Diploma Thesis

Assessing the impact of radiotherapy on local recurrence, distant metastasis, and overall survival in a multicentre cohort of extremity soft tissue sarcoma patients

submitted by

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in partial fulfillment of the requirements for the degree of

Doktor(in) der gesamten Heilkunde

(Dr^{in}. med. univ.)

at the

Medical University of Graz

executed at the

Department of Internal Medicine, Division of Oncology

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Graz, 29th May 2023

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University´s regulations and procedures concerning plagiarism.

Graz, 29th May 2023 *Judith Wölfel m.p.*

Acknowledgments

For me, as a medical student, the diploma thesis was my first contact with scientific work and at the same time the prerequisite for completing my medical studies and being able to work as a doctor. Without the encouragement and support of others, I might never have finished or even started this project. For this reason, it is important for me to thank my supervisors, family and friends at this point.

First of all, I would like to especially thank my two great supervisors, Priv.-Doz^{in}. Dr^{in}. med. univ. Joanna Szkandera and Priv.-Doz^{in}. Dr^{in}. med. univ. Dr^{in}. scient. med. Maria Anna Smolle. On the one hand, their professionalism and expertise motivated me to work on soft tissue sarcomas, which were rather unknown to me until then, and always gave me confidence in scientific work. On the other hand, with their incredible patience and calmness, they enabled me to continue working on the topic even after long breaks. Every question, no matter how trivial, was answered incredibly quickly and helpfully. They will remain great role models for me on my professional and personal journey.

From the bottom of my heart, I would like to thank my family. For the freedom I have received by undoubtedly financing my studies. And for the understanding, acceptance and unconditional love, which has given me invaluable security.
I would also like to thank my dear friends, who have mostly shown understanding for my cancellations, when I got bogged down in this work again. They have given me a lot of strength throughout my studies by making me feel that I am never alone.

Your support and contributions are irreplaceable, and I am deeply grateful to all of you.

Content

ACKNOWLEDGMENTS **3**

ABBREVIATIONS **6**

LIST OF FIGURES **9**

LIST OF TABLES **11**

ZUSAMMENFASSUNG **12**

ABSTRACT **14**

1 INTRODUCTION **15**

1.1 LITERATURE REVIEW 15

1.1.1 Epidemiology *15*

1.1.2 Aetiology *16*

1.1.3 Tumour entities *19*

1.1.4 Diagnostic Evaluation and Workup *26*

1.1.5 Prognostic factors *32*

1.1.6 Treatment *34*

1.2 AIM OF THE STUDY AND RESEARCH QUESTION 51

2 MATERIAL AND METHODS **52**

2.1 STUDY DESIGN 52

2.2 DATA COLLECTION AND VARIABLES 52

2.3 STATISTICAL ANALYSIS 53

2.3.1 Subsets *53*

2.3.2 Statistical Methods *54*

2.3.3 Statistical analysis methods for treatment comparisons *54*

3 RESULTS **56**

3.1 COHORT DESCRIPTION IN THE ENTIRE DATASET 56

3.2 DIFFERENCES BETWEEN TREATMENT PAIRS 61

3.2.1 Differences between No RTX and NRTX cohort *61*

3.2.2 Differences between NRTX and ARTX cohort *65*

3.2.3 Differences between ARTX and No RTX cohort *69*

..... *72*

3.2.4 Significant SMDs and IPTW-weighting *72*

3.3 IPTW ANALYSIS 73

3.3.1 Effect of NRTX in comparison to no RTX 73

..... 74

3.3.2 Effect of ARTX in comparison to no RTX 74

3.3.3 Effect of NRTX in comparison to ARTX 76

4 DISCUSSION 79

4.1 SUMMARY OF MAIN RESULTS 79

4.2 COMPARISON WITH PREVIOUS RESULTS 79

4.2.1 Differences in patient cohorts 79

4.2.2 Effect of RTX on outcome 80

4.3 LIMITATIONS OF THE STUDY 82

4.4 CLINICAL IMPLICATIONS 83

4.5 CONCLUSION 83

5 LITERATURE 84

Abbreviations

A+I	*Anthracycline + ifosfamide*
ACTX	*Adjuvant chemotherapy*
AJCC	*American Joint Committee on Cancer*
APC	*Adenomatous polyposis coli*
ARTX	*Adjuvant radiotherapy*
ASTRO	*American Society for Radiation Oncology*
CI	*Confidence interval*
CNB	*Core needle biopsy*
CT	*Computer tomography*
CTX	*Chemotherapy*
D/P-LPS	*Dedifferentiated/pleomorphic liposarcoma*
DDLPS	*Dedifferentiated liposarcoma*
DFS	*Disease-free survival*
DM	*Distant metastases*
DSS	*Disease specific survival*
EBRT	*External beam radiotherapy*
EBV	*Epstein-Barr virus*
ESMO	*European Society for Medical Oncology*
eSTS	*Soft tissue sarcoma of the extremity*
FAP	*Familial adenomatous polyposis*
FDG-PET	*Fluorodeoxyglucose-positron emission tomography*
FNA	*Fine needle aspiration*
FNCLCC	*French - Fédération Nationale des Centres de Lutte Contre le Cancer*
FUS	*Fused in Sarcoma*
G	*Grade*
GIST	*Gastrointestinal stromal tumour*
HDR	*High-dose rate*
HHV-8	*Human herpes virus 8*
HR	*Hazard ratio*
HT	*Histotype-tailored*

IG-IMRT	*Image-guided intensity modulated radiotherapy*
ILP	*Isolated limb perfusion*
IMRT	*Intensity modulated radiotherapy*
IORT	*Intraoperative radiotherapy*
IPTW	*Inverse-probability of treatment-weight*
IQR	*Interquartile range*
LE	*Lower extremity*
LFS	*Li-Fraumeni syndrome*
LMS	*Leiomyosarcoma*
LPS	*Liposarcoma*
LR	*Local recurrence*
LRFS	*Local recurrence free survival*
LSS	*Limb-sparing surgery*
MFH	*Malignant fibrous histiocytoma*
MFS	*Metastasis-free survival*
MFS	*Myxofibrosarcoma*
MPNST	*Malignant peripheral nerve sheath tumour*
MRI	*Magnetic resonance imaging*
MSKCC	*Memorial Sloan Kettering Cancer Centre*
MWC	*Major wound complication*
NCBD	*National Cancer Database*
NCCN	*National Comprehensive Cancer Network*
NCTX	*Neoadjuvant chemotherapy*
NOS	*Not otherwise specified*
NRTX	*Neoadjuvant radiotherapy*
OR	*Odds ratio*
ORR	*Overall response rate*
OS	*Overall survival*
PFS	*Progression free survival*
PR	*Partial response*
PS	*Propensity score*
R	*Resection margin*
RR	*Risk ratio*

RTX	*Radiotherapy*
SD	*Standard deviation*
SD	*Stable disease*
SEER	*Surveillance Epidemiology and End Results*
SHR	*Subhazard ratio*
SMD	*Standardised mean difference*
SS	*Synovial sarcoma*
STS	*Soft tissue sarcoma*
TLS	*Translocated in liposarcoma*
TNF-alpha	*Recombinant human tumour necrosis factor – alpha*
TNM	*Tumour-node-metastasis*
UE	*Upper extremity*
UICC	*Union for international cancer control*
UPS	*Undifferentiated pleomorphic tumour*
US	*Ultrasound*
USTS	*Undifferentiated/unclassified STS*
WC	*Wound complication*
WDLPS	*Well-differentiated liposarcoma*
WHO	*World Health Organisation*

List of Figures

Figure 1: Histologic subtype distribution in a modern database of 10.000 adult soft tissue sarcomas (MSKCC).(54) *23*
Figure 2: Anatomic distribution in 4550 adults reviewed by the American college of surgeons. (81)..... *26*
Figure 3: Diagnostic evaluation algorithm according to Smolle et al.. (3) *28*
Figure 4: Time interval between local therapy in weeks (w.) depending on the sequence according to the American Society for Radiation Oncology guidelines. *43*
Figure 5: Management of locally, clinically resectable extremity and superficial trunk STS according to ESMO guidelines. (1) *47*
Figure 6: Management of localised, clinically unresectable eSTS according to ESMO guidelines. (1)..... *48*
Figure 7: Management of advanced/metastatic, clinically resectable STS according to ESMO guidelines.(1) *49*
Figure 8: Management of advanced or metastatic, clinically unresectable STS according to ESMO guidelines. (1) *50*
Figure 9: Frequencies of the respective treatment regimens (left) and the mean age with standard deviation at surgery (right) in the entire dataset. *57*
Figure 10: Frequencies of the respective gender (left) and grading (right) in the entire dataset...... *57*
Figure 11: Frequencies of the histologic subtypes in the entire dataset. *58*
Figure 12: Median tumour size with interquartile range in the entire dataset. *59*
Figure 13: Frequencies of the respective depths (left) and localisations (right) in the entire dataset. *59*
Figure 14: Frequencies of the respective resection margins in the entire dataset. *60*
Figure 15: Outcome in the entire dataset. *60*
Figure 16: Comparison of mean patient age with standard deviation in NRTX and no RTX subgroups...... *62*
Figure 17: Comparison of frequencies of respective grading in NRTX and no RTX subgroups. *63*
Figure 18: Comparison of the frequencies of histologic subtypes within NRTX and no RTX subgroups. *63*
Figure 19: Comparison of median tumour size with respective interquartile ranges in NRTX and no RTX subgroups. *64*
Figure 20: Comparison of frequencies of respective tumour depths (left) and locations (right) in NRTX and no RTX subgroups. *64*
Figure 21: Comparison of the frequencies of respective resection margins in NRTX and no RTX subgroups. . *65*
Figure 22: Comparison of the frequencies of the respective grading in the NRTX and ARTX subgroups. *67*
Figure 23: Comparison of the frequencies of the respective histologic subtypes in the NRTX and ARTX subgroups. *67*
Figure 24: Comparison of mean tumour size with the corresponding interquartile range in the NRTX and ARTX subgroups. *68*
Figure 25: Comparison of the frequencies of the respective localisations (left) and the respective tumour depth (right) in the NRTX and ARTX subgroups. *68*

Figure 26: Comparison of mean age with corresponding standard deviation in the ARTX and no RTX subgroups. *70*
Figure 27: Comparison of the frequencies of the respective histologic subtypes in the ARTX and no RTX subgroups. *71*
Figure 28: Comparison of median tumour sizes with corresponding IQR (left) and frequencies of respective depths (right) in the ARTX and no RTX subgroups. *71*
Figure 29: Comparison of the frequencies of the respective resection margins in the ARTX and no RTX subgroups. *72*
Figure 30: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for LR for the no RTX vs. NRTX subgroups *73*
Figure 31: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for DM for the no RTX vs. NRTX subgroups *73*
Figure 32: Univariate naïve (left) and IPTW-weighted (right) Cox regression models for OS for the no RTX vs. NRTX subgroups *74*
Figure 33: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for LR for the no RTX vs. ARTX subgroups *74*
Figure 34: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for DM for the no RTX vs. ARTX subgroups *75*
Figure 35: Univariate naïve (left) and IPTW-weighted (right) Cox regression models for OS for the no RTX vs. ARTX subgroups *75*
Figure 36: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for LR for the NRTX vs. ARTX subgroups *76*
Figure 37: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for DM for the NRTX vs. ARTX subgroups *76*
Figure 38: Univariate naïve (left) and IPTW-weighted (right) Cox regression models for OS for the NRTX vs. ARTX subgroups *77*

List of Tables

Table 1: Classification of benign and malignant soft tissue sarcoma defined by the WHO 2020. (3) 22
Table 2: Rules for planning a biopsy according to Smolle et. al. 30
Table 3: Sarcoma grading according to French Federation of Cancer Centre Sarcoma Group. 32
Table 4: Tumour- node-metastasis system - AJCC 8th edition. 32
Table 5: Surgical procedure according to Enneking et al.. 36
Table 6: Comparison of R-Classification and UICC-Classification. 36
Table 7: Comparison of NRTX and ARTX according to Hoefkens et al. (136) 44
Table 8: Descriptive analysis of the entire dataset. 56
Table 9: Descriptive analysis of patients with no RTX and NRTX. 62
Table 10: Descriptive analysis in patients with NRTX or ARTX. 66
Table 11: Descriptive analysis of patients with no RTX or ARTX. 70
Table 12: Univariate naïve and IPTW-weighted Fine&Gray models for LR and DM and univariate naïve and IPTW-weighted Cox-regression model for OS 78

Zusammenfassung

Hintergrund: Die Strahlentherapie (engl. RTX) ist neben der Operation und der Chemotherapie (engl. CTX) ein wichtiger Bestandteil der Behandlung von Weichteilsarkomen der Extremitäten (engl. eSTS). Während ihr positiver Einfluss auf das Lokalrezidiv (engl. LR) gut beschrieben ist, ist ihr Effekt auf die Fernmetastasierung (engl. DM) und das Gesamtüberleben (engl. OS) nicht eindeutig belegt. Ziel dieser Studie war es, den unabhängigen Effekt von neoadjuvanter und adjuvanter Strahlentherapie (engl. NRTX und engl. ARTX) auf das LR-Risiko, das DM-Risiko und das OS zu untersuchen.

Methoden: In die multizentrische retrospektive Studie wurden 1200 Patient*innen mit lokalisierten, hochgradigen eSTS einbezogen, die in zehn verschiedenen tertiären Tumorzentren mit kurativem Ansatz behandelt wurden. Im gesamten Datensatz betrug das Durchschnittsalter der Patient*innen 60.7±16.8 Jahre und 44.4% waren weiblich. 216 (18.0%) hatten keine RTX, 194 (16.2%) eine NRTX und 790 (65.8%) eine ARTX erhalten. Die mediane Nachbeobachtungszeit betrug 70.5 Monate (engl. interquartile range [IQR]: 41.8-106.4 Monate). Für die statistische Auswertung wurde der Gesamtdatensatz in drei separate Datensätze aufgeteilt: 1. NRTX vs. keine RTX, (n=410); 2. ARTX vs. keine RTX, (n=1006); 3. NRTX vs. ARTX, (n=984). Relevante Unterschiede zwischen den Behandlungspaaren wurden durch standardisierte Mittelwertdifferenzen ermittelt und mittels „Propensity Score (engl. PS)“ und „Inverse Probability of Treatment Weight (engl. IPTW)” adjustiert. Für LR und DM wurden Fine&Gray-Modelle und für OS Cox-Regressionsmodelle angewendet.

Ergebnisse: In den univariaten IPTW-gewichteten Modellen waren sowohl NRTX als auch ARTX im Vergleich zu keiner RTX mit einem signifikant reduzierten LR-Risiko assoziiert (NRTX: engl. subhazard ratio [SHR] 0.236, p<0.001; ARTX: SHR 0.479, p<0.001). Weder NRTX noch ARTX zeigten einen signifikanten Unterschied auf das DM-Risiko (NRTX: SHR 1.329, p=0.192; ARTX: SHR 1.294, p=0.121) oder OS (NRTX: engl. hazard ratio [HR] 0.838, p=0.394; ARTX: HR 0.829; p=0.178) im Vergleich zu keiner RTX. NRTX zeigte im Vergleich zu ARTX ein signifikant geringeres LR-Risiko (SHR 3.433; p<0.001), aber keinen signifikanten Unterschied bezüglich DM-Risiko (SHR 0.985; p=0.936) oder OS (HR 1.312; p=0.213).

Schlussfolgerung: NRTX und ARTX haben einen signifikant positiven Effekt auf die Reduktion des LR-Risikos, scheinen aber DM oder OS nicht signifikant zu beeinflussen. Die Überlegenheit von NRTX gegenüber ARTX bei der lokalen Kontrolle ist ein Grund, NRTX bevorzugt anzuwenden.

Abstract

Background: Radiotherapy (RTX) is an important part of the treatment of extremity soft tissue sarcomas (eSTS), along with surgery and chemotherapy (CTX). While its positive effect on local recurrence (LR) has been clearly demonstrated in previous studies, the effect on distant metastasis (DM) and overall survival (OS) has not been conclusively shown. The aim of this study was to investigate the independent effect of neoadjuvant and adjuvant radiotherapy (NRTX and ARTX) on LR-risk, DM-risk and OS.

Methods: The multicentre retrospective study included 1200 patients with localised high-grade eSTS treated in ten different tertiary tumour centres with curative intent. Mean age of the patients was 60.7±16.8 years and 44.4% were female. 216 (18.0%) had received no RTX, 194 (16.2%) had received NRTX and 790 (65.8%) had received ARTX. The median follow-up was 70.5 months (interquartile range [IQR]: 41.8 - 106.4 months). For statistical analysis, the total dataset was divided into three separate sets: 1. NRTX vs. no RTX, (n=410); 2. ARTX vs. no RTX, (n=1006); 3. NRTX vs. ARTX, (n=984). Differences between treatment pairs were adjusted for using propensity score (PS) and inverse-probability of treatment-weight (IPTW). Fine&Gray models were used to assess the impact of prognostic variables on LR and DM, and Cox-regression models to analyse the effect of prognostic factors on OS.

Results*:* In the univariate IPTW-weighted models, both NRTX and ARTX were significantly associated with a reduced LR-risk (NRTX: subhazard ratio [SHR] 0.236, p<0.001; ARTX: SHR 0.479, p<0.001) compared to no RTX. Neither NRTX nor ARTX showed a significant impact on DM-risk (NRTX: SHR 1.329, p=0.192; ARTX: SHR 1.294, p=0.121) or OS (NRTX: hazard ratio [HR] 1.294, p=0.121; ARTX: HR 0.829, p=0.178) compared to no RTX. There was a significantly lower LR-risk for patients receiving NRTX compared to those administered ARTX (SHR 3.433; p<0.001), but no significant difference in DM-risk (SHR 0.985; p=0.936) or OS (HR 1.312; p=0.213).

Conclusion: Both NRTX and ARTX have a significant positive effect on LR risk-reduction, but do not appear to significantly affect DM-risk or OS. The superiority of NRTX over ARTX in local control is a reason to prefer NRTX when possible.

1 Introduction

1.1 Literature review

Soft tissue sarcomas (STS) are a rare group of malignant tumours with a heterogeneous appearance. (4, 5) Along with bone tumours, they belong to the group of sarcomas. (5) These arise from mesenchymal tissue which can differentiate into muscle tissue, connective tissue, fatty tissue, blood vessels and nerves, bone and cartilage tissue. In addition to malignant tumours, these include numerous benign tumours. (4, 6) The resulting broad histopathological spectrum and heterogeneous clinical presentation of STS, combined with their rarity, make them medically challenging tumours. (7) Patients with suspected soft tissue tumours should be referred to a centre as soon as possible for diagnosis and treatment by experienced medical professionals. (1, 6) Their treatment is based on the three pillars of surgery, chemotherapy (CTX) and radiotherapy (RTX) and is individualised according to histological subtype, size and location. (1, 6)

This diploma thesis will be dedicated to STS of the extremities (eSTS). In the following, I will refer to the epidemiology, aetiology, possibilities of clinical presentation and the diagnostic and therapeutic pathways based on the current guidelines. In particular, I will review the latest studies on the influence of RTX on the occurrence of local recurrence (LR), distant metastases (DM) and overall survival (OS).

1.1.1 Epidemiology

Sarcomas, as a supergroup of STS, account for about 1% of all malignant diseases in adulthood. (4) Malignant soft tissue tumours are significantly rarer than benign soft tissue tumours. (4) The annual incidence of malignant soft tissue tumours is described at approximately 5/100,000. (8) According to a population-based study from the Surveillance Epidemiology and End Results (SEER) database, most subtypes occur slightly more frequently in men than in women (1.5:1), exceptions being alveolar soft part sarcoma and leiomyosarcomas. (9)

1.1.2 Aetiology

An exact pathogenesis of STS is not clearly defined. (10) Numerous influencing factors have been identified, including genetic factors, viral infections, chemical carcinogens, local tissue damage, RTX and CTX. (6, 10) However, they are found in only a minority of STS. (10)

1.1.2.1 Genetic factors

A genetic predisposition in the form of syndromes or germline mutations plays a role in the development of STSs. (11, 12, 13, 14) This is the case in only a small proportion of STS patients and especially in young people with STS. (4, 11) A series of 151 families with children who developed STS suggested a genetic predisposition to cancer in 7-33% of the respondents. (11) Important genetic syndromes associated with STSs are Li-Fraumeni syndrome, neurofibromatosis I, familial adenomatous polyposis or Gardner syndrome, and retinoblastoma. (10, 14, 15, 16)

Li- Fraumeni syndrome (LFS) is inherited in an autosomal dominant manner. (15) A TP53 germline mutation is often found. (14) Patients with LFS have an increased risk of cancer, particularly STS, osteosarcoma, breast cancer and brain tumours. (17) They develop sarcomas earlier than sarcoma patients without LFS. (18)

Familial adenomatous polyposis (FAP) – **Gardner´s syndrome** is inherited in an autosomal dominant manner with an underlying gene mutation of the APC gene (adenomatous polyposis coli gene). (19, 20) Gardner´s syndrome has been characterised by the presence of extraintestinal growths in addition to the adenomatous intestinal polyps typical of FAP. (21) Extraintestinal manifestations include medulloblastoma, desmoid tumours, osteomas, fibromas, epidermal cysts and dental abnormalities. (20, 21, 22, 23)

Retinoblastoma survivors are at increased risk of developing soft tissue and bone sarcomas years later in life. (16) The risk of developing subsequent cancers is significantly higher in the hereditary form of retinoblastoma with a positive family history than in the non-hereditary form. (24) Furthermore, having received RTX contributes to an increased risk and a shorter latency period. (16, 24, 25) A longitudinal study with 1601 retinoblastoma survivors, 963 of whom had the genetic form, illustrates this point. (16) According to this study by Kleinerman et al., the cumulative incidence of developing a second cancer

(sarcomas, melanomas, cancers of the nasal cavities, and brain) 50 years after retinoblastoma diagnosis was 36% (95% confidence interval [CI], 30.9% to 41.1%) for the hereditary form compared to 5.7% (95% CI, 2.4% to 11%) for the non-hereditary form. (16) In addition, in the hereditary form, RTX increased the cumulative probability of developing a second cancer after 50 years to 38.2% (95% CI, 32.6% to 43.8%), compared with a cumulative probability of 21.0% (95% CI, 9.42% to 35.6%) in non-irradiated patients. (16)

Neurofibromatosis is associated with an increased risk of developing malignant peripheral nerve sheath tumours from the benign neurofibromas. (26)

1.1.2.2 Virus infection

Infections with **human herpes virus 8 (HHV-8)** and **Epstein-Barr virus (EBV**) are rarely implicated in the development of sarcomas. HHV-8 is considered an aetiological component of Kaposi's sarcoma. (27, 28) There are reports of EBV-associated smooth muscle tumours in patients with acquired immunodeficiency syndrome. (29, 30) In organ transplant patients, an association between EBV and the development of smooth muscle tumours has also been noted. (31)

1.1.2.3 RTX

The risk of developing a second sarcoma as a result of RTX has been demonstrated. (32, 33) Nevertheless, studies have shown that only a small proportion of all sarcomas are associated with RTX. (34, 35) The frequency increases with the radiation dose, (36) with the length of time observed after irradiation and the younger age at which RTX administered. (37, 38, 39) RTX-associated sarcomas are often diagnosed as high-grade lesions. (38, 40)

They occur as distinct histopathologic subtypes. (40) Undifferentiated/unclassified tumours (formerly called “malignant fibrous histiocytoma” – including now “undifferentiated pleomorphic sarcomas” and round and spindle cell forms (4)), angiosarcomas, leiomyosarcomas, and fibrosarcomas are common. (34, 40, 41) Among patients with breast cancer who have received RTX for this purpose, the most common histopathological secondary sarcoma is cutaneous angiosarcoma. (39, 42, 43)

1.1.2.4 Chemical carcinogens

Chemical carcinogens are thought to play a role in the development of sarcomas. (44) An association between exposure to arsenic and/or vinyl chloride and the development of angiosarcomas in the liver has been described, (45, 46) and phenoxyacetic acids are suspected to promote the development of STS. (47)

1.1.2.5 Chronic oedema, trauma, orthopaedic implants

There are case reports of STS developing after **chronic oedema**: For example, lymphangiosarcomas have been described in the lymphoedematous arm after mastectomy (48, 49) and in chronic lymphoedema caused by filarial infection. (50) There are also described STS developing on the back of **damaged tissue,** after **trauma,** or near **orthopaedic implants**. (4, 6, 51, 52) Although, physicians discuss the possibility of the patient´s attention being focused on pre-existing lesions due to trauma rather than a trauma directly influencing them. (6) However, Kirkpatrick et al. found cell changes similar to an adenoma-carcinoma sequence histologically adjacent to biomaterial sites in rats. (53)

1.1.3 Tumour entities

The current edition of the World Health Organisations (WHO) classification of soft tissue tumours includes more than 100 subtypes, which are summarised in **Table 1**. (4) They are named after the tissue the tumour most resembles and are classified as benign, intermediate 1/2, or malignant depending on LR-risk and metastatic behaviour. (4) For example, tumours that resemble fatty tissue are called liposarcomas and those that resemble synovium are called synovial sarcomas. (4) If this classification is not possible, they are named according to the architectural pattern, for example alveolar, clear cell or epithelioid. (4)

Benign means that the tumours usually do not recur locally and only very rarely form DM. (4) In the case of LR, they are usually not aggressive and cure is possible by complete removal. (4)
Intermediate tumours are divided into intermediate 1 (locally aggressive) and intermediate 2 (rarely metastasising). (4) *Intermediate 1* tumour is characterised by frequent infiltrative, destructive LRs, but only rarely by DM. (4) *Intermediate 2* tumour, on the other hand, is characterised by sporadic DM (mostly lung, lymph nodes) in addition to locally aggressive behaviour. (4)
Malignant tumours are characterised by frequent LRs, destructive growth and DM. (4)

In the following, the histological subtypes that occur in the study on which this diploma thesis is based are further described and are highlighted in **Table 1.**

Table 1. WHO classification of soft tissue tumours.

