



## PROMIS scores of patients undergoing neoadjuvant and adjuvant radiation therapy for surgically excised soft tissue sarcoma

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### A B S T R A C T

**Introduction:** Few recent studies have examined patient reported outcomes (PROs) during pre- or post-operative radiation therapy (RT) for soft tissue sarcoma (STS), and none have used PROMIS. This study aims to examine PROMIS scores across *peri*-operative time points for patients receiving pre- or post-operative RT.

**Methods:** Anxiety, depression, pain interference, and physical function PROMIS domains were collected at the pre-operative (1), immediate post-operative (2), and post-treatment completion (3) timepoints for patients undergoing surgery and either pre-operative or post-operative RT. Median scores were compared between groups using the Kruskal-Wallis test. The reliable change index was used to determine minimum important change in PROMIS scores and to compare scores between timepoints.

**Results:** 95 patients were included (19 pre-operative, 76 post-operative). Both groups had significant decreases in function during treatment. Patients with wound complications were more likely to have significant increases in anxiety (36.4% vs. 8.3%;  $p = 0.020$ ) and decreases in physical function (57.1% vs. 16.2%;  $p = 0.011$ ) independent of RT timing.

**Conclusions:** This study demonstrates minimum significant change thresholds to detect PROMIS changes in STS patients undergoing pre- and post-operative radiotherapy. As expected, more patients with pre-operative RT than post-operative RT had wound complications ( $p = 0.06$ ), but patients with complications in both groups had worse anxiety and function at the completion of treatment compared with those that did not. The association of wound complications with worse anxiety and physical function at completion of treatment should be considered when making individualized treatment recommendations regarding the timing of RT.

### Introduction

Wide surgical excision combined with radiotherapy (RT) is the preferred local treatment modality for patients with high-risk soft tissue sarcoma (STS) of the extremities [1–5]. However, personalized selection of optimal RT timing remains a challenge. RT can be administered either pre-operatively or post-operatively with equal efficacy but unique side effect profiles with respect to post-operative wound complications and physical function [1,6–12].

Compared with post-operative RT, pre-operative RT is associated with a reduced risk of late complications, such as fibrosis and joint stiffness [8,10,13–15]. These reduced late complications are potentially further associated with improved long-term functional outcomes and

decreased healthcare costs [16]. Yet, pre-operative RT also has disadvantages. It is associated with an increased risk of major wound complications that can limit post-operative function in the short term [8,14–15,17–20].

One prospective study investigated patient reported outcomes (PROs) for those who underwent pre-operative or post-operative RT for STS using the Musculoskeletal Tumor Society Scoring System (MSTS), the Toronto Extremity Salvage Score (TESS), and the Short Form-36 (SF-36) [14]. This study found that patients who underwent pre-operative versus post-operative RT had significantly worse function per TESS and MSTS at 6 weeks post-surgery but equivalent long-term outcomes. Moreover, this showed that several baseline factors such as tumor size (i. e. field size) were associated with long term worse PROs. Importantly,

