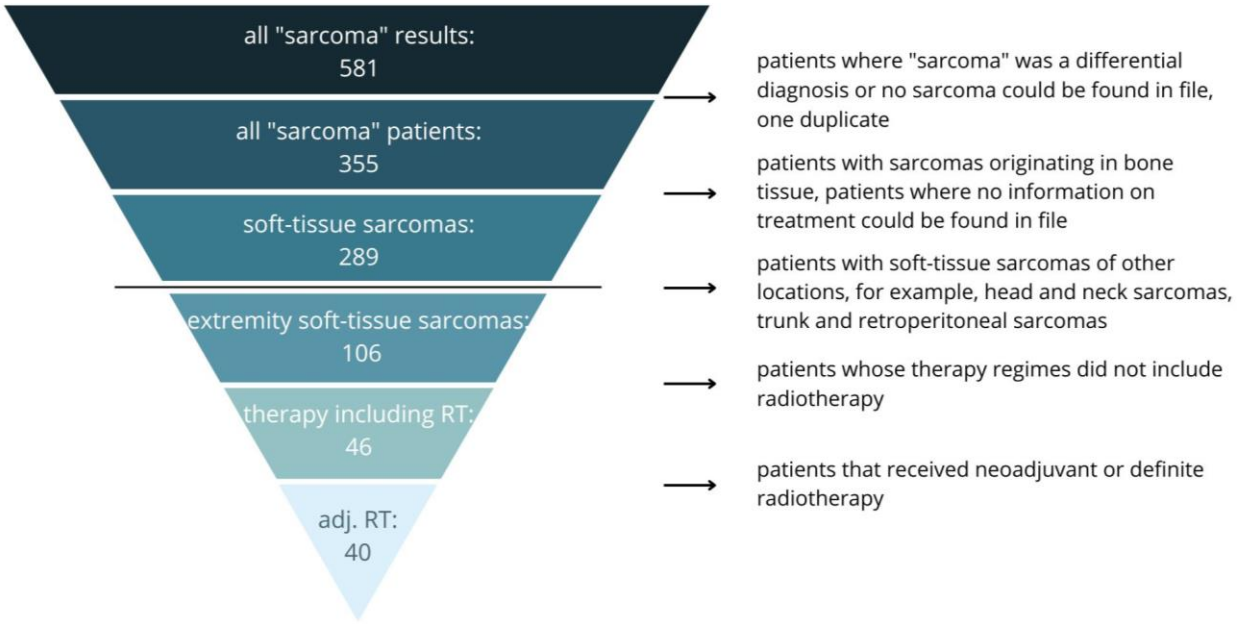


Fig. 2: Selection of patients. Exclusion criteria are listed on the right-hand side. Adapted and expanded from Koeksal et al. (2022).

In order to be able to establish the patient's age, the date of histological diagnosis was chosen as point of reference. If no exact date for the original histological report could be acquired, the middle of the month or the middle of the year was used to calculate age to minimise statistical error. This was not done though for all other time-sensitive endpoints to not impede accuracy.

Data that was collected included the date of birth, sex, nationality and date of diagnosis. Sarcoma-specific data collected included the location of the sarcoma, joint involvement, the histological type and grading, size, and disease stage based on the TNM-classification, as well as lymph vessel (L0 vs. L1) and vascular invasion (V0 vs. V1). In order to be able to group the patients, it was investigated whether patients underwent any neoadj. therapies (CHT or RT) and, if they did have CHT, what substances were used. The dates for the neoadj. therapies were also noted. For RT, categories included the

starting date, the dose, DpF, irradiation technique and the biologically effective dose (BED) and the equivalent dose in 2 Gy-fractions (EQD2). The latter two were estimated with the alpha/beta-ratio being 4, with the reasons stated above. When it came to surgery, it was important whether or not they had surgery at all and at what date, if there had to be a second resection, the resection status (sorted into R0, R1, and R2), the exact margin according to the pathological report and whether the wound was closed directly or with flap closure. For the adj. therapies, whether CHT or RT, the same data as referenced for neoadj. modalities was collected.

In order to be able to calculate disease-outcome endpoints, importantly, the date of a recurrence, if any, was also established from the date of imaging, as well as a date of last follow-up and death if this occurred. For local recurrence rates, patients who underwent a limb amputation were excluded. Patients whose data was missing on certain points were excluded casewise for only that particular analysis.

Adverse events associated with adjuvant RT were identified through a review of clinical notes and specific RT-related check-up documentation. To classify these events, the Common Terminology Criteria for Adverse Events (CTCAE) (National Cancer Institute, 2017) was used. The CTCAE is a standardised tool for grading the severity of adverse events in clinical trials and is implemented in clinical practice. Ratings range from grade 1 to grade 5 with the latter indicating the most severe outcome. Adverse events rated as grade 2 or higher are generally considered to be more severe and clinically significant, as they may require clinical intervention or management. In contrast, grade 1 events are typically mild or transient in nature. For this dissertation, the CTCAE version 5.0, published on November 27th of 2017 (National Cancer Institute, 2017) was used. The descriptions of the different ratings sorted by the relevant adverse events that occurred in the patient collective and directly cited from the CTCAE version 5.0 are provided in the following Table (Tab. 1). Information on the grade descriptions of limb oedema, joint stiffness, deep tissue fibrosis, radiation dermatitis, skin hyperpigmentation, pain, fatigue and RT-related colitis is provided. Generally, symptoms range from mild discomfort to very severe which can include death for some symptom classifications.

Tab. 1: Relevant adverse events to this dissertation with their CTCAE ratings. Grade descriptions cited from CTCAE version 5.0 (National Cancer Institute, 2017). ADL = activities of daily life, ROM = range of motion, BSA = body surface area.

Oedema limbs	
Grade 1	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection
Grade 2	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL
Grade 3	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL
Grade 4	-
Grade 5	-
Joint range of motion decreased	
Grade 1	<=25% loss of ROM (range of motion); decreased ROM limiting athletic activity
Grade 2	>25 - 50% decrease in ROM; limiting instrumental ADL
Grade 3	>50% decrease in ROM; limiting self care ADL
Grade 4	-
Grade 5	-
Fibrosis deep connective tissue	
Grade 1	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)
Grade 2	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL
Grade 3	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL
Grade 4	Generalized; associated with signs or symptoms of impaired breathing or feeding
Grade 5	Death

Radiation dermatitis	
Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
Grade 3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
Grade 4	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Grade 5	Death
Skin hyperpigmentation	
Grade 1	Hyperpigmentation covering <10% BSA; no psychosocial impact
Grade 2	Hyperpigmentation covering >10% BSA; associated psychosocial impact
Grade 3	-
Grade 4	-
Grade 5	-
Pain	
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self care ADL
Grade 4	-
Grade 5	-
Fatigue	
Grade 1	Fatigue relieved by rest
Grade 2	Fatigue not relieved by rest; limiting instrumental ADL
Grade 3	Fatigue not relieved by rest, limiting self care ADL
Grade 4	-
Grade 5	-

RT colitis	
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Abdominal pain; mucus or blood in stool
Grade 3	Severe abdominal pain; peritoneal signs
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

If the classification was not documented, the severity of side effects was estimated from given keywords, such as “minimal”, “moderate” and “severe”. Each unfavourable incident that occurred during the treatment documented in the patient files was noted for statistical analysis and a thorough search of every document in the patient's file was conducted. Routinely, patients underwent follow-up assessments to monitor their RT-related well-being so that these documents could be accessed. However, due to the Covid-19 pandemic, some of these follow-up appointments were conducted via telephone. In cases where patients failed to attend their scheduled RT-specific follow-up appointments, information about their adverse effects had to be extracted from clinical documentation that was done by non-radiology oncologists.

For wound complications, the criteria from O’Sullivan et al. (2002)’s trial were used as an orientation: secondary surgeries or invasive procedures, as well as prolonged dressing changes and infections within 120 days counting from the surgery date. Information regarding alternative methods for wound closures was also documented, including direct closure or the use of flaps obtained from a donor site to achieve a tension-free closure. It was also recorded if the wound was closed by the use of a vacuum drainage system (VAC). Furthermore, incidences of amputations were also noted.

Upon reviewing the standard treatment procedures for patients in this clinical setting, it was determined that the University hospital meets the criteria to be classified as a high-volume sarcoma centre, as previously defined. The current established guidelines for treating STES were strictly adhered to in this patient cohort, which spanned from 1997 to 2021 in terms of the dates of diagnosis. Given that this is a European treatment centre, radiation therapy was primarily administered postoperatively. Out of the 46 cases in which

patients underwent radiation therapy, 40 of them received adjuvant RT. The normofractionated approach was employed, mostly using a dosage of 1.8 Gy or 2 Gy as the DpF. Doses were covering 99 % of the CTV and 95 % of the PTV. The irradiation dose encompassed 95 % to 107 % of the originally prescribed irradiation dose. Current Radiation Therapy Oncology Group (RTOG) guidelines were used when it came to determining CTV and PTV margins. Over the years, the use of IMRT has progressively increased and is now the prevalent irradiation technique for the treatment of STES at this hospital. The first patient in the patient cohort that underwent RT, received this RT for the treatment of their STES in 2008.

2.2 Statistical methods

For data collection, Microsoft® Excel® was used, and for statistical analyses, IBM®'s SPSS® (version 28.0.1.1; IBM Corp., Armonk, NY, USA) was applied. Primarily, all data is laid out using descriptive statistics in absolute numbers and relative percentages. This includes the description of the patient collective, the characteristics of their sarcomas, the details of their therapy regimes and the adverse events. Importantly, the number of recurrences, especially local ones, is also pointed out.

Furthermore, the influence of different factors on irradiation therapy-related toxicity was evaluated using binary logistic regression. To facilitate this analysis, a binary variable was derived by categorising patients as either having experienced side effects or not, having experienced side effects of a certain grade or not, or having experienced a particular side effect or not. The same approach was used to evaluate surgery-related complications. A p-value of < 0.005 is generally considered to indicate a significant result.

Secondly, patients' overall survival (OS) was analysed concerning the whole patient collective of STES which is 106 patients, as well as for only the group of postoperatively irradiated patients. The OS was defined as the amount of time in months that patients could be followed-up starting from their diagnosis to the point of last follow-up or death. With that, the exact reason for their death was not taken into account. Since OS is a time-sensitive endpoint, Kaplan-Meier analysis was chosen which censors cases if patients are being lost to the follow-up, but the event "death" has not occurred, meaning they are still alive at the last follow-up date. This is paired with the log-rank test enabling grouping patients by characteristics and juxtaposing them by comparing their OS. Since Kaplan-

Meier analyses cannot account for multiple predictors or non-binary predictors, Cox proportional hazard regression was chosen to find the impact of polytomous or continuous variables. As with binary logistic regression, as statistically significant are regarded log-rank and Cox regression results with a p-value of < 0.05.

The same was done with the other time-sensitive endpoints like disease-free survival (DFS) and local control (LC). As common with literature (Cai et al., 2013; Lee et al., 2018), the former was defined as the time in months from diagnosis until either death or a recurrence of any location. LC focused specifically on endpoints including recurrences in the same location as the original sarcoma or patient death.

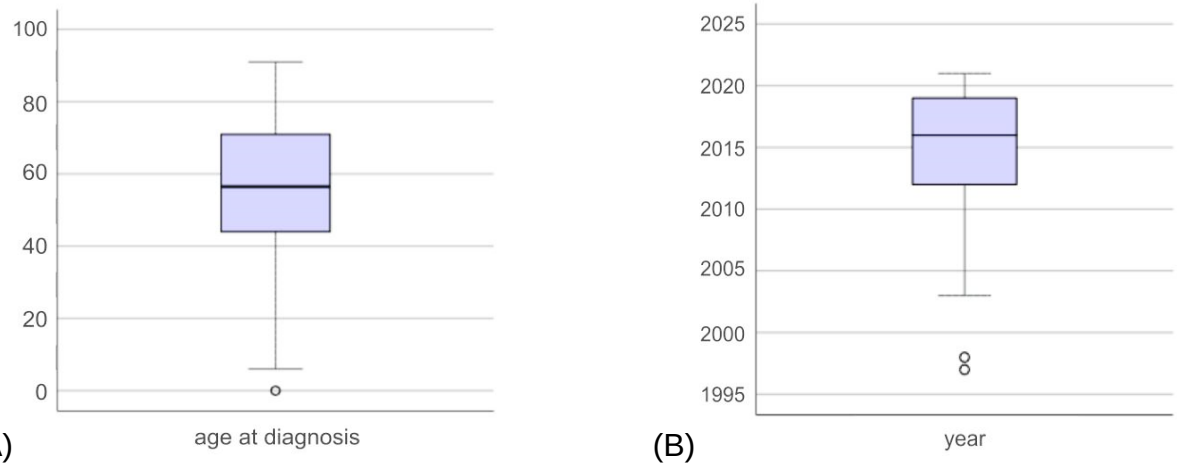
If appropriate, comparison group sizes are given in parentheses with the matching p-value.

3. Results

3.1 The patient collective - a statistical description

A cohort of 106 patients afflicted with a STES were successfully enrolled in the study. The follow-up period spanned a mean duration of 26 months, with an overall average of 41.28 months, encompassing a range of 1 to 288 months. The latter time value can be attributed to certain outlier patients whose onset of care was delayed, either for diverse diagnoses or to address treatment-related complications from their sarcoma.

The following numbers describe the patient collective of 106 STES patients. If numbers pertain to a certain subgroup it is made clear beforehand. As illustrated in Figure 3, the time of diagnosis spanned from 1997 to 2021, with a notable surge of diagnoses recorded in 2020 (12.3%) (Figure 3 A). Notably, the vast majority of diagnoses were established in recent years. The average age at diagnosis for patients was 55 years, as depicted in Figure 3 B. Within the entire cohort, there was no discernible disparity between male and female patients, with a near-even distribution of 53.8% and 46.2%, respectively. The average age of male patients was 56.35 years, while their female counterparts were slightly younger, with an average age of 53.82 years.



(A) (B)

Fig. 3: Boxplot graphs of (A) patients' age distribution and (B) distribution of the years of diagnosis. Outliers are marked with circles.

The majority of sarcomas were diagnosed on the leg (80.2 %), more precisely on the thigh (48.1 %) as can be seen in Figure 4 which depicts the spatial distribution of sarcomas within the patient collective (Figure 4 A). The second most prevalent sarcoma cluster was

observed in the hip and buttock region, comprising 18.9 % of cases. In contrast, sarcomas of the upper extremity were substantially less common, accounting for 19.8 % of cases, with 10.4 % and 9.4 % of sarcomas diagnosed on the upper and lower arms, respectively. Figure 4 B delineates the distribution pattern within the subset of patients who received adj. RT, revealing a similar predominance of sarcomas in the thigh (57.5 %). Furthermore and across both groups, the majority of sarcomas did not infiltrate the joint (38.6 %).

