A Phase II Trial of 5-Day Neoadjuvant Radiotherapy for Patients with High-Risk Primary Soft Tissue Sarcoma

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ABSTRACT

Purpose: In a single-institution phase II study, we evaluated the safety of a 5-day dose-equivalent neoadjuvant radiotherapy (RT) regimen for high-risk primary soft tissue sarcoma.

Patients and Methods: Patients received neoadjuvant RT alone (30 Gy in five fractions) to the primary tumor with standard margins. The primary endpoint was grade ≥2 late-radiation toxicity. Major wound complications, local recurrences, and distant metastases were also examined. In exploratory analysis, we evaluated germline biomarkers for wound toxicity and the effects of the study on treatment utilization.

Results: Over 2 years, 52 patients were enrolled with median follow-up of 29 months. Seven of 44 evaluable patients (16%) developed grade ≥2 late toxicity. Major wound complications occurred in 16 of 50 patients (32%); a signature defined by 19 germline SNPs in miRNA-binding sites of immune and DNA damage response genes, in addition to lower extremity tumor location, demonstrated strong predictive performance for major wound complications. Compared with the preceding 2-year period, the number of patients treated with neoadjuvant RT alone at our institution increased 3-fold, with a concomitant increase in the catchment area.

Conclusions: A shorter 5-day neoadjuvant RT regimen results in favorable rates of wound complications and grade ≥2 toxicity after 2-year follow-up. Five-day RT significantly increased utilization of neoadjuvant RT at our high-volume sarcoma center. With further validation, a putative germline biomarker for wound complications may guide safer RT utilization.

Introduction

Radiotherapy (RT) significantly improves local control for patients with high-risk primary extremity and trunk soft tissue sarcomas (STS; ref. 1). Neoadjuvant RT is generally preferred because of its favorable toxicity profile, shorter course, and potential operative benefits (2). Although widely considered a standard approach for high-risk STS, many patients do not receive RT, in part due to the difficulty of daily treatments for 5 or 6 weeks (3, 4).

More condensed RT regimens have been adopted in the treatment of several malignancies as radiation oncologists can more easily spare normal tissues with modern radiation techniques and image guidance (5, 6). There is also a biological rationale for this approach in sarcoma, a tumor that is less sensitive to smaller RT fraction sizes (lower α/β ratio; ref. 7). Although late toxicities are still a concern, these condensed RT regimens can be well-tolerated with appropriate dosimetry (8, 9).

For patients with STS who also receive neoadjuvant chemotherapy, a condensed (hypofractionated) form of neaodjuvant RT has been used at our institution for decades. This regimen of neoadjuvant chemoradiation (the "Eilber" protocol, 28 Gy over eight fractions with ifosfamide-based chemotherapy) demonstrated an actuarial local recurrence rate of 11% and 17% at 3 and 6 years (10, 11). Another Polish study utilizing 5-day neaodjuvant radiation (25 Gy over five fractions) for STS resulted in 19.1% rate of local recurrence at median follow-up of 35 months (12). The risk of local recurrence in these two studies was higher than modern studies using standard fractionation (50 Gy over 25 fractions in 5 weeks), which have reported <10% local recurrence rates (5, 13–15). We hypothesized that this may be due to the lower biologically equivalent or effective dose used in both hypofractionation studies.

We initiated a prospective phase II study to evaluate the safety and toxicity of a 5-day neoadjuvant RT regimen for STS that delivers 30 Gy over five fractions, a dose that may more closely mimic the biological effect of conventional 5-week RT (EQD_2 = 50 Gy). This calculation is based on a presumed $\alpha/\beta = 4$ for STS (7, 16), although this is a generalized estimate of a value that is more likely histology and tumor specific. Here, we report the feasibility, safety, and early oncologic outcomes of this prospective phase II study.

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Translational Relevance

A 5-day neoadjuvant radiotherapy (RT) regimen for primary soft tissue sarcoma (STS) of the extremity and trunk demonstrates a toxicity profile similar to modern studies using conventional 5-week neaodjuvant RT. This less-burdensome 5-day course of neoadjuvant RT increased access to care of STS at our high-volume sarcoma center, while early local control, pathologic and imaging outcomes support the bioactivity of this dose and fractionation scheme. We identified a putative germline biomarker profile for major wound complications; further validation of this profile may guide safer utilization of neoadjuvant RT. Together, these results support the evaluation of the 5-day neoadjuvant RT regimen and its associated germline toxicity biomarker in a larger multi-institutional study for patients with primary STS of the extremity and trunk.

