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The Interval Between Preoperative Radiation and Surgery Is Not Associated with Overall Survival for Soft-tissue Sarcomas: An Analysis of the National Cancer Database

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Abstract

Background Most cancer centers prefer preoperative radiation therapy (preRT) over postoperative therapy to treat soft-tissue sarcoma (STS) to limit long-term fibrosis, joint stiffness, and edema. Surgery is often delayed after preRT to allow for tissue recovery and to reduce wound complications. However, the association between the time interval between preRT and surgery and survival is unknown.

Questions/purposes (1) What factors are associated with the preRT-surgery interval in patients with STS? (2) Is the preRT-surgery interval associated with overall survival?

Methods The National Cancer Database, a nationwide registry that includes 70% of all new cancers in the United States with 90% follow-up, was reviewed to identify 6378 patients who underwent preRT and surgical resection for a localized extremity or pelvic STS from 2004 to 2014. Patients were excluded if they had lymphatic or metastatic disease at diagnosis (23%; n = 1438), underwent neoadjuvant chemotherapy (24%; 1531), were missing vital status (8%; 487), had chemosensitive histologies (9%; 603), underwent radiation other than external beam (1%; 92), were missing preRT-surgery interval (1%; 45), or had a preRT-surgery interval greater than 120 days (< 1%; 6). A total of 2176 patients were included for analysis, with a mean preRT-surgery interval of 35 ± 16 days. A multiple linear regression model was generated to assess demographic, clinicopathologic, and treatment characteristics associated with the preRT-surgery interval. A Kaplan-Meier survival analysis was then conducted, stratified by the preRT-surgery interval, to assess survival over 10 years. Finally, a multivariate Cox regression analysis model was constructed to further evaluate the association between the preRT-surgery interval and overall survival, adjusted for demographic, clinicopathologic, and treatment characteristics.

Results A longer preRT-surgery interval was associated with higher age (β = 0.002 per year [95% CI 0.0 to 0.004]; p = 0.026), tumor location in the pelvis (compared with the lower extremity; β = 0.15 [95% CI 0.082 to 0.22]; p < 0.001), and malignant peripheral nerve sheath tumor subtype (compared with undifferentiated pleomorphic sarcoma; β = 0.17 [95% CI 0.044 to 0.29]; p = 0.008). A shorter preRT-surgery interval was associated with higher facility volume (β = -0.002 per case [95% CI -0.003 to -0.002]; p = 0.026) and higher tumor stage (compared with Stage I; β = -0.066 [95% CI -0.13 to -0.006]; p = 0.03 for Stage II; β = -0.12 [95% CI -0.17 to -0.065]; p < 0.001 for Stage III). The 5-year overall survival rates were similar across all preRT-surgery interval groups: less than 3 weeks

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Each author certifies that his institution waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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(66% [95% CI 60 to 72]), 3 to 4 weeks (65% [95% CI 60 to 71]), 4 to 5 weeks (65% [95% CI 60 to 71]), 5 to 6 weeks (66% [95% CI 60 to 72]), 6 to 7 weeks (63% [95% CI 54 to 72]), 7 to 9 weeks (66% [95% CI 58 to 74]), and more than 9 weeks (59% [95% CI 48 to 69]). Over 10 years, no difference in overall survival was observed when stratified by the preRT-surgery interval (p = 0.74). After controlling for potentially confounding variables, including age, sex, Charlson/Deyo comorbidity score, histology, tumor size, stage and surgery type, the preRT-surgery interval was not associated with survival (hazard ratio = 1 per day [95% CI 1 to 1]; p = 0.88).

Conclusion With the numbers available, this study demonstrates that a delay in surgery up to 120 days after radiation is not associated with poorer survival. Therefore, clinicians may be able to delay surgery to minimize the risks of wound complications and modifiable comorbidities without affecting overall survival.

Level of Evidence Level III, therapeutic study.

Introduction

Treatment of extremity soft-tissue sarcoma (STS) formerly consisted of surgery alone, often in the form of amputation [8]. In the 1980s, the addition of radiation therapy expanded the indications for limb-sparing surgery, and many studies have established the role of radiation to decrease local recurrence [15, 20, 31, 34, 40, 44, 56, 60]. Direct comparisons of preoperative radiation therapy (preRT) and postoperative radiation therapy suggest that the delay in surgery to deliver preRT is safe and does not adversely affect local recurrence or survival [3, 36, 37, 61]. The advantages of preRT include smaller treatment volumes at lower doses, clearer delineation of tumor volumes, oxygenated tumors susceptible to free radical formation, and lower rates of permanent fibrosis, joint stiffness, and extremity edema [10, 11, 24, 27, 36, 50, 60, 61]. The major disadvantage of preRT is a higher rate of short-term wound complications [4, 10, 19, 28, 36, 38, 43, 50, 53, 62]. A recent analysis of national trends in the United States demonstrated a shift toward the delivery of preRT over postoperative radiation therapy for STS [29].

