Effect of radiotherapy on local recurrence, distant metastasis and overall survival in 1200 extremity soft tissue sarcoma patients: retrospective analysis using IPTW-adjusted models

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Original Article

Effect of radiotherapy on local recurrence, distant metastasis and overall survival in 1200 extremity soft tissue sarcoma patients. Retrospective analysis using IPTW-adjusted models

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ABSTRACT

Background and purpose: Neoadjuvant (NRTX) and adjuvant radiotherapy (ARTX) reduce local recurrence (LR) risk in extremity soft tissue sarcoma (eSTS), yet their impact on distant metastasis (DM) and overall survival (OS) is less well defined. This study aimed at analysing the influence of NRTX/ARTX on all three endpoints using a retrospective, multicentre eSTS cohort.

Materials and methods: 1200 patients (mean age: 60.7 ± 16.8 years; 44.4 % females) were retrospectively included, treated with limb sparing surgery and curative intent for localised, high grade (G2/3) eSTS. 194 (16.2 %), 790 (65.8 %), and 216 (18.0 %) patients had received NRTX, ARTX and no RTX, respectively. For the resulting three groups (no RTX vs. NRTX, no RTX vs. ARTX, NRTX vs. ARTX) Fine&Gray models for LR and DM, and Cox-regression models for OS were calculated, with IPTW-modelling adjusting for imbalances between groups.

Results: In the IPTW-adjusted analysis, NRTX was associated with lower LR-risk in comparison to no RTX (SHR [subhazard ratio]: 0.236; $p = 0.003$), whilst no impact on DM-risk ($p = 0.576$) or OS ($p = 1.000$) was found. IPTW-weighted analysis for no RTX vs. ARTX revealed a significant positive association between ARTX and lower LR-risk (SHR: 0.479, $p = 0.003$), but again no impact on DM-risk ($p = 0.363$) or OS ($p = 0.534$). IPTW-weighted model for NRTX vs. ARTX showed significantly lower LR-risk for NRTX (SHR for ARTX: 3.433; $p = 0.003$) but no difference regarding DM-risk ($p = 1.000$) or OS ($p = 0.639$).

Conclusion: NRTX and ARTX are associated with lower LR-risk, but do not seem to affect DM-risk or OS. NRTX may be favoured over ARTX as our results indicate better local control rates.

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Introduction

In the past four decades, radiotherapy (RTX) has been recommended in deep-seated, G2/3 STS as well as large tumours (>5 cm) in order to improve local control rate [1,2]. In the most recent ESMO guideline published in 2021, RTX is still proposed in G2 and G3 tumours, whilst size and depth are no more considered as decisive whether to administer RTX [3].

In order to independently analyse the effect of neoadjuvant (NRTX) and adjuvant radiotherapy (ARTX) on outcome of patients with extremity soft tissue sarcoma (eSTS), randomised trials are necessary. Both the low incidence and heterogenous patient population would significantly affect recruitment of sufficiently large STS cohorts, though. Consequently, randomised studies performed thus far assessing the effect of RTX have included less than 200 patients each [4–7]. Thus, the potential benefit of RTX on oncological outcome beyond local control rate – irrespective of its timing – could not be demonstrated in these studies [8,9]. On the other hand, some retrospective studies have reported on a strong association between RTX and development of local recurrence (LR), distant metastasis (DM) and overall survival (OS) [10–14]. Meta-analyses on this issue have revealed ambivalent results, consistently reporting on a positive impact of RTX on LR-risk [15], but conflicting evidence regarding influence on DM or OS [15–18].

Undeniably, it is of clinical importance to provide more evidence on the effects of both NRTX and ARTX on oncological outcome beyond local control. Apart from retrospective studies, propensity score methods may thus be used to compensate for treatment selection bias [19]. Furthermore, there is an ongoing debate whether RTX should be administered pre- or postoperatively in patients with eSTS [20]. Whilst the impact of both NRTX and ARTX on LR and OS is considered equivalent [21–23], differing toxicity profiles may be decisive for one or the other treatment option [1,20,21].

In light of this, we first aimed to analyse whether a treatment modality directly affecting LR-risk – as NRTX and ARTX – could potentially have an indirect protective effect on DM-risk and OS, using a retrospective, multi-centre cohort of eSTS patients. Second, we sought to investigate whether NRTX or ARTX is associated with a lower LR-risk.

Materials and methods

In the current retrospective study, all patients with localised, high-grade eSTS, treated with limb sparing surgery and curative intent between 1996 and 2016 at 10 tertiary tumour centres, were potentially eligible. Information on demographic variables (sex, age), tumour-specific parameters (grading, tumour size, histological subtype, superficial vs. deep location, upper vs. lower limb STS), resection margins (R0 vs. R1 vs. R2) and outcome variables (time to LR, DM, or death/last follow-up) derived from prospectively maintained databases at the respective centres. Due to the large patient number obtained from different centres, standardised re-evaluation of either histology, grading, or margins was impossible. Yet, all cases included had been treated at experienced sarcoma centres adhering to the ESMO guidelines for diagnosis, treatment, and follow-up of STS patients, as previously described [1,24].