Adipocytic tumours		
Benign	**Intermediate 1**	**Malignant**
▪ Lipoma NOS ▪ Lipomatosis ▪ Lipomatosis of nerve ▪ Lipoblastomatosis ▪ Angiolipoma NOS ▪ Myolipoma ▪ Chondroid lipoma ▪ Spindle cell lipoma ▪ Atypical spindle cell/ pleomorphic lipomatous tumour ▪ Hibernoma	▪ Atypical lipomatous tumour	▪ Liposarcoma, well-differentiated ▪ Dedifferentiated liposarcoma ▪ Myxoid liposarcoma ▪ Pleomorphic liposarcoma ▪ Myxoid pleomorphic liposarcoma

Fibroblastic/Myofibroblastic tumours			
Benign	**Intermediate 1**	**Intermediate 2**	**Malignant**
▪ Nodular fasciitis ▪ Proliferative fasciitis ▪ Proliferative myositis ▪ Myositis ossificans/ fibro-osseous pseudotumor of digits ▪ Ischaemic fasciitis ▪ Elastofibroma ▪ Fibrous hamartoma of infancy ▪ Fibromatosis colli ▪ Juvenile hyaline fibromatosis ▪ Inclusion body fibromatosis ▪ Fibroma of tendon sheath ▪ Desmoplastic fibroblastoma ▪ Myofibroblastoma ▪ Calcifying aponeurotic fibroma ▪ EWSR1-SMAD3-positive fibroblastic tumour (emerging) ▪ Angiomyofibroblastoma ▪ Angiofibroma NOS ▪ Nuchal fibroma ▪ Acral fibroma	▪ Palmar/plantar-type fibromatosis ▪ Desmoid-type fibromatosis ▪ Lipofibromatosis ▪ Giant cell fibroblastoma ▪ Solitary fibrous tumour, benign	▪ Dermatofibrosarcoma protuberans NOS ▪ Solitary fibrous tumour ▪ Inflammatory myofibroblastic tumour ▪ Myofibroblastic sarcoma ▪ Low-grade myofibroblastic sarcoma ▪ Superficial CD34-positive fibroblastic tumour ▪ Myxoinflammatory fibroblastic sarcoma ▪ Infantile fibrosarcoma	▪ Fibrosarcoma NOS ▪ Solitary fibrous tumour, malignant ▪ Myxofibrosarcoma ▪ Low-grade fibromyxoid sarcoma ▪ Sclerosing epithelioid fibrosarcoma

So called fibrohistiocytic tumours		
Benign	**Intermediate 2**	**Malignant**

▪ Tenosynovial giant cell tumour NOS ▪ Deep benign fibrous histiocytoma	▪ Plexiform fibrohistiocytic tumour ▪ Giant cell tumour of soft parts NOS	▪ Malignant tenosynovial giant cell tumour

Vascular tumours			
Benign	**Intermediate 1**	**Intermediate 2**	**Malignant**
▪ Haemangioma NOS ▪ Intramuscular haemangioma ▪ Arteriovenous haemangioma ▪ Venous haemangioma ▪ Epithelioid haemangioma ▪ Lymphangioma NOS/ Lymphangiomatosis ▪ Acquired tufted haemangioma ▪ Cystic lymphangioma	▪ Kaposiform haemangioendothelioma	▪ Retiform haemangioendothelioma ▪ Papillary intralymphatic angioendothelioma ▪ Composite haemangioendothelioma ▪ Kaposi sarcoma ▪ Pseudomyogenic (epithelioid sarcoma - like) haemangioendothelioma	▪ Epithelioid haemangioendothelioma NOS ▪ Angiosarcoma

Pericytic (perivascular) tumours	
Benign	**Malignant**
▪ Glomus tumour NOS ▪ Myopericytoma: Myofibroma, Myofibromatosis, Infantile Myofibromatosis ▪ Angioleiomyoma	▪ Glomus tumour, malignant

Smooth muscle tumours	
Benign and Intermediate	**Malignant**
▪ Leiomyoma ▪ Smooth muscle tumour of uncertain malignant potential	▪ Leiomyosarcoma NOS

Skeletal muscle tumours	
Benign	**Malignant**
▪ Rhabdomyoma NOS	▪ Embryonal rhabdomyosarcoma NOS ▪ Alveolar rhabdomyosarcoma ▪ Pleomorphic rhabdomyosarcoma NOS ▪ Spindle cell rhabdomyosarcoma ▪ Ectomesenchymoma

Gastrointestinal stromal tumours

Peripheral nerve sheath tumours	
Benign	**Malignant**

▪ Schwannoma NOS ▪ Neurofibroma NOS ▪ Perineurioma NOS ▪ Granular cell tumour NOS ▪ Nerve sheath myxoma ▪ Solitary circumscribed neuroma ▪ Meningioma NOS ▪ Hybrid nerve sheath tumour	▪ Malignant peripheral nerve sheath tumour NOS ▪ Melanotic malignant peripheral nerve sheath tumour ▪ Granular cell tumour, malignant ▪ Perineurioma, malignant

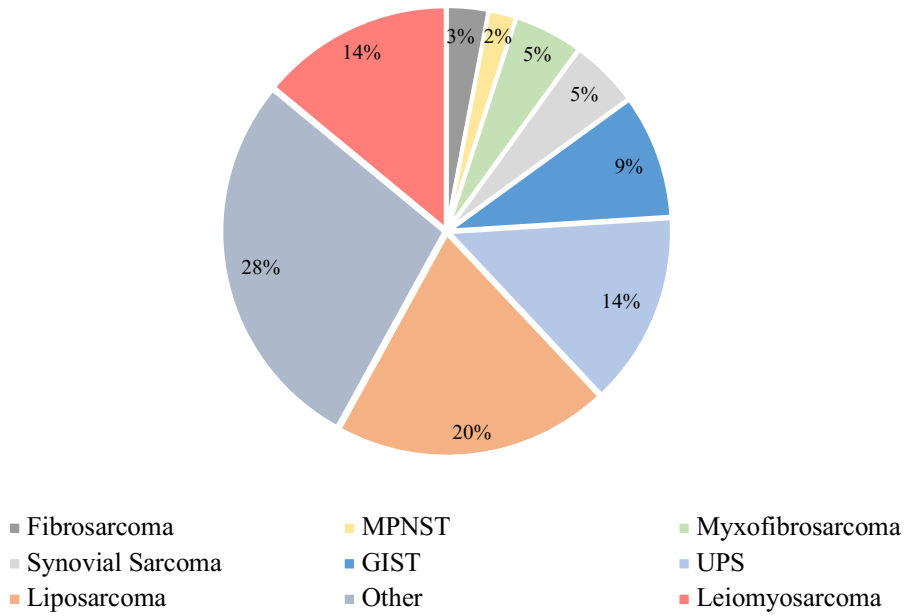
Chondro-osseus-tumour	
Benign	**Malignant**
▪ Chondroma NOS	▪ Osteosarcoma, extraskeletal

Tumours of uncertain differentiation			
Benign	**Intermediate 1**	**Intermediate 2**	**Malignant**
▪ Myxoma NOS ▪ Aggressive angiomyxoma ▪ Pleomorphic hyalinizing angiectatic tumour ▪ Phosphaturic mesenchymal tumour NOS ▪ Perivascular epitheloid tumour, benign ▪ Angiomyolipoma	▪ Haemosiderotic fibrolipomatous tumour ▪ Angiomyolipoma, epithelioid	▪ Atypical fibroxanthoma ▪ Angiomatoid fibrous histiocytoma ▪ Ossifying fibromyxoid tumour NOS ▪ Myoepithelioma NOS ▪ Mixed tumour, NOS ▪ Mixed tumours, malignant, NOS	▪ Phosphaturic mesenchymal tumour, malignant NTRK-rearranged spindle cell neoplasm (emerging) ▪ Synovial sarcoma NOS ▪ Epithelioid sarcoma NOS ▪ Alveolar soft part sarcoma ▪ Clear cell sarcoma NOS ▪ Extraskeletal myxoid chondrosarcoma ▪ Desmoplastic small round cell tumour ▪ Rhabdoid tumour NOS ▪ Perivascular epithelioid tumour, malignant ▪ Intimal sarcoma ▪ Ossifying fibromyxoid tumour, malignant ▪ Myoepithelial carcinoma ▪ Undifferentiated sarcoma ▪ Spindle cell sarcoma, undifferentiated ▪ Pleomorphic sarcoma, undifferentiated ▪ Round cell sarcoma, undifferentiated

Legend: *NOS – Not otherwise specified*

Table 1: Classification of benign and malignant soft tissue sarcoma defined by the WHO 2020. (4)

Figure 1 shows the most common histological subtypes according to a modern Memorial Sloan Kettering Cancer Centre (MSKCC) data series of 10,0000 STS in adults - liposarcomas, leiomyosarcomas and undifferentiated pleomorphic sarcomas. (54)



Legend: *MSKCC – Memorial Sloan Kettering Cancer Centre; MPNST – Malignant peripheral nerve sheath tumour; GIST – Gastrointestinal stromal tumour; UPS – Undifferentiated pleomorphic tumour*

Figure 1: Histologic subtype distribution in a modern database of 10.000 adult soft tissue sarcomas (MSKCC).(54)

1.1.3.1 Liposarcoma

Liposarcomas (LPS) are malignant tumours arising from adipocyte progenitor cells (4) and account for approximately 15% of STS. (55) There are three main morphological subtypes: myxoid/round cell, well-differentiated (WDLPS) / dedifferentiated (DDLPS) and pleomorphic liposarcomas, which differ in morphology, clinical behaviour and treatment sensitivity. (4, 56) The most frequent localisation is the extremities, WDLPS/DDLPS and pleomorphic liposarcomas also frequently occur in the retroperitoneum. (4, 57)

WDLPS is the most common LPS (about 40-50%) and is mostly localised in the extremities. (4) It carries a low risk of DM, LR, and is curable, if localised in the extremities and completely removable. (58) **DDLPS** is often localised in the retroperitoneum, and may arise de novo or occasionally from a WDLPS. (59) DDLPS is usually high-grade, has a locally

aggressive behaviour and a higher risk of LR and DM. (59, 60) MDM2 and CDK4 amplifications are often present in both tumours. (4)

Myxoid/round cell liposarcomas are more sensitive to CTX than WDLPS and DDLPS. (57) They contain a specific translocation t(12;16) (q13;p11), where the CHOP gene is inserted next to a new gene called TLS (translocated in liposarcoma) or FUS (fused in sarcoma). (61)

Pleomorphic liposarcoma is often aggressive, high grade and associated with higher risk of DM. (62, 63)

1.1.3.2 Myxofibrosarcoma

Myxofibrosarcoma (MFS) is a pleomorphic malignant fibroblastic neoplasm with variable myxoid stroma. (4) It has been described as one of the most common sarcomas in adult patients, approximately equally common in men and women. (64) It occurs mainly between the sixth and eighth decades of life, only rarely in those under thirty. (4, 64)

The patients usually present with a slowly growing painless mass. (4) MFS is usually localised in the limbs, more often in the lower than in the upper limbs. (4, 64) It rarely occurs in the trunk, head, neck, hands, or feet. (4) A special feature is that many are localised superficially, i.e., in the skin/subcutaneous tissue. (64, 65)

Superficially located MFS typically appear as multiple, variably fibrous or gelatinous nodules. (4) Tumour necrosis areas are usually associated with high-grade lesions. (4) The cell spectrum, pleomorphism and proliferative activity of MFS are highly variable. (4) Common features are usually multinodular growth with myxoid stroma and incomplete fibrous septa. (4)

1.1.3.3 Synovial sarcoma

Of all STS, synovial sarcoma (SS) account for approximately 5-10% (66, 67) and typically occur in young adulthood in the extremities, frequently in a juxta-articular position. (4) They are almost equally distributed in both sexes. (67)

There are monophasic and biphasic types depending on the presence or absence of epithelial cells. (4) In the monophasic type, only malignant spindle cells are present, whereas in the biphasic type, the malignant spindle cells often form glandular structures together with epithelial cells. (4)

SSs are usually characterised by the chromosomal translocation t(X;18) (p11.2; q11.2). (68) Different fusions of the SS18 gene with one of the homologous genes on the X chromosome are then associated with the corresponding histological subtype, monophasic (SS18-SSX2) or biphasic (SS18-SSX1). (68, 69) There are some reports of SS18-SSX2 positive SS having a lower proliferation rate, and a better outcome than SS18-SSX1 positive SS. (68, 69) An immunohistochemically detectable novel SS18-SSX antibody is described as a highly sensitive (95%) and specific (100%) marker for SSs. (70)

1.1.3.4 Leiomyosarcoma

The tissue of origin of leiomyosarcomas (LMS) is smooth muscle. (4) They can occur anywhere in the body, classically in the extremities, but also from the retroperitoneum, trunk, (71) big vessels, (72) or the uterus. (4, 73) Cutaneous LMS have a lower risk of DM compared to subcutaneous and deep-seated LMS. (73) LMSs arising from the uterus are subdivided from the others, because of their different gene expression patterns. (74)

1.1.3.5 Undifferentiated/unclassified soft tissue sarcoma

Undifferentiated/unclassified STS (USTS), a diagnosis of exclusion, have no specific lineage of differentiation. (4) They previously belonged to the large group of malignant fibrous histiocytomas (MFH), of which some sarcomas have been re-categorised after re-histologic and immunohistochemical analysis. (75)

1.1.3.6 Malignant peripheral nerve sheath tumour

Malignant peripheral nerve sheath tumours (MPNST) originate in the ectoderm and account for 3-5% of STS. (4) They commonly arise from peripheral nerves, from benign nerve sheath tumours, and in patients with neurofibromatosis type 1. (4) Furthermore, MPNSTs are frequently associated with RTX (4, 76) and are more prevalent in childhood cancer survivors. (77)

Typically, MPNSTs are diagnosed in the 20-50 years of age (4) and are commonly localised in the extremities and trunk, but also in the head or neck. (4, 78) Clinical suspicion exists in the case of rapid changes in pain, neurological deficits or enlargement of the mass. (4, 79, 80) This is particularly the case with pre-existing tumours or neurofibromatosis type 1. (4,

80) Diagnosis of MPNST can be challenging. (4) The expression of S100 protein can be helpful in diagnosis, but is not uniformly present. (4)

1.1.4 Diagnostic Evaluation and Workup

1.1.4.1 Clinical Presentation

The clinical presentation of STS is non-specific. (4) Most patients present with a slowly enlarging mass. (4, 81) STS can occur anywhere in the body, but most frequently in the extremities. (4, 81) **Figure 2** shows the anatomical distribution of STS in 4550 adults reviewed by the American College of Surgeons. (81)

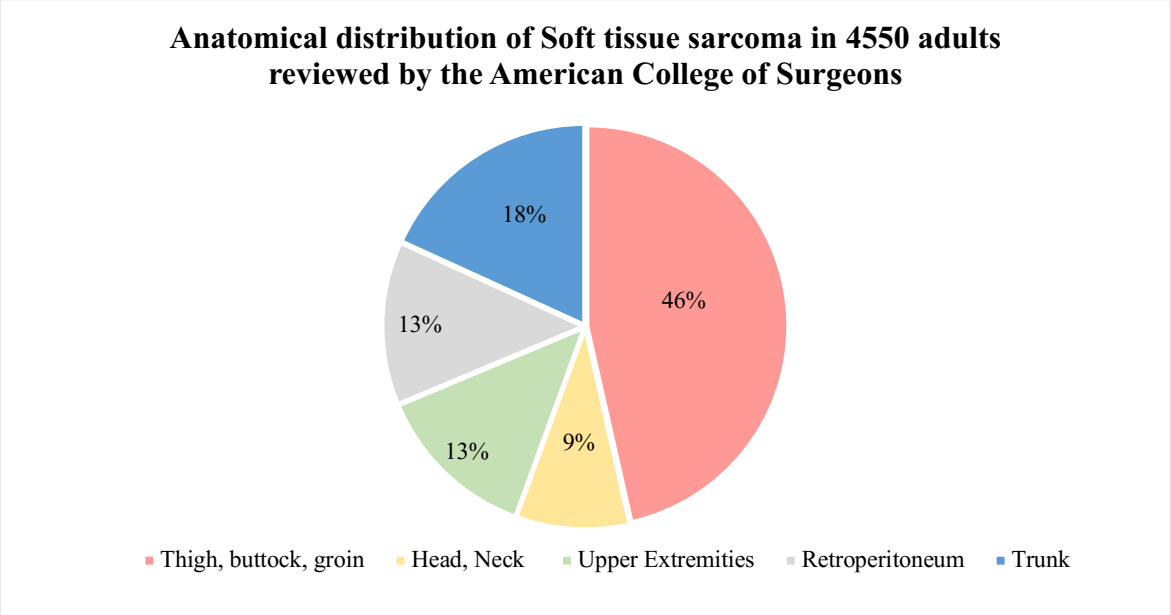


Figure 2: Anatomic distribution in 4550 adults reviewed by the American college of surgeons. (81)

At initial diagnosis, the presence of DM is uncommon, but more likely in deep-seated, large, histologically high-grade sarcomas and certain subtypes (e.g. MPNST). (82)
STS metastasise mainly hematogenous to the lungs. (83, 84, 85) Spread to regional lymph nodes is rare, (86) and more frequent in embryonal rhabdomyosarcomas, epithelioid sarcoma and angiosarcoma. (86)

1.1.4.2 Importance of early referral to a specialised centre

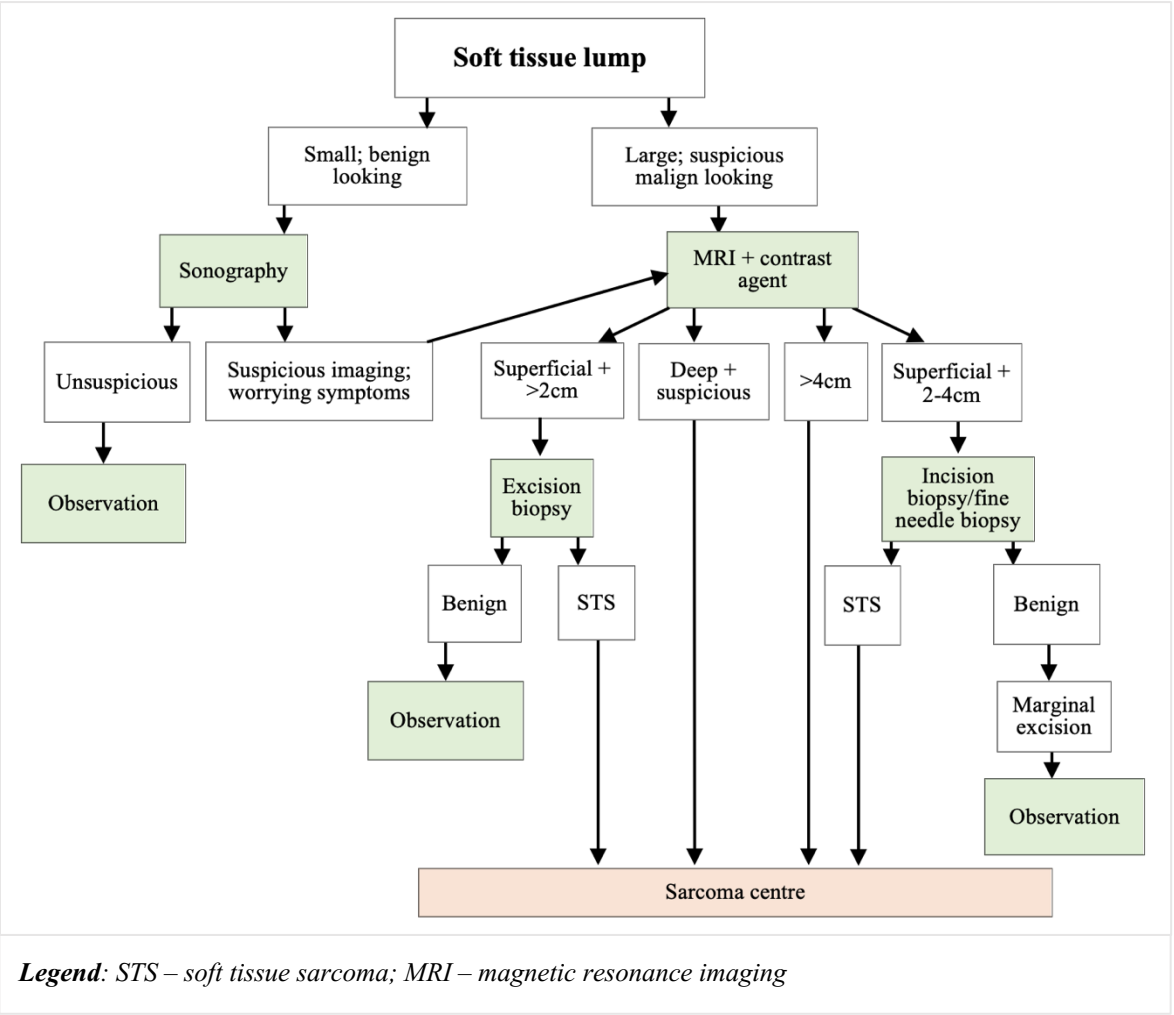
Due to the nonspecific symptoms and rarity of the tumours, a delay diagnosis is common. (87) Their nonspecific symptoms and rarity often lead to delayed presentation of the patient

to the primary care physician, to possibly delayed suspicion or diagnosis, and in delayed referral to a reference centre. (88, 89, 90) By the time a definite diagnosis can then be made by imaging and biopsy, a great deal of time has often elapsed since the patient's first symptoms. (88, 89, 90) Over time, the tumour grows, worsens surgical conditions and makes DM at initial presentation more likely. (91)

Multidisciplinary care by STS specialists improves adherence to guidelines and patient outcomes. (7, 92, 93) Gutierrez et al. reported a lower rate of limb amputation (9.4% vs. 13.8%; p=0.048) and significantly better survival (OR 1.292; p=0.047) in patients treated in so-called high-volume centres, where a large number of STS patients receive multidisciplinary care. (94) Venigalla et al. highlighted this effect with regards to OS (HR 0.87; 95% CI 0.80-0.95; p=0.001). (95)

1.1.4.3 Diagnostic pathway

The recommendations for the diagnostic evaluation described below are adapted from the National Comprehensive Cancer Network (NCCN) guidelines, (5) the European Society for Medical Oncology (ESMO) guidelines (1) and a review about diagnosis and treatment of STS of the extremities and trunk by Smolle et al.. (3) **Figure 3** shows a diagnostic pathway recommended by Smolle et al.. (3)



***Legend**: STS – soft tissue sarcoma; MRI – magnetic resonance imaging*

Figure 3: Diagnostic evaluation algorithm according to Smolle et al.. (3)

1.1.4.4 Patient history and clinical examination

Differentiating malignant from benign soft tissue tumours is difficult. (4) A detailed medical history as well as inspection and palpation can provide initial clues. (3)

Aspects that should be recorded in the **medical history** are: First appearance, age, duration of symptoms, size, size changes, (96) symptoms such as paraesthesia, pain or oedema. (96) No changes in shape or size over a long period of time (96) or a newly formed tumour in association with trauma are more indicative of a benign tumour (haematoma). (3, 97) Newly formed, growing tumours are often malignant. (96, 97) Pain has not been shown to be a sensitive marker of malignancy or benignity. (96) Benign haematoma associated with trauma can be very painful, (3) and MPNST can present with severe radicular pain and neurological deficit. (80)

