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Hypofractionated Preoperative Radiation Should Not Yet Be Used as Standard of Care for Extremity and Truncal Soft Tissue Sarcoma

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Soft tissue sarcomas (STS) represent <1% of all cancers and occur anywhere in the body, with 75% arising in extremities and trunk.¹⁻³ Landmark randomized trials for STS of extremities established the following: (1) combined limb-sparing surgery and radiation therapy (RT) is standard of care; (2) oncologic outcomes are similar with preoperative or postoperative RT, but toxicities differ.⁴⁻⁷ The American Society of Radiation Oncology, National Comprehensive Cancer Network, and European Society for Medical Oncology have endorsed (1) preference for preoperative RT over postoperative RT due to more favorable long-term toxicity profile and (2) conventional fractionation of 50 Gy in 25 fractions over 5 weeks as standard of care for preoperative RT for STS.⁸⁻¹⁰

There has been a paradigm shift in radiation oncology with randomized controlled studies showing noninferior oncologic outcomes for hypofractionated RT for several cancers, including breast, prostate, and rectal.¹¹⁻¹³ By comparing several RT prescriptions, regimens that increase the radiation dose per day, but decrease total dose delivered, were identified with similar toxicity. Compared with conventional fractionation (1.8-2 Gy per fraction), hypofractionated regimens deliver larger daily doses (>2 Gy per fraction) with fewer fractions over shorter treatment duration (1-3 weeks). Hypofractionation is appealing for several reasons: potential biological advantage for higher dose per fraction for tumors with lower α/β ratios like sarcoma,^{14,15} convenience of shorter treatment duration, reduction of time from RT completion to surgery, and optimization of hospital resources. Logically, we should ask whether we can safely deliver preoperative RT for STS using hypofractionation.

A group of expert sarcoma radiation oncologists convened at the 2023 Connective Tissue Oncology Society (CTOS) Annual Meeting to address the status of hypofractionation for STS and collaborated to put forward this consensus report. We reviewed the literature and included publications with at least 20 patients. Since the role of concurrent chemotherapy for localized STS is not well established,^{9,10} publications of concurrent chemotherapy and hypofractionation were excluded. As hypofractionation trials are predominantly in the setting of preoperative RT, this report focuses on hypofractionated preoperative RT for localized STS of extremity and trunk.

To adopt hypofractionation as a standard, the dose regimen must demonstrate noninferior efficacy and acute and long-term toxicity comparable with conventional 50 Gy in 25 fractions. The consensus from international experts at CTOS is that hypofractionated preoperative RT regimens should *not yet* be standard of care for STS of extremities and trunk *outside of clinical trials*.

Radiobiologic Principles of RT Dosing

Radiation dose fractionation regimens can be evaluated with regard to specific end points by comparing biologically equivalent doses calculated using cell survival models. These models are tissue-specific and sensitive to total dose and fraction size. Calculations of biologic equivalency differ on the basis of respective outcome end points (eg, tumor control or acute toxicity or late toxicity). Biologically equivalent doses in 2 Gy fractions (EQD2) for sarcoma tumor control are

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calculated using the EQD2 formula derived from the linear-quadratic model of cell killing and α/β ratio for STS approximated to 4 Gy.¹⁵⁻¹⁷ The typical α/β ratio for STS tumor control is approximately 3–5 Gy, whereas α/β ratios for normal tissue acute toxicity and late toxicity are approximately 10 Gy and 2 Gy, respectively.¹⁸ Importantly, when compared with conventional fractionation, hypofractionated STS regimens designed to be equivalent for local control (LC) will have higher biologically equivalent dose effect on the incidence and severity of late toxicities of normal tissues.

Treatment Efficacy for Preoperative Conventional and Hypofractionation Regimens

Conventional Fractionation (25 fractions, 5 weeks)

Presently, reports indicate that when using conventional fractionation, LC is consistently >85%.¹⁹⁻²³

Moderate Hypofractionation (15 fractions, 3 weeks)

Guadagnolo et al²⁴ conducted a single-institution phase II trial using a moderate hypofractionation regimen of 42.75 Gy in 15 fractions of 2.85 Gy over 3 weeks. The trial included 120 patients; the median follow-up was 24 months, and the 30-month actuarial local recurrence-free survival (LRFS) was 93%. The tumor control EQD2 for 2.85 Gy $\times$ 15 (with an α/β ratio of 4) is approximately 49 Gy; it is therefore not unexpected that the observed LC is similar to that for conventional dosing of 50 Gy.

