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Original Research Article

A neuropathic pain component as a predictor of improvement in pain interference after radiotherapy for painful tumors: A secondary analysis of a prospective observational study

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ABSTRACT

Background and purpose: We previously demonstrated that patients with a tumor-related neuropathic pain component were more likely to experience a pain response after radiotherapy (RT) than those without. It is unknown whether the presence of a neuropathic component also favorably influences pain interference. In a secondary analysis of our previous prospective observational study, we investigated if the presence of a neuropathic component of the index pain caused by the irradiated tumors predicts greater reduction in pain interference.

Material and methods: For patients scheduled for RT for painful tumors, Brief Pain Inventory data were collected at initiation of RT and 1, 2, and 3 months thereafter. Multivariable linear regression analyses were performed to investigate the effects of the presence of a neuropathic component on the changes in pain interference scores (i.e., follow-up minus baseline). We used 10 covariates as potential confounders.

Results: Of the 302 analyzable patients, 93 (31%) were diagnosed as having a neuropathic component of the index pain. Multivariable linear regression analyses revealed that all the point estimates of regression coefficients at 1-, 2-, and 3-month follow-up were negative values; some were statistically significant. At 2-month follow-up, patients with a neuropathic component experienced greater reductions in their pain interference scores for walking ability ($p = 0.048$), normal work ($p = 0.021$), sleep ($p = 0.001$), and enjoyment of life ($p = 0.010$) than those without it.

Conclusions: The presence of a neuropathic pain component predicted a greater reduction in pain interference after RT. Patients with neuropathic tumor-related pain should be offered the option of receiving palliative RT.

Neuropathic pain occurs in 19% to 39% of cancer patients [1–3]; it may be challenging therapeutically and have a substantial impact on patients' quality of life [4]. Neuropathic cancer pain may be directly caused by tumors or be treatment-related. Although pharmacotherapy is the mainstay of neuropathic pain management [3], it is important not to miss the opportunity to reverse the cause of the pain with appropriate oncological management, including radiotherapy (RT) [4]. A few studies have investigated the effects of RT on neuropathic tumor-related pain and have demonstrated that it can effectively palliate this type of pain [5,6].

When selecting patients to receive palliative RT for painful tumors, it is important to predict which patients would benefit from this treatment. In our previous study, we demonstrated that patients with a neuropathic component of the index pain caused by the irradiated tumors were more likely to experience a pain response after RT than those without it [7]. It is not known whether the presence of a neuropathic component also favorably influences pain interference. When assessing interventions for pain, reduced

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interference in daily activity rather than a simple reduction in pain intensity is a relevant endpoint that reflects the true benefits for patients [8]. Therefore, in a secondary analysis of our previous prospective observational study, we investigated if the presence of a neuropathic component of the index pain predicts a greater reduction in pain interference after RT for painful tumors.

Material and methods

Patients and study design

The present study is a secondary analysis of our previously published prospective observational study that was conducted at three medical centers [7]. In the primary study, we analyzed 302 patients (enrolled between July 2013 and September 2017) who were scheduled to receive RT for painful tumors (Fig. 1); we evaluated the characteristics of the patients, their tumors, and their pain to identify the predictors of pain palliation after RT [7]. The data of these 302 patients were used in this secondary study to investigate the effect of the presence of a neuropathic component on the change in pain interference scores after RT. This secondary study was approved by the participating centers' institutional review boards; written informed consent was obtained from all participants for the primary study.

Evaluation

We previously reported how the patients were assessed at baseline and follow-up evaluations [7]. In brief, immediately prior to RT, the treating radiation oncologist identified the pain caused by the irradiated tumor using physical examination and diagnostic imaging; this pain was recorded as the index pain for the study. The treating radiation oncologist recorded whether the index pain had a neuropathic component according to the definition provided by the International Association for the Study of Pain – Neuropathic Pain Special Interest Group [9]. Patients with definite and probable neuropathic pain were recorded as having a neuropathic component. The Brief Pain Inventory (BPI) short form (Japanese version) was used to evaluate the intensity of pain and its interference in the patient's life using an 11-point scale (0 to 10); higher scores indicate greater pain intensity and interference [10]. Patients assessed their worst pain (in terms of the index pain) experienced in the previous 3 days. Pain interference was assessed using seven subscales: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The BPI data and analgesic data were collected at baseline, and 1, 2, and 3 months (± 7 days) after initiation of RT.