Surgery after preRT is typically performed 3 to 6 weeks after the last radiation dose [4, 19, 27, 36, 53]. These practices are largely based on clinical anecdotes and laboratory studies finding that acute inflammation after radiation requires 3 weeks to decline to levels compatible with wound healing [12, 19, 42, 51]. Whether irradiated tissues continue to recover, and thereby improve wound healing, is unclear. It is also not clear whether the tumor undergoes further cell death over time, which has implications for the resection volume and margin status at the time of surgery. Although the association between the preRT-surgery interval and outcomes in patients with STS is not well understood, many providers and patients remain skeptical of delaying surgery for cancer because of the perceived risk of disease progression [13, 55].

This study therefore used a national oncology registry to ask: (1) What factors are associated with the preRT-surgery interval in patients with STS? (2) Is the preRT-surgery interval associated with overall survival?

Patients and Methods

Data Source

Data from 2004 to 2014 were captured from the STS participant use file of the National Cancer Database. Established in 1989 as a collaborative effort between the American Cancer Society and the American College of Surgeons' Commission on Cancer, the National Cancer Database is a nationwide cancer registry that includes information on approximately 70% of all new cancer diagnoses in the United States from more than 1500 Commission on Cancer-approved centers. Hospitals submitting patient data to the National Cancer Database are required to maintain a follow-up rate of 90% [57]. Because the National Cancer Database does not contain any patient-identifying information, this study was exempted from institutional review board review.

Inclusion and Exclusion Criteria

In all, 6378 patients met the inclusion criteria after undergoing preRT and surgical resection for localized extremity or pelvic STS between 2004 and 2014. A total of 4202 patients were excluded, leaving 2176 patients for analysis (Fig. 1). Patients were excluded if they had lymphatic or metastatic disease at the time of diagnosis (23%; 1438 of 6378) because preRT and surgery are treatments that target local control. Patients with missing vital status (deceased or alive) at last contact (8%; 487 of 6378) were excluded since the National Cancer Database outcome measure "last contact" alone does not distinguish between deceased or alive patients. Patients were also excluded if they received neoadjuvant chemotherapy (24%; 1531 of 6378) or had chemosensitive histologic subtypes (9%; 603 of 6378) because the administration of neoadjuvant chemotherapy may lengthen the preRT-surgery interval, including extraskeletal osteosarcoma, extraskeletal chondrosarcoma, extraskeletal Ewing's sarcoma, mesenchymal chondrosarcoma, and rhabdomyosarcoma. Finally, additional patients were excluded if they had a radiation modality other than external beam (1%; 92 of 6378), had missing preRT-surgery interval (1%; 45 of 6378), or had a

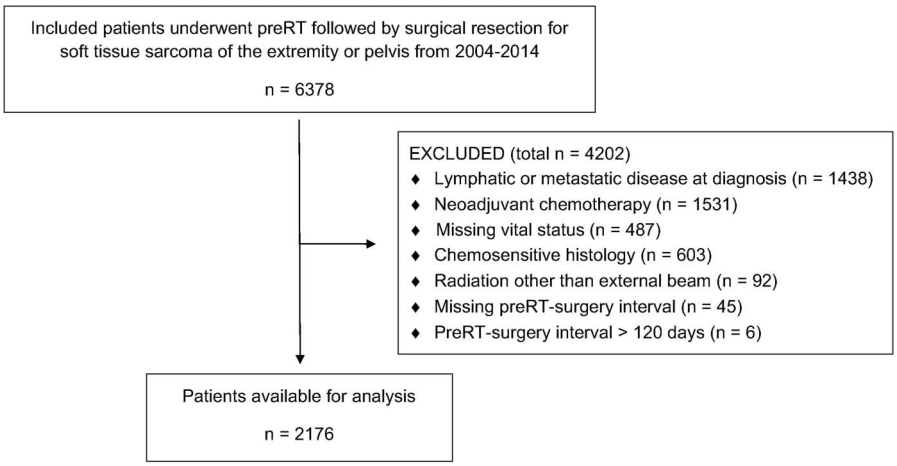


Fig. 1 The STROBE diagram demonstrates patient inclusion-exclusion criteria.

preRT-surgery interval greater than 120 days (< 1%; 6 of 6378), because this may represent a salvage attempt.

Extracted Data and Outcomes

Patient demographic information (age, sex, race, Charlson/Deyo comorbidity score, ZIP code-level median household income, ZIP code-level percentage of population with a high school degree, insurance type, urban or rural location, and distance from facility), tumor attributes (location, histologic type, size, grade, and stage), and treatment variables (facility volume, radiation modality, surgery type, and surgical margins) were extracted. Urban or rural location is categorized by the National Cancer Database using the United States Department of Agriculture Rural-Urban Continuum codes, which distinguishes rural counties (population less than 2500 and not metropolitan), urban counties (population greater than 2500 and not metropolitan) and metropolitan counties (as defined by the United States Office of Management and Budget). A composite socioeconomic score was calculated based on methodology from previous studies [14, 25, 33]. Malignant histologic subtypes were further organized into six categories: undifferentiated pleomorphic sarcoma, fibrosarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor, following previously published guidelines (see Appendix 1, Supplemental Digital Content, http://links.lww.com/CORR/A341) [1]. Facility volume was stratified by percentile into low (less than 25%), intermediate (25% to 75%), and high (greater than 75%) by procedure number during the study period. Radiation modality and surgery type were categorized (see Appendix 1, Supplemental Digital Content, http://links.lww.com/CORR/A341). Finally, margin status was considered negative only if all margins were grossly and microscopically free of residual tumor at the time of definitive surgery.