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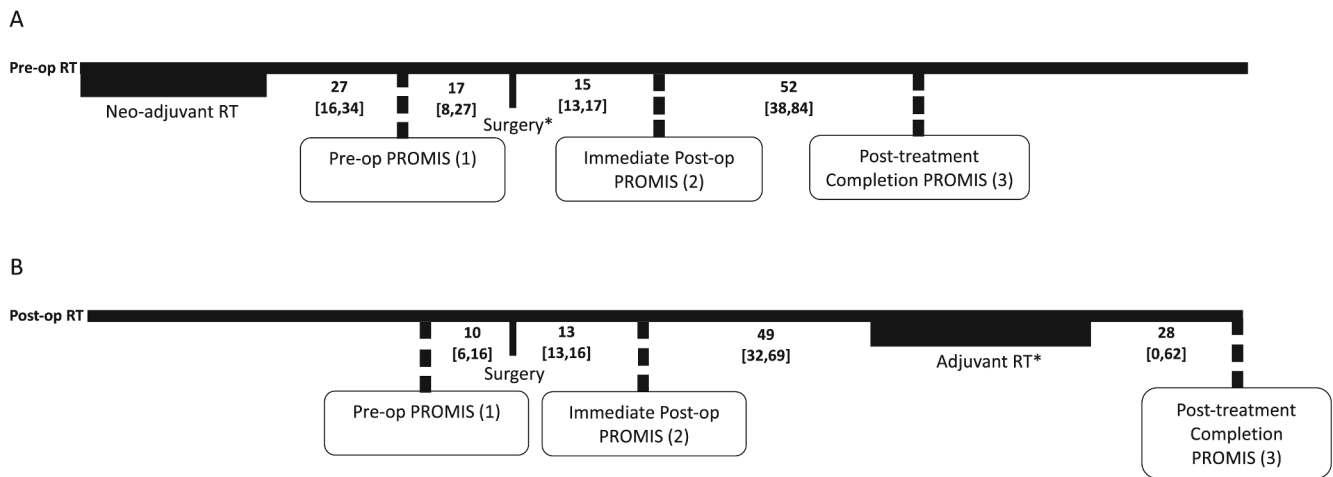
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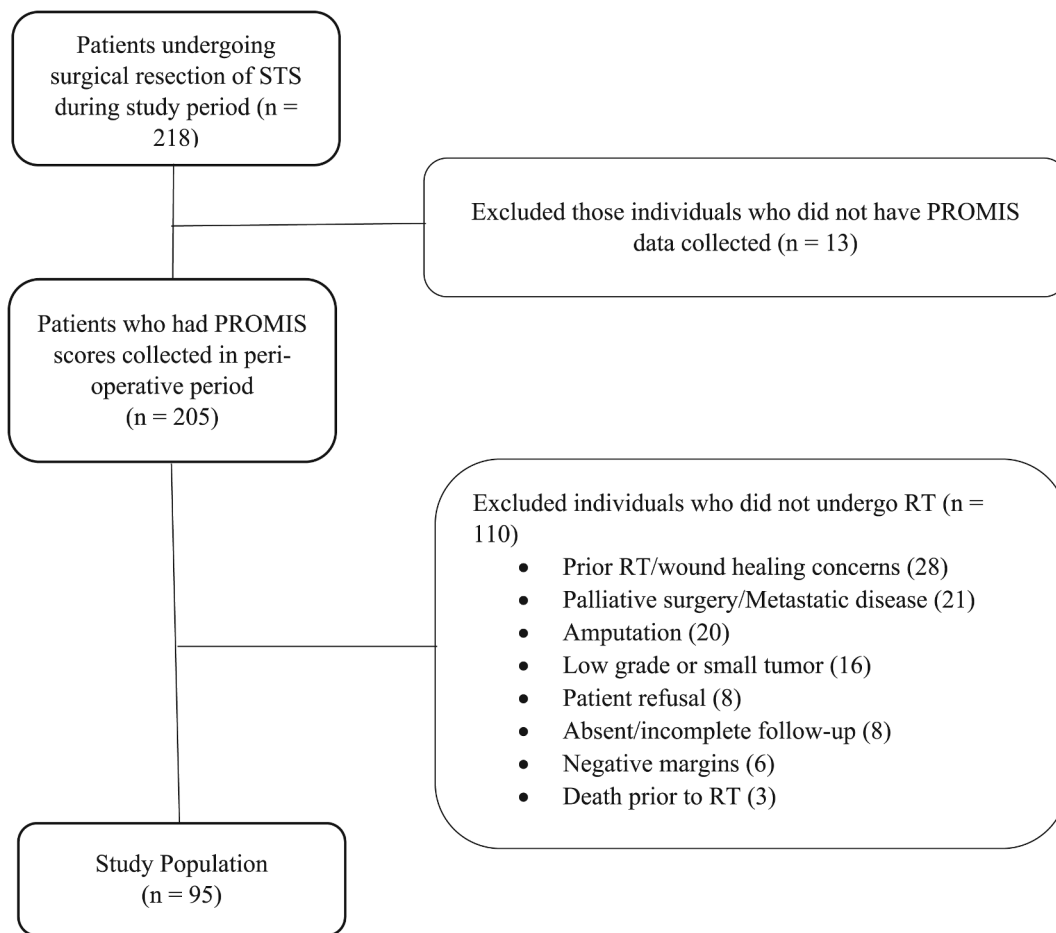
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**Fig. 1.** Timeline showing dates of RT, surgery, and PROMIS score collection of the pre-operative RT (A) and post-operative RT (B) groups. Numbers between timepoints indicate median number of days passed between events. The asterisks indicate the defined point of treatment completion: after surgery for the pre-operative RT group and after adjuvant RT for the post-operative RT group.



**Fig. 2.** Consort flow diagram of patient inclusions and exclusions.

modern pre-operative RT fields are smaller than those used in this study.

The recently developed Patient Reported Outcomes Measurement Information System (PROMIS) utilizes T-scores in order to standardize results across different medical conditions and with the general population [21]. PROMIS provides an advantage over previously used PRO measures such as the MSTs or TESS. PROMIS is supported by the National Cancer Institute and is being widely adopted for use in oncology

studies. PROMIS also allows for comparisons with other more common conditions or other cancer types [22–23]. No study has evaluated PROMIS data collected from patients with sarcoma during the peri-operative and radiation periods.

This study had two main objectives: (1) to compare PROMIS scores between patients who had undergone pre-operative versus post-operative RT for the management of STS, and (2) to investigate the