Statistical analysis

The patients' characteristics, analgesic use, and baseline pain interference scores were analyzed using the Mann–Whitney U test for continuous variables; the Fisher exact test was used for categorical variables. Univariable and multivariable linear regression analyses were performed to investigate the effects of the presence of a neuropathic component of the index pain on the change in pain interference scores. The outcome variables were the changes in the functional interference scores from baseline (i.e., follow-up minus baseline). In the multivariable analysis, we used 10 covariates as potential confounders: age, sex, Eastern Cooperative Oncology

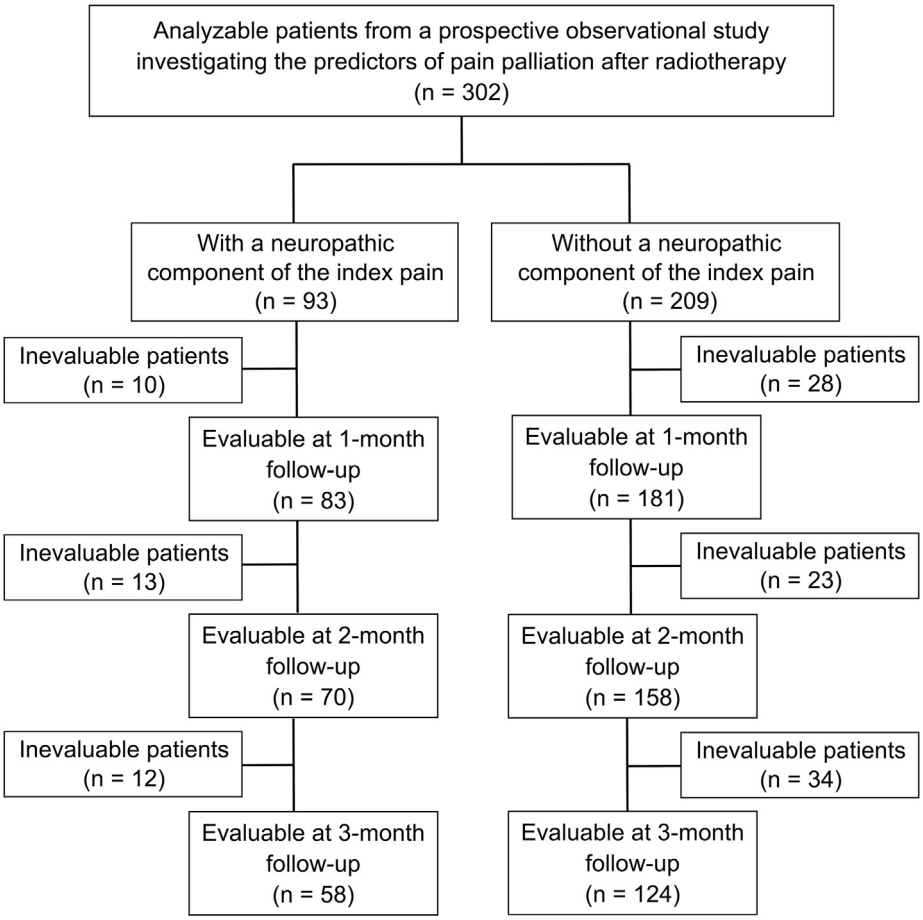

Fig. 1. Flow diagram of the study cohort. The index pain is the pain caused by the irradiated tumor.

Group (ECOG) performance status, hematologic tumor, tumor involvement of the bone, worst pain score at baseline, opioid analgesic use at baseline, adjuvant analgesic use at baseline, palliative intent of the RT, and total radiation dose. The ECOG performance status (≤1 vs. >1) and worst pain score at baseline (≤7 vs. >7) were treated as binary variables; age and total radiation dose were treated as continuous variables. Normality of residuals was assessed by inspection of Q-Q plots and histograms. The variance inflation factor was used to detect multicollinearity between independent variables. All tests were two-tailed; $p < 0.05$ was considered statistically significant. We did not adjust for multiple comparisons in this exploratory study. All statistical analyses were performed using SPSS software, version 24 (IBM SPSS, Armonk, NY).

