Title: Quality of Life Outcomes Associated with Primary Soft Tissue Sarcomas of the Extremity

Running Title: QOL in Soft Tissue Sarcoma

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Data Availability Statement

All data will be made available per the NCTN Data Archive rules. The link for the archive is: https://nctn-data-archive.nci.nih.gov/.

Keywords

Soft tissue sarcoma, IG-RT, Quality of life, Sexuality, Patient outcomes

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Abstract

Objectives: This clinical trial examined the effects of IG-RT without chemotherapy followed by limb-sparing resection on outcomes of physical disability and quality of life (QOL) in individuals with soft tissue sarcoma (STS) of either the upper or lower extremity.
Sample and Setting: Sixty-two participants, primarily white men with a median age of 60.5 years, completed measures in a NCIC clinical trial setting.

Methods and Variables: Three measures were completed four times over a two year period of time. Measures used were: Toronto Extremity Salvage Score (TESS); Functional Assessment of Cancer Therapy-General (FACT-G); and Sexual Adjustment Questionnaire (SAQ). Physicians scored functional performance using the Musculoskeletal Tumor Society Rating Scale (MSTS).

Results: No improvements were found in physical disability over the NCIC preoperative arm; while QOL measured by the FACT-G suggested limited improvement over time. Sexual adjustment appeared to worsen over time. MSTS scores weakly correlated with TESS results.

Implications for Nursing: Nurses must include discussions of impact of QOL, including sexuality, when educating about options for cancer treatments so patients can make informed decisions about costs/benefits of treatment choices.

Knowledge Translation statements:

1. More study of the impact of cancer treatments on sexuality is indicated.
2. Middle-aged patients with STS have concerns about their QOL, including sexuality.
3. The effects of physical disability on QOL in those with STS and other cancers is understudied.

Physical disability, sexuality and quality of life (QOL) as outcomes in patients after treatment for soft tissue sarcoma (STS) have been understudied. Instead, some investigators studying this population have used function and physical disability as a proxy for QOL (Davis et al., 1996; Schreiber et al., 2006) while others have examined physical performance, psychosocial adjustment and social acceptability as critical aspects of QOL (Hanley et al., 2004; Ide, Watanabe, & Toyonaga, 2002) In their classic study of QOL in sarcoma patients, Sugarbaker and colleagues (Sugarbaker, Barofsky, Rosenberg, & Gianola, 1982) were one of the first teams to include an assessment of sexuality. Although their findings on the impact of limb-sparing versus amputation on QOL were not conclusive, they did identify significant reduction in sexual functioning in the group treated with limb-sparing surgery and adjuvant radiation and chemotherapy. As yet, however, little definitive work has been completed related to physical disability, sexuality and general QOL in individuals with STS particularly those who are middle-aged. In this study, we aimed to explain the effects of Image Guided-Radiation Therapy (IG-RT) without chemotherapy followed by limb sparing resection (LSR) on the outcomes of physical disability, sexuality and global quality of life (QOL) in individuals diagnosed with soft tissue sarcoma (STS) of either the upper extremity (UE) or lower extremity (LE).

Introduction

Despite advances in understanding the impact of cancer treatments on sexuality in other types of cancer, such as breast and prostate, research remains scarce that investigates the impact of treatment of STS on the social/family well-being and emotional well-being aspects of QOL, which includes sexuality. The literature on re-integration into previous life activities has highlighted the continued lack of data on social discomfort, body-image anxieties, and sexuality in those with limb amputation (Pardasaney, Sullivan, Portney, & Mankin, 2006; Zahlten-Hinguranage, Bernd, Ewerbeck, & Sabo, 2004)

In one report on QOL in STS patient, researchers examined patients' perceptions of their ability to reintegrate into their life roles following treatment (Schreiber et al., 2006)]. Clinicians completed the Musculoskeletal Tumor Rating Scale (MSTS) evaluating each patient and patients completed the Toronto Extremity Salvage Score (TESS), the Reintegration to Normal Living Index (RNL) and the EQ-VAS, a one-item visual analog scale asking participants to rate their QOL on a scale of 0 to 100. The RNL measures patient perceptions about their ability to reintegrate into their lives. Study participants (n=100) were one year-post treatment; the majority were male, with a mean age of 55 years. Using a stepwise regression model, after adjusting for demographic and clinical variables, investigators found that restriction on resumption of previous life activities was the only variable with statistically significant impact on QOL, explaining 63% of the variance.

Davis and colleagues(Davis et al., 1996) evaluated the effect of late radiation morbidity on QOL in 194 patients with extremity sarcoma randomized to either preoperative or postoperative radiotherapy (the NCIC SR2 trial). The investigators measured patient function and physical disability using the TESS and the MSTS, and found no statistically significant differences between preoperative and postoperative radiotherapy groups in TESS and MSTS scores. However, patients with ≥ grade 2 fibrosis, joint stiffness, and edema reported significant physical disability measured by the TESS and significantly greater impairment measured by physicians using the MSTS.

