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Balancing the dose: A meta-analysis of preoperative radiotherapy strategies for soft tissue sarcomas

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ABSTRACT

Purpose: Soft tissue sarcomas (STS) are a rare and diverse group of tumors. Management of STS typically involves a multidisciplinary approach, including surgery, radiotherapy (RT), and chemotherapy, with surgery remaining the cornerstone of treatment. Radiotherapy, both preoperative and postoperative, has been shown to improve local control. Hypofractionation has shown promising results in other malignancies and may offer similar benefits in STS. This study systematically reviews the efficacy and safety of different preoperative RT fractionation schedules, focusing on major wound complications (MWC) and late toxicity.

Methods: A systematic review and meta-analysis were conducted following PRISMA guidelines. PubMed, Cochrane Library, and Embase were searched for studies on preoperative RT in STS. Included studies were categorized into conventional RT, moderate hypofractionation, and ultra-hypofractionation. Meta-analysis was performed on MWC and late toxicity (≥ grade 3) using a random-effects model. Statistical heterogeneity was assessed using I-squared and Tau statistics.

Results: Thirty studies with 2288 patients were included. The pooled overall rate of MWC was 18 % (95 % CI: 10–27 %) for conventional RT, and 29 % (95 % CI: 24–34 %) for moderate hypofractionation. The pooled overall rate of late toxicity was 5 % (95 % CI: 0–12 %) and 4 % (95 % CI: 2–6 %), respectively. Based on descriptive data, the MWC rates of the ultra-hypofractionated group did not exceed 41 %, with one study reporting a rate of 41 % and the remaining studies reporting rates no higher than 32 %. For toxicity, a wide range of toxicity rates (1–16 %) was reported.

Conclusion: Moderate hypofractionation appears to maintain oncological outcomes while balancing toxicity and wound complications. Reported MWC rates of ultra-hypofractionation regimens, based on descriptive data from heterogeneous individual studies remained below 41 %. However, these outcomes are not derived from pooled analysis. This approach should not yet be used in clinical practice, and randomized controlled trials are needed to establish its efficacy and safety in STS patients.

Introduction

Soft tissue sarcomas (STS) are a rare and heterogeneous group of tumors. Their treatment is influenced by factors such as tumor histology, grade, location, size, and the patient's overall performance status. The management of STS typically involves a multidisciplinary approach, including surgery, radiotherapy (RT), and chemotherapy, with surgery remaining the cornerstone of treatment. Radiotherapy, both preoperative and postoperative, has been shown to improve local control [1]. However, while radiotherapy improves local control, its addition is associated with an increased risk of toxicity.

Preoperative radiotherapy is associated with an increased risk of short-term complications, particularly wound complications after surgery. However, these short-term complications are generally transient

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and manageable with appropriate care. In contrast, postoperative radiotherapy carries a lower immediate risk of wound complications but is associated with an increased risk of long-term toxicities such as fibrosis, edema, and joint stiffness [1–3]. To balance these risks, the recommended treatment regimen is preoperative radiotherapy followed by surgery after a waiting period of 6–8 weeks. Current guidelines recommend a preoperative dose of 50 Gray (Gy), delivered in 25 fractions [4–8].

In recent years, there has been growing interest in hypofractionation, which involves delivering larger radiation doses in fewer fractions, thereby reducing the overall treatment duration. The primary aim of hypofractionated radiotherapy is to improve patient outcomes by maintaining or even enhancing treatment efficacy, while reducing treatment burden. Clinical studies in other malignancies, including breast, rectal, and prostate cancer, have already demonstrated hypofractionation, to reduce overall treatment time without compromising local control or long-term toxicity [9–11]. These findings suggest that hypofractionation could also be safe in terms of long-term toxicity in the treatment of STS.

