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Scientific Article

The Correlation Between Lymphocyte Nadir and Radiation Therapy for Soft Tissue Sarcoma: Defining Key Dosimetric Parameters and Outlining Clinical Significance

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Purpose: The objectives of this study were to identify key dosimetric parameters associated with postradiation therapy lymphopenia and uncover any effect on clinical outcomes.

Methods and Materials: This was a retrospective review of 69 patients (between April 2010 and January 2023) who underwent radiation therapy (RT) as a part of curative intent for soft tissue sarcoma (STS) at a single academic institution. All patients with treatment plans available to review and measurable absolute lymphocyte count (ALC) nadir within a year after completion of RT were included.

Results: Median follow-up was 22 months after the start of RT. A decrease in lymphocyte count was noted as early as during treatment and persisted at least 3 months after the completion of RT. On multivariable linear regression, the strongest correlations with ALC nadir were mean body dose, body V10 Gy, mean bone dose, bone V10 Gy, and bone V20 Gy. Five-year overall survival was 60% and 5-year disease-free survival was 44%. Advanced T-stage, chemotherapy use, use of intensity-modulated RT, lower ALC nadir, and the development of grade ≥2 lymphopenia at nadir were associated with worse overall survival and disease-free survival.

Conclusions: Post-RT lymphopenia was associated with worse outcomes in STS. There were associations between higher body V10 Gy and bone V10 Gy and lower post-RT ALC nadir, despite the varying sites of STS presentation, which aligns with the well-known radiosensitivity of lymphocyte cell lines. These findings support efforts to reduce treatment-related hematopoietic toxicity as a way to improve oncologic outcomes. Additionally, this study supports the idea that the effect of radiation on lymphocyte progenitors in the bone marrow is more significant than that on circulating lymphocytes in treatments with limited involvement of the heart and lung.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Introduction

The goal of radiation therapy (RT) in general is the balance between sufficient dose for tumor cell kill while limiting toxicity to organs at risk. Lymphocytes are particularly radiosensitive immune cells that play a vital role in both anti-infection as well as antitumor response.[1,2] There has been a recent interest in understanding the effects of radiation on the immune cell populations, especially with increasing use of immunotherapy treatments, which rely on normal lymphocyte function.

Prior studies have shown that pretreatment lymphocyte counts are associated with worse outcomes in numerous malignancies.[3] More recently, radiation-induced lymphopenia (RIL) has been correlated with worse survival outcomes in various solid tumors.[4-9] It is theorized that lymphocyte depletion compromises host antitumor response leading to worse treatment response.[4] This idea is supported by findings that show levels of tumor-infiltrating lymphocytes in pathologic samples after treatment are associated with worse survival outcomes.[10-13] The incidence and effects of RIL are less known in soft tissue sarcoma (STS).

STS presents a unique challenge in that the location of presentation is heterogenous, with the most common being in the extremities followed by the retroperitoneum, trunk, and head and neck regions.[14] Jin et al[15] developed a model to estimate radiation dose to circulating blood cells, which takes into account large blood-containing organs such as lung, heart, body, and vessels. Their model was validated using patients enrolled on Radiation Therapy Oncology Group 0617, a clinical trial that showed worse survival in patients with locally advanced lung cancer who were treated to a higher RT dose.[16] Their findings showed that higher dose to circulating blood was significantly and independently associated with worse overall survival (OS) and local progression-free survival. Work by Mell et al[17] also found higher bone marrow volume receiving 10 Gy to be associated with increased rates of grade ≥2 hematologic toxicity in patients undergoing RT for cervical cancer. There may be additional dosimetric factors associated with RIL in STS given the generally lower circulating blood radiation doses and decreased use of concurrent chemotherapy compared with thoracic and gynecologic malignancies.

Methods and Materials

Patient selection

Institutional review board approval was collected before the start of this study. Patients who underwent curative management of STS at our institution between September 2009 and January 2023 were retrospectively reviewed. All patients received RT with neoadjuvant, adjuvant, or definitive intent. Patients were excluded if they did not have RT at our institution or if they did not have complete blood cell count within 0 to 14 months after completion of RT. Patients underwent staging by the American Joint Committee on Cancer Staging (8th ed.) criteria.