Palpation and inspection can determine size and location as well as signs of inflammation. (3) Malignant soft tissue tumours are more likely to be deep-seated. (98) These tumours lie under the fascia or are fused to it and are difficult to move, while subcutaneous tumours can be easily moved under the skin. (3) Furthermore, tumours larger than about 4cm should be suspected of being malignant. (91, 96, 99) Signs of inflammation are redness, pain and hyperthermia. (3)

1.1.4.5 Imaging

In case of suspicious findings, diagnostic imaging should be performed prior to any biopsy. (3, 100) Various imaging techniques help to plan the further procedure by confirming the clinical findings and identifying the local extension and DM. (3) Later they are used as an aid in percutaneous biopsy and therapy controls. (1, 100) In primary soft tissue lesions of the limbs or trunk, cross-sectional imaging with magnetic resonance imaging (MRI) is performed for diagnostic clarification. (1)

Ultrasound (US) is useful for initial evaluation of the lesions. (101) It provides accurate information about the size, relationship to adjacent tissue and perfusion of the tumour using Doppler mode. (102) Cysts, abscesses and haematomas can be identified or excluded. (101, 103) Heavily perfused lesions with centripetal vessels and scattered peripheral vascularisation are indicative of malignancy. (102) If STS is likely, a computer tomography (CT) or MRI should be added. (1)

Radiographs are quick and easy to perform and provide few relevant information. They show intratumoural calcifications and bone involvement, (1) and detect soft tissue swelling caused by primary bone lesions. (104) However, they do not provide enough information about the tumour. (3)

MRI is mostly described as the method of choice for the diagnostic evaluation of soft tissue tumour of the extremities, superior to CT. (1, 105, 106) However, a multicentre prospective study with 326 participants, including 133 patients with STS and 183 patients with primary bone tumours, found no significant difference between CT and MRI in the detection of tumour involvement of muscles, bones, joints, nerves and vessels. (107)

1.1.4.6 Biopsy

A biopsy containing sufficient tissue for histological typing and grading is essential before starting therapy. (5) Adherence to the biopsy planning rules according to Leithner et al. (108) (3) described in **table 2** should help to plan and perform the biopsy appropriately. (3, 108)

Table 2. Rules for planning a biopsy.	
I.	**Do not hurry** → take time, carefully plan your next steps
II.	**Do not contaminate joints or neurovascular structures** → plan your biopsy based on anatomy and possible future surgery
III.	**Do adequate imaging before any surgery** → organise MRI with contrast agent
IV.	**Send biopsy sample to a pathologist specialised in soft tissue and bone tumours** → check with your nearby pathology department to find out who to contact
V.	**Take the shortest way through just one compartment** → remember to follow rules II, VI
VI.	**Plan your biopsy with a view to possible resections** → cut along the length of the limb
VII.	**Gain sufficient and representative tissue** → take samples from the peripheral area, not central necrotic regions
VIII.	**(If possible) store small fraction of tissue fresh frozen (ca. 80°) for research purposes** → get in contact with the pathologist
IX.	**Operate in the most atraumatic way possible** → keep incisions to a minimum or use CT-guided biopsy for deep lesions
X.	**Prevent post-operative haematoma** → ensure thorough haemostasis, use a drain (inserted directly through the skin incision) and apply a compression bandage
Legend: *MRI – magnetic resonance imaging; CT – computer tomography*	

Table 2: Rules for planning a biopsy according to Leithner et al.. (108)

Core needle biopsy (CNB) is the standard method in most cases. (1) When properly performed and interpreted by an experienced pathologist, CNB provides accurate diagnostic information regarding malignancy, grade and treatment planning, (109, 110, 111, 112) while having a low complication rate and cost. (113)

Excisional biopsy may be a good option for <3cm superficial lesions. (1)

CT- or US-guided biopsy may be helpful to place the biopsy site more precisely, especially in deeper lesions. (114, 115, 116)

Open biopsy is required if adequate tissue is not available, (109) and has been reported to be more accurate than CNB. (113) Subsequent open incisional biopsy is described in 20% of cases after CNB. (117)

Fine needle aspiration (FNA) cytology can be used to confirm recurrence, (118) but less so to make the initial diagnosis, as it is less accurate than CNB. (119)

1.1.4.7 Grading and Staging

In order to be able to predict the clinical course of STSs, grading and/or staging is required. (4) Several **grading systems** have been developed to represent the prognostic value of histological assessment. (4, 120, 121) The French Federation of Cancer Centre Sarcoma Group (FNCLCC) system is widely used. (120, 122, 123, 124) It classifies tumours into three grades based on tumour cell differentiation, extent of necrosis and mitotic count (**Table 3**). (4, 122)

a. Grade 1 (G1) = low grade, well differentiated
b. Grade 2 (G2) = intermediate grade, moderately differentiated
c. Grade 3 (G3) = high grade, poorly differentiated

High grades indicate more aggressive tumours, which are more likely to be associated with the occurrence of DM (125) and tumour mortality. (126) When using the grading system, it should be used for untreated tumours. (1, 4) Furthermore, its prognostic value depends on the histological subtypes. (127)

Table 3. Histological Grading according to FNCLCC.

Parameter	Assessment	Score
Differentiation	clearly visible	1
	not visible	2
	unclear	3
Necrosis	non	0
	<50 %	1
	>50 %	1
Mitosis (per 10 HPF)	<10	1
	10 - 19	2
	>20	3
Histologic grade	G1	Total score: 2, 3
	G2	Total score: 4, 5
	G3	Total score: 6, 7, 8

Legend: *FNCLCC – Fédération Nationale des Centres de Lutte Contre le Cancer; HPF – high power field; G1 – grade 1; G2 – grade 2; G3 – grade 3*

Table 3: Sarcoma grading according to French Federation of Cancer Centre Sarcoma Group. (122, 128).

Existing **staging manuals** are of limited clinical relevance. (1) The Union for International Cancer Control (UICC) – American Joint Committee on Cancer (AJCC) staging classification system for STS is often used. (1, 5) It takes into account tumour size (T), lymph node involvement (N), and the presence or absence of DM (M), as well as histologic grade (G) based on the FNCLCC grading system. (129, 130) The current 8th edition of AJCC Staging Manual is shown in **table 4**. (129)

Table 4. AJCC TNM-system - 8th edition.

Stage	Primary Tumour	Metastasis	Grading
I A	T1	N0; M0	G1
I B	T2; T3; T4		G1
II	T1		G2/G3
III A	T2		G2/G3
III B	T3; T4		G2/G3
IV	Any T	N1; M0	Any G
		Any N; M1	

Legend: *AJCC – american joint committee on cancer; TNM – tumour-node-metastasis;*
T1 – tumour size ≤5cm; T2 – tumour size 5-10 cm; T3 – tumour size 10-15cm; T4 – tumour size.
N0 – no regional lymph node metastasis or unknown lymph node status; N1- regional lymph node metastasis;
M0 – no distant metastasis; M1 – distant metastasis. G1 – grade 1; G2 – grade 2, G3 – grade 3

Table 4: Tumour- node-metastasis system - AJCC 8th edition.

1.1.5 Prognostic factors

Several factors that may influence the oncologic outcome of patients with eSTS have been reported in the literature. (126, 131) Surgical margins, tumour grade, tumour size, localisation, and histologic subtype have been reported to influence LR risk, whereas tumour size and histologic grade are critical for survival and DM. (126, 132, 133, 134)

High-grade tumours are described as negative prognostic factors for the occurrence of LR, DM (125, 131) and disease-specific survival (DSS). (126, 132, 135)

In a retrospective study of 1240 non-metastatic adult STS patient from the FNCLCC database, histologic grade appeared as an independent prognostic factor of metastasis development in MFH, LPS, LMS, SS and unclassified sarcoma type. (125)

Patients age has been described as a prognostic factor for LR-risk (126) and survival in some studies. (9, 132, 135) In a population-based study from the SEER database, for example, younger patient age (<50 years) was associated with significantly better survival (88.8 ± 0.2% vs. 40 ± 0.3% p<0.001). (9) In this regard, the decline in survival was gradual with increasing age and not abrupt with the onset of adulthood. (9)

Histopathologic subtypes also differ in their recurrence risk. (126, 135, 136) In a prospective study of 1041 patients with localised eSTS, Pisters et al. described the following histologic subtypes as independently prognostically unfavorable factors: MPNST and fibrosarcoma for LR risk, LMS and "non-liposarcomas" for DM risk, and LMS and MPNST for DSS. (126)

Tumour size and anatomical location were described as influencing factors for LR and DM and OS. (132, 137, 138)

In a retrospective analysis on prognostic factors in 1225 patients with localised STS treated with conservative surgery and RTX, tumour size of more than 10 cm in greatest extent was reported as a prognostic factor for the development of LR (risk ratio [RR] 1.7; 95% CI 1.6-3.0; p<0.001), and tumour size of more than 5 cm was reported as a prognostic factor for the occurrence of DM (RR 2.9; 95% CI 2.3-3.8; p<0.001) and poorer disease-free survival (DFS) (RR 2.9; 95% CI 2.3–3.7; *p*<0.001). (132)

In a prospective study, Gerrand et al. described a lower 5-year LR-free rate for sarcomas in the upper extremity (UE) than in the lower extremity (LE) (82% UE vs. 93% LE; p=0.002) and a higher 5-year metastasis-free rate in the UE than in the LE (82% UE vs. 69% LE; p=0.013). (137) It should be noted that UE tumours were smaller (6.0cm UE vs. 9.3cm LE; p<0.001), underwent more unplanned excision (64.0% UE vs. 46.9% LE; p<0.001), and less frequently received RTX (70.5% UE vs. 84.8% LE, p<0.001). (137)

The current TNM classification (AJCC eight edition) no longer considers superficial or deep location of STS. (130)

Marginal status has a significant impact on LR risk in patients eSTS (126, 131, 135, 139, 140) and is controversial in DSS and metastasis-free survival (MFS). (131, 135)
Inadequate surgical margin is described by Trovik et al. as an independent risk factor for LR (RR 2.9; 95% CI 1.8-4.6; p<0.001), but not for metastases (RR 1.1; 95% CI 0.8-1.7; p=0.6). (131) Intralesional and marginal margins were counted as inadequate margins. (131)
In contrast, Harati et al. showed in a retrospective study that positive margins were independently associated with a significantly increased risk of LR (HR: 2.66 [1.68–4.22]; p <0.001), DSS (HR 2.86 [95% CI: 1.45–5.61]; p=0.002)) and MFS (p=0.016). (135) They demonstrated an equal effect of narrow and wide margins on DSS, local recurrence free survival (LRFS), and MFS. (135)

Validated **dynamic prognostic nomograms** can be used to assess personalised risk on OS and DM after surgical resection on eSTS. (124, 141)

1.1.6 Treatment

The three main therapeutic pillars in the treatment of eSTS are surgery, RTX and CTX. (1) Until three decades ago, amputation was a common treatment option for eSTS given the lack of effective alternatives for local control. (142, 143, 144, 145, 146) Over the years, developments in multimodal therapy including the use of RTX, have led to the implementation of more limb-preserving therapies and a decrease in amputation rates. (142, 143, 144, 145, 146) As early as 1982, Rosenberg et al. described no significant differences in DFS (71% and 78% at five years; p=0.75) and OS (83% and 88% at five years; p=0.99) with limb-preserving surgery plus adjuvant radiotherapy (ARTX) compared to amputation in a prospective randomised trial with 43 adult patients with high-grade eSTS. (146)

The assessment and treatment of patients with STS should be carried out in a reference centre by a multidisciplinary team. (7, 147) Collaboration between specialised pathologists, radiologists, surgeons (orthopaedic surgeons, thoracic surgeons, plastic surgeons and general surgeons), medical oncologists, radiotherapists and physiotherapists is crucial. (7, 147, 148) Better adherence to guidelines and better quality of care in sarcoma centres have been described. (1, 7, 92, 93) Thus, patients treated in centres where many STS patients are treated with this multidisciplinary approach have a higher rate of limb salvage and better survival

than centres with a lower volume. (94, 95) Treatment must be individualised to the patient, depending on variables like tumour location, histology, tumour grade and size, and the patient's health status. (149)

The ESMO guidelines provide treatment pathways divided into: (1) localised, clinically resectable STS; (2) localised, clinically non-resectable STS; (3) advanced/metastatic, clinically resectable STS; (4) advanced/metastatic, clinically non-resectable STS. (1)

1.1.6.1 Surgery

Surgery is the standard treatment for all patients with localised eSTS arising in adults. (1) Currently, largely limp-sparing procedures are performed. (5, 146) Amputation plays a role in cases where the remaining limb is not functional. (1, 143) Examples include recurrent tumours located in the proximal thigh that have already undergone RTX and/or reconstruction, or primary tumours with severe neurovascular involvement. (143) If mutilating surgery is necessary, in cases of extensive tumour involvement, multimodality treatment approaches and plastic reconstruction options should be discussed in shared decision making with the patient. (1)
Various reconstructive procedures can be considered that may lead to satisfactory results. (150, 151)

1.1.6.1.1 Surgical procedure

In localised eSTS, the standard surgical procedure is an en bloc resection, meaning a single removal of the complete tumour, with R0-margins, i.e. is a margin of normal tissue. (1) Enneking et al. described surgical procedures according to the relationship of the plane of dissection to the lesion, its pseudocapsule and the surrounding normal tissue (**Table 5**). (152)

Table 5. Enneking et al. surgical procedures

Intralesional resection	Surgical opening of the tumour capsule to preserve important structures with the awareness of an increasing risk of LR.
Marginal resection	Planned resection close to the tumour capsule. Resection margins pass through a "reactive zone" or the "pseudotumour capsule" which contains vital tumour cells.
Wide resection	Resection with a clear safety distance to the tumour given by healthy muscle tissue or fascia.

Radical resection	Resection of the entire STS-affected anatomic compartment.
Legend: *STS – soft tissue sarcoma*	

Table 5: Surgical procedure according to Enneking et al. (152)

Wide surgical resection is recommended. (153) Marginal resection may be considered for atypical lipomatous tumours, despite knowledge of the increased risk of LR. (1, 154) If the tumour is in close proximity to critical structures such as important nerves, bones, or vessels, sparing them with predictable positive margins helps increase functional outcomes. (155)

1.1.6.1.2 Surgical margin

Resection with negative margin, called R0 resection, is usually the primary goal of curative surgical intervention. (1, 156) Still, there is no uniform definition of an adequate margin (157) given by the different anatomical locations and ways of achieving largely negative margins in STS. (158, 159, 160, 161)

So, the **R-Classification** speaks of an R0 resection for macroscopically and microscopically tumour-negative surgical margins, regardless of the tumour-free width of the margin, (145) the **UICC Classification** defines an R0 resection only from a tumour-free resection margin with a width of at least 1mm (**Table 6)**. (162)

Table 6. Comparison of R- and UICC- Classification.			
R- Classification (AJCC)		**UICC Classification**	
R0	Resection margin or intact barrier free of tumour cells	**R0**	Resection margin >1mm
R1	Tumour cells microscopically detectable at the margin or resection alongside pseudo-capsule	**R1**	Resection margin <1mm
R2	Macroscopic involvement of tumour cells	**R2**	Macroscopic involvement of tumour cells
Legend: *AJCC – american joint committee on cancer; UICC – union internationale contre le cancer*			

Table 6: Comparison of R-Classification (145) and UICC-Classification (162).

In the retrospective study of Kainhofer et al. is described a superiority of R0 resection according to the UICC classification (minimal clear resection margin ≥1mm) over R0

resection according to the R-classification (resection margin clear but <1mm possible) **(Table 6**). (163)

The necessary width of resection margin is described as depended on several factors: histologic subtype, neoadjuvant therapies, presence of resistant anatomic barriers (muscle fascia, periosteum, epineurium, vascular adventitia). (1) The type of tissue that forms the surgical margin plays a role in the safety against tumour cells. (1)

R1 resections may be tolerable in diligently selected cases. (1) For R2 surgery, the ESMO guidelines describe re-excision at a referral centre as mandatory. (1) Likewise, neoadjuvant treatments should be taken into account. (1)

In 2017, Gingrich et al. analysed independent predictors of R0 resection. (164) Positive paired indicators were performance in an academic/research centre (odds ratio [OR]1.366; 95% CI 1.204-1.554; p<0.0001) and the use of NRTX (OR 1.826; 95% CI 1.608-2.073; p<0.0001). (164) Several histologic subtypes, like MPNST and liposarcoma were associated with a lower likelihood of an R0 resection (liposarcoma, NOS: OR 0.154; 95% CI 0.442-0.597; p=0.000 MPNST: OR 0.646; 95% CI 0.548-0.762; p<0.000), as well as grade 2 tumours (OR: 0.878; 95% CI 0.788-0.978; p=0.018). (164)

1.1.6.1.3 Unplanned excision

An unplanned excision is the removal of a soft tissue lesion that was usually mistaken for benign and performed without adequate imaging. (165) Due to heterogeneity and rarity of STS unplanned excisions occur frequently (166, 167) and make options for subsequent appropriate oncologic management more challenging. (168) They can lead to haematoma formation, contamination of previously uninvolved compartments, inappropriate incision and/or drainage tube localisation and complicated appropriate assessment of STS. (169)

Re-resection at a referral centre should be considered, (1) if technically feasible and with acceptable morbidity. (170, 171, 172, 173, 174) Tumour biology should be considered in re-resection planning. (1) Thus, atypical lipomatous tumors and classic dermatofibrosarcoma protuberances do not require re-excision. (1)

1.1.6.2 CTX

There are no general treatment recommendations for the use of chemotherapeutic agents in the treatment of eSTS. (1) It should be decided on a case-by-case basis, taking into account the patient's health status, tumour histology, spread, and resectability. (1) Numerous agent-depended potential side effects should be noted, which may also lead to treatment discontinuation, such as nausea, fatigue, anorexia, dysgeusia, gastrointestinal disturbances, oral ulceration, as well as myelotoxicity, cardiotoxicity, cumulative renal injury, bladder toxicity and central encephalopathy. (175)

In **localised resectable eSTS**, the use of CTX is not a standard measure but may be considered for fit patients at high risk of death. (1) Anthracyclines+ifosfamide (A+I) regimen is commonly used. (1)

In **advanced or metastatic unresectable eSTS**, systemic treatment with mainly palliative intent may be suggested. (1) The standard treatment would be anthracycline based. (1) There is no evidence for improvement in OS with the use of multi-agent CTX than with doxorubicin alone, although a better overall response rate (ORR) and longer (progression-free survival) PFS was observed in specific histotypes. (175)

One randomised trial of Judson et al. compared doxorubicin alone with doxorubicin+ifosfamid in locally advanced, unresectable or metastatic high-grade STS and showed no significant benefit from the addition of ifosfamide in terms of OS (12.8 vs. 14.3 months; HR 0.83; p=0.076), but higher ORR and median PFS rates (ORR: 26% vs. 14%, p<0.0006 and for PFS: 7.4 vs. 4.6 months; HR 0.74 [95% CI 0.60-0.90], p=0.003). (175) However, in selected histological subtypes, particularly those that respond to ifosfamide, multi-agent CTX may be considered. (1) This requires the patient to have a good performance status. (1)

In LMS, doxorubicin + dacarbazine is the first-line combination therapy, due to lack of response to ifosfamide. (1, 176) For unresectable angiosarcomas, weekly paclitaxel has been shown to be clinically effective in a phase II trial. (177) An alternative for advanced angiosarcoma is gemcitabine, alone (178) or in combination with docetaxel. (1) In patients with inoperable and/or metastatic dermatofibrosarcoma protuberans, imatinib is considered the standard first-line treatment. (1, 179)

1.1.6.2.1 Neoadjuvant chemotherapy

Neoadjuvant chemotherapy (NCTX) may have a positive impact on further disease and treatment progression in locally advanced and high-risk STS of the trunk and extremities. (180, 181) Promising intentions are to shrink the tumour and thus increase the chance of limb-sparing surgery, to achieve potentially better negative histologic margins and thus reduce the incidence of LR, and to eliminate possible micro metastases, reduce postoperative complications and improve OS. (181, 182)

In a randomised, phase III trial by Gronchi et al., administration of histotype-tailored (HT) NCTX did not prove significantly superior to the A+I regimen in high-risk STS in terms of DFS (0.55 A+I vs. 0.47 HT; HR 1.23 [95% CI, 0.88-1.73]; p=0.32) and OS (0.76 A+I vs. 0.66 HT; HR 1.77 [95% CI 1.10-2.83; p=0.02). (183)

Chemoradiation, the combined use of CTX and RTX, concurrently or sequentially, may be aimed to reduce the risk of LR, distant recurrence, and mortality by intensifying therapy, or to minimise wound complications (WC) by de-intensifying RTX, or to evaluate response to treatment to assist in prognostic assessment and adjuvant treatment planning. (184) There is evidence that concomitant use of doxorubicin and RTX in advanced and/or metastatic tumour has a positive impact on response rate and OS. (185)

1.1.6.2.2 Adjuvant chemotherapy

For STS that typically occur in adults, there is no consensus on an overall benefit of adjuvant chemotherapy (ACTX). (186, 187, 188) NCCN and ESMO guidelines recommend offering ACTX for high-risk STS, (5, 154) weighing the benefit individually against the risk of anticipated treatment-related toxicity and considering factors such as health status, disease location, and histology. (5)

Two meta-analyses have shown conflicting results on this issue. (148, 189) The updated meta-analysis by Pervaiz et al. reported a significant benefit of a correct therapy regimen with anthracyclines in terms of a reduced LR- and DM risk and a trend towards an increased OS. (189) Improvement is described with additional administration of ifosfamide, but with consideration of the increased toxicity profile. (189) That analysis, however, did not consider the data from the largest negative trial, which didn´t report benefit in OS. (190)

A pooled analysis of two studies including the above that examined the value of A+I-based therapy failed to find any benefit of this treatment regimen in terms of OS. (191)
A long-term follow-up of the randomised clinical trial of the Italian and Spanish sarcoma groups found no inferiority of three cycles (neoadjuvant) of conventional full-dose CTX compared with five cycles (three neoadjuvant + two adjuvant) in patients with high-risk STS. (192)

1.1.6.2.3 Isolated hyperthermic limb perfusion

Isolated limb perfusion (ILP) with recombinant human tumour necrosis factor- alpha (TNF-alpha) and melphalan represents a potential treatment for selected patients with locally advanced STS of the limbs in whom resection in healthy tissue and/or preservation of the limb is not possible. (3)

An isolated circuit is created in the tumour-bearing limb using a heart-lung machine. (3) After induction of mild hyperthermia to enhance the effects of TNF-alpha and melphalan, the chemotherapeutic agents are administered. (3) Finally, a 90 min washout with crystalloid or colloid solution follows. (3) The vascular effect of TNF-alpha is critical. It destroys tumour-associated vessels by endothelial apoptosis and increases vascular permeability, leading to significantly higher uptake of cytotoxic agents into the tumour. (193, 194, 195) It can be administered via ILP at significantly higher doses than via the systemic route, with fewer systemic side effects. (196)

Due to the described effect of TNF-alpha, this method is particularly potent in well-vascularised tumours and, according to a retrospective study by Rastrelli et al., in LPSs. (197) In a systematic review, Bhangu et al. describe the outcome of patients with eSTS after treatment with ILP from 18 studies with a total of 1030 patients; TNF-alpha and melphalan were most commonly used. (198)When described, an overall response rate was observed in 72% of patients, with complete tumour response in 22%. (198) Limb salvage was achieved in 81% of patients initially threatened with amputation. (198)

1.1.6.3 RTX

When deciding whether to use RTX in the treatment of eSTS, factors impacting LR-risk should also be considered. (199) In selected patients, the local control achieved by surgery

alone is comparable to that achieved by a combination of RTX and surgery. (200, 201) The current ESMO guidelines recommend RTX in high-grade (G2 or G3) lesions as a standard adjunct to surgery. (1) However, after complete resection of the tumour within a compartment, RTX may be omitted. (1)

For low-grade tumours, RTX is particularly useful for resections with marginal margins. (202) Low-grade, small (≤5cm) and superficially located primary tumours where wide resection is feasible, for example, can be treated with surgery only. (200) In addition, various histopathologic subtypes respond differently to RTX. (203) MLPS, for example, are fairly sensitive to RTX, and ARTX can reduce the size of the tumour significantly. (136, 203, 204) In MFSs, the particularly high risk of LR justifies the use of RTX. (205, 206)

The debate about whether RTX should be administered neoadjuvant or adjuvant is ongoing. (207) Developed nomograms for prediction of LR rates depending on various factors can help with individual decisions for or against the use of RTX, whereby possible side effects of RTX must be weighed against the respective risk of LR with re-operations without RTX. (208)

In the following sections, I review the different types of RTX described in the literature, their differences in neoadjuvant and adjuvant use, and the described effects of RTX on the outcome of patients with eSTS.

