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Original Research Article

A pattern of local failure after preoperative 5 × 5 Gy in soft tissue sarcomas: A long-term real-world experience

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ABSTRACT

Introduction: Preoperative radiotherapy (RT) is used to improve local control (LC) and facilitate limb-sparing procedures in patients with localized soft tissue sarcomas (STS). While conventional preoperative RT delivers 50–50.4 Gy in 25–28 fractions, alternative hypofractionated regimens are under investigation. A 5x5 Gy regimen has been investigated in STS, but its long-term LC rates appear suboptimal. The aim of this study is to analyze the characteristics of patients with local recurrence (LR) after 5x5 Gy and to identify potential RT-related factors affecting efficacy.

Methods: We retrospectively analyzed patients who received 5x5 Gy and underwent surgery for localized extremity and truncal STS in three clinical trials and institutional records. Patient, tumor, and treatment characteristics were evaluated. We assessed the quality of RT plans and recurrence patterns.

Results: Among 174 patients who experienced LR after 5x5 Gy, pleomorphic sarcoma (23 %), myxofibrosarcoma (17.8 %), and malignant peripheral nerve sheath tumor (12 %) were the most common pathologic diagnoses. No LR was observed in patients with myxoid liposarcoma. Almost all analyzed plans met the quality criteria. Most patients (86.2 %) had in-volume recurrences, suggesting inadequate tumor cell eradication rather than insufficient margins or poor target coverage. Dose equivalence analysis suggested that 5x5 Gy (EQD2 = 37.5 Gy for STS, assuming alpha/beta ratio of 4 Gy) may be insufficient, especially for radioresistant subtypes.

Conclusions: The primary factor contributing to LR after 5x5 Gy appears to be insufficient total dose. Future clinical trials should explore dose escalation beyond 5 Gy per fraction, except in myxoid liposarcoma where 5x5 Gy remains effective.

Introduction

Soft tissue sarcomas (STS) are rare malignancies of mesenchymal and connective tissues characterized by high heterogeneity and morbidity [1]. Surgery remains the cornerstone of curative treatment, but combined therapy, namely neoadjuvant or adjuvant radiotherapy (RT), can significantly improve local control (LC) in high-risk patients or allow limb-sparing or conservative surgery [2,3]. Preoperative treatment is the preferred approach in the vast majority of clinical scenarios [4]. The recommended regimen is 50–50.4 Gy in 25–28 fractions [5–7]. However, there is an increasing number of phase 1 and 2 clinical trials investigating moderately and ultra-hypofractionated regimens in the preoperative setting [8,9]. These studies have consistently demonstrated the preliminary safety and efficacy of this approach.

Since 2009, we have implemented the 5 × 5 Gy preoperative regimen and published results from three clinical trials using this fractionation [10–13]. The choice of 5x5 Gy was justified by the similar regimen successfully and widely used in rectal cancer. Nevertheless, the mature data from the first trial showed a 5-year local recurrence-free survival rate of 81 %, which is at the low end of acceptable LC rates [13]. It appears to be higher in other studies with hypofractionation (over 90 %) [8]. Local control probability after preoperative RT in STS was discussed

Abbreviations: CTV, clinical target volume; ICRU, International Commission on Radiation Units and Measurements; IMRT, intensity modulated radiotherapy; IQR, interquartile range; MPNST, malignant peripheral nerve sheath tumor; LC, local control; LR, local recurrence; RT, radiotherapy; STS, soft tissue sarcomas; VMAT, volumetric modulated arc therapy.

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by Haas et al. The authors concluded that equivalent dose in 2-Gy fractions affects LC at total doses below 28 Gy [6]. It is uncertain whether this effect occurs between 28 Gy and 50 Gy. The equivalent dose in 2-Gy fractions of 5x5 Gy regimen assuming alpha/beta of STS as 4 Gy is 37.5 Gy. Thus, it is crucial for us to find the reason for presumably lower efficacy of 5x5 Gy.