Treatment

Treatment was a combination of surgery with neoadjuvant or adjuvant RT, as well as definitive RT alone. Chemotherapy indications were advanced stage disease or rhabdomyosarcoma histology. The median total RT dose was 50 Gy (range, 39-78 Gy) delivered in conventional 1.8 to 2 Gy fractions daily. Three dimensional conformal was more often used before increased intensity modulated RT (IMRT) utilization starting in 2015. In cases involving extremities, margins of 3 to 4 cm were employed in the superior and inferior directions, whereas 1- to 1.5-cm margins were used radially.

Follow-up and hematologic assessments

Follow-up consisted of physical examination, complete blood counts, and radiologic assessments done at provider discretion. Absolute lymphocyte counts (ALC) were assessed before start of RT (baseline), during RT (midtreatment), between 0 to 4 months post-RT (3 months), between 5 to 8 months post-RT (6 months), and between 9 to 14 months post-RT (12 months). ALC nadir was defined as lowest lymphocyte level post-RT within 0 to 14 months after completion of RT. Lymphopenia was graded by Common Terminology Criteria for Adverse Events v5.0 with grade 1 (800-1000 cells/μL), grade 2 (500-799 cells/μL), grade 3 (250-499 cells/μL), and grade 4 (<250 cells/μL).

Dosimetric analysis

Dosimetric data were calculated using RT plans. Organ volumes were contoured individually for body, bone, heart, and lung to calculate dose-volume histograms. Planning treatment volume (PTV) as well as mean dose and volume receiving 10, 20, and 30 Gy (V10, V20, V30 Gy) for individual organs were calculated.

Statistical analysis

Paired *t* tests were used to compare baseline ALC with follow-up ALC measurements, and effect size was estimated with Cohen's d. OS was defined as time from RT start to death. Disease-free survival (DFS) was defined as time from RT start to disease recurrence, progression, or

death. Associations between lymphopenia and survival outcomes were modeled with univariate and multivariate Cox proportional hazards regression. Additionally, a mixed effects Cox proportional hazards model was used to account for serial ALC measurement and patient-level random effects. Clinical and dosimetric parameters were evaluated for associations with lymphocyte nadir using Spearman rank correlation coefficient and multivariable linear regression. Receiver operating characteristics analysis was used to determine dosimetric cutoff values for predicting ALC nadir. Statistical analyses were performed using SPSS version 24.0 (IBM Corp, Armonk, NY) and R version 4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographics

Two hundred eighty-five patients with STS were reviewed, and 69 patients met criteria to be included in this study. Baseline demographic and disease characteristics are summarized in Table 1. Median age was 59 years (range, 23-89 years). T1 disease was present in 15% of patients (n = 10), T2 in 45% (n = 31), T3 in 22% (n = 15), and T4 in 19% (n = 13). There were 2 patients with node-positive disease. Grade 1 disease was found in 12% of patients (n = 8), grade 2 in 8.7% (n = 6), and grade 3 in 80% (n = 55). The most common histologies were liposarcoma (26%, n = 18) and undifferentiated pleomorphic sarcoma (22%, n = 15). Chemotherapy was given to 45%

Table 1 Baseline patient and disease characteristics

Characteristic	Value
Age, median (range), y	59 (23-89)
Follow-up, median (range), mo	22 (3-142)
Sex, no. (%)	
Male	41 (59%)
Female	28 (41%)
Location, no. (%)	
Head/neck	16 (23%)
Upper/lower extremity	44 (64%)
Trunk	9 (13%)
Tumor staging, no. (%)	
T1	10 (15%)
T2	31 (45%)
T3	15 (22%)
T4	13 (19%)
Nodal staging, no. (%)	
N0	67 (97%)
N1	2 (2.9%)
Grade, no. (%)	
Grade 1	8 (12%)
Grade 2	6 (8.7%)
Grade 3	55 (80%)
Histology, no. (%)	
Angiosarcoma	6 (8.7%)
Carcinosarcoma	1 (1.4%)
Clear cell sarcoma	1 (1.4%)
Leiomyosarcoma	8 (12%)
Liposarcoma	18 (28%)
Dedifferentiated liposarcoma	2 (2.9%)
Myxoid liposarcoma	11 (16%)
Pleomorphic liposarcoma	4 (5.8%)
Well-differentiated liposarcoma	1 (1.4%)
Malignant peripheral nerve sheath tumor	2 (2.9%)
Myxofibrosarcoma	1 (1.4%)
Pleomorphic dermal sarcoma	3 (4.3%)
Rhabdomyosarcoma	4 (5.8%)
Spindle cell sarcoma	4 (5.8%)
Synovial sarcoma	4 (5.8%)
Undifferentiated pleomorphic sarcoma	15 (22%)
Unknown histology	2 (2.9%)
Chemotherapy, no. (%)	31 (45%)
Surgery, no. (%)	59 (86%)
Radiation technique	
3DC, no. (%)	22 (32%)
IMRT, no. (%)	47 (68%)
Total RT dose, median (range), Gy	52 (39-78)
PTV, median (range), cc	840 (48-13,981)
ALC, median (range), cells/μL	
Pretreatment	1700 (600-5100)
Midtreatment	600 (30-2200)
3 mo post-RT	900 (40-2300)
6 mo post-RT	1000 (100-4700)
12 mo post-RT	1300 (130-2300)
ALC nadir	1000 (40-2300)