Patients and Methods

Patients

The protocol for this prospective study (NCT012701153) was approved by the University of California Los Angeles (UCLA) Institutional Review Board (Los Angeles, CA; IRB). Informed written consent was obtained from eligible patients with histologically confirmed STS of the extremity or trunk with planned neaodjuvant RT and surgery. The study was performed according to the institutional regulations as well as ethical principles summarized in the Belmont Report. All patients were 18 or older and had Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. Exclusion criteria included evidence of distant metastases, planned neoadjuvant, or adjuvant chemotherapy; prior RT to the area to be irradiated; and active treatment of a second malignancy.

Study design and treatments

Eligible patients were assigned to receive neaodjuvant RT followed by surgery 2–6 weeks later. Radiation CT and/or MRI simulation was performed with custom immobilization. The gross, clinical, and planning target volumes were defined according to RTOG 0630 (5): the gross tumor volume (GTV) was defined by T1 weighted MRI and CT. The clinical target volume (CTV) was defined as a margin of 3 cm in the longitudinal directions on the GTV and a 1.5 cm radial expansion on the GTV, in addition to any suspicious edema as seen on T2 weighted MRI, and cropped out of any uninvolved bone and nonadjacent muscle compartments. This CTV was then expanded to a planning treatment volume (PTV) using a 5-mm expansion. The PTV was cropped at least 2 mm from the skin for superficial lesions unless there was skin involvement.

A dose of 6 Gy × 5 fractions (30 Gy) was delivered on consecutive days to at least 95% of the PTV. Intensity modulated RT (IMRT), 3D conformal, or electron planning techniques were used. Radiation plans were deemed acceptable if they met dosimetric parameters outlined in Supplementary Table S1. All patients underwent daily image guidance except 2 patients receiving electron RT. All surgeries were performed at UCLA (Los Angeles, CA) by one of four dedicated sarcoma surgeons.

Assessments

The primary endpoint of this study was the rate of grade ≥ 2 radiation morbidity (fibrosis, lymphedema, or joint stiffness) at median 2-year follow-up (minimum 1 year). Fibrosis and joint stiffness were graded on the basis of Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) criteria, and lymphedema was graded by Stern scale. Other secondary endpoints included acute toxicities as assessed by the frequency and severity of adverse events using Common Terminology Criteria for Adverse Events (CTCAE) v4.0 toxicity criteria, the rate of major wound complications, pathologic treatment effect, and the rate of local and distant recurrences. Major wound complications were defined as per established criteria from prospective clinical trials of extremity STS (2, 13). We also evaluated patient- and physician-reported functional outcomes at baseline and 12, 18, and 24 months using the Toronto Extremity Salvage Score (TESS) and the Musculoskeletal Tumor Society (MSTS score), respectively (17, 18). Pathologic treatment effect was defined as the percentage of surgical tissue with hyalinization or necrosis relative to pretreatment biopsy (19). Time-to-event end points were measured from enrollment.

Patients were seen after the completion of radiation and prior to surgery by the radiation oncologist and/or the sarcoma surgeon. Patients were followed closely in the postoperative setting. The patients' status was reviewed 3 months after surgery, and then at least every 6 months thereafter. The patients were followed both clinically and radiographically after treatment with CT or MRI of the primary site and CT of the chest at least every 6 months for the first 2 years and then at least annually in the third year. Patients with myxoid liposarcoma were also evaluated with CT of the abdomen and pelvis.

A subset of patients was consented to a parallel imaging study under IRB approval from May 2016 to June 2018. Diffusion-weighted images (DWI) were acquired up to four times for each patient using a 0.35T MR-guided radiotherapy machine (ViewRay, MRIdian) including before the first fraction of treatment and at least 14 days after RT but prior to surgical resection.

Statistical analysis

The study was designed to evaluate the rate of grade ≥2 radiation-related morbidity (subcutaneous tissue fibrosis, joint stiffness, or edema at 2 years to mirror the initial design of RTOG-0630; ref. 5) with a target absolute improvement of 20% in the rate of grade ≥ 2 radiation-associated toxicity at 2 years compared with the historical neaodjuvant RT arm of the CAN-NCIC-SR2 study from 37% to 17%. Between May 2016 and May 2018, 52 patients with localized high-risk STS of the extremity or trunk were enrolled. Of these, 50 patients ultimately underwent neaodjuvant RT and surgery (Supplementary Fig. S1, CONSORT diagram).