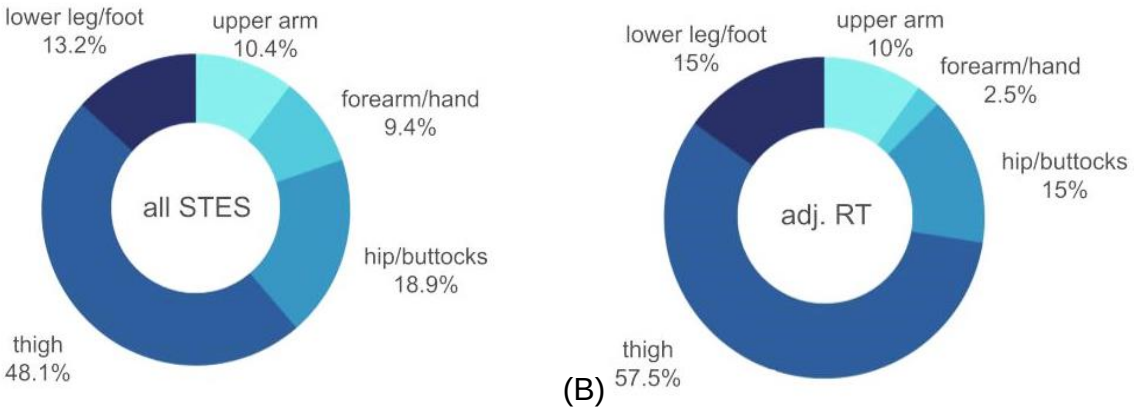


Fig. 4: Location distribution of sarcomas for (A) all 106 patients and (B) for the group of 40 patients that received postoperative radiotherapy (adj. RT). Adapted from Koeksal et al. (2022).

Undifferentiated (pleomorphic) sarcoma was the most frequent histological subtype observed, accounting for 37.7 % of cases. The subsequent most prevalent sarcomas were synovial sarcomas (11.3 %) and liposarcomas (7.5%), as illustrated in Figure 5. Notably, the subset of patients who received postoperative RT exhibited a higher incidence of liposarcomas (15.0 %) compared to those who did not (7.5 %).

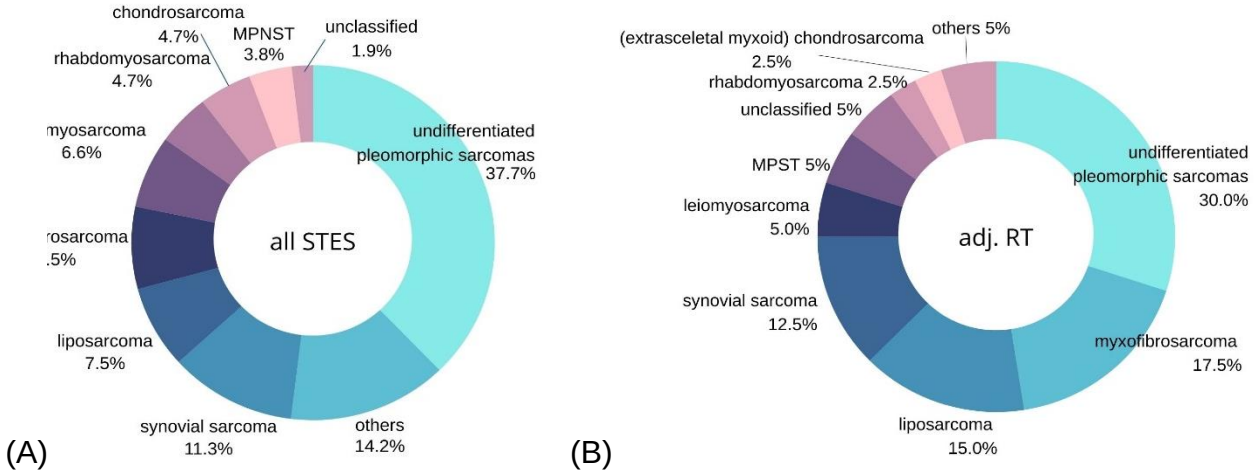


Fig. 5: Histological distribution of sarcomas for (A) all 106 patients and (B) for the group of 40 patients that received postoperative radiotherapy (adj. RT). Adapted from Koeksal et al. (2022).

For the whole of the patient collective, most sarcomas histologically were classified to be in the high-grade/poorly-differentiated G3 group (21.7 %), followed by the group of G2-rated sarcomas (intermediate) (16.0 %). G1-rated sarcomas accounted for only 8.5 % of all sarcomas. It has to be noted, that for some sarcomas, no histological grading could be acquired from the clinical records (21.7 %). This phenomenon was observed with greater frequency among patients whose diagnoses were established in earlier years, and potential reasons for this are explained below, within the purview of this study's limitations. The same limitation was apparent with regard to the parameter of sarcoma size. Specifically, 64.2 % of sarcomas had an average diameter greater than 5 cm, whereas only 18.9 % of STES were measured to be smaller than or equal to 5 cm. Tumours that did not fit into either of these categories constituted 16.98 % of cases.

Within the entire patient cohort, a total of 31 deaths were recorded, corresponding to a mortality rate of 29.2% in reference to the number of all included patients. Notably, 12.3% of patients included in the study succumbed to metastatic disease, while no deaths were attributed to localised disease. Due to the unavailability of complete death records for 17 patients, only the dates of death were obtainable from a cursory inquiry of the German Cancer Registry. One patient passed away due to a severe infection that was acquired during chemotherapy and resulting neutropenia. This was subsequently defined as “death from treatment complication”.

Table 2 summarises the key descriptive statistics pertaining to the patient cohort as outlined above. This includes statistical descriptions for both the entire patient cohort as well as for the subgroup that received postoperative RT, with the latter provided to highlight any similarities or differences. Notably, the rates for the irradiated group were found to be very similar to those of the entire patient cohort, with the exception of the aforementioned variables.

Tab. 2: Patient and sarcoma characteristics. MPNST = malignant peripheral nerve sheath tumour, adj. RT = adjuvant radiotherapy, n = total number of patients included. Numbers for the whole of the patient collective, as well as for the group that received adj. RT are provided in separate rows. Adapted and expanded from Koeksal et al. (2022).

Characteristic	all (106)	% (n = 106)	adj. RT (40)	% (n = 40)
Age				
Mean (years)	55.18		56.80	
Range (years)	0 - 91		22 - 85	
< 70 years	77	72.6 %	29	72.5 %
≥ 70 years	29	27.4 %	11	27.5 %
Sex				
Male	57	53.8 %	17	42.5 %
Female	49	46.2 %	23	57.5 %
Location of sarcoma				
Upper extremity	21	19.8 %	5	12.5 %
Upper arm	11	10.4 %	4	10.0 %
Forearm/hand	10	9.4 %	1	2.5 %
Lower extremity	85	80.2 %	35	87.5 %
Thigh	51	48.1 %	23	57.5 %
Lower leg/foot	14	13.2 %	6	15.0 %
Hip or buttocks	20	18.9 %	6	15.0 %
Joint infiltration				
Sarcomas infiltrating the joint	18	17.0 %	5	12.5 %
Sarcomas not infiltrating the joint	88	88.0 %	35	87.5 %

Characteristic	all (106)	% (n = 106)	adj. RT (40)	% (n = 40)
Histology				
Undifferentiated (pleomorphic) sarcoma	40	37.7 %	12	30.0 %
Synovial sarcoma	12	11.3 %	5	12.5 %
Liposarcoma	8	7.5 %	6	15.0 %
Myxofibrosarcoma	8	7.5 %	7	17.5 %
Leiomyosarcoma	7	6.6 %	2	5.0 %
Rhabdomyosarcoma	5	4.7 %	1	2.5 %
(Extraskeletal myxoid) chondrosarcoma	5	4.7 %	1	2.5 %
MPNST	4	3.8 %	2	5.0 %
Others	15	14.2 %	2	5.0 %
Unclassified	2	1.9 %	2	5.0 %
Histological grade				
Low-grade (G1)	9	8.5 %	3	7.5 %
Intermediate (G2)	17	15.1 %	10	25.0 %
High-grade (G3)	57	53.8 %	25	62.5 %
Unknown	23	21.7 %	2	5.0 %
Size (longest axis)				
≤ 5cm	20	18.9 %	6	15.0 %
> 5cm	68	64.2 %	31	77.5 %
Exact size unknown	18	17.0 %	3	7.5 %
Metastases				
No (M0)	57	53.8 %	31	77.5 %
Yes (M1)	22	20.8 %	4	10.0 %
Unknown	27	25.5 %	5	12.5 %
Deaths	31	29.2 %	9	22.5 %
Death from localised disease	0	0 %	0	0.0 %
Death from metastatic disease	13	12.3 %	4	10.0 %
Death from treatment complications	1	0.9 %	1	2.5 %
Death from other reasons / reason unknown	17	16.0 %	4	10.0 %

Descriptive statistics pertaining to the specific treatment modalities that were administered to patients during the course of their STES care are presented in Table 3 below. As previously mentioned, the three primary treatment modalities for sarcoma are surgery, CHT, and RT of which CHT and RT may be administered either before pre-surgery or post-surgery. Of 106 patients in the collective, 92 patients (86.8 %) underwent resective surgery and for most patients (64.1 %) a complete R0-rated resection could be achieved. 14 patients (13.2 %) did not undergo surgery, instead were either treated with definite CHT or RT or received palliative care. 39.6 % of patients received CHT, of which 24.5 % did so in a postoperative setting. 43.4 % underwent RT treatment with 40 patients receiving adj. RT compared with a group of only four patients that did so in a neoadj. manner. The average time between the start of neoadj. RT and surgery amounted to 62.25 days.

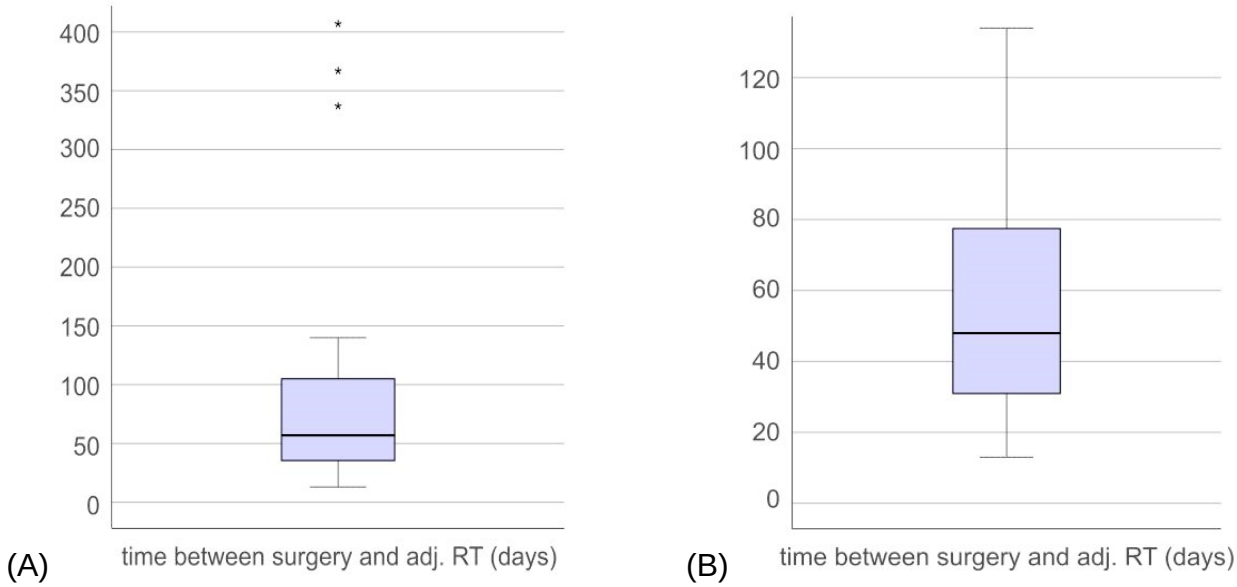
Therapy regime details for the adjuvantly irradiated group are also given in Table 3.1. All patients who received adjuvant RT underwent surgery prior to their irradiation treatment, but the details of surgery, such as margin status or flap closure rates, only differed slightly as can be observed below.

Tab. 3: Therapy regime details. n = number of patients, adj. = adjuvant, neoadj. = neoadjuvant, RT = radiotherapy, R0 = negative resection margins, R1 = microscopically positive resection margins, R2 = macroscopically positive resection margins. Numbers for the whole of the patient collective, as well as for the adjuvant radiotherapy group are provided in separate rows. Adapted from Koeksal et al. (2022).

Therapy regime details	**all**	**%**	**n**	**adj. RT (n = 40)**	**%**
Surgery	92	86.8 %	n = 106	40	100 %
Amputation	7	7.6 %	n = 92	0	0 %
Limb-sparing surgery	85	92.4 %	n = 92	40	100 %
Direct closure	64	75.3 %	n = 85	31	77.5 %
Flap closure	7	8.2 %	n = 85	3	7.5 %
R0	59	64.1 %	n = 92	22	55.0%
R1	22	23.9 %	n = 92	15	37.5 %
R2	5	5.4 %	n = 92	0	0 %
Margin status unknown	6	6.5 %	n = 92	3	7.5 %
No surgery	14	13.2 %	n = 106	0	0 %
Chemotherapy	42	39.6 %	n = 106	17	42.5 %
Neoadj. chemotherapy	16	15.1 %	n = 106	5	12.5 %
Adj. chemotherapy	26	24.5 %	n = 106	13	21.5 %
Definite chemotherapy	8	7.5 %	n = 106	-	-
No chemotherapy	64	60.4 %	n = 106	23	57.5 %
Radiotherapy	46	43.4 %	n = 106	40	100 %
Neoadj. radiotherapy	4	3.8 %	n = 106	-	-
Adj. radiotherapy	40	37.7 %	n = 106	40	100 %
Definite radiotherapy	3	2.8 %	n = 106	-	-
No radiotherapy	60	56.6 %	n = 106	-	-

When focussing on the timing of the adj. RT that patients underwent, please refer to Figure 6 for the following analysis: Among all patients who received adj. irradiation therapy (40 patients) (Figure 6 A), the median time interval between surgery and the start of postoperative RT was 57 days or approximately 8 weeks. Notably, the shortest interval between surgery and adj. RT amounted to 13 days or close to 2 weeks. A few patients, marked as outliers (marked with stars), underwent adj. RT after more than 300 days, which

could be attributed to prior adj. CHT. Excluding patients who received preoperative CHT before adj. RT and thus may have experienced a delayed initiation of RT due to other sarcoma treatment therapies (Figure 6 B), the median time interval was 48 days or a little less than 7 weeks (mean 57.63 days or 8.2 weeks, range 13-134 days), which falls outside of the recommended six weeks as the longest time interval between surgery and the start of adj. RT as outlined above.



(A) (B)

Fig. 6: Boxplot graph of the time interval between surgery and adjuvant radiotherapy (adj. RT) (in days) for (A) all patients having received adj. RT and (B) patients that did not undergo adj. CHT before adj. RT. Please note the different scales given. Outliers marked with stars.

Additional information regarding the parameters utilised in the adj. RT regimens can be found in Table 3.2. The average total dose of adj. RT was 58.74 Gy, with a BED of 86.76 Gy and an EQD2 of 58.19 Gy. The median DpF was 2.00 Gy, however, it ranged from 1.6 Gy to 3.0 Gy, the latter being classified as hypofractionated. Notably, 60 % of postoperatively irradiated patients underwent IMRT, while the technique was unknown for 11 patients due to RT therapy being performed at different hospitals or the technique not being documented within the RT-specific or clinical patient files.

