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

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ABSTRACT

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.
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
Radiotherapy was delivered per standard practices 1st 2015 and October 31st 2019. Exclusion criteria included absence of tissue sarcoma, and who were evaluated in the orthopedic oncology patients in the pre-operative RT group received a post-operative radiation operative RT was prescribed to 60
post-operative boost for positive margins (16
neoadjuvant or adjuvant RT. Patients who received pre-operative RT or
PROMIS scores at all orthopedic oncology visits and treatment without
Methods
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 RT 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. 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.

Table 1

| Demographic data of total patient population and of the two patient groups. |
|---------------------------------|----------|----------|----------|----------|
| Pathologic Diagnosis            | Total (N = 95) | Pre-op (N = 19) | Post-op (N = 76) | p-value |
| Liposarcoma                     | 37        | 15        | 22        | 0.11^c  |
| Liposarcoma                      | 37        | 15        | 22        | 0.11^c  |
| Diffuse fibrous sarcoma          | 21        | 10        | 11        | 0.059^c |
| Leiomyosarcoma                   | 9         | 9         | 0         | 0.008^a |
| Synovial Sarcoma                 | 7         | 7         | 0         | 0.045^a |
| Rhabdomyosarcoma                 | 5         | 5         | 0         | 0.008^a |
| Angiosarcoma                     | 5         | 3         | 2         | 0.014^a |
| Epithelioid Sarcoma              | 2         | 2         | 0         | 0.008^a |
| MPNST                             | 2         | 2         | 0         | 0.008^a |
| Other                            | 4         | 4         | 0         | 0.008^a |

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 metatases after surgical excision. Complication rate was defined consistent with the SR2 trial as secondary operation for wound repair (debridement, operative drainage, secondary wound closure), seroma aspiration, readmission 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 |
|--------------------------|--------------------------|---------|--------------------|----------|--------------|
| **A) Anxiety**           |                          |         |                    |          |              |
| 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         | 5.08    | 0.48               | 0.116    | 0.0166       | 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) Depression**        |                          |         |                    |          |              |
| 1 -> 2                   | Pre-operative RT         | 5.33    | 0.962              | -0.35    | -0.108       | Non-Significant |
|                          | Post-operative RT        | 5.57    |                     | -0.97    | 0.274        | Non-Significant |
| 1 -> 3                   | Pre-operative RT         | 5.83    | 0.17               | -0.37    | 0.47         | Non-Significant |
|                          | Post-operative RT        | 5.88    |                     | -0.05    | 0.015        | 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 |
| **C) Pain Interference** | Minimum Important Change |         | 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         | 6.05    | 1.06               | 0.265    | 0.0025       | Non-Significant |
|                          | Post-operative RT        | 6.65    |                     | 0.154    | 0.05         | Non-Significant |
| 2 -> 3                   | Pre-operative RT         | 6.08    | 0.822              | 4.17     | -1.699       | Significant Decrease |
|                          | Post-operative RT        | 5.73    |                     | -5.9     | -1.133       | Non-Significant |
| **D) Physical Function** | Minimum Important Change |         | Mean PROMIS Change | Mean RCI | Significance |
| 1 -> 2                   | Pre-operative RT         | 6.46    | 0.953              | -7.33    | -1.87        | Significant Decrease |
|                          | Post-operative RT        | 6.47    |                     | -7.09    | -1.81        | Non-Significant |
| 1 -> 3                   | Pre-operative RT         | 6.47    | 3.21               | -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        | Significant Increase |
|                          | Post-operative RT        | 6.73    |                     | 4.12     | 0.99         | Non-Significant |

\[ S_i = s_i \sqrt{1 - r_{xx}} \]

where \( S_i \) is the standard error of measurement of the test, \( s_i \) 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 the standard error of measurement of the test, \( s_i \) is the standard error of measurement of the test, \( r_{xx} \) 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].

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 0.43; \( p = 0.0017 \)) 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 Pre-op | Post-op | p-value |
|---------------|----------|-------------|---------|---------|
| Anxiety       | 30       | 54.0        | 52.6    | 56.0    | 0.28 |
| Depression    | 0        | 48.1        | 47.6    | 49.4    | 0.33 |
| Pain          | 0        | 56.0        | 57.4    | 56.0    | 0.72 |
| Function      | 0        | 42.5        | 43.4    | 42.3    | 0.63 |

2) Immediate Post-operative PROMIS Data

| PROMIS Domain | N missing | Total Pre-op | Post-op | p-value |
|---------------|----------|-------------|---------|---------|
| Anxiety       | 30       | 54.0        | 51.2    | 54.4    | 0.092 |
| Depression    | 0        | 48.2        | 46.2    | 48.2    | 0.42 |
| Pain          | 0        | 61.5        | 60.9    | 62.1    | 0.81 |
| Function      | 0        | 34.4        | 30.4    | 34.9    | 0.29 |

3) Post-treatment Completion PROMIS Data

| PROMIS Domain | N missing | Total Pre-op | Post-op | p-value |
|---------------|----------|-------------|---------|---------|
| Anxiety       | 12       | 51.2        | 51.2    | 51.2    | 0.37 |
| Depression    | 0        | 46.7        | 45.6    | 47.6    | 0.57 |
| Pain          | 0        | 56.0        | 54.4    | 56.0    | 0.87 |
| Function      | 0        | 41.7        | 38.6    | 43.1    | 0.057 |

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 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 MST5, 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].
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 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 that need enhanced functional and psychological interventions. Such interventions may help identify patients that need enhanced functional and psychological 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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