We examined whether major wound complications were related to relevant clinical variables, including tumor size, tumor site, tumor depth, time interval from radiation to surgery, and two radiation dosimetric variables using univariate logistic regression. Dosimetric variables included the maximum radiation dose (Gy) to the skin (minimum 0.5 cc volume), and volume of the skin (cc) receiving 12 Gy. Likelihood ratio test was used to assess the significance of categorical variables.

Pathologic outcomes were reported with descriptive statistics. Differences in pre- and post-treatment tumor volumes by diffusion-weighted MRI were assessed by paired *t* test. Comparisons of average distance traveled and volume of patients between the 2 years prior to study enrollment and the study period were made using unpaired *t* tests.

Exploratory germline biomarker analysis

Genomic DNA from blood or saliva was analyzed for SNPs disrupting miRNA-binding sites, promoter regions, or coding sequences

Table 1. Clinical characteristics and demographics of the study population.

	n (%)
All patients	50
Disease characteristics	
Tumor size	
≤5	13 (26)
>5 and ≤10	25 (50)
>10	12 (24)
Tumor depth	
Superficial	10 (20)
Deep	40 (80)
Tumor site	
Upper extremity	9 (18)
Lower extremity	34 (68)
Trunk/girdle	7 (14)
Tumor histology	
Undifferentiated	24 (48)
Myxofibrosarcoma	8 (16)
Myxoid liposarcoma	11 (22)
Angiosarcoma	2 (4)
Well-diff liposarcoma	2 (4)
Other	3 (6)
Tumor grade	
Low	1 (2)
Intermediate	19 (38)
High	30 (60)
Patient characteristics	
Age	
<50	14 (28)
50–64	11 (22)
65–79	20 (40)
>79	5 (10)
ECOG	
0	39 (78)
1	6 (12)
2	5 (10)
Diabetes	
No	46 (92)
Yes	4 (8)
Smoking	
No	41 (82)
Yes	9 (18)
Demographic	
Race	
White	36 (72)
Black	5 (10)
Hispanic/Latino	5 (10)
Asian	4 (8)
Sex	
Female	22 (44)
Male	28 (56)
Distance to facility	
≤10 miles	3 (6)
>10, ≤25 miles	10 (20)
>25, ≤50 miles	8 (16)
>50, ≤100 miles	9 (18)
>100, ≤200 miles	10 (20)
>200 miles	10 (20)
Treatment characteristics	
Radiation type	
3D-conformal	10 (20)
IMRT	38 (76)
Electron	2 (4)
Prior R1/R2 resection	
No	38 (76)
Yes	12 (24)
Adjuvant chemotherapy	
No	44 (88)
Yes	6 (12)

(Continued on the following column)

Table 1. Clinical characteristics and demographics of the study population. (Cont'd)

as identified previously (20). Biomarkers in binding sites in genes involved in the immune system and DNA damage response, as well as promoters and coding sequences of miRNAs that regulated key genes known to be critical in the DNA damage or immune response were enriched in our analysis. We reduced to a final list of approximately 116 variants (see Supplemental Materials and Methods). We evaluated the relationship of this set of 116 SNPs with the incidence of major wound complications. We also included lower extremity tumor site as a variable as it was the only clinical variable associated with major wound complications. The association between this panel of potential germline biomarkers and tumor site with wound toxicity was assessed using four classifiers: classification trees (ref. 21), random forests (RF; ref. 22), boosted trees (BT; ref. 23), and LASSO-regularized logistic regression (LASSO-LR; ref. 24), which were fit in R (version 3.6.0; ref. 25).

Retrospective analysis of neaodjuvant RT patients prior to clinical trial period

Patients treated with neaodjuvant RT alone prior to surgical resection during the 2-year period (May 2014 to May 2016) before study initiation were extracted from the facility electronic health record system. Distance to facility was calculated using the patients' residential zip codes and the facility zip code in R package *ggmap* (26).

