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Scientific Article

Index and Nonindex Pain Endpoints in Radiation Therapy for Painful Tumors: A Secondary Analysis of a Prospective Observational Study

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Abstract

Purpose: Improving pain interference in daily activities, rather than mere pain reduction, is a desirable endpoint for palliative radiation therapy. The association between pain response and pain interference has been studied almost exclusively in patients with painful bone metastases (PBMs), whereas nonindex pain has scarcely been explored in palliative radiation therapy. We investigated whether index and nonindex pain endpoints are associated with pain interference changes in patients with both PBMs and painful non-bone-metastasis tumors (PNTs).

Methods and Materials: Brief pain inventory data collected at baseline and at 2 months post-treatment were used to calculate differences in pain interference scores. Pain response in terms of the index pain was assessed using the international consensus endpoint. Patients were diagnosed with predominance of other pain (POP) if nonindex pain of malignant or unknown origin was present and had a greater pain score than the index pain.

Results: Of 302 patients, 127 (42%) had PBMs and 175 (58%) had PNTs. The median pain interference score, which is based on the mean of the 7 subscale items, decreased to a greater extent among responders than among nonresponders (PBM group: -3.43 vs -0.57 [$P = .005$]; PNT group: -2.43 vs -0.29 [$P < .001$]). Moreover, patients without POP experienced a greater reduction in their median pain interference score than did those with POP (PBM group: -2.71 vs $+0.43$ [$P = .004$]; PNT group: -2.00 vs $+1.57$ [$P = .007$]). The Jonckheere-Terpstra test showed a significant trend across 4 pain response categories in patients with PBMs and those with PNTs ($P < .001$ for both).

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Conclusions: The index and nonindex pain endpoints were positively and negatively associated with improvement in pain interference, respectively. There was no apparent difference between patients with PBMs and PNTs in terms of the associations of these endpoints with pain interference.

Introduction

Radiation therapy is an effective treatment option for tumor-related cancer pain.[1,2] Previous studies have demonstrated that radiation therapy not only reduces bone pain but also improves the interference of pain in the patient's daily life.[3] When evaluating interventions for cancer pain, improved interference in daily activities rather than merely reducing pain intensity is a desirable endpoint for patients.[4] However, the association between pain response and pain interference has been studied almost exclusively in patients with painful bone metastases (PBMs); patients who respond to radiation therapy for PBMs have been found to experience improved pain interference in daily activities and quality of life.[3] In contrast, it remains unknown if response to radiation therapy improves pain interference in patients with painful nonbone-metastasis tumors (PNTs).

Patients with tumor-related pain sometimes have more than a single pain location.[5,6] Even when the index pain (ie, pain caused by the irradiated tumor) is controlled, another tumor with more intense pain may negatively influence the pain interference score and impede the patient's daily functions. We previously studied such nonindex pain in patients who underwent palliative radiation therapy to identify predictors of its predominance.[7] However, data on the influence of nonindex pain on pain interference are scarce in patients with PBMs as well as those with PNTs.

The present study had 2 main objectives. First, we sought to determine whether the index pain endpoint is associated with an improvement in pain interference after radiation therapy in patients with PBMs as well as in those with PNTs. Second, we investigated the association between nonindex pain endpoint and an improvement in pain interference in patients with PBMs and those with PNTs. Pain interference scores were used to analyze the effect of radiation therapy on the daily life of patients with and without the aforementioned pain endpoints.

Methods and Materials

Patients and study design

The present study was based on data collected from a previously published 3-center prospective observational study. The primary study, the goal of which was to identify the predictors of pain response, included 302 patients who underwent radiation therapy for miscellaneous painful tumors.[8] Patients were excluded if the tumor scheduled to receive radiation therapy had been previously irradiated or if another tumor had more severe pain than the one scheduled to receive radiation therapy.[8] This secondary study was approved by the participating centers' institutional review boards; written informed consent was obtained from each of the patients who were enrolled in the primary study.

