Inconsistencies in assessment of pain endpoints in radiotherapy for painful tumors: Analysis of original articles in the Green and Red Journals

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Background and purpose: Consistent assessment of the pain response is essential for adequately comparing treatment efficacy between studies. We studied the assessment of pain endpoints in radiotherapy for painful bone metastases (PBM) and painful non-bone-metastasis tumors (PNT).

Material and methods: We performed a literature search in the Green (Radiotherapy and Oncology) and Red (International Journal of Radiation Oncology * Biology * Physics) Journals for full-length original articles published between 2009 and 2018. We only included articles that assessed palliation of tumor-related pain after radiotherapy. The data obtained included the definitions of pain response and assessment of non-index pain (pain other than that related to the irradiated tumors).

Results: Among the 1812 articles identified using the journals’ search function, 60 were included in the analysis. Thirty percent of the PBM articles and approximately half of the PNT articles did not report on analgesic use. Among the prospective studies, 68% of the articles on PBMs and 10% of the articles on PNTs used the International Consensus Endpoint. The PBM articles published in 2014–2018 utilized the International Consensus Endpoint more frequently than those published in 2009–2013 (p = 0.049). No articles reported information on non-index pain.

Conclusions: After the initial publication of the International Consensus Endpoint, the frequency of its use appears to have risen in PBM research; however, its use in PNT studies has been considerably limited. The International Consensus Endpoint should be consistently utilized in future studies on radiotherapy for painful tumors. Since none of the journal articles had investigated non-index pain, this issue may also need to be addressed.

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Pain is common in cancer patients, contributing to poor physical and emotional well-being [1]. A systematic review on pain prevalence and pain severity in cancer patients showed that the prevalence rates of pain were 39.3% after curative treatment; 55.0% during anticancer treatment; and 66.4% in advanced, metastatic, or terminal disease [2]. Pain caused by tumors, including bone metastases [3,4] and other tumors [5–8], are major causes of cancer pain. Consistent assessment of the pain response is essential for adequately evaluating the treatment efficacy of radiotherapy for painful tumors. An international consensus was achieved on palliative radiotherapy endpoints for clinical trials in bone metastases to ensure consistent assessment of the pain response [9]; this was initially published in 2002 [9] and updated in 2012 [10]. According to the International Consensus Endpoint, a...
partial response is defined as a reduction in the index pain score by $\geq 2$ without an increase in analgesic use, or a $\geq 25\%$ reduction in analgesic use from baseline without an increase in the pain score \[9,10\]. The International Consensus Endpoint, initially developed for research on painful bone metastases (PBMs), has also been shown to be associated with pain interference changes in treatment for painful non-bone-metastasis tumors (PNTs) \[11\]. To date, the frequency of the use of the International Consensus Endpoint is unknown in studies on both PBMs and PNTs. The presence of non-index pain, the cause of which is not treated with radiotherapy, was recently demonstrated to be associated with poorer pain interference after palliative radiotherapy \[12\]. Even when the index pain is alleviated after radiotherapy, non-index pain may preclude the patients from deriving full benefits from palliative radiotherapy. Among studies on radiotherapy for painful tumors, the proportion reporting non-index pain endpoints is unknown.

Since the initial publication of the International Consensus Endpoint, has the frequency of its use risen adequately? How often is non-index pain investigated? In the present study, we sought to determine the frequency of the use of the International Consensus Endpoint and non-index pain endpoints in studies on radiotherapy for PBMs and PNTs. We searched articles published in two of the largest and most influential radiation oncology journals, namely, the Radiotherapy and Oncology (Green Journal) and International Journal of Radiation Oncology * Biology * Physics (Red Journal).

1. Material and methods

1.1. Search strategy and article selection

We performed a literature search in the Green (Radiotherapy and Oncology) and Red (International Journal of Radiation Oncology * Biology * Physics) journals for full-length original articles published between 2009 and 2018; the last search was performed on November 17, 2019. As the International Consensus Endpoint was initially published in 2002 \[9\], we compared articles published in 2009–2013 and 2014–2018, considering the time frame between consensus agreement and its uptake by researchers. Articles that contained the term “pain” were identified using the online search function of each journal. For the present study, we only included articles that assessed palliation of tumor-related pain after radiotherapy. More specifically, we included articles in which the number or proportion of patients who experienced pain response (or other terms with similar meanings, such as pain alleviation, pain palliation, or improvement in pain) was described. We did not restrict the methods of assessing pain response to specific ones; i.e., we included studies in which pain response was assessed based on pain scales, one of the subscales of quality of life, and subjective patient evaluation. In addition to articles whose primary endpoint was pain response, those in which pain response was the secondary outcome measure were also included in the present analysis. The following articles were excluded: editorials or reviews, case reports (<10 patients), and studies using radiopharmaceuticals, particle radiotherapy, brachytherapy, radiotherapy for benign disease, intraoperative radiotherapy, and preoperative radiotherapy. The title/abstract screening and the subsequent assessment of full-text articles for eligibility were performed by one radiation oncologist (TS).