Results

Patients

Of the 302 analyzable patients, 93 (31%) were diagnosed as having a neuropathic component of the index pain (definite, 52 patients; probable, 41 patients; Fig. 1); 83 (89%) of the 93 patients also had nociceptive pain caused by the index tumors treated with RT. Patients with a neuropathic component had greater pain intensity and worse ECOG performance status than patients without (Table 1); they also reported significantly worse baseline pain interference scores for general activity, walking ability, relations with other people, and sleep (Table 2). There was no significant difference in the total radiation dose between the patients with a neuropathic component and those without (Table 1).

Analgesic use

At baseline, the patients with a neuropathic component were using opioid analgesics more frequently than those without the component (Table 3). At 1-month follow-up, patients with a neuropathic component were more frequently using opioid and adjuvant analgesics than those without. At 2- and 3-month follow-up, there was no significant difference in analgesic use between the two patient groups. At baseline and 1-, 2-, and 3-month follow-up, the median daily oral morphine equivalent doses were 23, 23, 15, and 19 mg, respectively, in patients with a neuropathic component; the doses were 0, 8, 0, and 0 mg, respectively, in the patients without a neuropathic component.

Pain

The mean worst pain scores at baseline and 1-, 2-, and 3-month follow-up are presented in Fig. 2. At baseline and 1-, 2-, and 3-month follow-up, the median worst pain scores (in terms of the index pain) were 8, 3, 2, and 2, respectively, in the patients with a neuropathic component; these scores were 7, 2, 1, and 1, respectively, in the patients without a neuropathic component.

BPI pain interference scores

The mean pain interference scores at baseline and 1-, 2-, and 3-month follow-up are presented in Fig. 2. For the patients with a neuropathic component, the median differences in scores (i.e., follow-up minus baseline) at 1-, 2-, and 3-month follow-up were

Table 1
Baseline patient characteristics (n = 302).

Characteristic	Neuropathic component (n = 93)		No neuropathic component (n = 209)		*p*
	No.	%	No.	%	
Age, years					0.003
Median	70		65		
Range	35–91		21–89		
Sex					0.033
Female	33	35	103	49	
Male	60	65	106	51	
ECOG performance status					0.023
0	11	12	52	25	
1	36	39	83	40	
2	25	27	51	24	
3, 4	21	23	23	11	
Irradiated tumor					0.36
Solid tumor	78	84	184	88	
Hematologic tumor	15	16	25	12	
Bone involvement by the tumor					<0.001
No	8	9	86	41	
Yes	85	91	123	59	
Worst pain score at baseline					0.006
1-2	2	2	8	4	
3-4	8	9	53	25	
5-7	32	34	70	33	
8-10	51	55	78	37	
Intent of radiation therapy					0.035
Curative	13	14	52	25	
Palliative	80	86	157	75	
Total radiation dose, Gy					0.93
Median	30		30		
Range	8–62		6–70.4		
≤20	17	18	59	28	
20-30	43	46	60	29	
30-45	17	18	32	15	
>45	16	17	58	28	

Table 2
Baseline pain interference scores from the Brief Pain Inventory.

Item	Neuropathic component			No neuropathic component			p^*
	No.	Median	IQR	No.	Median	IQR	
General activity	91	6	3 to 10	204	5	2 to 8	0.037
Mood	93	6	2 to 8	203	5	2 to 8	0.12
Walking ability	93	5	2 to 9	204	4	1 to 8	0.030
Normal work	91	6	3 to 10	201	5	1.5 to 9	0.065
Relations with other people	92	4.5	1 to 8	204	2.5	0 to 6	0.040
Sleep	92	5	2 to 8	205	3	1 to 6	0.016
Enjoyment of life	92	5.5	2 to 10	202	5	1 to 9	0.099

Abbreviation: IQR = interquartile range.
* Mann-Whitney U test.

Table 3
Analgesic use.

Analgesic use	Neuropathic component		No neuropathic component		p^*
	No.	%	No.	%	
Baseline	n = 93		n = 209		
Opioid analgesic use	64	69	101	48	0.001
Adjuvant analgesic use	38	41	67	32	0.15
1-month follow-up	n = 83		n = 181		
Opioid analgesic use	63	76	94	52	<0.001
Adjuvant analgesic use	47	57	75	41	0.024
2-month follow-up	n = 70		n = 158		
Opioid analgesic use	41	59	76	48	0.15
Adjuvant analgesic use	37	53	62	39	0.061
3-month follow-up	n = 58		n = 124		
Opioid analgesic use	33	57	56	45	0.16
Adjuvant analgesic use	28	48	49	40	0.33

