Unraveling the myth of radiation resistance in soft tissue sarcomas

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Unraveling the Myth of Radiation Resistance in Soft Tissue Sarcomas

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There is a misconception that sarcomas are resistant to radiotherapy. This manuscript summarizes available (pre-) clinical data on the radiosensitivity of soft tissue sarcomas. Currently, clinical practice guidelines suggest irradiating sarcomas in 1.8-2 Gy once daily fractions. Careful observation of myxoid liposarcomas patients during preoperative radiotherapy led to the discovery of this subtype's remarkable radiosensitivity. It resulted subsequently in an international prospective clinical trial demonstrating the safety of a reduced total dose, yet still delivered with conventional 1.8-2 Gy fractions. In several areas of oncology, especially for tumors of epithelial origin where radiotherapy plays a curative role, the concurrent application of systemic compounds aiming for radiosensitization has been incorporated into routine clinical practice. This approach has also been investigated in sarcomas and is summarized in this manuscript. Observing relatively low α/β ratios after preclinical cellular investigations, investigators have explored hypofractionation with daily doses ranging from 2.85-8.0 Gy per day in prospective clinical studies, and the data are presented. Finally, we summarize work with mouse models and genomic investigations to predict observed responses to radiotherapy in sarcoma patients. Taken together, these data indicate that sarcomas are not resistant to radiation therapy.
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Routine Clinical Practice, the Paradigm of 1.8-2 Gy Fractions

As a single modality, radiotherapy (RT) can be applied with curative intent in many epithelial malignancies (like inoperable cervical cancer, non-small cell lung cancer, and head-and-neck cancers, to name a few). Similarly, in the setting of hematologic malignancies, RT can be applied with curative intent given the high response rates of malignant lymphomas to RT. For the management of soft tissue sarcomas (STS), RT is usually prescribed in close conjunction with surgery, either pre- or postoperatively. In contrast to lymphomas and many epithelial cancers, most subtypes of STS do not show marked volumetric reductions with RT, which has contributed to the misperception of radiation resistance of STS.

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RT is prescribed in conjunction with limb-sparing surgery for extremity STS for tumor-specific and personalized indications (like size, grade, histological subtype, location, age, achieved or anticipated resection margins, anticipated RT-induced toxicities, co-morbidities etc.) because RT increases the local control probability as described by both NCCN-[1] and ESMO[2] clinical practice guidelines (CPG). The indications for perioperative RT are essentially the same for both the preoperative and postoperative phases of localized STS management. If RT is applied postoperatively, specifically after R1 resection margins, the aim is to sterilize potential (assumed, but unproven) residual microscopic disease, that is by definition invisible. Thereby, other than prolonged follow-up of patients irradiated postoperatively, for observing ongoing local control, there is no means of detecting a response of this microscopic tumor burden to radiation.

Conversely, if preoperative RT is delivered, the patient is treated with the primary tumor still *in situ* giving the opportunity to investigate histotype-specific sensitivity to RT by imaging and pathological examination, both during the course of RT and in the definitive resection specimen.

Based on vast clinical experience, an abundance of literature, as well as prospective randomized clinical studies, like the Canadian SR-2 trial,[3] these RT schedules are usually

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prescribed in 1.8-2.0 Gy once-daily fractions sizes. Deviation from this standard-of-care is only advised in the setting of well-designed clinical investigations.

In this manuscript, we summarize clinical trial efforts and (pre-) clinical investigations testing the appropriate total dose (eg, in myxoid liposarcomas), the value of concurrent radiosensitizers, and the growing knowledge of sarcoma radiobiology leading to hypofractionation. However, the timing of adjuvant RT (pre- vs postoperative) as well as the difference in both acute and late toxicity profiles with pre-versus postoperative RT will not be discussed. Instead, we focus on literature and clinical trials with RT delivered in the preoperative setting.

