Influence of pain duration on pain outcomes following palliative radiotherapy for painful tumors: the sooner the irradiation, the better?

Abstract

Purpose We assessed the influence of pre-radiotherapy pain duration on post-treatment outcomes.

Methods Patients who received palliative radiotherapy were analyzed in a prospective observational study investigating curative and palliative radiotherapy. Brief Pain Inventory data were acquired at baseline and 1, 2, and 3 months after commencing irradiation. The pain response in terms of the index pain (i.e., pain caused by the irradiated tumors) was assessed using the International Consensus Endpoint. Patients were diagnosed with predominance of other pain (POP) if non-index pain of malignant or unknown origin was present and showed a higher pain score than the index pain. Competing risk analyses were performed in which deaths without the pain endpoints were considered as competing events.

Results Of 229 patients analyzed, 123 (54%) experienced a pain response and 43 (19%) experienced POP. Multivariable analyses using the Fine-Gray model revealed that patients with shorter pain duration (< 1 month) had higher cumulative incidence of pain response (subdistribution hazard ratio, 2.43; 95% confidence interval [CI], 1.35–4.38) and POP (subdistribution hazard ratio, 4.22; 95% CI, 1.30–13.70) compared with patients with longer pain duration (≥ 4 months). For patients with a pain duration of less than 1 month, cumulative incidence of pain response was estimated to be 69% (95% CI, 53–85%) and cumulative incidence of POP was estimated to be 15% (95% CI, 3–28%) at 1-month follow-up.

Conclusion Commencing palliative radiotherapy earlier may improve the probability of patients achieving a pain response, although POP may be more frequent.

Keywords Palliative radiotherapy; Patient-reported outcome; Painful tumor; Pain interference; Pain duration

Introduction

Palliative radiotherapy is an effective treatment for tumor-related pain in patients with bone metastases [1], and for painful lesions in other locations [2–5]. Patients with painful tumors may receive palliative radiotherapy at different time points during their disease course, and the optimal time for such patients to begin treatment remains unclear; i.e., there is no consensus on whether irradiation should commence as soon as possible after the patient experiences pain or after a certain period of time has elapsed. Associations between the duration of pain before palliative treatment and the therapy's success have been investigated in patients with cancer-related and -unrelated pain syndromes (although none of these studies used radiotherapy as the palliative treatment) [6–10]. Some studies found that longer pain duration is associated with lower rates of treatment success [6–8], although other studies revealed no such associations [9, 10]. If shorter pain duration before intervention is associated with a higher probability of treatment success, earlier treatment may be more effective.

To our knowledge, the influence of pain duration on the success of palliative radiotherapy has never been studied in patients with cancer-related pain. Hence, we performed a post hoc analysis of a prospective observational study to assess the influence of pain duration before palliative radiotherapy on pain outcome thereafter. These pain outcomes were evaluated in terms of index pain (i.e., pain caused by the irradiated tumors themselves) and non-index pain (i.e., pain from other sources).

Materials and methods

Patients and study design

We used the data from a prospective observational study performed at 1 academic and 2 non-academic hospitals [11]. This primary, 3-center study included 302 patients for whom curative or palliative radiotherapy was prescribed to treat painful tumors with the aim of identifying the predictors of pain response. Radiotherapy was performed with palliative intent for 237 of these patients (Fig. 1). After excluding 8 patients whose data regarding pain duration were missing, 229 were included in the present study. Radiotherapy was defined as palliative if the primary purpose of treatment was pain relief or if the irradiation field did not cover all of the tumors identified by diagnostic imaging [11]. Immediately before the start of radiotherapy in the primary study, patients were asked to complete a questionnaire, which asked when the index pain (i.e., pain caused by the tumors for which radiotherapy was planned) began. In the present post hoc study, the interval between this patient-reported date of the beginning of index pain and the date of radiotherapy initiation was defined as the duration of pain. The present study was approved by the participating centers' institutional review boards; written informed consent was received from all patients for the primary study.

Evaluation

The methods used for patient evaluation and follow-up were described previously [11]. Briefly, the treating radiation oncologists identified the index pain caused by the irradiated tumors at baseline through physical examination and diagnostic imaging. The Brief Pain Inventory short form was used to evaluate the intensity of pain and its interference with the

patient's daily life on an 11-point scale [12]. Patients rated their worst pain during the preceding 3 days in terms of index pain, and if present, non-index pain. The Brief Pain Inventory and analgesic data were collected at baseline and at 1, 2, and 3 months (all ± 7 days) after the start of radiotherapy. Follow-up data were obtained from patients in the hospital, or by mail, fax, or telephone. The pain response in terms of the index pain was assessed using the International Consensus Endpoint for clinical trials in bone metastases [13]. Patients who received radiotherapy for painful tumors were categorized as responders (including patients showing complete or partial responses to radiotherapy) or nonresponders. A complete response was defined as an index pain score of 0, with no increase in the daily oral morphine equivalent dose (OMED) [13]. A partial response was defined as a ≥ 2 point reduction in the pain score without an increase in OMED, or a ≥ 25% reduction in the use of analgesics, without an increase in the pain score [13].

We previously described our method of evaluating non-index pain (i.e., pain other than the index pain) [14]. At baseline and during follow-up, the treating radiation oncologists prospectively determined whether the patients had non-index pain, and for those who did, recorded its intensity (the worst pain over the preceding 3 days) and its origin. When more than one non-index pain was present, that with the greatest intensity was recorded. Non-index pain was classified as having malignant (tumor-related), unknown, or benign origins or as treatment-related. Patients were diagnosed with predominance of other pain (POP) if non-index pain of a malignant or unknown origin was present and showed a greater pain score than the index pain [14]. When the treating radiation oncologists were unable to determine whether the reported pain was related to the tumor among the patients evaluated by mail or fax, they sought clarification by contacting them via telephone. We assessed the pain response and POP at 1-, 2-, and 3-month follow-up evaluations.

Statistical analysis

Explanatory and response variables for which normal distribution could not be assumed were log-transformed or transformed into categorical variables based on medians and quartiles. Linear regression was performed to identify variables associated with pain duration. In competing risk analysis, the events of interest were pain response and POP, and deaths in the absence of these pain endpoints were considered as the competing events. Because the 1-month evaluation was performed between ± 1 weeks of 1 month after the initiation of radiotherapy, estimates at 38 days after the start of radiotherapy were recorded as 1-month cumulative incidence of pain response and POP.

Competing risk endpoints were analyzed using proportional cause-specific hazard models (i.e., Cox proportional hazard models) and proportional subdistribution hazard models (Fine-Gray model) [15,16]. The cause-specific hazard model estimates the effect of covariates on the rate at which events occur in subjects who are currently event-free [17]. Subdistribution hazard ratios obtained from the Fine-Gray model describe the relative effect of covariates on the subdistribution hazard function; hence, the covariates in this model can also be interpreted as having an effect on the cumulative incidence function or on the probability of events occurring over time [17]. The cause-specific hazard may be better suited for studying the etiology of diseases, whereas the subdistribution hazard is useful in predicting an individual's risk of an outcome [18]. Our primary analysis utilized a Fine-Gray model to analyze the cumulative incidence of pain response and POP; i.e., we sought to investigate whether pain duration is associated with the cumulative proportion of patients who experienced the pain endpoints (pain response and POP).

The relationships between pain duration and outcomes were analyzed with univariable and multivariable analyses. In addition to pain duration, we assessed 12 other covariates: age, sex, Eastern Cooperative Oncology Group performance status, hematologic tumor, pain score at baseline, presence of an index pain neuropathic component, non-index pain of malignant or unknown origin at baseline, opioid analgesic use at baseline, adjuvant analgesic use at baseline, concurrent systemic therapy, concurrent use of a bone-modifying agent, and total radiation dose. The variance inflation factor was used to determine whether multicollinearity between independent variables existed. Covariates with a p value < 0.10 at univariable analysis were included in multivariable analysis. All statistical tests were two-tailed, and $p <$ 0.05 was considered significant. Statistical analyses were performed with R version 3.6.2.