* Fisher exact test.

as follows: −3, −3, and −4 for general activity; −2.5, −3, and −4 for mood; −2, −3, and −2 for walking ability; −2.5, −3, and −2 for normal work; −2, −1, and −1 for relations with other people; −2, −3, and −3 for sleep; and −2, −3, and −3 for enjoyment of life, respectively. The median differences in scores for the patients without a neuropathic component at 1-, 2-, and 3-month follow-up were as follows: −2, −2, and −2 for general activity; −2, −2, and −2 for mood; 0, −1, and −1 for walking ability; −2, −1.5, and −1 for normal work; −1, −1, and 0 for relations with other people; −1, −1, and −1 for sleep; and −1.5, −1, and −2 for enjoyment of life, respectively.

Effect of the presence of a neuropathic pain component on the changes in pain interference scores

There were no missing values in the 10 covariates. Inspection of the Q-Q plots and histograms revealed that the assumption of normality of residuals was not violated. The variance inflation factors ranged from 1.11 to 3.08, which indicated that there was no multicollinearity problem. The univariable and multivariable linear regression analyses demonstrated that the patients with a neuropathic component of the index pain tended to experience greater reduction in their pain interference scores than those without this pain component (Table 4). All the point estimates of regression coefficients at 1-, 2-, and 3-month follow-up were negative values, and some were statistically significant. Greater differences in the pain interference scores between the two groups were seen at 2- and 3-month follow-up than at 1-month follow-up.

Discussion

Our present study demonstrated that patients that had a neuropathic component of the index pain tended to experience greater reductions of their pain interference scores after RT than those without this pain component. We also observed that, at baseline, patients with a neuropathic component had greater pain intensity, worse ECOG performance status, and worse pain interference scores than patients without it, despite their more frequent use of opioid analgesics.

We found that the reduction of the pain interference scores after RT tended to be greater among patients with a neuropathic component. Our linear regression analyses demonstrated that greater differences in the pain interference scores between the two groups (i.e., those with and without neuropathic pain) were seen at 2-month follow-up than at 1-month follow-up. While more frequent analgesic use was observed in the patients having a neuropathic component at 1-month follow-up, no significant difference in analgesic use was observed between the two groups at 2-month follow-up. The difference in analgesic use between the two groups decreased between the 1- and 2-month follow-up evaluations; however, the differences in pain interference scores increased during this period. This increase in the difference in functional interference between the two groups may be due to the effects of RT.

In our previous study, which is the largest to date to examine the effects of neuropathic pain on the pain response to RT, patients with a neuropathic component were more likely to experience a pain response after RT [7]. In contrast, other smaller studies did not find significant differences in the pain response rates between patients with and without neuropathic pain [11,12]. In the present study, we observed that the presence of a neuropathic component predicts a greater improvement in pain interference. These findings reinforce the benefits that patients with neuropathic tumor-related pain may derive from RT.

A previous clinical study demonstrated that normalization of sensory abnormality after RT predicts greater improvement in pain

