



Contents lists available at ScienceDirect

# Clinical and Translational Radiation Oncology

journal homepage: [www.elsevier.com/locate/ctro](http://www.elsevier.com/locate/ctro)

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

Tetsuo Saito<sup>a,b,\*</sup>, Naoto Shikama<sup>c</sup>, Atsunori Yorozu<sup>d</sup>, Hikaru Kubota<sup>e</sup>, Kenta Murotani<sup>f</sup>, Kohsei Yamaguchi<sup>a</sup>, Natsuo Oya<sup>a</sup>, Naoki Nakamura<sup>g</sup>

<sup>a</sup> Department of Radiation Oncology, Kumamoto University Hospital, Kumamoto, Japan

<sup>b</sup> Graduate School of Medicine, Kurume University, Fukuoka, Japan

<sup>c</sup> Department of Radiation Oncology, Juntendo University, Tokyo, Japan

<sup>d</sup> Department of Radiation Oncology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan

<sup>e</sup> Department of Radiation Oncology, Kobe University Hospital, Hyogo, Japan

<sup>f</sup> Biostatistics Center, Graduate School of Medicine, Kurume University, Fukuoka, Japan

<sup>g</sup> Department of Radiology, St. Marianna University Hospital, Kawasaki, Japan

### ARTICLE INFO

#### Article history:

Received 1 July 2020

Accepted 20 July 2020

Available online 24 July 2020

#### Keywords:

Palliative radiotherapy

Painful tumors

Pain endpoint

Pain response

Analgesics

### ABSTRACT

**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 (PBMs) and painful non-bone-metastasis tumors (PNTs).

**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.

© 2020 The Author(s). Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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, meta-

static, 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

*Abbreviations:* PBM, painful bone metastasis; PNT, painful non-bone-metastasis tumor.

\* Corresponding author.

<https://doi.org/10.1016/j.ctro.2020.07.003>

2405-6308/© 2020 The Author(s). Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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

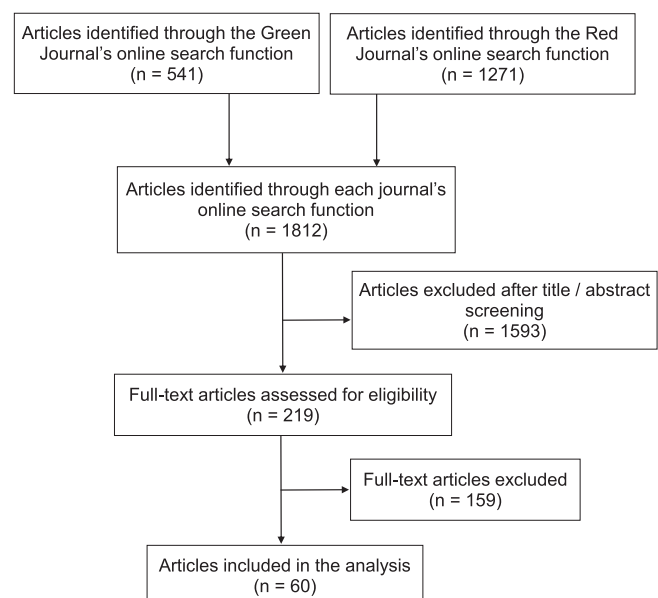


Fig. 1. Flow diagram of study inclusion.

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

Characteristic	Green Journal		Red Journal		Total	
	No.	%	No.	%	No.	%
Total number of articles that studied pain palliation owing to radiation therapy	10	100	27	100	37	100
Study design						
Prospective	10	100	15	56	25	68
Retrospective	0	0	12	44	12	32
Randomized controlled trial						
No	8	80	26	96	34	92
Yes	2	20	1	4	3	8
Symptom palliation as primary endpoint						
No	2	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	1	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	100	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.

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. While 64% articles on PBMs utilized the 11-point numeric rating scale, only 1 (10%) PNT article utilized this scale; 84% and 50% of the articles in the PBM and PNT groups, respectively, reported any information on analgesic use. Although the International Consensus Endpoint was most frequently used to define the pain response in articles on PBMs, 32% defined it differently. In the PNT group, the International Consensus Endpoint was utilized in only 1 (10%) article.

### 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 consen-

sus 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.

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.

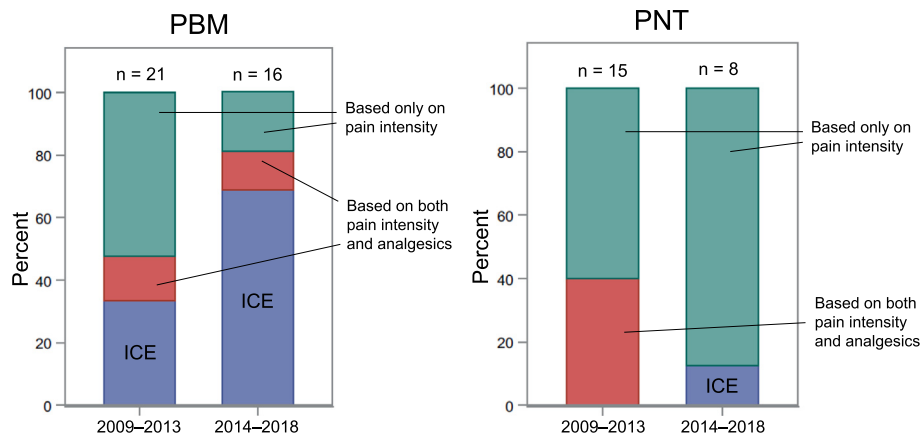
After radiotherapy for painful tumors, the presence of non-index pain, that is more intense than the index pain, negatively influences the interference with daily activities [12]. Information regarding non-index pain was not reported in any of the articles

