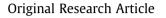
Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro



Using the revised Edmonton symptom assessment scale during neoadjuvant radiotherapy for retroperitoneal sarcoma



Russell F. Palm^{a,*}, Heather S.L. Jim^b, David Boulware^c, Peter A.S. Johnstone^a, Arash O. Naghavi^a

^a Department of Radiation Oncology. H. Lee Moffitt Cancer Center. Tampa, FL. USA

^b Health Outcomes and Behavior Department, H. Lee Moffitt Cancer Center, Tampa, FL, USA

^c Department of Biostatistics, H. Lee Moffitt Cancer Center, Tampa, FL, USA

ARTICLE INFO

Article history: Received 21 June 2019 Revised 20 February 2020 Accepted 25 February 2020 Available online 28 February 2020

Keywords: Sarcoma Retroperitoneal Radiation ESAS PRO Patient reported outcomes Toxicity

ABSTRACT

Background and purpose: Retroperitoneal sarcoma (RPS) is a rare, complex disease requiring multidisciplinary management. We have previously reported that use of the Revised Edmonton Symptom Assessment Scale (ESAS-r-CSS) allows for proactive symptom management, and we sought to report the results of ESAS-r-CSS screening during pre-operative radiotherapy (RT) for a cadre of patients with RPS.

Materials and methods: We reviewed records of 47 patients with RPS evaluated at our institution between 2015 and 2018. Of this group, 29 non-metastatic patients were treated with definitive intent neoadjuvant RT with at least 2 weekly ESAS-r-CSS reports. A generalized estimating equation model was used to compare 13 symptoms during weekly on-treatment visits compared to baseline scores at week 1 of RT. Additionally, covariate effects of age, gender, dose, tumor size and location were assessed.

Results: The population was predominantly male (66%) with median age of 65 years, KPS of 90, and tumor size of 12.8 cm. ESAS scores significantly decreased for anxiety at week 3 (P = 0.01), and pain at week 5 (P = 0.01). Worse constipation was reported at week 2 (P = 0.02). In an exploratory covariate analysis, female gender, age, high dose, and larger tumor size were associated with worse ESAS scores across all time points.

Conclusion: Patient reporting of symptoms during radiotherapy through weekly ESAS-r-CSS facilitates timely management in patients with this unique tumor type. Expectant care during RT offers the opportunity to minimize symptom progression or treatment interruptions in a population that generally has worsening side effects.

© 2020 The Authors. Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/ licenses/by-nc-nd/4.0/).

1. Introduction

Retroperitoneal sarcoma (RPS) is a rare disease that generally accounts for 10–20% of soft tissue sarcomas and with an incidence of less than 1% per 100,000 persons [1]. In reference to the results of radiotherapy for sarcoma of the trunk and extremities showing benefit in local control [2], radiation therapy has been used in preoperative treatment for RPS with support coming from retrospective analyses showing improved survival [3,4] and favorable results of small prospective phase II trials for disease control [5,6]. However, these findings have been called into question by conflicting retrospective evidence showing no improvement in survival or recurrence rate with radiotherapy [7] as well as the early outcomes from the STRASS trial that showed no benefit in preoperative radiotherapy to 50.4 Gy in its primary endpoint of abdominal relapse free survival [8]. While prospectively collected data mature, population-level reports have shown that the utilization of pre-operative radiotherapy has been increasing in both the academic and community setting [9].

To date, data are sparse regarding patient-reported symptoms during pre-operative radiotherapy for RPS. Patient symptom management during treatment can be challenging as the presenting symptoms for RPS can be variable due to tumor size and location, but classically include abdominal pain and a palpable mass [10]. However, poor appetite, dyspnea, changes in bowel habits, bleeding, or lower extremity edema can also be present [11]. A recent cohort study noted the most common reported physical symptoms

https://doi.org/10.1016/j.ctro.2020.02.007

^{*} Corresponding author at: Moffitt Cancer Center Magnolia Campus, Department of Radiation Oncology, 12902 USF Magnolia Drive Tampa, FL 33612, USA.

E-mail addresses: Russell.Palm@Moffitt.org (R.F. Palm), Heather.Jim@Moffitt.org (H.S.L. Jim), David.Boulware@Moffitt.org (D. Boulware), Peter.Johnstone@Moffitt. org (P.A.S. Johnstone), Arash.Naghavi@Moffitt.org (A.O. Naghavi).

^{2405-6308/© 2020} The Authors. Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

in RPS patients prior to starting radiotherapy were pain, fatigue, and appetite loss [12]. When utilizing 3D conformal radiotherapy, the University of Florida found that the rate of acute grade 1–2 enteritis dropped by more than half from 80% to 36% when implementing pre-operative rather than post-operative radiotherapy for RPS [13]. Other investigators have found common toxicities to be skin, fatigue, and nausea with a pre-operative approach without dose-limiting toxicity resulting in 75% of patients proceeding to surgery [14] however the temporal relationship of these toxicities during the course of radiotherapy were not reported.

To this end, the Edmonton Symptom Assessment System (ESAS) and its modifications have been used since 1991 in the palliative setting to systematically monitor patient symptomatology in the inpatient and outpatient settings [15], including the most common symptoms of fatigue, pain, loss of appetite, dyspnea, anxiety, and depression [16]. ESAS-reported symptom burden has been shown to be predictive of ER visits [17] and has been correlated with shorter survival in ambulatory cancer patients [18]. At our radiation oncology clinic, we have previously utilized the revised ESAS (ESAS-r-CSS) to explore symptom clusters for patients receiving palliative and definitive intent radiotherapy [19] and with expanded use across different oncology clinics we have reported our results on ESAS-driven screening for anemia [20]. The use of the ESAS questionnaire has also been explored in patients receiving definitive radiotherapy [21], particularly for breast [22] and esophageal cancer [23] as well as in sarcoma patients receiving chemotherapy [24]. Finally, studies have emphasized the use of symptom assessment tools such as ESAS to the reduce healthcare system burden due to treatment delays and costs of emergency room visits for breakthrough cancer pain management [25,26].