Horgan and MacLachlan (2004) suggested that the impact on QOL may be similar in both limb salvage surgical (LSS) patients and in those with an amputation for lower extremity sarcoma. The primary difference might be in how QOL is expressed with LSS patients reporting higher QOL in terms of physical performance status, and patients with limb amputations associate QOL with social acceptability. Still other researchers have suggested that the degree of alteration in QOL is independent of type of surgery (LSS v. amputation) but rather depends on the site of the surgery, i.e., patients may have lower QOL if either type of surgery is above the knee (Ide, 2004).

There has been limited study on the effects of LSS or limb amputation specifically on sexuality. Ide, Watanabe and Toyonaga (2002) described physical and psychosocial status in the sexual life of individuals following amputation. Of the 85 participants (83.5% male; median age 50), more than 40% reported discussing sexual issues with another person in their daily life and 60% reported they engaged in coitus. Having a partner was the key factor for participants who remained sexually active and who reported satisfaction in their sexual life. This study may have limited application because the questionnaire had weak psychometric properties and was used with a Japanese population.

Questions remain, however, about how the various components of QOL are affected by radiation and surgery on those with extremity sarcoma, as well as the relationship between patients' general QOL and sexuality. Furthermore, the relationship between physician rating of the patient function using the MSTS and patient self-reports of QOL and sexuality remains unclear. Building on previous research and with these unaddressed questions in mind, we speculated that image-guided radiation therapy followed by limb sparing resection would reduce late radiation morbidity and improve physical function and quality of life, including sexuality, as reported by patients.

These questions were imbedded in a prospective multi-institutional phase II trial for preoperative IG-RT for extremity STS (Wang et al., 2015). The primary endpoint was to measure the effect of reduced radiation volume through the use of IG-RT on radiation morbidity (≥ Grade 2 lymphedema, subcutaneous fibrosis, or joint stiffness) two years post-treatment. A secondary endpoint of this trial was to evaluate QOL and to describe the trend over time with respect to four variables: late radiation morbidity, FACT-G, TESS, and SAQ.

Methods

Study Design

This examination of the influence of IG-RT [either image-guided three-dimensional conformal radiation treatment (3DCRT) or image-guided intensity modulated radiation treatment (IG-IMRT)] with (cohort A) or without chemotherapy (cohort B) followed by LSS on physical disability, quality of life and sexuality was part of a larger, multi-institutional prospective phase II trial designed to assess late toxicities in STS treated preoperatively by IG-RT(Wang et al., 2015) [For this study, we hypothesized that the degree of late radiation morbidities and physical impairment measured by the MSTS would correlate positively with the TESS (Davis et al., 1996) and with the functional well-being component of the Functional Assessment of Cancer Therapy – General (FACT-G) (Cella et al., 1993) and the Sexual Adjustment Questionnaire(Waterhouse & Metcalfe, 1986; Wilmoth, Hanlon, Ng, & Bruner, 2014).

Following consent to participate in the QOL portion of the study, participants completed three assessments –FACT-G, TESS, SAQ – at four time points: pretreatment (baseline), and at 1, 1.5 and 2 years from initiation of radiation treatment. Late radiation morbidity subcutaneous tissue fibrosis and joint stiffness were scored by RTOG/EORTC criteria and edema by Stern's scale (Table 1). Physicians completed the MSTS on each patient at the same time points.

Participants

Twelve participants were enrolled to Cohort A in the larger clinical trial between March 2008 and January 2010, at which time Cohort A was closed due to poor accrual and results are not reported (Wang, et al, 2015). Eighty-six participants were enrolled to Cohort B between March 2008 and September 2010. Seven were retrospectively declared ineligible leaving 79 patients from Cohort B potentially eligible for the QOL substudy. Of these 79 participants, 62 (78.5%) consented to participate in the QOL portion of the trial. Participants who consented to the QOL portion had significantly smaller tumors (median 9.95cm vs. 14.5cm, p=0.03) but there were no other statistically significant differences in patient or tumor characteristics (Table 2). Participants were predominantly male (58.1%), white (91.9%), with Zubrod performance status 0 (80.6%), and had disease in the lower extremity (83.9%); median age was 60.5 years. Rates of radiation late toxicity such as edema, subcutaneous fibrosis and joint stiffness (primary endpoint of this study) were previously reported (Wang et al., 2015).

Procedures

Measures

Quality of life was measured from 3 perspectives: physical disability from the patient's perspective using the Toronto Extremity Salvage Score (TESS), global quality of life using the Functional Assessment of Cancer Therapy-General form (FACT-G), and the impact on sexuality of loss/alteration in a limb using the Sexual Adjustment Questionnaire. Widely used in cancer research, these measures acceptable psychometric properties.

The Toronto Extremity Salvage Score (TESS) (Davis et al., 1996) is a questionnaire completed by patients in which they describe their ability to perform activities of daily living based on difficulty of performance. There are 2 versions of the TESS: one for individuals with an upper extremity tumor (29 questions) and the other for lower extremity tumors (including hip and buttocks; 30 questions). Each item is scored 1 through 5.