Established factors for local recurrence (LR) regardless RT fractionation include postoperative margins, recurrent disease, tumor grade, tumor size, anatomic location, and pathologic subtype [14,15]. Among these, resection margin is the strongest, with microscopically and/or macroscopically positive margins being strong predictors of LR [16]. Intermediate and high-grade STS also tend to recur more frequently than low-grade tumors. Unfavorable anatomic sites include the head and neck, deep trunk, and lower extremity. LC is also worse in selected STS subtypes, namely undifferentiated pleomorphic sarcoma and myxofibrosarcoma (formerly both classified as malignant fibrous histiocytoma), malignant peripheral nerve sheath tumor (MPNST), leiomyosarcoma, and epithelioid sarcoma. Similar factors influencing on local relapse-free survival were identified in our prospective clinical trial 5x5 Gy and immediate surgery in primary resectable STS, namely pathologic subtype, resection margins and tumor stage according to TNM classification by AJCC 8th edition [13]. Unfavorable pathologic STS subtypes were MPNST and leiomyosarcoma. Thus, we can cautiously say that non-RT-related factors prognostic for LR are similar among different RT regimens, and the reason for lower local efficacy of 5x5 Gy should be explained in a different way.

Hypothesized reasons of RT-related factors of worse LC after 5x5 Gy include too narrow elective margins of the clinical target volume (CTV), poorer target volume coverage, and too low total dose.

The aim of this study was to analyze the characteristics of patients who experienced LR after 5x5 Gy, with an emphasis on RT-related factors, to suggest the RT-related reason for lower LC after 5x5 Gy and to guide the design of new clinical trials with preoperative hypofractionated RT for STS.

Materials and methods

We included consecutive patients who experienced LR after 5x5 Gy and surgery for localized STS. We analyzed patients who received 5x5 Gy and underwent surgery for localized extremity and superficial truncal STS from three clinical trials, namely 5x5 Gy and immediate surgery for localized resectable STS (n = 311), 5x5 Gy with extended interval to surgery for myxoid liposarcoma (n = 29), and combination of sequential 5x5 Gy with anthracycline-ifosfamide chemotherapy for marginally resectable tumors (n = 46) [11–13]. In addition, we identified all patients with local recurrences treated with 5x5 Gy outside the above-mentioned trials by searching the available electronic medical records using MedStream Designer software from Transition Technologies, Poland. The appropriate International Classification of Diseases code was C49, and the keywords “relapse” and “recurrence” were used.

We analyzed patient characteristics, pathologic diagnosis, primary tumor characteristics, RT technique, quality of RT plan, interval to surgery (immediate vs extended), concomitant systemic treatment, date of LR, type of LR, and salvage treatment.

To identify the most likely reason for the lower effectiveness of 5x5 Gy, we developed a factor-driven assessment, shown in Table 1. We set the threshold probability levels for each factor to no possibility (less than 20 % of positive results), minor possibility (20–40 % of positive results), and major possibility (more than 40 % of positive results).

The quality of RT plans was retrospectively assessed using the target volume coverage criteria recommended by the International Commission on Radiation Units and Measurements (ICRU) Report 62, namely 95 % dose coverage of 95 % of the target volume. Adequate margins were defined as the extension of gross tumor volume to the CTV of at least 1.5 cm radially and 3 cm longitudinally [17]. In-volume LR was defined as recurrence within the planned target volume and 1 cm margin in all directions. In all other cases, LR was classified as marginal LR. To assess this, we performed image registration of RT planning computed tomography with diagnostic imaging confirming LR for each identified recurrence if imaging files were available. An example of such a registration is shown in Fig. 1. If no imaging data were available, we relied on medical records and physical examination description.

The $\chi 2$ or Fisher’s exact test (if frequencies were < 5) were used to analyze proportions. The Wilson method was used for calculating confidence intervals for proportions. Data analysis was performed using the R software environment, version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and the jamovi project, version 2.5.4.0

Table 1
Methods for assessing radiotherapy-related factors.