Results

Patients

We analyzed 229 patients treated with palliative radiotherapy (Fig. 1, Table 1). The primary sites of the solid tumors (n = 195) were the lung (n = 66), gastrointestinal system (n = 50), gynecological system (n = 24), head and neck (n = 14), urogenital system (n = 15), breast (n = 13), skin (n = 3), soft tissues (n = 3), and others (n = 7). Of the 229 patients, 224 (98%) completed the planned radiotherapy. A wide range of dose fractionations were used, with a median 30 Gy (range, 6–60 Gy) total radiation dose delivered in a median 10 fractions (range, 1–30 fractions).

Pain response and POP

Of the 229 patients, 195 (85%), 164 (72%), and 128 (56%) were evaluable for both pain response and POP at 1-, 2-, and 3-month follow-up, respectively (Fig. 1). Two-hundred and one (88%) were evaluable at least once across the three follow-up time points and 126 (55%) were evaluable at all three. Most (28 [82%]) of the 34 patients inevaluable at 1 month were also inevaluable at the 2- and 3-month follow-up; most (64 [98%]) of the 65 patients inevaluable at 2 months were also inevaluable at the 3-month follow-up. In total, 123 (54%) of the 229 patients experienced a pain response within 3 months after the start of radiotherapy; 30 patients (13%) died without experiencing a pain response. A total of 43 (19%) of the 229 patients experienced POP; 26 (11%) died without experiencing POP. At the 1-, 2-, and 3-month follow-up, 99 (51%), 89 (54%), and 71 (55%), respectively, of the evaluable patients had a pain response, and 16 (8%), 18 (11%), and 20 (16%) had POP.

Relationship between pain duration and patient characteristics

There were 8 missing values in systemic therapy and 10 in bone-modifying agent use (Table 1); complete case analyses were performed since the amount of missing data was small. Pain duration was skewed to the right (median, 2 months; range, 0.3–48 months), and, therefore, log-transformed. The variance inflation factors indicated a lack of multicollinearity between the variables used in the multivariable analysis. The multivariable analysis identified that a hematologic tumor (vs. solid tumor) was significantly associated with a decrease of 1.58 months, and adjuvant analgesic use (e.g., steroids, anticonvulsants, and anti-anxiety agents, etc.) was significantly associated with an increase of 1.35 months, of pain duration (Table 2).

Relationship between pain duration and pain outcomes

Pain duration was skewed to the right, and initially transformed into categorical variable with four levels based on quartiles (i.e., < 1, 1–2, 2–4, and ≥ 4 months). Because there was no clinically relevant difference between the effects of the variable of the second and third levels on pain outcomes, these two levels were pooled to form the variable "pain duration" with 3 levels (i.e., < 1, 1–4, and ≥ 4 months). The variance inflation factors indicated a lack of multicollinearity between the explanatory variables employed in the multivariable analyses. A significance level of 0.05 was used in the analyses of relationship between pain duration and pain outcomes. Shorter pain duration before radiotherapy was associated with higher cause-specific hazards and higher cumulative incidence of pain response and POP (Fig. 2 and 3, respectively). Pain duration was not significantly associated with cause-specific hazards or cumulative incidence of death without pain response, or death without POP (Fig. 4 and 5,

respectively). Full details of the results of our analyses with regression models are provided as Online Resource 1. For patients with pain duration of ≥ 4 months, 1–4 months, and < 1 month, cumulative incidence of pain response at 1 month was estimated to be 35% (95% confidence interval [CI], 22%–49%), 47% (95% CI, 38%–56%), and 69% (95% CI, 53%–85%), respectively. For patients with a pain duration of ≥ 4 months, 1–4 months, and < 1 month, cumulative incidence of POP at 1 month was estimated to be 6% (95% CI, 0%–13%), 7% (95% CI, 2%–11%), and 15% (95% CI, 3%–28%), respectively.

Discussion

We found that patients with a shorter pain duration before radiotherapy more frequently experienced a pain response, in terms of the index pain. The link between pain duration and response indicates the possibility that earlier radiotherapy for painful tumors increases the likelihood of improving pain symptoms. In contrast, a shorter pain duration was associated with more frequent occurrences of POP after radiotherapy; this observation suggests that earlier treatment may not be favorable. Overall, however, earlier radiotherapy may still provide benefits for 2 reasons. One is that pain response (54%) was approximately 3 times more frequent than POP (19%), indicating that the pain response (i.e., the index pain outcome) is a more relevant condition in our patients than POP (the non-index pain outcome). The other reason is that even when patients experience POP, additional palliative radiotherapy or analgesics may ameliorate non-index pain.

Cause-specific hazards and cumulative incidence curves capture different aspects of the event histories in competing risk data [19,20]. When a difference is found in the cumulative incidence of an event of interest between patient groups, sometimes the difference in the cause-specific hazard of the event of interest is the main contributing factor to the difference in the cumulative incidence (direct effect); but on other occasions, the difference in a cause-specific hazard of a *competing event* is an important contributing factor to the difference in the cumulative incidence of the event of interest (indirect effect). To completely understand the event dynamics, it is recommended that the results of competing risk analyses for both the event of interest and the competing event be reported [16]. In the present study, Fig. 2 shows that shorter pain duration is associated with both the higher rate at which pain response occurs (i.e., the cause-specific hazard) and the higher probability of pain response occurring over time (i.e., the cumulative incidence); the same is shown for POP in Fig. 3. Fig.

4 and 5 show that the cause-specific hazards of the competing events (i.e., deaths without pain response and POP) do not significantly differ between the patient groups, and therefore, do not seem to contribute to the differences in cumulative incidence of the events of interest (i.e., pain response and POP) between the 3 groups; i.e., a direct effect was shown in the present analysis but not an indirect effect.

One explanation for why patients with shorter pain duration before radiotherapy were more likely to experience pain palliation may be pain chronicity; i.e., unless the causes and consequences of cancer-related pain are resolved, the pain becomes chronic [21]. Although acute pain is relatively responsive to pharmacologic and interventional treatments, persistent pain is more difficult to treat [22]. In the present study, patients who received radiotherapy earlier may have had acute tumor-related pain that was more amenable to palliation. The mechanisms by which acute pain becomes chronic are multifactorial and complex, and current evidence for the prevention of chronic pain is inconclusive and/or inconsistent [23]. Our findings suggest an approach that can prevent chronic pain. Shorter pain duration before treatment has been shown to be associated with higher rates of therapy success in epidural steroid injection [8], joint manipulation [6], and administration of topical capsaicin [24], placebo [25], and opioid analgesics [10]. Our present study is an addition to these existing studies.

The influence of pain duration on POP may be explained, at least partially, by patient selection. Some patients with long-lasting tumor-related pain may experience systemic pain progression, and are therefore, not referred to radiation oncologists; only patients with long-lasting localized pain without intense distant pain may be referred for palliative radiotherapy. Another explanation may be that in patients with shorter pain duration before radiotherapy, the index pain tends to be palliated by radiotherapy, thereby rendering pain in other areas more prominent.