Higher scores indicate better QOL. Partially completed questionnaires were included in analysis. Internal consistency for the TESS has been reported as 0.94 (LE version) and 0.92 (UE version) and construct validity was estimated by showing a moderate correlation with the MSTS (Enneking, Dunham, Gebhardt, Malawar, & Pritchard, 1993).

The Functional Assessment of Cancer Therapy-General (FACT-G)(Cella et al., 1993) is a patient-reported 27-item questionnaire with four subscales: Physical Well-Being (7 questions), Social/Family Well-Being (7 questions), Emotional Well-Being (6 questions), and Functional Well-Being (7 questions). Each item is scored 0 to 4 yielding subscale total scores of 0 to 28, 0 to 28, 0 to 24, and 0 to 28. The overall score is the sum of the subscale scores (range 0 to 108). Subscale total scores were calculated only if participants answered more than 50% of subscale questions and calculated the overall score only if participants answered more than 80% of all questions. Higher scores indicated better QOL.

The Sexual Adjustment Questionnaire (SAQ)(Waterhouse & Metcalfe, 1986; Wilmoth et al., 2014) is a patient-reported 16-item questionnaire with three subscales: Sexual Activity (6 questions), Sexual Function (5 questions), and Sexual Satisfaction (5 questions). Each question is scored 1 to 5 and the overall score is the sum of the 16 items (range 16 to 80). Higher scores indicate lower sexual adjustment . Both the 16-item male version of the SAQ (mSAQ) (Wilmoth et al., 2014) and the longer female version (Waterhouse & Metcalfe, 1986) have satisfactory reliability and validity in samples of individuals with cancer. For the current study, missing answers were assigned the mean of the non-missing answers.

The physician's subjective perception of clinical aspects of the patient's condition was rated on the Musculoskeletal Tumor Rating Scale (MSTS). This measure includes ratings of pain, joint range of motion, strength, joint stability, joint deformity, overall function and the clinician's perception of the patient's acceptance of the treatment. The MSTS has seven items rated on a scale of 0 – 5 with summary scores ranging from 0 – 35 (Enneking, Dunham, Gebhardt, Malawar, & Pritchard, 1993). Higher scores reflect a more positive perception of the patient's condition by the clinician. Questionnaires with fewer than six responses were not included in analysis.

Data Analysis

We compared mean scores for the TESS and MSTS against the NCIC trial preoperative arm using a two-sample t-test. QOL means in patients with Grade 0-1 and Grade 2+ late toxicity (lymphedema and/or subcutaneous fibrosis and/or joint stiffness) at 2 years were calculated with and without adjustment for one additional covariate (age, gender, race, performance status, tumor location, T stage, histology, tumor size, RT type, R status, or major wound complications) using Analysis of Covariance (ANCOVA). Due to relatively small sample sizes at 2 years, adjusting for more than one covariate was not possible. Patients dropped out of the study over time We evaluated trends over time using the generalized linear mixed model adjusting for baseline covariates (age, gender, race, performance status, tumor location, T stage, and histology). Pearson correlation coefficients were calculated between each pair of tools at each time point.

Results

Compliance

The pretreatment, 1-year, 1.5-year, and 2-year TESS assessments were completed and useable in 82.3%, 54.8%, 45.2%, and 43.5%, respectively (Table 3). For FACT-G, the percentages were 83.9%, 50.0%, 48.4%, and 43.5%. For SAQ, the percentages were 71.0%, 38.7%, 43.5%, and

29.0%. Reasons for the decreases in response rate over time for all measures included death prior to the time point for the administration of the measures, patient refusal due to illness or other reason, patient unable to be contacted or not completed for unknown reasons. For the physician-scored MSTS, the percentages were 85.5%, 37.1%, 35.5%, and 32.3%, with institutional error the most common reason assessments were missed. All four assessments were completed for the TESS, FACT-G, SAQ, and MSTS in 24.2%, 24.2%, 16.1%, and 14.5% of patients, respectively.

TESS

The pretreatment mean was 81.4 and the 2-year mean was 81.6 (Table 4) indicating little change in function overall. TESS scores at 2 years were not improved relative to the NCIC preoperative arm (mean 85.4, p=0.41). The four patients with reported Grade 2+ late toxicity had mean 2-year TESS score of 68.8 compared with 83.6 for the 22 patients with Grade 0-1 late toxicity (p=0.16). Adding a single covariate did not change the means appreciably and no covariates approached significance (p-values 0.10 to 0.91). The least squares means were stable from pretreatment to 2 years (87.28, 87.16, 87.11, 85.25), and none of the changes from pretreatment were statistically significant (p-values 0.97, 0.95, and 0.49).

FACT-G

The pretreatment mean was 81.0 and the 2-year mean was 89.3, with the increase due to improvements in emotional and functional well-being (Table 5). The three patients with Grade 2+ late toxicity had mean 2-year FACT-G score 84.9 compared with 89.9 for the 22 patients with Grade 0-1 late toxicity (p=0.63). No covariates approached significance at the 0.05 level, but RT type [IMRT (mean 84.6) vs. 3DCRT (mean 99.7)] approached significance (p=0.07) The least squares means increased over time (83.72, 87.72, 88.01, and 88.85) with the change from pretreatment to 2 years nearly statistically significant (5.13 point increase, p=0.07).