The goal of this study was to report RPS patient symptom progression through the duration of neoadjuvant radiotherapy to identify the timing of common symptoms and help initiate provider management. This information should be beneficial to educate treatment providers of the progression of symptoms during radiotherapy, improve anticipation, and increase uninterrupted treatment rates. Although sarcoma patients historically have symptom progression during radiation treatment, we believe the integration of ESAS-r-CSS into on-treatment-visits (OTVs) will provide an actionable tool for improving symptom management.

2. Materials and methods

2.1. Patients

Between 2015 and 2018, 47 patients were identified with a diagnosis of either primary or recurrent RPS who had been evaluated in the radiation oncology clinic. The inclusion criteria for this study included non-metastatic RPS, planned for neoadjuvant radiation followed by surgery with definitive intent, and >1 week of ESAS data. Of this population, 9 patients either did not receive radiation therapy or sought treatment at a different institution, 6 patients had no ESAS data available, 2 patients had a single week of ESAS data, and a single patient received palliative treatment. After exclusion of these cases, 29 patients had valid weekly radiotherapy ESAS scores (mean 4.2, range 2-6) obtained at OTVs by clinical staff and were included in analysis. Baseline symptoms were measured at the first week of therapy and were repeated weekly for up to 6 weeks on treatment. Radiation therapy treatment was performed with tomotherapy (80%) or intensity modulated radiotherapy, and daily on-line cone beam CT image guidance was utilized for all patients. The majority of patients were treated either to 50 Gy in 25 daily fractions of 200 cGy (33%) or with simultaneous integrated boost to 57.50 Gy in 25 fractions (48%) as previously described [27].

2.2. Data collection

Since 2015, the Radiation Oncology department of Moffitt Cancer Center has supported the ESAS-r-CSS questionnaire as a longitudinal clinical assessment for all patients seen in clinic and receiving radiation therapy [19]. Patients complete the ESAS-r-CSS inventory that includes nine common symptoms (pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, and overall wellbeing) experienced by oncology patients in the original ESAS [28] with modifications to include constipation, sleep disturbance, spiritual wellbeing, and a blank scale for other issues. This modified ESAS tool has improved clarity and formatting for admitted and ambulatory patients compared to the original ESAS [29], which has shown internal and test-retest reliability, high internal consistency, and convergent validity for ambulatory and inpatient non-hospice patients [30]. However, concerns have been raised regarding validity in the in the psychological and psychiatric domains, responsiveness, and interpretation outside of supportive care and palliative medicine [31]. Patients are asked to rate current symptoms on a scale of 0-10 (0 = none, 10 = worst possible). Per institutional policy, a value of 7 or greater was defined as the threshold for recommended practitioner intervention.

2.3. Statistical analysis

At the time of analysis, 14% of the symptom scores were missing. After examining the missing data, we used multiple imputation (predictive mean matching) on the survey data with missing values in weeks 1–5 of radiotherapy. A generalized estimating equation (GEE) model approach with repeated measures was used to analyze each of the thirteen scores across time. This approach was applied in a univariable fashion to assess the weekly effect relative to the first week established as the baseline symptom value. Graphical plots of the means across weeks and 95% confidence intervals were generated to help visualize the general trend of the scores over the course of radiotherapy. All models were adjusted for the baseline score. In addition, we tested for the covariate effects of age, dose, gender, and tumor location by the Wald Chi-Square test. As this was an exploratory analysis, we did not adjust for multiple testing. All analyses were performed in SAS version 9.4 (Cary, NC).

3. Results

Median age of the cohort was 65 years (range 22–86), 65.5% of the patients were male, median tumor size was 12.8 cm (range 3–40 cm), and 65.5% of cases were de-differentiated liposarcoma (Table 1). Survey compliance was 86% across the total course of treatment and no patients required treatment breaks. A total of 82.7% of patients were taken to surgery, while patients that did not undergo surgery were due to distant progression of disease (n = 4) and patient preference (n = 1).

Table 2 demonstrates the mean scores with standard deviation for all ESAS-r-CSS symptoms across the 5 weeks of radiotherapy with the generalized estimated difference score compared to the week 1 baseline. There were no statistically worse symptoms at the end of radiotherapy. Mean patient scores show that pain was decreased in week 5 (P = 0.01; Fig. 1A), and anxiety was decreased at week 3 (P = 0.01; Fig. 1B). Mean constipation scores were significantly worse at week 2 (P = 0.02; Fig. 1C) but improved to baseline thereafter. Twenty-one of 29 patients e-prescription records were able to be accessed for opioid prescriptions during radiotherapy, of which 9 (42.9%) had access to opioids during radiotherapy. Three patients of the analyzed cohort were referred to supportive care

Table 1

Descriptive statistics of retroperitoneal sarcoma patients (N = number of patients, % = percent of total patients, Gy = Gray, KPS = Karnofsky Performance Status).