Follow-up and evaluation

The patients' evaluation and follow-up procedures were described previously.[7,8] Before radiation therapy, the treating radiation oncologist identified the pain caused by the targeted tumor using physical examination and diagnostic imaging and noted it as the "index pain" for the study. When a patient had more than 1 painful tumor scheduled for irradiation, information on the tumor causing the most severe pain was recorded as the index pain. The treating radiation oncologists differentiated between index pain caused by the irradiated tumor and "nonindex pain," the cause of which was not treated with radiation therapy. The Brief Pain Inventory (BPI) short form was used to evaluate the intensity of pain and its interference with the patient's daily activity using an 11-point scale (0-10).[9] Patients rated their worst pain during the preceding 3 days (in terms of index pain as well as nonindex pain if present). A higher BPI score indicated greater disability and poorer well-being. Pain interference was evaluated using 7 subscales: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The mean of the pain interference scores was calculated if at least 4 of the 7 scores were available.[10] Many patients completed the questionnaire on their own; if required, a nurse or a family member assisted the patients in completing it. BPI data were collected at baseline and at 1, 2, and 3 months after the start of radiation therapy. Follow-up BPI data were obtained using patient self-reported questionnaires in the hospital, by mail, by fax, or by telephone.[8] The baseline and 2-month follow-up data were used to calculate the differences in pain interference scores. Radiation therapy was defined as *palliative* if the primary purpose of the treatment was pain relief or if the radiation field did not cover all tumors identified by diagnostic imaging; otherwise, the treatment was defined as *curative*.[8]

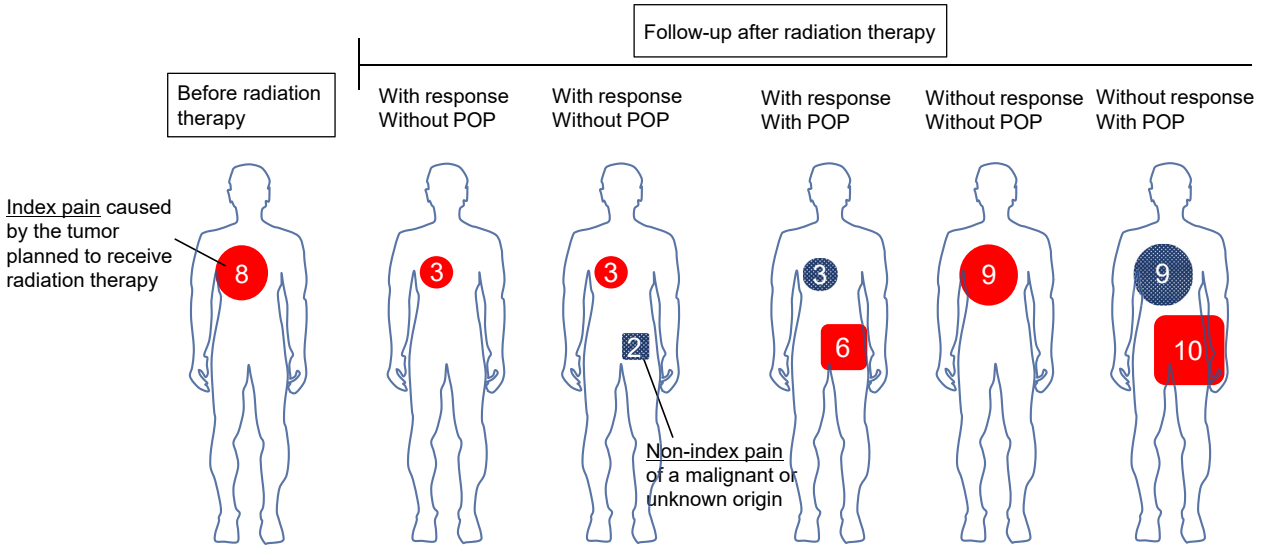

Figure 1 Diagrams showing various index and nonindex pain endpoint statuses. The numbers indicate pain intensity measured using an 11-point scale from 0 to 10. Assuming the daily oral morphine equivalent dose is constant before and after radiation therapy, the patient experiences pain response, referred to as the *index pain endpoint,* if there is a ≥2 point reduction in the pain score compared with baseline. Patients are diagnosed with predominance of other pain (POP), referred to as the *nonindex pain endpoint,* if an existing nonindex pain of a malignant or unknown origin has a greater pain score than the index pain at follow-up.