SAQ

The pretreatment mean was 41.5 and the 2-year mean was 45.3, with increases in all 3 subscales indicating worse sexual adjustment (Table 6). The three patients with Grade 2+ late toxicity had a mean 2-year SAQ score 43.3 compared with 45.0 for the 14 patients with Grade 0-1 late toxicity (p=0.84) indicating slightly worse levels of sexual adjustment. Older age was significantly associated with worse SAQ scores at 2 years, either as a continuous variable (p=0.002) or dichotomized as > 60 (mean 39.0) vs. ≤ 60 (mean 54.0; p=0.02). No other covariates approached significance. The model R^2 was largest (0.52) when age as a continuous variable was in the model. The least squares means were higher at all three post-treatment time points relative to pretreatment (36.25 to 41.49 to 42.34 to 40.60) with the 1-year and 1.5-year changes from pretreatment statistically significant (1-year: 5.24 point increase, p=0.02; 1.5-year: 6.09 point increase, p=0.005); although not significant, there was a 4.35 point increase from pretreatment to 2 years. Age (p=0.008), gender (p=0.05), and histology (p=0.03) were significantly associated with SAQ score.

MSTS

The pretreatment mean was 31.0 and the 2-year mean was 30.7 compared to 30.0 for the NCIC preoperative arm (p=0.68; Table 7). Patients with Grade 2+ late toxicity had mean 2-year MSTS of 25.0 compared to 31.3 for patients with Grade 0-1 late toxicity (p=0.07) though the latter group only had 2 patients. The least squares means were stable over time [31.34 to 30.56 (p=0.48) to 30.76 (p=0.61) to 30.89 (p=0.70)].

Correlation

We aimed to identify correlations among physical functioning, QOL and sexuality, and found a significant correlation between physical functioning and quality of life, although we recognize that the small sample size at the later time points may not reflect actual changes in scores on various measures. Scores on the TESS and FACT-G were highly correlated at all 4 time points: baseline r=0.62, p<0.001; 1 year: r=0.58, p<0.001; 1.5 years: r=0.51, p=0.005; 2 years: r=0.63, p<0.001. This pair of measures also had the largest sample size at each time point.

Physical functioning (TESS) and sexuality (SAQ) had a significant negative relationship at baseline (r= - 0.34, p = 0.03); and nonsignificant negative association at 1 year (r=-0.30). Relationships were positive, although nonsignificant, at 1.5 years (r=0.16) and 2 years (r=0.19).

We found no relationship between the FACT-G and SAQ at baseline (r=-0.02). At 1 year (r = -0.26and 1.5 years (r = -0.21), the relationship was negative but nonsignificant, and at 2 years there was only marginal relationship (r = 0.05). Finally, there was very little correlation between the MSTS and TESS at baseline (r = 0.10) or 1 year (r = 0.04). At 1.5 years there was a significant positive correlation (r = 0.74, p < 0.0001); at 2 years there was a positive but nonsignificant correlation (r = 0.43, p = 0.07).

Discussion

This is one of a very few studies on IG-RT/LSR on QOL in STS and one of even fewer to include sexuality as a patient outcome separate from generalized QOL in this population. Survival rates for Stage 1 diagnosis of soft tissue sarcoma in the upper or lower extremity are approximately 90% with an average survival rate of 50% in disease that remains confined to the primary tumor site (cancer.org, 2018). This survival rate highlights the importance of designing treatments for early stage sarcoma leading to improved physical functioning, improved QOL and stabilization or improvement sexual adjustment. This report on the exploration of the impact of treatment for soft tissue sarcoma by IG-RT followed by surgery did support the proposition that a less radical limb sparing resection would result in reduction of late radiation morbidity and patient reports of improved physical function and quality of life.

In the larger study in which the data we use were collected (RTOG 0630), (Wang, et al, 2015) we observed a significant reduction of late toxicities in extremity sarcoma patients treated with image-guided radiotherapy to a reduced target volume compared to conventional preoperative radiotherapy. In this separate analysis of QOL data, late radiation morbidities at 2 years from the start of radiation treatment were reported for only 4 patients, which may explain no difference in mean TESS scores (measurement of patients' self-reported physical function activities) at pretreatment and at 2 years (81.4 vs. 81.6). We did however observe a large but non-significant difference in the mean TESS scores (68.8 vs. 83.6) between patients with severe late radiation morbidity ($n = 4$) and patients who did not ($n = 22$). This suggests that those with less RT toxicity may experience better physical functioning. Furthermore, results of this QOL study in conjunction with treatment outcome results of the RTOG 0630 (Wang et al., 2015) suggest the importance of designing treatments for localized sarcoma leading to improved physical functioning and improved QOL. Importantly, the negative effects on function related to severe late radiation morbidity are likely not reversible.

