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Research Article

# The failures and challenges of bone metastases research in radiation oncology

Gillian Bedard, Edward Chow*

*Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada*

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ABSTRACT

Bone metastases affect a large portion of the cancer population. As treatment options continue to evolve, many added failures and challenges arise. This narrative review details such in palliative radiation therapy for bone metastases. We begin by describing the incidence rates of bone metastases in the cancer population, the current standards of practice in recent literature and clinical trial data. Inconsistencies in end point definitions along with difficulties in measuring response to treatment and controversial areas are outlined. Current literature suggests that there is a discrepancy in physician and patient perspective on treatment options as well as quality of life. The added challenges of treatment side effects are addressed and a review of recent trials is given. Stereotactic radiation therapy is a relatively new treatment option for patients with bone metastases. Therefore, a review of the safety and efficacy of this treatment is provided. Other new areas of bone metastases treatment and research such as high intensity focused ultrasound and nanoparticles are discussed. Physicians need to prevent unwanted side effects of treatment in addition to determining how to integrate many new upcoming treatment options for patients with bone metastases. A continued reluctance to practice evidence based medicine needs to be addressed.



## 1. Introduction

Bone metastases are a common complication of cancer, with breast and prostate cancers being the most common types to metastasize to bone [1]. 70–85% of cancer patients are diagnosed as having bone metastases at the time of autopsy [2,3]. These bone metastases and the primary cancer itself can cause patients great pain and functional interference. Radiation therapy has been well established for the treatment of symptomatic bone metastases [4].

Although radiation therapy is one of the most common treatments for pain palliation in patients with bone metastases, a number of issues exist. As the radiation oncology field has evolved, a number of added failures and challenges to bone metastases research in radiation oncology have been presented. Radiation oncologists have worked towards establishing evidence-based treatment guidelines; however whether or not these guidelines are followed is one area in which improvement is required. The purpose of this review is to outline the failures and challenges associated with bone metastases research in radiation oncology. As new treatment options become available, radiation oncologist need to work collaboratively with other health care professionals in order to deliver the most current treatments to their patients.

## 2. Failures

### 2.1. Different endpoints and controversial conclusions

Many bone metastases trials have been conducted in order to determine efficacy of radiation treatment; however each trial appears to have slightly different endpoints. With these differing endpoints, a number of different conclusions have been drawn. This is a major failure of bone metastases research, as results from trials are often times contradictory.

#### 2.1.1. Inconsistency in endpoints

A number of radiation therapy trials have been conducted over the past few decades to determine the efficacy of the palliation of bone pain due to bone metastases. Although these studies have been greatly beneficial and influential to the radiation oncology field, their inconsistency in endpoint definitions has left radiation oncologists and researchers unable to effectively compare the results of these trials.

Even within the same patient population, endpoints have differed. In a study by Tong et al. with the RTOG, the three

* Correspondence to: Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5. Tel.: +1 416 480 4998; fax: +1 416 480 6002.
*E-mail address:* edward.chow@sunnybrook.ca (E. Chow).

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endpoints of complete relief, partial relief and minimal relief were utilized [5]. Complete relief was defined as the pain score dropping to zero, partial relief defined as pain score dropping below four points and minimal relief defined as pain score dropping below the initial pain score. Whereas in a re-analysis by Blitzer et al. in the same patient population, four endpoints were utilized: complete pain relief (pain score falls to zero), complete pain relief prior to retreatment (pain score falls to zero before retreatment), retreatment (freedom from retreatment), and complete combined relief (pain score and narcotic score fell to zero) [6]. Although both of these studies included the same patient population, the conclusions drawn were different due to the differing endpoint definitions. The study by Tong et al. concluded that low dose, short course schedules are as effective as high dose protracted programs [5], whereas Blitzer et al. concluded that there was an improved complete response with protracted fractionation schedules [6].

In a Canadian trial by Kirkbride et al., yet another definition of response rates was utilized. This trial randomized patients between a single 8 Gy treatment and 20 Gy in 5 fractions for the palliation of painful bone metastases. The endpoint of this trial was the clinically significant pain relief, as defined by a reduction in pain score at the treated site with reduced analgesics or a pain score of zero at the treated site with no increase in analgesics at 3 months post treatment [7]. This trial was closed early; as it was determined that 20 Gy in 5 fractions was superior for pain control when compared to 8 Gy in 1 fraction. However, when pain score was assessed at 3 months independent of analgesic score, the two arms were almost identical.

The observed treatment response is also influenced by the type of pain scale employed, the inclusion of quality of life as an endpoint and the duration of follow-up. If very stringent criteria are utilized, response rates reported may be lower than traditionally accepted rates.