Index pain endpoint

The pain response in terms of the index pain was assessed using the international consensus endpoint for bone metastases.[11] Patients who received radiation therapy for painful tumors were categorized as *responders* versus *nonresponders*; *responders* included patients who experienced complete and partial responses. A complete response was defined as an index pain score of 0 with no increase in the daily oral morphine equivalent dose (OMED).[11] A partial response was defined as a $\geq$ 2 point reduction in the pain score without an increase in OMED or a $\geq$ 25% reduction in analgesic use without an increase in the pain score. Pain progression was defined as either a $\geq$ 2 increase in the index pain score without an OMED reduction or a $\geq$ 25% increase in the OMED without a decrease in the pain score. An indeterminate response was that which did not fit the definition of a complete response, partial response, or pain progression. Figure 1 shows the various statuses of the index and nonindex pain endpoints. For simplicity, the image in Figure 1 assumes that the daily oral morphine equivalent dose is constant before and after radiation therapy; thus the patient experiences pain response if there is a $\geq$ 2 point reduction in the pain score compared with baseline.

Nonindex pain endpoint

The treating radiation oncologists prospectively evaluated whether the patients had pain other than the index pain at both baseline and follow-up examination. The intensity (ie, the worst pain during the preceding 3 days) and origin of any such pain were noted.[7] When more than 1 nonindex pain was present, that with the greatest intensity was recorded. Nonindex pain was classified as having a malignant (tumor-related) origin, unknown origin, benign origin, or treatment-related cause. Patients were diagnosed with predominance of other pain (POP) if an existing nonindex pain of a malignant or unknown origin had a greater pain score than the index pain during follow-up visits. The intensity of the nonindex pain was compared with that of the index pain at follow-up to assess the presence or absence of POP (Fig 1).

Statistical analysis

The primary goal of this study was to determine whether the pain endpoints (ie, pain response and POP) are associated with the differences between the means of the 7 pain interference scores before and after radiation therapy. The Wilcoxon rank sum test with normal approximation was used to compare the changes in pain interference scores between responders and nonresponders, as well as between patients with POP and those without. The Jonckheere-Terpstra test was used to examine trends across the response categories. All tests were 2-tailed. Bonferroni correction was performed only in the primary analyses comparing the differences in the means of the 7 pain interference scores; statistical tests were performed 4 times (2 endpoints [pain response and POP] in 2 patient groups [PBMs and PNTs]), and the significance level was set at 0.0125. In the remaining statistical tests (which were exploratory), there were no adjustments for multiplicity, and the significance level was set at 0.05. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Table 1 Baseline patient characteristics (n = 302)

Characteristic	Painful bone metastases (n = 127)		Painful non-bone-metastasis tumors (n = 175)	
	No.	%	No.	%
Age, years				
Median	68		64	
Range	35-91		21-89	
Sex				
Female	43	34	93	53
Male	84	66	82	47
ECOG performance status				
0	13	10	50	29
1	58	46	61	35
2	39	31	37	21
3, 4	17	13	27	15
Worst pain score at baseline				
1-2	2	2	8	5
3-4	17	13	44	25
5-7	41	32	61	35
8-10	67	53	62	35
Neuropathic component of index pain				
No	85	67	124	71
Yes	42	33	51	29
Nonindex pain of malignant or unknown origin at baseline				
No	106	83	159	91
Yes	21	17	16	9
Opioid analgesic use at baseline				
No	62	49	75	43
Yes	65	51	100	57
Intent of radiation therapy				
Curative	2	2	63	36
Palliative	125	98	112	64
Total radiation dose, Gy				
Median	30		40	
Range	8-70.4		6-70	
≤20	52	41	24	14
20-30	54	43	49	28
30-45	18	14	31	18
45	3	2	71	41
Systemic therapy concurrent with radiation therapy*				
No	54	43	74	42
Yes	68	54	97	55
Not available	5	4	4	2

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

* Chemotherapy, molecular targeted therapy, or hormone therapy delivered from 1 week before to 1 month after the initiation of radiation therapy.