**Table 1**  
Demographic data of total patient population and of the two patient groups.

	Total (N = 95)	Pre-op (N = 19)	Post-op (N = 76)	p-value
Age	64.0 [52.0,76.0]	64.0 [54.0,73.0]	64.0 [50.5,76.0]	0.90 <sup>b</sup>
Gender				<b>0.048<sup>c</sup></b>
F	39(41.1)	4(21.1)	35(46.1)	
M	56(58.9)	15(78.9)	41(53.9)	
Race				0.064 <sup>c</sup>
Black	12(12.6)	0(0.0)	12(15.8)	
White	83(87.4)	19(100.0)	64(84.2)	
Marital Status				0.28 <sup>d</sup>
Divorced	7(7.4)	0(0.0)	7(9.2)	
Married	68(71.6)	17(89.5)	51(67.1)	
Single	14(14.7)	1(5.3)	13(17.1)	
Widowed	6(6.3)	1(5.3)	5(6.6)	
Size	7.8 [4.5,14.5]	8.8 [4.3,15.5]	7.8 [4.5,13.3]	0.74 <sup>b</sup>
Size, categorical				0.82 <sup>c</sup>
< 5 cm	28(29.5)	6(31.6)	22(28.9)	
> 5 cm	67(70.5)	13(68.4)	54(71.1)	
Margins				0.43 <sup>c</sup>
Negative	63(66.3)	14(73.7)	49(64.5)	
Positive	32(33.7)	5(26.3)	27(35.5)	
Re-operation				0.288 <sup>c</sup>
No	71(74.7)	16(84.2)	55(72.4)	
Yes	24(25.3)	3(15.8)	21(27.6)	
Metastatic				0.12 <sup>c</sup>
No	88(92.6)	16(84.2)	72(94.7)	
Yes	7(7.4)	3(15.8)	4(5.3)	
Upper/Lower				0.19 <sup>c</sup>
Upper	24(25.3)	7(36.8)	17(22.4)	
Lower	71(74.7)	12(63.2)	59(77.6)	
Complication				0.059 <sup>c</sup>
No	75(78.9)	12(63.2)	63(82.9)	
Yes	20(21.1)	7(36.8)	13(17.1)	
Pathologic Diagnosis				0.11 <sup>c</sup>
Undifferentiated pleomorphic sarcoma	37	27	10	
Liposarcoma	15	13	2	
Myxofibrosarcoma	11	10	1	
Leiomyosarcoma	9	5	4	
Synovial Sarcoma	7	7	0	
Rhabdomyosarcoma	5	5	0	
Angiosarcoma	3	2	1	
Epithelioid Sarcoma	2	2	0	
MPNST	2	1	1	
Other	4	4	0	

Values presented as Mean ± SD, Median [P25, P75], Median (min, max) or N (column %).

p-values: a = ANOVA, b = Kruskal-Wallis test, c = Pearson's chi-square test, d = Fisher's Exact test.

changes in PROMIS scores between different *peri*-operative timepoints.

## Methods

This study was approved by the local institutional review board. This study included all patients >18 years old who underwent surgical treatment for primary or repeat surgical resection of a malignant soft tissue sarcoma, and who were evaluated in the orthopedic oncology clinic at a single university-based tertiary care institution between July 1st 2015 and October 31st 2019. Exclusion criteria included absence of PROMIS scores at all orthopedic oncology visits and treatment without neoadjuvant or adjuvant RT. Patients who received pre-operative RT or post-operative RT were evaluated separately due to different expected side effect profiles. Radiotherapy was delivered per standard practices using 3D conformal or intensity-modulated radiotherapy [24]. Pre-operative RT was prescribed to 50–50.4 Gy in 25–28 fractions with a post-operative boost for positive margins (16–19.8 Gy) while post-operative RT was prescribed to 60–66 Gy in 30–33 fractions. No patients in the pre-operative RT group received a post-operative radiation

boost if margins were positive after surgery.

We collected PROMIS data at all orthopedic oncology visits beginning July 1st, 2015 as standard of care. PROMIS instruments were collected using a tablet computer (iPad mini; Apple Inc., Palo Alto, CA) on a secure wireless network, automatically converted from raw to T-scores, and deposited into the electronic medical record. Depression, Pain Interference, and Physical Function domains were collected for all patients, and Anxiety domains were added after May 1st, 2016. The additional major PROMIS profile domains (Pain Intensity, Fatigue, Sleep Disturbance, and Ability to Participate in Social Roles and Activities) were not available for collection at the study institution and were beyond the scope of the present study.

Electronic medical records were reviewed for patient demographic, surgical, pathologic, and RT data. Information on neoadjuvant or adjuvant chemotherapy was not collected. Potential confounding variables, such as age, tumor size, and grade, for the pre-operative RT group and the post-operative RT group were compared using the Kruskal-Wallis test for continuous variables and the Pearson's chi-square test or Fisher's Exact test for categorical variables. Disease progression was defined as local recurrences and/or development of metastases after surgical excision. Complication rate was defined consistent with the SR.2 trial as secondary operation for wound repair (debridement, operative drainage, secondary wound closure), seroma aspiration, re-admission for wound care, or deep packing of wound for 120 days or longer within 120 days of surgery [8].

PROMIS scores were collected at three time points depicted Fig. 1A and B for patients who received pre- and post-operative radiotherapy: pre-operative (time-point 1), immediate post-operative (time-point 2), and after completion of all treatment (time-point 3). Time-point 1 scores were collected at the pre-operative clinic visit nearest to the date of surgery. Time-point 2 scores were collected at the first clinic visit after surgery. Time-point 3 scores were collected after both RT and acute surgical recovery were completed, defined as >45 days.