**Table 2**  
Characteristics of articles that investigated painful non-bone-metastasis tumors.

Characteristic	Green Journal		Red Journal		Total	
	No.	%	No.	%	No.	%
Total number of articles that studied pain palliation owing to radiation therapy	5	100	18	100	23	100
Study design						
Prospective	3	60	7	39	10	43
Retrospective	2	40	11	61	13	57
Randomized controlled trial						
No	4	80	18	100	22	96
Yes	1	20	0	0	1	4
Symptom palliation as primary endpoint						
No	2	40	8	44	10	43
Yes	3	60	10	56	13	57
Scales for measuring pain intensity						
11-point numeric rating scale	0	0	2	11	2	9
Visual analog scale	0	0	3	17	3	13
Others	1*	20	4 †	22	5	22
Not reported	4	80	9	50	13	57
Assessment of analgesic usage						
No	4	80	8	44	12	52
Yes	1	20	10	56	11	48
Definition of pain response						
International Consensus Endpoint published in 2002	0	0	0	0	0	0
International Consensus Endpoint published in 2012	0	0	1	6	1	4
Based on both, pain intensity and analgesic use	0	0	6	33	6	26
Based only on pain intensity	5	100	11	61	16	70
Assessment of pain other than index pain caused by the irradiated tumors						
No	5	100	18	100	23	100
Yes	0	0	0	0	0	0
Assessment of quality of life or symptom interference						
No	2	40	13	72	15	65
Yes	3	60	5	28	8	35
Assessment of any symptoms other than pain						
No	0	0	7	39	7	30
Yes	5	100	11	61	16	70

\*A 4-point scale was used in 1 study.

†A 4-point scale was used in 3 studies, and the Kersh-Hazra scale was used in 1 study.



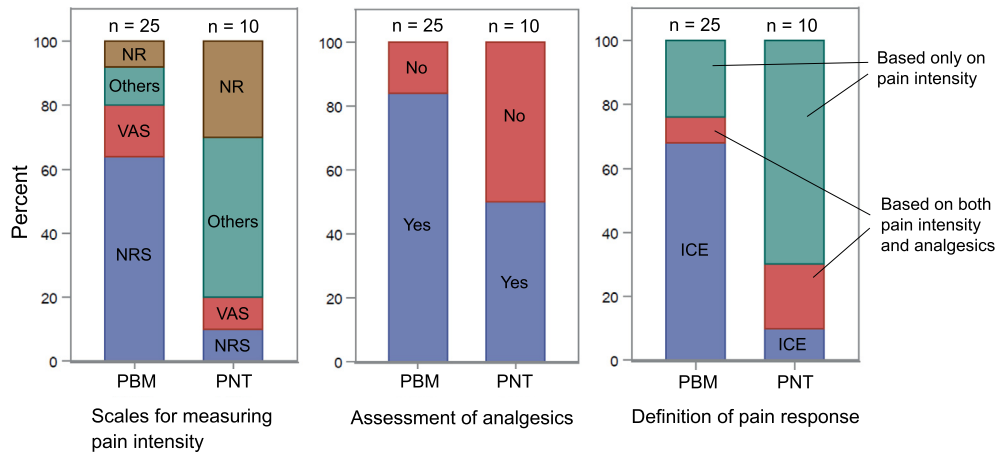
**Fig. 2.** Definition of pain response according to the years of publication. *Abbreviations:* ICE = International Consensus Endpoint; PBM = painful bone metastases; PNT = painful non-bone-metastasis tumors.

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



**Fig. 3.** Summary of prospective studies. Abbreviations: NRS = numeric rating scale; VAS = visual analog scale; NR = not reported; ICE = International Consensus Endpoint; PBM = painful bone metastases; PNT = painful non-bone-metastasis tumors.

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.