Clinician reports of functioning compared to patient reports of functioning showed a slight positive correlation but the clinical significance of these small relationships is unknown. Using the MSTS, Davis and colleagues (Davis et al., 2002; Davis et al., 1996) found improved functioning at the immediate post-operative visit in those who had had preoperative radiation therapy, but no significant differences at other times. The findings reported here as well as those by others underscore the concept that quality of life is measured more accurately by patient-reported measures rather than clinician-reported measures (Jacobsen & Jim, 2011).

Quality of life as measured by the FACT-G showed an average improvement in QOL over time, with improvements in both emotional and functional well-being. Improved emotional well-being scores over time may reflect patients' relief following their initial crisis response around receiving a cancer diagnosis. The improved functioning scores corroborate the improvement in physical functioning shown by the TESS in the majority, who experienced less severe radiation toxicity. Those who experienced Grade 2+ late toxicity had reduced QOL compared to those with less radiation toxicity, a finding we expected. In addition, our findings support those of Mason et.al, where they found significant differences between those with limb sparing had better QOL in areas such as job satisfaction, material wellbeing and occupational relationships compared to amputees (2013). Others have also shown advantage of limb sparing over amputation in functional quality of outcomes in younger populations (Ginsberg et al., 2007; Pardasaney et al., 2006). With these findings, our study suggests that there are benefits to limb sparing procedures compared to amputation in ensuring better QOL outcomes.

Although the number of participants who completed the SAQ was small, the trends we noted in worsening sexual adjustment over time are not necessarily unexpected in a sample of individuals in their late 50's and 60's with a chronic disabling and disfiguring disease that hinders movement. There are no data available on other chronic conditions in this sample, such as arthritis, chronic lung disease or heart disease, that may have contributed to a worsened sexual activity. Findings in this study that were intriguing yet difficult to explain were the reports of worse sexual adjustment in those with less severe symptoms of toxicity (n = 3 with Grade 2+ toxicity reported 2 year mean score of 43.3 and n = 14 with Grade 0-1 toxicity reported a 2 year mean score of 45.0). A possible explanation is that those with greater toxicity had ceased attempts at sexual activity while those with lesser degrees found that the joint stiffness and edema affected range of motion to a degree that made sexual activity uncomfortable if not difficult. However, the results we report here are consistent with those reported by Sugarbaker and colleagues (Sugarbaker et al., 1982) in their assessment of RT followed by LSR. The limb-spared patients in their study reported disturbed sexual functioning more often than those who had undergone amputation. One other study of patients undergoing limb sparing therapy found decreased sexual functioning and reports of decreased frequency of intercourse and interest in sex (Chang et al., 1989). A gap exists in the literature related to the impact of sexuality in individuals with STS and LSR, which warrants additional study. Although the findings reported here are not statistically significant (and might be explained by a small sample) and the small observed difference may not have clinical significance, they do indicate that more needs to be known about the effect of STS, current treatments and their effect on sexuality.

Analysis indicated that the patient self-reports of physical functioning on the TESS and on the FACT-G were significantly correlated at all four time points, a logical relationship because the FACT-G includes a 7-item Functional Well-Being scale. Based on the strength of this correlation, forgoing use of the 30-item TESS in this population and substituting the 27-item FACT-G may provide a more holistic evaluation of functioning with 3 fewer items, thus reducing patient burden somewhat. Given the small number of participants who completed the SAQ, correlations between the TESS and SAQ or the FACT-G and SAQ may be spurious and thus do not warrant further discussion.

Limitations to this study that preclude generalizing beyond this sample are the relatively small number of participants at the outset (n = 86) and the high participant attrition rate over the two year study period. In addition to the reasons for patient attrition identified in Table 3, we speculate that attrition may be related to the study burden in which participants were asked to complete the three QOL-related measures, which had a combined total of 73 items. One might also speculate that staff discomfort over asking middle-aged patients to complete a measure of sexuality could have affected patients and contributed to the relatively fewer number of completed SAQ over time. Eliminating use of the TESS in future studies in this population and using only the FACT-G and SAQ might increase patient participation and completion rates across time. All results should be considered hypothesis-generating given the small sample sizes.

Implications for Nursing

The findings from this clinical trial show that preoperative IG-RT followed by LSR led to a significantly reduced incidence of severe radiation toxicity at two years post treatment, which had a positive effect on gernalized quality of life in this sample of individuals with STS. This study adds new data about the physical functioning and quality of life impact of preoperative IG-RT followed by limb-sparing resection. Nurses working with these individuals need to be knowledgeable about the various treatment options and effects on patient outcomes while they educate patients about treatment side effects. Nurses also have the responsibility to speak knowledgeably about quality of life outcomes of cancer and its treatment. Given that little is known about sexuality in STS patients before, during or after treatment, and how this specific aspect of QOL is affected, nurses have the opportunity to lead further inquiry in this area.

Knowledge Translation

Pre-operative IG-RT followed by LSR can positively affect QOL in middle-aged patients, who remain concerned about living full lives. Despite the low response rate in this clinical trial, most people in their 50’s and 60’s remain interested in sexuality and nurses have the skills and knowledge to lead the research in this field.