The rationale for exploring hypofractionation in STS is based on the fact that tumors with a low α/β ratio, commonly seen in STS, may respond better to higher radiation doses per fraction [12]. Shortening the treatment duration has the potential to reduce the overall treatment burden on patients. Due to the rarity of STS, conducting large-scale non-inferiority, phase III randomized clinical trials (RCTs) remains challenging. Nevertheless, several phase 2 studies have demonstrated that hypofractionated treatment schedules can shorten treatment time without compromising local control or increasing wound complications [13,14].

This review aims to assess the current evidence for the use of hypofractionation in STS, by critically evaluating and comparing the clinical outcomes of different fractionation strategies, comparing conventional fractionation, moderate hypofractionation, and ultra-hypofractionation. The meta-analysis is specifically focused on late toxicity (grade 3 or higher) and wound complications as key outcomes.

Methods

This research was performed according to 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15]. The databases PubMed (NCBI), Cochrane Library (Wiley), Embase (Ovid) and Web of Science (Clarivate) were searched on January 1st, 2025. The search terms included various combinations of relevant keywords such as 'Radiotherapy', 'Soft tissue sarcomas', 'preoperative' and 'dose'. Only studies published in English were included. The full search strategy is outlined in the Supplementary (S1). The first and second reviewer screened articles together, excluded duplicates, studies on hyperthermia, postoperative RT, or trials with concurrent chemotherapy and immunotherapy. Studies with pediatric (<18 years) populations, studies including only myxoid liposarcoma, studies assessing metastatic disease and reviews were also excluded. For an overview of the in- and exclusion criteria see Table 1. In case of overlap of the study population, the paper with a larger study population or more extensive data of interest was chosen. Authors of studies included in the review who had published more than two papers were also searched to find additional studies not found through other sources. Studies were categorized into three groups based on the type of radiotherapy delivered: conventional radiotherapy, moderate hypofractionation, and ultra-hypofractionation. This classification was determined based on the number of fractions and dose per fraction, following the predefined criteria outlined in the study protocol.

The first reviewer (G.F.) examined all full texts thoroughly to maintain sufficient quality standards. The risk of bias for each study was assessed using the Risk of Bias In Non-randomized Studies of Interventions tool (ROBINS-I) developed by the Cochrane Bias Methods Group. For randomized studies, the Rob Tool was used [16,17]. After the initial evaluation by the first reviewer, the second reviewer (B.v.R.) critically reviewed the bias assessment, list of results and data. Disagreements were resolved in team discussions. Find Supplementary (S1–2) for the critical review of the risk of bias.

Table 1
In- and exclusion criteria of the systematic review.

Category	Inclusion criteria	Exclusion criteria
Study design	Any accept reviews Presented studies	Systematic reviews Narrative reviews Non-English
Population	Age ≥ 18 years Sex: any Race: any Disease: primary soft tissue sarcomas located at the extremities or trunk Histological grade: any except myxoid liposarcoma Stage: localized	Metastatic stage Non-human Myxoid liposarcoma studies only
Intervention	Conventional RT (1.8–2.2 Gy/fraction) Hypofractionated RT (>2.2 Gy/fraction) Surgical resection	Hyperthermia Postoperative RT (including boost)
Concurrent therapy		Concurrent chemotherapy Concurrent immunotherapy
Outcomes	Late toxicities including wound complications	
Date range	Until January 1st, 2025	

Meta-analysis was performed on major wound complications (MWC) and late toxicity as outcomes for each study included in the analysis. MWC were defined by the Canadian SR-2 trial [1]. The definition of MWC included surgery for wound repair, invasive procedures without anesthesia (e.g., seroma aspiration), hospital readmission for IV antibiotics, or ongoing deep packing within 120 days of surgery. If MWC were not defined by the Canadian SR-2 trial by the author and in the published paper, definition was changed to the Canadian SR-2 trial if possible. Late toxicity of interest was grade 3 or higher, scored by the CTCAE version 5.0 [18]. Toxicity of grade 3 or higher was classified as significant medical symptoms requiring medical intervention, hospitalization, or more severe consequences, including life-threatening conditions (grade 4) or fatal outcomes (grade 5). In case of missing data, additional information was requested from the authors. If no response or no longer available data, missing data was reported. When the outcomes MWC and toxicity could not be defined according to the Canadian SR2 trial definition or the CTCAE version 5.0, or when the data was not available, the study was not included in the meta-analysis.