The preRT-surgery interval was calculated using three variables from the National Cancer Database by subtracting the number of days between the date of diagnosis and the date on which radiation therapy was started, combined with the length of radiation therapy, from the number of days between the date of diagnosis and the date of the definitive surgical procedure. The outcome, overall survival, was defined as the patient's vital status (deceased or alive) at last contact.

Patient Demographic, Clinicopathologic, and Treatment Characteristics

Between 2004 and 2014, 2176 eligible patients were included. The mean age of all patients was 60 years ± 16 years, 55% (1193 of 2176) were men, and 86% (1876 of 2176) were white (Table 1). Most patients were treated at a high-volume institution (79%, 1727 of 2176) and lived in a metropolitan county (83%, 1810 of 2176). Tumors were located predominately in the lower extremity (73%, 1590 of 2176) with a mean tumor size of 11 cm ± 7 cm. Overall, 68% (1470 of 2176) of preRT was delivered by conventional external beam. The mean preRT-surgery interval was 35 days ± 16 days, most frequently 3 to 4 weeks (24%, 529 of 2176) or 4 to 5 weeks (23%, 491 of 2176). Most patients had local (23%, 499 of 2176) or radical (75%, 1629 of 2176) resections, as described by the National Cancer Database site-specific surgery codes. The number of patients with positive surgical margins was 9% (185 of 2176) overall and similar across preRT-surgery interval groups: less than 3 weeks (10%; 29 of 304), 3 to

Table 1. Demographic, clinicopathologic, and treatment characteristics of the study population(n = 2176)

Variable	Frequency
Age (years)	
Mean ± SD	60 ± 16
18-30	4% (89)
30-60	41% (898)
> 60	55% (1189)
Sex	
Male	55% (1193)
Female	45% (983)
Race	
White	86% (1876)
Black	10% (224)
Other	4% (76)
SES composite	
1	19% (403)
2	29% (636)
3	31% (675)
4	21% (462)
Insurance	
Private	50% (1090)
Medicaid	5% (114)
Medicare	39% (852)
Other	2% (47)
Uninsured	3% (73)
Facility volume (per case)	
Low	15% (14)
Intermediate	15% (335)
High	79% (1727)
Charlson/Deyo score	
0	80% (1740)
1	16% (350)
2 or more	4% (86)
Median distance, in miles (IQR)	26 (57)
Urban/rural	
Rural	2% (37)
Urban	15% (329)
Metropolitan	83% (1810)
Tumor location	
Lower extremity	73% (1590)
Upper extremity	17% (366)
Pelvis	10% (220)
Histologic findings	
UPS	36% (786)
Fibrosarcoma	13% (286)
Liposarcoma	30% (654)
Leiomyosarcoma	11% (239)
Synovial sarcoma	7% (144)
MPNST	3% (67)
Tumor size	
Mean ± SD (cm)	11 ± 7
< 5	12% (269)
5-10	40% (865)
> 10 cm	48% (1042)
Grade	
1	14% (308)
2	22% (470)
3	36% (785)
4	28% (613)
Stage	
I	27% (580)
II	27% (597)
III	46% (999)
Radiation modality	
Conventional	68% (1470)
IMRT	20% (432)
3-D Conformal	13% (274)
PreRT-surgery interval	
Mean ± SD (days)	35 ± 16
< 3 weeks	14% (304)
3-4 weeks	24% (529)
4-5 weeks	23% (491)
5-6 weeks	16% (344)
6-7 weeks	10% (210)
7-9 weeks	8% (181)
> 9 weeks	5% (117)
Surgery type	
Local resection	23% (499)
Radical resection	75% (1629)
Amputation	2% (48)
Margin status	
Negative	91% (1991)
Positive	9% (185)

Race data was reported by hospital registries to the American College of Surgeons' Commission on Cancer. Facility volume was stratified by percentile into low (less than 25%), intermediate (25% to 75%), and high (greater than 75%) by procedure number during the study period; SES = socioeconomic score; IQR = interquartile range; UPS = undifferentiated pleomorphic sarcoma; MPNST = malignant peripheral nerve sheath tumor; IMRT = intensity-modulated radiation therapy.

4 weeks (7%; 38 of 529), 4 to 5 weeks (10%; 48 of 491), 5 to 6 weeks (8%, 28 of 334), 6 to 7 weeks (12%, 25 of 210), 7 to 9 weeks (11%, 20 of 181), and more than 9 weeks (12%, 14 of 117).