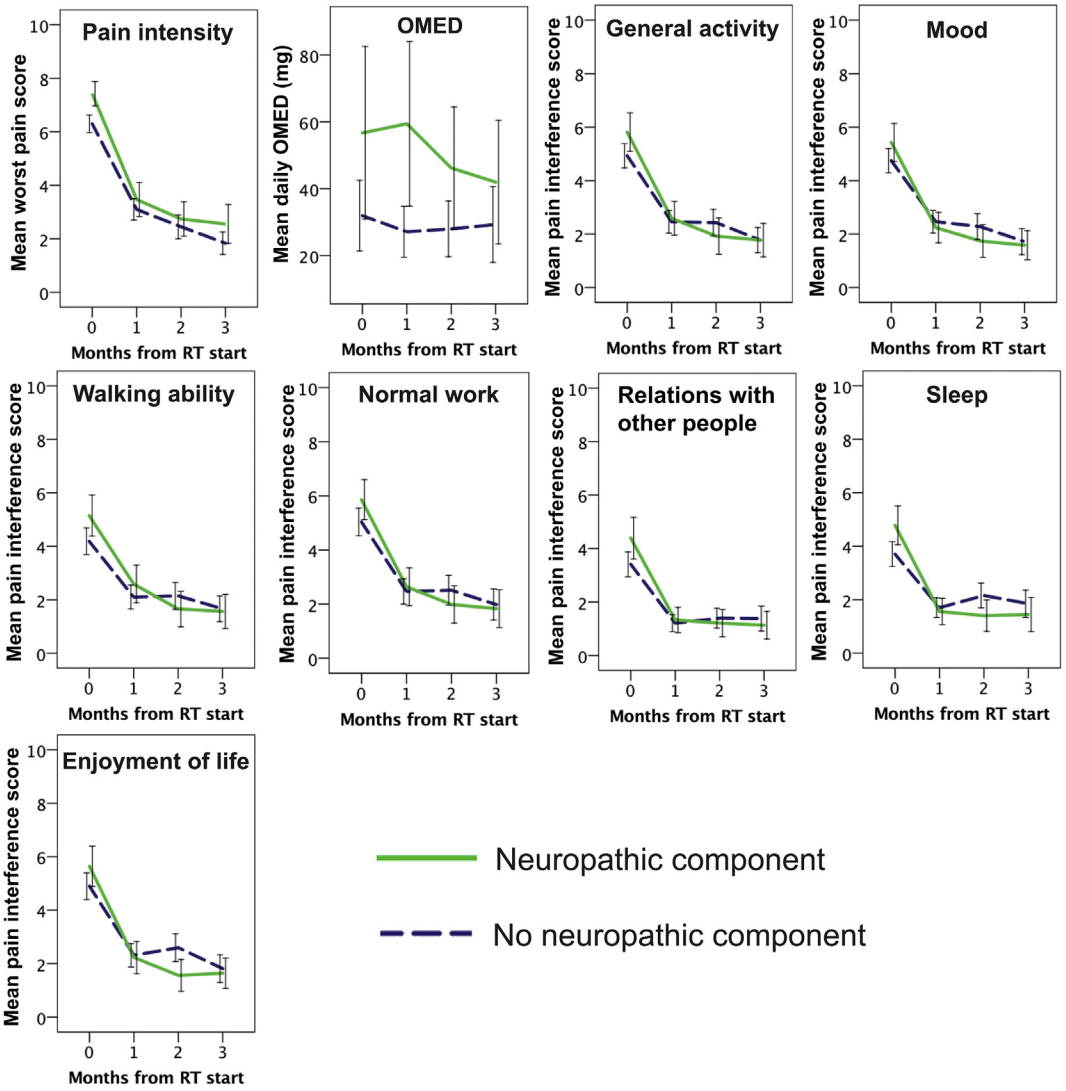

Fig. 2. Pain intensity, opioid analgesic dose, and pain interference at baseline and 1-, 2-, and 3-month follow-up. The error bars indicate the 95% confidence intervals. *Abbreviations:* RT = radiotherapy; OMED = oral morphine equivalent dose.

Table 4
Linear regression models to investigate the effect of the presence of a neuropathic pain component on the changes in pain interference scores from baseline.

Item	1-month follow-up				2-month follow-up				3-month follow-up			
	No.	β	95% CI	*p*	No.	β	95% CI	*p*	No.	β	95% CI	*p*
Univariable												
General activity	253	−0.63	−1.60 to 0.35	0.21	210	−1.24	−2.40 to −0.09	0.036	168	−1.32	−2.60 to −0.04	0.044
Mood	252	−0.89	−1.88 to 0.09	0.075	208	−0.87	−2.05 to 0.32	0.15	166	−1.32	−2.65 to 0.01	0.052
Walking ability	253	−0.36	−1.35 to 0.63	0.47	212	−1.35	−2.54 to −0.16	0.026	166	−1.44	−2.70 to −0.18	0.026
Normal work	241	−0.67	−1.78 to 0.45	0.24	204	−1.32	−2.57 to −0.07	0.039	166	−1.07	−2.41 to 0.28	0.12
Relations with other people	253	−0.71	−1.64 to 0.22	0.14	209	−0.95	−2.04 to 0.14	0.086	166	−1.14	−2.33 to 0.05	0.060
Sleep	255	−1.17	−2.14 to −0.20	0.018	212	−1.74	−2.87 to −0.61	0.003	167	−1.63	−2.93 to −0.33	0.014
Enjoyment of life	250	−0.79	−1.83 to 0.26	0.14	205	−1.62	−2.90 to −0.35	0.013	165	−1.08	−2.48 to 0.32	0.13
Multivariable*												
General activity	253	−0.48	−1.51 to 0.55	0.36	210	−1.31	−2.64 to 0.03	0.054	168	−1.24	−2.69 to 0.20	0.092
Mood	252	−0.89	−1.96 to 0.18	0.10	208	−1.18	−2.53 to 0.18	0.087	166	−1.25	−2.81 to 0.31	0.12
Walking ability	253	−0.49	−1.51 to 0.53	0.35	212	−1.33	−2.65 to −0.01	0.048	166	−1.48	−2.81 to −0.15	0.030
Normal work	241	−0.39	−1.57 to 0.79	0.52	204	−1.64	−3.03 to −0.25	0.021	166	−1.16	−2.64 to 0.32	0.12
Relations with other people	253	−0.38	−1.37 to 0.61	0.45	209	−0.43	−1.66 to 0.80	0.49	166	−0.58	−1.93 to 0.76	0.39
Sleep	255	−1.27	−2.33 to −0.21	0.019	212	−2.27	−3.56 to −0.98	0.001	167	−1.58	−3.13 to −0.03	0.046
Enjoyment of life	250	−0.66	−1.77 to 0.45	0.24	205	−1.92	−3.37 to −0.47	0.010	165	−0.66	−2.26 to 0.94	0.42