1.1.6.3.1 Types of RTX

Intensity modulated radiotherapy (IMRT) is the technique of choice for most STS cases. (199, 209) Image-guided IMRT (IG-IMRT) reduces uncertainty in daily positioning. (210) As a special computer-controlled technique, it allows precise irradiation of the target volume while minimising the high radiation dose to the surrounding healthy tissue. (211) Neoadjuvant IG- IMRT significantly reduces the need for tissue transfer, while the incidence of WC was not significantly reduced. (212) Another advantage is the significant reduced LR compared with conventional external beam radiation therapy (EBRT) for primary eSTS. (209, 213, 214) For example, a retrospective analysis of 41 eSTS patients treated with limb-preserving surgery and IMRT demonstrated a 5-year local control rate of 94%, regardless of marginal status. (209) The toxicity profile was lowered. (214)

Intraoperative radiotherapy (IORT) is performed at the time of surgery, after resection but before the wound is sutured. (142) In this way, the surgical field can be directly irradiated, and the healthy tissue spared. (142) Possible indications are recurrent tumours in a previously irradiated area or tumours near critical structures. (215) It is mainly used for STS in the pelvis and abdomen. (142) A study by Tran et al. showed that IORT in eSTS as adjunctive therapy to EBRT results in excellent local control with low acute toxicities. (215) This was confirmed by a 2016 study by Call et al. in which IORT also resulted in excellent local control and survival. (216)

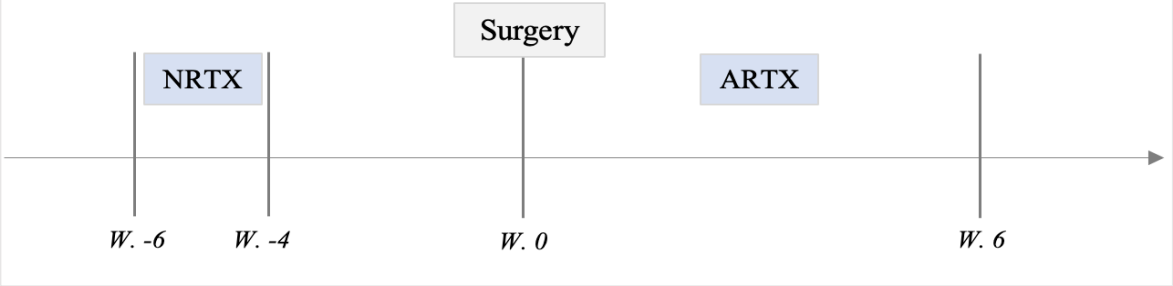
Brachytherapy is an internal RTX, where radioactivity is delivered directly into the tumour bed via a catheter placed during the operation. (142) Compared to external RTX, a higher concentrated dose of radiation can be delivered, whilst sparing the normal tissue. (142, 217) There are different types of brachytherapy: In high-dose rate (HDR) brachytherapy, a high dose of radiation is given over a short period of time. While in low-dose rate brachytherapy, a lower dose is administered over several days. The risk for LR is comparable for the two types. (5, 218) Brachytherapy is mostly used as a boost that is combined with EBRT, but can also be used alternative to EBRT as a form of ARTX, with reported advantages like shorter treatment duration and lower financial costs. (219) The availability of brachytherapy is restricted. (142)

Proton beam therapy belongs to the group of hadron therapies. (220) As charged particles, protons only lose energy very quickly in the last few millimetres of their range, leading to a sharp limited dose peak (Bragg peak) which is directly related to the initial energy of the proton. (220) Therefore, it is possible to place the desired dose in a targeted manner and normal tissue is spared more compared to photon beam therapies. (220)

1.1.6.3.2 NRTX vs. ARTX

RTX can be used in the neoadjuvant or adjuvant setting (**Figure 4**). (2, 5) **The optimal timing** is debated (221, 222) and should be determined for each patient, taking into account tumour and patient factors, such as tumour radiosensitivity, the possibility of achieving surgically negative margins and patient risk factors for short- and long-term morbidity. (2, 203, 223, 224, 225) If NRTX was performed, oncological resection is usually performed 4 to 6 weeks after completion of RTX (**Figure 4**). (1, 2, 226) After primary oncological

resection, ARTX follows within 6 weeks postoperatively if wound recovery is adequate (**Figure 4**). (2, 225)



Legend: *NRTX – neoadjuvant radiotherapy; ARTX – adjuvant radiotherapy; W. - weeks*

Figure 4: Time interval between local therapy in weeks (w.) depending on the sequence according to the American Society for Radiation Oncology guidelines. (2)

For NRTX the current ESMO guidelines recommend a total dose of 50Gy in 1.8-2Gy fractions. (1) For ARTX, higher doses up to 66Gy are recommended. (1)

The side effects of NRTX and ARTX differ in terms of their risk and frequency. (225, 227, 228) Previous studies have shown that patients receiving NRTX have an increased risk of major wound complications (MWC) compared to patients receiving ARTX. (225, 229, 230) This is further influenced by several tumour factors, such as its proximity to the skin surface, its size (>10cm), and location in the LE, as well as patient factors, such as smoking, diabetes and obesity. (223, 224, 231, 232) Several studies have been conducted to investigate ways of reducing the risk of MWC. (212, 226) No significant positive effect on MWC risk with the use of IG-IMRT was demonstrated. (212) Adjusting the time interval between NRTX and surgical resection had minimal effect on the development of MWC. (226)
On the other hand, the use of ARTX is associated with more late complications. (227, 228) These include fibrosis, oedema and joint stiffness which can affect patient function. (227) A possible explanation may be the higher treatment volumes and irradiation field sizes of ARTX. (225, 227)

Considering the described risk of MWC, current guidelines recommend NRTX whenever possible. (1, 2) NRTX may also facilitate R0-resection. (164) On the other hand, in patients at high risk of developing MWC (see factors above), these concerns may outweigh the long-term toxicities of ARTX and lead to the decision for primary surgery and ARTX. (223, 225)

Negative findings in the postoperative pathological assessment, such as insufficient margins, infiltrative or discontinuous margins or invasion of the fascia, require consideration of re-excision vs. ARTX. (1, 135) When the unplanned excision is treated by re-resection in combination with RTX, NRTX has been shown to improve LR and PFS. (233)

The following table contrasts the advantages and disadvantages of NRTX vs. ARTX according to Hoefkens et al. (**Table 7**). (142)

Table 7. Comparison of NRTX and ARTX in terms of advantages (green) and disadvantages (red).	
RTX Volume	
NRTX	**RTX**
Smaller RTX Volume	Larger RTX Volume
Complications	
NRTX	**ARTX**
Wound complications Fibrosis that could interfere with surgery Fewer late complications	Less scar formation
	More long-term complications (stiffness of the joint, oedema, fibrosis)
Consequences for surgery	
NRTX	**ARTX**
Easier resection Better oxygenation and vascularisation → larger effect	Need for demarcation of the surgery field (clips)
Delay of operation date	
Staging	
NRTX	**ARTX**
	Better staging options
Legend: *RTX – Radiotherapy; NRTX – neoadjuvant radiotherapy; ARTX – adjuvant radiotherapy*	

Table 7: Comparison of NRTX and ARTX according to Hoefkens et al. (142)

1.1.6.3.3 Effect of RTX on outcome

For LR, there is long-standing evidence that RTX has a beneficial effect in high-grade eSTS, (234, 235, 236, 237, 238) but it is controversial for DM and OS. (234, 237, 239, 240) In the 1990s, two randomised prospective trials demonstrated the efficacy of ARTX (EBRT and

brachytherapy) for local control of high-grade tumours. (235, 236) In 1996, Pisters et al. described in a randomised trial an improvement in local control with adjuvant brachytherapy compared with no further treatment in high-grade tumours (89% vs. 66%; p=0.0025), but not in low-grade lesions (p=0.49). (235) However, they reported no significant reduction in DM or DSS, regardless of tumour grade. (235) In 1998, Yang et al. showed in a prospective randomised trial a highly significant reduction in LR with adjuvant EBRT in high-grade eSTS (p=0.0028), but also no significant benefit in DM (p=0.64) and 10-year OS (75% vs. 74%; p=0.71). (236) In this study, all patients with high-grade tumours received ACTX. (236)

A 2008 Scandinavian study of 1,093 patients by Jebsen et al. described the efficacy of ARTX on local control regardless of malignancy grade, depth, and surgical margin of the tumour, with the most pronounced beneficial effect in high-grade, deep-seated tumours, even with a wider resection margin. (238)

Furthermore, an updated randomised prospective study by Beane et al. in 2014 demonstrated excellent local control with adjuvant EBRT with limb-sparing surgery (LSS) compared to surgery alone (1.4% vs. 25%; p=0.0001), with a statistically nonsignificant improvement in OS (p=0.22). (234)

Posch et al. recently showed a strong reduction in LR risk (sub hazard ratio [SHR] 0.42; 95% CI 0.19-0.91; p=0.03), but no significant relative risk reduction in DM risk (SHR 0.69; 95% CI 0.39-1.25; p=0.22) or improvement in OS (HR 0.76; 95% CI 0.44-1.30; p=0.32). (237) Furthermore, in a subgroup analysis, they found a positive effect of ARTX on OS for G3 tumours (HR 0.51; 95% CI 0.33-0.78; p=0.002), but discuss possible residual confounding. (237)

RTX has been associated with improved survival in some other studies. (164, 239, 240, 241) In a retrospective analysis of SEER data by Koshy et al., the addition of RTX to LSS in patients with high-grade eSTS showed a significant improvement in OS (HR 0.67; 95% CI 0.57-0.79) and cause-specific survival (CSS) (HR 0.76; 95% CI 0.63-0.91). (239) Of the patients who received RTX, 13.5% were treated neoadjuvant. (239)

Similarly, in a retrospective 1:1 matched-pair analysis of high-grade eSTS in two databases (SEER and National Cancer Database [NCDB]), Ramey et al. in 2018 demonstrated a significant survival benefit for RTX compared with LSS alone. (241)

Furthermore, Zhao et al. 2016 reported not only an association between the use of ARTX (vs. surgery alone) and a reduced risk of LR (HR 0.408; 95% CI 0.235-0.707; p=0.001), but also an improved OS (HR 0.512; 95% CI 0.296-0.886; p=0.017). (240)

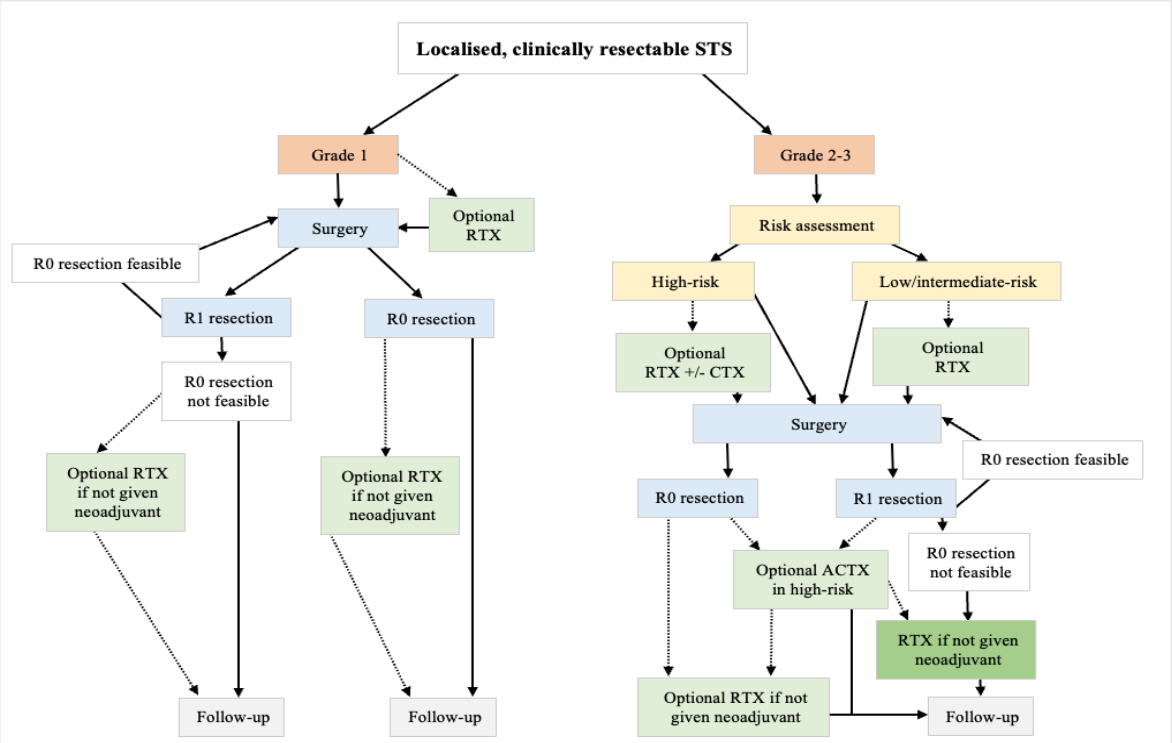
The influence of RTX-timing on oncologic outcome is also controversial. (164, 221, 222, 242) A meta-analysis by Yang et al., showed no difference in NRTX and ARTX according to LR (RR 0.84; 95% CI 0.58-1.21), DM and OS. (222)
However, a retrospective analysis by Sampath et al. in 2011 described a significant superiority of NRTX over ARTX in terms of OS (HR 0.72; 95% CI 0.56-0.91; p<0.01) and CCS (HR 0.64; 95% CI 0.46-0.88; p<0.01). (242) Furthermore, Gingrich et al. demonstrated a significantly higher likelihood of achieving R0 resections with NRTX (OR 1.83; 95% CI 1.61-2.07; p<0.0001) compared to an OR of 0.674 (95% CI 0.632-0.720; p<0.0001) for ARTX, with no RTX as a reference, and an associated improvement in OS. (164)
In contrast, a recent 2021 meta-analysis on this topic by Kungwengwe et al. showed a significant benefit of ARTX for OS (HR 1.15; 95% CI 1.0009-1.32; p=0.05), but no significant benefit for DFS (HR 1.25; 95% CI 0.87-1.78; p=0.22) and DSS (HR 1.06; 95% CI 0.92-1.22; p=0.43). (221)

1.1.6.4 Treatment algorithms according to ESMO guidelines

Figures 5 and 6 show algorithms of the treatment recommendations of the current ESMO guidelines for localised STS on the extremities and trunk. (1)

For localised, resectable **grade 1** STS, primary surgery is recommended. (1) In case of successful R0 resection, no further therapy is required and only follow-up is recommended. (1) In case of R1 resection and if R0 re-resection is not expected, the use of RTX may be considered. (1) In selected cases, R1 resection can also be regarded as justifiable. (1) For example, marginal excisions along the pseudocapsule are possible for atypical lipomatous tumour, as mentioned previously. (1)

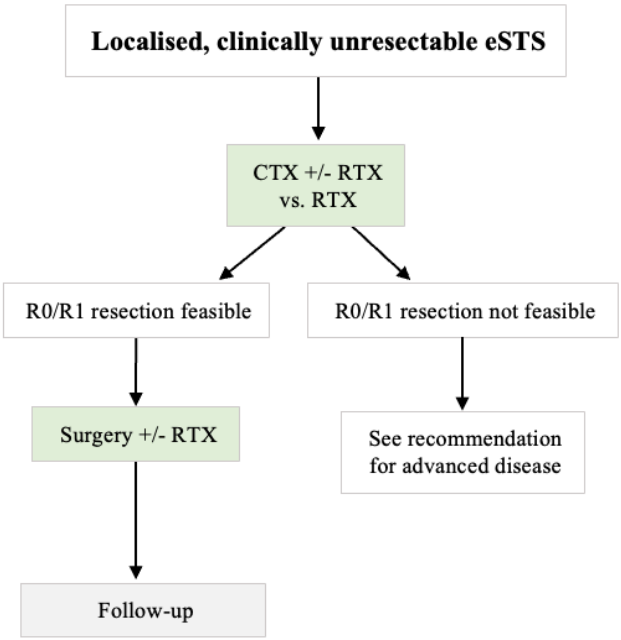
For patients with **grade 2 or 3** STS, risk assessment is suggested before intervention. (1) RTX is recommended as an adjunct to surgical removal in high grade STS, (1, 235) indicated by the operating surgeon and radiation oncologist. (124) For high-risk tumours, the use of NCTX or ACTX is considered adjunctively in CTX-naïve patients. (1) Low or intermediate risk tumours are usually treated with surgery alone. (1)



***Legend**: STS – soft tissue sarcoma; RTX – radiotherapy; CTX – chemotherapy; ACTX – adjuvant chemotherapy; R0 – resection margin; microscopically negative; R1 – resection margin, microscopically positive*

Figure 5: Management of locally, clinically resectable extremity and superficial trunk STS according to ESMO guidelines. (1)

In patients with **locoregional recurrences** including lymphnode metastases, more aggressive multimodality treatment can be indicated. (1) For sensitive histological subtypes, radical surgery can be supplemented by neoadjuvant RTX or CTX. (1)



Legend: *eSTS – soft tissue sarcoma of the extremities; RTX – radiotherapy; CTX – chemotherapy; R0 – no tumour at the margin; R1 – microscopic tumour at the margin*

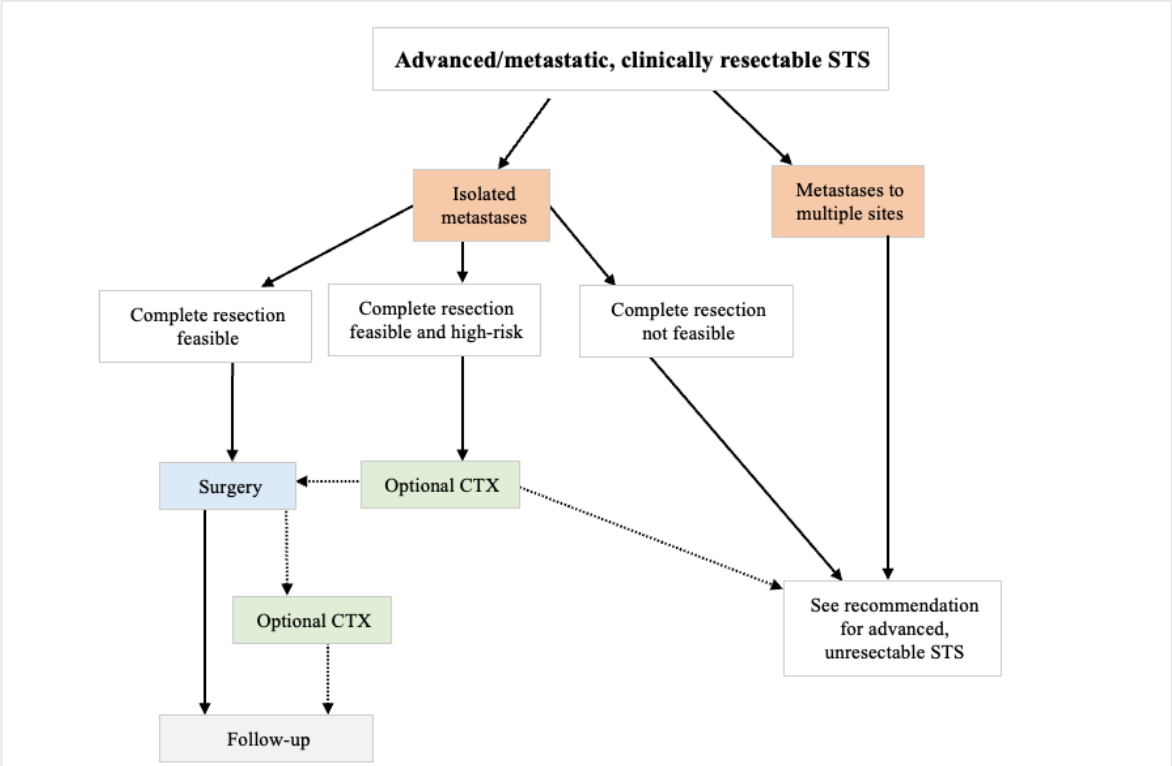
Figure 6: Management of localised, clinically unresectable eSTS according to ESMO guidelines. (1)

Figures 7 and 8 show the treatment recommendation algorithms of the ESMO guidelines in advanced STS of the extremities and trunk. (1)

Isolated metastases can be treated surgically. (1) For example, resectable isolated pulmonary metastases that appear after more than one disease-free year are treated by surgery as standard**.** (1, 243) Prior to surgery, the absence of extrapulmonary lesions must be confirmed by abdominal CT scan, and bone scintigraphy or fluorodeoxyglucose-positron emission tomography (FDG-PET) must be performed. (1) In the presence of unfavourable prognostic factors, such as multiple lesions and a short recurrence-free interval, additional CTX may be taken into consideration. (1)

If pulmonary metastases without extrapulmonary involvement are already present at the time of diagnosis of the STS, CTX, usually performed neoadjuvant, is considered as standard treatment. (1) Subsequently, especially if the tumour is responsive, surgical removal of residual lung metastases may be offered to the patient. (1)

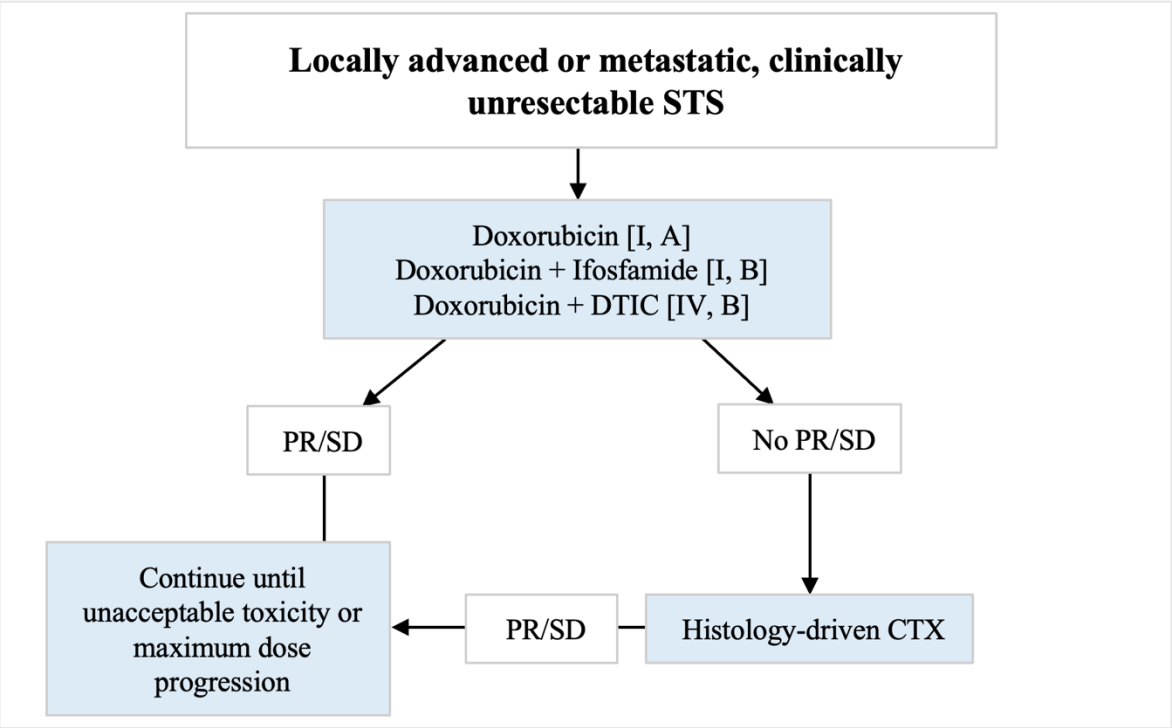
Pulmonary metastases that are not resectable and extrapulmonary metastases are primarily treated with CTX. (1) In selected cases, especially oligometastases, surgical resection or stereo-ablative RTX may be considered. (1)



***Legend**: STS – soft tissue sarcoma; CTX – chemotherapy*

Figure 7: Management of advanced/metastatic, clinically resectable STS according to ESMO guidelines.(1)

For **advanced or metastatic STS that are not resectable**, systemic treatment with palliative intent can be proposed (**Figure 8**). (1) In this context, the ESMO guidelines mention anthracycline-based therapy as first-line treatment. (1)



***Legend**: STS – soft tissue sarcoma; CTX – chemotherapy; PR – partial response; SD – stable disease*

Figure 8: Management of advanced or metastatic, clinically unresectable STS according to ESMO guidelines. (1)

1.2 Aim of the study and research question

In current guidelines, RTX is a relevant component of therapy for patients with high-grade eSTS. (1, 5) The positive impact on local control is well established. (234, 235, 236, 237, 238) However, the effect on DM risk and OS has been controversial in previous studies. (234, 237, 239, 240) Other studies have described a strong correlation between the development of LR, DM, and OS. (244, 245, 246) The debate about the timing of RTX use – neoadjuvant or adjuvant – is ongoing and is largely determined by the different side effect profiles. (225, 227)

Independent analysis of the effects of NRTX and ARTX on outcome, would require large, randomised trials that do not specifically distinguish between known prognostic factors such as histology, tumour size, depth and margins. However, due to the rarity of STS and the heterogeneous patient population, (4) it is difficult to recruit large study populations.