Table 2. Factors associated with the preRT-surgery interval (days), based on transformed values

Variable	Unstandardized β	95% CI	p value
Age (per year)	0.002	(0.0 to 0.004)	0.026
Sex			
Male	Ref		
Female	0.028	(-0.012 to 0.069)	0.17
Race			
White	Ref		
Black	0.059	(-0.01 to 0.128)	0.095
Other	-0.042	(-0.15 to 0.066)	0.45
SES composite			
1	Ref		
2	-0.021	(-0.082 to 0.039)	0.49
3	-0.008	(-0.07 to 0.055)	0.81
4	-0.017	(-0.086 to 0.052)	0.62
Charlson/Deyo comorbidity score			
0	Ref		
1	0.029	(-0.026 to 0.084)	0.30
2 or more	-0.051	(-0.155 to 0.052)	0.33
Distance from facility (per mile)	0	(0.0-0.0)	0.91
Urban/rural			
Rural	Ref		
Urban	-0.008	(-0.168 to 0.151)	0.92
Metropolitan	-0.006	(-0.162 to 0.15)	0.94
Insurance			
Private	Ref		
Medicaid	0.060	(-0.036 to 0.155)	0.22
Medicare	0.012	(-0.046 to 0.069)	0.70
Other	0.055	(-0.083 to 0.193)	0.44
Uninsured	0.052	(-0.061 to 0.165)	0.37
Facility volume (per case)	-0.002	(-0.003 to -0.002)	< 0.001
Tumor location			
Lower extremity	Ref		
Upper extremity	-0.002	(-0.058 to 0.053)	0.94
Pelvis	0.15	(0.082-0.217)	< 0.001
Histology			
UPS	Ref		
Fibrosarcoma	0.018	(-0.048 to 0.084)	0.60
Liposarcoma	0.052	(-0.004 to 0.107)	0.067
Leiomyosarcoma	0.039	(-0.03 to 0.108)	0.26
Synovial sarcoma	0.058	(-0.031 to 0.147)	0.20
MPNST	0.165	(0.044 to 0.286)	0.008
Tumor size (per mm)	0	(0.0 to 0.0)	0.50
Stage			
I	Ref		
II	-0.066	(-0.126 to -0.006)	0.030
III	-0.117	(-0.17 to -0.065)	< 0.001
Radiation modality			
Conventional	Ref		

Table 2. continued

Variable	Unstandardized β	95% CI	p value
IMRT	0.022	(-0.029 to 0.074)	0.39
3-D conformal	0.055	(-0.006 to 0.116)	0.077
Surgery type			
Local resection	Ref		
Radical resection	-0.040	(-0.087 to 0.008)	0.10
Amputation	-0.074	(-0.212 to 0.064)	0.29

Race data was reported by hospital registries to the American College of Surgeons' Commission on Cancer; SES = socioeconomic score; UPS = undifferentiated pleomorphic sarcoma; MPNST = malignant peripheral nerve sheath tumor; IMRT = intensity-modulated radiation therapy.

Statistical Analysis

We addressed missing variables through multiple imputation by chained equations, with the number of imputations based on the proportion of missing variables [18, 49]. In the overall data set, the proportion of missing variables was 3.7% for urban or rural location, 2.6% for tumor size, 16.8% for grade, 4.2% for stage, and 2.4% for margins. All other values needing imputation were missing for less than 2% of patients. There was no missing data for tumor location, histology, radiation modality, preRT-surgery interval, or surgery type because this data was required to satisfy the inclusion criteria.

We conducted a multiple linear regression analysis to assess demographic, clinicopathologic, and treatment characteristics associated with the preRT-surgery interval as a continuous variable in days. Because the preRT-surgery interval was not distributed normally, we performed the regression analysis after a natural log transformation of the interval. We provided β and confidence intervals derived from the log-transformed values because the focus of the analysis was factors that affected the interval length, not the absolute value of the coefficients. Then, we conducted a Kaplan-Meier survival analysis, stratified by preRT-surgery interval (binned into weekly intervals), to assess survival over 10 years. We combined The 7- to 8-week and 8- to 9-week groups to provide similarly sized groups. We then calculated 5- and 10-year survival rates with 95% CIs. We used a stratified log-rank test to compare groups included in the Kaplan-Meier analysis. Finally, to adjust for demographic, clinicopathologic, and treatment effects on survival, we performed a multivariate Cox regression analysis to evaluate the association between the preRT-surgery interval, as a continuous variable in days, and survival.

We pooled inferential estimates (β, hazard ratios, and CIs) from each imputed dataset according to Rubin's rules for inferences, after multiple imputation and as previously described [25, 47]. To examine collinearity in regression analysis, we calculated a variance inflation factor for each variable, and we found stage and grade to be collinear (variance inflation factor greater than 5). Because grade had a higher variance inflation factor, we included only stage in the models presented. The proportional hazard assumption of the multivariate Cox regression model was validated by examining Schoenfeld residuals, which must be independent versus time in a valid Cox model [58].