An analysis of data from two randomized trials of patients with head and neck cancer who were treated with fentanyl or methadone (one study was on radiation-induced nociceptive pain [n = 82] and the other study was on neuropathic pain [n = 52]) found no association between pain duration and opioid therapy success [10]. In contrast, our results showed that shorter pain duration was associated with a higher incidence of pain response. This discrepancy may be explained by the difference in the mechanism of pain between the previous study and ours. Another explanation may be that, in our study, index and non-index pain were assessed separately. From the standpoint of systemic pain control, a patient that experiences pain response but also has POP (patients with a short pain duration tended to be in this situation after radiotherapy) would not be considered to have good pain control.

We found that a hematologic tumor and adjuvant analgesic use were significantly associated with the duration of pain prior to referral to a radiation oncologist. Hematologic tumors tend to progress rapidly and be more radiosensitive than solid tumors, which might influence hematologists to refer patients for radiotherapy earlier to prevent massive tumor progression. Patients who have pain longer tend to take various adjuvant analgesics when they are referred to radiation oncologist. The association between long pain duration and the frequency of adjuvant analgesic use may reflect the long and complex trajectory of pain management in these patients.

The present study has limitations. One was the high attrition rate, and another was the uncertainty regarding the ability of patients to recall the date on which they started experiencing pain. Furthermore, our analyses were post-hoc. As such, our results should be confirmed in future studies. Another limitation was the observational study design, as the duration before radiotherapy may have been confounded by some unmeasured factors. In addition, the heterogeneous study population and non-standardized treatments might limit the internal validity of the study. On the other hand, the heterogeneity of the patients and

interventions might reflect the reality of palliative care settings and could contribute to a high generalizability of the study. Future studies should include more-homogeneous patient groups, including patients with bone metastases. Another limitation is that we focused on tumor-related pain, but other factors might have influenced a physician's clinical decision and been overlooked in the study. For example, patients with heterogeneous tumors might have had miscellaneous tumor-related symptoms such as bleeding or obstruction. Lastly, in this post hoc study, it is not known why some patients received early and others late radiotherapy; this point is worth researching in prospective studies.

In conclusion, a shorter pain duration pre-palliative radiotherapy was associated with a higher cumulative incidence of both pain response and POP. When the pain duration before palliative radiotherapy is short, a higher probability of both pain response and POP may be expected. Therefore, close follow-up is necessary after radiotherapy to identify any new pain, and repeat palliative radiotherapy or analgesics should be administered to control non-index pain, if it develops.

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Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical standards

The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Author Contribution

All authors contributed to the study conception and design. All authors were involved in material preparation, data collection, and analyses. The first draft of the manuscript was written by T. Saito and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figure captions

Fig. 1 Flow diagram of the study cohort.

Fig. 2 Pain response; analysis of cause-specific hazards and of cumulative incidence. The pain response was assessed in terms of the index pain (i.e., pain caused by the irradiated tumors).

HR hazard ratio, *CI* confidence interval

Fig. 3 Predominance of other pain (POP); analysis of cause-specific hazards and of cumulative incidence. Patients were diagnosed with POP if non-index pain of malignant or unknown origin was present and had a greater pain score than the index pain.
HR hazard ratio, *CI* confidence interval

Fig. 4 Death without pain response; analysis of cause-specific hazards and of cumulative incidence.

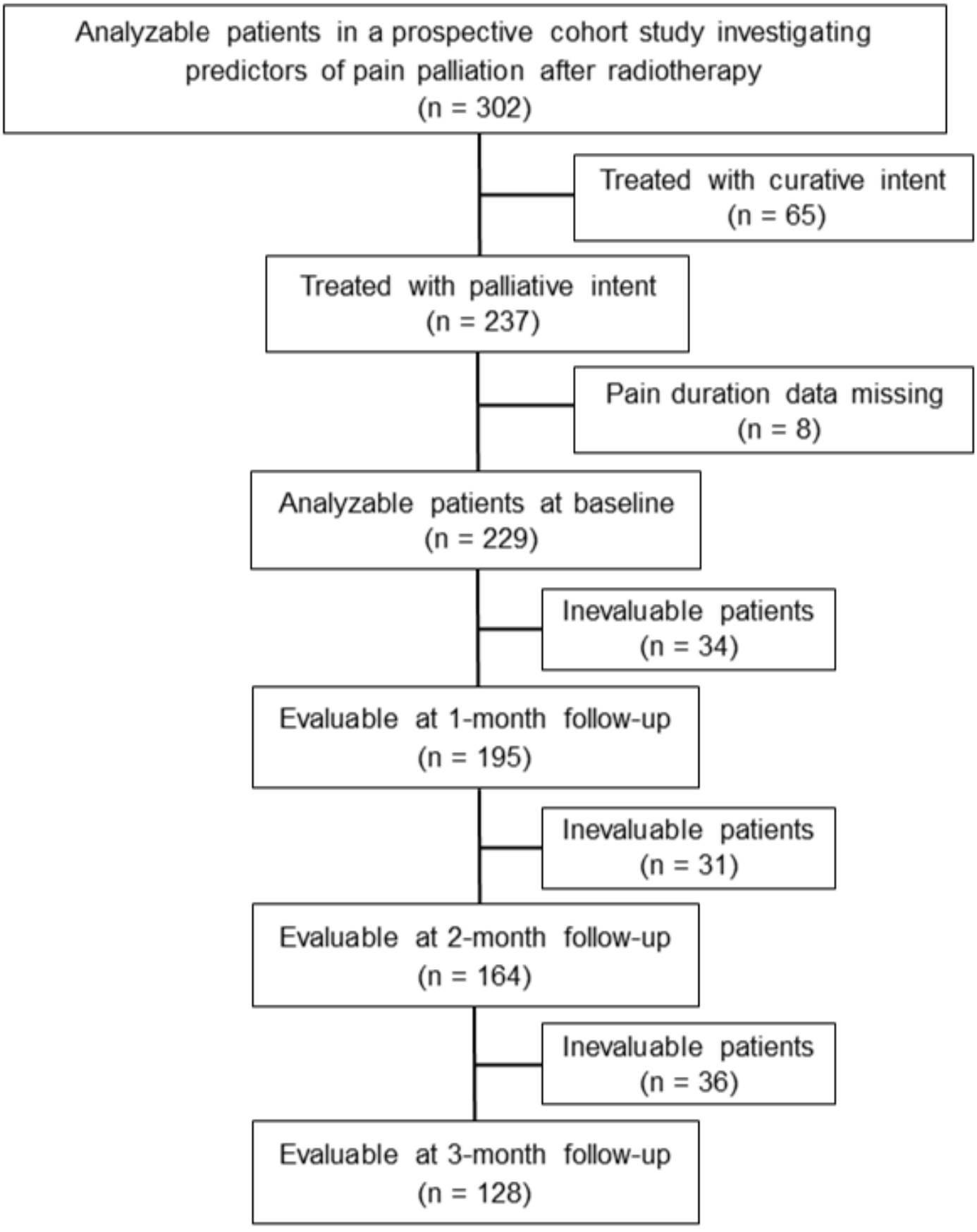
HR hazard ratio, *CI* confidence interval

Fig. 5 Death without predominance of other pain (POP); analysis of cause-specific hazards and of cumulative incidence.