Mean and individual changes in PROMIS scores between the above defined time-points were calculated and compared using RCI. A complete description of how RCI was calculated is available in the [supplementary materials](#). Mean RCI for each time-point and domain was calculated for both pre- and post-operative radiotherapy groups.

As an exploratory analysis, median PROMIS scores were compared between the pre- and post-operative radiotherapy groups at all three time-points for all four PROMIS domains using the Kruskal-Wallis test. Mean RCI at each time point was compared between the groups using Levene's Test of the Homogeneity of Variance [25–30]. Lastly, the proportion of individuals in the pre-operative and post-operative RT groups whose RCI indicated significant increase, significant decrease, or no change in PROMIS scores were compared for each PROMIS domain at each time-point using the Pearson Chi-Square test with p-value set at 0.05. Significance was set at <0.05 for all variables.

Mean and individual changes in PROMIS scores between the above defined time-points were calculated and compared using RCI. The RCI utilizes the known retest reliability and standard deviation of a test to calculate the standard error of measurement and standard error of the difference between scores [25]. This value represents the level of change associated with statistically significant change from baseline. RCI is calculated as follows:

$$RCI = \frac{x_2 - x_1}{S_{diff}}$$

where  $x_2 - x_1$  represents an individual's change between timepoints. This can also be reported as a difference in population mean.  $S_{diff}$ , the standard error of the difference between the two scores accounting for reliability of the test, is calculated as:

$$S_{diff} = \sqrt{2(S_E)^2}$$

**Table 2**

Minimum important change in PROMIS score to be considered significant at 90% CI and mean PROMIS changes for Anxiety (A), Depression (B), Pain Interference (C), and Physical Function (D). The most leftward column indicates timepoints with 1 = pre-operative; 2 = immediate post-operative; 3 = post-treatment completion. All p-values comparing minimum important change were calculated using Levene’s Test of the Homogeneity of Variance. Significant RCI change is defined as > 1.65 in either direction.

		Minimum Important Change	P-Value	Mean PROMIS Change	Mean RCI	Significance
<b>A) Anxiety</b>						
1 -> 2	Pre-operative RT	5.04	0.428	-2.08	-0.358	Non-Significant
	Post-operative RT	5.78		-1.71	-0.496	Non-Significant
1 -> 3	Pre-operative RT		0.091	0.48	0.116	Non-Significant
	Post-operative RT			-6.57	-1.369	Non-Significant
2 -> 3	Pre-operative RT	3.56	0.091	2.56	0.867	Non-Significant
	Post-operative RT	6.78		-4.85	-0.862	Non-Significant
<b>B) Depression</b>						
1 -> 2	Pre-operative RT	5.33	0.962	-0.35	-0.108	Non-Significant
	Post-operative RT	5.57		-0.87	-0.258	Non-Significant
1 -> 3	Pre-operative RT		0.124	-0.54	-0.168	Non-Significant
	Post-operative RT			-0.93	-0.274	Non-Significant
2 -> 3	Pre-operative RT	4.49	0.124	-0.19	-0.071	Non-Significant
	Post-operative RT	5.61		-0.05	-0.015	Non-Significant
<b>C) Pain Interference</b>						
	Minimum Important Change	P-Value	Mean PROMIS Change	Mean RCI	Significance	
1 -> 2	Pre-operative RT	6.59	0.864	5.23	1.309	Non-Significant
	Post-operative RT	6.98		6.56	1.549	Non-Significant
1 -> 3	Pre-operative RT		0.822	1.06	0.265	Non-Significant
	Post-operative RT			0.65	0.154	Non-Significant
2 -> 3	Pre-operative RT	6.08	0.822	-4.17	-1.699	<b>Significant Decrease</b>
	Post-operative RT	5.73		-5.9	-1.133	Non-Significant
<b>D) Physical Function</b>						
	Minimum Important Change	P-Value	Mean PROMIS Change	Mean RCI	Significance	
1 -> 2	Pre-operative RT	6.46	0.953	-7.33	-1.873	<b>Significant Decrease</b>
	Post-operative RT	6.47		-7.09	-1.81	<b>Significant Decrease</b>
1 -> 3	Pre-operative RT		0.791	-3.21	-0.819	Non-Significant
	Post-operative RT			0.99	0.253	Non-Significant
2 -> 3	Pre-operative RT	6.87	0.791	8.09	1.984	<b>Significant Increase</b>
	Post-operative RT	6.73		4.12	0.99	Non-Significant

$$S_E = s_1 \sqrt{1 - r_{xx}}$$

where  $S_E$  is the standard error of measurement of the test,  $s_1$  is the standard deviation of the test results at the initial time point, and  $r_{xx}$  is the test–retest reliability of the measure. The test–retest reliabilities of PROMIS domains used in this study have been previously evaluated in patients with musculoskeletal conditions and range from 0.85 to 0.92 [26].

The RCI was calculated for each individual patient for each PROMIS domain between time points 1 and 2, 1 and 3, and 2 and 3. In order for a change to be deemed statistically reliable at a 90% confidence interval, the Z-score of the RCI must be >1.645. The 90% confidence interval is standard use in the literature when calculating RCI because it increases the sensitivity in detecting reliable change and defines a change which occurs in only 5% of healthy individuals in either direction [27–30]. Changes that exceed this threshold in either direction are likely due to actual change rather than due to chance. Individual changes are reported as either significant increase, significant decrease, or no change.