Margins were subdivided into negative margins (R0; microscopically negative), marginal margins (R1; macroscopically negative but microscopically positive), and intralesional margins (R2; macroscopically positive). Histological subtypes were categorised into eight subgroups (leiomyosarcoma [LMS], dedifferentiated/pleomorphic liposarcoma [D/P-LPS], myxoid liposarcoma [M−LPS], myxofibrosarcoma [MFS], malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified [MFH/UPS & NOS], malignant peripheral nerve sheath tumour [MPNST], synovial sarcoma [SS], and “others”). Owing to several histological subtypes grouped together, the “others” category comprised the third largest histological subgroup, with spindle cell sarcomas accounting for the majority of cases. Grading was defined according to the FNCLCC system (*Fédération Nationale des Centres de Lutte Contre le Cancer*) as G2 or G3 eSTS (G1 tumours were not included in the current dataset).

From initially 2184 patients potentially eligible, patients with (neo) adjuvant chemotherapy (n = 274), as well as patients developing metastases within three months from definite surgery (n = 67), were excluded. The reason behind this was based on the fact that patients receiving chemotherapy are usually high-risk individuals in terms of sarcoma-specific outcome, and that those diagnosed with metastases within three months most likely already presented with (subclinical) systemic spread at initial presentation. Thus, exclusion of these patients resulted in a more uniform patient cohort. Furthermore, patients with missing information on histology, tumour depth, tumour size, localisation and type of surgical procedure (limb sparing surgery vs. amputation) were excluded (n = 643). This resulted in 1200 patients finally eligible.

The conduction of the present study was approved by the institutional review board of the primary study centre (IRB-number: [blinded for review]) and performed according to the Declaration of Helsinki.

Statistical analysis

All statistical analyses were performed with Stata Version 16.0 (*StataCorp, College Station, Texas, USA*). For statistical analysis, comparisons were made within three patient subsets, each comparing two treatment regimens (no RTX vs. NRTX; no RTX vs. ARTX; NRTX vs. ARTX).

In order to allow independent assessment of the treatment effect, inverse-probability of treatment-weight (IPTW)-adjusted statistical models were implemented. Strengths of the IPTW involve the possibility to assess balance of baseline characteristics between treatment groups, fewer statistical assumptions within the model, and inclusion of all patients in the analysis (in comparison to conventional propensity score [PS] matching) [25]. One major limitation of IPTW is its lack of robustness against outliers, as the required formula may generate patients with extreme scores [25].

Means and medians were reported with corresponding standard deviations (SDs) and interquartile ranges (IQRs), respectively. Overall differences between groups were compared with analysis of variance (ANOVA) and chi-squared tests for continuous and categorical variables, respectively. T-tests and Mann-Whitney-U tests were performed to assess differences between two treatment groups in normally and non-normally distributed continuous variables, respectively. Chi-squared tests were applied to analyse differences in binary and/or categorical variables between two treatment groups.

To estimate differences between each of the three treatment pairs at baseline, standardised mean differences (SMDs) were calculated [26]. SMDs are most commonly used after PS matching to assess balancing of parameter distribution [27]. Herein, SMDs $\geq$ 0.2 were regarded as showing marked difference between treatment groups [28]. For each treatment pair, unweighted SMDs exceeded 0.2, wherefore IPTW-adjusted statistical models were subsequently applied.

The PS was calculated separately for the no RTX vs. NRTX, NRTX vs. ARTX, and no RTX vs. ARTX treatment pairs using a logistic regression model with a subset of variables (sex, patient age, histological subtype, tumour location, grading, depth, tumour size, margin status). Variables were included in the logistic regression model irrespective of their association with clinical outcome [29,30]. Based on the PS, the IPTW was calculated (formula: RTX = 1/PS; no RTX = 1/[1-PS]), defined as the inverse probability of patients to receive the treatment they actually received [30].

After weighting the treatment pairs for their respective IPTW, univariate Fine&Gray models for LR and DM (with death as the competing event), and Cox-regression models for OS, were generated to assess the independent influence of the treatment modalities on end-points of interest. Time-to-event analyses were calculated from date of surgery to

Table 1
Baseline characteristics of the entire study population (n = 1200), together with p-values showing differences between no RTX and NRTX (n = 410), no RTX and ARTX (n = 1006), as well as NRTX and ARTX (n = 984). Continuous variables presented as medians with IQRs, categorical variables as absolute numbers with valid percentages. P-values in bold indicate significant results.