		Ν	%
Gender	Male	19	65.5
	Female	10	34.5
Tumor Location	Right abdomen	13	44.8
	Left abdomen	12	41.4
	Bilateral abdomen	2	6.9
	Other	2	6.9
Dose/Fraction (Gy)	1.5	1	3.4
	1.8	2	6.9
	2.0	9	31
	2.15	2	6.9
	2.3	14	48.3
	3.5	1	3.4
Total Dose	≤50 Gy	12	41.4
	>50 Gy	17	58.6
Disease Recurrence	No	22	75.9
	Yes	7	24.1
Histological Grade	G1	2	7.4
	G2	7	25.9
	G3	18	66.7
	GX	2	7.4
Race	White	23	79.3
	Black	2	6.9
	Chinese	2	6.9
	Filipino	1	3.4
	Kampuchean	1	3.4
Marital Status	Divorced	3	10.3
	Married	20	69
	Single	3	10.3
	Widow	3	10.3
KPS	100	6	20.7
	90	15	51.7
	80	5	17.2
	70	3	10.3

with two instances for pain management and one for depressive symptoms.

Covariate effect on ESAS symptom scores across all time points were performed for age, gender, tumor location, radiation dose, and tumor size (Table 3). Females were more likely to report higher mean nausea scores (P = 0.005) and have higher mean total symptomatology (P = 0.01). Older age was significantly associated with several ESAS symptoms, including higher mean total symptom score (P = 0.03), appetite (P = 0.02), shortness of breath (P = 0.02), depression (P = 0.03), anxiety (P = 0.01), and constipation (P = 0.047). Dose > 50 Gy was significantly associated with increased higher pain scores (P = 0.02). Tumor size was associated with higher overall total score ($P \le 0.001$), pain ($P \le 0.001$), tiredness (P = 0.007), shortness of breath (P = 0.03), and overall wellbeing (P = 0.001). When stratified by laterality in the abdomen, tumor location had no significant effect on symptoms.

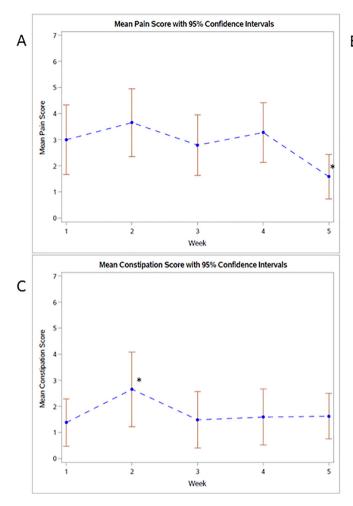
4. Discussion

Patient-reported symptoms during definitive radiation have been described, with patients reporting worse general wellbeing, tiredness, anxiety, and depression in a third of this population, with a quarter experiencing significant pain and lack of appetite [21]. However, data are limited specifically within pre-operative management of RPS. A publication regarding patient reported outcomes by Wong et al. [12] of 48 RPS patients from 2 cohorts that underwent pre-operative radiotherapy followed by surgery showed that 54% of RPS patients experience gastrointestinal toxicity at the completion of radiation therapy and symptom burden significantly associated with overall quality of life. However, they did not find a correlation between radiation dose, tumor size, age or gender on quality of life at 36 months. In contrast to this study, their analysis only included eleven patients with baseline quality of life data prior to radiation therapy and primarily focused on long term follow-up after radiation and surgical resection, offering little granularity on symptomatology during radiation delivery. In this regard, toxicity data from small trials and retrospective analyses in pre-operative external beam radiotherapy to 45-50 Gy for RPS have shown primarily grade 1 or 2 toxicity in a half of patients [12,32,33], and 15% grade 3 or 4 acute toxicity was reported in a trial that included preoperative IMRT with intraoperative radiotherapy [34]. However, 7–11% of patients have been unable to complete pre-operative radiotherapy underlying the potential

Table 2

Symptom score summary table for each week on treatment. Score reported are means with standard deviation followed by the generalized estimated difference from the baseline with level of significance bolded if $P \leq 0.05$ (SOB: shortness of breath).