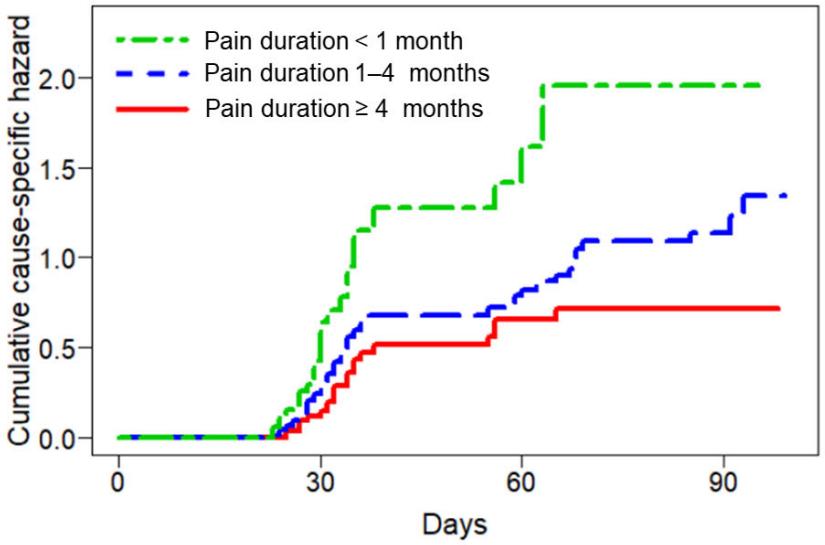
HR hazard ratio, *CI* confidence interval

Caption for Electronic Supplementary Material

Online Resource 1 Full details of the results of analyses with regression models


Analyzable patients in a prospective cohort study investigating predictors of pain palliation after radiotherapy
(n = 302)
Treated with curative intent
(n = 65)
Treated with palliative intent
(n = 237)
Pain duration data missing
(n = 8)
Analyzable patients at baseline
(n = 229)
Inevaluable patients
(n = 34)
Evaluable at 1-month follow-up
(n = 195)
Inevaluable patients
(n = 31)
Evaluable at 2-month follow-up
(n = 164)
Inevaluable patients
(n = 36)
Evaluable at 3-month follow-up
(n = 128)

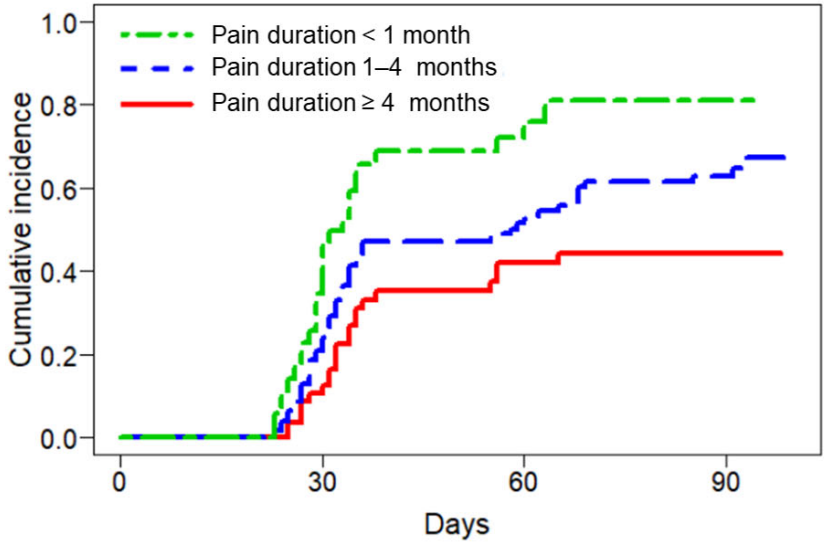
Analysis of cause-specific hazards



Number at risk				
Pain duration < 1 month	37	19	5	1
Pain duration 1–4 months	131	91	39	15
Pain duration ≥ 4 months	61	41	18	12

Cumulative number of censoring				
Pain duration < 1 month	0	3	5	6
Pain duration 1–4 months	0	7	15	27
Pain duration ≥ 4 months	0	6	12	17

Analysis of cumulative incidence



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Pain duration 1–4 months	131	91	39	15
Pain duration ≥ 4 months	61	41	18	12

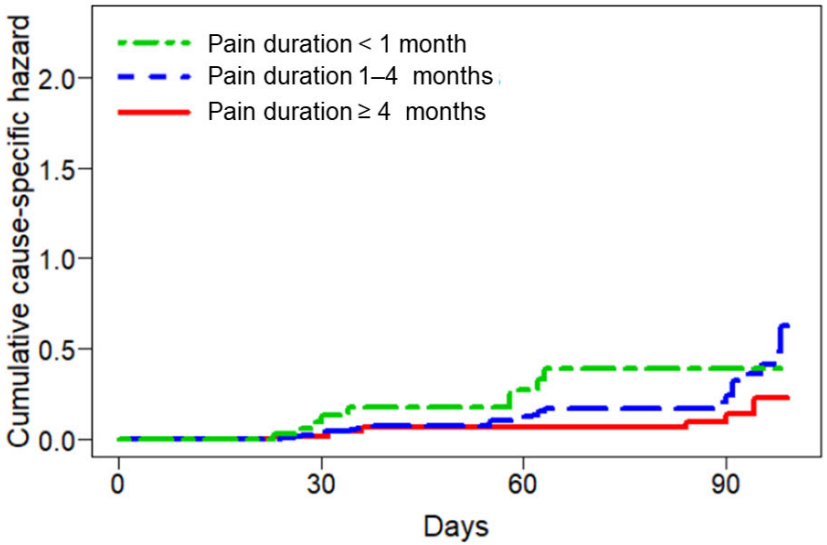
Cumulative number of censoring				
Pain duration < 1 month	0	3	5	6
Pain duration 1–4 months	0	7	15	27
Pain duration ≥ 4 months	0	6	12	17

Analysis of cause-specific hazards

Analysis of cumulative incidence

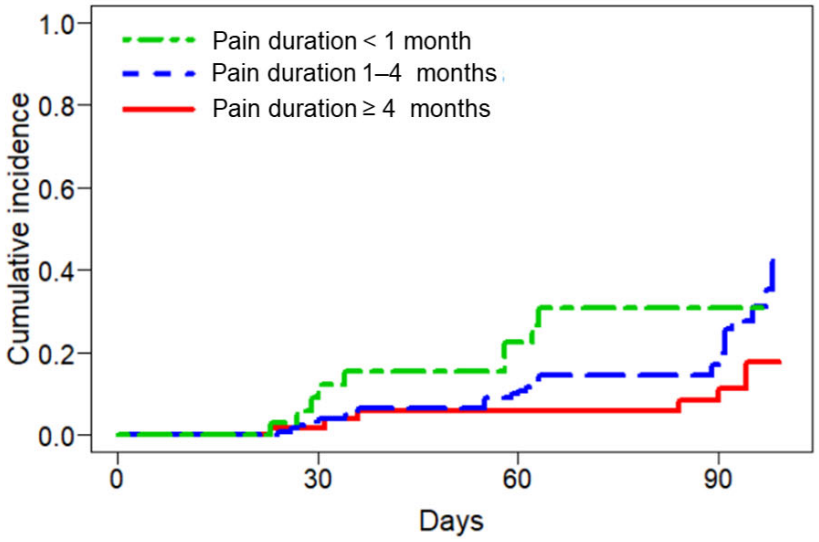
Variable	Cox proportional hazards model			Fine-Gray model		
	Cause-specific HR	95% CI	*P*	Subdistribution HR	95% CI	*P*
Univariable regression models						
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	1.56	0.97 to 2.51	.067	1.69	1.06 to 2.70	.027
< 1	2.92	1.65 to 5.17	< .001	2.89	1.64 to 5.10	< .001
Multivariable regression models						
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	1.47	0.90 to 2.41	.12	1.68	1.05 to 2.69	.031
< 1	2.29	1.28 to 4.14	.006	2.43	1.35 to 4.38	.003

Analysis of cause-specific hazards



Number at risk				
Pain duration < 1 month	37	26	19	8
Pain duration 1–4 months	131	111	91	47
Pain duration ≥ 4 months	61	46	34	24
Cumulative number of censoring				
Pain duration < 1 month	0	5	8	17
Pain duration 1–4 months	0	9	15	52
Pain duration ≥ 4 months	0	6	14	23