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Table 1: Late toxicity grading

RTOG/EORTC late radiation toxicity criteria					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Subcutaneous tissue (subcutaneous fibrosis)	None	Slight fibrosis; subcutaneous fat loss	Moderate fibrosis; slight field contracture	Severe fibrosis; field contracture > 10%	Necrosis
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Joint (joint stiffness)	None	Mild stiffness; slight range of motion loss	Moderate stiffness, pain, range of motion loss	Severe stiffness, pain, range of motion loss	Necrosis; complete fixation
Stern's scale					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Edema	None	Mild (but definite swelling)	Moderate	Severe (considerable swelling)	Very severe (skin shiny and tight +/- skin cracking

Table 2

RTOG 0630 Cohort B: Patient and Tumor Characteristics by QOL Consent

	Consented to QOL		
	No (n=17)	Yes (n=62)	p-value
Age (years)			0.25 [1]
Mean (standard deviation)	62.5 (16.6)	58.8 (13.9)	
Median (min-max)	65 (28-87)	60.5 (24-88)	
Gender			0.11 [2]
Male	6 (35.3%)	36 (58.1%)	
Female	11 (64.7%)	26 (41.9%)	
Race			0.36 [2]
White	14 (82.4%)	57 (91.9%)	
Other	3 (17.6%)	5 (8.1%)	
Zubrod performance status			0.20 [2]
0	11 (64.7%)	50 (80.6%)	

Table 2

RTOG 0630 Cohort B: Patient and Tumor Characteristics by QOL Consent

	Consented to QOL		
	No (n=17)	Yes (n=62)	p-value
1	6 (35.3%)	12 (19.4%)	
Disease location			0.44 [2]
Upper extremity	1 (5.9%)	10 (16.1%)	
Lower extremity/hip/buttocks	16 (94.1%)	52 (83.9%)	
Disease size (longest diameter, cm)			0.03 [1]
Mean (standard deviation)	15.0 (6.8)	11.6 (6.8)	
Median (min-max)	14.5 (6.2-29)	9.95 (3.5-30)	
T stage			0.19 [2]
T1	0 (0.0%)	9 (14.5%)	
T2	17 (100.0%)	53 (85.5%)	
Histology			1.00 [2]

Table 2

RTOG 0630 Cohort B: Patient and Tumor Characteristics by QOL Consent

	Consented to QOL		
	No (n=17)	Yes (n=62)	p-value
Liposarcoma	3 (17.6%)	14 (22.6%)	
Other	14 (82.4%)	48 (77.4%)	

[1] Wilcoxon rank-sum test.

[2] Fisher's exact test.

Table 3

RTOG 0630 Cohort B: Tool Completion Status

(n=62)

	TESS	FACT-G	SAQ	MSTS
Pretreatment				
Completed, useable	51 (82.3%)	52 (83.9%)	44 (71.0%)	53 (85.5%)
Completed, not useable	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Completed, useable, outside time window	3 (4.8%)	3 (4.8%)	1 (1.6%)	2 (3.2%)
Not completed, patient refused due to illness	1 (1.6%)	1 (1.6%)	1 (1.6%)	0 (0.0%)
Not completed, patient refused due to other reason	1 (1.6%)	0 (0.0%)	8 (12.9%)	0 (0.0%)
Not completed, institutional error	3 (4.8%)	3 (4.8%)	3 (4.8%)	3 (4.8%)
Not completed, other reason	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)
Not completed, unknown reason	0 (0.0%)	0 (0.0%)	2 (3.2%)	2 (3.2%)
Not received	3 (4.8%)	2 (3.2%)	2 (3.2%)	2 (3.2%)
1 year [1]				
Completed, useable	34 (54.8%)	31 (50.0%)	24 (38.7%)	23 (37.1%)
Completed, not useable	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (1.6%)

Withdrawn consent prior to time point	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)
Death prior to time point	6 (9.7%)	6 (9.7%)	6 (9.7%)	6 (9.7%)
Not completed, patient refused due to illness	2 (3.2%)	2 (3.2%)	2 (3.2%)	3 (4.8%)
Not completed, patient refused due to other reason	1 (1.6%)	2 (3.2%)	5 (8.1%)	0 (0.0%)
Not completed, patient unable to be contacted	3 (4.8%)	3 (4.8%)	3 (4.8%)	1 (1.6%)
Not completed, institutional error	4 (6.5%)	4 (6.5%)	6 (9.7%)	16 (25.8%)
Not completed, other reason	7 (11.3%)	7 (11.3%)	8 (12.9%)	5 (8.1%)
Not completed, unknown reason	1 (1.6%)	1 (1.6%)	2 (3.2%)	1 (1.6%)
Not received	3 (4.8%)	4 (6.5%)	5 (8.1%)	5 (8.1%)
1.5 years [1]				
Completed, useable	28 (45.2%)	30 (48.4%)	27 (43.5%)	22 (35.5%)
Withdrawn consent prior to time point	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)
Death prior to time point	8 (12.9%)	8 (12.9%)	8 (12.9%)	8 (12.9%)
Not completed, patient refused due to illness	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)
Not completed, patient refused due to other reason	4 (6.5%)	4 (6.5%)	6 (9.7%)	1 (1.6%)