Studies for conventional radiotherapy included in the meta-analysis were structured based on the Equivalent Dose in 2 Gy fractions (EQD2) of normal tissue taking an α/β ratio of 3 Gy [19]. After initial selection of data items by the first reviewer, the second reviewer checked for suitability and accuracy. Wherever multiple doses and fractions were used within the same study, the most used dose and fraction was applied as outcome for the meta-analysis.

A random effects model was employed to pool study-specific proportion of wound complication and toxicity to estimate overall proportions and their associated confidence intervals. Inverse variance method which gives more weight to larger study was used to pool outcomes for different studies. The overall effect corresponding to a fixed and random effects model are reported together in the same forest plots along with their confidence intervals. The sizes of the square boxes on the forest plot are proportional to the total number of patients in the selected trials. An overall test on heterogeneity between studies was performed for each separate meta-analysis (value I-squared in figures). To estimate the between-study variance which is represented as 'Tau' in the forest plots, DerSimonian-Laird's method has been employed [20]. The analysis was performed in R software environment with the library meta [21].

Results

Characteristics of included studies

The PRISMA flow chart (Fig. 1) illustrates the complete progress of the search and selection. In total, we included 30 studies with a total of 2288 patients. The majority of studies (n = 26) were included through the search strategy and database screening. Additionally, three studies were identified through snowballing, and one paper has not been published yet [22]. Of those studies, thirteen conventional radiotherapy studies were included, four studies were included with a moderate hypofractionated schedule and thirteen studies with an ultra-hypofractionated schedule [1,13,22–49].

Data extraction included essential information from all eligible studies and resulted in extensive overview tables (Supplementary S4–5, Tables 2 and 3). Tables includes information such as author, publication year, type of trial, number of patients, dose per fraction, age of the patients, median follow-up time, oncological outcomes, wound complications and late toxicity grade 3 or higher. After conducting the risk of bias assessment, one article was excluded due to a critical risk of bias. This study was not included in the meta-analysis (Supplementary S3). Meta-analysis on MWC and late toxicity was not performed for the ultra-hypofractionated group, since this group included a wide variety of radiotherapy regimens and follow-up time.

In Tables S4 and S5, different rates of survival outcomes are reported. Conventional radiotherapy showed local control rates from at least 93 %. Recurrence rates reported in the moderate hypofractionated studies showed a cumulative incidence of local recurrence of 7.6 % at 2 years minimum. In ultra-hypofractionation, the 5 × 5 Gy regimen demonstrated lower local control, with a 5-year LRFS rate of 81 %. In contrast, the 5 × 7 Gy and 5 × 8 Gy regimens achieved a 0 % local recurrence rate at 2 years.

In total, 12 studies were included in the meta-analysis of MWC for

Table 2
Overview of toxicity outcomes for conventional radiotherapy, classified by CTCAE v5.0 and Canadian SR-2 trial.

Author	EQD2 (Gy)	Schedule	Median follow-up (range)	Toxicity ≥ grade 3 (%)	Major wound complication (%)
Conventional					
O' Sullivan et al.	50.0	25 × 2	3.3 yr (0.27–5.6)	*Not available*	35
Canter et al.	50.0	25 × 2	19 mo (4–113)	*Not available*	28
Shah et al.	50.0	25 × 2	40 mo	*Not available*	23
Wang et al.	48.4	28 × 1.8	6.0 yr	14.7 %	25
Studer et al.	50.0	25 × 2	33 mo (4–106)	*Not available*	7
Abdallah et al.	50.0	25 × 2	7.3 mo (6.0–9.0)	*Not available*	10
Bonvalot et al.	50.0	25 × 2	> 24 mo	*Not available*	9
Green et al.	50.0	25 × 2	27 mo (19 to 59)	*Not available*	11
Huang et al.	50.0	25 × 2	14.3 mo (11.9–24.7)	0 %	16
Hui et al.	48.4	28 × 1.8	4.1 yr (0.6–6.9)	3 %	*Not available*
Seddon et al.	50.0	25 × 2	35.2 mo (32.9–36.6)	*Not available*	*Not available*
Shelby et al.	50.0	25 × 2	Unknown	*Not available*	*Not available*
J. González-Viguera et al.	50.0	25 × 2	24 mo (0–156)	0 %	*Not available*