Radiotherapy-related factor	Method of assessment	Positive result	Possibility
Too narrow elective margins	Assessment of delineation	The extension of gross tumor volume to the CTV less than 1.5 cm radially or 3 cm longitudinally	No possibility: less than 20 % of positive results Minor possibility: 20–40 % of positive results Major possibility: more than 40 % of positive results
	Assessment of the localization of local recurrence	Marginal recurrence (recurrence within the planned target volume and 1 cm margin in all directions)	No possibility: less than 20 % of positive results Minor possibility: 20–40 % of positive results Major possibility: more than 40 % of positive results
Poor target volume coverage	Assessment of plan quality	Less than 95 % dose coverage of 95 % of the target volume	No possibility: less than 20 % of positive results Minor possibility: 20–40 % of positive results Major possibility: more than 40 % of positive results
Inadequate dose	Representation of subtypes	Dominance of more radioresistant subtypes* (undifferentiated pleomorphic sarcoma, leiomyosarcoma, myxofibrosarcoma, malignant peripheral nerve sheath tumor, epithelioid sarcoma)	No possibility: less than 20 % of positive results Minor possibility: 20–40 % of positive results Major possibility: more than 40 % of positive results

* – those related to higher risk of local recurrence or considered radioresistant in the literature (https://doi.org/10.1200/JCO.1996.14.5.1679, https://doi.org/10.1002/cncr.11365, https://doi.org/10.1002/cncr.26296.

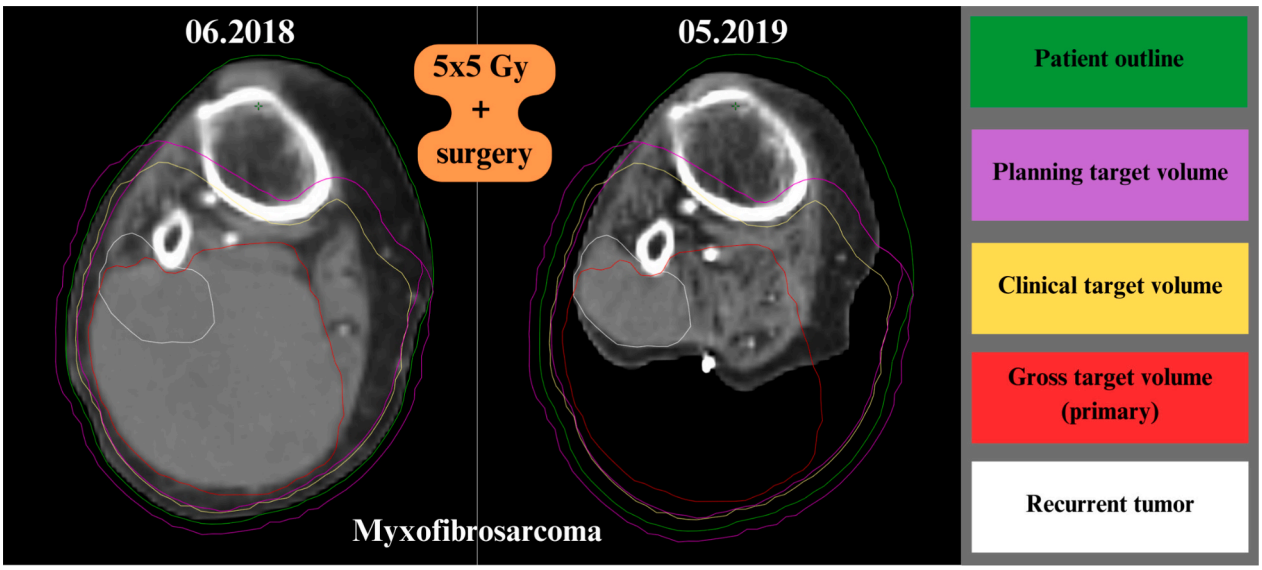

Fig. 1. A registration of planning computed tomography with diagnostic imaging that revealed recurrence.

(obtained from https://www.jamovi.org, Sydney, Australia).

Results

Patients' characteristics

We identified 174 patients (101 men and 73 women) who experienced LR after receiving preoperative radiotherapy (5x5 Gy) between 2010 and 2021. The results of the search are presented in Fig. 2. The median age was 59 years (interquartile range, IQR: 45–68 years). Among them, 83 (47.7 %) received radiation for treatment-naive primary disease, 91 (41.4 %) for local recurrence after prior surgery, and 19 (10.9 %) for a scar with margin following a non-oncological soft tissue sarcoma (STS) resection. Patients' characteristics are summarized in Table 2.