Abbreviations: β = regression coefficient (e.g., when β is −1, the presence of a neuropathic pain component predicts a 1-point greater reduction in the functional interference score from baseline); CI = confidence interval.
Outcome variables are the changes in the functional interference scores from baseline (i.e., follow-up minus baseline).
* The covariates are age, sex, Eastern Cooperative Oncology Group performance status, hematologic tumor, tumor involvement of the bone, worst pain score at baseline, opioid analgesic use at baseline, adjuvant analgesic use at baseline, palliative intent of the radiation therapy, and total radiation dose.

intensity [13]. The patients with bone metastases that experienced normalization of abnormal warm sensation on the skin over the area of cancer-induced pain had greater pain score reduction [13]. The authors of this previous study reported that alterations in specific sensory characteristics seem to be associated with an increased likelihood of successful analgesia from palliative RT [13]. They demonstrated which patients responded best using Quantitative Sensory Testing *after* RT. In contrast, we demonstrated which patients benefited most from RT by diagnosing the presence or absence of a neuropathic component *before* RT. Thus, our results will enable better patient selection for palliative RT.

In addition, we found that, at baseline, patients with a neuropathic component of the index pain had greater pain intensity, worse performance status, worse pain interference scores, and used opioid analgesics more frequently than patients without this component. Our findings are consistent with past studies that investigated neuropathic cancer pain, which demonstrated that patients with neuropathic pain were likely to have a higher pain intensity, worse performance status, worse pain interference, worse quality of life, and more frequent analgesic use [14–16]. Neuropathic cancer pain is associated with a negative impact on patients' life quality and functioning despite greater use of analgesics. Palliative RT may be a good intervention for this type of pain, considering its favorable influence on pain interference that was demonstrated in this study.

Diagnosis of a neuropathic component was performed by the treating radiation oncologists in the present study. Making a diagnosis based on the definition provided by the International Association for the Study of Pain [9] requires an experienced physician. We are uncertain if the results of our study will be reproducible in other medical facilities; thus this uncertainty in generalizability may be a limitation of our study. However, one advantage of our study is that the treating radiation oncologists diagnosed whether the neuropathic component was related to the index tumor that was scheduled to receive RT. Although screening questionnaires to diagnose neuropathic pain [17,18] can be used reproducibly at any facility, it is not certain if the neuropathic pain identified by use of the questionnaires is caused by the irradiated tumors. Additionally, these screening questionnaires are often insufficiently accurate [1,12,19]. Neuropathic cancer pain can have many causes other than tumors. When attempting to predict the effects of RT, it is necessary to know if the neuropathic pain component is caused by the index tumors treated with RT.

In conclusion, a secondary analysis of our previous prospective observational study demonstrated that the presence of a neuropathic component of the index pain predicted a greater reduction in pain interference after RT for painful tumors. This observation supports our previous findings that patients with a neuropathic component were more likely to experience a pain response after RT. Patients with neuropathic tumor-related pain should be offered the option of receiving palliative RT.

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The authors have no sources of support to report.

Conflict of interest

The authors have no conflicts of interest to declare.

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