Tab. 4: Details for adj. RT. n = number of patients included in analysis, adj. RT = adj. radiotherapy, BED = biologically effective dose, EQD2 = equivalent dose in 2 Gy fractions, IGRT = image-guided radiation therapy, IMRT = intensity-modulated radiation therapy, VMAT = volumetric-modulated arc therapy, 3DCRT = 3D conformal radiation therapy.

Adjuvant radiotherapy details		% (n = 40)
Timing		
Mean time between surgery and adj. RT	87.58 days	
Median time between surgery and adj. RT	57.00 days	
Range of time interval between surgery and adj. RT	13 - 407 days	
Dose		
Mean dose	58.74 Gy	
Mean BED	86.76 Gy	
Mean EQD2	58.19 Gy	
Median dose per fraction	2.00 Gy	
Range dose per fraction	1.60 - 3.00 Gy	
Technique		
IG-/IMRT	24 patients	60.0 %
IGRT	2 patients	5.0 %
Others including VMAT and 3DCRT	3 patients	7.5 %
Unknown	11 patients	27.5 %

3.2 Overall Survival

For the whole of the patient collective (106 patients), the 1-, 2- and 5-year OS-rates were calculated to be 89 %, 76.4 %, and 58.3 %, respectively. Please refer to Figure 7 below for a graphic representation in the form of a Kaplan-Meier curve.

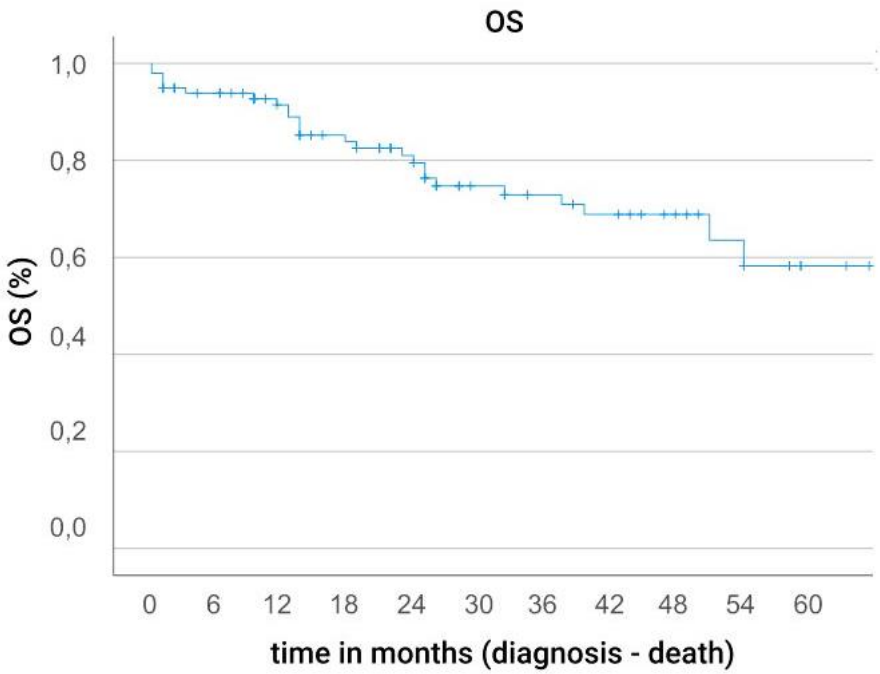


Fig. 7: Overall survival (OS) Kaplan-Meier curve for all 106 patients. Adapted from Koeksal et al. (2022).

The group of patients who underwent postoperative RT (40 patients) showed a 1-year OS rate of 91.3%, a 2-year OS rate of 79.3%, and a 3-year OS rate of 66.1%. Unfortunately, the 5-year OS rate for this subgroup could not be calculated due to an excess of patients being censored at that point.

The following statistics describe the whole of the patient collective (106 patients). Notably, patients with STES exhibiting lymph node infiltration ($p < 0.001$, 34 N0 vs. 8 N1) or blood vessel involvement (V1) ($p = 0.003$) had a significantly worse overall survival outcome. Additionally, late diagnosis, as characterised by sarcoma growth ≥ 8 cm ($p = 0.042$, 37 < 8 cm vs 45 ≥ 8 cm) (as shown in Figure 8), or the presence of metastases (M1) ($p < 0.001$, 56 M0 vs. 19 M1) also negatively impacted OS.

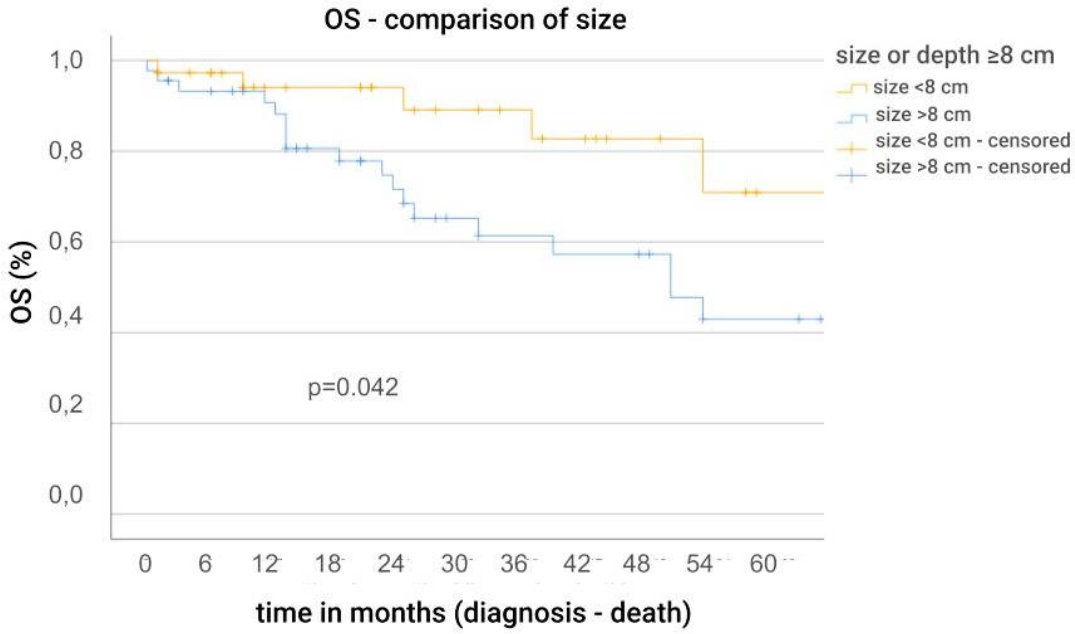


Fig. 8: Overall survival (OS) Kaplan-Meier curve, comparison of sarcomas < 8 cm (37 patients) and ≥ 8 cm (45 patients). Analysis included the whole of the patient collective (n = 106) in which appropriate data was available for 82 patients. Adapted from Koeksal et al. (2022).

However, no significant results were found for sarcoma location, even when certain locations were grouped together and sarcomas of the upper extremities were compared to ones occurring in the lower extremities (p = 0.662, 21 upper extremities vs. 78 lower extremities). Furthermore, the location of the sarcoma did not have a significant impact on OS, whether it was more proximal (hips/buttocks, thigh, upper arm vs. lower leg and lower arm). Significant results were not achieved either when comparing the larger group of 88 non-joint-infiltrating sarcomas to the group of 18 where the sarcomas did infiltrate the joint. In addition, older patients over the age of 70 could not be proven to exhibit worse survival (p = 0.082, 71 < 70 years old vs. 28 ≥ 70 years old). Notably, histological grading showed a clear and significant graphical trend, as shown in Figure 9 (p = 0.040, 9 G1 vs. 17 G2 vs. 56 G3). However, it is important to note the uneven distribution of patients across the grading spectrum, with the majority of patients having been diagnosed with high-grade sarcomas.

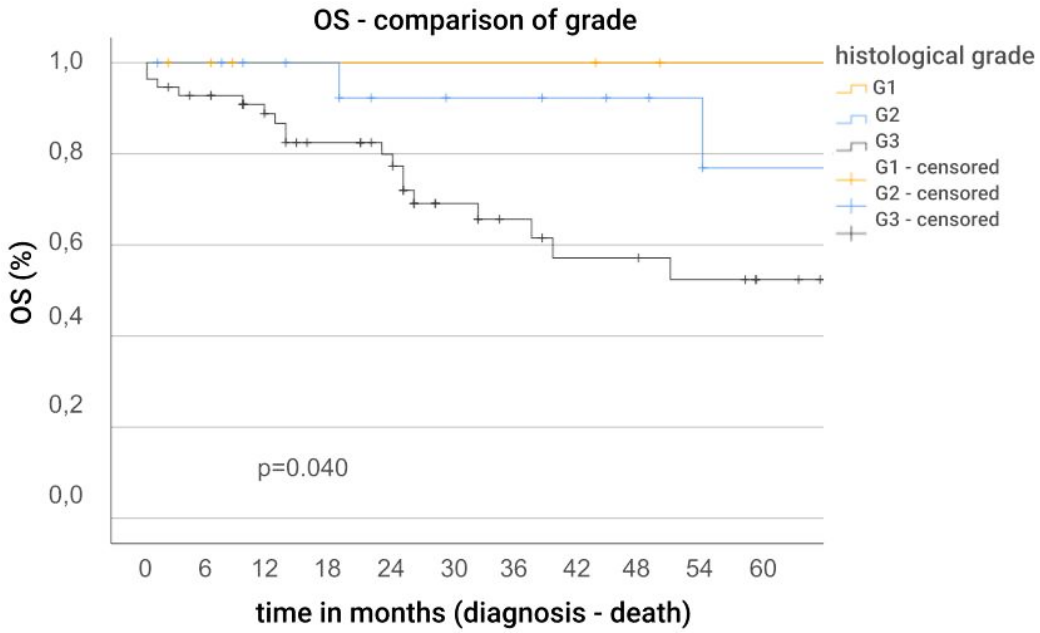


Fig. 9: Overall survival (OS) Kaplan-Meier curve comparing sarcomas by histological grade (9 patients for G1 vs. 17 patients for G2 vs. 56 patients for G3). Analysis included the whole of the patient collective (n = 106) in which appropriate data was available for 82 patients.

When looking at therapy options surgery was confirmed to be most vital to patients ($p < 0.001$, 88 with surgery vs. 11 without) although no statement can be made in regards to the resection margins ($p = 0.155$, 58 R0 vs. 22 R1 vs. 5 R2) (Figure 10) and the exact width of surgical margins if only looking at the subgroup of patients where an R0 could be achieved ($p = 0.467$). Figure 10 visually depicts a better outcome for R0-resected patients in comparison to those who underwent R1- or R2-graded resections. However, the significance of these results could not be established, and it should be noted that the distribution of patients among the R0, R1, and R2 groups was 59, 22, and 5, respectively.

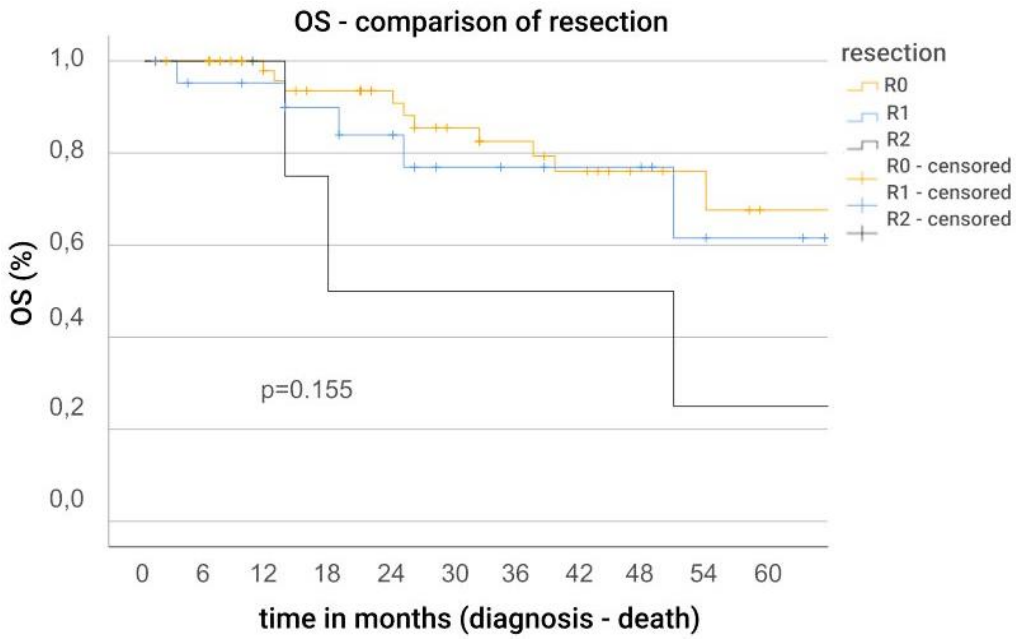


Fig. 10: Overall survival (OS) Kaplan-Meier curve comparing sarcomas by surgery margins. Analysis included the subgroup of patients who underwent surgery (n = 92) in which appropriate data was available for 85 patients (58 patients for R0, 22 patients for R1, 5 patients for R2).

When analysing the impact of adj. RT, a general significant impact to the OS failed to be reached (p = 0.397) as well. When examining the group of 40 patients that underwent adj. RT, however, it was found that higher irradiation doses resulted in significantly better survival rates (p = 0.016, HR = 0.952, 95 % CI: 0.915 - 0.991). The beneficial effect of high doses was also evident in the BED (p = 0.028, HR = 0.969, 95 % CI: 0.942–0.997) and EQD2 (p = 0.022, HR = 0.953, 95 % CI: 0.915 - 0.993). Nevertheless, no significant trend was found for the DpF (p = 0.067), indicating no preference for hypofractionation.

Of paramount importance, it should be noted that the time interval in days between surgery and adj. RT did not have a statistically significant impact on OS in this patient cohort (p = 0.477). This finding remained unchanged even after excluding patients who received adj. CHT before adj. RT (p = 0.671).

In summary, the best survival rates were observed in sarcomas with N0M0V0 status, which were less than eight centimetres in size, and were resected and irradiated with high doses.

3.3 Radiotherapy-related adverse effects

In the cohort of patients who underwent postoperative irradiation (40 patients), a multitude of adverse effects were documented and subsequently classified according to the CTCAE. Short-term effects, such as radiation dermatitis, skin hyperpigmentation, fatigue, pain, and RT-associated colitis were observed. Long-term effects were monitored as well, including limb oedema, hardened soft tissue, and joint stiffness, which are generally more prevalent in postoperative RT cases. Additionally, wound healing disorders were recorded, as previous findings indicated their higher incidence in neoadj. RT cases, as stated above.

As the number of patients who received neoadj. RT was limited to only four individuals within the observed patient cohort, statistical comparisons between neoadj. and adj. RT were not feasible due to the insufficient sample size in the preoperatively irradiated group. Consequently, the subsequent statistical analysis exclusively pertains to the group of 40 patients who underwent postoperative RT.

Table 4.1 provides a summary of the observed outcomes, indicating that a higher percentage of patients, specifically 87.5 % (35 out of 40), experienced adverse events related to adj. radiation compared to those who did not. Additionally, 40.0 % of patients (16 out of 40) experienced side effects categorised as second-degree or higher on the CTCAE scale, indicating a more severe manifestation. Of note, 12.5 % of patients required medical intervention for adverse events graded as third-degree. However, no side effect was reported to be of fourth-degree severity.

Tab. 5: RT adverse events sorted by severity according to CTCAE. Adapted from Koeksal et al. (2022).