Results

Patient characteristics and accrual

Patient clinical and pathologic details and demographics are summarized in **Table 1** and Supplementary Fig. S2. The study enrolled patients across a broad age spectrum, including 5 patients between age 80 and 90, 3 of whom had ECOG performance status of 2. With the exception of 1 patient's tumor, all were intermediate or high grade. Tumor size among enrolled patients was heterogeneous (1.2–28 cm), and 12 patients had tumors >10 cm. Twelve patients (24%) received neoadjuvant RT prior to re-resection for gross ($n = 9$, 18%) or microscopic ($n = 3$, 6%) residual disease. The median time between completion of RT and surgery was 28 days (range 14–55). Nine of 50 patients (18%) had initial R1 resection, of whom 5 underwent R0 re-resection.

Radiation-associated toxicities

The 5-day neaodjuvant RT regimen was well-tolerated without grade 3 or higher acute or toxicities. The most severe radiation dermatitis was grade 2 and occurred in 4 patients (8%); other grade 2 toxicities were pain flare ($n = 3$, 6%) and nausea ($n = 1$, 2%).

Radiation-associated toxicities (fibrosis, joint stiffness, or lymphedema) as measured by RTOG/EORTC criteria are summarized in **Table 2**. No grade 3 or higher toxicities were observed after 29 months median follow-up (minimum 17 months). Overall, 7 of

Table 2. Late toxicities of 5-day preoperative RT.

Number of patients		
Fibrosis		
G1	G2	G3
11 (24%)	5 (11%)	0 (0%)
Joint stiffness		
G1	G2	G3
5 (11%)	5 (11%)	0 (0%)
Lymphedema		
G1	G2	G3
2 (4%)	2 (4%)	0 (0%)

44 evaluable patients (16%) developed at least one grade 2 radiation-associated toxicity, which met the primary endpoint. Grade 2 fibrosis (11%) and joint stiffness (11%) were more frequent than grade 2 lymphedema (4%). Of evaluable patients, 34 patients had minimum 2 years follow-up; 5 (14.7%) developed grade ≥ 2 fibrosis, lymphedema, and/or joint stiffness. We observed a nonsignificant trend toward increased grade ≥2 radiation-associated toxicities in patients with tumors larger than the median size of 6.5 cm ($P = 0.101$, χ^2 test). We did not observe any association between RT modality (IMRT, 3D, or electron) and toxicities, but the limited number of patients treated with 3D-conformal and electron RT limits this comparison (data not shown).

We also examined patient- and physician-reported outcomes using TESS and MSTS score surveys, respectively, at baseline, 12, 18, and 24 months. Baseline and at least one evaluable follow-up data point were available in 34 of 50 patients. We did not observe a significant decline in functional outcome at 12, 18, or 24 months using either survey (Supplementary Fig. S2A and S2B).

Wound complications

Major wound complications were observed in 16 of 50 patients (32%). This rate is on par with rates of major wound complications observed in prospective studies of neaodjuvant RT (35% in the neoadjuvant RT arm of the NCIC phase III study; 30.5% in multi-institutional phase II study of image-guided IMRT, and 36.6% in RTOG 0630) as well as retrospective analyses (**Fig. 1A**; refs. 2, 5, 13, 27–29). By CTCAE criteria, 12 patients (24%) experienced grade 3 or higher wound complication or wound dehiscence, including 3 patients who required a reconstruction flap (grade 4 complication). In the 16 patients with major wound complications, 14 have achieved wound closure at a median time to closure of 6.4 months (**Fig. 1B**). There were more wound complications in patients with lower extremity tumors ($P = 0.01$; **Fig. 1C**; Supplementary Tables S2 and S3), including 5 of 9 patients with adductor compartment involvement. Wound complications were not associated with smoking history, time interval from radiation to surgery, tumor depth, tumor size, or either of two parameters for radiation dose to the skin (Supplementary Fig. S3A–S3D). The low rate of diabetes ($n = 4$) in our study population precluded meaningful statistical analysis. We did not find an association of prior R1/R2 surgery on the incidence of major wound complications ($P > 0.99$, Fisher exact test).

Association of germline biomarkers with wound complications

Given the paucity of clinical factors that predict for wound complications, we hypothesized that inherent patient radiosensitivity may contribute to the risk of wound complications after neaodjuvant RT. In exploratory analysis, among lower extremity tumor site and a panel of 116 annotated SNPs in miRNA-binding sites, tumor site and 19 SNPs were identified as the top 20 predictors for major wound complication rate (Supplementary Table S4). The prediction performance for four proposed classifiers (classification tree, RF, BT, and LASSO-LR) using these 20 predictors jointly were fairly similar (**Table 3**), with RFs performing the best, with an accuracy of 0.855, a specificity of 0.792, sensitivity of 0.917, AUC of 0.952, and F1 of 0.868.