Statistical analyses were performed with packages *mice* and *survival* in R (R Foundation, Vienna, Austria; https://www.r-project.org/) [9, 21, 52], and general data processing was conducted in Python programming language (Python Foundation, https://www.python.org/). All statistical testing was two-sided, with a p value less than 0.05 considered significant.

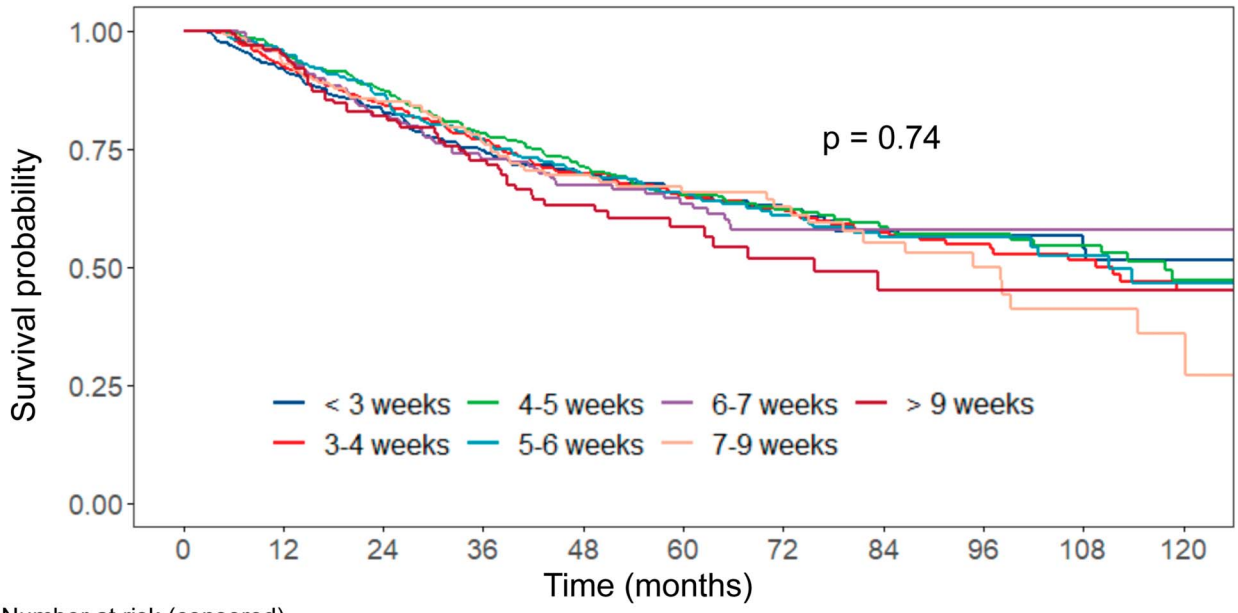
Results

Factors Associated with the preRT-surgery Interval

After controlling for potentially confounding variables including sex, race, Charlson/Deyo comorbidity score, distance from facility urban or rural location, and tumor size, a longer preRT-surgery interval was associated with higher age (β = 0.002 per year [95% CI 0.0 to 0.004]; p = 0.026), tumor location in the pelvis (compared with the lower extremity; β = 0.15 [95% CI 0.082 to 0.22]; p < 0.001), and malignant peripheral nerve sheath tumor subtype (compared with undifferentiated pleomorphic sarcoma; β = 0.17 [95% CI 0.044 to 0.29]; p = 0.008) (Table 2). A shorter preRT-surgery interval was associated with higher facility volume (β = -0.002 per case [95% CI -0.003 to -0.002]; p = 0.026) and higher tumor stage (compared with Stage I; β = -0.066 [95% CI -0.13 to -0.006]; p = 0.03 for Stage II; β = -0.12 [95% CI -0.17 to -0.065]; p < 0.001 for Stage III).

Association Between the preRT-surgery Interval and Survival

Survival analysis over 10 years demonstrated no difference in overall survival with the numbers available when patients were stratified by the preRT-surgery interval in



Number at risk (censored)

< 3 weeks	304 (0)	268 (8)	218 (31)	167 (61)	120 (97)	88 (125)	55 (153)	40 (166)	18 (187)	8 (197)	1 (204)
3-4 weeks	529 (0)	370 (5)	302 (42)	221 (97)	159 (135)	106 (183)	74 (211)	45 (237)	19 (261)	11 (268)	7 (268)
4-5 weeks	491 (0)	413 (15)	336 (50)	245 (122)	169 (178)	117 (216)	74 (253)	37 (284)	24 (296)	11 (308)	6 (309)
5-6 weeks	344 (0)	320 (10)	270 (41)	201 (81)	147 (118)	92 (162)	52 (191)	28 (212)	15 (224)	10 (229)	2 (235)
6-7 weeks	210 (0)	169 (5)	127 (26)	90 (55)	53 (82)	37 (96)	22 (106)	13 (115)	10 (118)	7 (121)	3 (125)
7-9 weeks	181 (0)	187 (6)	146 (28)	107 (56)	82 (72)	54 (94)	32 (115)	16 (128)	9 (133)	4 (135)	2 (135)
> 9 weeks	117 (0)	116 (0)	92 (12)	68 (25)	45 (37)	27 (51)	15 (60)	8 (65)	3 (70)	0 (73)	0 (73)