As a result, many randomised trials investigating the effect of RTX on outcome in eSTS patients have enrolled fewer than 150 patients. (146, 225, 227, 234, 236) Propensity score (PS) statistical methods can be used to adjust for differences in observed characteristics between treatment pairs. (247)

Based on studies describing a correlation between LR, DM and OS, (244, 245, 246) it was hypothesised that RTX might have an indirect protective effect on DM risk and OS through its positive effect on LR risk. The aim of this study was to further investigate the effects of NRTX and ARTX, and the possible superiority of either, on LR risk, DM risk, and OS independent of confounding factors.

For this purpose, patients with high-grade eSTS treated in tertiary sarcoma centres were included in this retrospective study and divided into three separate datasets: 1. NRTX and no RTX dataset; 2. ARTX and no RTX dataset; 3. NRTX and ARTX dataset. PS- and IPTW-adjusted statistical methods were applied to the three datasets separately.

2 Material and Methods

2.1 Study design

The retrospective data analysis was performed in collaboration with eight departments from a total of ten tertiary tumour centres in five countries of the European Union and United Kingdom. The participating tumour centres were as follows:

1. Medical University of Graz (Austria)
2. Leiden University Medical Centre (Netherlands)
3. Radboud University Medical Centre (Netherlands)
4. The Netherlands Cancer Institute (Netherlands)
5. University Medical Centre Groningen (UMCG) (Netherlands)
6. Erasmus MC Cancer Institute (Netherlands)
7. Aarhus University Hospital (Denmark)
8. HELIOS Klinikum Berlin-Buch (Germany)
9. Royal Orthopaedic Hospital Birmingham NHS Foundation Trust (United Kingdom)
10. Royal National Orthopaedic Hospital (United Kingdom)

This study retrospectively included 1200 patients who were treated for localised eSTS with curative intent at one of the above-mentioned tertiary tumour centres between 1996 and 2016. Initially, 2184 patients were potentially eligible. Of these, those who received CTX (neoadjuvant or adjuvant) (n=274) or developed metastases within three months of definitive surgery (n=67) were excluded. Patients with incomplete information on histology, location, tumour size, tumour depth and amputation status were also excluded (n=643).

2.2 Data collection and variables

The following baseline and outcome data were documented in the respective internal medical records:

- Demographic variables: Age at surgery; gender
- Tumour-specific characteristics: Tumour size; **histologic subtype**; depth (superficial vs. deep); localisation (upper vs. lower limb); **grading**

- Treatment modality: RTX (neoadjuvant/adjuvant); surgery (limb separation/amputation; **resection margins**)
- Outcome variables: Time to LR, time to DM, or last follow-up/death

Histological subtypes were organised into eight subgroups: 1 - Leiomyosarcoma [LMS], 2 - dedifferentiated/pleomorphic liposarcoma [D/P-LPS], 3 - myxoid liposarcoma [M-LPS], 4 - myxofibrosarcoma [MFS], 5 - malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified [MFH/UPS & NOS], 6 - malignant peripheral nerve sheath tumour [MPNST], 7 - synovial sarcoma [SS], and 8 - "Other" (multiple histological subtypes – largest proportion being spindle cell sarcomas) .

Grading of the tumours into G2 and G3 was based on the FNCLCC – (Fédération Nationale des Centres de Lutte Contre le Cancer) system. Two groups were formed for the statistical analysis: G2 and G3.

Resection margins were categorised as negative margins (R0; microscopically negative), marginal margins (R1; macroscopically negative but microscopically positive) and intralesional margins (R2; macroscopically positive).

Reassessment of cases in terms of grading, histology or margins was not feasible given the large number of patients from different sarcoma centres. However, because all included cases were from experienced sarcoma centres, diagnosis, treatment, and follow-up can generally be considered ESMO-compliant. (1, 156)
Approval for the present study was obtained from the institutional review boards of the respective participating centres. All methods and analyses were conducted in accordance with relevant local and national guidelines and regulations and the Declaration of Helsinki.

2.3 Statistical Analysis

2.3.1 Subsets

To compare the independent effects of NRTX and ARTX on the outcome parameter LR, DM and OS, the dataset was divided into three subgroups, each comparing two treatment modalities: (1) patients who had not received radiotherapy versus patients who had received adjuvant radiotherapy (no RTX vs. ARTX (n=1006)), (2) patients who had not received

radiotherapy versus patients who had received neoadjuvant radiotherapy (no RTX vs. NRTX (n=410)), and (3) patients who had received neoadjuvant radiotherapy versus patients who had received adjuvant radiotherapy (NRTX vs. ARTX; (n=984)). Statistical analyses were then performed separately for each of these subgroups.

2.3.2 Statistical Methods

Stata version 16.0 (*StataCorp., College Station, Texas, USA*) was used for statistical analyses.

Means, medians, t-tests, Mann-Whitney-U tests and chi-square tests were performed in the study.

For the means and medians, the respective standard deviations and interquartile ranges were given to quantify the dispersion of the data.

T-tests and Mann-Whitney-U tests were used to examine differences in continuous variables between two groups - t-test for normally distributed data and Mann-Whitney-U test for non-normally distributed data.

Chi-square tests were used to examine differences in categorical variables.

The statistical models were inverse-probability of treatment-weight (IPTW)-adjusted to allow independent assessment of the treatment effect.

2.3.3 Statistical analysis methods for treatment comparisons

Standardised mean differences (SMD) were calculated to estimate significant differences between the three treatment pairs at baseline, by dividing the difference between the means of the two groups by their common standard deviation.

An SMD of ≥ 0.2 was considered to indicate a significant difference between the treatment groups. If more than one variable had an SMD of 0.2 or more, an inverse-probability treatment-weight (IPTW) was applied, based on a propensity score (PS).

The PS, a method to control for confounding variables in the analysis of observational data, allows estimation of the probability of assignment to a particular treatment group. It was calculated separately for each of the three treatment pairs using a logistic regression model with a subset of variables including sex, patient age, histological subtype, tumour location,

grading, depth, tumour size and margin status. These variables were selected independently of their association with clinical outcome. (248, 249)

Based on this PS, the authors calculated the IPTW, which is defined as the inverse-probability that patients received the treatment they actually received. (248, 249) Fine&Gray and Cox regression models were then applied to assess the impact of treatment modalities on the outcomes of interest. Univariate Fine&Gray models were used in the assessment of treatment on the risk of LR and DM, with death as a competing event. Cox regression models were used to assess the impact of treatment on OS. For the Fine&Gray models, SHRs with corresponding 95% CI were provided. For Cox-regression models, HRs with 95% confidence intervals were given.

Median LR and DM-free survival were calculated using the Marubini and Valsecchi (250) estimator for cumulative incidence and median follow-up using the inverse Kaplan-Meier estimator of Schemper and Smith. (251) A p-value of less than 0.05 was considered statistically significant.

3 Results

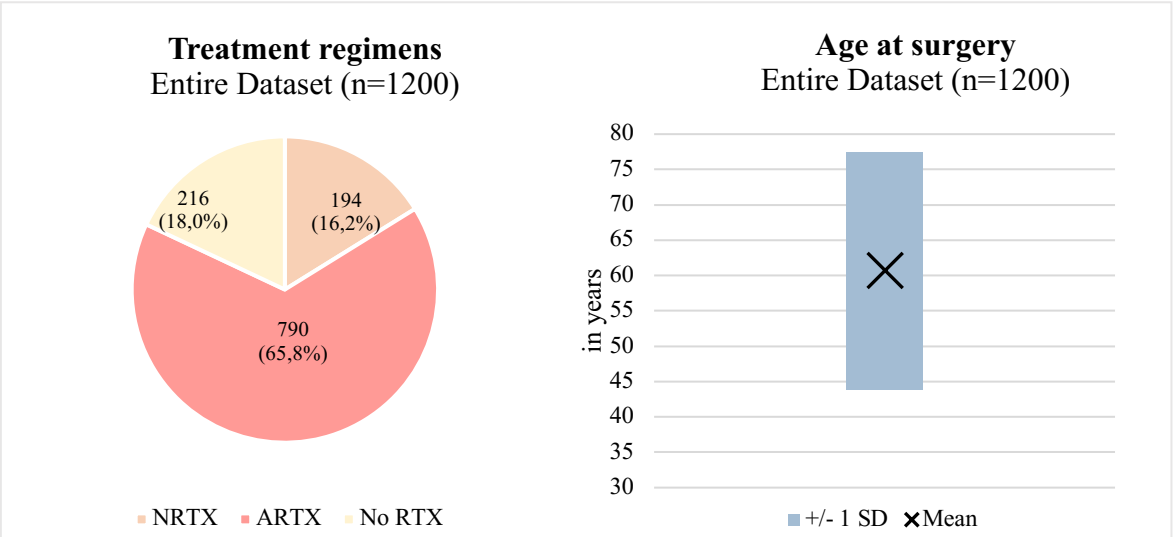
3.1 Cohort description in the entire dataset

Table 8 displays all the variables for the entire dataset. Subsequently, key variables are illustrated in diagrams.

Table 8. Descriptive analysis of the entire patient cohort.			
		Missing	**Entire Dataset (n=1200)**
Treatment regime	*NRTX*	0	194 (16.2)
	ARTX	0	790 (65.8)
	No RTX	0	216 (18.0)
Age at surgery (in years; mean, SD)		0	60.7 ± 16.8
Gender	*Male*	0	667 (55.6)
	Female	0	533 (44.4)
Grading	*G2*	0	236 (19.7)
	G3	0	964 (80.3)
Histology	*LMS*	0	68 (5.7)
	D/P-LPS	0	68 (5.7)
	MFS	0	322 (26.8)
	MFH/UPS & NOS	0	266 (22.2)
	MPNST	0	96 (8.0)
	SS	0	122 (10.2)
	Other	0	185 (15.4)
	M-LPS	0	73 (6.0)
Tumour size (in cm; median, IQR)		0	7.5 [5 – 12]
Localisation	*Upper Limb*	0	272 (22.7)
	Lower limb	0	928 (77.3)
Depth	*Superficial*	0	331 (27.6)
	Deep	0	869 (72.4)
Margins	*R0*	0	565 (47.1)
	R1	0	439 (36.6)
	R2	0	196 (16.3)
Follow-Up (median; IQR)		0	70.5 [41.8 – 106.4]
***Legend**: IQR – interquartile range; NRTX – neoadjuvant radiotherapy; ARTX – adjuvant radiotherapy; No RTX – no radiotherapy; LMS – leiomyosarcoma; D/P-LPS - dedifferentiated/pleomorphic liposarcoma; M-LPS - myxoid liposarcoma; MFS – myxofibrosarcoma; MFH/UPS & NOS - malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified; MPNST - malignant peripheral nerve sheath tumour; SS - synovial sarcoma*			

Table 8: Descriptive analysis of the entire dataset.

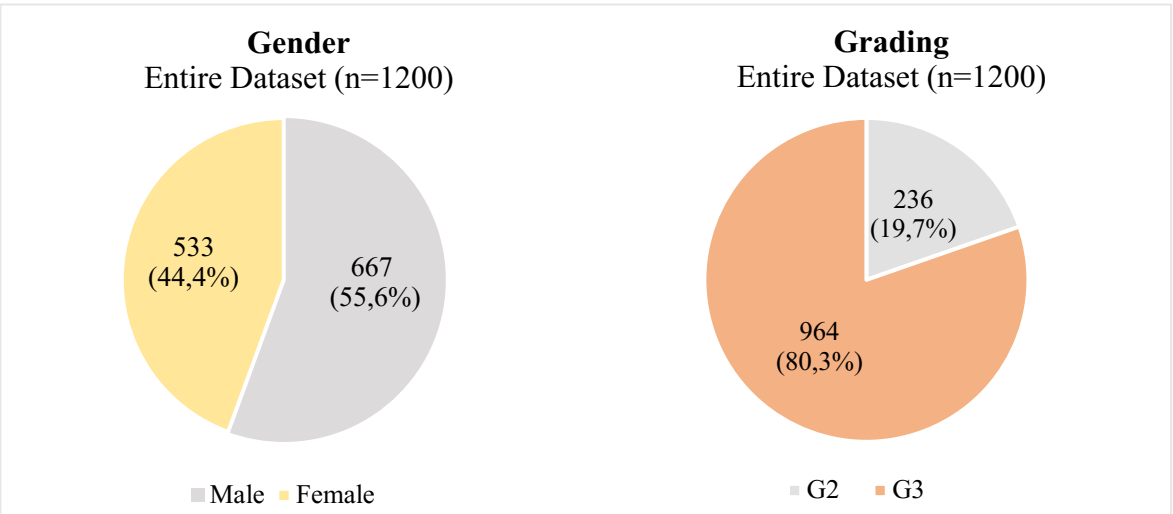
The retrospective study included 1200 patients with localised eSTS. Of these, 216 had received no radiotherapy (No RTX), 194 had received neoadjuvant radiotherapy (NRTX) and 790 had received adjuvant radiotherapy (ARTX) (**Figure 9**). The mean age of patients at the time of surgery across the dataset was 60.7 years with a standard deviation (SD) of 16.8 years (**Figure 9; Table 8**).



Legend: *NRTX – neoadjuvant radiotherapy; ARTX – adjuvant radiotherapy; No RTX – no radiotherapy; SD – standard deviation*

Figure 9: Frequencies of the respective treatment regimens (left) and the mean age with standard deviation at surgery (right) in the entire dataset.

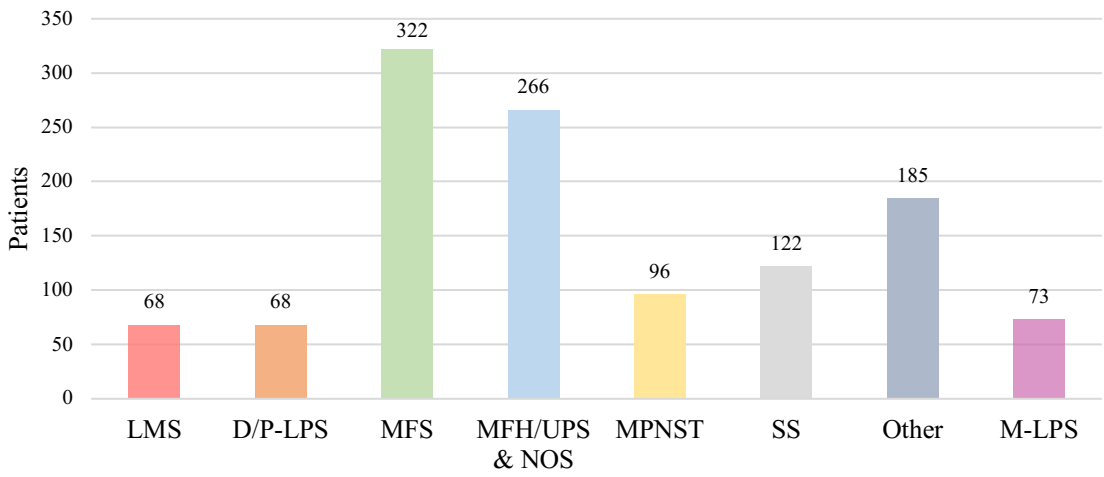
The entire data set was composed of 533 (44.4%) females and 667 (55.6%) males (**Figure 10; Table 8**). G3 tumours were more frequent (80.3%) than G2 tumours (n=19.7%) (**Figure 10; Table 8**).



Legend: *G2 – Grade 2; G3 – Grade 3*

Figure 10: Frequencies of the respective gender (left) and grading (right) in the entire dataset.

Histologic subtypes represented in the entire data set were leiomyosarcoma (LMS), dedifferentiated/pleomorphic liposarcoma (D/P-LPS), myxofibrosarcoma (MFS), malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not other specified (MFH/UPS & NOS), malignant peripheral nerve sheath tumour (MPNST), synovial sarcoma (SS), and myxoid liposarcoma. In addition, the group "other" was created for soft tissue sarcomas other than the above-mentioned ones (**Table 8**). **Figure 11** provides an overview of the frequencies of named subtypes in the entire dataset (**Table 8**).



Legend: *LMS – leiomyosarcoma; D/P-LPS - dedifferentiated/pleomorphic liposarcoma; M-LPS - myxoid liposarcoma; MFS – myxofibrosarcoma; MFH/UPS & NOS - malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified; MPNST - malignant peripheral nerve sheath tumour; SS - synovial sarcoma*

Figure 11: Frequencies of the histologic subtypes in the entire dataset.

In the entire dataset, tumours had a median size of 7.5 cm with an IQR of [5-12] **(Figure 12, Table 8).**

Legend: *IQR – interquartile range*

Figure 12: Median tumour size with interquartile range in the entire dataset.

STSs were more frequently localised in the depth than on the surface and in the lower extremities than in the upper extremities (**Figure 13; Table 8**).

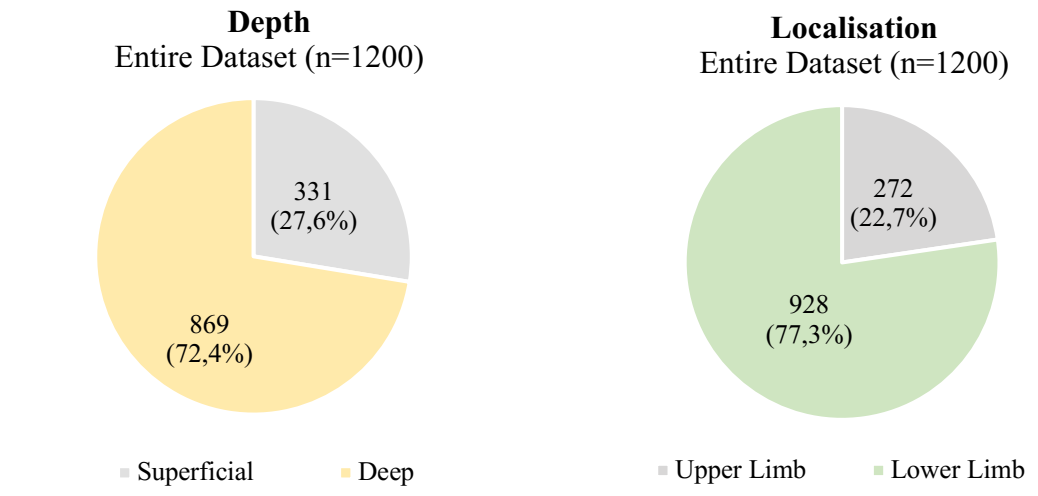
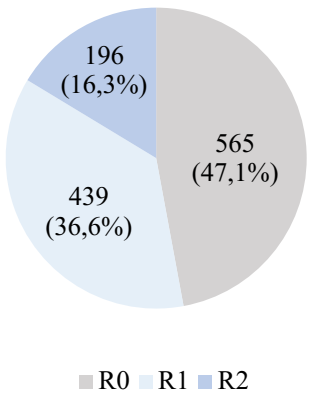


Figure 13: Frequencies of the respective depths (left) and localisations (right) in the entire dataset.

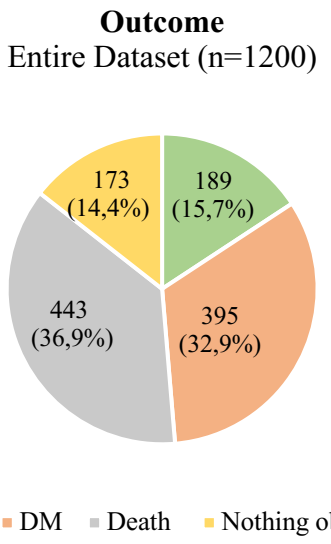
Overall, R0 resections were the most commonly performed (47.1%), followed by R1 resections (36.6%) and R2 resections (16.3%) (**Figure 14; Table 8**).



Legend: *R0 – resection margin, microscopically negative; R1 – resection margin, macroscopically negative, microscopically positive; R2 – macroscopically positive*

Figure 14: Frequencies of the respective resection margins in the entire dataset.

In the whole population, median follow-up time from time of surgery was 70.5 months (IQR: 41.8 - 106.4 months). During this observation period, 189 LRs (15.8%), 395 DMs (32.9%) and 443 deaths (36.9%) were reported (**Figure 15**). This corresponded to a 5-year cumulative LR risk of 15.5% (IQR: 13.3-17.8%) and DM risk of 34.6% (IQR: 31.7-37.5%). The 5-year cumulative OS chance was 64.4 % (IQR: 61.3-67.3) (**Figure 15**).



Legend: *LR – local recurrence; DM – distant metastasis*

Figure 15: Outcome in the entire dataset.

3.2 Differences between treatment pairs

3.2.1 Differences between No RTX and NRTX cohort

Table 9 contains the variables of the subgroup comparing treatment modalities NRTX and no RTX. The cohort consisted of 410 patients, of whom 194 had received NRTX and 216 had received no RTX (**Table 9**).

Table 9. Descriptive analysis of patients with no RTX and NRTX

N=410		**Missing**	**Overall**	**No RTX (n=216)**	**NRTX (n=194)**	**p-value***
Age at surgery (in years; mean, SD)		0	61.0 ± 16.7	63.6 ± 17.9	58.2 ± 16.7	**0.002**
Gender	*Male*	0	217 (52.9)	111 (51.4)	106 (54.6)	0.510
	Female	0	193 (47.1)	105 (48.6)	88 (45.4)	
Grading	*G2*	0	121 (29.5)	34 (15.7)	87 (44.8)	**<0.001**
	G3	0	289 (70.5)	182 (84.3)	107 (55.2)	
Histology	*LMS*	0	33 (8.0)	20 (9.3)	13 (6.7)	**<0.001**
	D/P-LPS	0	38 (9.3)	8 (3.7)	30 (15.5)	
	MFS	0	91 (22.2)	55 (25.5)	36 (18.6)	
	MFH/UPS & NOS	0	110 (26.8)	58 (26.8)	52 (26.8)	
	MPNST	0	24 (5.9)	20 (9.3)	4 (2.0)	
	SS	0	31 (7.6)	18 (8.3)	13 (6.7)	
	Other	0	39 (9.5)	29 (13.4)	10 (5.1)	
	M-LPS	0	44 (10.7)	8 (3.7)	36 (18.6)	
Tumour size (in cm; median, IQR)		0	9 [5.6 – 14]	6 [4 – 10]	9 [5.6 – 14]	**<0.001**
Localisation	*Upper Limb*	0	80 (19.5)	50 (23.2)	30 (15.5)	**0.050**
	Lower limb	0	330 (80.5)	166 (76.8)	164 (84.5)	
Depth	*Superficial*	0	116 (28.3)	90 (41.7)	26 (13.4)	**<0.001**
	Deep	0	294 (71.7)	126 (58.3)	168 (86.6)	
Margins	*R0*	0	235 (57.3)	142 (65.7)	93 (47.9)	**<0.001**
	R1	0	122 (29.8)	43 (19.9)	79 (40.7)	
	R2	0	53 (12.9)	31 (14.3)	22 (11.4)	
Follow-Up (median; IQR)		0	60.6 [31.3 – 97.3]	70.1 [38.8 – 108.1]	51.8 [27.4 – 88.3]	

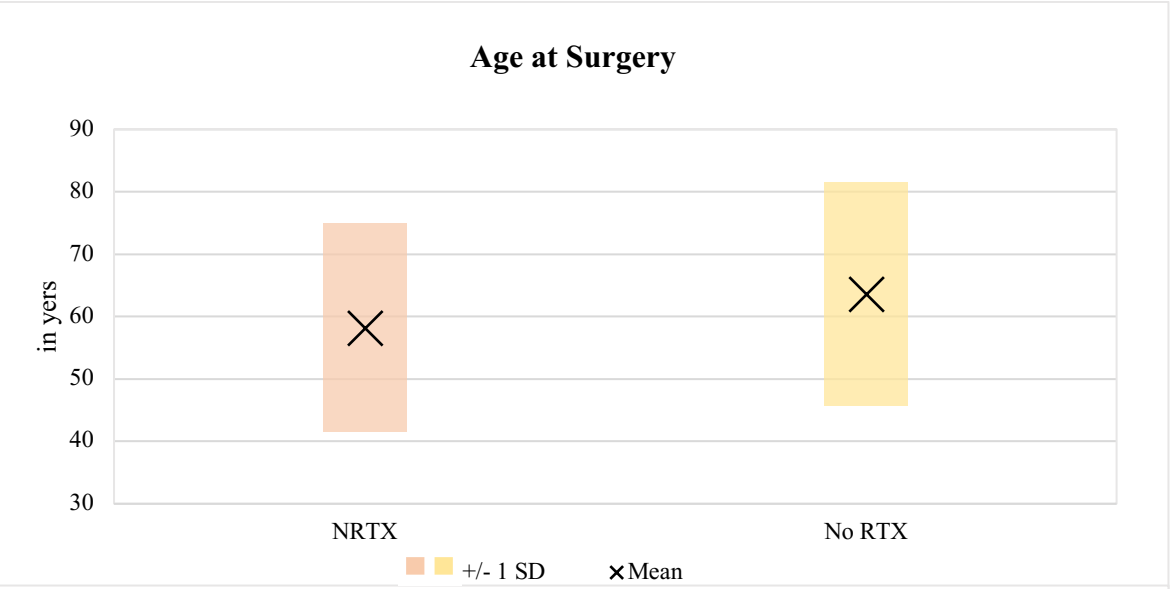
Continuous variables presented as medians with IQRs, categorical variables as absolute numbers with percentages. P-values in bold indicate significant results

***Legend**: IQR – interquartile range; RTX – radiotherapy; LMS – leiomyosarcoma; D/P-LPS - dedifferentiated/pleomorphic liposarcoma; M-LPS - myxoid liposarcoma; MFS – myxofibrosarcoma; MFH/UPS & NOS - malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified; MPNST - malignant peripheral nerve sheath tumour; SS - synovial sarcoma*

** p-values based on t-tests/Mann-Whitney-U-tests for normally/non-normally distributed continuous variables and chi-squared tests for categorical variables*

Table 9: Descriptive analysis of patients with no RTX and NRTX.