Results

Patients

Of the 302 patients at baseline, 127 (42%) had PBMs and 175 (58%) had PNTs. (Table 1). In patients with PBMs, the primary tumor sites were the lung (n = 49), gastrointestinal system (n = 35), gynecologic system (n = 12), head and neck (n = 6), urogenital system (n = 10), breast (n = 9), and others (n = 6). Among patients with PNTs, there were 135 solid painful tumors including the primary tumor lesion (n = 69), lymph node metastasis (n = 30), hematogenous metastasis other than bone metastasis (n = 7), pleural dissemination (n = 12), and others (n = 17); moreover, there were 40 hematologic

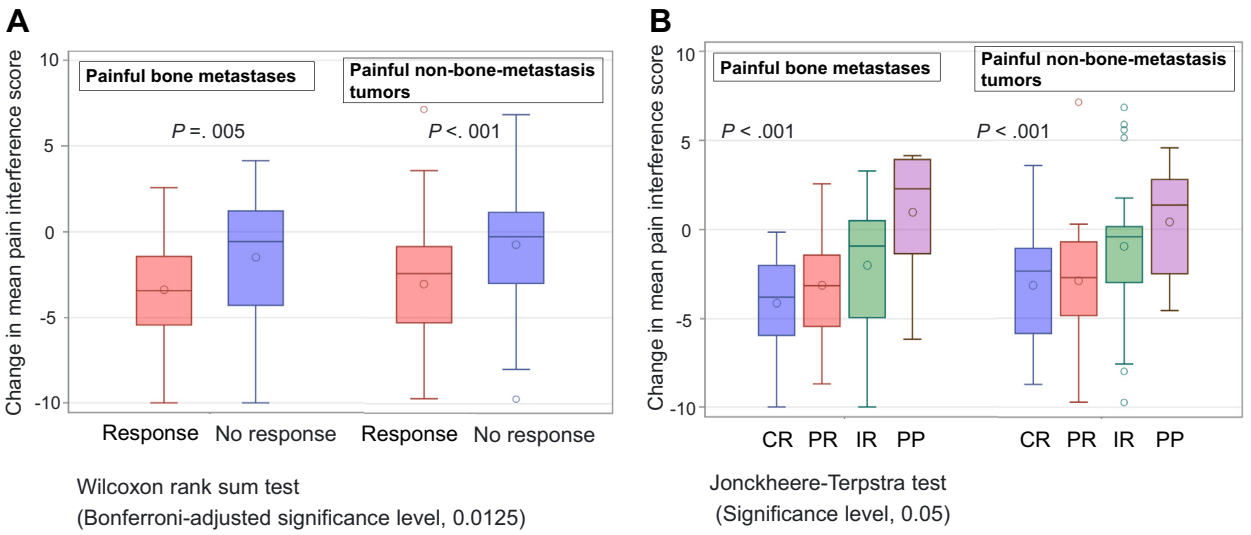

Figure 2 Changes in the mean of the pain interference scores between baseline and 2-month follow-up in patients with painful bone metastases versus those with painful nonbone-metastasis tumors according to response status (A) and individual response categories (B). Responders included patients who experienced CR and PR, and nonresponders included patients who experienced IR and PP. *Abbreviations:* CR = complete response; IR = indeterminate response; PP = pain progression; PR = partial response.

Table 2 Changes in pain interference scores between baseline and the 2-month follow-up in responders and nonresponders

Item	All evaluable patients	Responders			Nonresponders			*P* value
	No.	No.	Median	Interquartile range	No.	Median	Interquartile range	
Painful bone metastases								
Mean of the 7 pain interference items	87	43	−3.43	−5.43 to −1.43	44	−0.57	−4.29 to 1.21	.005*
General activity	87	43	−4	−7 to −2	44	−2	−5.5 to 1	.016†
Mood	84	42	−4	−8 to −1	42	−1	−4 to 1	.007†
Walking ability	88	44	−3	−6 to 0	44	−0.5	−5 to 1	.024†
Normal work	86	43	−3	−7 to −1	43	−1	−6 to 1	.041†
Relations with other people	86	43	−3	−6 to 0	43	−1	−5 to 1	.20†
Sleep	88	44	−1.5	−4 to 0	44	0	−3 to 1.5	.14†
Enjoyment of life	83	41	−3	−7 to −1	42	0	−5 to 1	.039†
Painful non-bone-metastasis tumors								
Mean of the 7 pain interference items	124	77	−2.43	−5.29 to −0.86	47	-0.29	−3.00 to 1.14	<.001*
General activity	123	77	−2	−6 to −1	46	−1	−3 to 1	.003†
Mood	124	77	−3	−6 to −1	47	−1	−2 to 1	<.001†
Walking ability	124	77	−2	−6 to 0	47	0	−2 to 2	<.001†
Normal work	117	74	−2	−6 to 0	43	−1	−4 to 1	.018†
Relations with other people	123	77	−1	−5 to 0	46	0	−2 to 1	<.001†
Sleep	124	77	−2	−5 to 0	47	0	−3 to 1	.006†
Enjoyment of life	122	77	−2	−5 to −1	45	0	−3 to 1	.003†

The Wilcoxon rank sum test was used to compare the changes in the Brief Pain Inventory scores between responders and nonresponders.