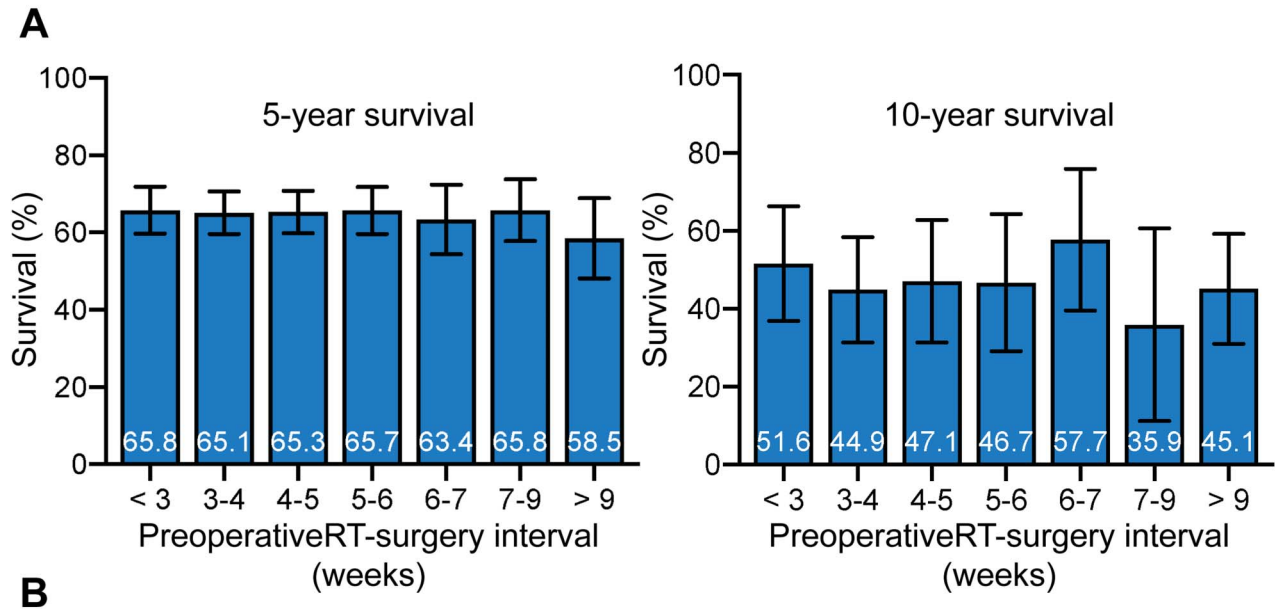


Fig. 2 A-B This figure shows the unadjusted survival analysis versus the preRT-surgery interval. (**A**) A Kaplan-Meier survival curve is shown, with the number at risk (censored) for each group, with p = 0.74. (**B**) Five-year and 10-year survival, stratified by the preRT-surgery interval, is shown with 95% CIs.