	Overall (n = 1200)	**No RTX (n = 216)**	**Neoadjuvant RTX (n = 194)**	**Adjuvant RTX (n = 790)**	**p-value** (over all three groups)*	**p-value** (no vs. NRTX; n = 410)**	**p-value** (no vs. ARTX; n = 1006)**	**p-value** (NRTX vs. ARTX; n = 984)**
Age at surgery (in years)					0.004	**0.002**	**0.016**	0.079
Mean, SD	60.7 ± 16.8	63.6 ± 17.9	58.2 ± 16.7	60.5 ± 16.4				
Range (min–max)	18 – 100	19 – 96	19 – 100	18—94				
Sex					0.330	0.510	0.144	0.559
Male	667 (55.6 %)	111 (51.4 %)	106 (54.6 %)	450 (57.0 %)				
Female	533 (44.4 %)	105 (48.6 %)	88 (45.4 %)	340 (43.0 %)				
Grading					**< 0.001**	**< 0.001**	0.664	**< 0.001**
G2	236 (19.7 %)	34 (15.7 %)	87 (44.8 %)	115 (14.6 %)				
G3	964 (80.3 %)	182 (84.3 %)	107 (55.2 %)	675 (85.4 %)				
Histology					**< 0.001**	**< 0.001**	**0.023**	**< 0.001**
LMS	68 (5.7 %)	20 (9.3 %)	13 (6.7 %)	35 (4.4 %)				
D/LPS	68 (5.7 %)	8 (3.7 %)	30 (15.5 %)	30 (3.8 %)				
MFS	322 (26.8 %)	55 (25.5 %)	36 (18.6 %)	231 (29.2 %)				
MFH/UPS & NOS	266 (22.2 %)	58 (26.8 %)	52 (26.8 %)	156 (19.8 %)				
MPNST	96 (8.0 %)	20 (9.3 %)	4 (2.0 %)	72 (9.1 %)				
SS	122 (10.2 %)	18 (8.3 %)	13 (6.7 %)	91 (11.5 %)				
Other	185 (15.4 %)	29 (13.4 %)	10 (5.1 %)	146 (18.5 %)				
M–LPS	73 (6.0 %)	8 (3.7 %)	36 (18.6 %)	29 (3.7 %)				
Tumour size (in cm)					**< 0.001**	**< 0.001**	**0.019**	**0.001**
Median, IQR	7.5 [5 –12]	6 [4 –10]	9 [5.6 – 14]	7.1 [5 – 11.5]				
Range (min–max)	0.2 – 35	0.4 – 26	1.1 – 25	0.2—35				
Localisation					**0.031**	**0.050**	0.725	**0.008**
Upper Limb	272 (22.7 %)	50 (23.2 %)	30 (15.5 %)	192 (24.3 %)				
Lower Limb	928 (77.3 %)	166 (76.8 %)	164 (84.5 %)	598 (75.7 %)				
Depth					**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Superficial	331 (27.6 %)	90 (41.7 %)	26 (13.4 %)	215 (27.2 %)				
Deep	869 (72.4 %)	126 (58.3 %)	168 (86.6 %)	575 (72.8 %)				
Margins					**< 0.001**	**< 0.001**	**< 0.001**	0.060
R0	565 (47.1 %)	142 (65.7 %)	93 (47.9 %)	330 (41.8 %)				
R1	439 (36.6 %)	43 (19.9 %)	79 (40.7 %)	317 (40.1 %)				
R2	196 (16.3 %)	31 (14.4 %)	22 (11.4 %)	143 (18.1 %)				
5-Year Outcome (%; IQR)					N/A	N/A	N/A	N/A
LR-Risk	15.5 % (13.3 % – 17.8 %)	15.4 % (13.3 % – 17.6 %)	15.6 % (13.4 % – 17.8 %)	15.1 % (13.0 % – 17.3 %)				
DM-Risk	34.6 % (31.7 % – 37.5 %)	34.6 % (31.7 % – 37.5 %)	36.0 % (33.1 % – 39.0 %)	34.4 % (31.6 % – 37.3 %)				
Overall Survival	64.4 % (61.3 % – 67.3 %)	62.6 % (55.0 % – 69.2 %)	69.3 % (60.8 % – 76.3 %)	63.9 % (60.2 % – 67.4 %)				

*p-values based on analysis of variance (ANOVA) and chi-squared tests; ** p-values based on t-tests/Mann-Whitney-U-tests for normally/non-normally distributed continuous variables and chi-squared tests for categorical variables.
ARTX – adjuvant radiotherapy; D/P-LPS - dedifferentiated/pleomorphic liposarcoma; DM – distant metastasis; IQR – interquartile range; LMS – leiomyosarcoma; LR – local recurrence; M–LPS - myxoid liposarcoma; MFH/UPS & NOS - malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma and not otherwise specified; MFS – myxofibrosarcoma; MPNST - malignant peripheral nerve sheath tumour; NRTX - neoadjuvant radiotherapy; RTX – radiotherapy; SS - synovial sarcoma.

date of LR, DM, death or last clinical follow-up. Subhazard ratios (SHR) for competing-risk regression models, and hazard ratios (HR) for Cox-regression models with corresponding 95 % confidence intervals (CIs) were provided. Bonferroni-adjusted p-values were calculated for outcome parameters LR, DM, and OS to ensure a controlled probability of generating a type I error in light of multiple testing. Results on naïve univariate analyses for the three treatment pairs regarding end-points LR, DM and OS are outlined in Supplementary Table 1. Median LR- and DM-free survival was calculated with the competing risk cumulative incidence estimator according to *Marubini and Valsecchi* [31]. Median follow-up was estimated applying the inverse Kaplan-Meier estimator according to *Schemper and Smith* [32], as previously described [33]. A p-value of < 0.05 was considered statistically significant.

Results

Mean patient age was 60.7 years (SD: 16.8 years) and 533 patients were female (44.4 %). Two-hundred-sixteen had received no RTX (18.0 %), 194 patients NRTX (16.2 %), and 790 patients ARTX (65.8 %). The resulting treatment pairs comprised 410 (no RTX vs. NRTX), 1006 (no RTX vs. ARTX), and 984 patients (NRTX vs. ARTX). Further baseline characteristics of patients included are depicted in Table 1. The

contribution of cases per each of the 10 tertiary sarcoma centres to RTX groups was significantly different, owing to the varying local treatment preferences and policies (***Supplementary*** Fig. 1; $p < 0.001$).