Two similar trials are ongoing: Mayo Clinic is conducting a phase II trial with the same 2.85 Gy $\times$ 15 fraction regimen (ClinicalTrials.gov identifier: [NCT04562480](#)); Netherlands Cancer Institute is performing a randomized phase II trial of 2 Gy $\times$ 25 fraction conventional fractionation versus 3 Gy $\times$ 14 fraction moderate hypofractionation (ClinicalTrials.gov identifier: [NCT04425967](#)). Results of these studies are eagerly anticipated.

Ultra-Hypofractionation (5 fractions, 1–1.5 weeks)

Several single-institution phase II studies have used ultra-hypofractionation with five fractions of ≥ 5 Gy per fraction delivered over 1–1.5 weeks. These studies differ in dose regimens used, treatment delivery (daily or every other day), and time after RT to resection (immediate or delayed) and will be reviewed in order of increasing biologically effective dose.

Koseła-Paterczyk et al²⁵ assessed 311 patients treated with 5 Gy $\times$ 5 fractions delivered over 1 week. With a median follow-up of 57 months, the 5-year LRFS was 81%. This is lower than the benchmark LC rates >85% for conventional fractionation. The EQD2 for 5 Gy $\times$ 5 is 37.5 Gy (with an α/β ratio of 4), which may explain the inferior LC compared with conventional dosing of 50 Gy.

Two trials have been conducted using 6 Gy $\times$ 5 fractions delivered over 1 week. Kalbasi et al²⁶ treated 50 patients with this regimen. Crude LC among 35 patients with a minimum 2-year follow-up was 94%. Mayo et al²⁷ reviewed 22 patients treated with the same regimen. With a median follow-up of 24.5 months, LC was 100%. Both report LC rates comparable with conventional fractionation in alignment with the EQD2 for 6 Gy $\times$ 5 (with an α/β ratio of 4) of 50 Gy.

Bedi et al²⁸ treated 32 patients with 7 Gy $\times$ 5 fractions delivered over 1.5 weeks. With a median follow-up of 36 months, LC was 100%. The EQD2 for 7 Gy $\times$ 5 (with an α/β ratio of 4) is 64 Gy (28% higher than conventional 50 Gy).

A final study of 25 patients by Leite et al²⁹ further escalated the dose to 8 Gy $\times$ 5 fractions delivered over 1.5 weeks using smaller radiation volumes. With a median follow-up of 21 months, LC was 100%. The EQD2 for 8 Gy $\times$ 5 (with an α/β ratio of 4) is 80 Gy (60% higher than conventional 50 Gy). As discussed below, this regimen led to unacceptable toxicities.

It is the consensus opinion of this group of experienced sarcoma radiation oncologists that the appropriate ultra-hypofractionation dose per fraction for preoperative RT appears to be 6 Gy given that (1) 6 Gy $\times$ 5 has an EQD2 of 50 Gy (for an α/β ratio of 4), and (2) published LC rates are comparable with those for conventional fractionation. All these publications contain small sample sizes and short follow-up. Further study is necessary before such treatment is adopted as standard of care. An important caveat to these comparisons is that LC is not the only outcome of concern.

Acute Treatment Toxicities for Conventional and Hypofractionation Regimens

Conventional Fractionation (25 fractions, 5 weeks)

The most relevant acute toxicity for preoperative RT followed by resection is major wound complication (MWC).⁷ For preoperative treatment with conventional fractionation to 50 Gy, rates of MWC range from 31% to 37%.^{7,20-22,30}

Moderate Hypofractionation (15 fractions, 3 weeks)

Guadagnolo et al²⁴ reported an MWC rate of 31% in their trial of moderate hypofractionation.

Ultra-Hypofractionation (5 fractions, 1–1.5 weeks)

As shown in [Table 1](#), in the series of preoperative ultra-hypofractionation, rates of MWCs ranged from 24% to 41%.²⁵⁻²⁹ Excluding the study in which patients underwent surgery 0–5 days after RT,²⁴ MWC rates (24%–32%) were comparable with those reported for conventional and moderate hypofractionation. However, study heterogeneity and small sample sizes limit firm conclusions.