Abbreviations: 3DC = 3-dimensional conformal; ALC = absolute lymphocyte count; IMRT = intensity modulated RT; PTV = planning treatment volume; RT = radiation therapy.

(*continued on next page*)

(n = 31) of patients. Surgery was performed on 86% (n = 59) of patients. Median total RT dose was 50 Gy (range, 39-78 Gy) given in conventional 1.8 to 2 Gy fractions daily. IMRT was used in 68% (n = 47).

ALC nadir

Complete blood cell counts for ALC nadir analysis were available for 60 patients at pretreatment, 27 patients at midtreatment, 53 patients at 3 months post-RT, 46 patients at 6 months post-RT, 31 patients at 12 months post-RT, and 69 patients at ALC nadir. Median pretreatment, midtreatment, 3 months post-RT, 6 months post-RT, 12 months post-RT, and ALC nadir lymphocyte counts were 1700 cells/μL (range, 600-5100 cells/μL), 600 cells/μL (30-2200 cells/μL), 900 cells/μL (40-2300 cells/μL), 1000 cells/μL (100-4700 cells/μL), 1300 cells/μL (130-2300 cells/μL), and 1000 cells/μL (40-2300 cells/μL), respectively (Fig. 1).

ALC was decreased as early as during midtreatment and persisted until 3 months post-RT as reflected by larger effect sizes (d > 0.8) noted at midtreatment and 3 months post-RT timepoints (Fig. 1). Fifty-nine of 69 patients (86%) reached ALC nadir within 6 months post-RT. Distribution of lymphopenia toxicity at ALC nadir was 9 (13%) with grade 1, 7 (10%) with grade 2, 12 (17%) with grade 3, and 7 (10%) with grade 4 (Fig. E1). Long-term ALC follow-up was available for 19 of the 25 patients who developed grade ≥2 lymphopenia. Among these 19 patients, 9 experienced a recovery in their lymphocyte counts (ALC ≥ 1000 cells/μL), with a median time to recovery of 9.5 months (range, 1.7-19 months).

Factors associated with development of grade ≥3 lymphopenia included head and neck primary disease, T3-T4 versus T1-T2 disease (odds ratio [OR], 6.2; 95% CI, 1.9-21), receipt of chemotherapy (OR, 7; 95% CI, 2.0-25), and use of IMRT technique (OR, 12; 95% CI, 1.5-96). Disease grade, surgery, definitive versus neoadjuvant or adjuvant RT goal, RT dose, and PTV were not significantly associated.

Dosimetric parameters

Strongest correlations with lower ALC nadir were increased mean body dose (r_s = 0.39; P < .01), body V10 Gy (r_s = 0.36; P < .01), mean bone dose (r_s = 0.51; P < .01), bone V10 Gy (r_s = 0.58; P < .01), and bone V20 Gy (r_s = 0.56; P < .01) (Table 2). Other statistically significant correlations included body V20 Gy, body V30 Gy, and bone V30 Gy. Lung and heart parameters as well as total dose did not show significant correlations. PTV approached significance (r_s = 0.22; P = .07).

On multivariable linear regression, controlling for surgical resection and chemotherapy use, strongest correlations with ALC nadir were body V10 Gy (β = 0.38; P < .01), bone V10 Gy (β = 0.49; P < .01), and bone V20 Gy (β = 0.46; P < .01) (Table 2). Other statistically significant correlations included mean body dose, body V20 Gy, body V30 Gy, mean bone dose, and bone V30 Gy. Figure 2 shows an axial image of a treatment plan for a patient who developed grade 3 lymphopenia.