**Results**

A consort diagram for this study is shown in Fig. 2. Two hundred eighteen patients underwent surgical resection of a malignant STS during the study period. Of those patients, 13 were excluded due to an absence of PROMIS data at all of the collected time points. 110 patients were excluded because they did not undergo RT. Ninety five patients were included in the final analysis. 19 patients underwent pre-operative RT and 76 underwent post-operative RT. Demographic, surgical, and pathologic data are shown in table 1. There were no significant differences in any of these variables other than gender between the two groups (21.1% female, 78.9% male in pre-operative group; 46.1% female, 53.9% male in post-operative group;  $p = 0.048$ ).

One pre-operative RT patient and five post-operative RT patients had incomplete pre-operative PROMIS data, leaving a total of 18 pre-operative RT patients and 71 post-operative RT patients in this

analysis. One pre-operative RT patient and two post-operative RT patients had incomplete immediate post-operative PROMIS data, leaving a total of 18 pre-operative RT patients and 74 post-operative RT patients in this analysis. Four pre-operative RT patients and 37 post-operative RT patients had incomplete post-treatment completion PROMIS data, leaving a total of 14 pre-operative RT patients and 39 post-operative RT patients in this analysis. Similarly, 30 patients had their pre-operative and immediate post-operative PROMIS collection dates prior to the start of anxiety PROMIS score collection, while 12 of those patients had their post-treatment completion PROMIS collection date prior to anxiety collection. Those patients were included in the depression, pain interference, and physical function analyses, but not the anxiety analyses.

**PROMIS score changes between Peri-operative timepoints**

Multivariate analysis was completed to determine if any of the covariates in table 1 were associated with PROMIS scores (supplemental table 1) and whether PROMIS scores significantly differed between each of the three timepoints (supplemental table 2). Anxiety scores were significantly lower at the post-treatment completion timepoint when compared to the other two time-points (effect size -5.91;  $p = 0.0015$ ). None of the variables were significantly associated with depression scores at any timepoint, and they were similar across timepoints. The physical function scores were also significantly lower at the immediate post-operative timepoint when compared to the other two time-points (effect size - 6.94;  $p < 0.0001$ ). Physical function scores were significantly lower with increased patient age (effect size -0.14;  $p = 0.0163$ ) and increased tumor size (effect size -0.44;  $p = 0.0011$ ). Pain scores were significantly higher with larger tumor size (effect size 0.433;  $p = 0.0017$ ) and during the immediate post-operative timepoint when compared to the other two time-points (effect size 6.48;  $p < 0.001$ ). All of these effects were similar for the pre-operative and post-operative radiotherapy groups

Table 2 demonstrates the minimum important change in individual PROMIS score to be considered significant at a 90% confidence interval

**Table 3**

PROMIS scores comparisons in all 4 PROMIS domains at the pre-operative (2.1), immediate post-operative (2.2), and post-treatment completion time points (2.3). 30 patients had their pre-operative and immediate post-operative visits prior to anxiety score collection, and 12 patients had their post-treatment completion visits prior to anxiety score collection. These patients were excluded from the anxiety analysis at the time-points where data was missing. All PROMIS scores are reported as Median [P25, P75]. All p values calculated using the Kruskal-Wallis test.

1) Pre-operative PROMIS Data					
PROMIS Domain	N missing	Total (N = 89)	Pre-op (N = 18)	Post-op (N = 71)	p-value
Anxiety	30	54.0 [51.2,59.8]	52.6 [51.2,58.0]	56.0 [51.2,61.6]	0.28
Depression	0	48.1 [42.5,51.3]	47.6 [39.3,49.9]	49.4 [42.5,51.3]	0.33
Pain	0	56.0 [46.6,61.6]	57.4 [47.1,62.7]	56.0 [46.6,61.5]	0.72
Function	0	42.5 [35.4,49.3]	43.4 [34.7,46.1]	42.3 [35.7,50.5]	0.63
2) Immediate Post-operative PROMIS Data					
PROMIS Domain	N missing	Total (N = 93)	Pre-op (N = 18)	Post-op (N = 74)	p-value
Anxiety	30	54.0 [46.0,58.6]	51.2 [44.6,54.0]	54.4 [50.2,59.7]	0.092
Depression	0	48.2 [41.7,51.1]	46.2 [42.7,49.9]	48.2 [40.7,52.0]	0.42
Pain	0	61.5 [56.0,66.9]	60.9 [56.0,66.9]	62.1 [56.0,66.9]	0.81
Function	0	34.4 [26.9,41.0]	30.4 [26.7,36.1]	34.9 [28.0,41.3]	0.29
3) Post-treatment Completion PROMIS Data					
PROMIS Domain	N missing	Total (N = 53)	Pre-op (N = 14)	Post-op (N = 39)	p-value
Anxiety	12	51.2 [43.9,54.0]	51.2 [49.3,53.9]	51.2 [42.1,56.0]	0.37
Depression	0	46.7 [34.2,54.1]	45.6 [34.2,50.0]	47.6 [41.2,55.0]	0.57
Pain	0	56.0 [46.8,62.6]	54.4 [52.6,64.0]	56.0 [46.6,62.6]	0.87
Function	0	41.7 [36.0,46.8]	38.6 [30.3,44.7]	43.1 [37.3,48.5]	0.057