Analysis of cumulative incidence



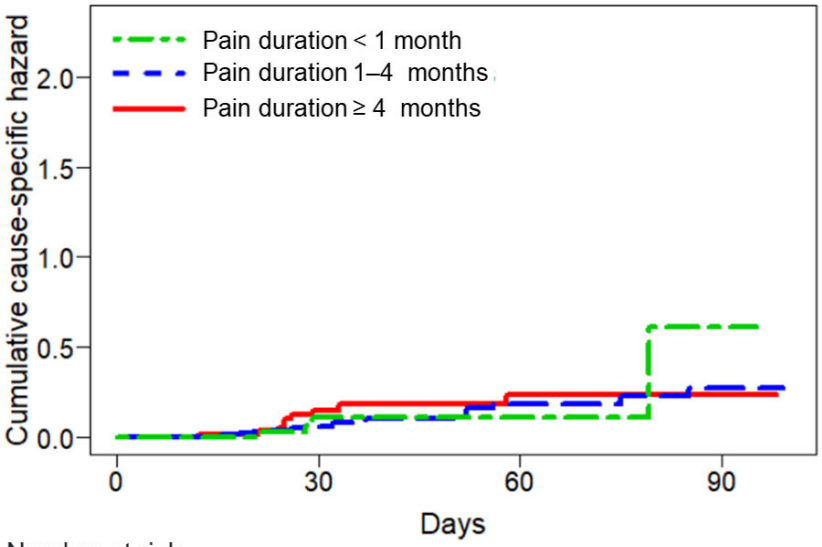
Number at risk				
Pain duration < 1 month	37	26	19	8
Pain duration 1–4 months	131	111	91	47
Pain duration ≥ 4 months	61	46	34	24
Cumulative number of censoring				
Pain duration < 1 month	0	5	8	17
Pain duration 1–4 months	0	9	15	52
Pain duration ≥ 4 months	0	6	14	23

Analysis of cause-specific hazards

Analysis of cumulative incidence

Variable	Cox proportional hazards model			Fine-Gray model		
	Cause-specific HR	95% CI	*P*	Subdistribution HR	95% CI	*P*
Univariable regression model						
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	1.93	0.80 to 4.67	.14	2.11	0.88 to 5.04	.095
< 1	2.97	1.06 to 8.38	.039	3.17	1.10 to 9.08	.032
Multivariable regression model						
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	2.49	1.01 to 6.13	.047	2.47	0.96 to 6.34	.060
< 1	4.80	1.60 to 14.40	.005	4.22	1.30 to 13.70	.016

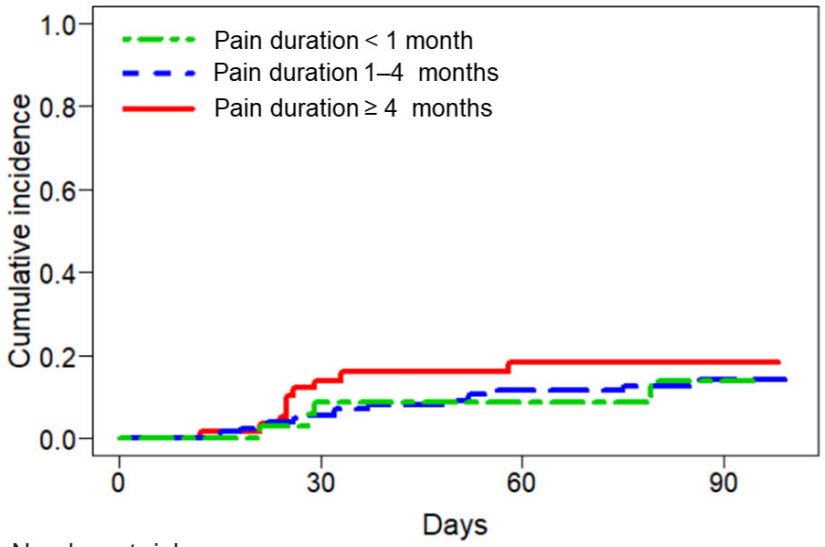
Analysis of cause-specific hazards



Number at risk				
Pain duration < 1 month	37	19	5	1
Pain duration 1–4 months	131	91	39	15
Pain duration ≥ 4 months	61	41	18	12

Cumulative number of censoring				
Pain duration < 1 month	0	3	5	6
Pain duration 1–4 months	0	7	15	27
Pain duration ≥ 4 months	0	6	12	17

Analysis of cumulative incidence



Number at risk				
Pain duration < 1 month	37	19	5	1
Pain duration 1–4 months	131	91	39	15
Pain duration ≥ 4 months	61	41	18	12

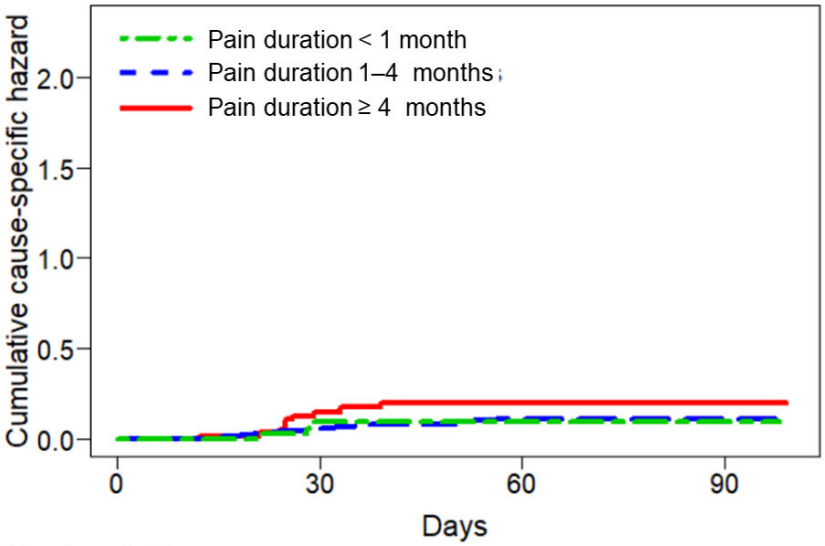
Cumulative number of censoring				
Pain duration < 1 month	0	3	5	6
Pain duration 1–4 months	0	7	15	27
Pain duration ≥ 4 months	0	6	12	17

Analysis of cause-specific hazards

Analysis of cumulative incidence

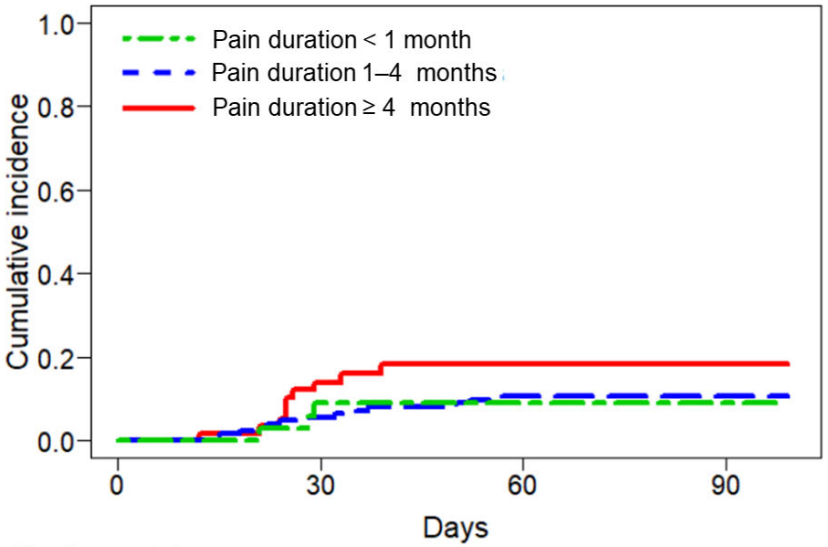
Variable	Cox proportional hazards model			Fine-Gray model		
	Cause-specific HR	95% CI	*P*	Subdistribution HR	95% CI	*P*
Univariable regression model						
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	0.76	0.34 to 1.67	.49	0.68	0.31 to 1.48	.33
< 1	0.89	0.28 to 2.86	.84	0.61	0.19 to 1.92	.40
Multivariable regression model						
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	0.74	0.33 to 1.67	.47	0.64	0.28 to 1.47	.30
< 1	0.93	0.28 to 3.05	.90	0.62	0.18 to 2.16	.46