TABLE 1. Local Control, Wound Complications, Amputation, and Late Toxicity Data for Preoperative Conventional, Moderate, and Ultra-Hypofractionation Regimens for Localized Soft Tissue Sarcoma of Extremity and Trunk

Author (year)	n	Median Follow-up	Total Dose Gy/ No. fx	EQD2	Local Control	Major Wound Complication	Any Amputation	Amputation for Reason Other Than LR	≥G2 Late Toxicity	Late Skin/ Wound Complication	Bone Toxicity
Conventional fractionation											
O'Sullivan et al ^{7,19} Davis et al ³¹ (2002, 2004, 2005)	88 73 ^a	3.3 years	50/25 fx daily	50 Gy	5 years 93% (6.9 years updated follow-up)	35%	NS	NS	Any 37% (fibrosis 32%, edema 15%, joint stiffness 18%)	NS	NS
Wang et al ^{22,23} (2015, 2023)	57	3.6 years	50/25 fx daily	50 Gy	5 years 87.3% (6 years updated follow-up)	37%	NS	NS	Any 11% (fibrosis 5%, edema 5%, joint stiffness 4%)	NS	NS
O'Sullivan et al ²¹ (2013)	59	49 months	50/25 fx daily	50 Gy	Crude 93%	31%	NS	NS	Fibrosis 9%, edema 11%, joint stiffness 6%	NS	None
Lansu et al ³⁰ (2019)	191	21 months	50/25 fx daily	50 Gy	3 years 93%	31%	NS	NS	NS	NS	NS
Moderate hypofractionation											
Guadagnolo et al ²⁴ (2022)	120	24 months	42.75/15 fx daily	49 Gy	3 years 93%	31%	1%	None	Any 11% (fibrosis 11%, edema 3%, joint stiffness 3%)	≥G2 3% (skin ulcer at 180 days)	Fracture 2%
Ultra-hypofractionation											
Koseła-Paterczyk ²⁵ (2021)	311	57 months	25/5 fx daily	37.5 Gy	5 years 81%	24%	3%	None	Any 9% (severe fibrosis 0.3%, edema 3%)	NS	Fracture <1% (n = 3)
Kalbasi et al ²⁶ (2020) Kendal et al ³² (2022) ^b	50	29 months	30/5 fx daily	50 Gy	Crude 94%	32%	3% ^b	None	Any 16% (fibrosis 11%, edema 4%, joint stiffness 11%)	≥G2 16% open wound at 180 days	Fracture 3% ^b Osteo-radio-necrosis 1% ^b
Mayo et al ²⁷ (2023)	22	25 months	30/5 fx daily	50 Gy	Crude 100%	41%	5%	5% fracture/trauma after treatment	Any 18% (fibrosis 14%, edema 5%, joint stiffness 5%)	NS	Fracture 5%
Bedi et al ²⁸ (2022)	35	36 months	35/5 fx every other day	64 Gy	Crude 100%	25%	6%	6% (1 for traumatic fracture: 1 for persistent infection)	Fibrosis 35%	NS	Fracture 3%
Leite et al ²⁹ (2021)	25	21 months	40/5 fx every other day	80 Gy	2 years 100% (1 LR at 26 months)	28%	16%	16% (3 for vascular occlusion, 1 for limb dysfunction)	Any 41% (fibrosis 4%, edema 4%, joint stiffness 13%)	12% vascular occlusion and necrosis	Fracture 4% (2 months postoperatively)

NOTE. Table adapted from Guadagnolo et al.³³

Abbreviations: EQD2, equivalent dose in 2 Gy fractions with $\alpha/\beta = 4$ Gy; fx, fractions; LR, local recurrence; NS, not stated.

^aEvaluable patients on the preoperative arm of NCIC SR2, n = 88 for oncologic outcome and wound data and n = 73 for late toxicity data.

^bKendal et al³²: data presented in abstract update of published report by Kalbasi et al.²⁶

Late Treatment Toxicities for Conventional and Hypofractionation Regimens

Conventional Fractionation (25 fractions, 5 weeks)

The most common reported late toxicities after conventional preoperative RT followed by resection are $\geq$ grade 2 subcutaneous fibrosis, edema, and joint stiffness. Amputation due to toxicity and bone fracture is much less common but highly significant given the adverse effect on function. Davis et al reported late toxicities³⁴ at 2 years among patients on the NCIC-SR2 trial preoperative RT arm who received 50 Gy in 25 fractions³¹. Rates for $\geq$ grade 2 fibrosis, edema and joint stiffness were 32%, 15%, and 18%, respectively. Of note, NCIC-SR2 trial was conducted before the modern era of intensity modulated RT and daily pretreatment image guidance, both of which reduce dose delivered to adjacent normal tissues. More recent series that form a better basis for comparison document rates of 5%–9%, 5%–11%, and 4%–6% for $\geq$ grade 2 fibrosis, edema, and joint stiffness, respectively.^{21,22}