Patients with an ALC nadir < 1000 cells/μL exhibited worsened OS compared with those with an ALC nadir ≥ 1000 cells/μL (hazard ratio [HR], 3.2; 95% CI, 1.1-9.0).

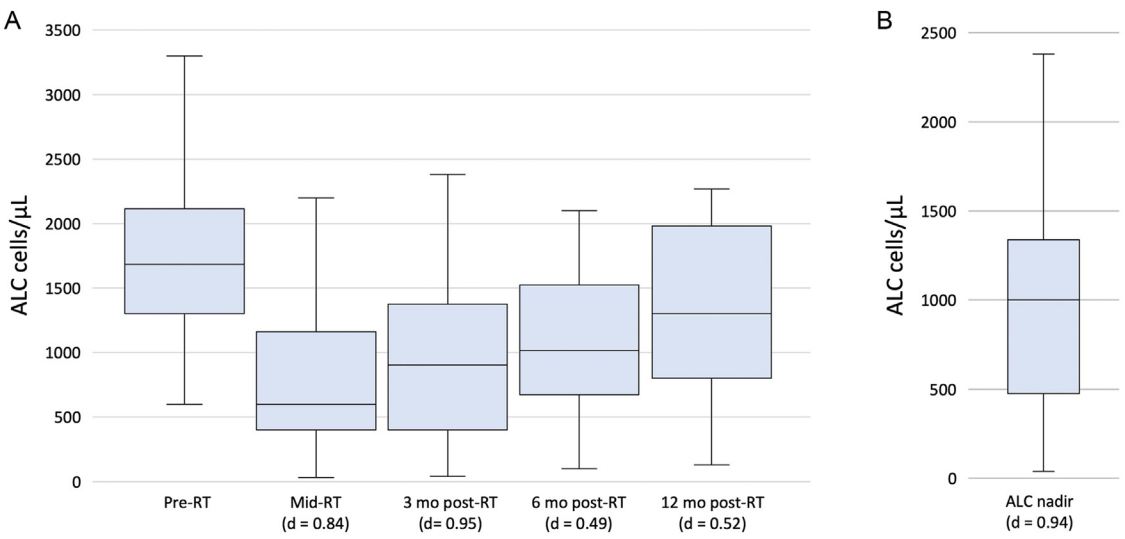

Figure 1 Box and whisker plot showing absolute lymphocyte count at pretreatment, midtreatment, 3 months post-RT, 6 months post-RT, 12 months post-RT, and absolute lymphocyte count nadir timepoints. The lines inside the boxes represent median, the boxes represent the interquartile range, and the whiskers represent the 95% range.
Abbreviations: ALC = absolute lymphocyte count; RT = radiation therapy.

Table 2 Spearman rho correlation and linear regression between clinical and dosimetric parameters and absolute lymphocyte count nadir

Parameter	Correlation, r_s	Linear regression, β	
		Univariable	Multivariable
T3-T4 vs T1-T2	-	0.44*	0.29†
High-grade disease	-	0.19	-
Chemotherapy	-	0.45*	0.43*
Surgery	-	−0.23	−0.10
Definitive vs neoadjuvant/adjuvant RT	-	0.21	-
IMRT vs 3DC	-	0.38*	0.31*
Total RT dose	0.21	0.21	-
PTV	0.22	0.24	-
Body mean dose	0.39*	0.39*	0.27†
Body V10	0.36*	0.36*	0.38*
Body V20	0.33*	0.33*	0.36*
Body V30	0.30†	0.29†	0.32*
Bone mean dose	0.51*	0.50*	0.37*
Bone V10	0.58*	0.58*	0.49*
Bone V20	0.56*	0.55*	0.46*
Bone V30	0.47*	0.44*	0.36†
Heart mean dose	−0.15	−0.50	-
Heart V10	−0.23	−0.029	-
Lung mean dose	0.27	0.26	-
Lung V10	0.20	0.15	-

Abbreviations: 3DC = 3-dimensional conformal; IMRT = intensity modulated radiation therapy; PTV = planning treatment volume; RT = radiation therapy.
*$P < .01$.
†$P < .05$.