ESAS-r-CSS Symptoms	Week 1 Mean (Std Dev)	Estimated Difference (P- value)	Week 2 Mean (Std Dev)	Estimated Difference (P- value)	Week 3 Mean (Std Dev)	Estimated Difference (P- value)	Week 4 Mean (Std Dev)	Estimated Difference (P- value)	Week 5 Mean (Std Dev)	Estimated Difference (P- value)
Total Score	24.41 (17.37)	ref	29.9 (22.33)	6.00 (0.12)	24.93 (18.02)	0.47 (0.91)	27.52 (18.88)	3.14 (0.29)	23.76 (17.93)	-0.95 (0.81)
Pain Score	3 (3.49)	ref	3.66 (3.42)	0.61 (0.27)	2.79 (3.05)	-0.26 (0.56)	3.28 (3.02)	0.22 (0.70)	1.59 (2.24)	-1.43 (0.01)
Tired Score	4.34 (3.23)	ref	5.31 (3.2)	1.09 (0.06)	5.1 (3.06)	0.69 (0.26)	4.86 (3.01)	0.51 (0.41)	3.9 (2.91)	-0.42(0.53)
Drowsiness Score	1.52 (2.75)	ref	2.86 (3.43)	1.35 (0.07)	2.45 (3.08)	0.92 (0.25)	2.38 (2.66)	0.84 (0.20)	2.14 (2.43)	0.59 (0.42)
Nausea Score	2.41 (3.41)	ref	3.14 (3.94)	0.82 (0.26)	2.86 (3.19)	0.56 (0.42)	3.1 (3.54)	0.80 (0.16)	2.66 (3.18)	0.26 (0.70)
Appetite Score	2.24 (2.9)	ref	3.1 (3.19)	0.91 (0.21)	3.14 (3.2)	0.88 (0.24)	2.97 (3.46)	0.72 (0.22)	3.07 (3.06)	0.84 (0.10)
SOB Score	0.9 (1.82)	ref	1.1 (2.3)	0.26 (0.56)	0.97 (2.32)	0.08 (0.86)	0.9 (1.95)	-0.02 (0.96)	0.76 (2.06)	-0.12 (0.74)
Depression Score	1.45 (2.59)	ref	1.24 (1.96)	-0.16 (0.68)	0.86 (1.77)	-0.57 (0.23)	1.41 (2.54)	0.03 (0.95)	1.07 (2.05)	-0.45 (0.39)
Anxiety Score	1.79 (3.02)	ref	1.86 (2.84)	0.02 (0.96)	0.66 (1.63)	-1.12 (0.01)	1.45 (2.86)	-0.34 (0.54)	1.14 (2.5)	-0.81 (0.12)
Overall Wellbeing Score	2.03 (2.49)	ref	2.34 (2.69)	0.33 (0.63)	2 (2.36)	0.06 (0.91)	2.41 (2.6)	0.40 (0.32)	2.59 (3.1)	0.68 (0.28)
Spiritual Wellbeing Score	0.38 (1.57)	ref	0.1 (0.56)	-0.23 (0.19)	0.34 (1.52)	-0.04 (0.91)	0.45 (1.33)	0.09 (0.87)	0.34 (0.97)	-0.05 (0.87)
Constipation Score	1.38 (2.38)	ref	2.66 (3.77)	1.34 (0.02)	1.48 (2.85)	0.30 (0.56)	1.59 (2.83)	0.26 (0.54)	1.62 (2.31)	0.45 (0.48)
Sleep Score	2.52 (3.09)	ref	1.72 (2.9)	-0.73 (0.27)	1.93 (2.96)	-0.64 (0.38)	2.41 (3.24)	0.006 (0.99)	1.86 (2.64)	-0.59 (0.40)



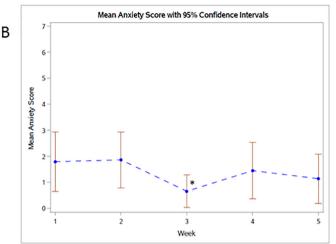


Fig. 1. Line graphs demonstrate mean symptom scores across weeks of treatment with standard deviation for pain (A), anxiety (B) and constipation (C). Asterisks indicate statistical significance from baseline week 1 scores with $P \le 0.05$.

Table 3

Generalized estimate of overall covariate effect on symptom scores across radiotherapy treatment course. Positive values indicate a correlation with increased symptom scores and are bolded if $P \leq 0.05$. Tumor location is based on lateralization with right abdomen as reference.

ESAS-r-CSS Symptom	Age (P-value)	Female Gender (P-value)	Tumor Location (P-value)	Dose > 50 Gy (P-value)	Tumor Size (P-value)
Total Score	0.37 (0.03)	8.08 (0.01)	5.51 (0.33)	7.2 (0.19)	0.67 (<0.0001)
Pain Score	0.03 (0.17)	1.28 (0.15)	0.32 (0.71)	1.69 (0.02)	0.12 (0.0003)
Tired Score	0.03 (0.20)	0.93 (0.30)	1.08 (0.25)	0.92 (0.29)	0.09 (0.007)
Drowsiness Score	<-0.01 (0.98)	0.66 (0.20)	0.91 (0.09)	0.65 (0.20)	0.02 (0.51)
Nausea Score	0.006 (0.81)	2.70 (0.005)	0.80 (0.47)	0.62 (0.54)	0.06 (0.27)
Appetite Score	0.05 (0.02)	1.10 (0.14)	-0.43 (0.62)	1.30 (0.09)	0.05 (0.27)
SOB Score	0.03 (0.02)	-0.25 (0.67)	0.20 (0.64)	0.07 (0.91)	0.09 (0.03)
Depression Score	0.04 (0.03)	-0.08 (0.90)	0.89 (0.17)	0.39 (0.55)	0.05 (0.18)
Anxiety Score	0.06 (0.01)	1.22 (0.21)	0.69 (0.36)	0.45 (0.59)	0.04 (0.34)
Overall Wellbeing Score	0.03 (0.07)	0.31 (0.60)	0.24 (0.68)	0.75 (0.15)	0.07 (0.001)
Spiritual Wellbeing Score	0.01 (0.15)	0.05 (0.89)	0.27 (0.16)	0.14 (0.61)	0.02 (0.13)
Constipation Score	0.04 (0.047)	0.05 (0.94)	-0.14 (0.85)	-0.05 (0.95)	-0.02(0.62)
Sleep Score	0.03 (0.15)	0.12 (0.89)	0.61 (0.49)	0.24 (0.78)	0.06 (0.06)

acute toxicity of this treatment and potential benefit of anticipatory care [5,34]. Importantly, other retrospective analyses have shown no increased short-term perioperative morbidity associated with pre-operative external beam radiation [35,36] but has been noted in patients receiving post-operative interoperative radiotherapy [34] and brachytherapy boosts [33].

From our clinical experience following twenty-nine patients with baseline symptom scores, the utilization of weekly ESAS evaluations allowed for close monitoring of symptoms while on treatment with notable findings of decreased pain and anxiety from baseline, and worsening constipation at week 2 of radiotherapy. Our findings contrast with other reports assessing pre- and postradiotherapy ESAS scores for patients undergoing definitive radiotherapy that have shown increased pain and impairment of wellbeing after radiotherapy [21] as well as increased physical complaints when measured by the Screening Inventory of Psychosocial Problems (SIPP) [37]. While the patients from these studies were not stratified by type of disease or disease location, this exemplifies the potential benefit of utilizing ESAS-r-CSS during OTVs for proactive management of patient concerns and symptoms prior to the need for treatment breaks as all of our patients were able to complete treatment uninterrupted.