Not completed, patient unable to be contacted	4 (6.5%)	4 (6.5%)	2 (3.2%)	4 (6.5%)
Not completed, institutional error	5 (8.1%)	3 (4.8%)	4 (6.5%)	14 (22.6%)
Not completed, other reason	7 (11.3%)	7 (11.3%)	7 (11.3%)	7 (11.3%)
Not completed, unknown reason	0 (0.0%)	0 (0.0%)	2 (3.2%)	1 (1.6%)
Not received	4 (6.5%)	4 (6.5%)	4 (6.5%)	3 (4.8%)
2 years [1]				
Completed, useable	27 (43.5%)	27 (43.5%)	18 (29.0%)	20 (32.3%)
Completed, useable, outside time window	2 (3.2%)	2 (3.2%)	3 (4.8%)	1 (1.6%)
Withdrawn consent prior to time point	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)
Death prior to time point	11 (17.7%)	11 (17.7%)	11 (17.7%)	11 (17.7%)
Not completed, patient refused due to illness	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)
Not completed, patient refused due to other reason	4 (6.5%)	5 (8.1%)	8 (12.9%)	1 (1.6%)
Not completed, patient unable to be contacted	4 (6.5%)	5 (8.1%)	6 (9.7%)	4 (6.5%)
Not completed, institutional error	1 (1.6%)	2 (3.2%)	3 (4.8%)	9 (14.5%)
Not completed, other reason	6 (9.7%)	5 (8.1%)	6 (9.7%)	8 (12.9%)
Not completed, unknown reason	1 (1.6%)	0 (0.0%)	2 (3.2%)	2 (3.2%)
Not received	4 (6.5%)	3 (4.8%)	3 (4.8%)	4 (6.5%)

[1] Window: +/- 3 months. Measured from start of treatment.

Table 4

Comparison of TESS with NCIC Trial Preoperative Arm

Time point	Cohort	n	Mean	Standard deviation	Standard error of the mean	p-value (t-test)
Pretreatment	RTOG 0630 cohort B	51	81.4	19.49	2.73	0.25
	NCIC preoperative arm	91	85.1	17.70	1.86	
1 year	RTOG 0630 cohort B	34	83.2	15.64	2.68	0.82
	NCIC preoperative arm	77	82.4	18.10	2.06	
1.5 years	RTOG 0630 cohort B	28	86.0	15.31	2.89	N/A
	NCIC preoperative arm	N/A	N/A	N/A	N/A	

Table 4

Comparison of TESS with NCIC Trial Preoperative Arm

Time point	Cohort	n	Mean	Standard deviation	Standard error of the mean	p-value (t-test)
2 years	RTOG 0630 cohort B	27	81.6	18.64	3.59	0.41
	NCIC preoperative arm	34	85.4	17.10	2.93	

Table 5

RTOG 0630 Cohort B: FACT-G Scores over Time

Score	Time point	Sample size	Mean	SD [1]	SEM [2]	Min	Max
Total score	Pretreatment	52	81.0	16.31	2.26	45.7	108.0
	1 year	31	87.2	16.76	3.01	44.0	108.0
	1.5 years	30	88.1	12.81	2.34	58.0	107.0
	2 years	27	89.3	18.27	3.52	48.5	107.0
Total score, change [1]	1 year	29	2.2	20.24	3.76	-62.8	45.3
	1.5 years	26	4.0	13.12	2.57	-19.0	35.8
	2 years	24	4.8	12.43	2.54	-16.5	42.3
Physical well-being	Pretreatment	53	23.0	5.21	0.72	7.0	28.0
	1 year	32	23.9	4.78	0.85	8.0	28.0
	1.5 years	30	23.8	4.07	0.74	11.0	28.0
	2 years	27	23.6	4.63	0.89	9.0	28.0
Physical well-being, change [1]	1 year	29	-0.4	6.48	1.20	-18.8	18.0

Table 5

RTOG 0630 Cohort B: FACT-G Scores over Time

Score	Time point	Sample size	Mean	SD [1]	SEM [2]	Min	Max
	1.5 years	26	-0.3	5.03	0.99	-9.0	17.0
	2 years	24	-0.2	4.55	0.93	-9.7	12.0
Social well-being	Pretreatment	53	23.2	4.38	0.60	11.0	28.0
	1 year	31	22.9	6.02	1.08	0.0	28.0
	1.5 years	30	23.5	4.46	0.81	12.8	28.0
	2 years	27	23.9	4.80	0.92	11.0	28.0
Social well-being, change [1]	1 year	29	-0.7	6.36	1.18	-28.0	14.0
	1.5 years	26	0.2	3.44	0.68	-8.0	7.0
	2 years	24	-0.1	3.62	0.74	-7.0	14.0
Emotional well-being	Pretreatment	53	16.7	4.98	0.68	2.0	24.0
	1 year	32	19.3	4.37	0.77	7.0	24.0
	1.5 years	30	19.7	3.66	0.67	11.0	24.0
	2 years	27	19.8	4.43	0.85	5.0	24.0