Abbrevations: EQD2, equivalent dose in 2 Gy per fraction with an α/β ratio of 3 Gy; Gy, Gray; yr, years; mo, months.

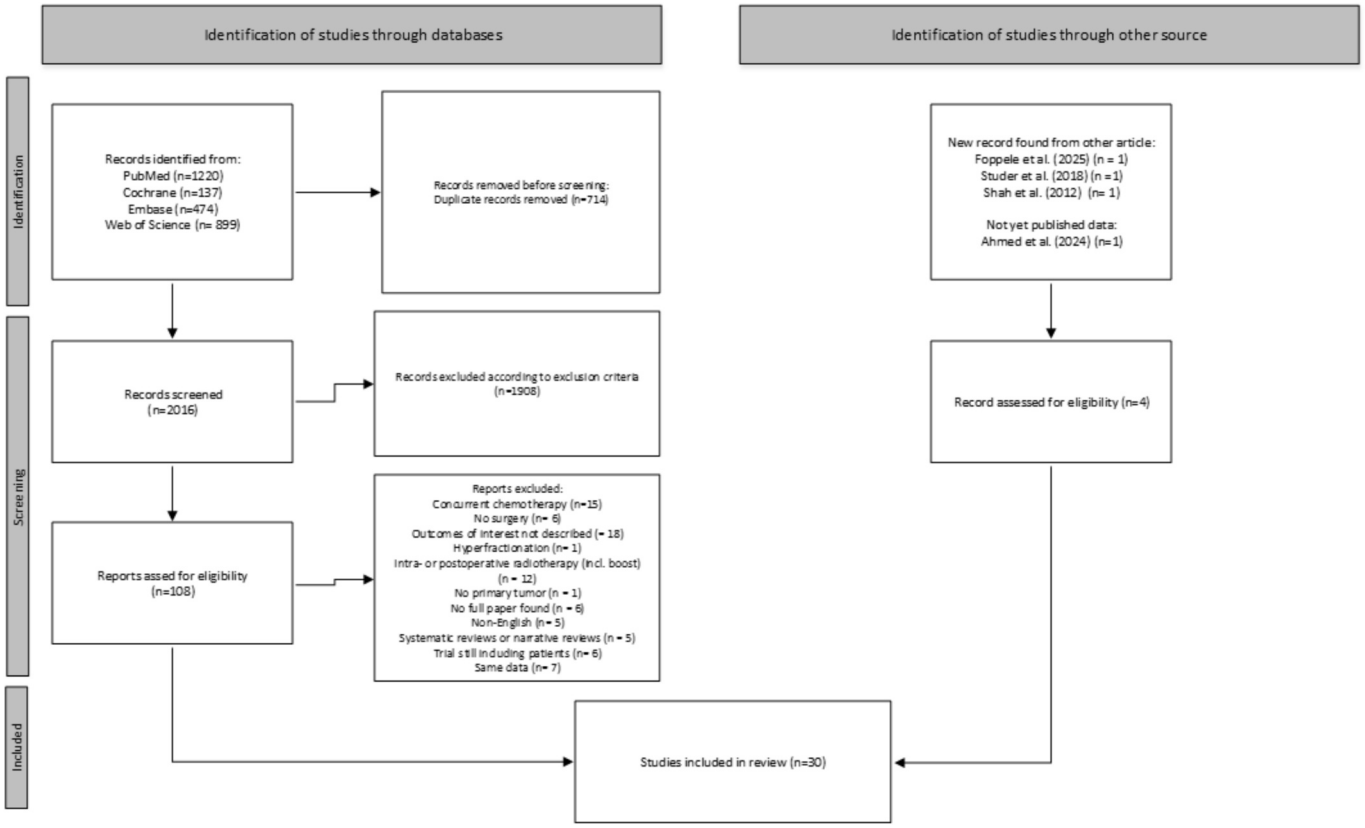

Fig. 1. PRISMA Flowchart depicting the selection process of articles included in the meta-analysis.