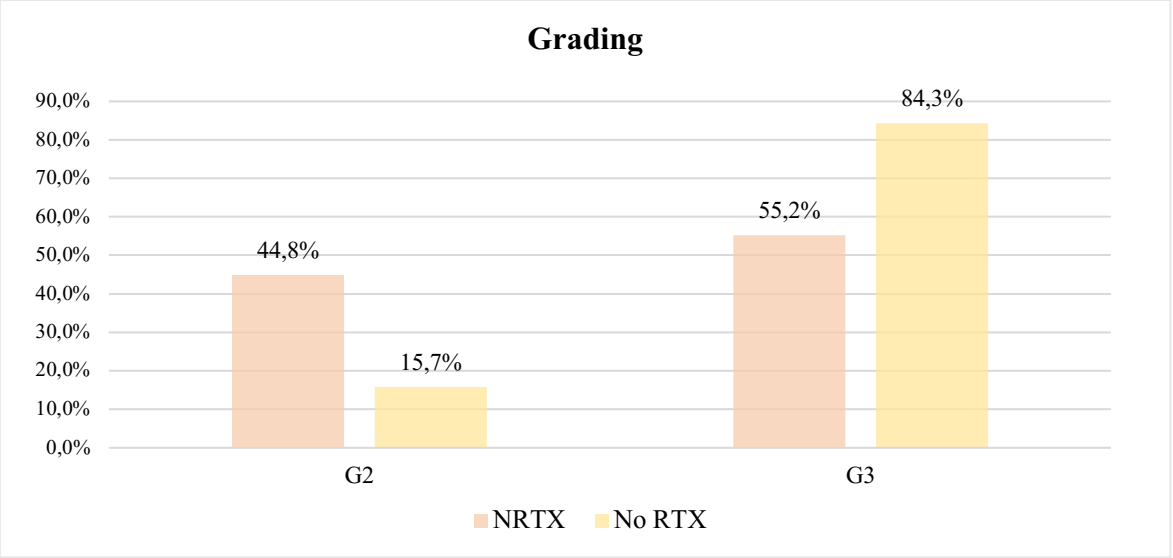
Patients who had received NRTX were slightly younger in mean than those who had not received RTX (**p=0.002; Table 9; Figure 16**).



***Legend:** NRTX – neoadjuvant radiotherapy; No RTX – no radiotherapy; SD – standard deviation*

Figure 16: Comparison of mean patient age with standard deviation in NRTX and no RTX subgroups.

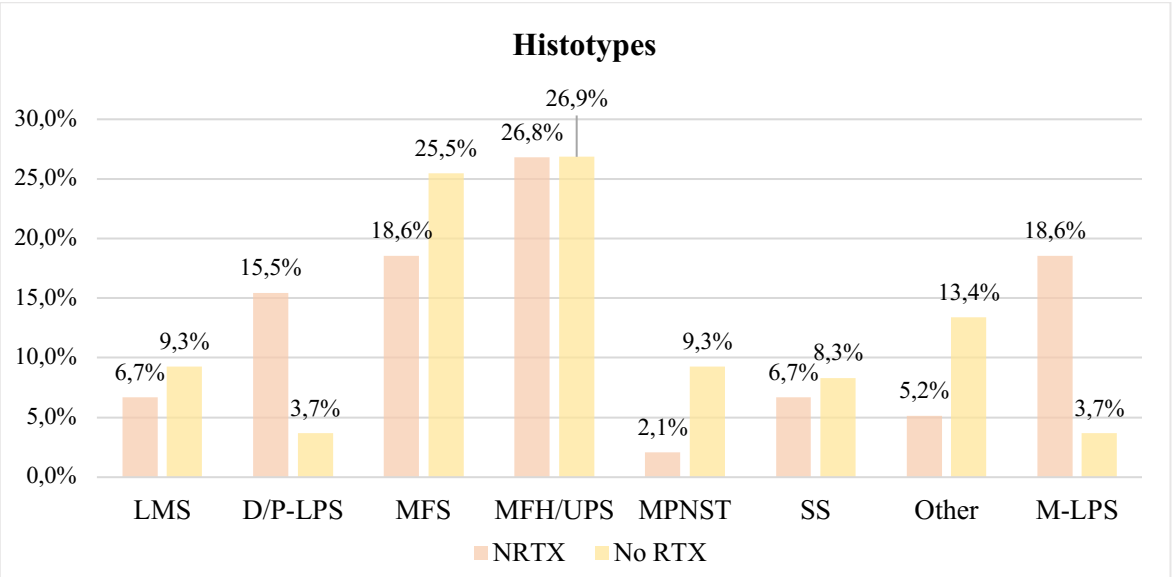
As shown in **Figure 17**, patients who had received NRTX were significantly more likely to have G3 tumours than patients who had not received RTX (**p<0.001; Table 9; Figure 17**).



Legend: *NRTX – neoadjuvant radiotherapy; No RTX – no radiotherapy; G2 – Grade 2; G3 – Grade 3*

Figure 17: Comparison of frequencies of respective grading in NRTX and no RTX subgroups.

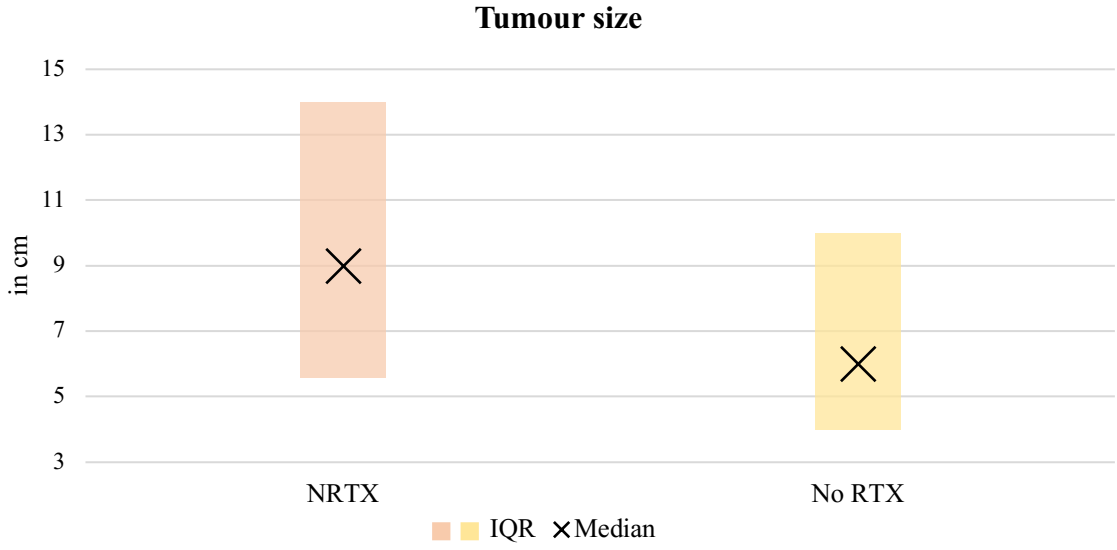
Furthermore, there were different frequencies of histologic subtypes between the two treatment groups. Patients who had received NRTX were significantly more likely to have the D/P-LPS and M-LPS histologic subtypes than those who had received no radiotherapy and less likely to have the LMS, MFS, MPNST, SS, and other histologic subtypes (**p<0.001; Table 9; Figure 18**).



Legend: *NRTX – neoadjuvant radiotherapy; No RTX – no radiotherapy; LMS – leiomyosarcoma; D/P-LPS - dedifferentiated/pleomorphic liposarcoma; M-LPS - myxoid liposarcoma; MFS – myxofibrosarcoma; MFH/UPS & NOS - malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified; MPNST - malignant peripheral nerve sheath tumour; SS - synovial sarcoma*

Figure 18: Comparison of the frequencies of histologic subtypes within NRTX and no RTX subgroups.

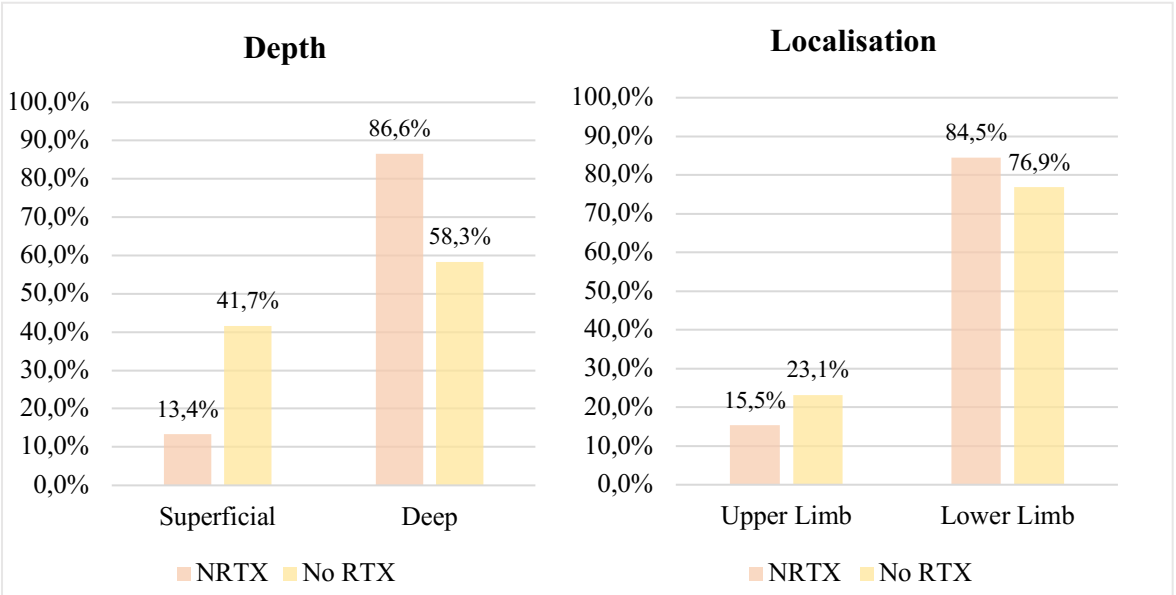
Tumours of the patients who had received NRTX were significantly larger than the tumours of the patients who had received no RTX (**p<0.001; Table 9; Figure 19**).



Legend: *NRTX – neoadjuvant radiotherapy; No RTX – no radiotherapy; IQR – interquartile range*

Figure 19: Comparison of median tumour size with respective interquartile ranges in NRTX and no RTX subgroups.

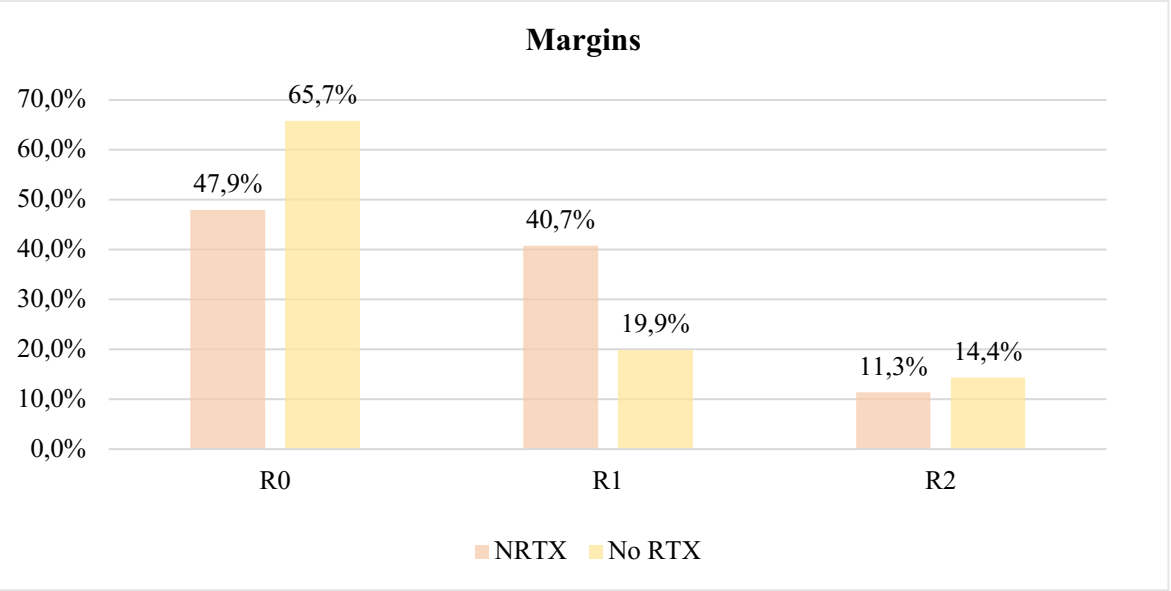
STS occurred significantly more frequently in depth in the NRTX group (**p<0.001; Figure 20**) and were rather localised in the lower extremities (**p=0.050; Figure 20; Table 9**).



Legend: *NRTX – neoadjuvant radiotherapy; No RTX – no radiotherapy*

Figure 20: Comparison of frequencies of respective tumour depths (left) and locations (right) in NRTX and no RTX subgroups.

Tumours in the NRTX subgroup were more likely resected with R1 than those in the no RTX subgroup. Correspondingly, R0 and R2 resections were less frequent in the NRTX-subgroup than in the subgroup without RTX (**p<0.001; Table 9; Figure 21**).



Legend: *NRTX – neoadjuvant radiotherapy; No RTX – no radiotherapy; R0 – resection margin, microscopically negative; R1 – resection margin, macroscopically negative, microscopically positive; R2 – macroscopically positive*

Figure 21: Comparison of the frequencies of respective resection margins in NRTX and no RTX subgroups.

3.2.2 Differences between NRTX and ARTX cohort

Table 10 contains the variables of the NRTX vs. ARTX subgroup. The cohort consisted of 984 patients, of whom 194 had received NRTX and 790 ARTX (**Table 10**). No significant differences were found between the two treatment groups at study onset in age at surgery (p=0.079), gender (p=0.559) and margins (p=0.060; **Table 10**).

Table 10. Descriptive analysis of patients with NRTX or ARTX.

N=984		**Missing**	**Overall (n=984)**	**NRTX (n=194)**	**ARTX (n=790)**	**p-value***
Age at surgery (in years; mean, SD)		0	60.1 ± 16.5	58.2 ± 16.7	60.5 ± 16.4	0.079
Gender	*Male*	0	556 (56.5)	106 (54.6)	450 (57.0)	0.559
	Female	0	428 (43.5)	88 (45.4)	340 (43.0)	
Grading	*G2*	0	202 (20.5)	87 (44.8)	115 (14.6)	**<0.001**

	G3	0	782 (79.5)	107 (55.2)	675 (85.4)	
Histology	*LMS*	0	48 (4.9)	13 (6.7)	35 (4.4)	**<0.001**
	D/P-LPS	0	60 (6.1)	30 (15.5)	30 (3.8)	
	MFS	0	267 (27.1)	36 (18.6)	231 (29.2)	
	MFH/UPS & NOS	0	208 (21.1)	52 (26.8)	156 (19.8)	
	MPNST	0	76 (7.7)	4 (2.1)	72 (9.1)	
	SS	0	104 (10.6)	13 (6.7)	91 (11.5)	
	Other	0	156 (15.9)	10 (5.2)	146 (18.5)	
	M-LPS	0	65 (6.6)	36 (18.6)	29 (3.7)	
Tumour size (in cm; median, IQR)		0	8 [5 – 11.5]	9 [5.6 – 14]	7.1 [5 – 11.5]	**0.001**
Localisation	*Upper Limb*	0	222 (22.6)	30 (15.5)	192 (24.3)	**0.008**
	Lower limb	0	762 (77.4)	164 (84.5)	598 (75.7)	
Depth	*Superficial*	0	241 (24.5)	26 (13.4)	215 (27.2)	**<0.001**
	Deep	0	743 (75.5)	168 (86.6)	575 (72.8)	
Margins	*R0*	0	423 (43.0)	93 (47.9)	330 (41.8)	0.060
	R1	0	396 (40.2)	79 (40.7)	317 (40.1)	
	R2	0	165 (16.8)	22 (11.4)	143 (18.1)	
Follow-Up (median; IQR)			70.6 [43.4 – 106.1]	51.8 [27.4 – 88.3]	74.5 [50.1 – 109.0]	

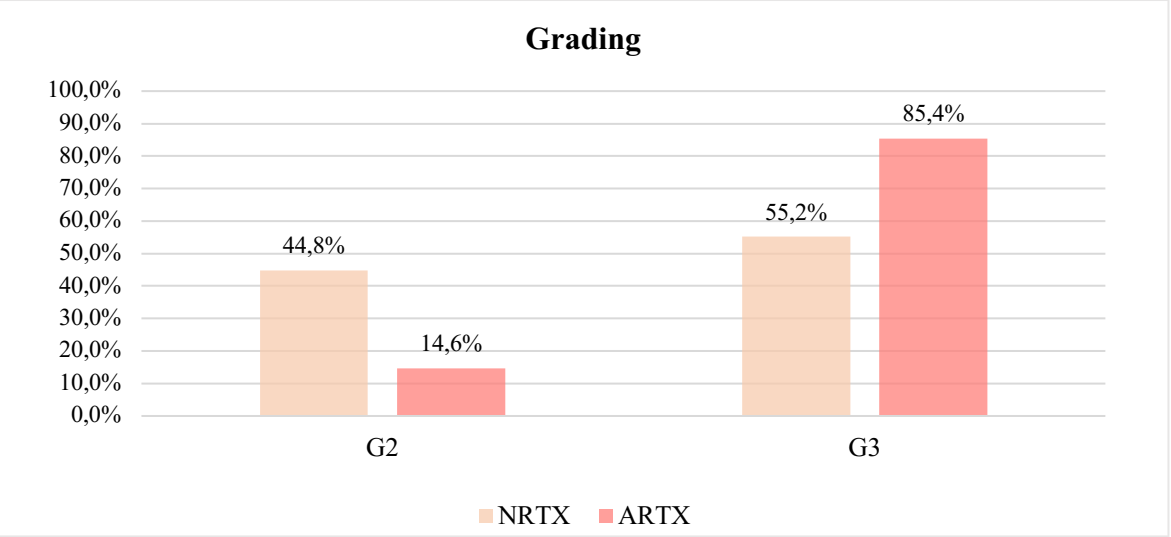
Continuous variables presented as medians with IQRs, categorical variables as absolute numbers with percentages. P-values in bold indicate significant results

***Legend**: IQR – interquartile range; NRTX – neoadjuvant radiotherapy; ARTX – adjuvant radiotherapy; LMS – leiomyosarcoma; D/P-LPS - dedifferentiated/pleomorphic liposarcoma; M-LPS - myxoid liposarcoma; MFS – myxofibrosarcoma; MFH/UPS & NOS - malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified; MPNST - malignant peripheral nerve sheath tumour; SS - synovial sarcoma*

** p-values based on t-tests/Mann-Whitney-U-tests for normally/non-normally distributed continuous variables and chi-squared tests for categorical variables*

Table 10: Descriptive analysis in patients with NRTX or ARTX.

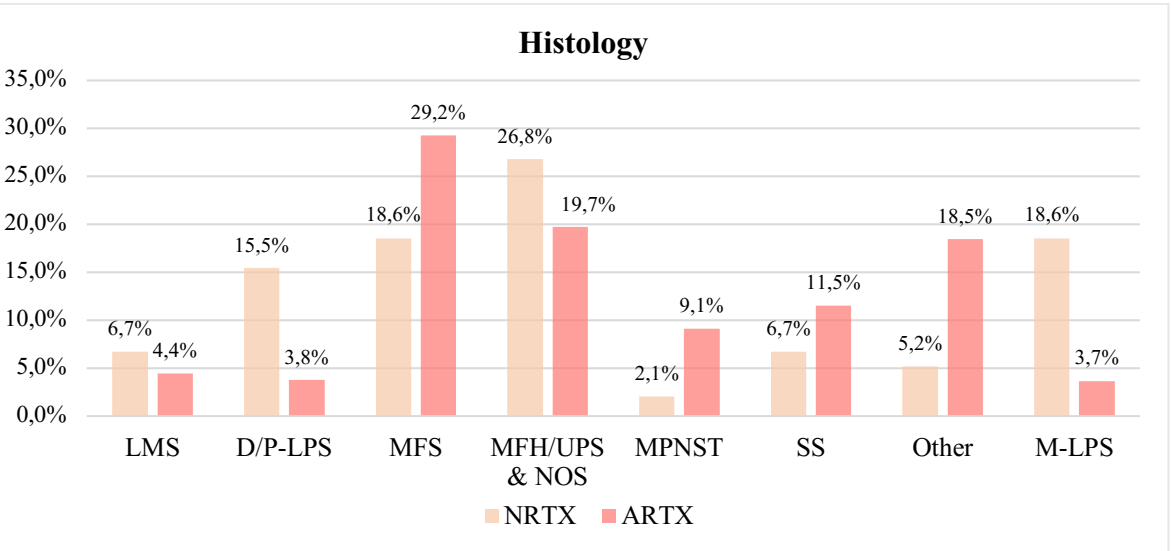
Tumours of the patients who had received ARTX were significantly more often G3 than those of patients who had received NRTX (**p<0.001; Table 10; Figure 22**).



Legend: *NRTX – neoadjuvant radiotherapy; ARTX – adjuvant radiotherapy; G2 – Grade 2; G3 – Grade*

Figure 22: Comparison of the frequencies of the respective grading in the NRTX and ARTX subgroups.

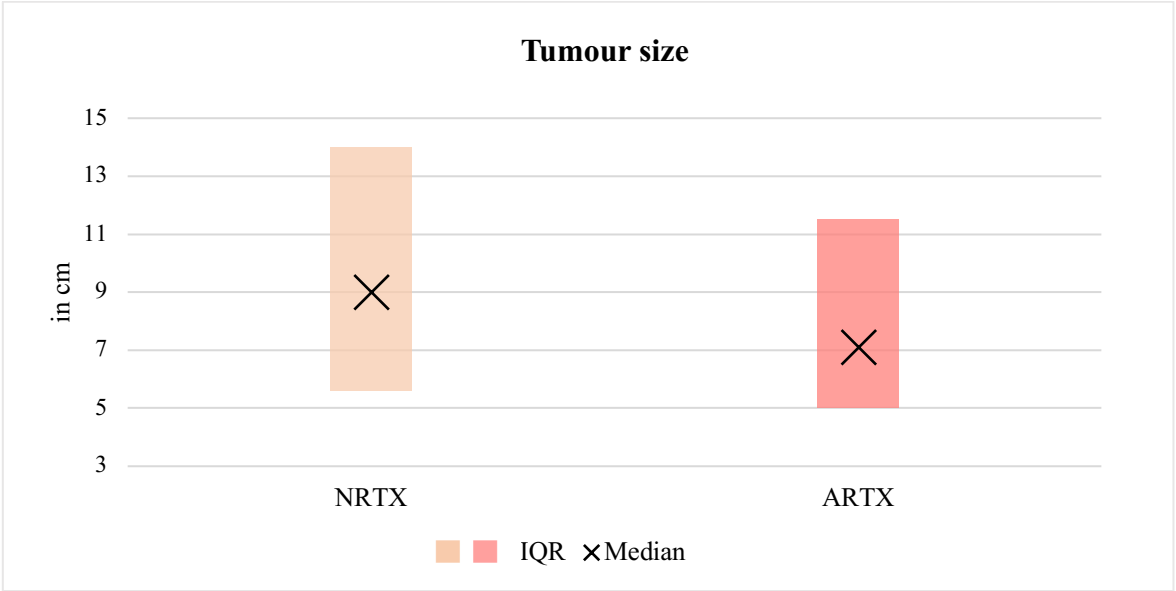
There were significant differences in the frequency of histological subtypes between patients who had received NRTX and ARTX (**p<0.001**). The subtypes MFS, MPNST, SS and "other" occurred more frequently in the ARTX group than in the NRTX group. In contrast, the subtypes LMS, D/P-LPS, MFH/UPS & NOS and M-LPS were more common in patients who had received NRTX than in those who had received ARTX (**Table 10; Figure 23**).