#### 2.1.2. Difficulty in measuring response

An example of the differing response rates when different pain scales are employed is observed in the Danish Bone Pain Trial. Pain relief was assessed utilizing a categorical scale and a visual analog scale. Using the categorical scale, an improvement of at least one category on the 5-point scale was seen in 62% of patients at 4 weeks, whereas a 50% reduction in pain was only seen in 49% of patients at 4 weeks using the analog scale [8]. A difference in response rates was also seen in the timing of follow-up. Fifteen percent of patients had a complete response at 4 weeks post treatment, while 25% of patients had a complete response at any time during the entire 20 week follow-up period. In this same population, complete response dropped to 12% when “no use of morphine” was added to the definition, and complete response rates dropped to 4% when “complete well-being” was included in the definition [8].

It is evident through the Danish trial and other key bone metastases trials that there is a large inconsistency in the definition of response, therefore a number of different conclusions have been reached, many of which contradict each other. Other difficulties in measuring response rate include the fact that radiation therapy is a local treatment, and cancer pain can originate from multiple sites. Other systemic treatments such as analgesics, chemotherapy, hormonal therapy and bisphosphonates also work at the treatment site and can contribute to the response rates seen from radiation therapy.

#### 2.1.3. Controversial areas

Currently, many controversial areas exist, such as the role of analgesic use in assessing treatment response, the definition of “partial response” and the interpretation of retreatment. Wu et al. addressed the end point inconsistency in their review of 12 randomized control trials for palliative radiotherapy. They concluded that although pain relief is a consistent primary outcome, a consensus on the features of treatment endpoints is needed to establish common grounds for future trials [9].

In response to these inconsistencies, Chow et al. surveyed a number of radiation oncologists and established an international consensus on palliative radiotherapy endpoints [10]. Experts were in agreement that pain assessment at the treatment site should be on a scale of 0 (no pain) to 10 (maximal pain). Incorporation of quality of life questionnaires such as the EORTC QLQ-BM22 and/or the QLQ-C15 was recommended for all clinical trials. A period of 1 week between analgesic dosing adjustment and start of radiation was also recommended to minimize risk of analgesic effects confounding radiation treatment effects [10]. It was also recommended that re-irradiation only be considered at least 4 weeks after the radiation treatment. A consensus on response rate definitions was also reached. A complete response was defined as a pain score of 0 at the treated site with no increase in analgesics, while a partial response was defined as a pain score reduction of 2 or more at the treated site without an analgesic increase, or an analgesic reduction of 25% without an increase in pain. Pain progression was defined as an increase in pain score of 2 or more above baseline at the treated site with stable analgesics, or an analgesic increase of 25% above baseline. Lastly, an indeterminate response was defined as any response that does not fit into any of the other three categories [10]. It was concluded that these recommendations should be taken into consideration for all future bone metastases trials.

In order to determine the optimal treatment schedule, Chow et al. have recently published an update on the systematic review of palliative radiotherapy [11]. In their meta-analysis, they compared single and multiple fraction treatment and determined that there is no difference between the response rates of single fraction (60% overall response, 23% complete response), and multiple fraction treatments (61% overall response, and 24% complete response). Pathological fracture and spinal cord compression rates were not statistically different between either arm; however, the likelihood of requiring retreatment was 2.6 times higher in the single fraction arm [11]. Thus, it was recommended that a single 8 Gy fraction be used to treat all patients with uncomplicated bone metastases.

### 2.2. Reluctance to practice evidence-based medicine

There have been a number of systematic reviews and meta-analyses to determine which treatment is more beneficial for patients with painful uncomplicated bone metastases [10–12]. Of which, it has been determined that there is no difference between single and multiple fractions in terms of pain response. Thus, it has been recommended that physicians prescribe single fraction treatment to patients with uncomplicated bone metastases where possible. However, a reluctance to practice evidenced based medicine still exists [13,14].

#### 2.2.1. Which regimen?

Although it has been recommended that a single 8 Gy fraction be employed for patients with painful uncomplicated bone metastases, the majority of radiation oncologists are still treating patients with multiple fraction regimens [14]. In Canada, the most common fractionation delivered to patients is 20 Gy in 5 fractions, and among American radiation oncologists it is 30 Gy in 10 fractions [14]. Another study on the international patterns of practice has globally demonstrated that despite the abundance of evidence, radiation oncologists still prescribe multi-fractionated

treatment for patients with painful uncomplicated bone metastases [13]. Roos et al. have also reported the continuing reluctance to use single fraction radiation therapy in their group of radiation oncologists in New Zealand and Australia [15].