Table 3
Overview of outcomes for moderate- and ultra-hypofractionated radiotherapy, classified by CTCAE v5.0 and Canadian SR-2 trial.

Author	EQD2 (Gy)	Schedule	Median follow-up (range)	Toxicity ≥ grade 3 (%)	Major wound complication (%)
Moderate					
Bishop et al.	50.0	15 × 2.85	43 mo (37–52)	4 %	31
Ahmed et al.	50.0	15 × 2.85	17 mo (3.1–37.5)	*Not available*	23.1
Montero et al.	68.3	15 × 3.5	14 mo (1–40)	5.5 %	39
Foppele et al.	54.0	14–15 × 3	29 mo (2–50)	3 %	33
Ultra-hypofractionated					
Kilic et al.	36.4	8 × 3.5	37 mo (11–66)	*Not available*	*Not available*
Kosela et al. (2021)	40.0	5 × 5	57 mo (95 % CI 55.1–61.0)	1.3 %	7
Kosela et al. (2014)	40.0	5 × 5	35 mo (6–94)	2.9 %	*Not available*
Heesen et al.	40.0	5 × 5	2.2 yr	*Not available*	13
Potkrajcic et al.	40.0	5 × 5	5.1 ± 1.6 mo	*Not available*	29.4
Mayo et al.	54.0	5 × 6	24.5 mo (17.0–35.7)	4.5 %	41
Parasai et al.	54.0	5 × 6	10.7 mo (1.7–33.2)	0 %	19
Kalbasi et al.	54.0	5 × 6	29 mo	0 %	32
Bedi et al.	70.0	5 × 7	36.4 mo (3–56)	13 %	25
Novikov et al.	70.0	5 × 7	Average 21.5 mo (13–30)	14 %	14
Kubicek et al. (2021)	88.0	5 × 8	1719 d (983–2327)	6.7 %	20
Kubicek et al. (2018)	88.0	5 × 8	279 d (54–506)	0 %	29
Leite et al.	88.0	5 × 8	20.7 mo (6.9–55.7)	16 %	28

Abbrevations: EQD2, equivalent dose in 2 Gy per fraction with an α/β ratio of 3 Gy; Gy, Gray; yr, years; mo, months; d, days.

conventional radiotherapy and moderate hypofractionated radiotherapy. Six studies were excluded due to missing data or other definitions of wound complications, one study was excluded due to a critical risk of bias.

In the meta-analysis for conventional radiotherapy, eight studies were included with a total of 413 patients (Fig. 2). The pooled overall major wound complication rate estimated with a random effect model was equal to 18 % [95 % CI 10–27]. Heterogeneity within studies estimated by the I squared was 79.5 % and the between study variance (Tau) equal to 0.0099. Cochran's Q test for heterogeneity provided a p-value < 0.0001.

In the analysis of the moderate hypofractionated studies, 312 patients were included across four studies (Fig. 3). The pooled overall major wound complication rate estimated with a random effect model was 29 % [95 % CI 23–34]. I squared was 18.0 %, Tau equal to 0.0006 and a p-value of 0.3009 for the Cochran's Q test.

The MWC rates of the ultra-hypofractionated group are descriptively reported in Table 3. Regardless of the specific regimen used, the MWC rate did not exceed 41 % with one study reporting a rate of 41 % and the remaining studies reporting rates not higher than 32 %.