### References

- Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines iv166-iv191. *Ann Oncol* 2018;29. <https://doi.org/10.1093/annonc/mdy152>.
- van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, et al. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *J Pain Symptom Manage* 2016;51(1070–1090). <https://doi.org/10.1016/j.jpainsymman.2015.12.340e9>.
- Lutz S, Spence C, Chow E, et al. Survey on use of palliative radiotherapy in hospice care. *J Clin Oncol* 2004;22:3581–6. <https://doi.org/10.1200/JCO.2004.11.151>.
- Culleton S, Kwok S, Chow E. Radiotherapy for pain. *Clin Oncol (R Coll Radiol)* 2011;23:399–406. <https://doi.org/10.1016/j.clon.2010.11.011>.
- Rutten EH, Crul BJ, van der Toorn PP, et al. Pain characteristics help to predict the analgesic efficacy of radiotherapy for the treatment of cancer pain. *Pain* 1997;69:131–5. [https://doi.org/10.1016/s0304-3959\(96\)03253-8](https://doi.org/10.1016/s0304-3959(96)03253-8).
- MacLeod N, Chalmers A, O'Rourke N, et al. Is radiotherapy useful for treating pain in mesothelioma?: A phase II trial. *J Thorac Oncol* 2015;10:944–50. <https://doi.org/10.1097/ITO.0000000000000499>.
- Rudzianskiene M, Inciura A, Gerbutavicius R, et al. Single vs. multiple fraction regimens for palliative radiotherapy treatment of multiple myeloma: a prospective randomised study. *Strahlenther Onkol* 2017;193:742–9. <https://doi.org/10.1007/s00066-017-1154-5>.
- Ashton M, O'Rourke N, Macleod N, et al. SYSTEMS-2: a randomised phase II study of radiotherapy dose escalation for pain control in malignant pleural mesothelioma. *Clin Transl Radiat Oncol* 2018;8:45–9. <https://doi.org/10.1016/j.ctro.2017.11.004>.
- Chow E, Wu JS, Hoskin P, Coia LR, Bentzen SM, Blitzer PH. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Radiother Oncol* 2002;64:275–80. [https://doi.org/10.1016/s0167-8140\(02\)00170-6](https://doi.org/10.1016/s0167-8140(02)00170-6).
- Chow E, Hoskin P, Mitera G, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Int J Radiat Oncol Biol Phys* 2012;82:1730–7. <https://doi.org/10.1016/j.ijrobp.2011.02.008>.
- Saito T, Toya R, Tomitaka E, et al. Predictors of pain palliation after radiation therapy for painful tumors: a prospective observational study. *Int J Radiat Oncol Biol Phys* 2018;101:1061–8. <https://doi.org/10.1016/j.ijrobp.2018.04.072>.
- Saito T, Toya R, Tomitaka E, et al. Predictors of the predominance of nonindex pain after palliative radiation therapy for painful tumors. *Adv Radiat Oncol* 2019;4:118–26. <https://doi.org/10.1016/j.adro.2018.08.006>.
- Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458–65. <https://doi.org/10.1001/jama.282.15.1458>.
- Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;362:1225–30. [https://doi.org/10.1016/S0140-6736\(03\)14546-1](https://doi.org/10.1016/S0140-6736(03)14546-1).
- Chow E, Davis L, Holden L, et al. A comparison of radiation therapy outcomes of bone metastases employing international consensus endpoints and traditional endpoints. *Support Cancer Ther* 2004;3:173–8. doi: unavailable.
- Chow E, Meyer RM, Chen BE, et al. Impact of reirradiation of painful osseous metastases on quality of life and function: a secondary analysis of the NCIC CTG SC.20 randomized trial. *J Clin Oncol* 2014;32:3867–73. <https://doi.org/10.1200/JCO.2014.57.6264>.
- McDonald R, Chow E, Rowbottom L, et al. Quality of life after palliative radiotherapy in bone metastases: a literature review. *J Bone Oncol* 2015;4:24–31. <https://doi.org/10.1016/j.jbo.2014.11.001>.
- Harris K, Li K, Flynn C, Chow E. Worst, average or current pain in the Brief Pain Inventory: which should be used to calculate the response to palliative radiotherapy in patients with bone metastases?. *Clin Oncol (R Coll Radiol)* 2007;19:523–7. <https://doi.org/10.1016/j.clon.2007.04.007>.
- Nguyen J, Chow E, Zeng L, et al. Palliative response and functional interference outcomes using the Brief Pain Inventory for spinal bony metastases treated with conventional radiotherapy. *Clin Oncol (R Coll Radiol)* 2011;23:485–91. <https://doi.org/10.1016/j.clon.2011.01.507>.
- Khan L, Uy C, Nguyen J, et al. Self-reported rates of sleep disturbance in patients with symptomatic bone metastases attending an outpatient radiotherapy clinic. *J Palliat Med* 2011;14:708–14. <https://doi.org/10.1089/jpm.2010.0491>.
- Zeng L, Chow E, Zhang L, et al. Comparison of pain response and functional interference outcomes between spinal and non-spinal bone metastases treated with palliative radiotherapy. *Support Care Cancer* 2012;20:633–9. <https://doi.org/10.1007/s00520-011-1144-6>.
- McDonald R, Ding K, Brundage M, et al. Effect of radiotherapy on painful bone metastases: a secondary analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23. *JAMA Oncol* 2017;3:953–9. <https://doi.org/10.1001/jamaoncol.2016.6770>.
- Chow R, Hoskin P, Schild SE, et al. Single vs multiple fraction palliative radiation therapy for bone metastases: cumulative meta-analysis. *Radiother Oncol* 2019;141:56–61. <https://doi.org/10.1016/j.radonc.2019.06.037>.