RT adverse events	No.	% of n = 40
Patients with radiation side effects	35	87.5 %
Patients with ≥ 2nd-grade radiation side effects	16	40.0 %
Patients with ≥ 3rd-grade radiation side effects	5	12.5 %
Patients with ≥ 4th-grade radiation side effects	0	0.0 %

Continuing from that, Table 6 presents a detailed breakdown of the observed adverse events, sorted by their severity. Radiation dermatitis was the most frequently occurring adverse event overall, affecting 67.50 % of patients. Pain was the third most commonly

reported event, affecting 25.0 % of patients. In total, the three long-term effects affected 45.0% of patients, with only 10 % experiencing a long-term effect graded as second-degree or higher. Oedema was the most commonly reported long-term adverse event with 37.50 % of patients experiencing this, followed by joint stiffness and hardened soft tissue (7.5 % each).

Tab. 6: Adj. RT-related adverse events and severity details sorted by frequency and long-term vs. short-term. RT = radiotherapy, No. = number of patients per grade, n = number of patients included, adj. = adjuvant, CTC° = Common Terminology Criteria grade. Adapted from Koeksal et al. (2022).

Detailed listings of RT adverse effects	No. CTC° 1 / 2 / 3 / 4	Total in %, n=40
Radiation dermatitis	15 / 10 / 2 / 0	67.50 %
Long-term: oedema	12 / 2 / 1 / 0	37.50 %
Pain	8 / 1 / 1 / 0	25.00 %
Hyperpigmentation	6 / 0 / 0 / 0	15.00 %
Long-term: joint stiffness	2 / 0 / 1 / 0	7.50 %
Long-term: hardened soft tissue	2 / 1 / 0 / 0	7.50 %
Fatigue	2 / 1 / 0 / 0	7.50 %
Wound healing disorder after adj. RT	3 in total	7.50 %
RT colitis	1 / 0 / 0 / 0	2.50 %

When examining all side effects across all grades, regardless of their potential for long-term consequences, several predictors emerged while others were excluded. Specifically, a longer time interval between sarcoma resection and the initiation of adj. RT was associated with a lower likelihood of adverse events (measured in days, $p = 0.013$, HR = 0.984, 95 % CI: 0.972 - 0.997), suggesting that allowing more time for the surgical wound to heal before starting RT significantly reduced the risk of adverse events. However, it is important to note that the timing of RT measured in days could not prevent the occurrence of wound healing disorders, which were experienced by 7.5 % of patients who underwent postoperative irradiation ($p = 0.784$).

Regarding patients who may be particularly susceptible to adverse events, those with sarcomas affecting the nearest joint were found to be at a significantly higher risk of

experiencing adverse events graded as second-degree or higher that carried long-term consequences (p = 0.040, HR = 11.0, 95 % CI: 1.115 - 108.448).

Intrinsic patient factors failed to prove as predictors for side effects across all grades with patient sex (p = 0.904), age (0.591) and age under 70 (p = 0.690) failing to reach significance. Tumour characteristics like histology, lymph node involvement (p = 0.246), the presence of metastases (p = 0.999), sarcoma grade (0.977), stage (p = 0.999) and sarcoma size over 5 cm (p = 0.999) or 8 cm (p = 0.999) did not reach significance either. When looking at therapy regime details as possible predictors, the impact of going through CHT (p = 0.999) or RT (p = 0.999) before surgery could also not be observed. This finding may be attributed to the limited sample size of the cohort sample, as previously mentioned. Crucially, none of the adj. RT-specific parameters, including RT technique, total irradiation dose (p = 0.090), DpF (p = 0.170), boost to the CTV2 region (p = 0.832), BED (p = 0.121), and EQD2 (p = 0.111), as well as the size of the CTV2 area (p = 0.958), CTV1 area (p = 0.725), and PTV area (p = 0.855), were found to have a significant impact on adverse events graded as second-degree or higher, regardless of the long-term consequences.

It is worth noting that when specifically analysing potential predictors for wound healing disorders occurring only after the start of postoperative irradiation therapy, no significant factors were identified, including total irradiation dose (p = 0.771).

In summary, while the timing between resection and the initiation of adj. RT was found to have a mitigating effect on adverse effects, but the RT parameters themselves were not found to be significant predictors or preventatives of adverse effects.

3.4 Recurrences

In this section, a summary of the recurrence rates in the study population and related descriptive statistics will be provided, followed by an analysis of potential predictors. Table 5 summarises the occurrence of recurrence in the study population. Out of the total 106 patients, 30 patients (28.3 %) had a recurrence. Among them, 17 patients (16.0 %) had a local recurrence, while 13 patients (12.3 %) had a distant recurrence. In the group of irradiated patients (40 patients), only four patients (10.0 %) developed a local recurrence after the same area was previously irradiated. For all patients (106), the time interval between a patient’s diagnosis and the occurrence of a recurrence, both for anywhere and local recurrences, is presented in Figure 11. Figure 11 A displays the distribution for all

recurrences, while Figure 11 B illustrates the distribution of local recurrences, facilitating visual comparison.

Tab. 7: Recurrences sorted by location and timing, including after adjuvant radiotherapy (adj. RT)

Recurrences	No.	% of n=106
All recurrences	30	28.3 %
Distant recurrences	13	12.3 %
Local recurrences	17	16.0 %
Local recurrences after receiving adj. RT	4	
Mean time from diagnosis to recurrence (any)	18.35 months	
Mean time from diagnosis to local recurrence	16.12 months	

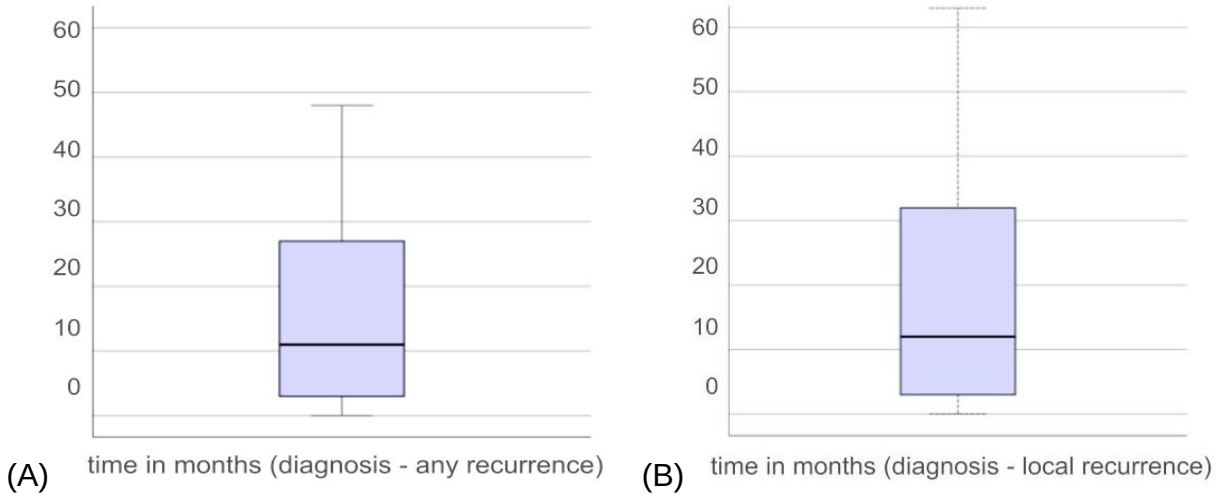


Fig. 11: Boxplot graphs of the timeframe until the recurrences occurred for (A) all recurrences and (B) local recurrences. Analysis included the whole of the patient collective (106 patients).

3.4.1 Disease-free survival

Out of the 106 patients included in this study, 30 patients (28.3 %) presented with a recurrence at any location, with a mean time of 18.35 months, which is just over 1 ½ years (median time 12 months, see Figure 11). In total, the 1-, 3-, and 5-year DFS referring to recurrences or death of any cause was estimated to be 74.1 %, 49.2 %, and 38.5 % if measured from the point of diagnosis. For graphic illustration in the form of a Kaplan-Meier curve please refer to Figure 12.

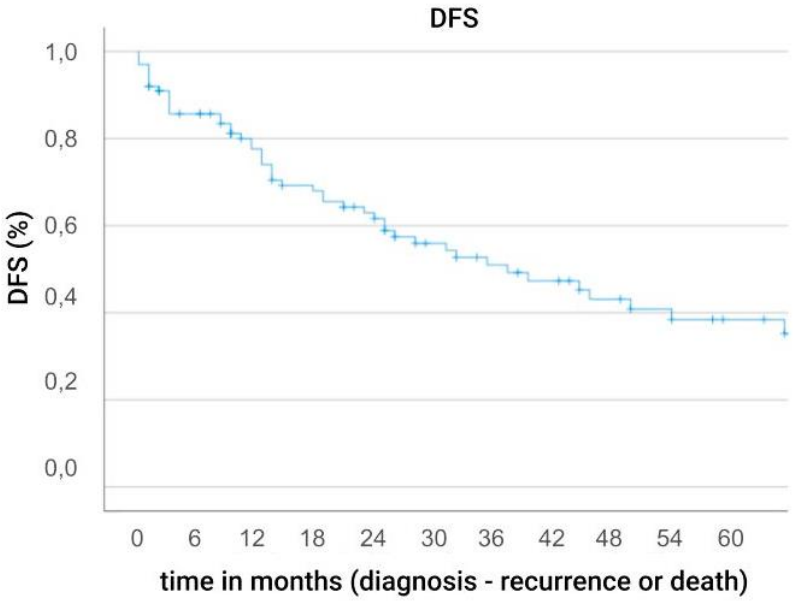


Fig. 12: Disease-free survival (DFS) Kaplan-Meier curve for all 106 patients. Adapted from Koeksal et al. (2022).

Table 6 displays location-specific recurrence rates. When comparing upper and lower extremity recurrences, the rates were 25.88 % and 33.33 %, respectively. It can be observed that the lower leg had the highest recurrence rate with 42.86 %, followed by the upper arm with 36.36 %.

Tab. 8: recurrence rates sorted by their anatomical location. Recurrences given in relation to total number of sarcomas of that particular location.

Location	recurrences	%
Upper extremity	7 of 21	33.33 %
Upper arm	4 of 11	36.36 %
Lower arm	3 of 10	30.00 %
Lower extremity	21 of 85	25.88 %
Hips/Buttocks	3 of 20	15.00 %
Thigh	13 of 51	25.49 %
Lower leg	6 of 14	42.86 %

For the 106 patients, it was found that older patients in the group of ≥ 70 years old had a worse outcome in regards to DFS (p = 0.019, 72 < 70 years vs. 28 ≥ 70 years); however, the patient gender did not have an impact (p = 0.517). In terms of the sarcoma stage, it was found that patients with N1 (p = 0.004, 34 N0 vs. 8 N1) V1 (p < 0.001, 28 V0 vs. 9 V1) M1 (p < 0.001, 56 M0 vs. 20 M1) classified sarcomas did rate significantly worse as well. The histological sarcoma rating, as well as the anatomical location, whether the sarcoma infiltrated the joint (p = 0.123, 83 without joint involvement vs. 17 with joint involvement), and the size of the tumour (≥ 5 cm: p= 0.083, 18 < 5 cm vs. 67 ≥ 5 cm) were not proven to be significant predictors of DFS. It is important to note that the surgery itself was found to be a crucial factor for a positive outcome of the patients' therapy regime (p < 0.001, 11 without surgery vs. 89 with surgery). Additionally, it was shown that the use of adj. RT was highly beneficial (p = 0.015, 50 without adj. RT vs. 39 with adj. RT) as well, as demonstrated in Figure 13. The latter was especially true for G2 and G3 sarcomas, rated as high-grade (p = 0.012) (Figure 14), whereas the same effect could not be shown for only G1 (low-grade) sarcomas (p = 0.414). For the latter analysis, the grading distribution presents as follows: 8 G1-rated STES, 17 G2-rated STES and 49 G3-rated STES. In conclusion, only the definite effect of adj. RT on high-grade sarcomas for the prevention of recurrences could be proven.

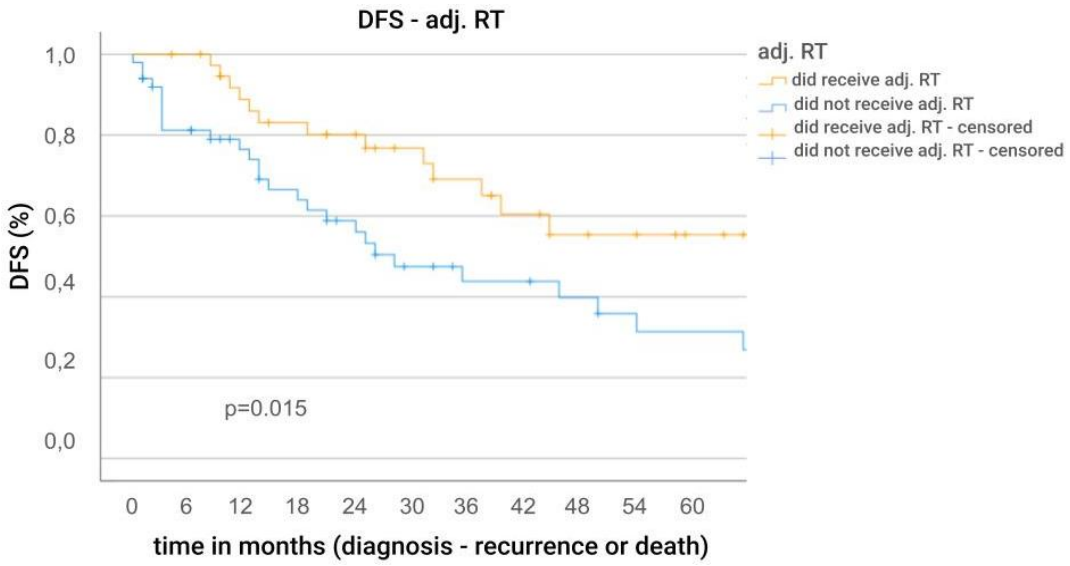


Fig. 13: Disease-free survival (DFS) Kaplan-Meier curve comparing patients with or without adj. RT. Apropriate data was available for 90 patients (50 patients who did not undergo adj. RT and 40 patients who did). Adapted from Koeksal et al. (2022).