Receiver operating characteristics analysis was used to determine the predictive accuracy of dosimetric parameters for an ALC nadir < 1000 cells/μL. The area under the curves for mean body dose, body V10 Gy, mean bone dose, bone V10 Gy, and bone V20 Gy were statistically significant, with values of 0.68, 0.70, 0.76, 0.78, and 0.79, respectively (Fig. E2). Optimal cutoff values were determined to be a mean body dose of 7.48 Gy, body V10 Gy of 3355 cc, mean bone dose of 6.57 Gy, bone V10 Gy of 231 cc, and bone V20 Gy of 178 cc (Table E1).

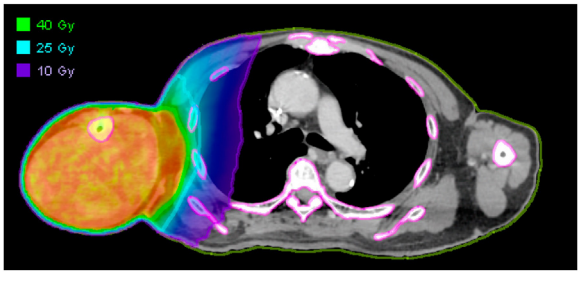

Figure 2 Axial computed-tomography image of radiation treatment plan showing dose wash and isodose lines for a patient who developed grade 3 lymphopenia. Ten Gy isodose line is in purple. Bone is contoured in magenta and body is contoured in light green.

Survival outcomes

Median follow-up was 22 months (range, 3-142 months) after start of RT. Median OS was 84 months (95% CI, 57-110). Five-year OS was 60%. Male sex, head and neck primary disease, chemotherapy use, and use of IMRT technique were associated with worse OS on Cox proportional hazard regression (Table 3). ALC at 3 months post-RT, 6 months post-RT, 12 months post-RT, and ALC nadir as well as development of grade ≥2 lymphopenia at ALC nadir were associated with worse OS. Pretreatment and midtreatment ALC were not associated with worse OS. On multivariate regression, accounting for chemotherapy use and surgical resection, ALC at 3

Table 3 Univariate Cox proportional hazards regressions of clinical factors associated with survival outcomes

Clinical factor	HR (95% CI)	
	Overall survival	Disease-free survival
Age	1.02 (0.99-1.0)	1.0 (0.98-1.0)
Female vs male	0.32 (0.11-0.98)*	0.38 (0.18-0.83)*
T3-T4 vs T1-T2	2.8 (1.1-7.2)*	3.0 (1.5-6.0)†
High-grade disease	24 (0.032-19,000)	26 (0.34-1900)
HN vs ext, trunk	2.0 (1.2-3.3)†	1.4 (0.93-2.1)
Chemotherapy	4.6 (1.5-14)†	5.6 (2.5-13)†
Surgery	0.36 (0.12-1.1)	0.39 (0.17-0.91)*
Definitive vs neoadjuvant/adjuvant RT	2.7 (0.74-9.5)	1.4 (0.50-4.1)
IMRT vs 3DC	3.3 (1.0-11)*	3.0 (1.2-7.6)*
RT total dose	1.0 (0.98-1.1)	1.0 (0.97-1.1)
ALC (cells/μL)		
Pretreatment ALC	1.0 (0.95-1.1)	1.0 (0.99-1.1)
Midtreatment ALC	1.1 (0.95-1.2)	1.1 (0.95-1.2)
3 mo post-RT ALC	1.3 (1.1-1.5)†	1.2 (1.1-1.3)†
6 mo post-RT ALC	1.2 (1.1-1.4)†	1.1 (1.0-1.2)†
12 mo post-RT ALC	1.2 (1.0-1.3)*	1.1 (1.0-1.2)
ALC nadir	1.2 (1.1-1.4)†	1.2 (1.1-1.2)†
G2-G4 lymphopenia	4.4 (1.6-12)†	3.5 (1.7-7.0)†
G3-G4 lymphopenia	5.0 (1.9-14)†	3.5 (1.7-7.2)†

Abbreviations: 3DC = 3-dimensional conformal; ALC = absolute lymphocyte count; HN = head and neck; HR = hazard ratio; IMRT = intensity modulated radiation therapy; RT = radiation therapy.
*$P < .05$.
†$P < .01$.

months post-RT (HR, 1.2; 95% CI, 1.0-1.4), 6-months post-RT (HR, 1.2; 95% CI, 1.1-1.4), 12-months post-RT (HR, 1.2; 95% CI, 1.0-1.3), ALC nadir (HR, 1.2; 95% CI, 1.0-1.3), and development of grade ≥2 lymphopenia at ALC nadir (HR, 2.5; 95% CI, 1.2-5.2) remained statistically significantly associated with OS. Kaplan-Meir curves of OS stratified by development of grade ≥2 lymphopenia are shown in Fig. 3A.