Decreases in patient psychological unease on treatment are multifactorial with the benefit of weekly on-treatment visits, acclimation to the routine of the radiation schedule, therapeutic response of their disease, adjustment to the diagnosis, and referral to supportive care services (e.g. behavioral health, social work). By week three, patients reported significantly less anxiety than at the beginning of radiation therapy. Other series have also noted that prior to starting radiation therapy 41% of patients have high anxiety and 33% of patients report depression that decrease over the course of their radiation treatment [38]. Further investigations involving radiation therapist led interventions [39] and music therapy [40] have also shown promise in managing patient anxiety while on treatment. These symptoms are important to note as cancer patients have a higher risk of psychological distress than healthy controls and patients with chronic diseases in a population level analysis [41], and elevations in anxiety and depression have been significantly associated with unmet needs in cancer patients [42]. Specifically within sarcoma, the psychosocial impact of diagnosis and treatment is poorly understood [43] with a high proportion of patients reporting psychological distress at disease presentation [44]. Patient reported measures of psychosocial health may help to identify these symptoms and enable providers to improve patients' psychological wellbeing through a multifaceted and multidisciplinary approach with involvement of supportive care and behavioral medicine.

Older patients and patients with large tumors appeared to have the greatest symptom burden in our exploratory multivariate analysis. There was a significant association of increasing age with several ESAS scores including appetite, constipation, shortness of breath, depression, and anxiety. This subpopulation should be closely monitored while on treatment as their symptoms are likely amplified due to a lower physiological reserve, and a reduced threshold for symptom management should be recommended. Additionally, patients with larger tumors also reported higher pain, tiredness, shortness of breath, and worse overall wellbeing; symptoms that can be frequently associated with increased mass effect of the tumor or higher organ at risk bystander radiation from treating larger volumes of disease.

It is important to note that many patients experience increased discomfort during treatment, likely due to inflammation and edema from tumor response to radiotherapy. Perhaps due to this effect, mean symptom scores increased in the second week of therapy in ten of thirteen ESAS domains, and significantly differed from baseline in constipation which is possibly explained by use of opioid medication and showed subsequent management with bowel regimen. Studies of radiographic response of sarcoma patients to pre-operative radiation have shown that tumor volume is primarily stable, however individual response can vary dramatically with a range in tumor percent diameter decreases to -25%, and increases from +31% to +86% volume [45,46]. We believe that the induction of intra-tumoral necrosis often softens the tumor and decreases mass effect symptoms, which is another possible explanation of improved mean pain scores by week 5 of radiotherapy. While therapeutic effect is certainly considered, recent studies in managing cancer-related pain have noted a benefit in patient screening [47], which the standardized use of ESAS symptom reporting has allowed.

Drowsiness, tiredness, and sleep quality are inherently related symptoms that can be affected by therapy-associated fatigue [19]. This is a well-established side effect of radiation that can be debilitating to patients who intend to work or maintain a high level of activity during treatment. Delineating between these symptoms may be difficult for patients, and clarification of this symptom cluster may show benefit in future studies. After behavioral modification and assessment of sleep hygiene, depending on performance status, we recommend daily mild to moderate physical activity to manage sleep cycle regulation prior to initiating pharmacotherapy. Combating fatigue with exercise has been most thoroughly described in breast cancer patients [48,49], with a mechanism of action thought to be due to downregulation of cytokines [50]. Although other disease sites may see improvement in these side effects with adoption of hypofractionation, retroperitoneal sarcoma treatment regimens commonly involve at least 5 weeks of therapy due to the proximity to organs at risk (e.g. small bowel, stomach, etc.). Therefore, understanding the progression of these symptoms in this population will continue to be pertinent.

Strengths of the study are a focus on an understudied population and utilization of patient reported outcomes encompassing a time period during the delivery of radiotherapy. Limitations include a retrospective, observational study design as well as a lack of comparison group not receiving radiotherapy. As CTC and RTOG toxicity was not systematically collected in this cohort, correlations with provider-assessed toxicity was unable to be performed and is an area of further inquiry. It is important to note that ESAS symptom severity and patient concern has been shown to correlate in only 42% of patients, with pain and tiredness being among the most frequent bothersome symptoms [51]. As postulated by these authors, modifying our data collection to add patient prioritization of symptoms may help further focus provider management even if the institutional threshold for intervention is not met. Moreover, revisions to symptom score severity thresholds have been proposed with an optimal cutoff at 8 for severe fatigue and 6 for dyspnea [52] and lower thresholds or qualitative measures [53] for anxiety and depression may lead to improved detection and enable earlier intervention. Finally, the ESAS-r-CSS does not systematically include a measurement for diarrhea symptoms which can be expected in radiotherapy to large volumes of the abdomen, although diarrhea is generally managed in the ambulatory setting and toxicity requiring hospitalization was not encountered in this cohort. Other investigators have proposed a physician and patient driven sarcoma 12-point inventory that also did not report on diarrhea symptoms [54] but underlies the potential for disease and tumor location specific tools.

5. Conclusions

This study provides temporally sensitive information to the multidisciplinary oncology teams managing this rare cancer population during neoadjuvant radiotherapy. In addition, we believe that implementation of ESAS-r-CSS during weekly radiotherapy OTVs facilitates proactive symptom management for providers and minimizes treatment breaks to allow patients to complete their prescribed course of treatment and proceed with further definitive therapy.