Early oncologic outcomes

Of the 50 patients who underwent surgery, a minimum of 2-year follow-up is available for 38 patients, of whom 35 are evaluable for local control (3 patients have died). To date, two of these evaluable patients with minimum 2-year follow-up developed a local recurrence after surgery (5.7%); both local recurrences occurred within the first year of study enrollment. Ten of 47 evaluable patients (21.2%) have developed metastatic disease. There was a preponderance of high-grade tumors among patients who developed metastatic disease (80% vs. 54%; $P = 0.16$), but no difference in size, tumor depth, or re-excision status (data not shown). Forty-two of 50 patients (84%) are alive, including 6 patients with metastatic disease. Of eight deaths, 4 patients have died because of causes unrelated to sarcoma or treatment (median age 81, range 70–90). Among 45 patients with evaluable pre- and post-treatment tumor, the average pathologic treatment effect was 44.2% (range 0%–100%, SD 31.6%; **Fig. 2A**; ref. 10).

Twenty-five patients had matched pre- and post-treatment MRI available for analysis on the parallel imaging study (Supplementary Table S5). The median time between pre- and post-treatment scans was 20 days (range 16–35). Overall, there was no difference in DWI tumor volume between pre- and post-treatment scans, and there was no association between time interval between scans and change in DWI tumor volume. We observed a significant decrease in DWI tumor volume between pre- and post-treatment myxoid liposarcoma specimens ($\Delta = -43.2\ cm^3 \pm 13.7\ cm^3$; $P = 0.025$), but not in nonmyxoid liposarcoma tumors (**Fig. 2B**).

Study-associated changes in access and utilization of RT

In the 2-year period just prior to the initiation of this study, 14 patients were treated with neaodjuvant RT at our institution. This value increased by 3-fold ($n = 52$) during the subsequent 2-year study period (**Fig. 3A**). In the 2-year period just prior to the initiation of this study, patients treated with neaodjuvant RT lived at a median distance of 11 miles from our facility, and there were no patients who traveled over 100 miles to receive treatment. During the study period, the size of the catchment area increased; enrolled study patients traveled a median 56 miles from their primary residence to receive treatment ($P < 0.0001$; **Fig. 3B**) and 40% of patients traveled over 100 miles to receive treatment.

Discussion

STS is a rare malignancy and treatment at high-volume sarcoma centers has been associated with improved outcomes (30–32). Conventional 5-week RT is known to have poor utilization among patients traveling a long distance (33, 34) and is a barrier to treatment at high-volume sarcoma centers. Shorter RT regimens are not only preferred by the patients (35), but they reduce travel burden and increase the access to care at high-volume centers. To date, limited data exist on the morbidity of shorter, condensed neoadjuvant RT for the treatment of STS of the extremities and trunk. In our single-institution phase II study, 5-day neoadjuvant RT to a total of 30 Gy was well-tolerated.