* Bonferroni correction was performed with an adjusted significance level of 0.0125.

† Significance level was set at 0.05.

tumors including myeloma (n = 18), plasmacytoma (n = 6), lymphoma (n = 13), and others (n = 3). In patients with solid tumors in the PNT group (n = 135), the primary tumor sites were the lung (n = 31), gastrointestinal system (n = 27), gynecologic system (n = 38), head and neck (n = 14), urogenital system (n = 7),

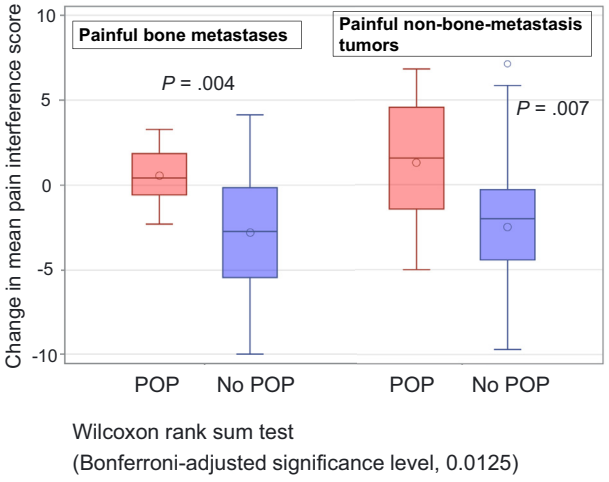

Figure 3 Change from baseline in the mean of the pain interference scores at 2-month follow-up in patients with painful bone metastases versus those with painful nonbone-metastasis tumors according to POP status. *Abbreviation:* POP = predominance of other pain.

breast (n = 5), and others (n = 13). In all patients including the PBM and PNT groups, the main location of treatment was head and neck (n = 37), chest (n = 85), abdomen/pelvis (n = 146), and extremity (n = 34), as we previously reported.[8] A wide range of dose fractionation regimens was used in both the PBM and PNT groups (Table 1). Patients with PNTs tended to receive treatment with higher dose fractionation regimens than those with PBMs. At the 2-month follow-up, 96 (76%) of the 127 patients with PBM and 132 (75%) of the 175 patients with PNT were evaluable. The reasons for not being evaluated were death (n = 27), deteriorated or unable to contact (n = 45), and temporarily missed for minor reasons (n = 2), as we previously reported.[8]

Pain response

At the 2-month follow-up point, 50 (52%) of the 96 evaluable patients with PBM experienced pain response; 14 (15%) experienced complete response, 36 (38%) experienced partial response, 37 (39%) experienced indeterminate response, and 9 (9%) experienced pain progression. Of the 132 evaluable patients with PNT, 81 (61%) experienced pain response; 46 (35%) experienced complete response, 35 (27%) experienced partial response, 43 (33%) experienced indeterminate response, and 8 (6%) experienced pain progression. Responders

Table 3 Changes in pain interference scores between baseline and the 2-month follow-up in patients with and without a predominance of other pain

Item	All evaluable patients	Predominance of other pain*			No predominance of other pain			*P* value
	No.	No.	Median	Interquartile range	No.	Median	Interquartile range	
Painful bone metastases								
Mean of the 7 pain interference items	87	9	0.43	−0.57 to 1.86	78	−2.71	−5.43 to −0.14	.004†
General activity	87	9	1	−2 to 5	78	−3	−7 to 0	.004‡
Mood	84	9	2	1-4	75	−3	−7 to 0	<.001‡
Walking ability	88	9	0	−1 to 1	79	−2	−6 to 0	.012‡
Normal work	86	9	0	−2 to 0	77	−2	−6 to 0	.089‡
Relations with other people	86	9	−3	−5 to 0	77	−1	−5 to 0	.84‡
Sleep	88	9	1	0-7	79	−1	−4 to 0	.006‡
Enjoyment of life	83	9	0	−1 to 1	74	−3	−7 to 0	.057‡
Painful non-bone -metastasis tumors								
Mean of the 7 pain interference items	124	10	1.57	−1.43 to 4.57	114	−2.00	−4.43 to −0.29	.007†
General activity	123	10	2.5	−5 to 3	113	−2	−5 to −1	.051‡
Mood	124	10	1	−4 to 4	114	−2	−5 to 0	.020‡
Walking ability	124	10	2	0-6	114	−1	−6 to 0	.002‡
Normal work	117	8	1.5	−3 to 4.5	109	−2	−5 to 0	.045‡
Relations with other people	123	10	−0.5	−3 to 6	113	−1	−3 to 0	.24‡
Sleep	124	10	1	0-4	114	−2	−5 to 0	.007‡
Enjoyment of life	122	9	3	2-6	113	−2	−5 to 0	.003‡