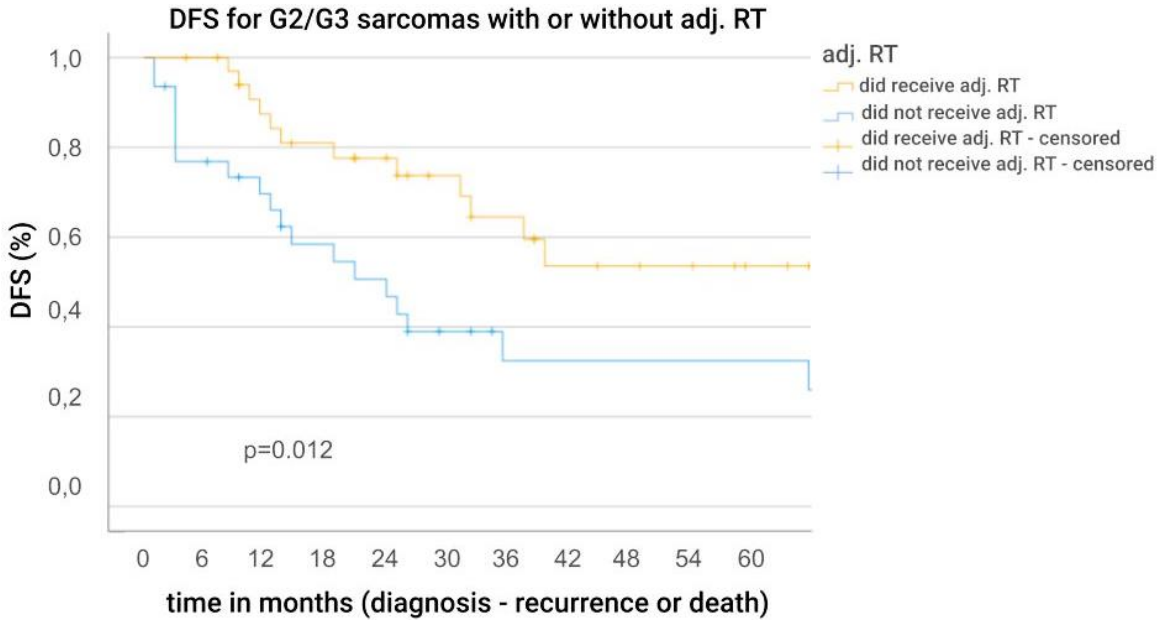


Fig. 14: Disease-free survival (DFS) Kaplan-Meier curve comparing patients diagnosed with an intermediate-grade (G2) or high-grade (G3) sarcoma with or without adj. RT. Appropriate data was available for 66 patients (31 patients who did not undergo adj. RT and 35 patients who did).

Since adj. RT proved significantly beneficial, a comprehensive analysis of the RT parameters was done within the group of 40 postoperatively irradiated patients: DFS was favourably influenced by higher total doses ($p = 0.26$, HR = 0.963, 95 % CI: 0.931 - 0.995), translating to a higher BED ($p = 0.43$, HR = 0.976, 95 % CI: 0.953 - 0.999) and a higher EQD2 ($p = 0.029$, HR = 0.963, 95 % CI: 0.930 - 0.996). The latter was still beneficial when the analysis was adjusted for sarcoma grade and resection status ($p = 0.02$, HR = 0.955, 95 % CI: 0.919 - 0.993). Crucially, the time in days between surgery and adj. RT failed to show a significant impact ($p = 0.820$) on DFS.

In short, the effect of high-dose adj. RT, especially for high-grade G2 and G3-rated sarcomas was able to be shown.

3.4.2 Local Control

During the follow-up period, a total of 17 patients with local recurrences were observed, representing 16.0 % of the study population (106 patients). The average time until local recurrences occurred was 16.12 months, with a median of 11 months (as shown in Table 5 and Figure 11). The estimated LC rates, which include local recurrences or death as

endpoints, were 78.7 % at one year, 51.6 % at three years, and 42.8 % at five years, as illustrated in Figure 15.

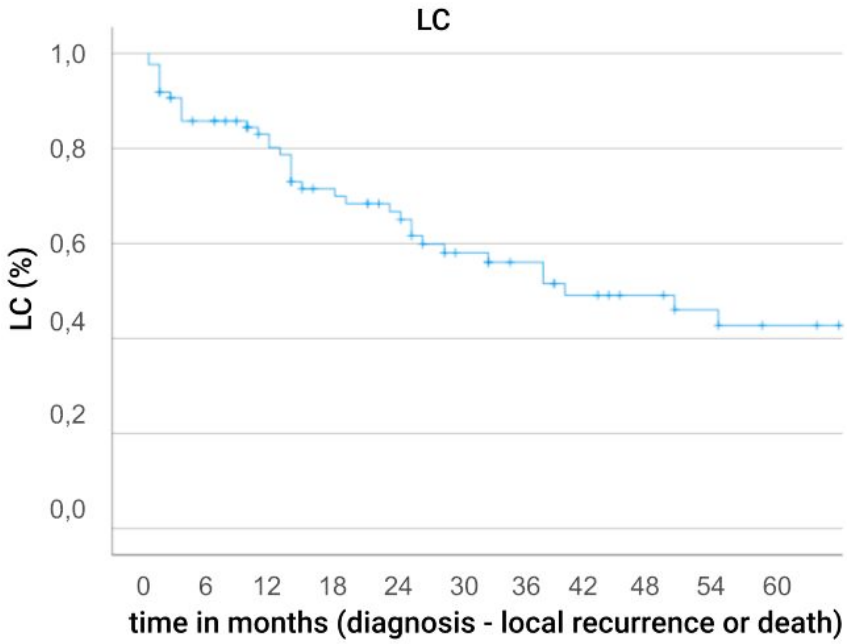


Fig. 15: Local control (LC) Kaplan-Meier curve for all 106 patients. Adapted from Koeksal et al. (2022).

When examining this subgroup of patients who experienced a local recurrence and stratifying them by their resection status, it was found that ten patients underwent R0-resections, while five patients had R1-resections and one patient had an R2-rated resection, meaning that more people had negative margins (R0) compared to positive margins (R1, R2) after resection.

For all 106 patients, the same factors that positively impacted DFS were found to have a beneficial effect on LC as well: age of < 70 years ($p = 0.010$, 64 < 70 years vs. 22 ≥ 70 years), N0-status ($p = 0.001$, 30 N0 vs. 8 N1), V0-status ($p < 0.001$, 28 V0 vs. 8 V1), M0-status ($p < 0.001$, 49 M0 vs. 19 M1), surgery ($p < 0.001$, 10 without surgery vs. 76 with surgery) and adj. RT after surgery ($p = 0.011$, $n = 92$, 41 without adj. RT vs. 35 with adj. RT) (Figure 16).

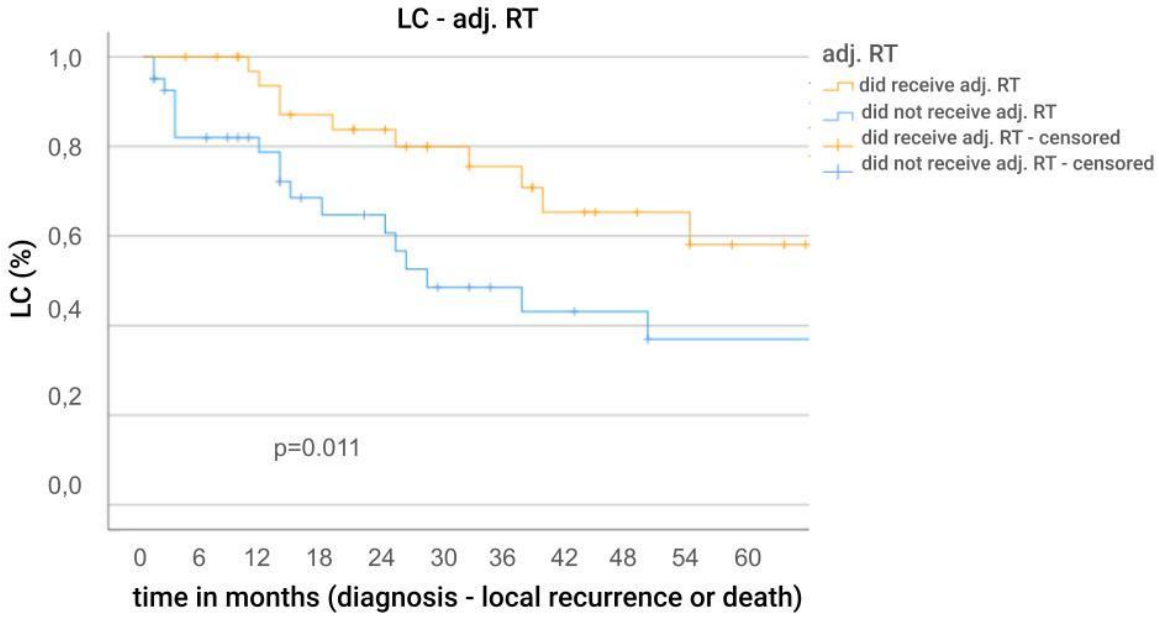


Fig. 16: Local control (LC) Kaplan-Meier curve comparing patients with or without adj. RT. Analysis included the subgroup of patients who underwent surgery (n = 92) in which appropriate data was available for 76 patients (41 patients who did not undergo adj. RT and 35 patients who did). Adapted from Koeksal et al. (2022).

No significant effect could be demonstrated for sarcoma location, joint involvement, histological sarcoma group, oncological stage, and sarcoma size.

A higher total irradiation dose (p = 0.024, HR = 0.961, 95 % CI: 0.928 - 0.995), BED (p = 0.042, HR = 0.975, 95 % CI: 0.951 - 0.999), EQD2 (p = 0.029, HR = 0.960, 95 % CI: 0.926 - 0.996), and EQD2 with grade and resection margin taken into account (p = 0.012, HR = 0.949, 95 % CI: 0.910 - 0.988) were beneficial to LC, same as with DFS, as well, when analysing the group of postoperatively irradiated patients (40). However, the time in days between surgery and initiation of adj. RT failed to show a significant impact (p = 0.199,) as was also the case for DFS, as explained above, signifying that a longer wait time before starting adj. irradiation did not lead to a higher risk of recurrences, even local ones.

In the following, the effect of adj. RT, proven to be effective above, is shown in regard to certain groups at high risk of developing a local recurrence. The beneficial effect of adj. RT in regards to the LC could be proven especially for high-grade sarcomas (p = 0.026, 27 without adj. RT vs. 32 with adj. RT) (Figure 17), but, again, not for G1-sarcomas with possible reasons stated above. With respect to resection margins, the benefit of adj. RT for patients that underwent complete R0-resections with negative margins could be shown

as well (p = 0.018, 30 without adj. RT vs. 20 with adj. RT) (Figure 18). Specifying that analysis due to the grading distribution (G1: 5, G2: 8, G3: 31, unknown: 6), the effect could be retained for high-grade G2/G3-sarcomas (p = 0.030).

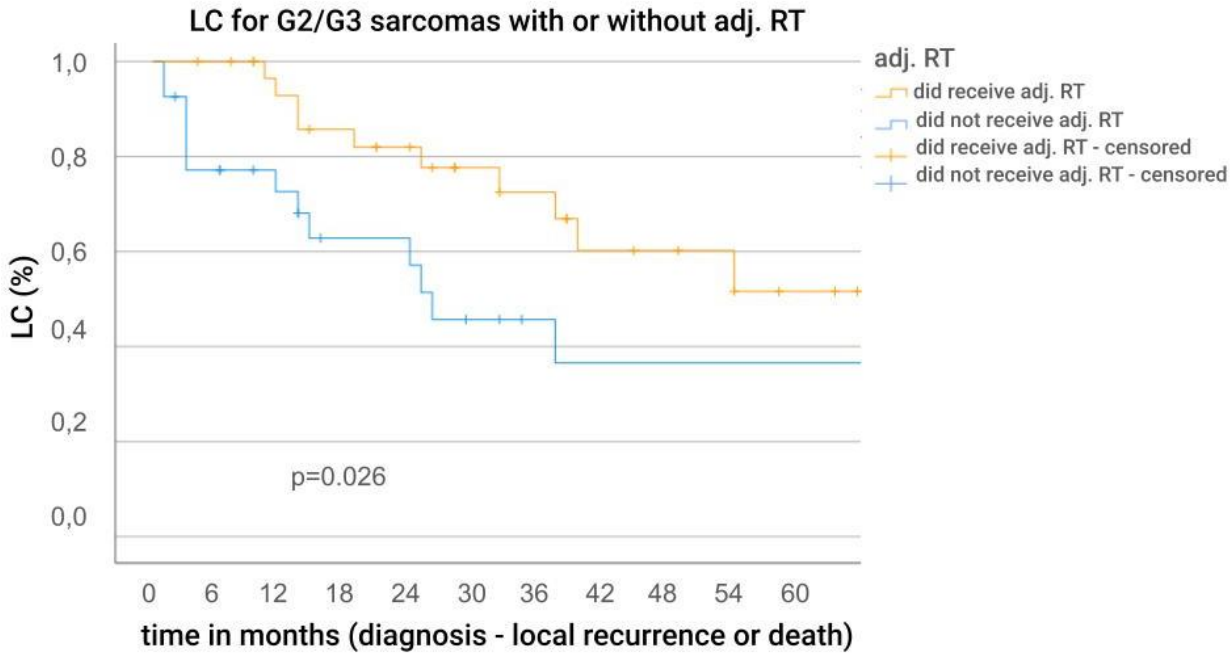


Fig. 17: Local control (LC) Kaplan-Meier curve comparing patients diagnosed with an intermediate-grade (G2) or high-grade (G3) sarcoma with or without adj. RT. Appropriate data was available for 59 patients (27 patients who did not undergo adj. RT and 32 patients who did).

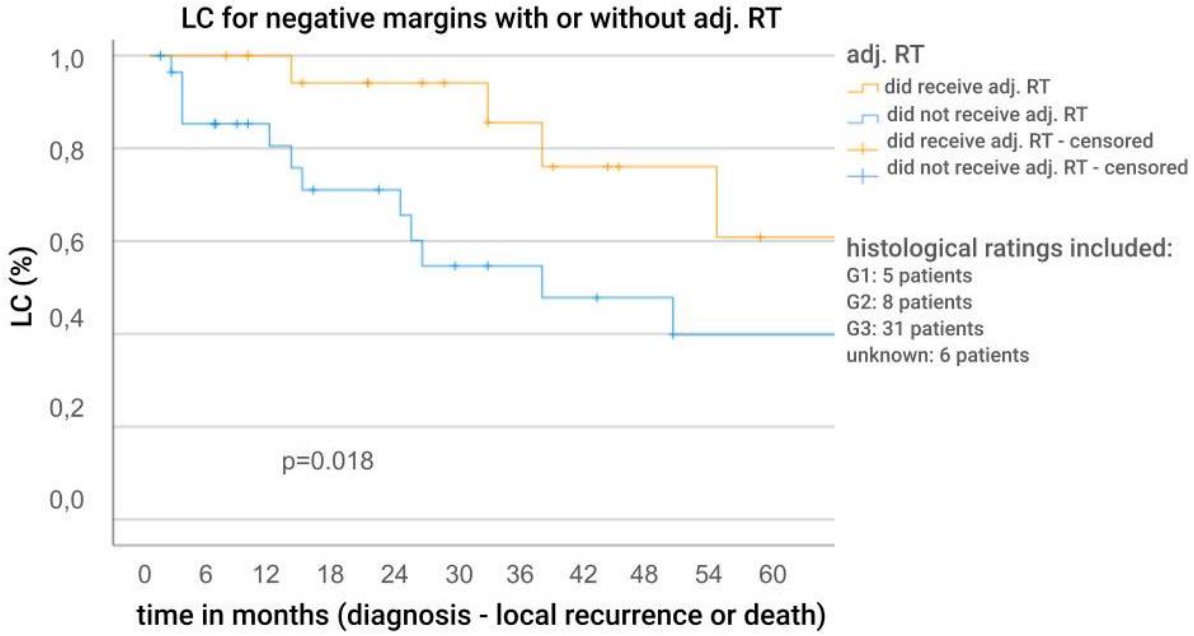


Fig. 18: Local control (LC) Kaplan-Meier curve comparing patients with or without adj. RT after complete R0 resection. Histological grade distribution is listed. Appropriate data was available for 50 patients (30 patients who did not undergo adj. RT and 20 patients who did).