1.2. Data extraction

We grouped articles based on the painful tumor types, for which radiotherapy was administered as follows: PBMs and PNTs. Studies that included both PBMs and PNTs were included in the PNT group. Our primary goal was to investigate the definition of the pain response after radiotherapy for painful tumors. Additional information obtained included the study design (i.e., prospective or retrospective and randomized controlled trial or not), primary endpoints of the study, scales for measuring pain intensity, assessment of analgesic use, assessment of non-index pain (i.e., pain other than that caused by the irradiated tumors), assessment of quality of life or pain interference with daily activities, and assessment of symptoms other than pain. Articles that utilized prospectively collected databases were classified as prospective studies. Those involving secondary analyses of previously published randomized controlled trial data were not classified as randomized controlled trials in the present study.

1.3. Statistical analysis

The proportion of articles that used the International Consensus Endpoint were compared between the articles published in 2009–2013 and 2014–2018, using the Fisher’s exact test. The statistical tests were two-tailed, and $p$ values $< 0.05$ were considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

2. Results

Among the 1812 articles identified through the journals’ online search function, 60 were included in the study (Fig. 1). The characteristics of the included studies are presented in Table 1 (PBMs) and Table 2 (PNTs). Approximately 70% of the PBM articles and 40% of the PNT articles had a prospective study design. As a scale for measuring pain intensity, the 11-point numeric rating scale was utilized in approximately half of the articles that investigated PBMs; in contrast, only 2 (9%) studies in the PNT group utilized the numeric rating scale. Over a half of the articles on PNTs did not report on scales measuring pain intensity. In approximately half of the articles on PBMs, the International Consensus Endpoint was employed to define the pain response; conversely, it was utilized in only 1 article (4%) on PNTs. Among the PNT articles, 70% assessed the pain response based only on pain intensity. The PBM articles published in 2014–2018 utilized the International
Consensus Endpoint more frequently than those published in 2009–2013 ($p = 0.049$); however, this trend was not observed for PNT articles ($p = 0.35$) (Fig. 2). No PBM or PNT articles reported data on non-index pain, the cause of which was not irradiated.

Pain assessment in the included prospective articles is presented in Fig. 3. In 11 (31%) of the 36 articles published in 2009–2013, enrollment started earlier than 2002, when the International Consensus Endpoint was initially published. In 6 (25%) of the 24 articles published in 2014–2018, enrollment started earlier than 2002, and thus, were not able to use the International Consensus Endpoint to assess pain response. In contrast, the International Consensus Endpoint was scarcely utilized in the articles on PNTs.

When evaluating the effect of radiotherapy on tumor-related pain, data on analgesic use is of particular value. Radiotherapy effectively relieves pain in weeks to months; during the period, analgesic usage may be increased in certain cases. This increase in analgesic use may confound the analgesic effect of radiotherapy, and lead to overestimation of the response to irradiation [15,16]. The present study demonstrated that 30% of the PBM articles and approximately half of the PNT articles did not report on analgesic usage. Information on analgesic usage should be recorded and evaluated in future studies, if the additional requirement of study resources is acceptable.

The International Consensus Endpoint considers both pain intensity and analgesic use, thus enabling adequate estimation of the pain response [9,10]. According to the International Consensus Endpoint, responders to radiotherapy have been demonstrated to experience an improvement in both quality of life and pain interference for PBMs [16–22]; improvements have also been noted for painful tumors in general, including both PBMs and PNTs [11]. Further studies are warranted for investigating the association between the pain response with quality of life and pain interference after radiotherapy for PNTs; available data in this regard are limited.