Recently, ASTRO has published an evidence-based guideline to better help physicians in their prescription of treatment for individuals with painful uncomplicated bone metastases. The guideline states that external beam radiation be used for the treatment of bone metastases and that a single 8 Gy should be employed where possible. They also state that no further clinical trials are required to confirm that a single treatment should be used in these circumstances [16].

To further bring attention to this reluctance, a number of editorials have been published that address this issue [17–19]. These authors question the reasoning of radiation oncologists who continue to employ multi-fractionated schedules when it is known that a single fraction holds the same efficacy. Chow et al. suggest that single fraction radiotherapy should be adopted as department policy in order to maximize social justice by decreasing wait times [19].

#### 2.2.2. Retreatment fractionation

There currently is no recommended retreatment fractionation; however a Canadian study is assessing this research question. A National Cancer Institute of Canada clinical trial (NCIC CTG SC 20) has closed accrual and is analyzing the results. This study randomized patients between a single 8 Gy and 20 Gy in 5 or 8 fractions for retreatment. Patients completed a follow-up assessment every month for 6 months after the start of radiation, and months 9 and 12. Follow-up assessments included a pain and medication assessment. Arm one included a single 8 Gy treatment, and arm two was comprised of 20 Gy in 5 fractions or 20 Gy in 8 fractions for spine retreatment. The planned sample size for this trial was 850 patients.

A correlational study, SC20U, took place in conjunction with this retreatment study. The correlational study was used to determine the effect of re-irradiation for bone pain on urinary markers of osteoclast activity. Previous study in this area with breast and prostate bone metastases patients demonstrated that pyridinoline and deoxypridinoline levels in those who responded to treatment were lower at baseline than those who did not respond. 4 weeks post treatment, levels in responders only slightly increased, while levels in nonresponders dramatically increased [20].

The results of these two studies are greatly anticipated, and perhaps may be able to provide further insight into the most appropriate radiation therapy fractionation regimen for retreatment of bone metastases.

## 3. Difference in physician vs. patient perspectives

It has been identified in a number of trials that patient and physician preferences differ. Often times, patients have different wants and needs for treatment and do not value the same aspects of treatment as do physicians.

### 3.1. Treatment preferences

A trial conducted by Szumacher et al. assessed patient preference of treatment with palliative radiation therapy for bone metastases. The purpose of this trial was to determine the proportion of patients who wanted to partake in the decision-making process and to determine the proportion of patients who preferred 8 Gy in 1 fraction to 20 Gy in 5 fractions. The majority of patients determined they wanted to decide either by themselves or with their radiation oncologist on which treatment option they preferred. 8 Gy in 1 fraction was the preferred treatment regimen regardless of site treated. The convenience of this treatment and the likelihood of bone fracture were the most important influencing factors on the patient's decision [21].

### 3.2. QOL perspectives

With the main goal of palliative radiotherapy for bone metastases being to alleviate symptoms and improve quality of life, a way to determine quality of life and issues prevalent to patients is essential. Thus, key issues to bone metastases patients have been determined through a number of studies pertaining to the development of a quality of life questionnaire designed specifically for this patient population [22–25].

The objective for the development of this tool was to develop a set of items and scales for assessing quality of life issues not sufficiently covered by the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire core 30 (QLQ-C30). Disease symptoms, side-effects, complications and other issues related to treatment of bone metastases are included in this bone metastases module, the EORTC QLQ-BM22 [26]. The development of this module underwent four phases: generation of relevant QOL issues, operationalization of the QOL issues into a set of items, pre-testing of the module questionnaire, and large scale international field testing.

Generation of relevant QOL issues included literature searches, interviews with health care professionals (HCPs) and patient interviews. This yielded a 61 item list that was then formatted into a questionnaire. 413 patients then completed the questionnaire rating the relevancy of each item from 1 (not relevant) to 4 (very relevant). Patients also determined if each item should be included in the final module (yes/no) and picked their top 5–10 items [23]. Top 10 QOL issues for patients included long-term chronic pain, psychological issues and worry about losing independence, while the majority of issues selected by HCPs were associated with pain [27]. A study by Harris et al. on the comparison of HCP and patient responses to the BM22 outlines the significant differences between patient and HCP ideals of QOL issues pertinent to bone metastases patients [27].

The final QOL module includes four sections that patients and HCPs have agreed upon: painful sites, painful characteristics, functional interference and psychological aspects. This module has successfully undergone validation testing and should be utilized in bone metastases clinical trials [24]. It has also undergone meaningful change testing to determine the degree of change that is meaningful to patients, the point at which they consider their symptoms to have improved or deteriorated [22].