The Wilcoxon rank sum test was used to compare the changes in the Brief Pain Inventory scores between patients with predominance of other pain and those without.

* Defined as pain of malignant (ie, tumor-related) or unknown origin being more intense than the index pain.

† Bonferroni correction was performed with an adjusted significance level of 0.0125.

‡ Significance level was set at 0.05.

experienced a greater decrease in the mean BPI interference scores than did nonresponders in both PBM and PNT groups at the 2-month follow-up (Fig 2A, Table 2). There was a significant trend toward higher pain interference scores among patients in worse response categories (ie, complete response, partial response, indeterminate response, and pain progression) (Fig 2B).

Predominance of other pain

At the 2-month follow-up, 10 (10%) of the 96 evaluable patients with PBM and 11 (8%) of the 132 evaluable patients with PNT experienced POP. Patients without POP experienced a greater decrease in the mean of the pain interference scores than did patients with POP in both the PBM and PNT groups (Fig 3, Table 3).

Discussion

We found that patients with pain response experienced a greater improvement in pain interference than did nonresponders in both the PBM and PNT groups. Moreover, patients in both these groups who had no POP after radiation therapy experienced a greater improvement in pain interference compared with those with POP.

Previous studies of index pain palliation in patients with PBM using radiation therapy, as assessed using the international consensus endpoint,[11] demonstrated that the pain response was associated with an improvement in pain interference.[3,12-17] In contrast, our present study, which may have been the first to investigate the association between pain response (as assessed using the international consensus endpoint) and pain interference in patients with PNT, found that poorer responses trended significantly toward worse pain interference changes irrespective of the irradiated tumors. Furthermore, there appeared to be no difference between PBM and PNT in terms of the ability of the international consensus endpoint to discriminate patients who experience improvement in pain interference from those who do not.

The assessment of pain palliation only in terms of index pain may be inadequate for estimating the extent of a patient's benefit from palliative radiation therapy. Treatment of pain at 1 site might unmask pain at other sites, possibly resulting in a limited quality-of-life benefit.[18,19] Our comparison of patients with POP to those without suggests that nonindex pain negatively influences patients' pain interference. For patients likely to experience POP, early intervention with new palliative radiation therapy or analgesics should be performed when required. Follow- up after palliative radiation therapy is important to help identify and assess pain in other sites that could require either radiation therapy or other interventions, given that approximately 1 in 10 patients have POP that interferes with activities. Data on nonindex pain as related to radiation therapy for painful tumors are very limited and worth collecting in future studies. In addition, our study did not record the number of nonindex painful lesions, which may be helpful to investigate further the incidence of the "pain unmasking phenomenon"; we recommend that future studies collect this information alongside the index painful lesions.

There were limitations to our study. First, it was explorative in nature, and the results should be validated in other prospective studies. Second, patient attrition may have biased the study results. Third, patients with PNTs were heterogeneous in terms of disease type. The association between pain endpoints and pain interference should be investigated in patients with specific cancer types in future studies.

In summary, our data showed that the index and nonindex pain endpoints were associated with a change in pain interference after radiation therapy. Our findings may be useful for predicting the extent to which patients with and without these endpoints would derive benefits from radiation therapy, indicating that the findings may be helpful in shared decision-making in palliative radiation therapy. The BPI was shown to be useful in assessing the significance of pain endpoints for the patients. In the next update of the international consensus on palliative radiation therapy endpoints for bone metastases, it may be worth exploring whether nonindex pain endpoints should be used in clinical trials for patients with PBMs and whether the international consensus endpoint can be used to assess pain palliation in patients with PNTs.

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