Radiotherapy Improves Local Control When Added to Surgery: Implications for Radiosensitivity of STS

It is a common perception that carcinomas as a group are radiosensitive compared to sarcomas. However, a comparison of randomized trials of surgery with or without radiotherapy for carcinomas and sarcomas demonstrates that these data do not support this perception. Over the past decades, results from clinical trials in breast cancer patients have shown that radiotherapy in addition to breast conserving surgery can replace the need for mastectomy. Nomograms like the "IBTR!"[4] can estimate the difference in local control rates for breast cancer after 10 years follow-up, when prescribing or refraining from additional RT. Only in relatively high-risk breast cancer patients that difference exceeds an absolute 10% gain. In rectal cancer, the TME trial investigated the value of preoperative short-term radiotherapy in combination with total mesorectal excision (TME). Here, the 10-year cumulative incidence of local relapse dropped by 6% with the addition of RT.[5] After 15 years follow-up of the POR-TEC-1 trial,[6] the absolute gain in pelvic disease control of stage I endometrial cancer was 9.5% comparing radical surgery only to radical surgery plus postoperative external beam RT.

Compared to these examples in carcinomas, the absolute gain in local control rates after perioperative RT for STS frequently exceeds 10%. For individual patient counseling, this absolute gain can be estimated using the freely available PERSARC-app.[7] These relatively large gains in local control were also found in the 2 randomized trials comparing surgery alone to surgery plus brachytherapy[8]; 23% difference in high-grade sarcomas and surgery alone to surgery plus external beam RT[9]; 19% difference.

Therefore, the overall benefit of RT in the limb- and function-sparing management for STS patients is at least as large as the benefit of RT observed for managing carcinoma patients. These clinical trials demonstrate that it is a misconception that sarcomas are radioresistant.

Radiation Sensitivity of Myxoid Liposarcomas

While the average radiosensitivity of STS may be similar to epithelial cancers, some subtypes of STS can have exquisite radiosensitivity. For example, in several clinical patient cohorts,[10-13] the subtype of myxoid liposarcomas (MLS) was shown to be highly radiosensitive as a marked volume shrinkage[14] as well as an early histological response[15] could be readily observed during RT.

These clinical observations led to the hypothesis that a conventionally fractionated RT dose of 50 Gy in 5 weeks was overtreatment for MLS, which could be tested in a clinical trial of a dose reduction. Since 2010, the DOREMY study (dose reduction of preoperative radiotherapy in myxoid liposarcomas; ClinicalTrials.gov Identifier: NCT02106312) investigated a reduced dose of 36 Gy in 18 once-daily fractions of 2 Gy. The analysis of the primary endpoint (early toxicity being the rate of postoperative wound complications) was subsequently published in 2021.[16] In brief, among 77 evaluable patients having undergone surgery after preoperative RT, the rate of wound complications after surgery was only 17%, and extensive pathological treatment response was observed in 91%. Local control after a median follow-up of 25 months was 100%. Twenty-six of these patients were treated at the Netherlands Cancer Institute (NCI). Currently, after a median follow-up of 61 months (range 44-126 months), the local control rate for the patients treated at NCI remains at 100% until the date of the last continued follow (Haas RL, unpublished). The DOREMY investigators intend to update the local control from all patients enrolled in the trial after a minimum follow-up of 5 years for the entire study population. These results have led to this regimen being included in the latest ESMO-CPG[2] as well as in the design of an International Prospective MLS Registry (NCT04699292).

Past and Current Experience With Radiation Sensitizers

In the past, several studies have been published on systemic therapies given concurrently with RT, and such trials are currently recruiting participants. Several classes of drugs have been tested for radiosensitization of STS.[17] Table 1 provides examples of investigations of concurrently applied systemic agents in the preoperative phase (sequential designs and interdigitation of drugs and RT are left out of consideration).

Several arguments for pursuing this approach include:

- Throughout oncology, predominantly in the field of carcinomas, the addition of radiosensitizers frequently increases the rates of local control, but at the cost of increased toxicity (eg, rectal-, esophageal-, cervical- and non−small-cell lung cancer).
- Where local control rates are already high by RT alone, the addition of radiosensitizers may enable a

Table 1 Overview of Classes of Drugs Investigated for Their Radiosensitization Properties