Median follow-up of the entire population from date of definite surgery was 70.5 months (IQR: 41.8 – 106.4 months). During that time, 189 LRs (15.8 %), 395 DMs (32.9 %), and 443 deaths (36.9 %) were observed. This amounted to a cumulative 5-year LR- and DM-risk of 15.5 % (IQR: 13.3 % − 17.8 %) and 34.6 % (IQR: 31.7 % − 37.5 %), as well as cumulative 5-year OS probability of 64.4 % (IQR: 61.3 % − 67.3 %). Cumulative 5-year event rates for patients with NRTX, ARTX and no RTX are provided in Table 1. Fig. 1 depicts cumulative OS for the three treatment groups.

Many statistically significant differences in baseline characteristics were found between the no RTX and NRTX cohort (Table 1). In comparison to patients receiving NRTX, those without RTX were significantly older ($p = 0.002$), had smaller ($p < 0.001$) and more often G3 tumours ($p < 0.001$), presented more often with MFS, MPNST or "other" histology but less often with D/P-LPS and M−LPS ($p < 0.001$), rather had upper limb ($p = 0.050$) and superficially located STS ($p < 0.001$), and had more often wide surgical margins ($p < 0.001$).

Most baseline variables also differed significantly for the NRTX vs. ARTX cohort (Table 1). Patients with NRTX had more often G2 STS ($p < 0.001$), MFH/UPS & NOS, D/L-LPS or M−LPS as underlying histological subtype ($p < 0.001$), presented with significantly larger ($p < 0.001$), lower limb ($p = 0.008$), and deep STS ($p < 0.001$). No significant difference regarding resection margin status between NRTX and ARTX could be found (Table 1).

Differences between the no RTX and ARTX group were likewise present (Table 1); patients administered ARTX were significantly younger than patients without RTX ($p = 0.016$), had more often synovial sarcoma, MFS or "other" but less frequently MFH/UPS & NOS as histological subtype ($p = 0.023$), presented with larger ($p = 0.019$), and deeply located STS ($p < 0.001$), and had more often R1 or R2 margins ($p < 0.001$).

Converted into SMDs, the following SMDs in the no RTX vs. ARTX treatment pair exceeded the threshold of 0.2 (depth, SMD = 0.31; R0 margin, SMD = 0.49; R1 margin, SMD = 0.45; ***Supplementary*** Fig. 2). In the no RTX vs. NRTX cohort, this was the case for age (SMD = 0.31), grading (SMD = 0.67), histological subtypes D/P-LPS (SMD = 0.41), MPNST (SMD = 0.31), "others" (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) (***Supplementary*** Fig. 2). In the NRTX vs. ARTX cohort the following SMDs exceeded 0.2: grading (SMD = 0.70), histological subtypes D/P-LPS (SMD = 0.40), MFS (SMD = 0.25), MPNST (SMD = 0.31), "others" (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; ***Supplementary*** Fig. 2). After IPTW-weighting of the no RTX vs. NRTX as well as of the NRTX vs. ARTX treatment pairs, the SMDs could be reduced considerably (***Supplementary*** Fig. 2).

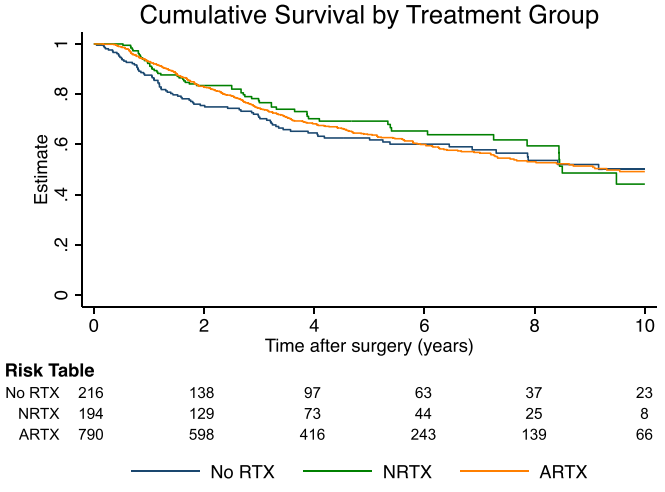

Fig. 1. Kaplan-Meier curve for overall survival, separated by the three treatment groups (no RTX, NRTX, ARTX). Risk table shows patients of each treatment group at risk at specific time points during follow-up. ARTX – adjuvant radiotherapy; NRTX – neoadjuvant radiotherapy; RTX – radiotherapy.

Using IPTW-weighting, a significant association between NRTX and lower LR-risk in comparison to no RTX was revealed (SHR: 0.236; $p = 0.003$; Table 2; Fig. 2). No significant impact on DM-risk (SHR: 1.329; $p = 0.576$), or OS was found (HR: 0.838; $p = 1.000$; Table 2; Fig. 2).

In the IPTW-weighted analysis, ARTX was associated with lower LR-risk as compared with no RTX (SHR: 0.479; $p = 0.003$; Table 2; Fig. 3). No significant association regarding DM-risk (SHR: 1.294; $p = 0.363$) or OS was found (HR: 0.829; $p = 0.534$; Table 2; Fig. 3).