for both the pre-operative RT and post-operative RT groups. The differences in minimum important change between the two RT groups was not significant for any PROMIS domain or time-point. Table 3 also shows the mean RCI for the pre-operative RT and post-operative RT groups at each timepoint and PROMIS domain. Both groups had a significant decrease in physical function between the pre-operative and post-operative timepoints. The pre-operative RT group had a significant decrease in pain interference (4.17 decrease; RCI = -1.699) and a significant increase in physical function (8.09 increase; RCI = 1.984) between the immediate post-operative and post-treatment completion time-points. No other groups at any time-point saw a significant change at a 90% confidence interval for any of the four PROMIS domains.

RCI was analyzed on an individual level to determine which patients are driving changes in mean PROMIS scores between time-points. The proportion of patients in both the pre-operative and post-operative RT groups who showed an increase, decrease, or no change in each of the four PROMIS domains are shown in supplemental table 2.1. Given the results of the above multivariate analysis, the proportion of patients with significant RCI deviation was also analyzed based on patients grouped by presence of major wound complication (supplemental table

2.2), tumor size (supplemental table 2.3), and age (supplemental table 2.4).

Patients who had major wound complications were more likely to have an increase in anxiety (36.4% vs. 8.3% without wound complication) and a decrease in physical function (57.1% vs. 16.2% without wound complications) between the pre-operative (1) and post-treatment completion (3) time-points (Fig. 3). Patients with tumors > 5 cm were also more likely to have a decrease in depression (27.4% vs. 4.2% with tumor < 5 cm) between the pre-operative and immediate post-operative time-points. No other groups showed a significant difference in proportions of increase, decrease, and no change in PROMIS scores.

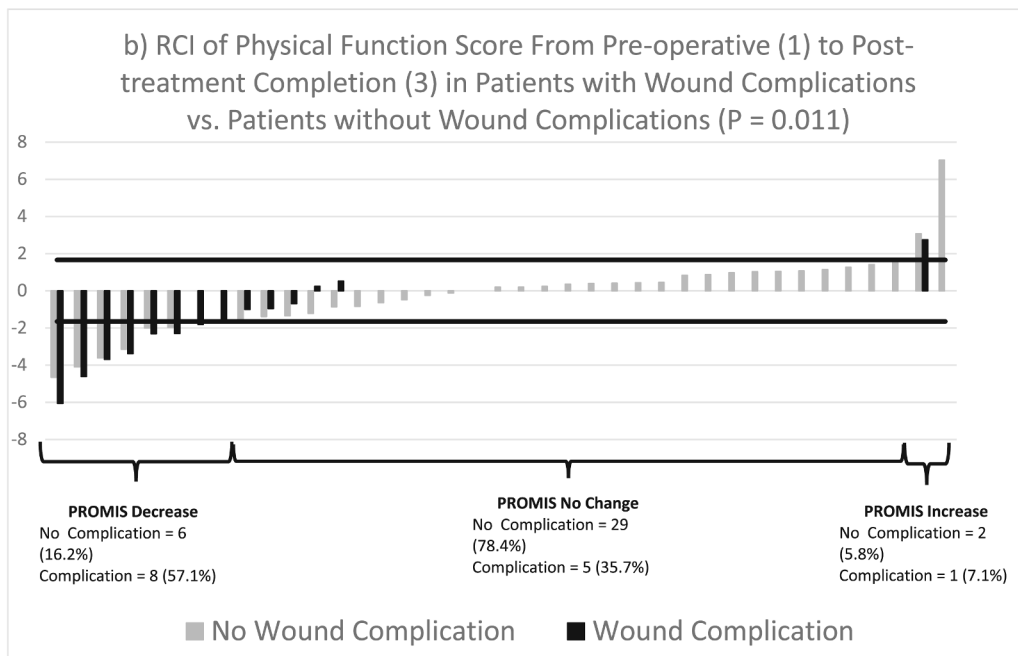
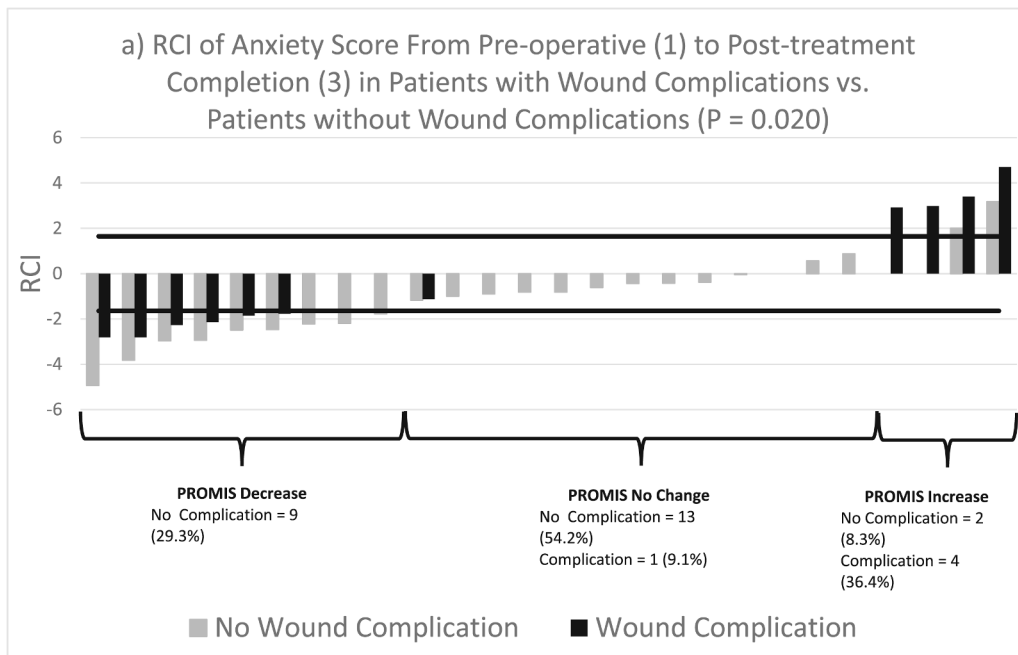
### PROMIS score comparison between Pre-operative and Post-operative RT