Legend: *NRTX – neoadjuvant radiotherapy; ARTX – adjuvant radiotherapy; LMS – leiomyosarcoma; D/P-LPS - dedifferentiated/pleomorphic liposarcoma; M-LPS - myxoid liposarcoma; MFS – myxofibrosarcoma; MFH/UPS & NOS - malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified; MPNST - malignant peripheral nerve sheath tumour; SS - synovial sarcoma*

Figure 23: Comparison of the frequencies of the respective histologic subtypes in the NRTX and ARTX subgroups.

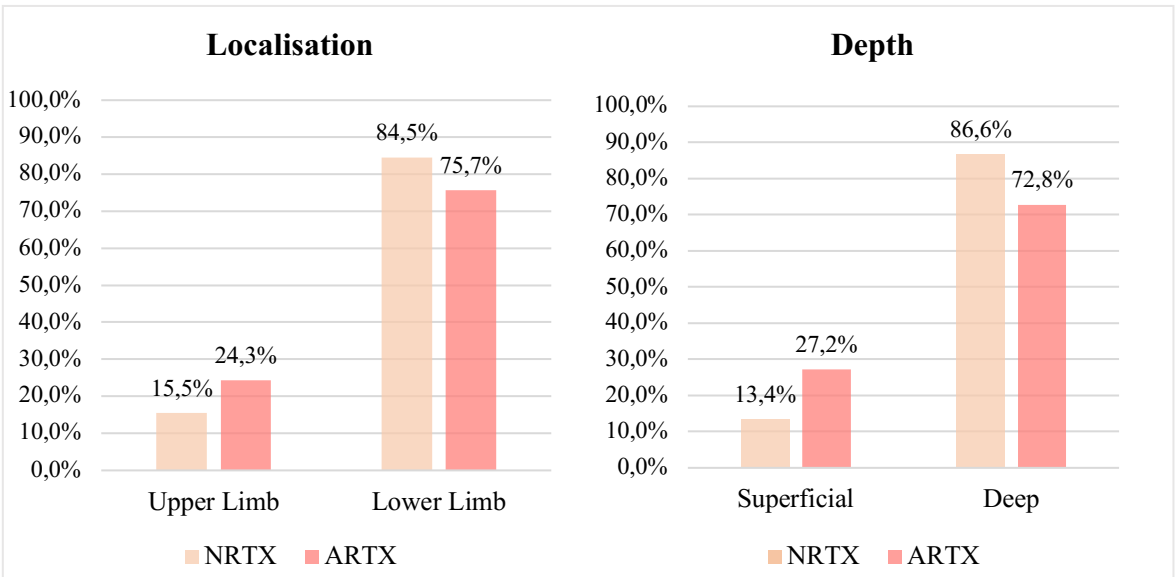
Median tumour size of patients who had received NRTX was significantly larger than the median tumour size of patients who had received ARTX (**p=0.001; Table 10; Figure 24**).



Legend: *NRTX – neoadjuvant radiotherapy; ARTX – adjuvant radiotherapy; IQR – interquartile range*

Figure 24: Comparison of mean tumour size with the corresponding interquartile range in the NRTX and ARTX subgroups.

Moreover, STS were significantly more frequent in the lower extremities (**p=0.008; Table 10; Figure 25**) and localised in deeper tissue layers (**p<0.001; Table 10; Figure 25**) in patients who had received NRTX compared to those who had received ARTX.



Legend: *NRTX – neoadjuvant radiotherapy; ARTX – adjuvant radiotherapy*

Figure 25: Comparison of the frequencies of the respective localisations (left) and the respective tumour depth (right) in the NRTX and ARTX subgroups.

3.2.3 Differences between ARTX and No RTX cohort

Table 11 contains the variables of the ARTX vs. no RTX subgroup. The subgroup consisted of 1006 patients, including the 790 patients who had received ARTX and 216 patients who had not received RTX. No significant differences between treatment groups were found for gender (p=0.144), grading (0.664) and location (p=0.725; **Table 11**).

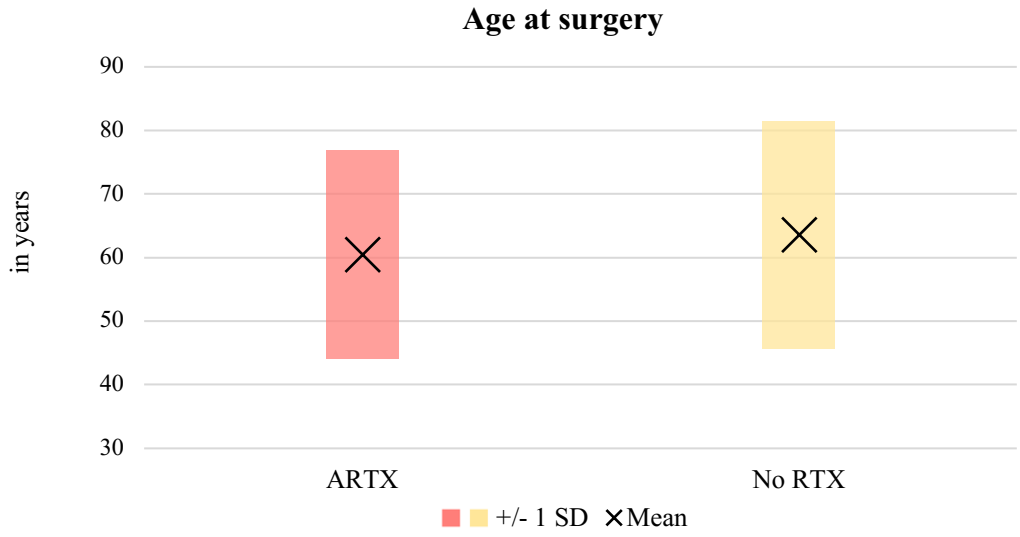
Table 11. Descriptive analysis of patients with no RTX or ARTX.

N=1006		**Missing**	**Overall (n=1006)**	**No RTX (n=216)**	**ARTX (n=790)**	**p-value***
Age at surgery (in years; mean, SD)		0	61.2 ± 16.4	63.6 ± 17.9	60.5 ± 16.4	**0.016**
Gender	*Male*	0	561 (55.8)	111 (51.4)	450 (57.0)	0.144
	Female	0	445 (44.2)	105 (48.6)	340 (43.0)	
Grading	*G2*	0	149 (14.8)	34 (15.7)	115 (14.6)	0.664
	G3	0	857 (85.2)	182 (84.3)	675 (85.4)	
Histology	*LMS*	0	55 (5.5)	20 (9.3)	35 (4.4)	**0.023**
	D/P-LPS	0	38 (3.8)	8 (3.7)	30 (3.8)	
	MFS	0	286 (28.4)	55 (25.5)	231 (29.2)	
	MFH/UPS & NOS	0	214 (21.3)	58 (26.8)	156 (19.8)	
	MPNST	0	92 (9.1)	20 (9.3)	72 (9.1)	
	SS	0	109 (10.8)	18 (8.3)	91 (11.5)	
	Other	0	175 (17.4)	29 (13.4)	146 (18.5)	
	M-LPS	0	37 (3.7)	8 (3.7)	29 (3.7)	
Tumour size (in cm; median, IQR)		0	7 [5 – 11.5]	6 [4 – 10]	7.1 [5 – 11.5]	**0.019**
Localisation	*Upper Limb*	0	242 (24.1)	50 (23.2)	192 (24.3)	0.725
	Lower limb	0	764 (75.9)	166 (76.8)	598 (75.7)	
Depth	*Superficial*	0	305 (30.3)	90 (41.7)	215 (27.2)	**<0.001**
	Deep	0	701 (69.7)	126 (58.3)	575 (72.8)	
Margins	*R0*	0	472 (46.9)	142 (65.7)	330 (41.8)	**<0.001**
	R1	0	360 (35.8)	43 (19.9)	317 (40.1)	
	R2	0	174 (17.3)	31 (14.4)	143 (18.1)	
Follow-Up (median; IQR)		0	73.4 [48.6 – 109.0]	70.1 [38.8 – 108.1]	74.5 [50.1 – 109.0]	

***Legend**: IQR – interquartile range; ARTX – adjuvant radiotherapy; No RTX – no radiotherapy; LMS – leiomyosarcoma; D/P-LPS - dedifferentiated/pleomorphic liposarcoma; M-LPS - myxoid liposarcoma; MFS – myxofibrosarcoma; MFH/UPS & NOS - malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified; MPNST - malignant peripheral nerve sheath tumour; SS - synovial sarcoma*

Table 11: Descriptive analysis of patients with no RTX or ARTX.

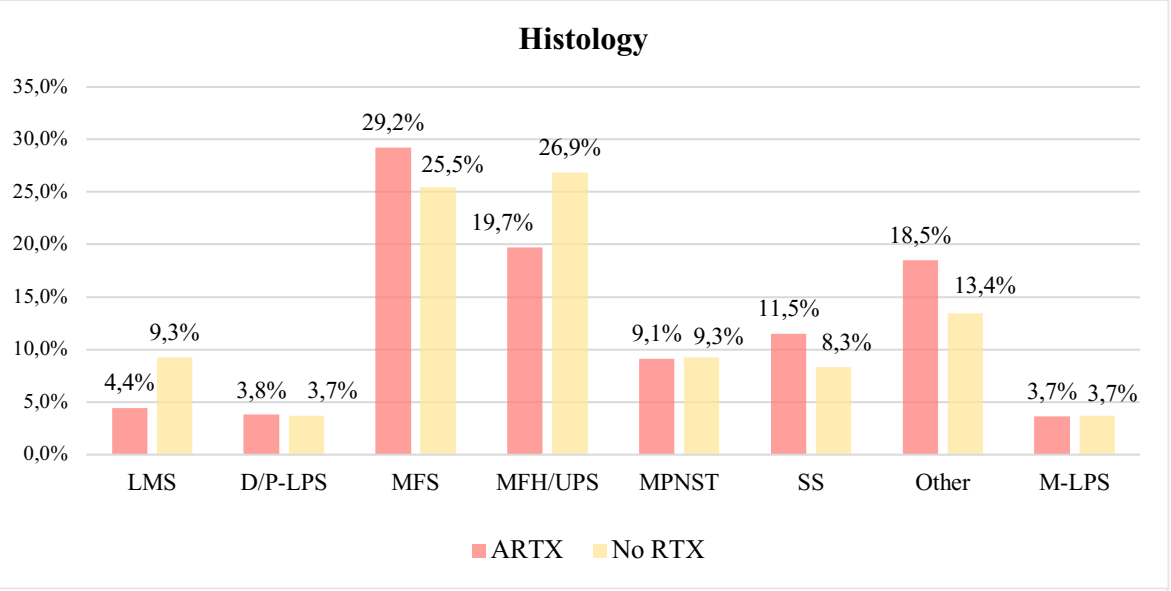
Patients who had received no RTX were significantly older at baseline than those who had received ARTX (**p=0.016; Table 11; Figure 26**).



***Legend:** ARTX – adjuvant radiotherapy; No RTX – no radiotherapy; SD – standard deviation*

Figure 26: Comparison of mean age with corresponding standard deviation in the ARTX and no RTX subgroups.

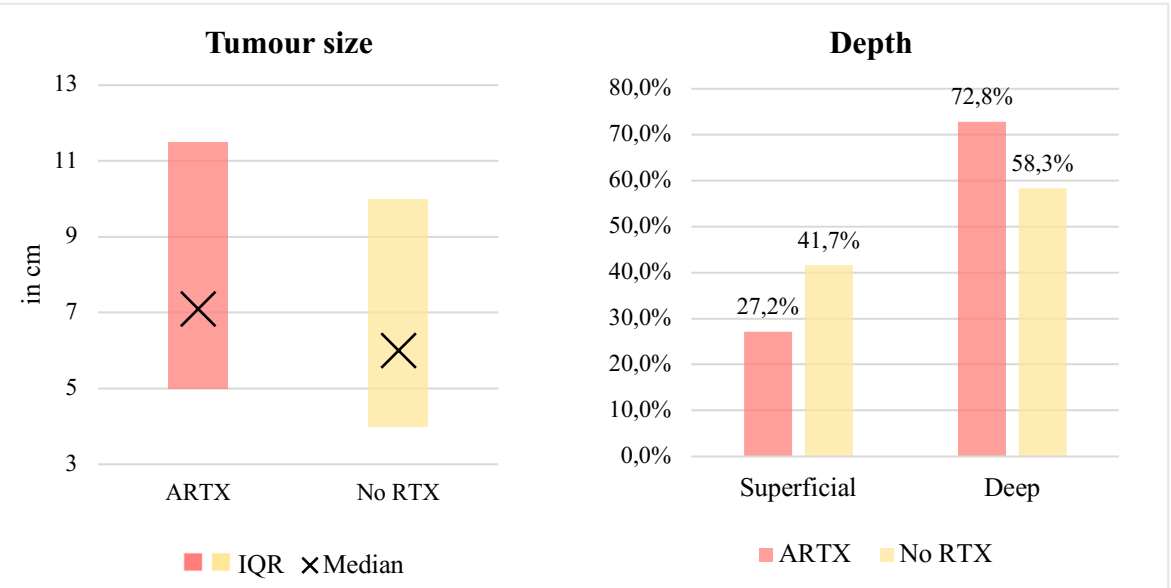
Furthermore, there were significant differences in the frequency of histologic subtypes between the two treatment groups at baseline, as shown in **Figure 27** (**p=0.023; Table 11**).



Legend: *ARTX – adjuvant radiotherapy; No RTX – no radiotherapy; LMS – leiomyosarcoma; D/P-LPS - dedifferentiated/pleomorphic liposarcoma; M-LPS - myxoid liposarcoma; MFS – myxofibrosarcoma; MFH/UPS & NOS - malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified; MPNST - malignant peripheral nerve sheath tumour; SS - synovial sarcoma*

Figure 27: Comparison of the frequencies of the respective histologic subtypes in the ARTX and no RTX subgroups.

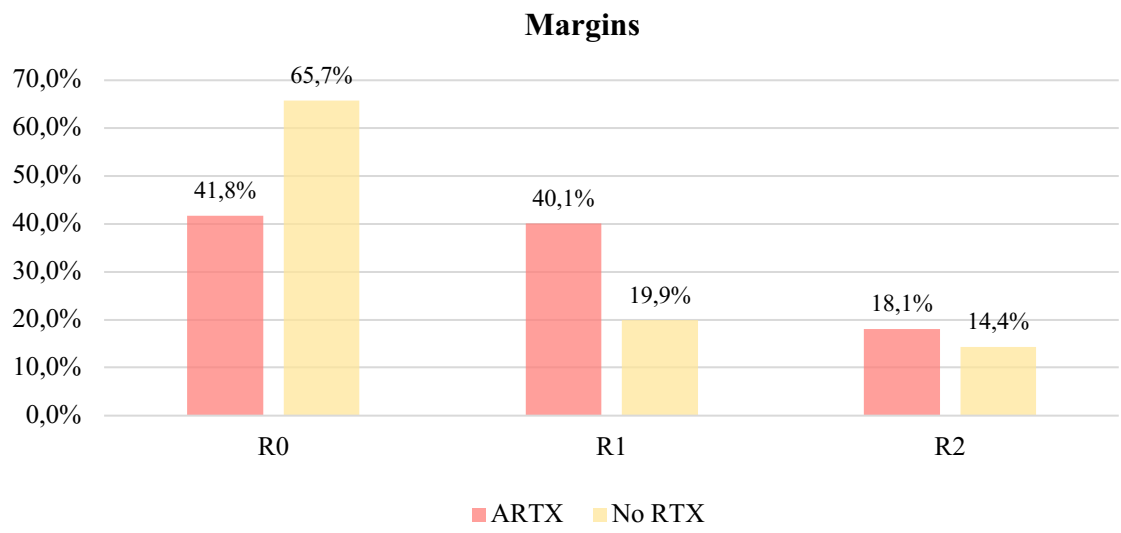
Tumours in patients having received ARTX were larger (**p=0.019**) and more frequently localised in the depth (**p<0.001**) than STS in patients not having received RTX (**Table 11; Figure 28**).



Legend: *ARTX – adjuvant radiotherapy; No RTX – no radiotherapy; IQR – interquartile range*

Figure 28: Comparison of median tumour sizes with corresponding IQR (left) and frequencies of respective depths (right) in the ARTX and no RTX subgroups.

Furthermore, tumours in the ARTX group less frequently had R0 margins than patients who had not received RTX (**p<0.001; Table 11; Figure 29**).



Legend: *ARTX – adjuvant radiotherapy; No RTX – no radiotherapy; R0 – resection margin, microscopically negative; R1 – resection margin, macroscopically positive, microscopically negative; R2 – resection margin, macroscopically positive*

Figure 29: Comparison of the frequencies of the respective resection margins in the ARTX and no RTX subgroups.

3.2.4 Significant SMDs and IPTW-weighting

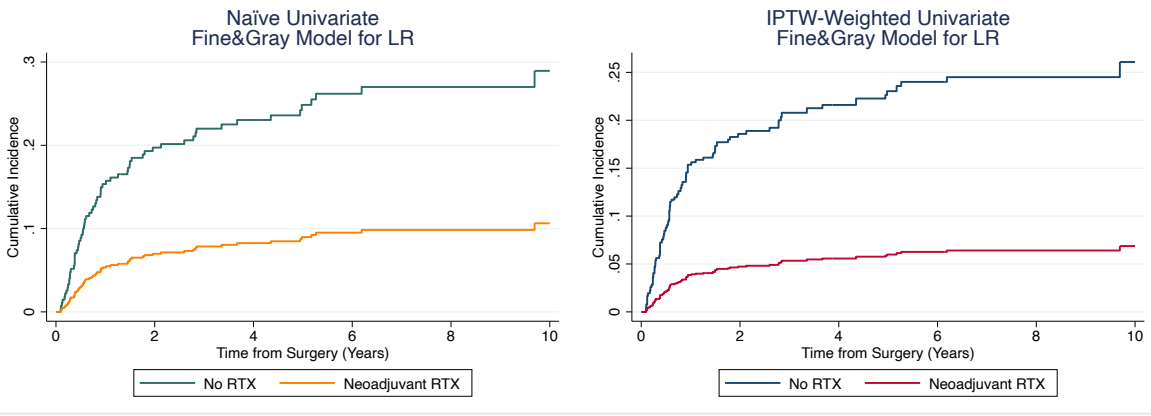
The SMD threshold of 0.2 was exceeded in the treatment pair no RTX vs. NRTX for age (SMD = 0.31), grading (SMD = 0.67), histological subtypes D/P-LPS (SMD = 0.41), MPNST (SMD = 0.31), "other" (SMD = 0. 29) and M-LPS (SMD = 0.48), tumour size (SMD = 0.38), tumour location (SMD = 0.20), depth (SMD = 0.67), R0 margin (SMD = 0.39) and R1 margin (SMD = 0.46).

In the NRTX vs. ARTX cohort, grading (SMD = 0.70), histological subtypes D/P-LPS (SMD = 0.40), MFS (SMD = 0.25), MPNST (SMD = 0.31), "other" (SMD = 0. 42) and M-LPS (SMD = 0.49), tumour size (SMD = 0.25), tumour location (SMD = 0.22) and tumour depth (SMD = 0.35) exceeded the same threshold.
In the cohort no RTX vs. ARTX, the defined threshold of 0.2 was exceeded for variables depth (SMD = 0.31), R0 margin (SMD = 0.49) and (R1 margin, SMD = 0.45).
After IPTW-weighting of the treatment pairs, the SMDs were significantly reduced, indicating a sufficient balancing of variables.

3.3 IPTW analysis

3.3.1 Effect of NRTX in comparison to no RTX

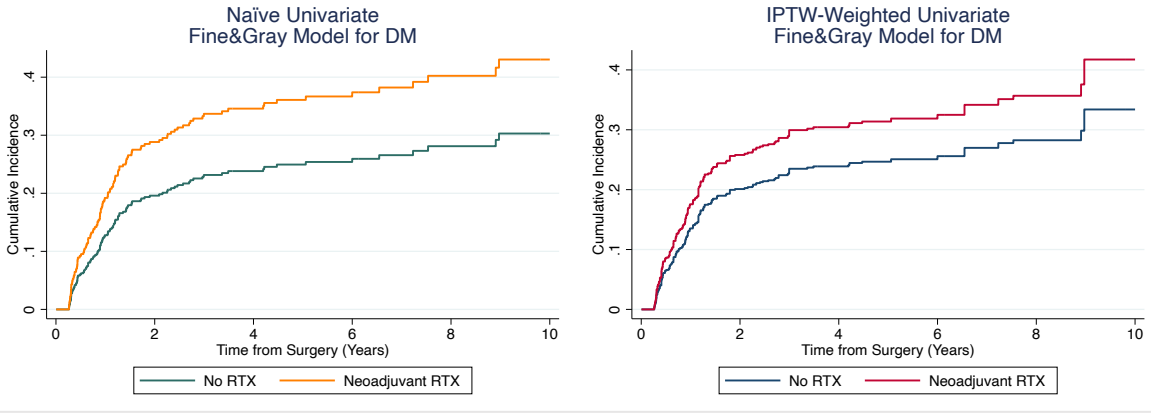
NRTX was associated with a significantly lower LR-risk in comparison to no RTX, both in the univariate naïve Fine&Gray model (SHR: 0.329; **p<0.001; Table 12; Figure 30**) and the IPTW-weighted univariate Fine&Gray model (SHR: 0.236; **p<0.001; Table 12; Figure 30**).



Legend: *LR – local recurrence; IPTW – inverse probability treatment weighting; RTX – radiotherapy*

Figure 30: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for LR for the no RTX vs. NRTX subgroups

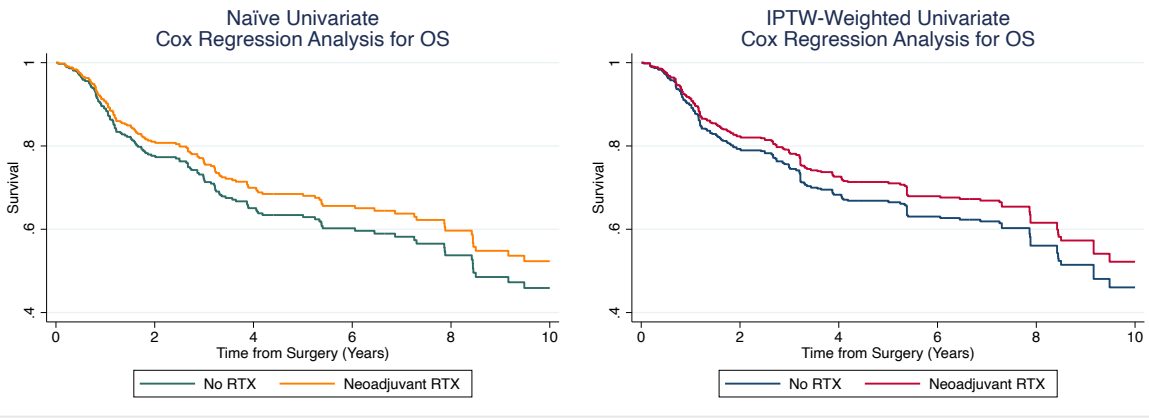
Univariate Fine&Gray model for DM showed a significantly increased risk for distant spread in patients with NRTX compared to those without RTX (SHR: 1.560; **p=0.018; Table 12; Figure 31**). However, this correlation was not significant after IPTW weighting (SHR: 1.329; **p=0.192; Table 12; Figure 31**).



Legend: *DM – distant metastasis; IPTW – inverse probability treatment weighting; RTX – radiotherapy*

Figure 31: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for DM for the no RTX vs. NRTX subgroups

Regarding OS, both univariate naïve and IPTW-weighted Cox regression models showed no significant association between NRTX and altered survival (HR: 0.831; p=0.289 and HR: 0.838; p=0.394; **Table 12; Figure 32**).

