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Original Article

Neuropathic Pain Features in Patients with Bone Metastases☆

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Abstract

Aims: The results of previous randomised controlled trials suggest that radiation oncologists should consider the presence of neuropathic pain when they prescribe dose fractionations for painful bone metastases. Although validated screening tools for neuropathic pain features are currently available, the prevalence of such features among patients with painful bone metastases is still poorly understood. The purpose of this study was to estimate the prevalence of neuropathic pain features among patients who received palliative radiotherapy for painful bone metastases.

Materials and methods: We conducted a cohort survey of consecutive patients who received palliative radiotherapy for painful bone metastases at St Luke's International Hospital between 2013 and 2014. Patients were prospectively assessed before radiotherapy using the validated screening questionnaire to identify neuropathic pain components in Japanese patients. Pain with neuropathic features was prospectively defined using the total score of the seven-item questionnaire and a cut-off score ≥9. The pain response was assessed 2 months after the start of radiotherapy according to the criteria defined by the International Bone Metastases Consensus Working Party.

Results: Eighty-seven patients were assessed. Twenty-four per cent of patients (95% confidence interval: 16–35%) were diagnosed as having pain with neuropathic features. On multivariate analysis, no significant correlations were seen between neuropathic pain features and patient characteristics. Sixty-four patients (74%) were assessable 2 months after the start of radiotherapy. Overall response rates were 59% (95% confidence interval: 33–82%) in patients with neuropathic features and 55% (95% confidence interval: 40–70%) in those without such features.

Conclusions: A considerable proportion of the patients were proven to have bone pain with neuropathic features. Further investigations are warranted to validate symptom assessment tools in cooperation with pain distribution and image findings, and to clarify if the presence of neuropathic pain affects the response to palliative radiotherapy.

Key words: Bone metastases; neuropathic pain; palliative radiotherapy; radiotherapy

Introduction

Radiotherapy provides successful palliation of painful bone metastases, with 50–80% overall response rates [1]. Numerous prospective randomised controlled trials have shown the equivalence of multifraction and single-fraction radiotherapy for the palliation of painful bone metastases [2–8]. Owing to patient convenience, available resource advantage and cost-effectiveness, clinical practice guidelines have recommended that single-fraction radiotherapy should be standard care [9–11].

Neuropathic pain due to bone metastases has been the subject of one randomised trial comparing an 8 Gy single-fraction arm with a multifraction arm (20 Gy in five fractions) [12]. The intention-to-treat overall response rates for all 272 patients were 53% for the 8 Gy single-fraction arm and 61% for the multifraction arm ($P = 0.18$), whereas response rates for the 245 patients treated according to protocol were 53% for the 8 Gy single-fraction arm and 64% for the multifraction arm ($P = 0.092$). Although the

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response rates were not significantly different between the two arms, the lower limit of the 90% confidence interval for the difference in response rates (−18 to +2%) was below the pre-defined lower level of −15%. Furthermore, the trial may have been underpowered to detect a true effect for dose escalation due to an erroneously small sample size. The authors concluded that the 8 Gy single fraction was neither as effective as, nor less effective than, 20 Gy in five fractions, and that it may be reasonable in general to recommend a multifraction regimen for patients with bone metastases causing neuropathic pain.

According to these findings, radiation oncologists should consider the presence of neuropathic pain when they prescribe dose fractionations for painful bone metastases.

Recently, neuropathic pain was strictly defined [13–15], and validated screening and measurement tools are now available [16–18]. However, the presence of neuropathic pain features among patients with painful bone metastases is still poorly understood.

The primary objective of this study was to estimate the prevalence of neuropathic pain features among patients who received palliative radiotherapy for painful bone metastases. We also assessed patient characteristics and the pain response to radiotherapy associated with neuropathic features.

Materials and Methods

We conducted a cohort survey of consecutive patients who received palliative radiotherapy for painful bone metastases at St Luke's International Hospital between 2013 and 2014. The study was approved by the Institutional Review Board.

Screening Tool

Patients were prospectively assessed before radiotherapy using the validated screening questionnaire to identify neuropathic pain components in Japanese patients [18]. This consists of a seven-item questionnaire with a maximum total score of 28 (Table 1). The contents are very similar to the Self-reported Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS), which is commonly used in Western countries [16].

Response to Radiotherapy

Radiation oncologists prescribed dose fractionations based on their own discretion, considering the outcomes of the questionnaire. Pain scores and the use of analgesics were recorded before and 2 months after radiotherapy. Pain scores were assessed according to the worst pain over the previous 3 days at the irradiated site using a patient-assessed 0–10 numerical rating scale (NRS). All narcotic analgesics, including regular and breakthrough doses, were converted to the daily oral morphine equivalent dose (OMED) for analgesic scoring. The pain response was assessed 2 months after the start of radiotherapy according to the criteria defined by the International Bone Metastases Consensus Working Party [19,20].

Statistical Considerations

Pain with neuropathic features was prospectively defined using the total score of the seven-item questionnaire and a cut-off score $\geq$9. Multivariate logistic regression analyses were used to examine the potential associations between pain with neuropathic features and patient characteristics, including gender, age, primary site, irradiated site, NRS, OMED and the administration of bone-modifying agents. We used EZR [21] version 1.27 for statistical analysis. Differences were deemed significant when two-tailed P values were less than 0.05. Because the sample size was not large enough in this single institutional study, we show the 95% confidence intervals for the percentage of neuropathic pain and response rates.

Results

All eligible patients completed the screening questionnaire. Eighty-seven patients were assessed. Patient characteristics are shown in Table 2. Pain medication use in evaluated patients is detailed in Table 3. Twenty-four per cent of patients (95% confidence interval: 16–35%) were diagnosed as having pain with neuropathic features. On multivariate analysis, higher NRS pain scores before radiotherapy ($P = 0.08$) and no use of bone-modifying agents ($P = 0.054$) were marginally correlated with neuropathic pain features. However, no significant correlations were seen between neuropathic pain features and patient characteristics (Table 4).

Table 1
The questions and scores to identify neuropathic pain components

	No	Yes, a little	Yes	Yes, strongly	Yes, very strongly
Do you have a 'pins and needles' prickling sensation?	0	1	2	3	4
Does your pain come on suddenly like 'electric shock'?	0	1	2	3	4
Do you have skin irritation like 'burning'?	0	1	2	3	4
Does your pain accompany distinguishable numbness?	0	1	2	3	4
Does your pain get stronger when your skin is contacted by clothes or pressure?	0	1	2	3	4
Does the painful area feel different from the non-painful area?	0	1	2	3	4
Does the painful area swell or change colour to red or purple?	0	1	2	3	4