To evaluate the adequacy of security margins for adj. RT, the incidence of local recurrences within the irradiation field was carefully monitored. Among the cohort of 40 patients who underwent adj. RT, only four cases of local recurrence after adj. RT were observed during the follow-up period. It is noteworthy that all four cases were observed in the lower extremities. Importantly, three recurrences occurred in patients who had previously undergone R1-resections, meaning with positive histological margins, and were localised within the 90 % isodose contour. On the other hand, only one recurrence was documented in a patient who had undergone R0-resection with negative margins, and was situated within the 25 % isodose border. Comprehensive details on these cases are provided in Table 7.

Tab. 9: Parameters for local recurrences after adj. RT (4 out of 40) with the distance of the recurrence to the original sarcoma and the isodose of the original irradiation field given. R = resection margin (0 = negative resection margins, 1 = microscopically positive resection margins), G = histological grading (2 = intermediate, 3 = high-grade), PTV = planning target volume, long. = longitudinal, IGRT = image-guided radiation therapy, IMRT = intensity-modulated radiation therapy. Adapted from Koeksal et al. (2022).

Age	Location	Histology	≥ 8cm	R	G	Dose (Gy)	Tech-nique	PTV long.	Dis-tance	Iso-dose
28	Thigh	Synovial sarcoma	Yes	1	3	66	IG-/IMRT	3.5 cm	0 cm	90 %
22	Lower leg	Other	Yes	1	3	44.80	IGRT	3.5 cm	0 cm	90 %
83	Thigh	Pleomorphic sarcoma	Yes	1	2	60	IG-/IMRT	Unknown	0 cm	95 %
56	Buttocks/ hip	Synovial sarcoma	Yes	0	3	60	IG-/IMRT	3 cm	3 cm	25 %

The final patient who experienced a recurrence within the 25 % isodose is presented here as an illustrative case to showcase the IMRT technique and its relationship with the isodoses in the context of the recurrence (refer to Figure 19 and 20 for visual representation).

Regarding the MRI shown in Figure 19, the patient was positioned on a flat surface and underwent IG-/IMRT adj. RT. The irradiation field, which includes the GTV (small orange outline), CTV (large orange outline), and PTV (red outline), is clearly marked. In addition, a graphic overlay is superimposed on the image, which shows the irradiation volumes with decreasing irradiation doses, represented by a gradient of colours from red/orange to green/blue. The colour scale on the left-hand side of the interface indicates the amount of irradiation in Gray (Gy) associated with each colour.

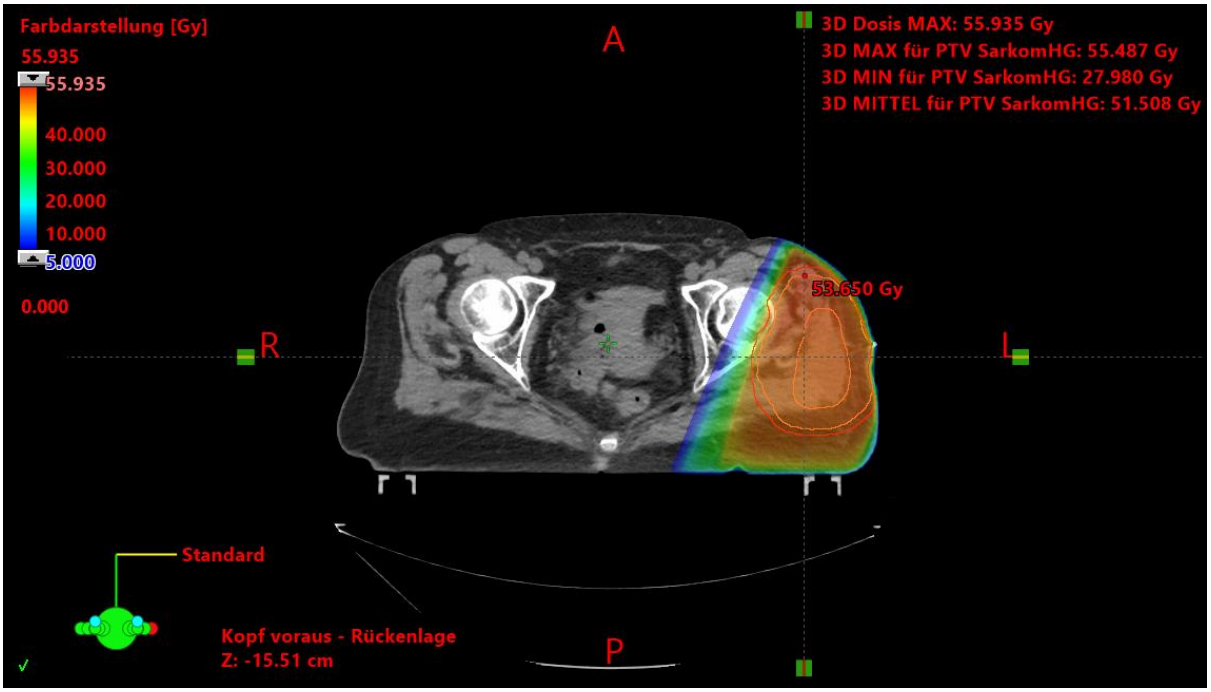


Fig. 19: Imaging interface of an MRI of the synovial sarcoma patient whose tumour occurred within the 25 % isodose

The patient subsequently developed a recurrence approximately 2 ½ years later, which is depicted in Figure 20. The same graphic overlay of the adj. RT irradiation field is illustrated in the red-to-blue gradient, with the location of the recurrence indicated by the red outline. In contrast to Figure 19, the radiation gradient is quantified in terms of different percentages of the originally prescribed dose, called isodoses, using the scale on the left-

hand side. The recurrence was observed to be slightly outside the original irradiation field but had reached the 25 % isodose mark. For the second MRI, the patient was positioned on a curved surface, resulting in slight variations in the graphic representation of the irradiation field that matched the contour of the patient's body.

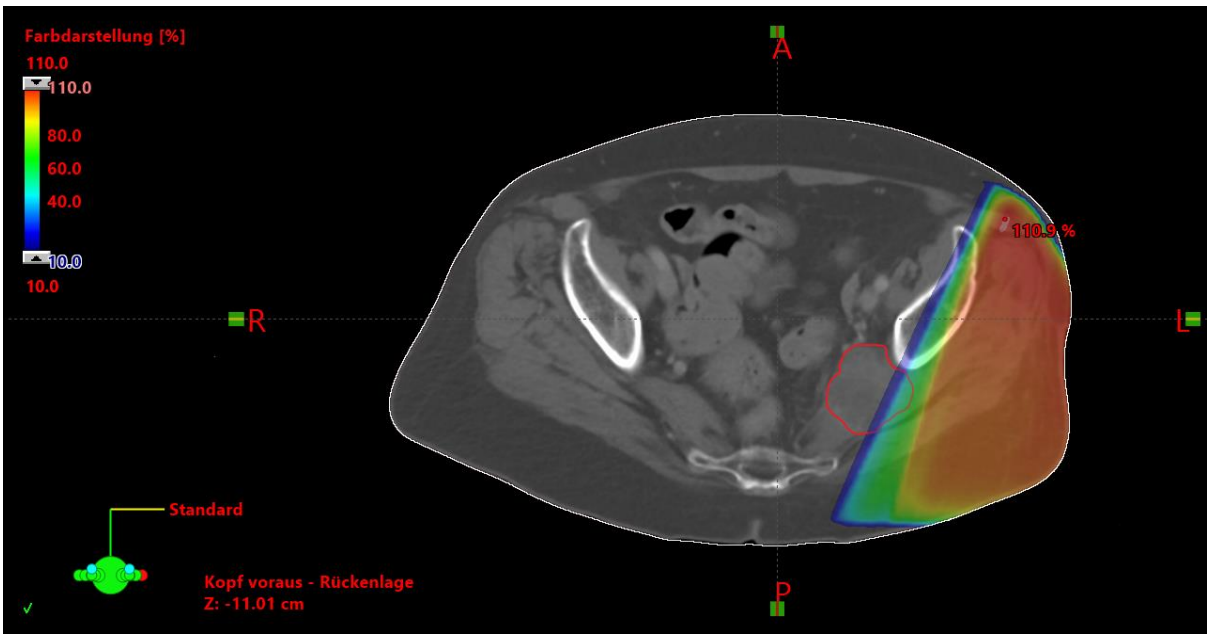


Fig. 20: Imaging interface of the patient from Figure 19 918 days (about 2 ½ years) later. Adapted from Koeksal et al. (2022).

3.5 Surgery complications

After outlining the benefits of surgical intervention for OS, it is imperative to explicate the potential complications that may ensue from these surgical procedures.

Focussing on different closure methods, this data was available from 78 patients out of 92 patients that underwent surgery. In this study cohort, direct wound closure was performed in 64 individuals, constituting 82.05 % (n = 78) of the sample size. Closure via a flap technique was employed in 8.97 % (7 patients), whereas sarcoma resection necessitated limb or partial limb amputation in 3.85 % (3 patients) of cases.

Out of the total cohort of 92 patients who underwent sarcoma resection, a notable proportion of 29.3 % experienced one or more of the aforementioned wound complications, as summarised in Table 8. Specifically, 25.0 % of patients, equivalent to 23 out of 92, necessitated a secondary surgical intervention or invasive procedure to facilitate proper wound healing. Within the initial 120-day postoperative period, the

incidence of both prolonged dressing changes and wound infections was found to be 7.6 %. Moreover, 5.4 % of patients required management via vacuum-assisted closure method.

In the subset of patients who received adj. RT (40 patients), the rates of some wound complications were slightly elevated compared to the overall cohort, as delineated in Table 8. Notably, 7.5 % of patients in this subgroup developed wound complications that only materialised after the end of RT.

Tab. 10: Surgery complications rates. VAC = vacuum-assisted closure, n = number of patients included, adj. RT = adjuvant radiotherapy.

Wound complications after surgery and VAC	All (92)	% of n = 92	Adj. RT (n = 40)
All wound complications	27	29.3 %	40.0 %
Requiring secondary operations or invasive procedures for wound care	23	25.0 %	35.0 %
Prolonged dressing changes	7	7.6 %	7.5 %
Infections within 120 days of surgery	7	7.6 %	15.0 %
Use of vacuum-assisted closure	5	5.4 %	7.5 %
Wound healing disorders after adj. RT	-	-	7.5 %

The subsequent analyses pertain to the entire cohort of patients who underwent surgical resection (n = 92): With respect to patient factors like sex and age, those could not be established as predictors with the p-values for those analyses being 0.776 and 0.986, respectively. Additionally, wound complications occurred more frequently in the lower extremity (22 patients out of 70 (31.4 %) with lower extremity sarcomas compared to 5 out of 21 patients (23.8 %) with upper extremity sarcomas). This difference did not prove to be a significant contrast, though (p = 0.527). Analysing other location variations like location in general or proximal compared with distal extremity (p = 0.510) did not yield significant results either.

In regard to preoperative therapies (p = 0.870), the incidence of wound complications was not significantly higher in patients who received neoadjuvant chemotherapy (p = 0.675), nor in those who were treated with Doxorubicin/Ifosfamide as opposed to other

chemotherapy regimens (p = 0.756). However, due to the limited number of patients (n = 4) who received neoadj. RT, a statistical analysis could not be performed for this subgroup. However, a significant association was observed between the preoperative size of the sarcoma and the incidence of wound complications, with an escalating risk correlated with increasing size. Specifically, for sarcomas measuring ≥ 8 cm in any direction (meaning width, length, or depth), the hazard ratio for developing complications was 2.88 (p = 0.047, 95 % CI: 1.015 - 8.180), whereas for sarcomas measuring ≥ 10 cm, the hazard ratio was 2.93 (p = 0.038, 95 % CI: 1.062 - 8.056).

None of the analysed factors were found to be predictive of the type of closure used (direct or flap closure), as indicated by the non-significant p-values for sex (p = 0.365), age (p = 0.206), age under 70 (p = 0.644), upper compared to lower extremity sarcomas (p = 0.644), joint involvement (p = 0.999), lymph node involvement (p = 0.999), vascular invasion (p = 0.999), size ≥ 5 cm (p = 0.447), size ≥ 8 cm (p = 0.378), and preoperative CHT (p = 0.466).

When focussing on the group that received adj. RT (40 patients), it is important to note however, that the occurrence of wound complications themselves was a significant predictor for a delayed start of adj. RT after six weeks (p = 0.025, HR = 7.5, 95 % CI: 1.288 - 43.687). Specifically, of the 20 patients who did not experience wound complications, 12 (60.0 %) were able to start their adj. RT within six weeks, whereas only two (16.6 7%) of the 12 patients with wound complications could start their postoperative irradiation therapy within the same time frame. It should be noted that patients who received adj. CHT prior to their adj. RT were excluded from this analysis as to not include delays that were caused by other therapies.

4. Discussion

In summary, this retrospective study aimed to identify prognostic factors for OS, DFS and LC, as well as to evaluate the adverse events associated with adj. RT and wound complications. The study was conducted at a high-volume treatment centre as previously defined and included 106 patients with a median age of 55 who were diagnosed with STS of the extremities and underwent multiple treatment approaches. The study had an average follow-up period of 26 months. Of note, 37.74 % of the patients underwent postoperative irradiation treatment, while only 3.77 % received RT prior to surgery.

4.1 Study size and Overall Survival

With 106 patients overall and 40 postoperatively irradiated patients, this study can be compared with other thematically fitting studies as illustrated in Figure 21. Since sarcomas are a quite rare form of adult malignancies, a retrospective design was chosen to allow for the inclusion of a larger patient cohort within a shorter timeframe. This investigation may also be classified as a single-centre study as data collection was facilitated from one hospital location possible, that being a high-volume treatment location. Illustrated by Figure 21 below, multiple studies are juxtaposed against this one and grouped according to their inclusion criteria: different inclusion criteria for different studies impede comparability of their outcomes, necessitating the listing of various results reported, along with the associated OS in percentages and the number of patients included in parentheses. Some studies included in the comparison had exclusion criteria for patients with metastatic disease at presentation, while others followed specific treatment regimens, such as the use of RT. Upon examining studies that excluded patients with metastatic disease (Abarca et al., 2018; Folkert et al., 2014; Sugiura et al., 2018), the 5-year OS rate of 69.6 % for the whole of the patient collective of 106 patients in this study is slightly lower. However, this discrepancy may be attributed to a different distribution of multiple therapy regimes represented. In the case of adj. RT, the inclusion criteria of Sampath et al. (2010) closely resemble this study and yielded a similar 5-year OS rate, albeit slightly lower at 60.0 % for the 40 postoperatively irradiated patients.

For the subset of irradiated patients, this study's sample size of 40 is relatively small. Nevertheless, the study produced significant results that contribute to the existing

literature. Similarly, the patient collective of 56 that initially presented without metastatic disease is smaller than in other studies, but as can be seen, in some groups OS even compares favourably.

As stated in the introduction, high-volume treatment centres produced better survival rates (Abarca et al., 2018) which proves true for this hospital which can be classified as such. Based on Abarca et al.'s study and confirmed by this one, there can be a recommendation made to diagnose and treat sarcoma patients at specialised hospitals with extensive experience in managing sarcoma due to their high sarcoma case volume. In cases where such specialised facilities are not available, patients may be referred to such hospitals. Abarca et al.'s study is noteworthy for its inclusion of a large number of patients. However, its focus on adj. RT produced different results in terms of OS compared to studies that included various treatment regimes, as shown in the figure below.