After radiotherapy for painful tumors, the presence of non-index pain, that is more intense than the index pain, negatively influences the interference with daily activities [12]. Information regarding non-index pain was not reported in any of the articles

### Table 1
Characteristics of articles that investigated painful bone metastases.

| Characteristic                                | Green Journal | Red Journal | Total |
|-----------------------------------------------|--------------|------------|-------|
| Total number of articles that studied pain palliation owing to radiation therapy | 10 100 | 27 100 | 37 100 |
| Study design                                  | 10 100 | 15 56 | 25 68 |
| Prospective                                   | 0 0 | 12 44 | 12 32 |
| Randomized controlled trial                   | No 80 | 26 96 | 34 92 |
| Yes                                           | 2 20 | 1 4 | 3 8 |
| Symptom palliation as primary endpoint        | No 20 | 10 37 | 12 32 |
| Yes                                           | 8 80 | 17 63 | 25 68 |
| Scales for measuring pain intensity           | 11-point numeric rating scale | 5 50 | 14 52 | 19 51 |
| Visual analog scale                           | 2 20 | 5 19 | 7 19 |
| Others                                        | 3 30 | 0 0 | 3 8 |
| Not reported                                  | 0 0 | 8 30 | 8 22 |
| Assessment of analgesic usage                 | No 10 | 10 37 | 11 30 |
| Yes                                           | 9 90 | 17 63 | 26 70 |
| Definition of pain response                   | International Consensus Endpoint published in 2002 | 3 30 | 5 19 | 8 22 |
| International Consensus Endpoint published in 2012 | 5 50 | 5 19 | 10 27 |
| Based on both, pain intensity and analgesic use | 1 10 | 4 15 | 5 14 |
| Based only on pain intensity                  | 1 10 | 13 48 | 14 38 |
| Assessment of pain other than index pain caused by the irradiated tumors | No 10 | 27 100 | 37 100 |
| Yes                                           | 0 0 | 0 0 | 0 0 |
| Assessment of quality of life or symptom interference | No 3 30 | 18 67 | 21 57 |
| Yes                                           | 7 70 | 9 33 | 16 43 |
| Assessment of any symptoms other than pain    | No 8 80 | 19 70 | 27 73 |
| Yes                                           | 2 20 | 8 30 | 10 27 |

*Overall, 4-point scales were used in 2 studies, and a 5-point scale was used in 1 study.*

3. Discussion

We found that the assessment of pain intensity, analgesic use, and pain response was not sufficiently consistent between the included studies. This inconsistency was demonstrated in some and many of the articles on PBMs and PNTs, respectively. After the initial publishing of the International Consensus Endpoint in 2002, the frequency of its use appears to have risen for more than ten years in PBMs. This increase in the frequency of use of the consensus endpoint is encouraging, in view of the difficulties in introducing evidence and clinical guidelines into routine practice [13,14]. The proportion of studies that commenced accrual before 2002 shows one of the reasons why uptake of consensus by papers can be slow. Future studies might more frequently use the consensus endpoint, considering that 31% of the studies published in 2009–2013 and 25% of those published in 2014–2018 commenced enrollment before 2002, and thus, were not able to use the International Consensus Endpoint to assess pain response. In contrast, the International Consensus Endpoint was scarcely utilized in the articles on PNTs.

When evaluating the effect of radiotherapy on tumor-related pain, data on analgesic use is of particular value. Radiotherapy effectively relieves pain in weeks to months; during the period, analgesic usage may be increased in certain cases. This increase in analgesic use may confound the analgesic effect of radiotherapy, and lead to overestimation of the response to irradiation [15,16]. The present study demonstrated that 30% of the PBM articles and approximately half of the PNT articles did not report on analgesic usage. Information on analgesic usage should be recorded and evaluated in future studies, if the additional requirement of study resources is acceptable.

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After radiotherapy for painful tumors, the presence of non-index pain, that is more intense than the index pain, negatively influences the interference with daily activities [12]. Information regarding non-index pain was not reported in any of the articles
included in the present study, and is worth recording and reporting in the future.

The scope of our study is limited by the inclusion of articles published in only 2 radiation oncology journals for analysis. In a cumulative meta-analysis, only one third (9/27) of the included randomized trials on single vs multiple fractions for metastatic bone pain were published in these 2 journals [23], suggesting the presence of significant potential bias in our study. Since our findings are based on articles published in high-impact radiation oncology journals, they may be biased in favor of pain assessment of high quality. There may still be further scope for improvement in pain evaluation in studies published in these journals. In general, pain assessment in radiation oncology may be equivalent or worse. Another limitation of our study is that only one author screened and evaluated the articles.

We demonstrated insufficient consistencies in the assessment of pain response in articles on both PBMs and PNTs. In evaluating the palliative effect of radiotherapy, consistent assessment of endpoints is crucial with both conventional radiotherapy and advanced technical therapy, including stereotactic body radiotherapy. In future studies on painful tumors, the International Consensus Endpoint should be utilized for both PBMs and PNTs to ensure...
consistency. In addition, data on non-index pain should be reported to enable comprehensive evaluation of patients’ pain.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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