Class of Drugs	Compound	Reference or Trial Identifier
Conventional chemotherapy	Anthracyclins (e.g adriamycin, epirubicin)	[40]
	Ifosfamide	[40,41], NCT01102608
	Gemcitabine	[42]
	Trabectedin	[43,44]
Monoclonal antibodies directed against angiogenesis	Bevacizumab	[45]
Tyrosine Kinase Inhibitors (inhibitors of neoangiogenesis)	Sunitinib	[46,47]
	Sorafenib	[48,49]
	Pazopanib	[50,51,52]
PARP inhibitors	Olaparib	[53], NCT02787642
DNA damage response inhibitors	AZD1390	NCT05116254
Modulators of the immune response	Atezolizumab	[54] NCT03474094
	Nivolumab +/- Ipilimumab	NCT03463408, NCT03307616
Others	Intratumoral nanoparticles	[55]

reduction in the dose of RT and thereby decrease RT-associated acute and late toxicities (eg,[18,19]).

- The radiosensitizer dose might be potentially high and intense enough to exhibit a clinical response against micrometastatic disease.

Although not yet shown in STS, ongoing clinical trials may show that radiation sensitizers improve outcomes for STS patients.

Cellular Radiobiology of Sarcomas

The paradigm of 1.8-2.0 Gy fraction sizes in daily clinical practice has been alluded to above. Given the wide variety of histological subtypes, all being an STS,[20] it may easily be questioned whether this "one size fits all" approach is justified. Moreover, prescribing RT for STS in conventional fraction sizes is based on the assumption that the α/β ratio is high, for example, 10 Gy or above. However, until recently there was only very limited radiobiological data available to substantiate initiatives aimed at optimizing sarcoma RT, both with respect to the total dose to apply as well as to a more evidence-based fraction size.

Haas et al.[21] have investigated a panel of 14 sarcoma cell lines, derived from synovial sarcoma, leiomyosarcoma, fibrosarcoma, and liposarcoma origin. These cells were submitted to clonogenic survival assays after exposure to single radiation doses (1-8 Gy). Surviving fractions (SF) were calculated from the resulting response data. Cellular radiosensitivities varied widely in this panel, indicating a considerable degree of heterogeneity. The median SF after 2 Gy (SF2) was 0.52 (range 0.27-0.76) with evidence of a particular radiosensitive phenotype in only a few cell lines. $D_{37\%}$ on the mean data was 3.4 Gy. Importantly, the median α/β ratio was 4.9 Gy and in 6 cell lines, the α/β ratio was below 4 Gy. These results suggest that hypofractionation (daily radiation dose) above 2 Gy would be useful for STS.

Translational Radiobiology

The challenge in determining response to radiation therapy lies in the numerous histological subtypes, intratumoral and interpatient heterogeneity within and between these subtypes, and the rarity of each subtype. Beyond cell lines evaluating SF which reports limited outcome data, there is an inherent need to evaluate tumor heterogeneity, intrinsic radiosensitivity, and immunogenicity to refine the understanding of the biological effect of radiation on the variety of soft tissue sarcomas. Soft tissue sarcomas rely on the loss of tumor suppressor pathways and the activation of oncogenic pathways to drive tumor growth and induce the tumor microenvironment to support this growth. The evolution of preclinical cancer models from 2D in vitro cell lines to 3D in vitro organoids (patient-derived organoids, PDO) to in-vivo animal models, including patient-derived xenografts (PDX), can faithfully mimic the original tumor within the patient to different degrees.

Early PDO investigations have studied the ability to predict responses to chemoradiation in rectal cancer. Yao et al.[22] demonstrated highly matched PDO response to corresponding patient outcomes. Driehuis et al.[23] reported correlation between postradiotherapy sensitivity of patient response to PDO in head and neck squamous cell cancer. A pilot study exposed 2 soft tissue sarcoma patient-derived 3D cell cultures (undifferentiated pleomorphic sarcoma (UPS) and pleomorphic liposarcoma, LPS) to different doses of photon or proton radiation. The proportion of viable cells were significantly higher for UPS compared to LPS but displayed minor nonsignificant differences when comparing photon versus proton treatment, as published by Roohani et al.[24] The potential limitation of these analyses is that they exclude the impact of the tumor microenvironment. The challenges in handling fresh viable tumors limits the routine use of PDO in translational radiation research but the results thus far are encouraging.