Tumor characteristics

The most common type of recurrent tumor was pleomorphic sarcoma (n = 40, 23 %), followed by myxofibrosarcoma (n = 31, 17.8 %), MPNST (n = 21, 12 %), and synovial sarcoma (n = 19, 10.9 %). Most recurrent STS cases were high-risk primary tumors, namely large (median size 8 cm, IQR: 5–13 cm) and high-grade (G3: n = 105, G2: n = 39, 82.8 %). The most frequent localization of primary tumor was a thigh (n = 58, 33.5 %). Tumor characteristics are summarized in Table 2.

Treatment characteristics

All but two plans fulfilled the criteria of target volume coverage recommended by the International Commission on Radiation Units and Measurements (ICRU) report 62, namely a 95 % dose coverage of 95 % of the target volumes. Only 12.6 % of patients (n = 22) were treated with intensity modulated radiation therapy or volumetric modulated arc

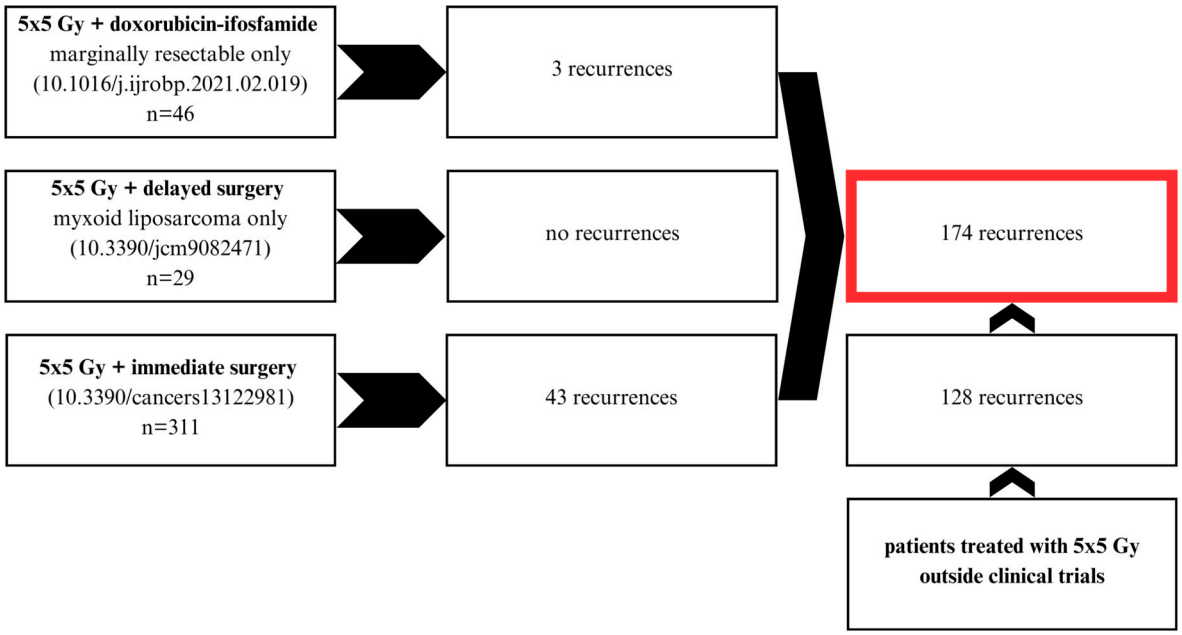

Fig. 2. Data extraction results.

Table 2
Patients' and tumor characteristics.