In total, 6 studies were included in the analysis of grade 3 or higher toxicities for conventional radiotherapy and moderate hypofractionated radiotherapy. Thirteen studies were excluded due to missing data on only grade 3 or higher toxicities, one study was excluded due to a critical risk of bias.

In the meta-analysis of conventional radiotherapy, three studies were included with a total of 167 patients (Fig. 4). The pooled overall toxicity rate estimated with a random effect model was 5 % [95 % CI 0.0–12.1]. I2 was equal to 78.3 % and Tau 0.0029. Cochran's Q test for heterogeneity showed a p-value equal to 0.0100.

In the analysis of the moderate hypofractionated studies, 209 patients were included across three studies (Fig. 5). The pooled overall toxicity rate estimated with a random effect model was 4 % [95 % CI 1.2–6.3]. I squared was equal to 0.0 % meaning that the variability can be explained by chance alone, Tau equal to 0 and a p-value of 0.8834 for the Cochran's Q test.

The late toxicities of the ultra-hypofractionated schedule are reported in Tables 3 and 4. As shown in these tables, a wide range of toxicitiy rates (1–16 %) and median follow-up periods (5–57 months) are listed.

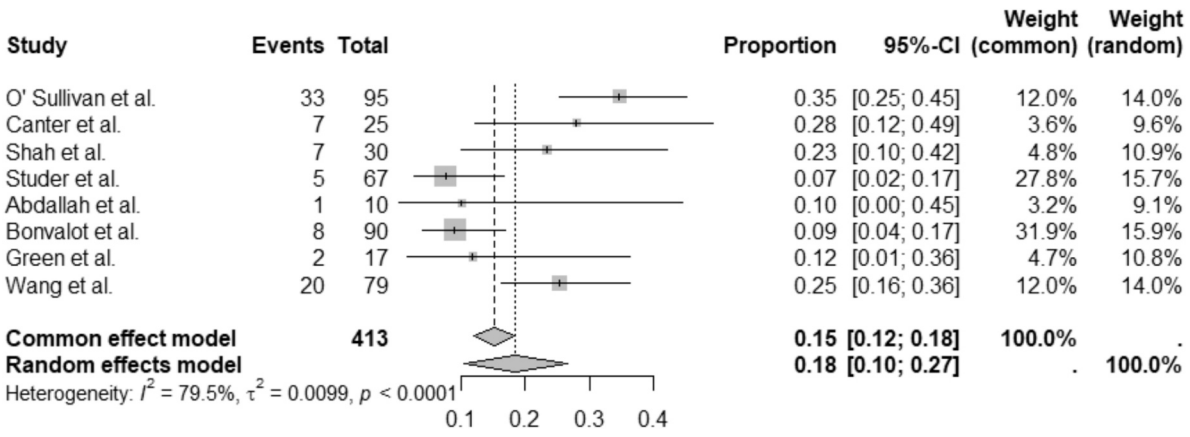

Fig. 2. Forest plot of the conventional radiotherapy studies and MWC.

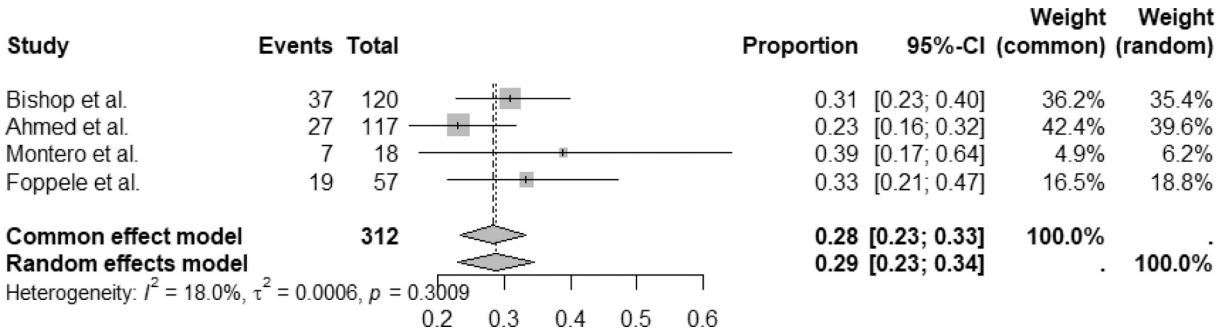

Fig. 3. Forest plot of the moderate hypofractionated studies and MWC.