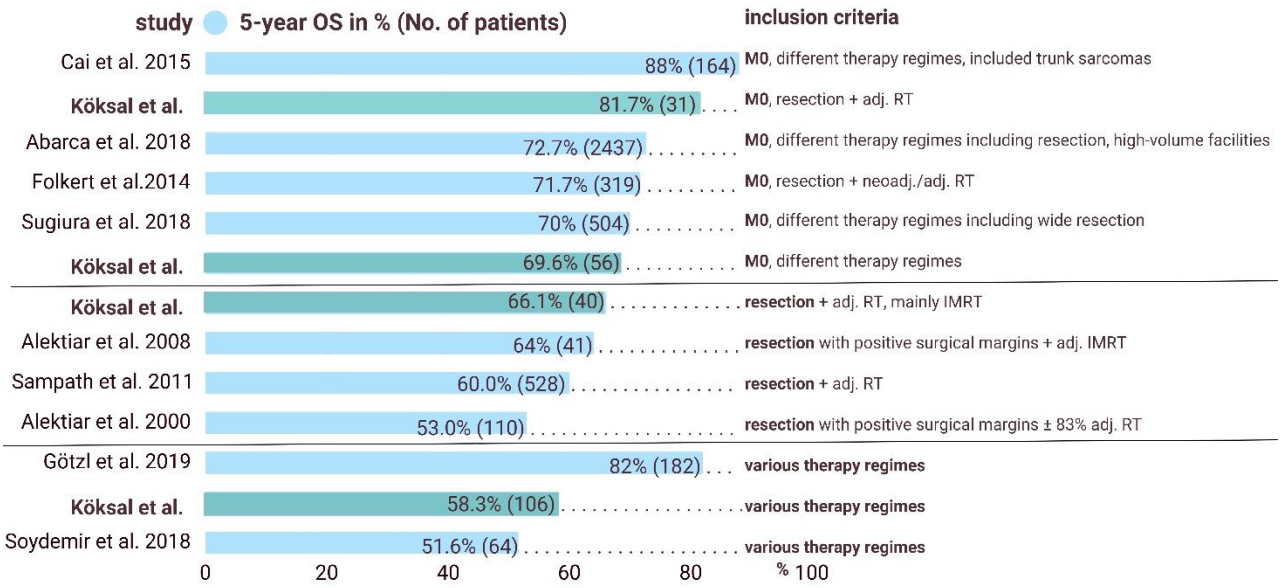


Fig. 21: Comparison of 5-year OS: different studies presented with their observed 5-year OS and the number of patients included, as well as inclusion criteria. This study's results marked by "Köksal et al.". Figure adapted from Koeksal et al. (2022).

Lymph node involvement, vascular invasion, and metastatic disease at the time of diagnosis, as well as a tumour size of ≥ 8cm, all alluding to a late diagnosis, were identified as negative prognostic factors for OS for all 106 patients. Therefore, further research on these high-risk factors is warranted to improve therapy. On the other hand, no differential

recommendations can be made for certain sarcoma locations as no improved survival for a certain location group was demonstrated in this study.

The results of this study highlight the crucial role of surgery in improving OS and emphasise its significance in the planning of a patient's treatment. However, the study was unable to replicate the results from Gronchi et al. (2017), which suggested that a greater surgical margin improves OS (HR for cause-specific death positive compared to negative margins 1.7). The lack of replicability could be attributed to differences in patient distribution regarding R0/R1/R2 margins. The findings of this study, however, align more closely with those of Dickinson et al., which suggest that with clean margins (R0) regardless of the distance, OS is comparable across groups (Dickinson et al., 2006).

The 5-year OS rates for the entire patient cohort differed from the OS rate of the subgroup who received adj. RT (40 patients), with 58.3 % and 66.1 %, respectively. This difference may be due to the fact that all patients who received adj. RT underwent surgery first. On the other hand, for high-grade sarcomas, Koshy et al. (2010) could prove a significant benefit of RT on patients' OS with most of their patients receiving RT in a postoperative manner. This same benefit could not be confirmed by this study, but this might be due to specific patient collective characteristics.

However, regarding adj. RT, efforts have been made over the last few decades to determine the appropriate radiation dose for STES treatment. This study demonstrated a significant benefit of the total radiation dose on OS for the 40 postoperatively irradiated patients, which translated into a higher BED and EQD2. Therefore, if RT is indicated and planned in a patient's treatment, higher doses of radiation with a tendency toward doses of 60 Gy or higher or even over 64 Gy should be targeted as they have the potential to significantly improve a patient's survival. These doses are in line with the guideline recommendations if an additional boost to the CTV2 is prescribed (50 Gy or 50.4 Gy plus a boost of 10 - 16 Gy) (Salerno et al., 2021). This renders the boost an imperative measure to attain the aforementioned irradiation doses. While other studies have correlated these elevated doses with certain adverse events as described below, the latter must be assessed in the context of the manifest benefit conferred by high-dose adj. RT.

4.2 Discussion of radiotherapy-related adverse events

In the following, a comprehensive summary of the incidence of unfavourable RT-related events in this study is provided and discussed in light of techniques to circumvent such events along with a comparative evaluation of other studies' results. Numbers are given in reference to the subgroup of 40 patients that underwent postoperative RT.

Adverse events of varying severity manifested in 87.5% of the adjuvantly irradiated patient cohort, with radiation dermatitis being the most commonly observed. This finding is disconcerting in light of LeBrun et al. (2017)'s report, which identified radiation dermatitis as a prognostic indicator for surgical wound complications, discussed subsequently. Notably, 40.0 % of patients were diagnosed with an RT-related event graded as 2 or higher, indicative of a more severe outcome that can markedly impede the patient's quality of life. Therefore, it is imperative to minimise the incidence of such events.

Over the past decade, the utilisation of IMRT has witnessed a substantial surge in hospitals, as was also the case in the present study institution. Notably, IMRT constituted the predominant technique employed for treating 60% of adjuvantly irradiated patients in this study. Due to its precise irradiation application that can accurately assign lower doses to surrounding healthy tissue, it has been proven to decrease adverse events, as elaborated subsequently. Another potential approach to reducing the incidence of adverse events is the adoption of smaller margins, as suggested by Wang et al. (2015)'s RTOG study, which investigated the use of IMRT or 3DRT techniques in irradiated patients. At this facility, the at the date of diagnosis current RT guidelines pertaining to dose and margins were followed at all times. In comparison, as an example, the incidence of radiation dermatitis was higher in this study (30 % with ≥ grade 2) than in Wang et al.'s study (16.46 % with ≥ grade 2). However, this could be attributed to the inclusion of older patient records or inaccuracies in describing the findings. Nonetheless, it should be emphasised that RT-related side effects can transpire regardless of whether the irradiation is applied within a neoadj. or adj. setting.

These short-term side effects named above are generally seen as treatable and, therefore, less worrisome than the long-term side effects which are often function-limiting themselves. Due to its precision, compared with conventional RT, IMRT was shown to have a significant mitigating effect on the reduction of late adverse events as well, as studied by Demitri et al. (2005). Given the prevalent use of precise-planning IMRT in this

patient cohort, the incidence of late toxicities, such as oedema, joint stiffness, and hardened soft tissue, was recorded at 45.0 % across all grades. However, for adverse events ≥ grade 2 that occurred over an extended period, the incidence was only 10 %. Nonetheless, these events can substantially affect the patient's quality of life (O'Sullivan et al., 2002). Of that 10 % of patients, 7.5 % suffered from severe limb oedema ≥ grade 2 and 2.5 % each suffered from joint stiffness ≥ grade 2 and more severe tissue fibrosis (≥ grade 2). The incidence rates of adverse events reported in this study are substantially lower compared to those reported in other studies, as summarised in Table 9. The studies listed in the table are primarily focused on investigating the effects of adj. RT and are sorted based on patient cohort size, with the smallest study listed first. In the second section of the table (last three rows), two studies that examined the effects of neoadj. RT, Peeken et al. (2019) and Wang et al. (2015) are included for comparative purposes. For adj. RT, for example, the rate of more severe limb oedema ranged from 11.3 % to 25 % which is undercut by this study as stated above. With respect to joint stiffness ≥ grade 2, this ranged from 10 % to 23.2 %, again underbid by the rate in this study. For fibrosis, a lot of studies did not report on this separately which impairs the comparison of that particular unfavourable event. Upon examining the neoadj. RT studies included in Table 9, the incidence of complications observed in this study is comparable to the presented results from literature, although it has been suggested that neoadj. RT may lead to fewer long-term function-limiting adverse events compared to the rate arising from adj. RT by Davis et al. (2005). Despite this study's limitations discussed below, the observed low incidence rates may be attributed to the widespread employment of IMRT and the adherence to the contemporary RTOG RT guidelines, which were improved constantly after Davis et al.'s study was published. Due to the above-given reasons, IMRT is to be considered the predominant RT technique that should be employed in the treatment of sarcomas, as is currently implemented at this institution.

Tab. 11: Comparison of the adj. RT-related rate of adverse events to other studies. This study's results marked by "Köksal et al.". No = Number, RT = radiotherapy, adj. = adjuvant, neoadj. = neoadjuvant, IMRT = intensity-modulated radiotherapy, IGRT = image-guided radiotherapy. Adapted and expanded from Koeksal et al. (2022).

Study	No of patients, RT	oedema ≥ 2nd grade	joint stiffness ≥ 2nd grade	fibrosis ≥2nd grade
Beane et al. (2014)	28 adj. RT	25 %	10 %	Not reported
Alektiar et al. (2008)	7 neoadj.,+ 34 adj. RT	12.2 %	17.1 %	Not reported
Koeksal et al. (2022)	40 adj. RT	7.5 %	2.5 %	2.5 %
Davis et al. (2005)	56 adj. RT	25.0 %	23.2 %	48.2 %
Folkert et al. (2014)	319 adj. RT	11.3 %	12.9 %	Not reported
Peeken et al. (2019)	38 neoadj. IMRT-IGRT	7.5 %	2.5%	Not reported
Wang et al. (2015)	57 neoadj. IMRT	5.3 %	3.5 %	5.3 %
Davis et al. (2005)	73 neoadj. RT	15.1 %	17.8 %	31.5 %

Looking at high-risk groups that had an increased risk of these severe long-term side effects ≥ grade 2 that significantly impacted the function of the limb, special attention should be placed on patients whose sarcomas infiltrated a joint. For these patients, it is particularly crucial to ensure optimal distribution of irradiation to spare healthy surrounding tissue in order to minimise the incidence of adverse events.

Patients who undergo postoperative RT in close temporal proximity to their surgery must be regarded as high-risk as well, given the substantially elevated incidence of adverse events associated with a shorter interval between these two treatment procedures. This underscores the need for surgical wounds to be given adequate time to heal prior to subjecting the tissue to the additional trauma of radiation. This finding has to be seen in

the light of contemporary guidelines recommending a three to six week interval between surgery and the start of adj. RT. However, it is important to note that the wound healing complications occurring after having already undergone adj. RT (7.5 %) could not be avoided by a longer time between surgery and adj. RT. Underlying mechanisms need to be studied further.

Upon evaluation of the DpF, it was observed that the majority of patients received a DpF of 2 Gy. Interestingly, no correlation between DpF and adverse events could be found. This means that Roohani et al. (2022)'s results showing that hypofractionated RT did not have worse adverse event rates cannot be confirmed. Bigger patient cohort samples with a hypofractionated group and a clear control group might be needed.

In addition to demonstrating the beneficial impact of high-dose adj. RT on OS, the effect on the incidence of adverse events was also evaluated. Surprisingly, no correlation was found between the occurrence of adverse events and other adj. RT parameters, such as the total dose administered, even at doses exceeding 60 Gy or 64 Gy. This finding suggests that high radiation doses should be aimed for to achieve maximum therapeutic benefit on the OS, as higher doses do not appear to be associated with an increased incidence of documented adverse effects or long-term functional limitations. Lee at al. (2012) showed no impact of radiation dose on the acute RT-related complication risk either. Additionally, this study failed to demonstrate any significant impact on the occurrence of long-term adverse events, thereby reinforcing the conclusion that higher radiation doses can be safely utilised without increasing the risk of either acute or long-term adverse events.

Adj. RT, however, is still underused in patients' treatment plans and neoadj. RT is on the rise compared to the use of postoperative RT. This is due to the higher needed irradiation doses for adj. RT which are said to result in more long-term side effects. In this study, this could not be proven true which signifies that while irradiation sites need to be evaluated constantly, high-dose adj. RT provides a clear benefit with no correlation to the incidence of adverse events that some patients develop. This can be related to the abovementioned modern techniques with high target conformity that make these high doses over 60 Gy possible.

While additional research is needed to further validate these findings, the results of this study provide further support for the effectiveness of adj. RT as a vital treatment option, meaning the significant benefits of this therapy should not be overlooked.

4.3 Discussion of the recurrence rate

As shown above, for the whole of the patient collective of 106, the recurrence rate regardless of location, meaning local, regional and distant recurrences, was 28.3 % which is highly concerning considering that the occurrence of recurrences is one of the main factors that significantly negatively impacts patients' OS (Alektiar et al., 2011). With this, the 5-year DFS was calculated to be 38.5 %. Therefore, it is imperative to include patients in structured follow-up programs in order to facilitate early detection of recurrences as soon as possible. This should be implemented every three months for the first two years, and then at increasing time intervals for a total of at least six years, in accordance with established guidelines (Leitlinienprogramm Onkologie, 2022). As could be shown by Jebsen et al. (2008) who studied extremity and trunk sarcomas, the 5-year local recurrence rate came out to 15 % in their study. Similarly, this finding is consistent with the observation that 16 % of all 106 patients in this study experienced a local recurrence, resulting in a 5-year LC rate of 42.8 %. These results further underscore the importance of diligent monitoring and follow-up care for patients. These local recurrences occurred with a mean time of 16.12 months which confirms Eiber et al. (2005)'s study that found 65 % of local recurrences to develop within the first two years and 90 % within the first four years with a median of 16 months. Folkert et al. (2014) observed a median time of 28 months for local recurrences. These slight differences could be due to differences within the particular patient collective, but yield the same conclusion, namely the need for diligent and structured follow-up visits that all patients should be highly advised to attend. Regular medical examinations and radiological imaging are important for detecting potential recurrences in patients and enabling prompt treatment as needed.

With regards to prognostic factors, similar to Alektiar et al. (2008)'s study, there could be no impact proven for sarcoma size and histological grade when it came to LC. Instead, other factors such as patient age, particularly if over 70 years, as well as N1-, V1- and M1-classified sarcomas also play a significant role in determining LC rates and should be taken into account in clinical decision-making. These high-risk groups should be closely

monitored and might receive even more regular follow-up appointments within the first years after initial diagnosis.