Median DFS was 20 months (95% CI, 0-76 months). Five-year DFS was 44%. Male sex, T3-T4 versus T1-T2 disease, chemotherapy use, lack of surgical resection, and use of IMRT technique were associated with worse DFS (Table 3). Three months post-RT, 6months post-RT, and ALC nadir as well as development of grade ≥2 lymphopenia at ALC nadir were associated with worse DFS. On multivariate regression, 3 months post-RT ALC (HR, 1.1; 95% CI, 1.0-.13), 6 months post-RT ALC (HR, 1.1; 95% CI, 1.0-1.2), ALC nadir (HR, 1.1; 95% CI, 1.0-1.2), and the development of grade ≥2 lymphopenia at ALC nadir (HR, 2.5; 95% CI, 1.2-5.2) remained statistically significantly associated with DFS. Kaplan-Meir curves of DFS stratified by development of grade ≥2 lymphopenia are shown in Fig. 3B.

After accounting for chemotherapy use, surgical resection, and pretreatment ALC on mixed effects multivariate regression, ALC nadir remained significantly associated with both OS ($P = .006$) and DFS ($P = .01$).

Discussion

We found that patients with STS treated with conventional radiation were at high risk for lymphopenia. Grade ≥2 lymphopenia was seen in 36% of patients in our cohort after radiation, and the most highly associated dosimetric parameters were bone V10 Gy and body V10 Gy. The clinical significance of lymphopenia were associations with OS and DFS, which were seen on multivariate analysis adjusting for chemotherapy use and surgical resection.

Our work contributes to the increasing evidence that RIL can have adverse consequences on treatment outcomes in solid tumor malignancies, although this is the first study to our knowledge in STS.[4,9] In contrast to other studies, we did not find survival outcomes to be influenced by lower pretreatment ALC.[18-21] These results support the monitoring of post-RT blood work as a

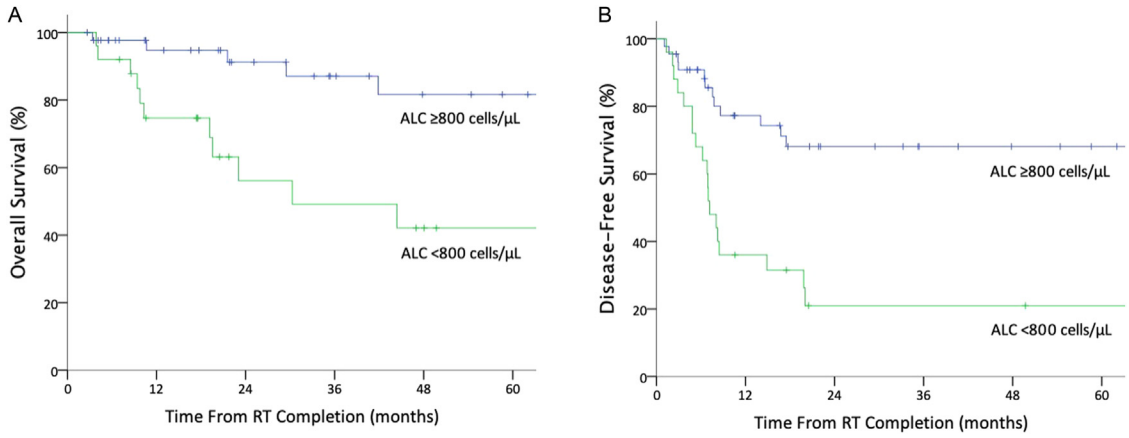

Figure 3 Kaplan-Meier curves of (A) overall survival and (B) disease-free survival for patients stratified by development of grade ≥2 lymphopenia at absolute lymphocyte count nadir. *Abbreviations*: ALC = absolute lymphocyte count; RT = radiation therapy.

commonly available and easily employed biomarker for treatment response and prognosis.