Characteristic		Value
Age	Median (range)	59 (17–88)
		Number of enrolled patients (%)
Sex	Female	73 (42)
	Male	101 (58)
Status at the time of preoperative radiotherapy	Primary	83 (47.7)
	Recurrent tumor after surgery in our center	6 (3)
	Recurrent tumor after surgery outside our center	66 (38)
	Scar and tumor bed after prior "whoops" surgery	19 (11)
Sarcoma pathology	Epithelioid sarcoma	3 (1.7)
	Leiomyosarcoma	12 (7)
	Liposarcoma	20 (11.5)
	Malignant peripheral nerve sheath tumor	21 (21.1)
	Myxofibrosarcoma	31 (17.8)
	Other	19 (10.9)
	Sarcoma not otherwise specified	9 (5.1)
	Synovial sarcoma	19 (10.9)
	Undifferentiated pleomorphic or pleomorphic sarcoma	40 (23)
Grade	1	13 (7.5)
	2	39 (22.4)
	3	105 (60.3)
	X	17 (9.8)
Tumor site	Arm	24 (17.8)
	Calf	17 (9.8)
	Foot	12 (6.9)
	Forearm	22 (12.7)
	Hand	4 (2.3)
	Other	7 (4)
	Thigh	58 (33.3)
	Thorax	30 (17.2)

therapy (IMRT/VMAT), which has been widely adopted in our sarcoma center in 2018, while the remaining 152 patients received three-dimensional (3D) conformal radiotherapy. All but three patients underwent immediate surgery three to seven days after completion of 5x5 Gy treatment. Preoperative chemotherapy was not commonly used (n = 48, 27.6 %), although it became the preferred option for high-risk sarcomas since 2016. Treatment characteristics are shown in Table 3.

Local recurrence characteristics and management

The proportion of patients experiencing local recurrence did not differ significantly between years (p = 0.085). Fig. 3 visualizes the data.

Table 3
Treatment characteristics.

Characteristic		Number of enrolled patients (%)
Technique	Static three-dimensional conformal	152 (87.4)
	Intensity modulated radiotherapy or volumetric modulated arc therapy	22 (12.6)
Gap to surgery	Yes	3 (1.7)
	No	171 (98.3)
Preoperative chemotherapy	Yes	48 (27.6)
	No	126 (72.4)
Resection results	R0 (microscopically negative)	116 (66.7)
	R1 (microscopically positive)	57 (32.6)
	R2 (macroscopically positive)	1 (0.7)

The majority of enrolled patients (n = 150, 86.2 %) experienced in-volume LR rather than marginal recurrence (n = 24, 13.8 %). LR occurred more than 12 months after surgery in 62 % of cases. Thirty-four patients (19.5 %) presented synchronous distant metastases. A total of 113 patients with LR (64.9 %) were eligible for curative salvage surgery, either limb preservation or amputation in the case of unresectable recurrence. The characteristics of local recurrence are summarized in Table 4.

Assessment of radiotherapy-related factors

We calculated confidence intervals for all proportions analyzed for each factor. The results are shown in Table 5. We excluded all RT-related factors except too low total dose.

Discussion

We presented the results of in-depth analysis of the pattern of recurrence after preoperative 5x5 Gy in patients with STS. We found that the most likely cause of local failure was too low total dose delivered to the target volume. We excluded other possible RT-related explanations, namely too narrow elective margins of the clinical target volume (CTV) or inadequate quality of RT plans.

All tumors were delineated with wide margins of at least 1.5 cm radially and 3 cm longitudinally. The quality of RT plans was acceptable and consistent with ICRU recommendations. In addition, the introduction of IMRT/VMAT to preoperative RT for STS did not reduce the number of local recurrences, which remained stable over the years (Fig. 3). Moreover, 85.6 % of patients experienced in-volume recurrences, suggesting inadequate RT-related sarcoma cell killing rather than too small margins or poor target volume coverage.

The most common subtype of recurrent STS was pleomorphic sarcoma, which is consistent with the results of the 5x5 Gy followed by immediate surgery trial and the general representation of STS subtypes localized to the extremities and trunk wall (see Table 6). The second most common subtypes were myxofibrosarcoma and malignant peripheral nerve sheath tumor, which are considered radioresistant. It can be said that they are overrepresented in our cohort. All the above-mentioned subtypes have the highest risk of LR. The distribution of other tumor-related factors that affect LC such as resection margin, grade, and tumor diameter appear to be similar to those reported in the above study.

The hypothesis of inadequate dose was also confirmed by the lack of local recurrences in the myxoid liposarcoma study LIPOMYX, which is considered to be more radiosensitive than other STS [11]. In this trial patients with localized resectable myxoid liposarcomas received 5x5 Gy followed by a gap to surgery. Similar results were obtained in the DOREMY trial with preoperative 36 Gy in 2 Gy fractions for localized myxoid liposarcoma [18]. This may also suggest an equivalence of 5x5 Gy and 18x2 Gy and consequently an alpha/beta ratio of myxoid liposarcomas between 4 and 5 Gy.