Historically, tumor xenografts from 10 sarcoma lines were irradiated to determine intrinsic radiosensitivity and relative biological effectiveness by measuring tumor growth delay. Considerable variability in radiation response was seen between the different subtypes.[25] Further progress in the development of PDX has been established in many malignancies to aid translational research. In a single institution cohort of 188 patients with soft tissue sarcoma, the tumor engraftment was 32% (range 0-%100%) and was variable between histological subtypes.[26] This platform has been established to aid further study of sarcoma biology and *in vivo* preclinical drug and radiation dose testing. A multicenter collaboration is currently open to accrue patient samples for further PDX development (NCT02910895).

A limitation of xenograft models of sarcomas is the need to transplant the human tumor cells into immunodeficient mice. To study the radiation response of STS sarcomas with an intact immune system, investigators frequently inject mouse sarcoma cells into immunocompetent mice from the same genetic background. However, mouse sarcoma transplantation into an orthotopic site like the muscle activates the immune system in ways that do not recapitulate the tumor microenvironment for a tumor that co-evolves with the immune system.[27] To address this limitation, investigators have utilized genetically engineered mouse models of sarcoma where a primary tumor co-evolves with the immune system.[28] These models have been useful to study the role of endothelial cells in mediating the response of tumors to radiotherapy.[29,30] and to investigate the RBE of carbon ion radiotherapy.[31]

To unify the impact of the biological effect of therapeutic radiation dose rather than the impact of physical dose alone, it will be important to understand the heterogeneous genomic features and gene expression across all malignancies. This is challenging for cancers with low incidence like soft tissue sarcomas, especially given the high heterogeneity within this population of tumors. A genome-based radiosensitivity index, RSI, has been clinically tested in several malignancies including soft tissue sarcomas.[32] A low RSI score suggests high radiosensitivity. A preliminary analysis of RSI by Torres-Roca et al.[33] in soft tissue sarcomas suggested a nonsignificant association of radio-resistance and local failure compared to epithelial malignancies. Further still, Scott et al.[34] have utilized RSI and the linear quadratic model to derive a genomic adjusted radiation dose (GARD). This signature has been developed through multi-institutional collaboration evaluating soft tissue sarcomas. Compared to other malignancies, sarcomas recorded a low GARD suggesting relative radio-resistance. Yang et al applied the concept of RSI and GARD to 217 sarcoma specimens and observed heterogeneity on a genomic scale. They proposed using a dose to optimize outcomes in highly radio-resistant (HRR) soft tissue sarcomas compared to conventionally radio-resistant (CRR) soft tissue sarcomas.[35] When the GARD was modeled for a total delivered dose of 50 Gy in 2 Gy fractions, Yang and colleagues observed a wide range of GARD distributed across sarcoma histologies. The median delivered GARD was 16 which was significantly lower for HRR (11.9) when compared to CRR (18.0) ($P < 0.01$). The median α/β ratio of the entire cohort was 5.42 Gy, which was significantly lower in HRR (3.29 IQR 2.1-5.0) when compared to CRR (5.98 IQR 4.0-7.7, $P < 0.01$). The application of PDX to determine response to radiation and incorporating gene-expression-based RSI has the potential to identify subgroups of soft tissue sarcoma with differences in the α/β ratio. Future clinical trials of GARD may help identify an appropriate biological effective dose for each soft tissue sarcoma subtype and aid in dose-escalation or de-escalation strategies.

Paving the Way to Hypofractionation for Sarcomas

Hypofractionation has already been widely adopted in daily clinical practice to treat prostate and breast cancer patients. Hypofractionation offers several advantages. For patients, the shorter overall treatment time might be associated with a lower treatment-related burden. Approximately 40% of all sarcoma patients are 70 years of age and above. A meaningful reduction in treatment burden will not only benefit elderly patients themselves but will also have an impact on society, including caregivers accompanying the older patient.

For health care providers in areas of the world with poor access to radiotherapy services, and as experienced during the recent COVID-19 pandemic, hypofractionation relieves pressure on health care systems and decreases costs to the health care system.