Table 5

RTOG 0630 Cohort B: FACT-G Scores over Time

Score	Time point	Sample size	Mean	SD [1]	SEM [2]	Min	Max
Emotional well-being, change [1]	1 year	29	2.0	5.42	1.01	-17.0	12.0
	1.5 years	26	2.5	4.43	0.87	-7.0	12.0
	2 years	24	2.8	3.10	0.63	-2.0	11.0
Functional well-being	Pretreatment	53	18.5	6.58	0.90	5.0	28.0
	1 year	32	21.1	6.70	1.18	5.0	28.0
	1.5 years	30	21.1	5.62	1.03	7.0	28.0
	2 years	27	22.0	6.36	1.22	8.0	28.0
Functional well-being, change [1]	1 year	29	1.3	7.72	1.43	-23.0	14.3
	1.5 years	26	1.5	5.24	1.03	-10.0	13.0
	2 years	24	2.3	5.05	1.03	-8.0	13.3

SD: standard deviation; SEM: standard error of the mean.

[1] Change from pretreatment value.

Table 6

RTOG 0630 Cohort B: SAQ Scores over Time

Score	Time point	Sample size	Mean	SD [1]	SEM [2]	Min	Max
Total score	Pretreatment	44	41.5	12.35	1.86	23.0	72.0
	1 year	24	48.5	15.31	3.13	24.0	75.4
	1.5 years	27	46.4	16.28	3.13	23.0	80.0
	2 years	18	45.3	12.54	2.95	27.0	72.0
Total score, change [1]	1 year	21	4.4	7.96	1.74	-9.0	19.0
	1.5 years	21	7.3	13.88	3.03	-15.0	50.0
	2 years	14	6.9	6.41	1.71	-1.0	20.0
Sexual activity	Pretreatment	44	17.7	4.83	0.73	8.0	29.0
	1 year	24	19.3	5.91	1.21	10.0	29.4
	1.5 years	27	19.6	5.83	1.12	11.0	30.0
	2 years	18	18.6	5.31	1.25	11.0	30.0
Sexual activity, change [1]	1 year	21	1.3	2.46	0.54	-2.0	7.0
	1.5 years	21	3.0	4.57	1.00	-3.0	16.0

Table 6

RTOG 0630 Cohort B: SAQ Scores over Time

Score	Time point	Sample size	Mean	SD [1]	SEM [2]	Min	Max
	2 years	14	2.3	2.30	0.61	0.0	7.0
Sexual function	Pretreatment	44	11.7	4.22	0.64	5.0	19.8
	1 year	24	14.1	5.04	1.03	6.0	23.9
	1.5 years	27	13.3	5.42	1.04	5.0	25.0
	2 years	18	13.2	4.74	1.12	6.0	22.5
Sexual function, change [1]	1 year	21	1.5	2.96	0.64	-3.0	6.5
	1.5 years	21	2.8	5.01	1.09	-4.0	18.0
	2 years	14	2.3	3.53	0.94	-3.2	8.0
Satisfaction	Pretreatment	44	12.1	4.35	0.66	6.0	24.0
	1 year	24	15.2	5.28	1.08	7.0	23.3
	1.5 years	27	13.4	5.77	1.11	5.0	25.0
	2 years	18	13.5	3.52	0.83	6.0	19.7
Satisfaction, change [1]	1 year	21	1.6	3.73	0.81	-6.0	9.5

Table 6

RTOG 0630 Cohort B: SAQ Scores over Time

Score	Time point	Sample size	Mean	SD [1]	SEM [2]	Min	Max
	1.5 years	21	1.6	5.01	1.09	-8.0	16.0
	2 years	14	2.4	2.28	0.61	-1.0	6.5

SD: standard deviation; SEM: standard error of the mean.

[1] Change from pretreatment value.

Table 7

Comparison of MSTS with NCIC Trial Preoperative Arm

Time point	Cohort	n	Mean	Standard deviation	Standard error of the mean	p-value (t-test)
Pretreatment	RTOG 0630 cohort B	53	31.0	4.10	0.56	<0.001
	NCIC preoperative arm	91	27.1	4.00	0.42	
1 year	RTOG 0630 cohort B	23	30.3	4.62	0.96	0.14
	NCIC preoperative arm	80	28.3	8.50	0.95	
1.5 years	RTOG 0630 cohort B	22	30.5	5.74	1.22	N/A
	NCIC preoperative arm	N/A	N/A	N/A	N/A	
2 years	RTOG 0630 cohort B	20	30.7	4.66	1.04	0.68

Table 7

Comparison of MSTS with NCIC Trial Preoperative Arm

Time point	Cohort	n	Mean	Standard deviation	Standard error of the mean	p-value (t-test)
	NCIC preoperative arm	35	30.0	7.90	1.34	

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