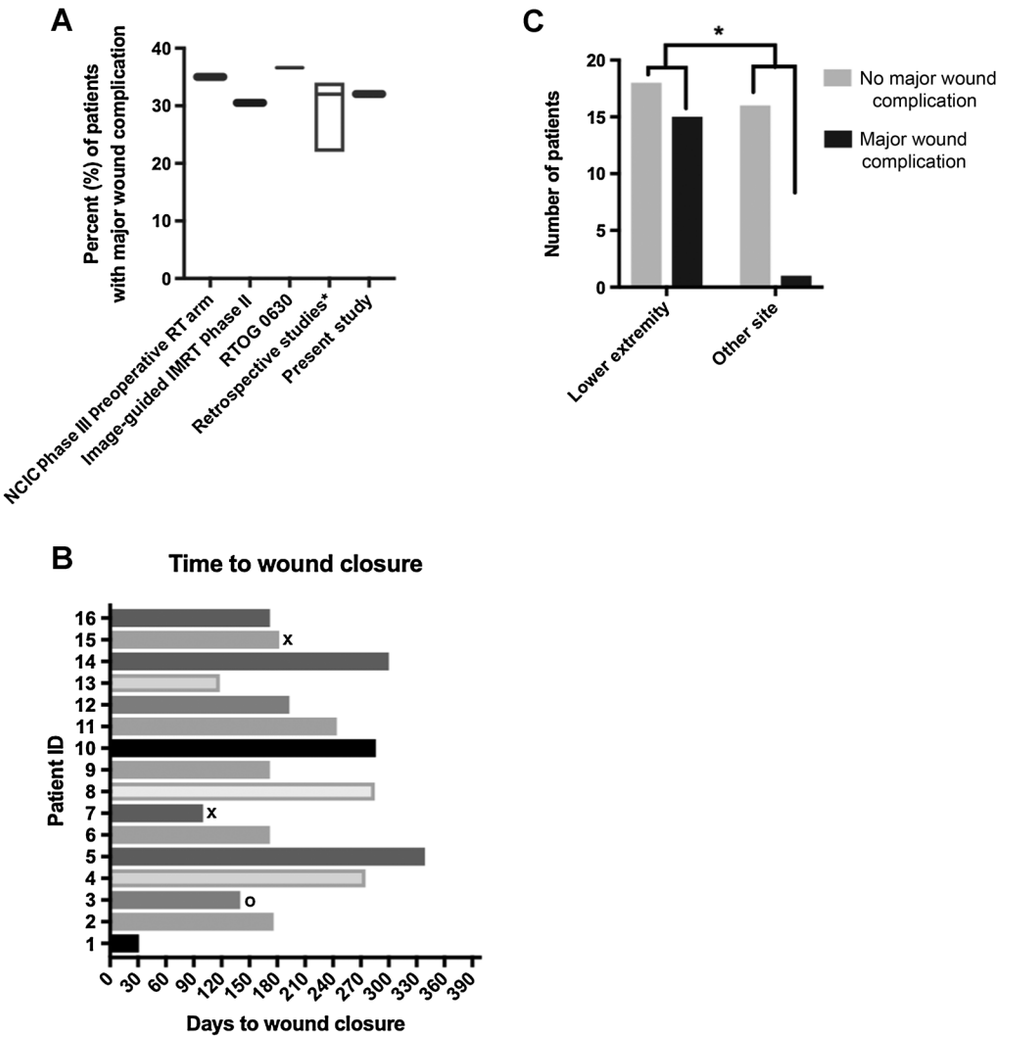

Figure 1.

Characteristics of major wound complications. **A,** The rate of major wound complications in this study, alongside major wound complication rates from prospective studies (preoperative RT arm of the NCIC randomized phase II study; image-guided IMRT phase II study of preoperative RT; and RTOG 0630; refs. 2, 5, 13) and modern retrospective studies (27–29). **B,** Time to wound closure in days. Patients who died (x) or underwent amputation (o) prior to wound closure are labeled. **C,** Frequency of wound complications according to lower extremity tumor location compared with other sites (upper extremity and trunk). *, $P < 0.05$ (likelihood ratio test).

Shorter, condensed RT regimens with higher daily dose historically have not been used due to concerns about toxicities. The rate of grade ≥2 radiation-associated toxicity (fibrosis, joint stiffness, or lymphedema) after median follow-up of 2 years was tolerable (16%). However, while these rates are favorable compared with the CAN-NCIC-SR2 study (2) against which our study was powered (16% vs. 37%), and comparable with a more recent multi-institutional phase II study using modern image-guided RT (5) that used 5-week neoadjuvant RT, longer follow-up is needed for a more robust comparison.

Table 3. Performance measures for prediction of major wound toxicity using germline biomarker and lower extremity tumor site.

	Acc	Specificity (TNR)	Sensitivity (TPR)	npv	ppv	AUC	F1
Classification Tree	0.692	0.650	0.733	0.750	0.757	0.757	0.696
RF	0.855	0.792	0.917	0.922	0.850	0.952	0.868
BT	0.792	0.667	0.917	0.875	0.770	0.798	0.827
LASSO-LR	0.780	0.667	0.892	0.917	0.767	0.839	0.790

Abbreviations: Acc, accuracy; npv, negative predictive value; ppv, positive predictive value.