This study demonstrated the failure of physicians in choosing items that are relevant to patients. It demonstrates the disparity between patient and HCP thoughts on QOL issues, and promotes the inclusion of patients in these decision making processes.

## 4. Challenges

### 4.1. Improve side effects

There are a number of side effects associated with radiation treatment for bone metastases. Most commonly, patients experience pain flare, and/or radiation induced nausea and vomiting.

#### 4.1.1. Pain flare

Pain flare is one of the most common side effects associated with radiation therapy of bone metastases. It occurs in up to 40% of patients who receive conventional radiation treatment and up to

70% of patients who receive stereotactic body radiotherapy [28]. Pain flare is defined as a 2-point increase in the worst pain score on a 0–10 scale in comparison to baseline with no decrease in analgesic intake, or a 25% analgesic intake increase with no decrease in worst pain score [28]. Typically, this pain flare occurs within the first 10 days following treatment. This side effect however can be reduced and treated. In a phase II study by Hird et al., it was concluded that a single dose of dexamethasone is quite effective in the prophylaxis of radiation-induced pain flare [29].

Dexamethasone as a prophylactic treatment against pain flare has been proven effective. For a single 8 Gy treatment, 8 mg of dexamethasone before treatment and for 3 days after radiation has greatly reduced pain flare rates. With this prescription, patients have pain flare free rates of 83% on days 1–5 post-treatment and 95% on days 6 through 10 post-treatment [30]. In the phase II study by Hird et al. only 9 of 41 patients experienced a pain flare, and most commonly flares occurred on day 5 post-treatment [30].

In order to create a change in standard of practice, the prophylaxis of dexamethasone is now undergoing a phase III double-blind placebo controlled study through the National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG). In this study (NCIC CTG SC 23), eligible patients who are receiving a single 8 Gy radiation treatment for painful uncomplicated bone metastases are randomized to receive either placebo or dexamethasone. Patients take the medication 1 h prior to treatment and once a day for 4 days following treatment. A 10 day pain diary is then completed to record pain scores and medication. Patients also complete the EORTC QLQ-BM22, QLQ-C15-Pal and a dexamethasone questionnaire at baseline, day 10 post-treatment and day 42 post-treatment. The expected sample size for this trial is approximately 250 patients.

#### 4.1.2. Radiation-induced nausea vomiting

Radiation-induced nausea and vomiting (RINV) occurs in an estimated 40–80% of patients undergoing radiation therapy. The incidence rate depends on the anatomical region irradiated and the treatment volume [31]. In a study by Dennis et al., patients undergoing moderately emetogenic radiation therapy were prescribed Ondanestron and daily rates of nausea and vomiting were collected. Daily incidence rates of at least one episode of nausea ranged from 19% to 44% and daily incidence rates of at least one episode of vomiting ranged from 0% to 25% [31]. Through this study it was concluded that despite prophylaxis, RINV affected a significant portion of patients undergoing radiation therapy for bone metastases.

To better prevent this side effect, our group is conducting a phase II study with Granisetron and Aprepitant for prophylaxis against RINV. Early analysis of this cohort shows that less than 30% of patients undergoing single fraction radiation experience any nausea or vomiting, and less than 33% of patients undergoing multiple fraction radiation experience nausea or vomiting up to 10 days post-treatment.

The outcomes of these two studies on pain flare and RINV are greatly anticipated to determine a remedy for this side-effect challenge of radiation therapy treatment.

### 4.2. Evaluating radiosurgery

Stereotactic body radiotherapy (SBRT) has increasingly become more common in the management of spinal metastases. A recent systematic review of 31 studies utilizing SBRT for spinal metastases has quoted an overall local control rate of 90% [32]. It was concluded that spine SBRT was highly effective in reducing pain regardless of prior treatment, and this type of treatment may be preferred in those patients who have been previously received treated and radiation tolerance of the spinal cord is a concern. It was concluded that any complications associated with SBRT were self-limited and mild [32].

Additional challenges with spine SBRT have been evident in the literature. The most drastic complication is vertebral compression fractures that can occur after spine SBRT. Fracture rates in patients who underwent spine SBRT were fairly high. One retrospective study identified 11% of patients treated with spine SBRT who subsequently developed a fracture [33]. The median follow-up time was 7.4 months. Another study reported a fracture rate of 39% in their patients post-SBRT [34]. Patients who experienced fractures were more likely to have higher pain scores and subsequently had a decrease in performance status.

In addition to high rates of vertebral compression fracture, spine SBRT also has high rates of pain flare. In one study of pain flare after SBRT for bone metastases, it was determined that 66% of patients experienced a flare, most commonly on the first day post-treatment [35]. Patients who underwent a single treatment had a slightly higher incidence (71%) than those who received multiple fractions (63%). It was also noted that patients who were on steroids prior to SBRT did not have a pain flare.