Analysis of cause-specific hazards



Number at risk				
Pain duration < 1 month	37	26	19	8
Pain duration 1–4 months	131	111	91	47
Pain duration ≥ 4 months	61	46	34	24
Cumulative number of censoring				
Pain duration < 1 month	0	5	8	17
Pain duration 1–4 months	0	9	15	52
Pain duration ≥ 4 months	0	6	14	23

Analysis of cumulative incidence



Number at risk				
Pain duration < 1 month	37	26	19	8
Pain duration 1–4 months	131	111	91	47
Pain duration ≥ 4 months	61	46	34	24
Cumulative number of censoring				
Pain duration < 1 month	0	5	8	17
Pain duration 1–4 months	0	9	15	52
Pain duration ≥ 4 months	0	6	14	23

Analysis of cause-specific hazards

Analysis of cumulative incidence

Variable	Cox proportional hazards model			Fine-Gray model		
	Cause-specific HR	95% CI	*P*	Subdistribution HR	95% CI	*P*
Univariable regression model						
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	0.54	0.24 to 1.23	.14	0.54	0.24 to 1.22	.14
< 1	0.49	0.13 to 1.77	.28	0.47	0.13 to 1.69	.25
Multivariable regression model						
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	0.44	0.19 to 1.01	.053	0.45	0.20 to 1.02	.056
< 1	0.43	0.12 to 1.58	.20	0.42	0.11 to 1.68	.22

Table 1 Baseline patient characteristics (n = 229)

Characteristic	No.	%
Age, years		
Median	67	
Range	21–91	
Sex		
Female	92	40
Male	137	60
ECOG performance status		
0	33	14
1	90	39
2	70	31
3, 4	36	16
Pain duration, months		
Median	2	
Range	0.3–48	
< 1	37	16
1–4	131	57
≥ 4	61	27
Interval from first tumor diagnosis to radiotherapy, months		
Median	11	
Range	0–317	
Missing	1	0.4
Irradiated tumor		
Solid tumor	195	85

Primary tumor lesion	23	10
Lymph node metastasis	24	10
Hematogenous metastasis	128	56
Bone metastasis	122	53
Other	6	3
Other	20	9
Hematologic tumor	34	15
Myeloma	18	8
Plasmacytoma	5	2
Lymphoma	8	3
Other	3	1
Bone involvement by the tumor		
No	46	20
Yes	183	80
Worst pain score at baseline		
0–2	7	3
3–4	34	15
5–7	79	34
8–10	109	48
Neuropathic component of index pain		
No	150	66
Yes	79	34
Opioid analgesic use at baseline		
No	100	44
Yes	129	56
Adjuvant analgesic use at baseline		

No	149	65
Yes	80	35
Chemotherapy, molecular targeted therapy, or hormone therapy concurrent with radiotherapy		
No	100	44
Yes	121	53
Data not available	8	3
Bone-modifying agent used concurrent with radiotherapy		
No	154	67
Yes	65	28
Data not available	10	4
Total radiation dose, Gy		
Median	30	
Range	6–60	
≤ 10	38	17
10–20	37	16
20–30	98	43
> 30	56	24
Equivalent dose 2 Gy (alpha/beta = 10), Gy		
Median	32.5	
Range	6–60	
Institution type		
Academic	194	85

Non-academic	35	15

ECOG Eastern Cooperative Oncology Group

Table 2 Linear regression models to identify variables associated with ln (pain duration)* (n = 229)

	Univariable analysis			Multivariable analysis		
Variable	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
Age (per 1 year increase)	-0.01	-0.02 to 0.01	.29			
Sex (male vs. female)	-0.25	-0.52 to 0.03	.075	-0.27	-0.53 to 0.00	.051
ECOG performance status (2–4 vs. 0,1)	-0.17	-0.44 to 0.10	.21			
Irradiated tumor (hematologic vs. solid)	-0.47	-0.84 to -0.10	.014	-0.46	-0.82 to -0.09	.016
Interval from first tumor diagnosis to radiotherapy (per 10 months increase)	0.02	-0.01 to 0.05	.11			
Pain score at baseline (8–10 vs. 0–7)	-0.01	-0.28 to 0.26	.93			
Neuropathic component of index pain (yes vs. no)	-0.13	-0.41 to 0.15	.37			
Non-index pain of malignant or unknown origin at baseline (yes vs. no)	0.18	-0.19 to 0.54	.35			
Opioid analgesic use at baseline (yes vs. no)	0.20	-0.07 to 0.47	.14			
Adjuvant analgesic use at baseline (yes vs. no)	0.30	0.02 to 0.58	.037	0.30	0.02 to 0.57	.035
Chemotherapy, molecular targeted therapy, or hormone	0.01	-0.27 to 0.28	.96			

therapy concurrent with radiotherapy (yes vs. no)			
Bone-modifying agent used concurrent with radiotherapy (yes vs. no)	0.07	-0.23 to 0.37	.63
Total radiation dose (per 1 Gy increase)	0.01	0.00 to 0.02	.17

ECOG, Eastern Cooperative Oncology Group; CI, confidence interval.

Covariates with a *P* value < 0.10 at univariable analysis were included in multivariable analysis.

* ln denotes natural logarithm.

Online Resource 1

Table S1
Cox proportional hazards models for pain response (n = 229)

Variable	Univariable analysis			Multivariable analysis		
	Cause specific HR	95% CI	*P*	Cause specific HR	95% CI	*P*
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	1.56	0.97 to 2.51	.067	1.47	0.90 to 2.41	.12
< 1	2.92	1.65 to 5.17	< .001	2.29	1.28 to 4.14	.006
Age, years (continuous)	1.00	0.99 to 1.02	.63			
Sex						
Female	1.00 (reference)					
Male	0.93	0.65 to 1.33	.69			
ECOG performance status						
0,1	1.00 (reference)			1.00 (reference)		
2–4	1.64	1.15 to 2.34	.007	1.31	0.89 to 1.94	.17
Irradiated tumor						
Solid tumor	1.00 (reference)			1.00 (reference)		
Hematologic tumor	1.69	1.07 to 2.67	.024	1.57	0.95 to 2.60	.081
Pain score at baseline						
0–7	1.00 (reference)					
8–10	1.21	0.85 to 1.73	.29			
Neuropathic component of index pain						
No	1.00 (reference)			1.00 (reference)		
Yes	1.42	0.99 to 2.04	.055	1.17	0.80 to 1.70	.41
Non-index pain of malignant or unknown origin at baseline						
No	1.00 (reference)			1.00 (reference)		
Yes	0.41	0.22 to 0.75	.004	0.50	0.26 to 0.96	.036
Opioid analgesic use at baseline						
No	1.00 (reference)					
Yes	0.94	0.66 to 1.34	.75			
Adjuvant analgesic use at baseline						
No	1.00 (reference)					
Yes	0.92	0.63 to 1.34	.68			
Chemotherapy, molecular targeted therapy, or hormone therapy concurrent with radiotherapy						
No	1.00 (reference)					

Yes	0.96	0.67 to 1.38	.81			
Bone-modifying agent used concurrent with radiotherapy						
No	1.00 (reference)					
Yes	0.87	0.58 to 1.30	.49			
Total radiation dose, Gy (continuous)	1.01	1.00 to 1.03	.056	1.02	1.00 to 1.03	.056

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.
Covariates with a *P* value < 0.10 at univariable analysis were included in multivariable analysis.