Regarding treatment options, surgery and complete removal of the STES have been proven to be vital for this patient collective in order to avert recurrences, particularly local ones, as well as improve OS as discussed above. Although statistical significance was not established in this specific patient cohort regarding the influence of surgical margins on local control (LC), the literature (Dickinson et al., 2006; Gronchi et al., 2017; Novais et al., 2010; Vraa et al., 2001) widely confirms their fundamental role in patient management. Therefore, negative resection margins are considered a critical component in a patient's therapeutic regimen. For the majority of the 16 % of patients who experienced the development of a local recurrence, it is noteworthy that their surgical resections were classified as complete R0-resections. It is worth considering that postoperative RT may potentially enhance the prognosis for these patients, as will be discussed below.

In general, and in accordance with existing literature, including studies by Yang et al. (1998) as well as others (Delaney et al., 2007; Zagars et al., 2003), the present study unequivocally demonstrates a significantly positive impact of adj. RT on DFS and LC within the whole of the patient collective that underwent surgery. Consequently, adj. RT must be considered a valuable treatment option that attending physicians ought to consider when designing a patient's therapeutic strategy. The highest benefit could be shown for high-grade G2- and G3-sarcomas confirming, for one, Alektiar et al. (2000)'s study that showed a benefit for high-grade sarcomas after positive margin resections, as well as the current guidelines (Leitlinienprogramm Onkologie, 2022; Salerno et al., 2021). When researching the possible benefits of adj. RT for other groups as well, Jebsen et al. (2008) conducted research showing that it even had a positive effect on G1-rated sarcomas and even if confirmation of wide resection margins after surgery was given by pathology. However, with the findings of this study and possibly due to the small patient sample size, a benefit from adj. RT on G1-rated sarcomas was not possible to be confirmed just on their own Instead, STES benefited from adj. RT even after negative margins were achieved. It has to be noted though, that in this patient collective, the majority of patients suffered from high-grade sarcomas. This is why it could be shown that G2/G3-rated sarcomas benefitted from adj. RT even when they had previously undergone complete removal (R0). Further studies with a bigger patient collective are needed in order

to confirm Jebsen et al.'s result for low-grade sarcomas as well, which was not possible within the scope of this study. As stated above, since most patients developed a recurrence after R0-resections, the histological grading of G2/G3 for most of those patients may have served as an indicator for the use of adj. RT which may, in turn, have prevented those recurrences. Only four patients developed a local recurrence after having already gone through adj. RT which was significantly lower than the 17 patients that developed a local recurrence overall. Based on these findings, it can be concluded that adj. RT as a beneficial treatment option should be implemented particularly for high-grade sarcomas to improve patient outcomes.

When considering the optimal irradiation doses required for adj. RT, it was shown on a group of 40 postoperatively irradiated patients that higher doses led to a reduction of the incidence of recurrences. Based on the findings of Delaney et al. (2007) who established a desired dose of > 64 Gy for an improved OS, as well as a reduction in both recurrences of any location and local recurrences, it is evident that adj. RT needs to be implemented with high doses in order to achieve the aforementioned benefits. While adverse events related to high-dose RT have been discussed above, it should be noted that the dose did not significantly impact the rate of adverse events in this patient cohort. Nonetheless, RT should be administered with due regard for these potential side effects. At this point, it can be concluded, however, that while high-dose postoperative RT has a positive impact on preventing recurrences of high-grade sarcomas and improving OS when indicated, the lack of a clear correlation with related adverse events leads to its benefit to be considered immense. As RT still remains underused (Bagaria et al., 2014) this further strengthens the case for the use of high-dose adj. RT.

Referring to neoadj. RT, this was only part of treatment for four patients so no statements can be made about the impact of RT when applied in a preoperative manner. Other studies like Sampath et al. (2010) and Al-Absi et al. (2010) studied neoadj. RT and also came to the conclusion that neoadj. RT had a significant benefit on the prevention of recurrences as well. Within the scope of this study, no comparison of pre- and postoperative RT can be made.

When discussing RT margins, as stated in the introduction of this dissertation, Wang et al. (2015) proved the benefit of reduced CTV margins with five local recurrences out of 74 patients included in their IGRT study that all occurred within the 95 % isodose. Although

their study focussed on neoadj. RT, reduced margins have become standard. This study can report that three out of the four local recurrences that occurred after patients had undergone adj. RT were within the 90 % isodose and only one bordered on the 25 % isodose. This supports Wang et al.'s results that reduced margins are safe, but more studies with a bigger patient collective, especially concerning patients that were diagnosed with local recurrences after having been treated with adj. RT, are necessary.

After examining the effects of RT timing, dose, and margins, it was found that the technique did not have a significant effect on recurrences in this patient cohort. However, it is worth noting that the majority of patients in the cohort received IMRT, which may have influenced the lack of significant effect. Alektiar et al. (2011) and Folkert et al. (2014) studied the benefit of this technique and could show a reduction of the recurrence rate in comparison with a patient group that received conventional RT. The precision of IMRT, a technique known for its high target conformity and ability to spare healthy tissue (Griffin et al., 2006; Stewart et al., 2009), may have contributed to the low rate of adverse effects at this treatment institution that could be shown in this patient collective. Adverse RT-related events can be minimised with IMRT making it one of the best available RT techniques, but it is also the technique of choice when aiming to prevent recurrences due to its high precision and ability to deliver high doses of radiation directly to the tumour.

Based on these findings, when it comes to adj. RT for STES, high-dose IMRT-based irradiation therapy should be the preferred treatment approach.

4.4 Discussion of wound complications

Wound complications are generally understood to be much more commonly associated with RT that is applied preoperatively (Beane et al., 2014; O'Sullivan et al., 2002; Peat et al., 1994; Peeken et al., 2019; Wang et al., 2015) which is one of the reasons why there is an ongoing discussion about the timing of RT. When looking at Götzl et al. (2019)'s study, they reported wound complications in 28 % of cases that underwent preoperative RT, but only 8 % for patients that received postoperative RT which was comparable to the 7 %-rate of patients that did not undergo RT at all. Complications included in their study were severe complications that brought about a second operation or in-hospital treatment and were classified Clavien-Dindo ≥ 3 ("requiring surgical, endoscopic or radiological treatment" (Clavien et al., 2009)). Included were wound necrosis, healing disorders,

thrombosis and bleedings among others. In this study, slightly different complications were included in the count, but it was found that 25 % of patients needed to be treated with a second surgery or other invasive interventions for wound care. This number was even higher with 29.3 % when including vacuum-assisted wound closures. When only focussing on the wound healing disorders though that arose after adj. RT which happened in 7.5 %, this number is again comparable to the rate that Götzl et al. found (10.11 % for neoadj. RT). In a different study by Rene et al. (2021) 45.5 % of patients with neoadj. RT vs. 53.8 % of patients with adj. RT suffered from complications of any grade (dehiscence, infection, wound necrosis and spontaneously draining seroma) with no significant difference. In this study, due to the small patient collective of four patients that underwent preoperative RT, no definite statement can be made in order to be compared to that number with regards to neoadj. RT. The widely differing numbers between studies could be due to the different complications included, but also show how the question of RT and its impact on wound complications has not been fully answered.

As previously mentioned, the preoperative measurement of sarcoma size was established as a significant predictor for the incidence of wound complications within the patient collective that underwent surgery, particularly when the size exceeded 8 cm or 10 cm. This finding is consistent with prior assertions made by Peat et al. (1994) and O'Sullivan et al. (2002). Therefore, it is imperative to exercise meticulous surgical planning and ensure sterile surgical environments to mitigate the risk of complications, including wound infections.

The location of the sarcoma diagnosis did not appear to exert any influence on the wound complication rate in this cohort of patients. The study revealed a wound complication rate of 31.4 % for lower extremity sarcomas and 23.8 % for upper extremity sarcomas, with no significant difference between the two groups. This is contrary to the above-mentioned study by O'Sullivan et al. (2002) where the anatomical site was a significant risk factor for wound complications. However, this could not be confirmed within the scope of this study. It is possible that the lack of significant difference in recurrence rates between lower and upper extremity sarcomas observed in this study could be attributed to the specific characteristics of the patient cohort and the relatively small sample size. However, it is noteworthy that the trend of increased incidence of wound complications in lower extremity sarcomas persists, even if not statistically significant. Further investigations are necessary

to explore this difference more comprehensively and devise effective strategies to minimise complications, particularly in the context of lower extremity sarcomas, as previously mentioned.

Further predictors of such complications like comorbidities like diabetes (LeBrun et al., 2017) and obesity (Houdek et al., 2019) were not investigated in this study, but certainly provide more areas of interest for further studies.

It is very important to note, that, as shown in literature (Rosenberg et al., 2013) while wound complications provide impediments to the patient's clinical treatment, they did not impact the oncological outcome like the recurrence rate or the OS in this study. However, what could indeed impact the oncological outcome is the delay of the RT treatment completion that is at risk when planning to apply RT in a postoperative manner: while Rene et al. (2021) found a timing between the start of preoperative RT and surgery in this study that came out to 66 days adj. RT, in this study, this came out to 62.25 days for the four patients. Rene et al. showed that 15.4 % of patients who adj. RT was planned for could not go through with it due to wound complications. As demonstrated above, adj. RT had a significant benefit on LC and DFS and those outcomes, in turn, impacted OS. The impossibility to go through with adj. RT could therefore be detrimental to the patient's outcome. It should be noted that some patients in this study received both adj. CHT and adj. RT. In cases where CHT was scheduled prior to RT, the administration of RT was delayed accordingly. For all patients who underwent postoperative irradiation, a timing interval between surgery and adj. RT was calculated, with a median of 57 days. However, when patients with adj. CHT prior to RT were excluded, the median time interval was reduced to 48 days. Nonetheless, this duration still exceeds the recommended time interval of three to six weeks after surgery, with a maximum duration of 42 days, as specified by existing guidelines. Such delays may be attributed to logistical reasons related to patient scheduling, as well as the resolution of wound complications that require time to heal before radiation therapy can be initiated. Similar to Rene et al. (2021), as stated above, wound complications were a major significant predictor, that adj. RT did not start within six weeks which could have resulted in the median time interval stated above. This means that while adj. RT carries a hugely positive impact for a patient, there is a risk of it being delayed if the patient suffers from complications with their surgical site. Implications are discussed in the following.

The time intervals observed in this study are consistent with the findings of Fourquet et al. (2016)'s study on the French Sarcoma Group, which involved 1131 patients and reported a median time interval of 87 days and a range of 18 - 356 days. Fourquet et al. also reported a decline in OS with longer time intervals between surgery and adj.RT, although the significance of this observation was not retained. Similarly, in the current study, the timing of adj. RT did not appear to impact OS, DFS, or LC in the group of postoperatively irradiated patients either.

In conclusion, further prospective studies are needed to determine the optimal timing of adj. RT for improving OS while considering the occurrence of wound complications. Nevertheless, it is evident that avoiding wound complications is crucial to ensure that adj. RT can be administered in a timely manner, which may lead to a better oncological outcome. The impact of a longer interval between surgery and adj. RT on OS still requires further investigation.

4.5 Limitations

It is important to acknowledge that this study has limitations due to its nature as a single-centre study and its relatively small sample size compared to other studies, as shown in Figure 21. The histological heterogeneity of the sarcoma group also adds complexity, as multiple histological diagnoses can fall under this definition. Despite this, the treatment approaches in this study remain consistent with guidelines recommended by ASTRO and ESMO. However, it is important to consider the potential impact of histological diversity when interpreting the results. In line with literature, different histological diagnoses were grouped in order to facilitate statistical analysis.

This study was conducted as a retrospective cohort study, which inherently presents challenges pertaining to the documentation of patient treatment, particularly since the electronic documentation system was introduced at the beginning of the century. Consequently, pertinent information particularly concerning sarcoma size and grading may have been omitted from the clinical documentation, potentially attributable to patients receiving their diagnoses at other medical institutions prior to their referral to the present facility. The sometimes incomplete and inadequate documentation of patient medical records has also resulted in the possibility of underreporting a range of adverse events that patients may have experienced. This underreporting aspect was tried to be minimised

by looking at multiple data sources and by taking into account all the available information for a patient. The retrospective nature of this study also presented the challenge of patients receiving follow-up care at different institutions or being referred to other facilities during the course of their treatment, potentially leading to incomplete event documentation. Doctors' notes and documents from another hospital were taken into account if present in the digital documentation from this hospital.

Some follow-up appointments could not be conducted in person due to distancing guidelines due to the Covid19-pandemic leading to a handful of interviews having been led over the phone. This, naturally, comes with a risk of adverse events not being described with enough detail and not being able to be subject to a physical examination.

Due to the range of diagnosis dates, it has to be taken into account that sarcoma treatment has come a long way over the last years. This means that with improving survival patients diagnosed in later years are more likely to survive longer due to better treatment regimes based on more evidence. In order to be transparent on this issue, a graph with the patient distribution in relation to their year of diagnosis is provided (Figure 3B).

5. Summary

Despite their rarity, managing STES clinically poses a considerable interdisciplinary challenge. This retrospective cohort study focused on the practical aspects and implications of postoperative RT, examining its impact on disease outcome. It also highlighted RT-related adverse events and identified prognostic factors. This study strongly supports integrating postoperative RT into a comprehensive treatment approach involving surgery, CHT, and RT.

Older patients with belated diagnoses, larger sarcomas of high histological grading that might have already metastasised, exhibit a diminished prognosis concerning both recurrence and overall survival. This underscores the critical need for vigilant medical supervision and expedited referral to a high-volume treatment centre for optimal care. In terms of recurrence, elevated rates were noted in the lower leg and upper extremity regions. Therefore, comprehensive and frequent follow-up programs, especially during the initial two years of post-sarcoma care, are imperative.

Postoperative irradiation therapy with high irradiation doses often exceeding 60 Gy was found to be highly beneficial in terms of disease outcome and positively prevented recurrences, both local and distant ones, contributing to improved overall survival. It must be noted, that the benefit was especially observed for intermediate- and high-grade sarcomas even when their sarcomas were previously completely resected with R0-rated margins. An effort should be made to incorporate high-dose adj. RT into the treatment regimes of those high-risk STES patients. Postoperative irradiation therapy is especially crucial for patients who undergo primary surgery and have not received any prior treatment.

Importantly, RT is associated with a risk of adverse events, especially for patients with sarcomas invading the adjacent joint as those are at risk of experiencing more severe adverse events. Irradiation sites should be regularly monitored. Despite the lower rate of adverse events with long-term consequences observed in this study compared to previous literature, it is still essential to remain cognisant of the possibility of such events. The only parameter found to affect the rate of these side effects was the time interval between surgery and adj. RT. With the recommended three to six weeks as the appropriate time window, sufficient time should be given to surgical wounds to heal prior to irradiation.

Patients larger STES are more at risk of wound complications and therefore, more at risk of delays with their adj. RT regime. Importantly, if having planned adj. RT, the risk of this being delayed due to those surgery complications must be kept in mind impeding a patient's treatment timing. Although the timing could not be shown to have an impact on disease outcome, it did have a significant impact on mitigating RT-related adverse events. For those patients, consideration should be given to neoadjuvant therapy regimens aimed at reducing the size of the sarcoma and meticulous surgical planning.

Although the dose itself as well as the dose per fraction did not exhibit a significant correlation with the rate of adverse events in this patient population, the advancement of tighter irradiation safety margins and precise radiation therapy techniques such as IMRT should be viewed as positive developments and have been shown to be advantageous in other studies. Further research into this as well as confirmation of low rates of long-term adverse events through prospective studies is needed. Meanwhile, the goal should be to strive for these high doses to improve the oncological outcome for patients with STES.

6. List of figures

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8. References

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