Several reports have assessed risk of femur fracture among patients treated with conventional RT for proximal lower extremity STS. Bishop et al³⁵ reviewed 596 patients and reported a crude fracture rate of 2%, noting all fractures occurred in patients who received 50 Gy to the entire circumference of femur. Dickie et al³⁶ reported a crude fracture rate of 4% among 691 patients treated and identified relationships between the dose to femur and volume of femur irradiated and subsequent fracture. The median time to fracture was 38 and 40 months in these two publications and studies show increased fracture rates with prolonged follow-up.^{35–37}

Using conventional fractionation, the need to perform amputation for indications other than local recurrence, such as intractable pain or limb dysfunction, is a rare occurrence.

Moderate Hypofractionation (15 fractions, 3 weeks)

Late $\geq$ grade 2 toxicities for the moderate hypofractionation trial were 11%, 3%, and 3% for fibrosis, edema, and joint stiffness, respectively.²⁴ Late $\geq$ grade 2 skin toxicity was seen in one patient (3%) who had an MWC with delayed healing and ulcer after 6 months. Two patients (2%) experienced fractures. No patients required amputation for treatment-related complications. The short median follow-up of 24 months limits firm conclusions regarding late toxicity. The toxicities appear comparable with those seen for conventional fractionation, but late skin and bone toxicities are notable. Further follow-up and additional trials will be informative.

Ultra-Hypofractionation (5 fractions, 1–1.5 weeks)

Late toxicities for ultra-hypofractionation series are shown in Table 1.^{25–29,32} Kosela-Paterczyk et al²⁵ used the lowest

dose regimen (5 Gy $\times$ 5) and demonstrated late toxicities comparable with or lower than those reported for conventional fractionation. Rates of $\geq$ grade 2 fibrosis for the series using higher dose regimens (6–8 Gy per fraction) range from 4% to 35%.^{26–29} The 35% rate reported by Bedi et al is an outlier. Rates for $\geq$ grade 2 edema and joint stiffness are in line with what might be expected, ranging from 4% to 5% and 5% to 13%, respectively.^{26–29}

Rates of other late toxicities raise questions. Amputations performed for treatment-related complications were necessary for 5% in the Mayo et al series (6 Gy $\times$ 5), 6% in the Bedi et al series (7 Gy $\times$ 5), and 16% in the Leite et al series (8 Gy $\times$ 5) and may further increase with longer follow-up; amputation for complications following conventional fractionation is very rare.^{27–29}

In the Kalbasi et al²⁶ series, (6 Gy $\times$ 5), late skin complications were described in 14% of patients, all of whom had open wounds 6 months following surgery. In the Leite et al²⁹ series (8 Gy $\times$ 5), 12% of the aforementioned amputations were related to skin necrosis arising from vascular occlusion.

Early fracture rates appear higher than expected given the short median follow-up times. Kalbasi et al updated their series in abstract form, describing fractures for 3% of patients and osteoradionecrosis requiring surgery for 1%³²; Mayo et al²⁷ described fracture associated with trauma for 5%; Bedi et al²⁸ also described fracture associated with trauma for 3%; and Leite et al²⁹ reported fractures for 4%. Additional monitoring is warranted given that fracture rates typically increase with time.³⁵

In conclusion, this consensus report summarizes publications for preoperative hypofractionated RT (without concurrent chemotherapy) for extremity and truncal STS. The data are not robust enough to change current standard of care. Moderate hypofractionation appears promising with reasonable LC and toxicity outcomes, but data are only available from a single trial; results of two similar ongoing trials are awaited. Of the ultra-hypofractionation regimens, the 5 Gy $\times$ 5 regimen is likely too low of a dose on the basis of inferior LC, and 8 Gy $\times$ 5 is too high a dose given the unacceptable amputation rate. Assuming an α/β ratio of 4, the 6 Gy $\times$ 5 regimen is the most biologically equivalent to conventional fractionation for tumor control and is appropriate for further study in randomized trials. However, as normal tissue late effects have an estimated α/β ratio <4 , a regimen of 6 Gy $\times$ 5 may lead to increased late toxicities that include amputation, skin necrosis/nonhealing wound, and bone fracture. On the basis of these limited data, our consensus opinion is that hypofractionated preoperative RT regimens should *not yet* be standard of care for localized STS of extremities and trunk. We advocate these dose regimens be tested in a three-arm multi-institutional randomized trial comparing conventional fractionation, moderate hypofractionation, and ultra-hypofractionation.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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