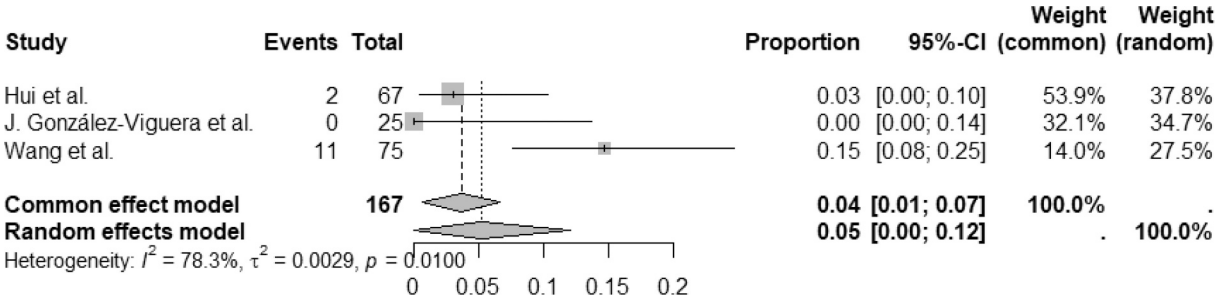

Fig. 4. Forest plot of conventional radiotherapy and late toxicity grade 3 or higher.

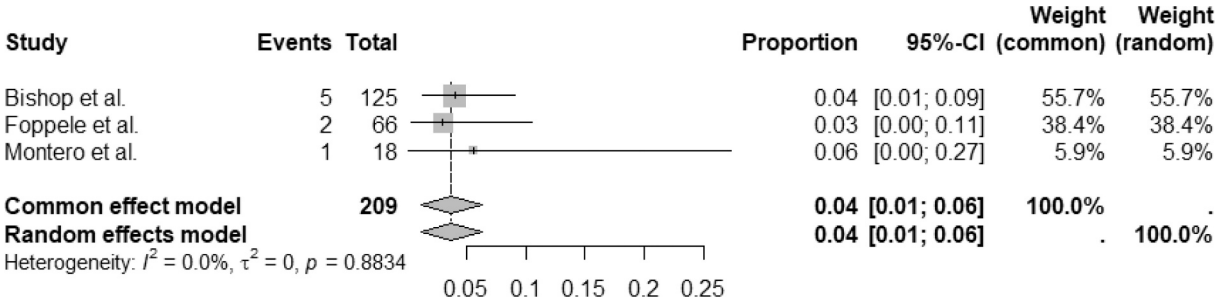

Fig. 5. Forest plot of the moderate hypofractionated studies and late toxicity grade 3 or higher.

Discussion

Moderate hypofractionated radiotherapy is a safe treatment in terms of toxicity and oncological outcomes. The outcomes of ultra-hypofractionated radiotherapy are still premature and heterogeneous, making it difficult to draw conclusions about this regimen. This study included a total of thirty studies, consisting of thirteen conventional radiotherapy studies, four studies on moderate hypofractionation, and thirteen studies on ultra-hypofractionation with multiple fractionation schedules. To the best of our knowledge, this is the first meta-analysis that incorporates conventional radiotherapy, moderate hypofractionation, and ultra-hypofractionated radiotherapy, focusing on MWC and late toxicities in the context of hypofractionation for STS.