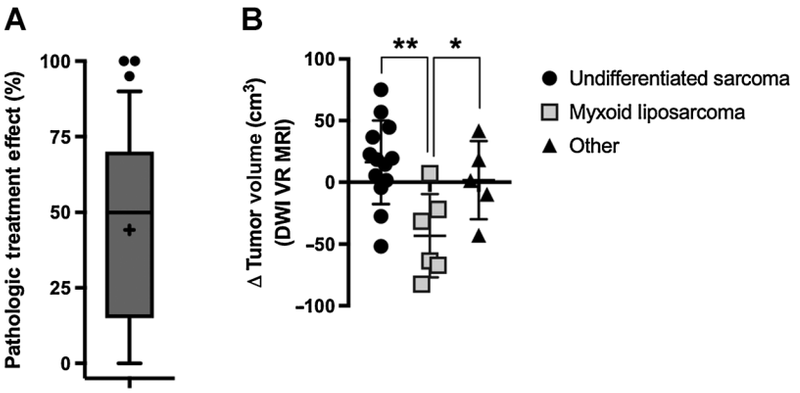

Figure 2.
Early surrogates for clinical response to 5-day neoadjuvant RT. **A,** Treatment effect as measured by the percentage of necrosis and hyalinization in the surgical specimen relative to the biopsy specimen in patients treated on the 5-day neoadjuvant RT protocol. Box plot represents 10th to 90th percentile, with mean (+), median, and outliers shown. **B,** Pre-to-post treatment change in tumor volume by diffusion-weighted ViewRay MRI for $n = 25$ patients with available data, according to histology (undifferentiated sarcoma, myxoid liposarcoma, and other; *, $P < 0.05$; **, $P < 0.005$ according to unpaired t test).

Another concern with RT dose intensification in the neoadjuvant setting was the rate of wound complications, which is the primary drawback of neaodjuvant RT for STS (2). The rate of major wound complications in our study (32%) is consistent with results from previous prospective and retrospective studies that used conventional 5-week neaodjuvant RT (22% to 37%; refs. 2, 5, 27). The pattern of wound complications was also consistent with what is observed using 5-week neaodjuvant RT, with a propensity for complications in the lower extremity (5). However, the median duration prior to wound closure was prolonged compared with a retrospective study of patients receiving conventionally fractionated RT (36).

Given the complex and multifactorial nature of wound complications (37), we examined whether specific clinical or dosimetric predictors could better identify patients at greatest risk. While clinical or dosimetric predictors other than lower extremity tumor location were not associated with wound toxicity, an exploratory analysis of germline SNPs in miRNA-binding sites suggests a role for patient-intrinsic biology as a factor in the development of wound complications after neaodjuvant RT. There are indeed germline differences in radiosensitivity of normal tissues between individuals (38–47). The majority of existing evidence on this topic centers on late skin and tissue response to RT of the breast. Our exploratory analysis identified a set of 19 germline alterations in miRNA-binding sites in genes with roles in immune and DNA damage response that, in combination with lower extremity tumor location, are associated with major wound complications. These data are limited by the sample size of our phase II study, and validation of this set is necessary and ongoing. Nonetheless, these data highlight the potential for using patient germline features to stratify the risk of major wound complications prior to treatment. For these at-risk patients, more aggressive dosimetric constraints, consideration of adjuvant RT, alternative surgical approaches, or changes in postsurgical wound care may be warranted.

We observed both an increase in the number of patients treated with neoadjuvant RT and the distance traveled by patients to our high-volume center that coincided with study initiation. These results are consistent with prior studies demonstrating that shorter RT regimens are preferred by patients (35) and suggest that 5-day neoadjuvant RT would increase the utilization of neaodjuvant RT and access to care at high-volume sarcoma centers.

While local control results have yet to mature, early results are promising with two (5%) local failures among 35 evaluable patients with at least 2 years follow-up. The pathologic treatment effect observed in our study may serve as an early indicator of the antitumor efficacy of this regimen. Because the time interval from treatment initiation to surgery in our study is shorter, we anticipated pathologic response rates would be slightly lower than results from studies using standard 5-week neoadjuvant RT (19, 48) or studies using neoadjuvant chemoradiation (49). As a secondary early indicator of clinical efficacy, we evaluated longitudinal diffusion-weighted MRI imaging of a subset of 25 patients. In the brief period between radiation and surgery (median 28 days), a brisk decrease in DWI tumor volume was noted in