Table S2
Fine-Gray models for pain response (n = 229)

Variable	Univariable analysis			Multivariable analysis		
	Subdistribution HR	95% CI	*P*	Subdistribution HR	95% CI	*P*
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	1.69	1.06 to 2.70	.027	1.68	1.05 to 2.69	.031
< 1	2.89	1.64 to 5.10	< .001	2.43	1.35 to 4.38	.003
Age, years (continuous)	1.00	0.99 to 1.02	.62			
Sex						
Female	1.00 (reference)					
Male	0.84	0.59 to 1.18	.32			
ECOG performance status						
0,1	1.00 (reference)			1.00 (reference)		
2–4	1.36	0.96 to 1.93	.082	1.14	0.78 to 1.68	.50
Irradiated tumor						
Solid tumor	1.00 (reference)			1.00 (reference)		
Hematologic tumor	1.69	1.06 to 2.67	.026	1.74	1.06 to 2.86	.030
Pain score at baseline						
0–7	1.00 (reference)					
8–10	1.18	0.83 to 1.66	.36			
Neuropathic component of index pain						
No	1.00 (reference)			1.00 (reference)		
Yes	1.44	1.01 to 2.05	.041	1.25	0.87 to 1.79	.23
Non-index pain of malignant or unknown origin at baseline						
No	1.00 (reference)			1.00 (reference)		
Yes	0.44	0.24 to 0.79	.006	0.50	0.27 to 0.92	.026
Opioid analgesic use at baseline						
No	1.00 (reference)					
Yes	0.84	0.60 to 1.18	.31			
Adjuvant analgesic use at baseline						
No	1.00 (reference)					
Yes	0.93	0.65 to 1.35	.72			
Chemotherapy, molecular targeted therapy, or hormone therapy concurrent with radiotherapy						
No	1.00 (reference)					
Yes	1.07	075 to 1.52	.72			
Bone-modifying agent used concurrent with radiotherapy						

No	1.00 (reference)					
Yes	093	0.64 to 1.35	.69			
Total radiation dose, Gy (continuous)	1.02	1.00 to 1.03	.007	1.02	1.01 to 1.03	.005

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.
Covariates with a *P* value < 0.10 at univariable analysis were included in multivariable analysis.

Table S3

Cox proportional hazards models for death without pain response (n = 229)

Variable	Univariable analysis			Multivariable analysis		
	Cause specific HR	95% CI	*P*	Cause specific HR	95% CI	*P*
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	0.76	0.34 to 1.67	.49	0.74	0.33 to 1.67	.47
< 1	0.89	0.28 to 2.86	.84	0.93	0.28 to 3.05	.90
Age, years (continuous)	0.99	0.96 to 1.03	.69			
Sex						
Female	1.00 (reference)			1.00 (reference)		
Male	2.49	1.07 to 5.81	.035	2.97	1.20 to 7.35	.019
ECOG performance status						
0,1	1.00 (reference)					
2–4	1.48	0.72 to 3.05	.29			
Irradiated tumor						
Solid tumor	1.00 (reference)					
Hematologic tumor	0.77	0.23 to 2.55	.67			
Pain score at baseline						
0–7	1.00 (reference)					
8–10	0.86	0.41 to 1.79	.69			
Neuropathic component of index pain						
No	1.00 (reference)					
Yes	0.86	0.39 to 1.87	.70			
Non-index pain of malignant or unknown origin at baseline						
No	1.00 (reference)					
Yes	0.87	0.33 to 2.28	.77			
Opioid analgesic use at baseline						
No	1.00 (reference)			1.00 (reference)		
Yes	2.08	0.95 to 4.54	.067	2.00	0.88 to 4.55	.099
Adjuvant analgesic use at baseline						
No	1.00 (reference)					
Yes	0.93	0.44 to 1.99	.86			
Chemotherapy, molecular targeted therapy, or hormone therapy concurrent with radiotherapy						
No	1.00 (reference)			1.00 (reference)		
Yes	0.44	0.21 to 0.94	.034	0.41	0.19 to 0.87	.020
Bone-modifying agent used concurrent with radiotherapy						

No	1.00 (reference)		
Yes	0.57	0.23 to 1.40	.22
Total radiation dose, Gy (continuous)	0.98	0.96 to 1.01	.28

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.
Covariates with a *P* value < 0.10 at univariable analysis were included in multivariable analysis.

Table S4

Fine-Gray models for death without pain response (n = 229)

Variable	Univariable analysis			Multivariable analysis		
	Subdistribution HR	95% CI	*P*	Subdistribution HR	95% CI	*P*
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	0.68	0.31 to 1.48	.33	0.64	0.28 to 1.47	.30
< 1	0.61	0.19 to 1.92	.40	0.62	0.18 to 2.16	.46
Age, years (continuous)	0.99	0.97 to 1.02	.67			
Sex						
Female	1.00 (reference)			1.00 (reference)		
Male	2.49	1.07 to 5.79	.034	3.04	1.22 to 7.54	.017
ECOG performance status						
0,1	1.00 (reference)					
2–4	1.19	0.59 to 2.42	.63			
Irradiated tumor						
Solid tumor	1.00 (reference)					
Hematologic tumor	0.63	0.19 to 2.07	.45			
Pain score at baseline						
0–7	1.00 (reference)					
8–10	0.78	0.38 to 1.60	.50			
Neuropathic component of index pain						
No	1.00 (reference)					
Yes	0.76	0.35 to 1.65	.49			
Non-index pain of malignant or unknown origin at baseline						
No	1.00 (reference)					
Yes	1.11	0.44 to 2.84	.82			
Opioid analgesic use at baseline						
No	1.00 (reference)			1.00 (reference)		
Yes	2.05	0.95 to 4.44	.068	1.85	0.82 to 4.19	.14
Adjuvant analgesic use at baseline						
No	1.00 (reference)					
Yes	0.93	0.44 to 1.97	.85			
Chemotherapy, molecular targeted therapy, or hormone therapy concurrent with radiotherapy						
No	1.00 (reference)			1.00 (reference)		
Yes	0.46	0.22 to 0.98	.043	0.43	0.21 to 0.90	.024
Bone-modifying agent used concurrent with radiotherapy						

No	1.00 (reference)		
Yes	0.61	0.25 to 1.50	.28
Total radiation dose, Gy (continuous)	0.98	0.95 to 1.01	.11

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.
Covariates with a *P* value < 0.10 at univariable analysis were included in multivariable analysis.