Interestingly, superior local control was seen after a combination of doxorubicin-ifosfamide with 5x5 Gy in marginally resectable STS with a median primary tumor size of up to 17.4 cm [12]. This may suggest a benefit in LC after the addition of chemotherapy. However, the results regarding LC in this study should be interpreted with caution because many patients may not have developed LR due to rapid distant progression of bulky high-grade primary STS followed by sarcoma-related death. This was confirmed by the poor 2-year local relapse-free survival of 67 % with only three LR events (7 % of patients enrolled).

On the other hand, the 5x5 Gy regimen was found to be effective in terms of local control in rectal cancer [19,20]. Excellent LC after 5x5.2 Gy was also confirmed in adjuvant RT for breast cancer [21]. Possible explanations for the lower efficacy of 5x5 Gy in STS could be the much higher heterogeneity of radiosensitivity as well as the much higher tumor volume compared to rectal and breast cancers [22,23].

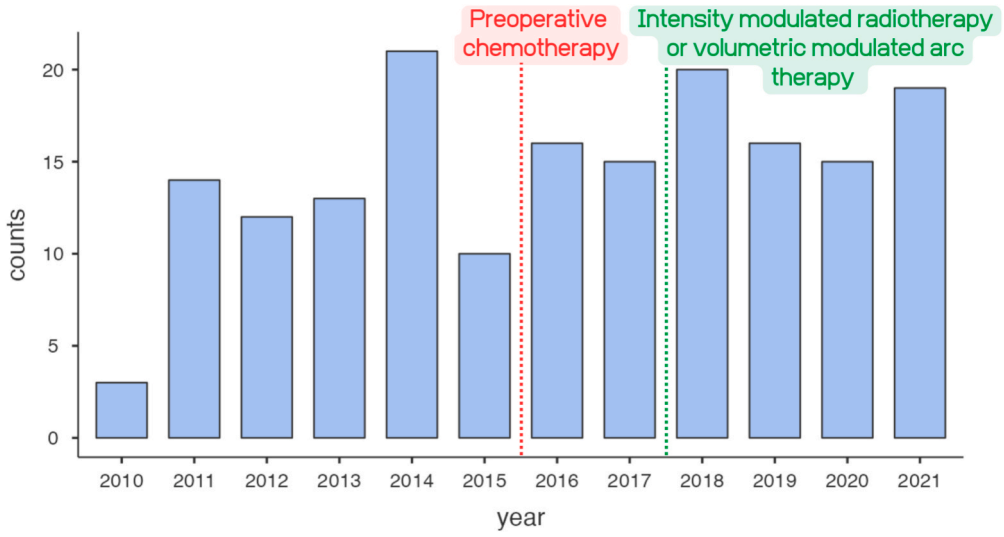

Fig. 3. Number of local recurrences per year.

Table 4
Local recurrences characteristics.

Characteristic		Number of enrolled patients (%)
Time to recurrence	Early (3–12 months from surgery)	55 (31.6)
	Late (>12 months from surgery)	119 (68.4)
Type of local recurrence	In-volume	150 (86.2)
	Marginal	24 (13.8)
Synchronous distant metastases	Yes	34 (19.5)
	No	140 (80.5)
Salvage surgery	Yes	113 (64.9)
	No (due to unresectability)	27 (15.5)
	No (due to synchronous multiple distant metastases)	34 (19.6)

Finally, other studies that evaluated doses per fraction greater than 5 Gy in the preoperative setting for STS patients showed superior LC of more than 90 % after five fractions, regardless of time to surgery, techniques used, and population characteristics [24–26]. These findings were summarized in a *meta*-analysis of 5-fraction preoperative RT trials, which demonstrated the positive impact of a total dose of at least 30 Gy on LC [9]. Importantly, in a study with 8 Gy per fraction up to a total dose of 40 Gy, the authors reported unacceptable toxicity from late-responding tissues, namely vascular damage in three of 25 enrolled patients and grade 3 movement disability, all of which required limb amputation [27]. It can be concluded that the optimal dose in 5-fraction regimens should be greater than 5 Gy but less than 8 Gy per fraction.