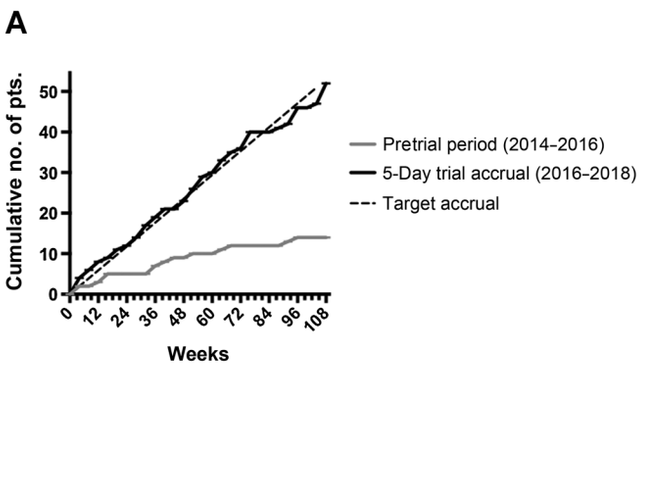

Figure 3.
Impact of 5-day protocol on utilization of neoadjuvant RT at a high-volume sarcoma center. **A,** Cumulative accrual of patients to the phase II prospective study of 5-day neoadjuvant RT, shown alongside target accrual rate and accrual of patients treated with standard 5-week neoadjuvant RT alone during the 2-year period preceding study initiation. **B,** Distance traveled to our high-volume sarcoma center for neoadjuvant RT by patients enrolled on the 5-day phase II study and by patients in the 2-year period preceding study initiation (****, $P < 0.0001$; Mann–Whitney test).

patients with myxoid liposarcoma, a histologic subtype characterized by inherent radiosensitivity, supporting the antitumor efficacy of the 5-day radiation dose and fractionation.

Although we routinely incorporate neoadjuvant systemic therapy for high-risk extremity and trunk STS, systemic therapy is not always recommended by our multidisciplinary conference due to age, comorbidities, clinicopathologic characteristics, and patient preference. The data presented here are not generalizable to patients with planned neoadjuvant or adjuvant chemotherapy. We are currently accruing to an expansion cohort of this phase II study to evaluate the safety of a 5-day neoadjuvant RT regimen in combination with systemic therapy.

In conclusion, our results demonstrate that 5-day neoadjuvant RT in extremity and trunk STS shows a favorable radiation toxicity profile at a median follow-up of 29 months and an acceptable rate of major wound complications. Importantly, we found a statistically significant increase in the number of patients treated with this short course of neoadjuvant RT at our high-volume sarcoma treatment center, which suggests this protocol could improve neoadjuvant RT use and access to care of STS at high-volume sarcoma centers. Early local control, pathologic treatment effect, and imaging outcomes support the bioactivity of this dose and fractionation scheme, although longer follow-up is needed. Finally, we identified a putative germline biomarker profile for major wound complications; further validation of this profile may guide safer utilization of neoadjuvant RT. In summary, 5-day neoadjuvant RT is a safe, effective, and accessible alternative for patients with localized STS of the extremity and trunk that warrants evaluation in a larger multi-institutional study.

Disclosure of Potential Conflicts of Interest

Y. Yang reports receiving speakers bureau honoraria from ViewRay. B. Chmielowski is an employee/paid consultant for Merck, Genetech/Roche, Iovance, HUYA, Compugen, Array, Regeneron, Biothera, Janssen, Novartis, IDEAYA, Epizyme, and Deciphera, reports receiving commercial research grants from Lilly, Incyte, AstraZeneca, Bristol-Myers Squibb, Macrogenics, Array, EMD Serono, Daiichi Sankyo, Merck, Karyopharm, Infinity, Rgenix, Immunocore, Biothera, Aeglea, Advenchen, Idera, Neon, Xencor, Compugen, FLX Bio, Iovance, and PACT Pharm, and speakers bureau honoraria from Regeneron, Sanofi, Janssen, and Genentech/Roche. A.S. Singh is an employee/paid consultant for Daiichi-Sankyo, Deciphera, Eisai, Roche, and Blueprint Medicines, reports receiving commercial research grants from Eli Lilly, Deciphera, Blueprint Medicines, and Nanocarrier, speakers bureau honoraria from Novartis, OncLive, and Eli Lilly, and holds ownership interest (including patents) in Certis Oncology Solutions. J.B. Weidhaas is an advisory board member/unpaid consultant for MiraDx. F.C. Eilber holds ownership interest (including patents) in and is an advisory board member/unpaid consultant for Certis Oncology. No potential conflicts of interest were disclosed by the other authors.

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