Table S5

Cox proportional hazards models for POP (n = 229)

Variable	Univariable analysis			Multivariable analysis		
	Cause specific HR	95% CI	*P*	Cause specific HR	95% CI	*P*
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	1.93	0.80 to 4.67	.14	2.49	1.01 to 6.13	.047
< 1	2.97	1.06 to 8.38	.039	4.80	1.60 to 14.40	.005
Age, years (continuous)	0.98	0.96 to 1.01	.16			
Sex						
Female	1.00 (reference)					
Male	1.59	0.85 to 2.99	.15			
ECOG performance status						
0,1	1.00 (reference)					
2–4	1.12	0.61 to 2.06	.71			
Irradiated tumor						
Solid tumor	1.00 (reference)					
Hematologic tumor	1.46	0.67 to 3.15	.34			
Pain score at baseline						
0–7	1.00 (reference)					
8–10	1.11	0.61 to 2.02	.74			
Neuropathic component of index pain						
No	1.00 (reference)					
Yes	0.58	0.29 to 1.15	.12			
Non-index pain of malignant or unknown origin at baseline						
No	1.00 (reference)			1.00 (reference)		
Yes	2.55	1.32 to 4.93	.005	3.52	1.75 to 7.06	< .001
Opioid analgesic use at baseline						
No	1.00 (reference)					
Yes	0.65	0.35 to 1.21	.17			
Adjuvant analgesic use at baseline						
No	1.00 (reference)					
Yes	0.66	0.33 to 1.31	.23			
Chemotherapy, molecular targeted therapy, or hormone therapy concurrent with radiotherapy						
No	1.00 (reference)					
Yes	1.04	0.55 to 1.95	.91			
Bone-modifying agent used concurrent with radiotherapy						

No	1.00 (reference)		
Yes	0.91	0.46 to 1.83	.80
Total radiation dose, Gy (continuous)	1.00	0.97 to 1.02	.74

POP, predominance of other pain; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.

Covariates with a *P* value < 0.10 at univariable analysis were included in multivariable analysis.

Table S6
Fine-Gray models for POP (n = 229)

Variable	Univariable analysis			Multivariable analysis		
	Subdistribution HR	95% CI	*P*	Subdistribution HR	95% CI	*P*
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	2.11	0.88 to 5.04	.095	2.47	0.96 to 6.34	.060
< 1	3.17	1.10 to 9.08	.032	4.22	1.30 to 13.70	.016
Age, years (continuous)	0.98	0.96 to 1.01	.18			
Sex						
Female	1.00 (reference)					
Male	1.37	0.74 to 2.56	.32			
ECOG performance status						
0,1	1.00 (reference)					
2–4	1.00	0.56 to 1.82	.99			
Irradiated tumor						
Solid tumor	1.00 (reference)					
Hematologic tumor	1.49	0.69 to 3.20	.31			
Pain score at baseline						
0–7	1.00 (reference)					
8–10	1.11	0.61 to 2.01	.74			
Neuropathic component of index pain						
No	1.00 (reference)					
Yes	0.63	0.32 to 1.23	.18			
Non-index pain of malignant or unknown origin at baseline						
No	1.00 (reference)			1.00 (reference)		
Yes	2.53	1.28 to 5.00	.008	3.27	1.61 to 6.63	.001
Opioid analgesic use at baseline						
No	1.00 (reference)			1.00 (reference)		
Yes	0.59	0.32 to 1.08	.087	0.60	0.33 to 1.10	.097
Adjuvant analgesic use at baseline						
No	1.00 (reference)					
Yes	0.67	0.34 to 1.30	.24			
Chemotherapy, molecular targeted therapy, or hormone therapy concurrent with radiotherapy						
No	1.00 (reference)					
Yes	1.16	0.63 to 2.16	.63			
Bone-modifying agent used concurrent with radiotherapy						

No	1.00 (reference)		
Yes	0.95	0.48 to 1.88	.88
Total radiation dose, Gy (continuous)	1.00	0.98 to 1.02	.90

POP, predominance of other pain; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.

Covariates with a *P* value < 0.10 at univariable analysis were included in multivariable analysis.

Table S7
Cox proportional hazards models for death without POP (n = 229)

Variable	Univariable analysis			Multivariable analysis		
	Cause specific HR	95% CI	*P*	Cause specific HR	95% CI	*P*
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	0.54	0.24 to 1.23	.14	0.44	0.19 to 1.01	.053
< 1	0.49	0.13 to 1.77	.28	0.43	0.12 to 1.58	.20
Age, years (continuous)	1.00	0.97 to 1.03	.96			
Sex						
Female	1.00 (reference)			1.00 (reference)		
Male	4.19	1.44 to 12.15	.008	4.02	1.35 to 11.97	.012
ECOG performance status						
0,1	1.00 (reference)					
2–4	1.89	0.87 to 4.12	.11			
Irradiated tumor						
Solid tumor	1.00 (reference)					
Hematologic tumor	0.78	0.24 to 2.61	.69			
Pain score at baseline						
0–7	1.00 (reference)					
8–10	0.84	0.39 to 1.84	.67			
Neuropathic component of index pain						
No	1.00 (reference)					
Yes	0.54	0.22 to 1.34	.18			
Non-index pain of malignant or unknown origin at baseline						
No	1.00 (reference)					
Yes	1.06	0.36 to 3.07	.92			
Opioid analgesic use at baseline						
No	1.00 (reference)			1.00 (reference)		
Yes	2.02	0.88 to 4.64	.098	1.44	0.61 to 3.37	.41
Adjuvant analgesic use at baseline						
No	1.00 (reference)					
Yes	0.81	0.35 to 1.86	.62			
Chemotherapy, molecular targeted therapy, or hormone therapy concurrent with radiotherapy						
No	1.00 (reference)			1.00 (reference)		
Yes	0.47	0.21 to 1.04	.061	0.38	0.17 to 0.86	.019

Bone-modifying agent used concurrent with radiotherapy						
No	1.00 (reference)					
Yes	0.71	0.28 to 1.77	.46			
Total radiation dose, Gy (continuous)	0.96	0.93 to 0.99	.010	0.96	0.93 to 1.00	.028

POP, predominance of other pain; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.

Covariates with a *P* value < 0.10 at univariable analysis were included in multivariable analysis.

Table S8

Fine-Gray models for death without POP (n = 229)

Variable	Univariable analysis			Multivariable analysis		
	Subdistribution HR	95% CI	*P*	Subdistribution HR	95% CI	*P*
Pain duration, months						
≥ 4	1.00 (reference)			1.00 (reference)		
1–4	0.54	0.24 to 1.22	.14	0.45	0.20 to 1.02	.056
< 1	0.47	0.13 to 1.69	.25	0.42	0.11 to 1.68	.22
Age, years (continuous)	1.00	0.97 to 1.03	.98			
Sex						
Female	1.00 (reference)			1.00 (reference)		
Male	4.16	1.42 to 12.20	.009	4.01	1.29 to 12.43	.016
ECOG performance status						
0,1	1.00 (reference)					
2–4	1.89	0.88 to 4.07	.10			
Irradiated tumor						
Solid tumor	1.00 (reference)					
Hematologic tumor	0.77	0.24 to 2.53	.67			
Pain score at baseline						
0–7	1.00 (reference)					
8–10	0.84	0.39 to 1.82	.66			
Neuropathic component of index pain						
No	1.00 (reference)					
Yes	0.54	0.22 to 1.34	.18			
Non-index pain of malignant or unknown origin at baseline						
No	1.00 (reference)					
Yes	0.97	0.34 to 2.76	.96			
Opioid analgesic use at baseline						
No	1.00 (reference)			1.00 (reference)		
Yes	2.00	0.88 to 4.54	.098	1.39	0.60 to 3.24	.44
Adjuvant analgesic use at baseline						
No	1.00 (reference)					
Yes	0.84	0.37 to 1.92	.68			
Chemotherapy, molecular targeted therapy, or hormone therapy concurrent with radiotherapy						
No	1.00 (reference)			1.00 (reference)		
Yes	0.47	0.22 to 1.04	.061	0.38	0.17 to 0.84	.017
Bone-modifying agent used concurrent with radiotherapy						

No	1.00 (reference)					
Yes	0.70	0.28 to 1.73	.44			
Total radiation dose, Gy (continuous)	0.96	0.93 to 0.99	.005	0.96	0.93 to 0.99	.015

POP, predominance of other pain; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.

Covariates with a *P* value < 0.10 at univariable analysis were included in multivariable analysis.