A decrease in lymphocyte count was noted as early as midtreatment, with the majority of patients reaching ALC nadir within 6 months post-RT. ALC at 6 and 12 months post-RT remained lower than pretreatment levels, and lymphopenia at these timepoints remained associated with mortality. Among the patients who developed grade ≥2 lymphopenia and eventually recovered their lymphocyte counts, the median time to recovery was 9.5 months. These findings suggest a chronic component to hematopoietic injury may be contributing to worsened survival. RT is known to cause long-term sequalae in lymphoid-containing tissues and blood vessels leading to chronic lymphopenia.[22] In STS, the lag to lymphocyte improvement is likely related to the detrimental effect on bone marrow progenitor cells, rather than lymphocytes already released into circulation. Interestingly, the model proposed by Jin et al[15] was recently adapted to explain how ultrahigh dose-rate FLASH RT might provide a means for limiting toxicity to circulating lymphocytes because of the minimal exposure of a given blood volume.[23] However, the limited involvement of adaptive immunity in FLASH-irradiated tumor growth delay cast doubts on this model, and current work here argues that total dose to the hematopoietic stem cell compartments has a larger effect on clinical outcome than radiation-induced ablation of circulating lymphocytes.

The detrimental association between lymphopenia and DFS is not necessarily self-evident. One hypothesis is that RIL may limit the ability to give additional systemic therapy or even decrease the efficacy of additional therapies. Some work has shown RIL may hinder the effectiveness of treatments that rely on a functional immune system, such as immune checkpoint inhibitors.[24-27]

The dosimetric parameters associated with lower ALC nadir included both mean and volumetric doses (V10 Gy) to the body and bone. These findings are consistent with the known radiosensitivity of lymphocyte cell lines and suggest that radiation effects on lymphocyte progenitors in the bone marrow may dominate those of circulating lymphocytes for treatments with minimal contribution to heart and lung.[2,15] Prior research has demonstrated that V10 Gy to pelvic bone marrow is a predictor of worse hematologic toxicity in patients receiving chemoradiation for cervical and anal cancers, and integral body dose is associated with worse lymphopenia in patients undergoing RT for lung cancer.[17,28,29]

This work supports ongoing initiatives to develop constraints to lymphoid-rich organs with the goal of improving efficacy of RT with immune checkpoint inhibitors.[30] For example, a phase 1 study of stereotactic body RT in non-small cell lung cancer is currently evaluating the use of a lymphodepletion- predictive algorithm to decrease circulating blood and lymphocyte dose.[31] Other efforts have focused on novel drug therapy approaches to reduce RIL. For example, an ongoing phase 1/2 clinical trial of chemoradiation for high-grade glioma is looking at the safety and tolerability of a recombinant interleukin-7 drug as well as its potential to increase ALC.[32] The current study points to a clinical need and opportunity for improved radiation and drug therapy investigations in STS. Such techniques that may be able to lower the body V10 Gy and bone V10 Gy include static field IMRT and proton beam therapy.

This study is limited by its small sample size and retrospective design, which is susceptible to selection bias. Surveillance laboratory work and imaging were ordered at provider discretion as part of normal standard of care. Additionally, there was significant heterogeneity within the patient population given differences in disease characteristics and presentation as well as treatment used, including chemotherapy regimens, surgical approaches, and differences in standard practices over 2 decades. In

addition, further validation is necessary as we did not consider the dose to other lymphoid-rich tissues such as the spleen and lymph nodes as well as to other circulating lymphocyte-containing tissues such as large blood vessels that could also contribute to the development of lymphopenia.[19,33] Despite the relative rarity and diversity of presentation in STS, we made efforts to create a well-designed study through the implementation of clear inclusion criteria and multivariable analysis.

Conclusion

Our study supports the use of post-RT blood counts as a means of improving prognostication as well as efforts to reduce treatment-related hematopoietic toxicity to improve oncologic outcomes. Further work to mitigate the effects of RIL include modification of RT volumes, fractionation, lowering dose to body and bone marrow, dose-rate modulation, and using techniques to lower integral dose for select patients. Potential dosimetric constraints to be considered in future studies include mean body dose < 7.48 Gy, body V10 Gy < 3355 cc, mean bone dose < 6.57 Gy, and bone V10 Gy < 231 cc. Nonetheless, RIL and lower lymphocyte nadir may help identify patients at high risk for recurrence.

Disclosures

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.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101309.

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