Following weighting of the data for the IPTW, there was a significantly higher LR-risk for ARTX in comparison to NRTX (SHR: 3.433; $p = 0.003$; Table 2; Fig. 4). No association for ARTX in comparison to NRTX regarding DM-risk (SHR: 0.985; $p = 1.000$) or OS (HR: 1.312; $p = 0.639$) was found (Table 2; Fig. 4).

Discussion

In this retrospective multicentre study involving 1200 eSTS patients, we analysed the impact of RTX on oncological outcome in eSTS patients. According to the IPTW-adjusted time-to-event models for no RTX vs. NRTX, and for no RTX vs. ARTX, administration of either pre- or post-operative RTX was associated with a significantly reduced risk for LR, whilst no statistically significant impact on DM or OS was found. Furthermore, the positive effect on local control was higher for NRTX in comparison to ARTX.

As it is to be expected in a retrospective multicentre cohort without random treatment assignment, we observed significant differences at baseline between patients without RTX and those administered NRTX, those with NRTX or ARTX, as well as between patients without RTX and those with ARTX. Specifically, patients administered NRTX or ARTX in comparison to no RTX were significantly younger, presented with deep-seated eSTS, and differed with regards to histological subtypes. Furthermore, patients undergoing NRTX or ARTX significantly more often presented with large STS as compared with patients not being administered RTX. Similar results have been obtained by others, with

Table 2
IPTW-weighted univariate Fine&Gray models for local recurrence and distant metastasis, as well as IPTW-weighted univariate Cox-regression model for overall survival, calculated each of the three treatment pairs. SHRs and HRs with corresponding 95% confidence intervals are based on univariate, IPTW weighted models.

IPTW-weighted Fine&Gray Model - Local Recurrence			
	SHR	**95 %CI (Lower - Upper)**	**p-value***
No RTX (ref.) vs. *NRTX*	0.236	0.127 – 0.436	**0.003**
No RTX (ref.) vs. *ARTX*	0.479	0.335 – 0.684	**0.003**
NRTX (ref.) vs. *ARTX*	3.433	1.820 – 6.475	**0.003**
IPTW-weighted Fine&Gray Model – Distant Metastasis			
	SHR	**95 %CI (Lower - Upper)**	**p-value***
No RTX (ref.) vs. *NRTX*	1.329	0.867 – 2.039	0.576
No RTX (ref.) vs. *ARTX*	1.294	0.935 – 1.791	0.363
NRTX (ref.) vs. *ARTX*	0.985	0.690 – 1.408	1.000
IPTW-weighted Cox-Regression Model – Overall Survival			
	HR	**95 %CI (Lower - Upper)**	**p-value***
No RTX (ref.) vs. *NRTX*	0.838	0.559 – 1.257	1.000
No RTX (ref.) vs. *ARTX*	0.829	0.631 – 1.089	0.534
NRTX (ref.) vs. *ARTX*	1.312	0.855 – 2.015	0.639

ARTX – adjuvant radiotherapy; CI – confidence interval; HR – hazard ratio; IPTW – inverse probability of treatment weight; NRTX – neoadjuvant radiotherapy; RTX – radiotherapy; SHR – subhazard ratio.
*Bonferroni-adjusted p-values.