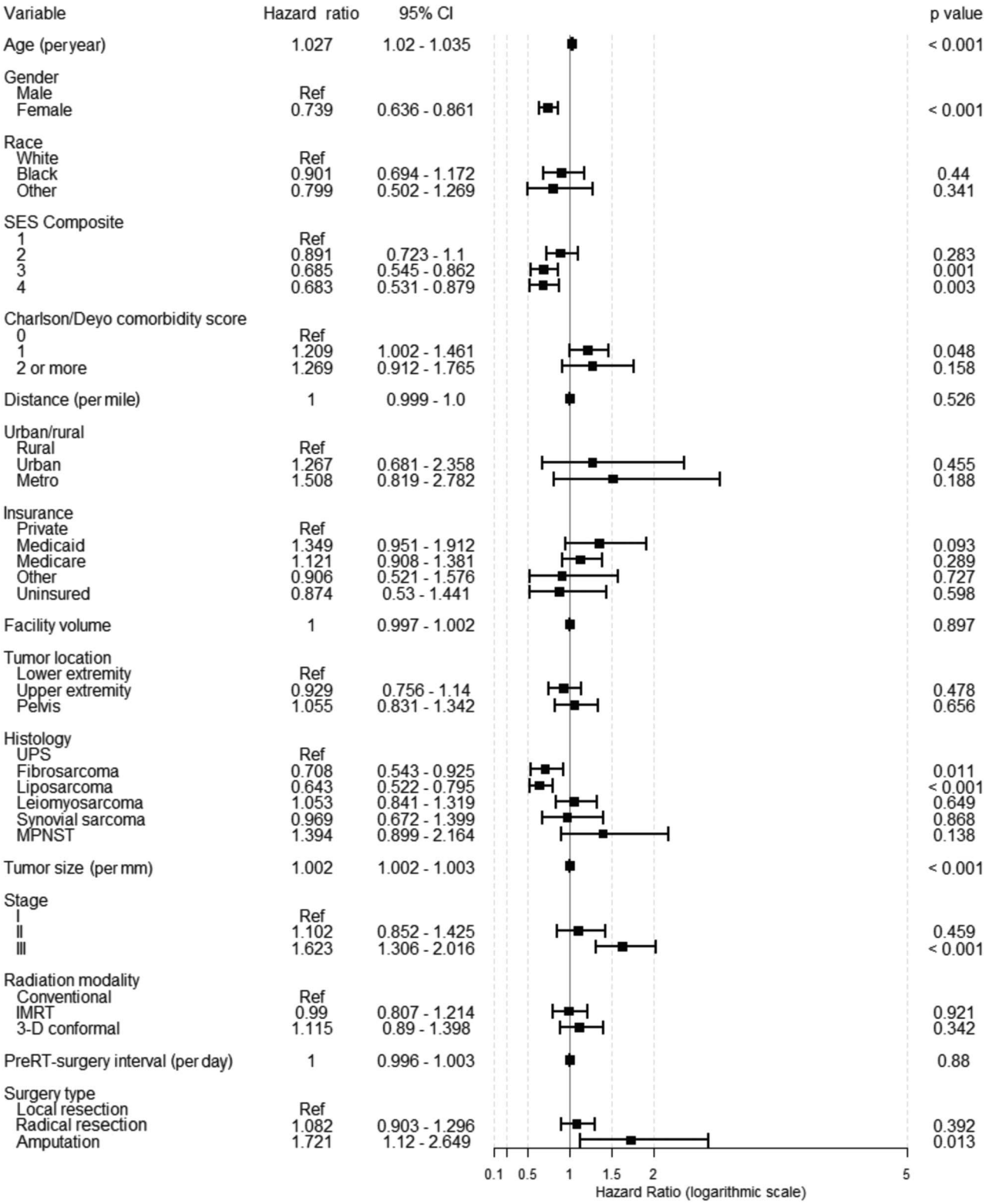


Fig. 3 This figure shows the multivariate Cox regression analysis of factors affecting overall survival. Hazard ratios are displayed on a logarithmic scale; SES = socioeconomic score; UPS = undifferentiated pleomorphic sarcoma; MPNST = malignant peripheral nerve sheath tumor; IMRT = intensity-modulated radiation therapy.

weeks (p = 0.74) (Fig. 2A). Accordingly, the 5-year overall survival rates were no different for preRT-surgery intervals less than 3 weeks (66% [95% CI 60% to 72%]), 3 to 4 weeks (65% [95% CI 60 to 71]), 4 to 5 weeks (65% [95% CI 60 to 71]), 5 to 6 weeks (66% [95% CI 60 to 72]), 6 to 7 weeks (63% [95% CI 54 to 72]), 7 to 9 weeks (66% [95% CI 58 to 74]), and more than 9 weeks (59% [95% CI 48 to 69]) (Fig. 2B). The same was true for 10-year overall survival rates for preRT-surgery intervals less than 3 weeks (52% [95% CI 37 to 66]), 3 to 4 weeks (45% [95% CI 31 to 58]), 4 to 5 weeks (47% [95% CI 31 to 63]), 5 to 6 weeks (47% [95% CI 29 to 64]), 6 to 7 weeks (58% [95% CI 40 to 76]), 7 to 9 weeks (36% [95% CI 11 to 61]), and more than 9 weeks (45% [95% CI 31 to 59]) (Fig. 2B). After controlling for potentially confounding variables, including age, sex, Charlson/Deyo comorbidity score, histology, tumor size, stage and surgery type, the preRT-surgery interval was not associated with survival with the numbers available (hazard ratio = 1 per day [95% CI 1 to 1]; p = 0.88) (Fig. 3).

Discussion

Surgery for STS is often delayed after preRT to allow for tissue recovery and reduction of wound complications. The preRT-surgery interval that provides the best balance of risk and benefit, however, is unknown. This study therefore investigated 2176 patients from a national oncology registry to evaluate factors associated with the preRT-surgery interval and whether the preRT-surgery interval is associated with overall survival. Factors associated with a longer preRT-surgery interval were higher age, lower facility volume, location in the pelvis, malignant peripheral nerve sheath tumor, and lower stage. The preRT-surgery interval in this population was not associated with overall survival. Therefore, clinicians may be able to delay surgery to minimize risk without affecting overall survival.