Our analysis shows that studies on moderate hypofractionation report a comparable wound complication rate to the standard treatment of 25 × 2 Gy. The guideline for conventional radiotherapy has been based on the 35 % MWC rate reported by O'Sullivan et al. in 2002 [1]. Accordingly, studies reporting a MWC rate below 35 % may be designated as clinically safe. In our meta-analysis, the moderate hypofractionation studies show a wound complication rate of 29 %, which aligns with this historical reference. When comparing MWC with the ultra-hypofractionation group, outcomes were not meta-analyzed due to the different hypofractionation schedules. Additionally, timing of surgery after radiotherapy varied, ranging from a few days after the final RT fraction to a waiting period of 6–8 weeks, potentially influencing complication rates. While descriptive findings of the included studies suggest that the rate of MWC does not exceed 41 %, regardless of the dose, these results are derived from individual heterogeneous studies and should be interpreted with caution.

Regarding late grade $\geq$ 3 toxicity, moderate hypofractionation showed comparable toxicity rates to conventional radiotherapy, with pooled estimates of 4 % (95 % CI 1.2–6.3) and 5 % (95 % CI 0.0–12.1), respectively. However, only four studies specifically reported grade 3 toxicity or higher and these studies reported heterogeneous toxicity results, varying from 0 up to 15 %. For the ultra-hypofractionated group, toxicities were not meta-analyzed. The ultra-hypofractionated studies are showing a wide variety of rates, ranging from 1 % up to 16 %. However, these rates are potentially misleading due to different follow up periods. It is important to note that the EQD2 calculations in this meta-analysis reflect the dose delivered to the planning target volume (PTV). The actual dose of the normal tissue within or near by the PTV may differ from the dose received by the tumor, potentially influencing the incidence of wound complications and late toxicities.

The oncological outcomes showed that moderate hypofractionation is associated with not only acceptable MWC rates and comparable late toxicity but also similar local control rates between 90 % and 95 %. In

ultra-hypofractionation, the 5 × 5 Gy regimen showed lower local control with a 5-year local recurrence-free survival (LRFS) of 81 %, while the 5 × 7 Gy and 5 × 8 Gy regimens show a 2-year local recurrence rate of 0 %. It is important to note that most of the studies used Kaplan-Meier's methodology to estimate the cumulative incidence of local recurrence. However, this method does not account for the presence of competing risks, such as death from other causes, which may lead to an overestimation of the cumulative incidence of local recurrence. The stronger the competition between the two competing events, the greater the bias [50].

This meta-analysis has several strengths, including its comprehensive inclusion of various studies across different hypofractionation schedules, offering broad insights into MWC and late toxicities in STS. However, there are notable limitations. Most of the included studies had small patient populations, limiting interpretation. Differences in fractionation schedules, surgery timing, patient demographics, and evolving radiotherapy techniques over time further complicate comparisons. Follow-up periods varied significantly, potentially underestimating long term toxicities. Additionally, most studies were phase 2 studies, single-center trials or retrospective studies, introducing potential biases. These factors underscore the need for caution when interpreting the findings of this meta-analysis.

In conclusion, moderate hypofractionation seems to be safe and effective. In all moderate hypofractionated studies, the MWC, late toxicities and oncological outcomes are comparable. In ultra-hypofractionation, a balance must be found between major wound complications and oncological outcomes, which is difficult to interpret due to the heterogeneity across studies. The need for larger cohorts and longer follow up is necessary to evaluate the ultra-hypofractionated regimens. As previously noted by Baldini et al., it is still necessary to avoid implementing hypofractionation outside of study settings [51]. A RCT is needed to compare outcomes in moderate and ultra-hypofractionated regimens. Currently, the randomized SCOPES trial (Short Course Of Preoperative Radiotherapy in Head and Neck-, Trunk- and Extremity Soft Tissue Sarcomas; NTC04425967; comparing 14 × 3 Gy vs 25 × 2 Gy) is accruing patients to evaluate this question.

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Registration and protocol

This meta-analysis was not registered and no protocol was prepared.

CRediT authorship contribution statement

G.F. Foppele: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **M. Fiocco:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **B.H.G. van Riet:** Writing – review & editing, Validation, Methodology, Formal analysis. **R.L.M. Haas:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **L.M. Wiltink:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.111034.

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