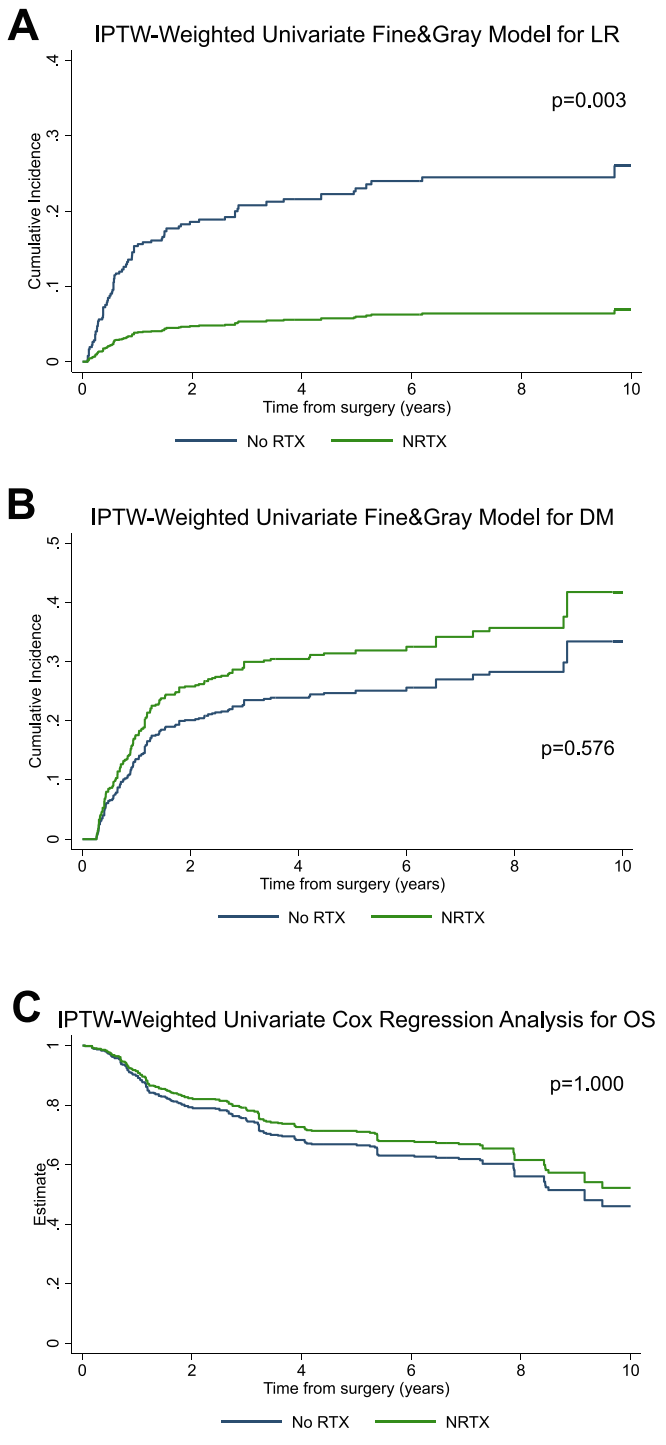

Fig. 2. Comparison of patients with no RTX and NRTX regarding LR-risk (A), DM-risk (B), and OS (C) after IPTW-weighting. No risk tables are displayed along the graphs as number of patients at respective time points are non-integers in IPTW-weighted samples. DM – distant metastasis; IPTW – inverse probability of treatment weight; LR – local recurrence; NRTX – neoadjuvant radiotherapy; OS – overall survival; RTX – radiotherapy.

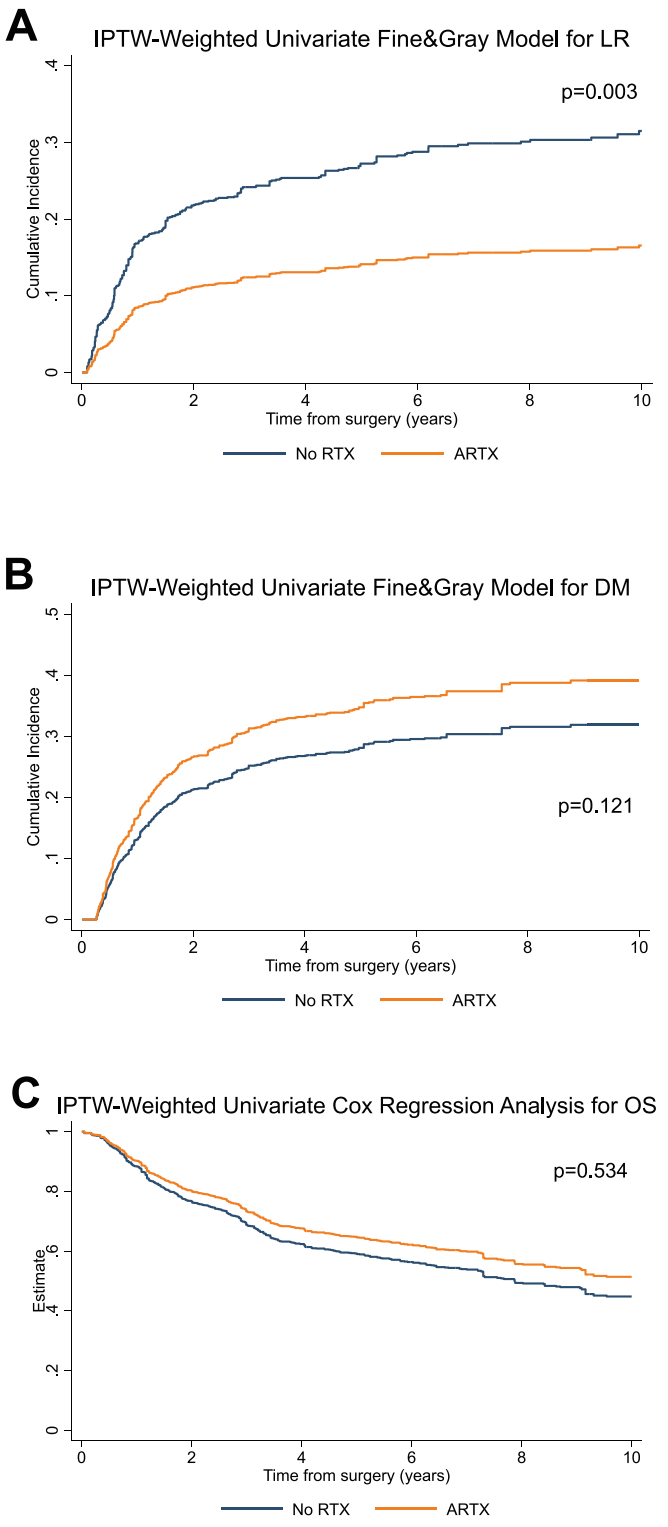

Fig. 3. Comparison of patients with no RTX and ARTX with regards to LR-risk (A), DM-risk (B), and OS (C) after IPTW-weighting. No risk tables are displayed along the graphs as number of patients at respective time points are non-integers in IPTW-weighted samples. ARTX – adjuvant radiotherapy; DM – distant metastasis; IPTW – inverse probability of treatment weight; LR – local recurrence; OS – overall survival; RTX – radiotherapy.