There are several limitations to this study. First, the analysis was limited to the variables and outcomes captured by the National Cancer Database and therefore cannot report on patterns of local recurrence, local recurrence-free survival, and disease-specific survival. However, patients with regional or metastatic disease were excluded to focus the analysis on the survival effects, if any, of local control. Second, this study did not include other outcomes of interest such as pathologic response, wound complications, joint fibrosis and stiffness, or patient satisfaction. Whether the preRT-surgery interval affects these outcomes was not the focus of this study. Third, the extensive exclusion criteria used here may limit the applicability of these findings to certain populations. The study population was restricted to minimize variables with clear effects on the preRT-surgery interval—such as neoadjuvant chemotherapy, which is often administered between radiation and surgery—and on survival, including the presence of metastatic disease. Fourth, though this study includes a relatively large population of STS patients, it may still be underpowered and susceptible to Type II errors. Fifth, this study could not account for all variations in reporting and treatment protocols, including the rationale for the preRT-surgery interval across different institutions and individual patients. Despite these limitations, this study is strengthened by the number of patients included while limiting the analysis to a contemporary time period with strict inclusion and exclusion criteria.

This study identified that several factors were associated with a longer preRT-surgery interval, including age and lower facility volume. Older age has been associated with wound complications, and surgery may be delayed to allow for tissue recovery and presurgical risk mitigation with respect to modifiable medical comorbidities [27]. Compared with low-volume facilities, high-volume facilities may have improved coordination between radiation oncologists and surgeons, thereby expediting surgical resection after completion of radiation therapy. Alternatively, high-volume facilities may be more likely to adopt shortened hypofractionated radiation protocols followed by immediate surgery, as previously described [23, 26]. It is less clear, however, why location in the pelvis, malignant peripheral nerve sheath tumor, and lower stage were associated with a longer preRT-surgery interval. Importantly, factors that may affect access to care, including sex, race, socioeconomic status, distance from facility, urban or rural location, and insurance status, were not associated with the preRT-surgery interval. Nevertheless, clinicians should remain mindful of how these factors shape practice patterns, as black race was recently associated with poor survival in STS [30].

This study demonstrated that the preRT-surgery interval, and thus a delay in surgery, is not associated with overall survival in patients with STS. Previous investigations have suggested that waiting for surgery after a cancer diagnosis can be a major source of patient frustration and anxiety [13, 55]. The widely held assumption is that earlier diagnosis and treatment of cancer improves survival; however, despite the rise in cancer screening programs and early detection, diagnostic cancer screening has been questioned recently because the expected reductions in overall mortality have not been realized [2, 41]. In fact, several studies have addressed this issue in patients with sarcoma and found that a delay in diagnosis did not affect survival [45, 46, 59]. One likely explanation is that efforts to identify and treat cancer early are thwarted by the biology of the tumor itself; that long before the diagnosis is made, metastasis has occurred at undetectable levels. Evidence for this exists already in STS, where the delivery of radiation has been shown to improve local control but

not overall survival [60]. Similarly, in the setting of postoperative RT, a delay in radiation after surgery is not associated with survival [6, 16]. These studies, together with the current one, suggest that the timing of local control does not determine overall survival in patients with STS. Therefore, it appears safe, and at times it may be prudent, to delay surgery after radiation.

One reason to delay surgery after preRT is to allow for tissue recovery and reduce the risk of wound complications, which have been reported to occur in 30% to 40% of patients [4, 10, 19, 28, 38, 43, 50, 53, 62]. Acute inflammation caused by radiation is well-described, and radiation-induced dermatitis has been directly associated with wound complications [12, 19, 32, 42, 51]. Waiting for these effects to subside before surgery may improve wound healing, although this possibility has not been directly assessed in a prospective study. A second reason to lengthen the preRT-surgery interval is to permit more time for the medical management of modifiable comorbidities including diabetes, smoking, poor nutrition, anemia, and cardiovascular disease. The time elapsed from diagnosis to the end of radiation treatment is typically 2 months; therefore, a preRT-surgery interval of 8 weeks would allow a total of 4 months for medical intervention. Examples of successful interventions to reduce complications after surgery exist for a number of other conditions [7, 17, 22, 35, 48, 54]. Considering the high rate of complications after the resection of STS, time to implement similar presurgical protocols could be beneficial. A third reason is to allow for a continued response to radiation, as has been explored in rectal cancer [39]. One meta-analysis reported that for rectal cancer patients, a preRT-surgery interval longer than 6 to 8 weeks was associated with a pathologic complete response at the time of surgery [39]. However, no differences were observed in margin status, sphincter preservation, surgical complications, or survival. Equivalent studies in STS have not been performed. Finally, although the role of neoadjuvant chemotherapy for STS is controversial, the development of novel agents, including radiosensitizers, may improve the efficacy of this approach and require a longer preRT-surgery interval for safe delivery [5, 56].

Conclusions

With the numbers available, this study demonstrates that a delay in surgery up to 120 days after radiation is not associated with poorer survival. Therefore, clinicians may be able to delay surgery to minimize the risks of wound complications and modifiable comorbidities without affecting overall survival. It also supports the safety of future study designs in which surgery is delayed to explore the effect on wound complications, implement presurgical interventions, or administer neoadjuvant chemotherapy. These efforts are needed to reduce complications and improve both function and survival for patients with STS.

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