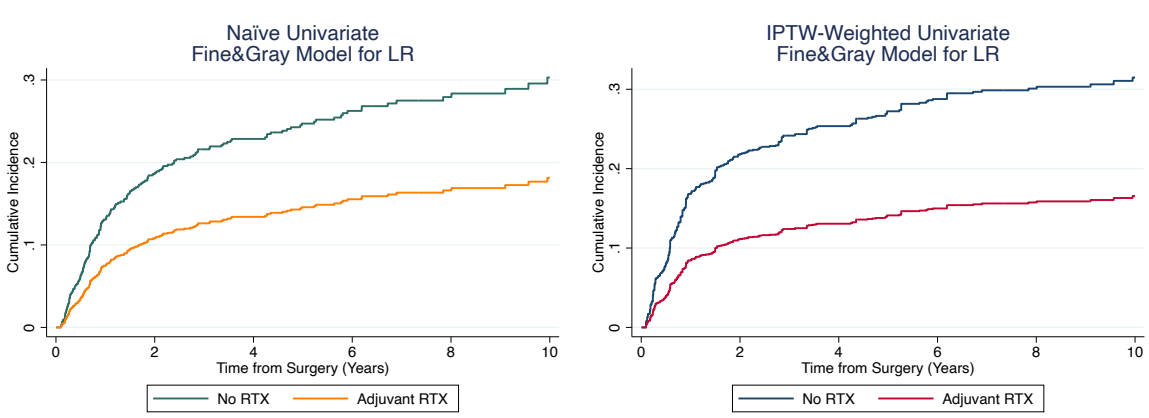


Legend: *OS – overall survival; IPTW – inverse probability treatment weighting; RTX - radiotherapy*

Figure 32: Univariate naïve (left) and IPTW-weighted (right) Cox regression models for OS for the no RTX vs. NRTX subgroups

3.3.2 Effect of ARTX in comparison to no RTX

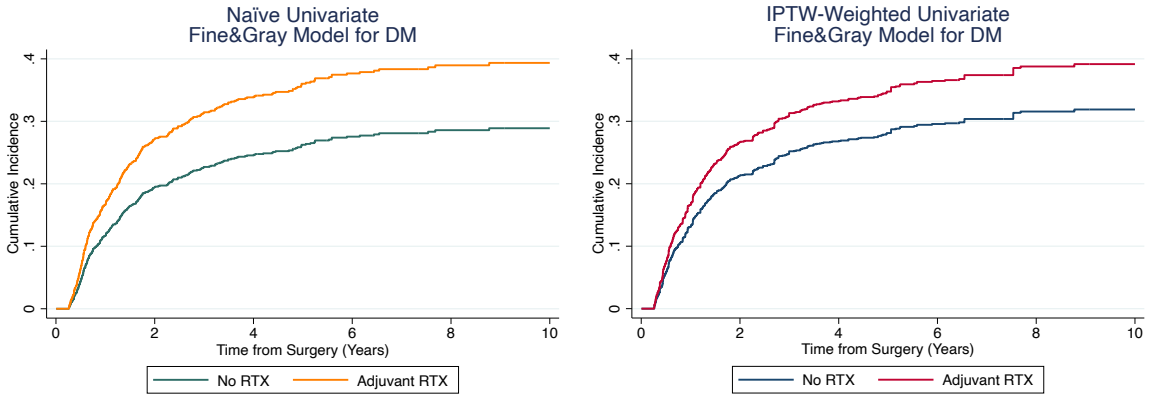
Both univariate naïve and IPTW-weighted Fine&Gray models showed a significantly lower risk of LR in case of ARTX in comparison to no RTX (SHR: 0.555; **p=0.001** and SHR: 0.479; **p<0.001; Table 12, Figure 33**).



Legend: *LR – local recurrence; IPTW – inverse probability treatment weighting; RTX – radiotherapy*

Figure 33: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for LR for the no RTX vs. ARTX subgroups

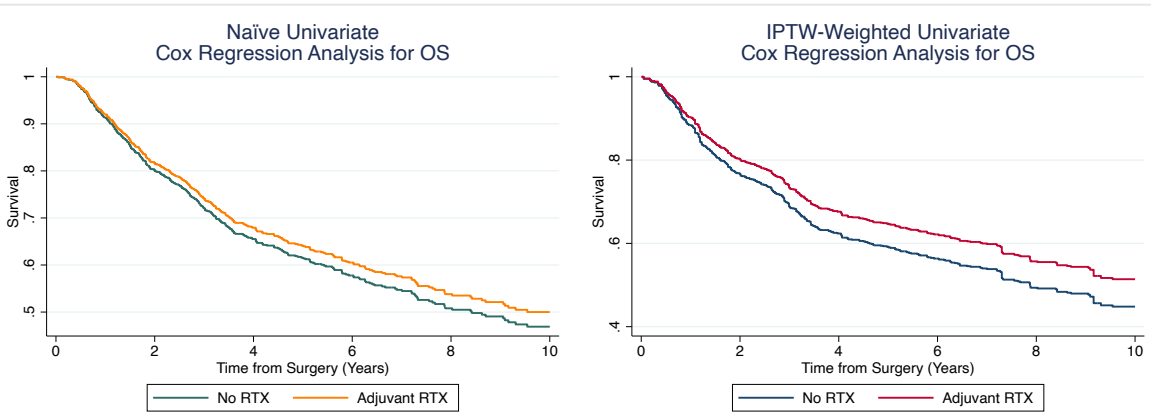
Univariate naïve Fine&Gray model showed a significantly increased risk for DM for ARTX compared to no RTX (SHR: 1.467; **p=0.013; Table 12; Figure 34**). This correlation, though, was found to be non-significant after IPTW weighting (SHR: 1.294; p=0.121; **Table 12; Figure 34**).



Legend: *DM – distant metastasis; IPTW – inverse probability treatment weighting; RTX –radiotherapy*

Figure 34: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for DM for the no RTX vs. ARTX subgroups

Regarding OS, both naïve univariate and IPTW-weighted Cox regression analysis showed no association between ARTX and improved OS (HR: 0.915; p=0.483 and HR: 0.829; p=0.178, respectively; **Table 12; Figure 35**).

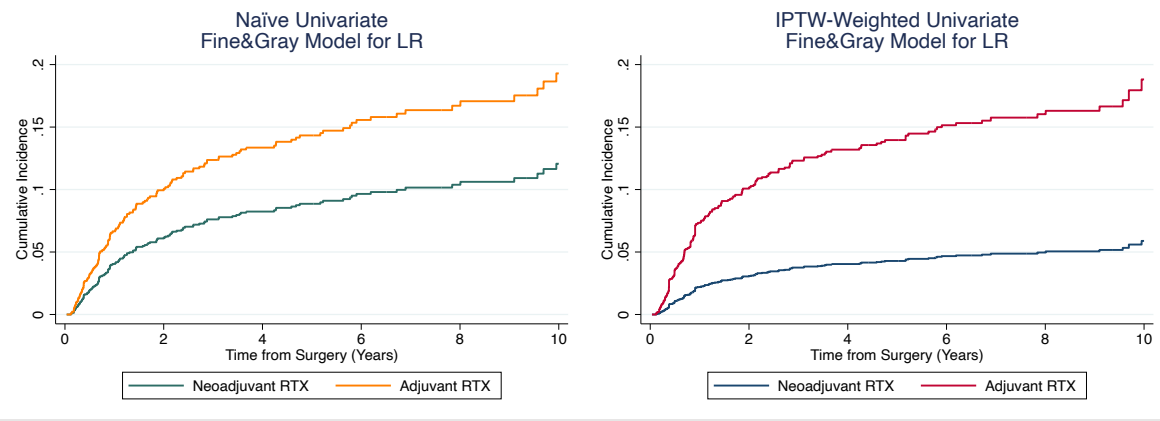


Legend: *OS – overall survival; IPTW – inverse probability treatment weighting; RTX - radiotherapy*

Figure 35: Univariate naïve (left) and IPTW-weighted (right) Cox regression models for OS for the no RTX vs. ARTX subgroups

3.3.3 Effect of NRTX in comparison to ARTX

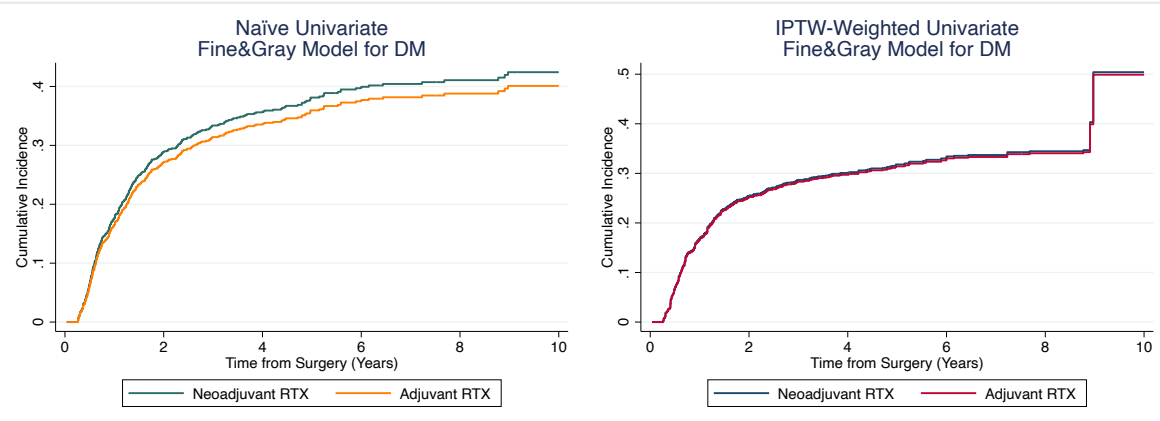
In univariate naïve Fine&Gray model, there was no significant effect of ARTX vs. NRTX with respect to the occurrence of LR (SHR: 1.667; p=0.055; **Table 12; Figure 36**). However, after IPTW weighting, ARTX showed a significantly increased risk of LR occurrence compared to NRTX (SHR:3.433**; p<0.001; Table 12; Figure 36**).



Legend: *LR – local recurrence; IPTW – inverse probability treatment weighting; RTX – radiotherapy*

Figure 36: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for LR for the NRTX vs. ARTX subgroups

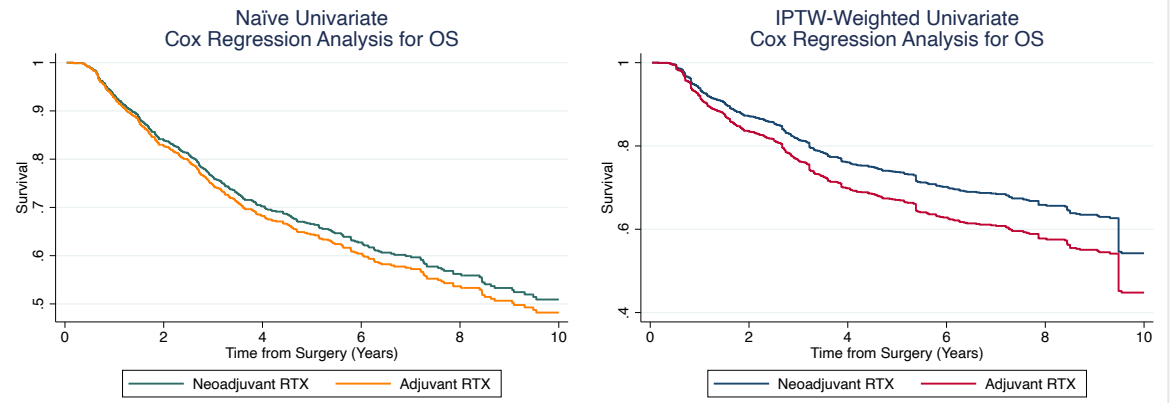
Regarding DM risk, neither univariate naïve nor IPTW-weighted Fine&Gray models showed a significant association between NRTX and ARTX towards increased risk for distant spread (SHR: 0.928; p=0.588 and SHR: 0.985; p=0.936; **Table 12; Figure 37**).



Legend: *DM – distant metastasis; IPTW – inverse probability treatment weighting; RTX –radiotherapy*

Figure 37: Univariate naïve (left) and IPTW-weighted (right) Fine&Gray models for DM for the NRTX vs. ARTX subgroups

Similarly, neither univariate naïve nor IPTW-weighted Cox regression analysis showed a significant association between NRTX or ARTX in terms of altered OS (HR: 1.081; p=0.591 and HR: 1.312; **p=0.213; Table 12; Figure 38**).



Legend: *OS – overall survival; IPTW – inverse probability treatment weighting; RTX – radiotherapy*

Figure 38: Univariate naïve (left) and IPTW-weighted (right) Cox regression models for OS for the NRTX vs. ARTX subgroups

Table 12. Univariate naïve and IPTW-weighted Fine&Gray models for LR and DM and univariate naïve and IPTW-weighted Cox-regression model for OS

LR								
Subgroups	**Naïve Fine&Gray model**				**IPTW-weighted Fine&Gray model**			
	SHR	**95%CI**		**p-value**	**SHR**	**95%CI**		**p-value**
		Lower	**Upper**			**Lower**	**Upper**	
No RTX (ref.) vs. NRTX	0.329	0.188	0.577	**<0.001**	0.236	0.127	0.436	**<0.001**
No RTX (ref.) vs. ARTX	0.555	0.397	0.775	**0.001**	0.479	0.335	0.684	**<0.001**
NRTX (ref.) vs. ARTX	1.667	0.990	2.810	0.055	3.433	1.820	6.475	**<0.001**
DM								
Subgroups	**Naïve Fine&Gray model**				**IPTW-weighted Fine&Gray model**			
	SHR	**95%CI**		**p-value**	**SHR**	**95%CI**		**p-value**
		Lower	**Upper**			**Lower**	**Upper**	
No RTX (ref.) vs. NRTX	1.560	1.080	2.251	**0.018**	1.329	0.867	2.039	0.192
No RTX (ref.) vs. ARTX	1.467	1.084	1.985	**0.013**	1.294	0.935	1.791	0.121
NRTX (ref.) vs. ARTX	0.928	0.709	1.215	0.588	0.985	0.690	1.408	0.936
OS								
Subgroups	**Naïve Cox Regression model**				**IPTW-weighted Fine&Gray model**			
	HR	**95%CI**		**p-value**	**HR**	**95%CI**		**p-value**
		Lower	**Upper**			**Lower**	**Upper**	
No RTX (ref.) vs. NRTX	0.831	0.591	1.170	0.289	0.838	0.559	1.257	0.394
No RTX (ref.) vs. ARTX	0.915	0.714	1.173	0.483	0.829	0.631	1.089	0.178
NRTX (ref.) vs. ARTX	1.081	0.814	1.435	0.591	1.312	0.855	2.015	0.213

***Legend**: HR – hazard ratio; SHR – subhazard ratio; RTX – radiotherapy; NRTX – neoadjuvant radiotherapy; ARTX – adjuvant radiotherapy; LR – local recurrence; DM – distant metastasis; OS – overall survival; IPTW- inverse-probability of treatment-weight*

Table 12: Univariate naïve and IPTW-weighted Fine&Gray models for LR and DM and univariate naïve and IPTW-weighted Cox-regression model for OS

4 Discussion

4.1 Summary of main results

The present retrospective multicentre study investigated the independent effect of NRTX and ARTX on oncological outcome (LR, DM, and OS) in patients with high-grade (G2/G3) localised eSTS. For this purpose, 1200 patients were retrospectively included, all of whom had been treated with primarily curative intent at altogether ten tertiary tumour centres.
Baseline differences between treatment groups were evaluated using SMDs and thereafter adjusted with statistical methods using PS and IPTW, resulting in sufficient reduction of SMDs.
IPTW-adjusted analysis showed that RTX improved local control both in the neoadjuvant and adjuvant setting in comparison to no RTX. Furthermore, NRTX showed a greater effect on local control than ARTX. On the other hand, neither NRTX nor ARTX had a significant positive impact on the development of DM or OS and finally, the hypothesis of an indirect association between improved local control and lower risk of DM or improved OS could not be confirmed.

4.2 Comparison with previous results

4.2.1 Differences in patient cohorts

The differences in the oncological profile between all treatment pairs observed at baseline were to be expected given the retrospective, non-randomised design of the study. Nevertheless, they need to be discussed as they may suggest that the prognostic influence is greater than effects of the respective treatment modalities.

In the present study, patients receiving RTX were significantly younger (NRTX: $p=0.002$; ARTX: $p=0.016$), had larger (NRTX $p<0.001$; ARTX $p=0.019$) and deeper located tumours (NRTX and ARTX: $p<0.001$), as well as less often R0 resections (NRTX and ARTX: $p<0.001$) compared to patients receiving no RTX. Histological subtypes also differed notably between treatment groups (NRTX: $p<0.001$; ARTX $p=0.023$). In addition, there were significantly more G2 and fewer G3 tumours in patients receiving NRTX ($p<0.001$) compared to patients not receiving RTX, noting that only high-grade (G2/G3) eSTS were included in this study (and no G1 eSTS). When comparing the NRTX and ARTX treatment

pairs, it was noticeable that patients receiving ARTX had significantly more often G3 tumours ($p<0.001$), which were smaller ($p=0.001$) and more likely superficially located ($p<0.001$). There was also a significant difference in the frequency distribution of histological subtypes.

Consistent with these findings, Gingrich et al. (164) showed in a 2017 analysis that tumours were larger ($p<0.001$) in patients receiving NRTX compared to patients receiving no RTX or ARTX, and Ramey et al. (241) demonstrated in 2018 that tumours were larger ($p<0.001$) and deeper ($p<0.001$) in patients receiving RTX in comparison to those receiving surgery alone. Furthermore, Gingrich et al. (164) observed significantly more high-grade tumours in patients receiving NRTX or ARTX ($p<0.001$), being consistent with the recommendation for RTX in current guidelines. (1)

In contrast to the observations of the present study, Gingrich et al. described significantly more R0 resections in patients receiving NRTX compared to patients receiving no RTX ($p<0.0001$). (164)

The described differences between patient cohorts are considered to be important prognostic factors in eSTS. (126, 131) It is therefore reasonable to argue that the different oncological profiles in treatment pairs may outweigh the influence of the treatment modality on patient outcome. In the present study, therefore, significant differences were present that could be balanced for using PS and IPTW statistical methods.

4.2.2 Effect of RTX on outcome

The statistical approach chosen allowed to analyse the effects of RTX on oncological outcome independent of confounding factors.

The positive effect of RTX on local control observed in this study is supported by a number of previous studies. (234, 235, 236, 237) For example, the randomised trials by Pisters et al., (235) Beane et al., (234) and Yang et al., (236) also reported on an improvement in local control with ARTX and, in addition, no significant improvement in survival. Similarly, a 2018 observational study by Posch et al. using IPTW-weighting statistical analysis showed a strong reduction in LR risk (SHR 0.42; 95% CI 0.19-0.91; $p=0.03$), but no significant positive effect on DM (SHR 0.69; 95%CI 0.39-1.25; $p=0.22$) and OS (HR 0.76; 95% CI 0.44-1.30; $p=0.32$). (237)

The superior effect of NRTX compared to ARTX found in this study is consistent with the observations reported by Sampath et al. (2019) who discovered in their retrospective study that the use of NRTX compared with ARTX was significantly associated with a lower risk of LR (HR 0.5, 95% CI 0.46-0.88, p<0.05) (242). On the other hand, these observations are contradicted by a meta-analysis published in 2020 by Yang et al., describing no significant difference between NRTX and ARTX in terms of local control (RR 0.84, 95% CI 0.58-1.21). (222)

The effect of RTX on survival has been discussed controversially in previous studies: In the above-mentioned randomised trials by Pisters et al. (1996), Beane et al. (2014) and Yang et al. (1998), no significant positive effect of RTX on DM and OS was found, being in line with the results of the present study. (234, 235, 236, 237)
On the other hand, a number of non-randomised studies have reported a beneficial effect of RTX on survival. (164, 239, 240, 241, 242) For example, in 2016, Zhao et al. (240) described a significantly improved OS in patients in whom ARTX had been applied (HR 0.512; 95% CI 0.296-0.886; p=0.017) compared to LSS alone. In 2017, Gingrich et al. (164) reported on better OS in case ARTX (HR 0.80, 95% CI 0.78-0.82; p<0.001) and NRTX (HR 0.94, 95% CI 0.91-0.98, p<0.001) had been applied, with superiority of ARTX. Ramey et al. made similar observations in 2018 for NRTX (median survival times NRTX+LSS: 8.9 years [95% CI 7.9 – not estimable] vs. LSS alone: 6.6 years [95% CI 5.4 – 7.8 years]) and ARTX (LSS alone: 7.2 years [95% CI 6.5-8.9] vs. LSS+ARTX: 9.8 years [95% CI 9.0-11.2 years]), using PS statistical methods. (241)

The hypothesis that there is an indirect association between local control and a reduced risk of DM as well as improved OS, based on the observations made in previous studies by Posch et al. (244), Gronchi et al. (245) and Rueten-Budde et al. (252) cannot be supported by results of the present study, albeit herein predominantly the effects of RTX on the outcome parameters mentioned were analysed. Another possible explanation for these conflicting results may be the observational nature of most of the studies mentioned, which introduces a possible selection bias. (253)
Large, randomised trials or advanced statistical analyses, such as IPTW-weighting, are needed to prevent or compensate for treatment selection bias. (248, 254) However, due to the heterogeneity and rarity of STS, (4, 5) previous randomised trials have included small

patient populations, with a maximum of 190 participants. (146, 225, 234, 235, 236) IPTW-analyses were used by Ramey et al., but with one-to-one PS matching, resulting in significant patient exclusion, whereas we could include all patients using IPTW-weighting. (241)

4.3 Limitations of the study

When considering the results of this study, it is important to be aware of some existing limitations.

The first limitation is the retrospective design of the study. Firstly, there is an increased risk of confounding and selection bias, eventually distorting the results and their interpretation. (253, 255) However, in this study, this bias was compensated for at best possible by the use of complex statistical methods (PS and IPTW). (248) Furthermore, statistical analyses were carried out in three separate datasets. One dataset, for the analysis of NRTX vs. no RTX, excluded all patients who had received ARTX. The second, for the analysis of ARTX vs. no RTX, excluded those who had received NRTX. And the third dataset, for the comparison of NRTX vs. ARTX, excluded those who had not received RTX. As the validity of the IPTW model depends on the precise specification of PS, (248, 254) in addition to factors that differed between treatment pairs, known prognostic factors were included in the analysis to avoid missing confounders.

In addition, retrospective studies are dependent on the quality of the data provided that may not always be accurate or complete. For example, in this study, 29.4% of patients were excluded due to missing and/or incomplete clinical data. Moreover, it is difficult to reconstruct decisions made in the past. In this study, for example, some patients had not received RTX although it would have been recommended according to the international guidelines based on their clinical profile. (1) Reasons for these decisions remain of speculative nature, eventually including patient refusal, difficult surgical circumstances or differing local treatment strategies. The latter theory is reinforced by the multicentre study design that may be associated with a more heterogeneous local treatment strategy. The different proportions of patients receiving RTX per centre in this study suggest at least slightly different local strategies. However, as all cases included were from experienced sarcoma centres, the clinical management can be considered ESMO-compliant. (1)

Nevertheless, the advantages of multicentricity, such as the large sample size, the geographical diversity and the broader patient population, outweigh the disadvantages.

Data on short- and long-term side effects of NRTX and ARTX were also not available for patients included in the present study. However, these play an important role in the indication and timing of RTX, as the main reason for the use of ARTX is the increased incidence of wound complications observed upon NRTX. (225, 227) Since the focus of this study was to assess the effect of RTX on LR, DM and OS, however, this is not a limitation in answering the research question.

4.4 Clinical implications

The decision to use neoadjuvant or adjuvant RTX remains controversial. (221) The higher wound complication rate with neoadjuvant use (225, 229) and the higher secondary toxicity rate with adjuvant use (227, 228) should be considered in the decision-making process. The present study demonstrated the positive effects of both NRTX and ARTX on local control, with NRTX being superior. Based on these results, the indication for RTX should be determined according to the ability to resect negative margins, tumour radiosensitivity and individual risk factors for short- and long-term morbidity. (2, 203, 223, 224, 225) The timing should take into account the superiority of NRTX in terms of local control. It should be noted that in the present study, the protective effect of NRTX and ARTX on LR risk was assessed independently of known prognostic factors.

4.5 Conclusion

In summary, this retrospective, multicentre study confirms the significant positive impact of RTX on the risk of LR in patients with high-grade eSTS, with the effect of NRTX being superior to ARTX. However, a significant positive effect of RTX on DM and OS could not be demonstrated. The hypothesis of an indirect benefit of RTX through a reduced LR risk for DM and OS could not be confirmed. In clinical practice, the use of NRTX may be preferred over ARTX due to its superiority in terms of local control, taking into account the individual factors.

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