Gingrich et al. [34] discovering that patients receiving NRTX had more often large, high-grade eSTS in comparison to patients undergoing no RTX, while *Ramey et al.* [21] reported on a higher rate of deep-seated and large eSTS in patients receiving NRTX or ARTX in comparison to patients undergoing surgery only. Consequently, one may argue that the differing oncological profile of patients receiving RTX rather than the treatment itself contributes to differences in prognosis, owing to the differences at baseline between patient groups.

Some previous studies have discovered not only a positive effect of NRTX and ARTX on local control, but also improved OS [13,14,21,22,34,35]. Herein, IPTW-weighting was used to account for

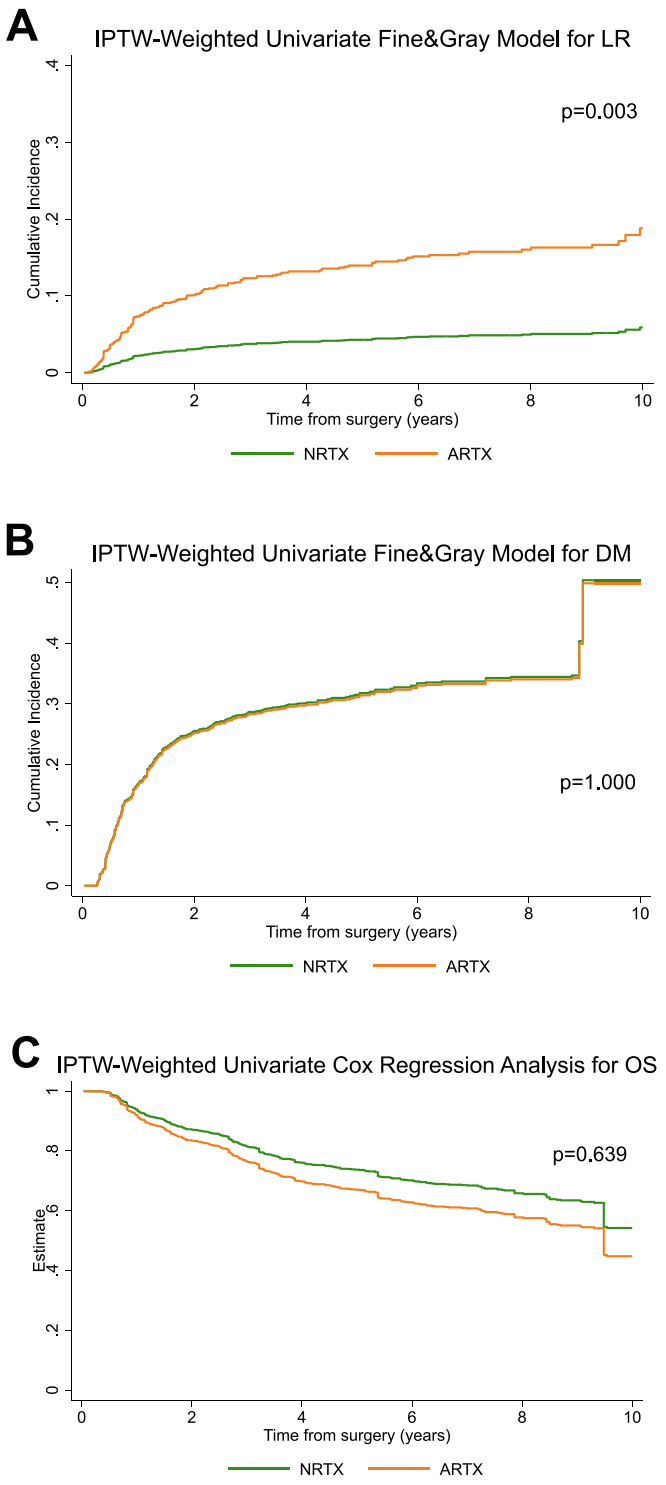

Fig. 4. Comparison of LR-risk (A), DM-risk (B), and OS (C) between patients with NTX and ARTX after IPTW-weighting. No risk tables are displayed along the graphs as number of patients at respective time points are non-integers in IPTW-weighted samples. ARTX – adjuvant radiotherapy; DM – distant metastasis; IPTW – inverse probability of treatment weight; LR – local recurrence; NRTX – neoadjuvant radiotherapy; OS – overall survival.

imbalances between treatment groups. Adjusted analyses revealed a consistently positive association between RTX (both pre- and post-operative) and reduced LR-risk, being in line with previous observations [21,36]. On the other hand, no significant impact on development of DM or OS could be demonstrated. This contradicts observations made by *Ramey et al.* [21] in a retrospective, one-to-one PS-matched study involving STS patients from two North American databases (SEER and NCBD) discovering a significant survival benefit in patients who had received ARTX [21]. Also, results obtained by *Kneisl et al.* [13] and *Zhao et al.* [14], reporting that any RTX and ARTX only, respectively, are associated with reduced LR-risk and improved OS, are in contrast to our observations. These conflicting findings highlight the limitations of retrospective analyses, being prone to several sources of bias [37,38]. In order to overcome especially the treatment-selection bias regarding RTX administration, IPTW-analyses were carried out. This approach has not been utilised in previous studies on this topic [14,22,34–36], except for the study by *Ramey et al.* [21]. However, one-to-one PS matching naturally results in patient drop-out (e.g. 44.6 % in the study by *Ramey et al.* [21]), whereas the herein used IPTW allows for inclusion of all patients. For PS-calculation, we carefully included observed confounders, and our balance diagnostics after IPTW weighting showed that differences in baseline covariates between each treatment pair (i.e. no RTX vs. NRTX, no RTX vs. ARTX, NRTX vs. ARTX), were reduced to negligible levels.