Table 3 shows the PROMIS score comparisons between the pre-operative RT and post-operative RT groups at the pre-operative, immediate post-operative, and post-treatment completion timepoints, respectively. There were no significant differences in PROMIS scores between the two groups at any of the timepoints for any of the four PROMIS domains.

### Discussion

This study is the first to evaluate PROs using PROMIS in patients undergoing pre- and post-operative RT with curative surgery for soft tissue sarcoma. There were several important findings. First, this study establishes reference PROMIS values and the amplitude of significant change for PROMIS physical function, pain interference, anxiety, and depression inventories for patients undergoing radiation and surgery for sarcoma. Since, PROMIS is endorsed by the NCI and increasingly being used across centers, this study may serve as a comparator for future work. Second, a sub-group analysis demonstrated that a significantly higher proportion of patients with wound complications had negative changes in anxiety and physical function from baseline to treatment completion than patients without wound complications. Third, despite the association of pre-operative RT with wound complications, the results suggest that, generally, the timing of RT is not associated with differences in patient-reported depression, anxiety, function, and pain outcome measures at the pre-operative, immediate post-operative, and post-treatment completion time-points.

The minimum important change at the 90% confidence interval for each time-point and PROMIS domain did not differ significantly between the pre-operative and post-operative RT groups. This indicates that changes in PROMIS scores can be interpreted similarly no matter which RT method is used. Yost et al. examined the minimally important differences of similar PROMIS domains in a cohort of patients with advanced cancer; they determined clinically meaningful differences of 3–4.5 for anxiety, 3–4.5 in depression, 4–6 in pain interference, and 4–6 in physical function, though they did not use RCI for their calculation [31]. This study included very few patients with musculoskeletal tumors which could explain why our data appears to consistently require slightly greater changes in score in order to detect meaningful change. The present study did not find any significant differences in the physical function or pain outcomes at any time point between patients who received pre- versus post-operative RT. A prior study directly compared functional and health status outcomes in a similar patient group receiving pre- and post-operative RT. They found that the post-operative RT group had improved scores in the MSTs, TESS, and bodily pain subset of SF-36 at 6 weeks after surgery [14], but found no differences in any outcome measures beyond 6 weeks after surgery. The current study seems consistent, as it found no difference in PROMIS outcomes in patients undergoing pre- versus post-operative RT at later timepoints of median 52 and 72 days, respectively. Indeed, multiple studies have shown functional recovery in patients following STS resection that continues for up to two years after an initial decline [32–35].



**Fig. 3.** Waterfall plot of anxiety (a) and physical function (b) RCI of patients grouped by presence of wound complication between pre-operative (1) and post-treatment completion (3) time points. Patients with wound complications were significantly more likely to have increases in anxiety and decreases in physical function between these time points than patients without wound complications. Similar analysis for other variables, time-points, and PROMIS domains were completed and are shown in the.

Multivariate analysis showed significantly worse pain and function scores in patients with larger tumors as well as worse function scores in older patients. Previous studies have reported similar results in large, deep tumors for MSTs and TESS scores in STS patients, while age has been shown to negatively impact SF-36 scores [14,32,36–37]. The current study extends these findings by demonstrating that these patients do not experience significant change in their PROMIS pain and physical function scores across *peri*-operative timepoints.