Conflicts of interest

None of the authors report conflicts of interest.

References

- Mettlin C, Priore R, Rao U, Gamble D, Lane W, Murphy P. Results of the national soft-tissue sarcoma registry. J Surg Oncol 1982;19:224–7.
- [2] Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998;16:197–203. <u>https://doi.org/10.1200/JCO.1998.16.1.197</u>.
- [3] Nussbaum DP, Rushing CN, Lane WO, Cardona DM, Kirsch DG, Peterson BL, et al. Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database. Lancet Oncol 2016;17:966–75. https://doi.org/10.1016/S1470-2045(16)30050-X.

- [4] Turner BT, Hampton L, Schiller D, Mack LA, Robertson-More C, Li H, et al. Neoadjuvant radiotherapy followed by surgery compared with surgery alone in the treatment of retroperitoneal sarcoma: a population-based comparison. Curr Oncol 2019;26:e766-72. <u>https://doi.org/10.3747/co.26.5185</u>.
- [5] Pawlik TM, Pisters PWT, Mikula L, Feig BW, Hunt KK, Cormier JN, et al. Longterm results of two prospective trials of properative external beam radiotherapy for localized intermediate- or high-grade retroperitoneal soft tissue sarcoma. Ann Surg Oncol 2006;13:508–17. <u>https://doi.org/10.1245/ ASO.2006.05.035</u>.
- [6] Smith MJF, Ridgway PF, Catton CN, Cannell AJ, O'Sullivan B, Mikula LA, et al. Combined management of retroperitoneal sarcoma with dose intensification radiotherapy and resection: long-term results of a prospective trial. Radiother Oncol 2014;110:165–71. <u>https://doi.org/10.1016/j.radonc.2013.10.041</u>.
- [7] Chouliaras K, Senehi R, Ethun CG, Poultsides G, Grignol V, Clarke CN, et al. Role of radiation therapy for retroperitoneal sarcomas: An eight-institution study from the US Sarcoma Collaborative. J Surg Oncol 2019;120:1227–34. <u>https:// doi.org/10.1002/iso.25694</u>.
- [8] Bonvalot S, Gronchi A, Le Pechoux C, Swallow CJ, Strauss DC, Meeus P. STRASS (EORTC 62092): a phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma. J Clin Oncol 2019;37(Suppl; Abstr 11001). <u>https://doi.org/10.1200/</u> <u>ICO.2019.37.15_suppl.11001</u>.
- [9] Lazarev S, McGee H, Moshier E, Ru M, Demicco EG, Gupta V. Preoperative vs postoperative radiation therapy in localized soft tissue sarcoma: nationwide patterns of care and trends in utilization. Pract Radiat Oncol 2017;7:e507–16. <u>https://doi.org/10.1016/j.prro.2017.04.010</u>.
- [10] Bolin TE, Bolin SG, Wetterfors J. Retroperitoneal sarcomas. An analysis of 32 cases. Acta Chir Scand 1988;154:627–9.
- [11] Windham TC, Pisters PWT. Retroperitoneal sarcomas. Cancer Control 2005;12:36–43. <u>https://doi.org/10.1177/107327480501200105</u>.
- [12] Wong P, Kassam Z, Springer AN, Gladdy R, Chung P, Ringash J, et al. Long-term quality of life of retroperitoneal sarcoma patients treated with pre-operative radiotherapy and surgery. Cureus 2017;9:e1764. <u>https://doi.org/10.7759/ cureus.1764</u>.
- [13] Zlotecki RA, Katz TS, Morris CG, Lind DS, Hochwald SN. Adjuvant radiation therapy for resectable retroperitoneal soft tissue sarcoma: the University of Florida experience. Am J Clin Oncol 2005;28:310–6. <u>https://doi.org/10.1097/ 01.coc.0000158441.96455.31</u>.
- [14] Alford S, Choong P, Chander S, Henderson M, Powell G, Ngan S. Outcomes of preoperative radiotherapy and resection of retroperitoneal sarcoma. ANZ J Surg 2013;83:336-41. <u>https://doi.org/10.1111/j.1445-2197.2012.06211.x</u>.
- [15] Hui D, Bruera E. The Edmonton symptom assessment system 25 years later: past, present, and future developments. J Pain Symptom Manage 2017;53:630–43. <u>https://doi.org/10.1016/j.ipainsymman.2016.10.370</u>.
- [16] Portenoy RK, Thaler HT, Kornblith AB, Lepore JM, Friedlander-Klar H, Coyle N, et al. Symptom prevalence, characteristics and distress in a cancer population. Qual Life Res 1994;3:183–9.
- [17] Barbera L, Atzema C, Sutradhar R, Seow H, Howell D, Husain A, et al. Do patient-reported symptoms predict emergency department visits in cancer patients? A population-based analysis. Ann Emerg Med 2013;61(427–437):. https://doi.org/10.1016/i.annemergmed.2012.10.010e5.
- [18] Barbera L, Seow H, Howell D, Sutradhar R, Earle C, Liu Y, et al. Symptom burden and performance status in a population-based cohort of ambulatory cancer patients. Cancer 2010;116:5767–76. <u>https://doi.org/10.1002/cncr.25681</u>.
- [19] Johnstone PAS, Lee J, Zhou J-M, Ma Z, Portman D, Jim H, et al. A modified Edmonton symptom assessment scale for symptom clusters in radiation oncology patients. Cancer Med 2017;6:2034–41. <u>https://doi.org/ 10.1002/cam4.1125</u>.
- [20] Johnstone PAS, Alla R, Yu H-HM, Portman D, Cheng H, Mitchell R, et al. Patientreported outcomes: using ESAS to screen for anemia. Support Care Cancer 2019. <u>https://doi.org/10.1007/s00520-019-05238-6</u>.
- [21] Körner P, Ehrmann K, Hartmannsgruber J, Metz M, Steigerwald S, Flentje M, et al. Patient-reported symptoms during radiotherapy: clinically relevant symptom burden in patients treated with palliative and curative intent. Strahlenther Onkol 2017;193:570–7. <u>https://doi.org/10.1007/s00066-017-1146-5</u>.
- [22] Chow S, Wan BA, Pidduck W, Zhang L, DeAngelis C, Chan S, et al. Symptoms predictive of overall quality of life using the Edmonton symptom assessment scale in breast cancer patients receiving radiotherapy. Clin Breast Cancer 2019;19:405–10. <u>https://doi.org/10.1016/j.clbc.2019.05.007</u>.
- [23] Gupta V, Allen-Ayodabo C, Davis L, Zhao H, Hallet J, Mahar AL, et al. Patientreported symptoms for esophageal cancer patients undergoing curative intent treatment. Ann Thorac Surg 2020;109:367–74. <u>https://doi.org/10.1016/j. athoracsur.2019.08.030</u>.
- [24] Granda-Cameron C, Hanlon AL, Lynch MP, Houldin A. Experience of newly diagnosed patients with sarcoma receiving chemotherapy. Oncol Nurs Forum 2011;38:160–9. <u>https://doi.org/10.1188/11.ONF.160-169</u>.
- [25] Pérez-Hernández C, Jiménez-López AJ, Sanz-Yagüe A, Mar-Medina J, Larrañaga I, Soler-López B. Observational study evaluating the economic impact of breakthrough pain in cancer patients in clinical practice in Spain: the IMDI study. Pain Ther 2018;7:227–40. <u>https://doi.org/10.1007/s40122-018-0102-0</u>.
- [26] Camps Herrero C, Batista N, Díaz Fernández N, Escobar Álvarez Y, Gonzalo Gómez A, Isla Casado D, et al. Breakthrough cancer pain: review and calls to action to improve its management. Clin Transl Oncol 2020. <u>https://doi.org/ 10.1007/s12094-019-02268-8</u>.