As previously outlined, the debate whether to administer RTX pre- or postoperatively is usually driven by the fact that NRTX is associated with fewer long-term toxicities, but higher wound complication rate (particularly in lower limb STS) [6,39], whilst ARTX has a higher risk for long-term secondary toxicities as fibrosis, joint stiffness, oedema, and eventually development of radiation-induced malignancies [6,7,20]. Furthermore, a lower total RTX-dose (50 Gy vs. 66 Gy) and a smaller RTX-field can be applied preoperatively [6].

Although in the present study both NRTX and ARTX were associated with decreased LR-risk in comparison to no RTX, NRTX reduced LR-risk to a greater amount than ARTX. This contradicts results of a recent *meta*-analysis, observing comparable local control rates for NRTX and ARTX [15], but is in line with another *meta*-analysis reporting on improved local control rate for NRTX in comparison to ARTX [16]. Even though based on a retrospective analysis, the present results generally strengthen the notion to rather administer RTX prior to surgery, when possible [3]. Nevertheless, timing of radiation therapy should be chosen based on radiosensitivity, ability to primarily achieve clear margins, and the impact wound complications might have on the further patient management [40].

Several limitations should be considered when interpreting the results of the current study. First, some patients had not received RTX, albeit it would have been recommended by international guidelines based on their clinical profile [1,3]. As no information on reasons to omit RTX was available, it can only be hypothesised that factors as patient refusal, precarious surgical circumstances and comorbidities have had an influence on treatment decision. In this respect, lack of more detailed patient-related information as ECOG performance status, prevailing comorbidities and surgery-associated complications impair further exploration on this issue. Second, the missingness of complete clinical data in the original dataset owing to its multicentre and retrospective design, leading to a drop-out rate of 29.4 %, has to be regarded as a limiting factor. Third, one has to consider the varying contribution of participating centres to the respective treatment cohorts when interpreting the results. Albeit the structure of data does not allow to elaborate the exact underlying reasons, it can be hypothesised that structural peculiarities and variances in local treatment policies played a role. Nevertheless, this does not necessarily impact the results obtained, given that all participating centres constitute experienced sarcoma-treating institutions, and that the research question was to analyse the influence of RTX on outcome parameters. In order to account for treatment-related bias, elaborate statistical methods (PS and IPTW) were applied to allow accurate evaluation of the stated hypothesis. In order to enable more independent evaluation of the effect of NRTX and ARTX in comparison to no RTX, as well as the effect of NRTX in comparison to ARTX, the authors decided to construct three separate statistical models. As the validity of IPTW modelling depends on correct

specification of the PS, we included both variables differing between treatment groups and those having a known prognostic impact in order not to miss any unmeasured confounders [29,41].

Further, detailed information on dose and timing of RTX (beyond pre- or postoperative administration) precludes from in-depth analysis of these parameters on patient outcomes. Related to this, we could not assess the potential impact of RTX on development of postoperative complications, as this information was not available in the dataset used for this study.

In conclusion, the results of this retrospective, multicentre study strengthen the notion to administer perioperative RTX in eSTS patients in order to minimise LR-risk. On the other hand, there does not seem to be an indirect effect of pre- or postoperative RTX on DM-risk or OS. Whenever possible, NRTX may be favoured over ARTX, as our findings imply better local control rates.

Declaration of interests

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Maria A. Smolle: Methodology, Formal analysis, Writing – original draft, Visualization, Project administration. **Dimosthenis Andreou:** Methodology, Investigation, Writing – original draft, Supervision. **Judith Wölfel:** Investigation, Data curation, Writing – review & editing. **Ibtissam Acem:** Investigation, Data curation, Writing – review & editing. **Michiel Aj Van De Sande:** Conceptualization, Validation, Writing – original draft, Supervision, Project administration. **Lee Jeys:** Validation, Investigation, Writing – review & editing. **Han Bonenkamp:** Validation, Investigation, Writing – review & editing. **Rob Pollock:** Validation, Data curation, Writing – review & editing. **Per-Ulf Tunn:** Validation, Data curation, Writing – review & editing. **Rick Haas:** Conceptualization, Data curation, Writing – review & editing, Supervision. **Florian Posch:** Methodology, Formal analysis, Writing – original draft, Visualization. **Robert J. Van Ginkel:** Validation, Data curation, Writing – review & editing. **Cornelis Verhoef:** Investigation, Data curation, Writing – review & editing. **Bernadette Liegl-Atzwanger:** Validation, Investigation, Writing – review & editing. **Dalia Moustafa-Hubmer:** Validation, Investigation, Writing – review & editing. **Philipp J. Jost:** Validation, Investigation, Writing – review & editing. **Andreas Leithner:** Conceptualization, Writing – review & editing, Supervision. **Joanna Szkandera:** Conceptualization, Investigation, Writing – original draft, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109944.

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