Similar to pain and function scores, the present study found no significant differences between the two RT groups with respect to mental health outcomes, PROMIS anxiety and depression. This is similar to the prior randomized study of pre- versus post-operative RT, which found no differences between groups in the mental health and emotional subsets of the SF-36 [14]. It is also consistent with a 2019 qualitative report of 19 patients undergoing treatment for STS. These patients did not express

concerns based on the order of treatment in interviews conducted after the initial clinic visit. Instead, they reported uncertainties regarding treatment delays and side effects as their top concerns [38]. Similarly, two studies have found that uncertainty, expectation of a difficult recovery, or frustration with communication from the healthcare system were shown to negatively impact quality of life and mental health outcome measures after STS resection [39–40]. These studies therefore suggest that communication and management of expectations may be more important for psychosocial health in STS patients than the sequence of treatment itself.

These data may help guide individualized approaches to optimizing mental health throughout STS treatment. For both groups, anxiety PROMIS scores were high prior to treatment in both RT groups and decreased after treatment completion. This likely occurs because patients no longer anticipate future therapies [40]. Interestingly,

depression scores were more likely to improve immediately after surgery for patients with larger tumors, and this was similar for both RT groups. This may be due to a sense of relief that the major part of their treatment has ended. Financial difficulty, pain, limited physical and social function, and depression or anxiety at baseline have been shown to be the most important predictors of poor mental health outcomes after STS resection [39,40]. Yet, there is significant noteworthy heterogeneity in the literature regarding the variables that can predict psychosocial outcomes after STS resection [41]. It remains an important area for further study.

The most common reason for avoiding pre-operative RT is due to the increased risk of wound complications, consistently reported to be between 30 and 40% vs. 10–20% in post-operative RT setting, even with decreasing field size and the use of intensity-modulated radiation therapy [1,8,14–15,17–20]. Similar complication rates were reported in this study, although these differences did not reach significance. A prior randomized study on pre- and post-operative RT reported worsening TESS scores for 6 weeks and MSTs scores for up to 2 years when patients experienced major wound complications [14]. Wound complications have been shown to negatively impact functional outcomes in other studies as well [32]. In contrast, this study did not demonstrate that the presence of a wound complication was independently associated with a worse PROMIS score in any domain at any *peri*-operative timepoint. However, RCI analysis found that a higher proportion of patients with wound complications had significantly decreased physical function and increased anxiety from baseline to treatment completion than patients without a complication. These findings suggest that the association of a discrete toxicity, such as wound healing complications, with worse PROMIS scores is heterogeneous across STS patients. Likewise, the association between increased radiation fibrosis, which can be more common with post-operative RT, and worse long-term patient reported outcomes may also be heterogeneous [14]. In the future, computer-based data collection of patient-reported outcomes may help identify patients who are expected to be more likely to tolerate side effects that are more commonly to be associated with pre- or post-operative RT.

There are multiple limitations to this study. First, due to its retrospective design, there was no control over patient group assignment. Selection of therapy may have been biased by factors such as significant pain at initial visit, rapidly growing tumors, or fungating massed that had penetrated the skin. This limited the amount of patients in the pre-operative RT group compared to the post-operative RT group, though there were no demographic differences between the groups other than a gender bias, potentially due to the small sample sizes. Second, patients who underwent resections only received PROMIS surveys at orthopedic oncology visits. The follow up for orthopedic oncology was not consistent across patients during the study period. This limited collection of PROMIS data for some patients, especially in the post-treatment completion time period. For example, patients with post-operative difficulty likely had many orthopedic visits while others may follow only with Radiation Oncology. Certain major PROMIS domains were available at the study institution for analysis (Pain Intensity, Fatigue, Sleep Disturbance, and Ability to Participate in Social Roles and Activities). Future collection of data in these domains may expand on the differences between groups found in this study. Information regarding neo-adjuvant and adjuvant chemotherapy was not collected and may have had an impact on treatment outcomes and PROMIS data. Investigation of the impact of chemotherapy may be a target of future study. Lastly, follow up for this study was short and PROMIS scores were only collected at two post-treatment time points. It is likely that more frequent assessments during treatment as well as longer follow-up will add important data. Future study should focus on mid- and long-term outcomes in each of the patient groups to assess for differences between the groups that only appear farther out from the initial therapies.

In conclusion, this retrospective study of PROMIS functional and mental health outcomes in STS patients after surgical resection provides novel data about PROMIS scores during the *peri*-operative period for

patients undergoing pre- and post-operative radiotherapy and resection for STS. These data provide context for future studies of PROs in STS and may help identify patients that need enhanced functional and psychosocial intervention, such as older patients or those with larger tumors. Importantly, these data show that, on average, there is no difference in PROMIS scores at the pre-operative, immediate post-operative, and post-treatment completion time points for pre-operative versus post-operative radiotherapy. However, this study found that individuals with wound complications were more likely to have significantly decreased physical function and increased anxiety from baseline to treatment completion. Therefore, while pre-operative RT should be used for most patients, sequence of therapy should be carefully considered in patients at a high risk of a wound complication (i.e. patients with large thigh tumors, those who smoke, or patients with diabetes). In such patients undergoing pre-operative RT, care teams should be diligent in monitoring for functional and mental health declines when wound complications do occur and should target those patients for increased interventions.

### Declaration of Competing Interest

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### Data sharing statement

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

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2021.08.008>.

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