Our study has limitations, including the potential for selection bias due to its retrospective design. To mitigate this, two authors (K.Z. and M. J.S.) independently reviewed all data. In addition, the patient sample analyzed is heterogeneous and may pose a risk of non-representativeness, especially when compared to other studies using ultra-hypofractionation. In addition, we did not retrieve all data for each patient treated with 5x5 Gy outside of clinical trials. However, this could significantly prolong the time required for analysis, and the data obtained are not necessary to provide a general overview of STS patients because of the availability of results from the 5x5 Gy followed by immediate surgery trials with the large sample size [10,13]. In addition, the proposed evaluation of RT-related factors may contain confirmation bias. Nevertheless, we tried to avoid it by using the objective numerical criteria and available literature data. Despite these limitations, the study provides valuable insights into this important topic, supported by the number of events and the site's extensive experience with hypofractionation over more than a decade.

In conclusion, the total dose in equivalent 2 Gy fractions, assuming an alpha/beta of 4 Gy, should be higher than 37.5 Gy in five-fraction regimens. Thus, the design of new clinical trials of five-fraction preoperative RT for patients with STS should plan for a higher dose than 5 Gy per fraction as in ongoing trials. The only currently known exception is a group of patients with myxoid liposarcoma, where a dose in equivalent 2 Gy fractions of approximately 36 Gy is satisfactory to achieve excellent local control.

CRediT authorship contribution statement

Konrad Zasadziński: Data curation, Investigation, Formal analysis, Visualization, Writing – original draft. **Aneta Borkowska:** Data curation, Resources, Writing – review & editing. **Tadeusz Morysiński:** Data curation, Resources, Writing – review & editing. **Hanna Koseła-Paterczyk:** Resources, Writing – review & editing. **Piotr Rutkowski:** Validation, Writing – original draft, Writing – review & editing. **Mateusz Jacek Spałek:** Conceptualization, Data curation,

Table 5
Methods for assessing radiotherapy-related factors.

Radiotherapy-related factor	Method of assessment	Number of patients with positive result	Proportion of patients	95 % confidence interval	Possibility
Too narrow elective margins	Assessment of delineation	0	0	0–0.0216	No possibility
	Assessment of the localization of local recurrence	24	0.1379	0.0945–0.197	No possibility
Poor target volume coverage	Assessment of plan quality	2	0.0115	0.0032–0.0409	No possibility
Inadequate dose	Representation of subtypes	107	0.6149	0.5409–0.684	Major possibility

Table 6
Distribution of sarcoma subtypes between our study and a study of 5x5 Gy followed by immediate surgery.

Sarcoma pathology	The number of patients in the current study (%) n = 174	The number of patients in the trial with 5x5 Gy followed by immediate surgery (%) n = 311
Epithelioid sarcoma	3 (1.7)	No data
Leiomyosarcoma	12 (6.9)	15 (4.8)
Liposarcoma	20 (11.5)	29 (9.3)
Malignant peripheral nerve sheath tumor	21 (12.1)	26 (8.4)
Myxofibrosarcoma	31 (17.8)	No data
Other subtypes	19 (10.9)	50 (16.1)
Sarcoma not otherwise specified	9 (5.2)	No data
Synovial sarcoma	19 (10.9)	49 (15.8)
(Undifferentiated) pleomorphic sarcoma	40 (23)	142 (45.7)

Investigation, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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none.

Ethical approval

Each patient provided routine informed consent for treatment and data processing at the start of treatment. Patients who participated in included trials provided separate consents, which are described in detail in the relevant articles. The study was conducted in accordance with the tenets of the Declaration of Helsinki. It does not report the use of experimental or novel protocols. This study, as part of a series of projects, was approved by the Institutional Ethics Committee at the Maria Sklodowska-Curie National Research Institute of Oncology (approval number KB/9/2011) to publish these data without additional patient consent, as patient consent was deemed unnecessary.

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Availability of data and materials.

Upon approval of data transfer by corresponding authors and relevant authorities.

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