A systematic review of studies of preoperative hypofractionation for STS has recently been published,[36] and here we highlight some of these studies and trials currently open for patient accrual in Table 2. In brief, after the current standard preoperative regimen of 25 × 2 Gy, in 5 weeks, one-third of all patients may expect delayed wound healing[3,37] after surgery with a high local control rate of 90% or more. Hypofractionated regimens with fraction sizes of 3 Gy up to as large as 8 Gy and with EQD2 total dose levels of 30-75 Gy (assuming an α/β ratio of 4.9 Gy) have been designed. Results have been mixed with unacceptable rates of amputation after 5 × 8 Gy,[38] but phase 2 data with more moderate schedules of hypofractionated radiotherapy suggesting the rate of delayed wound healing as well as local control after 2-5 years approximating the historical rates after 50 Gy in 5 weeks. Most of these studies have relatively short follow-up for observation of late toxicities such as fibrosis, joint impairments, edema, amputation due to vascular complications, and long bone fractures. Additionally, it is currently unknown whether a shortening of the overall treatment time translates into a lesser impact on health-related quality of life. Finally, hypofractionated RT regimens will also need to study cost-effectiveness. To the best of our knowledge, only the currently accruing NCT04425967 ("SCOPES") trial

Table 2 Hypofractionated Preoperative RT Schedules in Sarcoma Studies and Trials, Compared to Conventionally Fractionated Regimens

Reference / Trial Identifier	n	Time Frame	RT Schedule	Recalculated EQD2 (*)	Wound Complication Rate	Local Control	Comments (**)
[3]	94	1994-1997	25 × 2 Gy	50 Gy	35%	93% @ 3 y	"gold standard"
[37]	191	2003-2017	25 × 2 Gy	50 Gy	31%	93% @ 5 y	"gold standard"
[56]	120	2018-2021	15 × 2.85 Gy	48.0 Gy	31%	93% @ 2.5 y	
[57]	40	1984-1994	10 × 3 Gy	34.3 Gy	15%	97% at 5 y	1, 2
[58]	-	closed	10 × 3.25 Gy	38.4 Gy	-	-	Phase I,[15]
[59,60]	77	1974-1981	10 × 3.5 Gy	42.6 Gy	23%	95% @ 8 y	1
[59,60]	137	1981-1984	5 × 3.5 Gy	21.3 Gy	5%	88% @ 4 y	1
[59,60]	97	1984-1987	8 × 3.5 Gy	34.1 Gy	10%	95% @ 2 y	1
[61]	25	2002-2005	8 × 3.5 Gy	34.1 Gy	20%	88% @ 2 y	3
[41]	34	1995-2008	8 × 3.5 Gy	34.1 Gy	17%	89% @ 5 y	4
[49]	16	2009-2011	8 × 3.5 Gy	34.1 Gy	38%	100% @ 2 y	5
[62]	272	2006-2011	5 × 5 Gy	35.9 Gy	32.4%	81% @ 3 y	6
[63]	29	2015-2019	5 × 5 Gy	35.9 Gy	28%	100% @ 2 y	7
[64]	52	2016-2018	5 × 6 Gy	47.4 Gy	32%	94% @ 2 y	
[65]	32	2016-2020	5 × 7 Gy	60.4 Gy	25%	100% @ 3 y	
[38]	25	2015-2019	5 × 8 Gy	74.8 Gy	28%	100% @ 2 y	8
NCT03972930	-	open	60 Gy in 3-8 fractions		-	-	Recruiting
NCT04330456	-	open	5 × 5 Gy + 25 × 2 Gy	35.9 Gy	-	-	Recruiting, 9
NCT02812654	-	open	5 × 5 Gy	35.9 Gy	-	-	Recruiting, 10
NCT03651375	-	open	5 × 5 Gy	35.9 Gy	-	-	Recruiting, 10
NCT04425967	-	open	14 × 3 Gy	48.1 Gy	-	-	Recruiting

Overview of completed and/or currently accruing clinical studies investigating RT schedules diverging from the standard conventionally fractionated 50 Gy regimen.

Note: (*) using an average α/β ratio of 4.9 Gy.[21] Calculations making use of an α/β ratio of 10 Gy or higher result in EQD2 dose levels nominally almost equal to the physical dose in the column "RT schedule."