- [27] Baldini EH, Wang D, Haas RLM, Catton CN, Indelicato DJ, Kirsch DG, et al. Treatment guidelines for preoperative radiation therapy for retroperitoneal sarcoma: preliminary consensus of an international expert panel. Int J Radiat Oncol Biol Phys 2015;92:602–12. <u>https://doi.org/10.1016/j. ijrobp.2015.02.013</u>.
- [28] Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The edmonton symptom assessment system (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991;7:6–9.
- [29] Watanabe SM, Nekolaichuk C, Beaumont C, Johnson L, Myers J, Strasser F. A multicenter study comparing two numerical versions of the Edmonton symptom assessment system in palliative care patients. J Pain Symptom Manage 2011;41:456–68. <u>https://doi.org/10.1016/j.</u> ipainsymman.2010.04.020.
- [30] Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton symptom assessment scale. Cancer 2000;88:2164–71. <u>https://doi.org/10.1002/(sici)</u> 1097-0142(2000501)88:9<2164::aid-cncr24>3.0.co;2-5.
- [31] Richardson LA, Jones GW. A review of the reliability and validity of the Edmonton symptom assessment system. Curr Oncol 2009;16:55. <u>https://doi. org/10.3747/co.v16i1.261</u>.
- [32] El-Bared N, Taussky D, Mehiri S, Patocskai E, Roberge D, Donath D. Preoperative intensity modulated radiation therapy for retroperitoneal sarcoma. Technol Cancer Res Treat 2014;13:211–6. <u>https://doi.org/10.7785/ tcrt.2012.500371</u>.
- [33] Jones JJ, Catton CN, O'Sullivan B, Couture J, Heisler RL, Kandel RA, et al. Initial results of a trial of preoperative external-beam radiation therapy and postoperative brachytherapy for retroperitoneal sarcoma. Ann Surg Oncol 2002;9:346–54. <u>https://doi.org/10.1007/bf02573869</u>.
- [34] Roeder F, Ulrich A, Habl G, Uhl M, Saleh-Ebrahimi L, Huber PE, et al. Clinical phase I/II trial to investigate preoperative dose-escalated intensity-modulated radiation therapy (IMRT) and intraoperative radiation therapy (IORT) in patients with retroperitoneal soft tissue sarcoma: interim analysis. BMC Cancer 2014;14:617. https://doi.org/10.1186/1471-2407-14-617.
- [35] Bartlett EK, Roses RE, Meise C, Fraker DL, Kelz RR, Karakousis GC. Preoperative radiation for retroperitoneal sarcoma is not associated with increased early postoperative morbidity. J Surg Oncol 2014;109:606–11. <u>https://doi.org/ 10.1002/jso.23534</u>.
- [36] Nussbaum DP, Speicher PJ, Gulack BC, Ganapathi AM, Keenan JE, Stinnett SS, et al. The effect of neoadjuvant radiation therapy on perioperative outcomes among patients undergoing resection of retroperitoneal sarcomas. Surg Oncol 2014;23:155–60. <u>https://doi.org/10.1016/j.suronc.2014.07.001</u>.
- [37] Braeken APBM, Kempen GIJM, Eekers D, van Gils FCJM, Houben RMA, Lechner L. The usefulness and feasibility of a screening instrument to identify psychosocial problems in patients receiving curative radiotherapy: a process evaluation. BMC Cancer 2011;11:479. <u>https://doi.org/10.1186/1471-2407-11-479</u>.
- [38] Maurer J, Schäfer C, Maurer O, Kölbl O. Anxiety and depression in cancer patients during the course of radiotherapy treatment. Strahlenther Onkol 2012;188:940–5. <u>https://doi.org/10.1007/s00066-012-0143-y</u>.
- [39] Elsner K, Naehrig D, Halkett GKB, Dhillon HM. Reduced patient anxiety as a result of radiation therapist-led psychosocial support: a systematic review. J Med Radiat Sci 2017;64:220-31. <u>https://doi.org/10.1002/imrs.208</u>.
- [40] Rossetti A, Chadha M, Torres BN, Lee JK, Hylton D, Loewy JV, et al. The impact of music therapy on anxiety in cancer patients undergoing simulation for radiation therapy. Int J Radiat Oncol Biol Phys 2017;99:103–10. <u>https://doi. org/10.1016/i.ijrobp.2017.05.003</u>.
- [41] Rao W-W, Yang M-J, Cao B-N, You Y-Y, Zhang Y-Y, Liu Y-Y, et al. Psychological distress in cancer patients in a large Chinese cross-sectional study. J Affect Disord 2019;245:950–6. <u>https://doi.org/10.1016/j.jad.2018.11.089</u>.
- [42] Ferrari M, Ripamonti CI, Hulbert-Williams NJ, Miccinesi G. Relationships among unmet needs, depression, and anxiety in non-advanced cancer patients. Tumori 2019;105:144–50. <u>https://doi.org/10.1177/0300891618765546</u>.
- [43] Storey L, Fern LA, Martins A, Wells M, Bennister L, Gerrand C, et al. A critical review of the impact of sarcoma on psychosocial wellbeing. Sarcoma 2019;2019:9730867. <u>https://doi.org/10.1155/2019/9730867</u>.
- [44] Srikanthan A, Leung B, Shokoohi A, Smrke A, Bates A, Ho C. Psychosocial distress scores and needs among newly diagnosed sarcoma patients: a provincial experience. Sarcoma 2019;2019:5302639. <u>https://doi.org/10.1155/ 2019/5302639</u>.
- [45] Canter RJ, Martinez SR, Tamurian RM, Wilton M, Li C-S, Ryu J, et al. Radiographic and histologic response to neoadjuvant radiotherapy in patients with soft tissue sarcoma. Ann Surg Oncol 2010;17:2578–84. <u>https:// doi.org/10.1245/s10434-010-1156-3</u>.
- [46] Winfield JM, Miah AB, Strauss D, Thway K, Collins DJ, deSouza NM, et al. Utility of multi-parametric quantitative magnetic resonance imaging for characterization and radiotherapy response assessment in soft-tissue sarcomas and correlation with histopathology. Front Oncol 2019;9:280. <u>https://doi.org/10.3389/fonc.2019.00280</u>.
- [47] Koesel N, Tocchi C, Burke L, Yap T, Harrison A. Symptom distress: implementation of palliative care guidelines to improve pain, fatigue, and anxiety in patients with advanced cancer. Clin J Oncol Nurs 2019;23:149–55. <u>https://doi.org/10.1188/19.CION.149–155</u>.
- [48] Arya R, Siamakpour-Reihani S, Palta M, Massa L, Broadwater G, Blitzblau RC, et al. Exercise behavior and patient-reported outcomes in women with early breast cancer receiving locoregional radiation therapy. Pract Radiat Oncol 2015;5:e275–81. https://doi.org/10.1016/j.pro.2015.01.003.

- [49] Schmidt ME, Wiskemann J, Schneeweiss A, Potthoff K, Ulrich CM, Steindorf K. Determinants of physical, affective, and cognitive fatigue during breast cancer therapy and 12 months follow-up. Int J Cancer 2018;142:1148–57. <u>https://doi. org/10.1002/ijc.31138</u>.
- [50] Sprod LK, Palesh OG, Janelsins MC, Peppone LJ, Heckler CE, Adams MJ, et al. Exercise, sleep quality, and mediators of sleep in breast and prostate cancer patients receiving radiation therapy. Community Oncol 2010;7:463–71.
- [51] Li B, Mah K, Swami N, Pope A, Hannon B, Lo C, et al. Symptom assessment in patients with advanced cancer: are the most severe symptoms the most bothersome?. I Palliat Med 2019. https://doi.org/10.1089/ipm.2018.0622.
- bothersome?. J Palliat Med 2019. <u>https://doi.org/10.1089/ipm.2018.0622</u>.
 [52] Selby D, Cascella A, Gardiner K, Do R, Moravan V, Myers J, et al. A single set of numerical cutpoints to define moderate and severe symptoms for the

Edmonton symptom assessment system. J Pain Symptom Manage 2010;39:241-9. https://doi.org/10.1016/j.jpainsymman.2009.06.010. [53] Hewitt L, Powell R, Zenginer K, Coyle C, Murray H, Cooper L, et al. Patient

- [53] Hewitt L, Powell R, Zenginer K, Coyle C, Murray H, Cooper L, et al. Patient perceptions of the impact of treatment (surgery and radiotherapy) for soft tissue sarcoma. Sarcoma 2019;2019:9581781. <u>https://doi.org/10.1155/2019/</u> 9581781.
- [54] Skalicky AM, Ghate SR, Perez JR, Rentz AM. Results of a qualitative study to develop a patient reported outcome measure for patients with 4 subtypes of soft tissue sarcoma. Sarcoma 2017;2017:6868030. <u>https://doi.org/10.1155/ 2017/6868030</u>.