Comments: (1) RT schedules with either intravenous or intra-arterial doxorubicin, (2) Overall wound complication rate of 15% of which 2.5% were designated as "major" and 12.5% as "minor", (3) Epirubicin 30 mg/m^2/d on days 1-4 and ifosfamide 2.5 g/m^2/d on days 1-4 every 21 days for 3 preoperative and 3 postoperative cycles; concurrent RT with cycle 2 preoperative, (4) Concurrent ifosfamide 2.5g/m^2/d for 5 days, (5) Concurrent sorafenib, escalating dose in phase 1 design, (6) In total 32.4% acute treatment related toxicities, of which 11.8% was managed by oral antibiotics, (7) Study only recruiting myxoid liposarcomas,[18]; NCT04425967, (8) one local failure after 26 month resulting in a 88% LRFS @ 3 years (estimated from graph) and furthermore an exceptionally high 16% rate of amputations (4/25; 3 as a result of vascular occlusions and 1 because of a grade 3 limb dysfunction), (9); Sequential design of 5 × 5 Gy stereotactic preoperative RT to the gross tumor volume with narrow margins (intended dose exposure only to tissues to be removed by subsequent surgery) followed by postoperative RT to the entire surgical bed of 25 × 2 Gy (last update posted 2016), (10); Doxorubicin 75mg/m^2 (cycles 1, 2, and 3), and ifosfamide 9 g/m^2 (cycles 1 and 3). Radiotherapy: RT 25 Gy / 5 × 5 Gy/d, beginning at Cycle 2/Day 1, 9; Preoperative RT 10 × 3.25 Gy (5 consecutive days in a week, 2 weeks), in combination with deep hyperthermia, twice a week, if unresectable after 6 weeks a boost of 4 × 4 Gy is applied, 10; 1xAI (doxorubicin 75 mg/m^2 and ifosfamide 10 g/m^2) + 5 × 5 Gy radiotherapy + 2xAI + surgery.

harbors all these three fields of research. First published results are to be expected in 2025 and beyond.

Definitive RT for STS (Without Surgery)

Definitive RT is well described in the literature in several indication areas, for instance as local management in localized Ewing sarcoma, in desmoid type fibromatosis, and even in angiosarcomas of the scalp. Far less clear is the role of definitive RT in large, deep-seated, and/or high grade STS where the patient is inoperable based on size and site or where the patient is medically inoperable or both. In this setting, Allignet et al.[39] have recently performed a meta-analysis. Summarizing 29 studies involving over 1400 patients, 5-year local control rates of 28%-73% with photon beam and 52%-69% with particle therapies can be expected. The majority of local failures will occur within 3 years. Although a total equivalent dose of 64 Gy with standard fractionation or above seems to be associated with better outcomes, it also substantially increases the risk for severe adverse events, suggesting that an external beam RT dose of 64-66 Gy is relatively safe with some efficacy as definitive treatment for unresectable STS, particularly for tumors less than 5 cm in size.

Conclusions and Future Perspective

When radiotherapy is to be applied to sarcoma patients in routine daily practice, these regimens should be delivered in 1.8-2.0 Gy once-daily fractions. This prescription is based on decades of clinical experience and is thereby described in several clinical practice guidelines around the globe. However, until recently, such regimens are not so much based upon thorough scientific investigations, in part due to the rarity and heterogeneity of the disease. Nevertheless, deviations from these standard fraction sizes, larger, not smaller (by definition hypofractionation), deserve further investigation and these efforts are already being undertaken in carefully designed prospective randomized studies. Taking modern radiobiological observations of sarcoma cells into account, all these efforts have the potential to change the landscape of preoperative radiotherapy in the future. If this research is successful, not only will these new hypofractionated regimens be more evidence-based, but they will also serve patients by requiring less visits to radiotherapy facilities. Importantly, hypofractionated RT reduces healthcare costs because it utilizes fewer radiotherapy treatments. However, before hypofractionated radiotherapy becomes a standard of care, carefully designed randomized clinical studies with prolonged follow-up are needed. Time will tell.

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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