Although spine SBRT may appear to be a superior treatment than palliative radiotherapy for patients with bone metastases, there are a number of adverse events that are not as widely studied and documented. Physicians need to take these limitations and adverse events into consideration before treating patients with this approach.

### 4.3. How to integrate ultrasound/MRI with external beam radiation

High intensity focused ultrasound (HIFU) has proven to be effective in the treatment of solid tumors. Utilizing energy levels much higher than the diagnostic dose, it is a noninvasive treatment that utilizes high frequencies to ablate tumors. During treatment, the temperature at the focus can rise rapidly to above 80 °C, which effectively kills cells [36]. A pilot study of 10 patients with bone metastases treated with HIFU has been completed at the Sunnybrook Odette Cancer Centre, and results are greatly anticipated.

Another new way to use ultrasound to enhance radiation has been discovered; microbubbles passed through the body's circulation. Normally used as a contrast agent for ultrasound to detect cancer or new growth, in this study microbubbles are used as resonating agents inside the tumor blood vessels to destabilize structures and create greater sensitivity to low doses of radiation. With these microbubbles, a 40%–50% tumor volume cell death after a single 2 Gy radiation dose combined with ultrasound and microbubbles can be achieved [37]. This is compared to a 5% cell death utilizing microbubbles and ultrasound alone. Thirty-five 2 Gy treatments are required to achieve a comparable cell death [38]. This is an exciting new area of research that scientists are actively pursuing. Perhaps in the future, it will be possible to treat bone metastases patients with very low doses of radiation in the presence of ultrasound and microbubbles in hopes of ablating tumors.

Radiation oncologists and ultrasound imaging radiologists will need to work together in order to best treat patients with these new techniques.

### 4.4. Treating metastatic cancer with nanotechnology

Nanoparticles are becoming more common in the field of medicine. In a recent review, authors have outlined the current status of these particles and their role in cancer treatment [39]. With these particles, different biological pathways are stimulated and apoptosis can be achieved. Greater knowledge of these particles and how they operate is required before treatment with nanotechnology can be adopted into daily practice.

A recent study with Radium 223 chloride has demonstrated overall improved survival by 44% in patients with bone metastases from castrate resistant prostate cancer [40]. This treatment prolonged median time to first skeletal related event by 64%. There appears to be a benefit in using these new technologies, however radiation oncologists will need to work alongside other health care professionals in order to deliver the most effective and up to date treatment to their patients.

## 5. Conclusion

There are a number of failures and challenges to treating patients with radiation therapy for bone metastases. In the future, there will need to be great collaboration between health care professionals in order to effectively determine the optimal treatment for this patient population. It is hoped that through collaboration, upcoming new treatments will be further developed, and new methods for treatment will be discovered. In the meantime, radiation oncologists should work to find solutions to the current failures of radiation therapy, and consciously work towards practicing evidence based medicine.

## Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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## References

[1] Chow E, Nguyen J, Zhang L, Tseng LM, Hou MF, Fairchild A, et al. International field testing of the reliability and validity of the EORTC QLQ-BM22 module to assess health-related quality of life in patients with bone metastases. Cancer 2011;118(5):1457–65.
[2] Tubiana-Hulin M. Incidence, prevalence and distribution of bone metastases. Bone 1991;12(1):S9–10.
[3] Janjan N. Bone metastases: approaches to management. Seminars in Oncology 2001;28(4 Suppl. 11):28–34.
[4] Chow E, Fan G, Hadi S, Filipczak L. Symptom clusters in cancer patients with bone metastases. Supportive Care in Cancer 2007 Sep;15(9):1035–43.
[5] Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group. Cancer 1982;50(5):893–9.
[6] Blitzer PH. Reanalysis of the RTOG study of the palliation of symptomatic osseous metastasis. Cancer 1985;55(7):1468–72.
[7] Kirkbride P, Warde P., Panzeralla T., Aslanidis J., McKenzie M., Sun A.A. Randomised trial comparing the efficacy of a single radiation fraction with fractionated radiation therapy in the palliation of skeletal metastases. In: Proceedings of the 42nd annual ASTRO meeting 2000.
[8] Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. Radiotherapy and Oncology 1998;47(3):233–40.
[9] Wu JS, Bezjak A, Chow E, Kirkbride P. Primary treatment endpoint following palliative radiotherapy for painful bone metastases: need for a consensus definition? Clinical Oncology (Royal College of Radiologists) 2002;14(1):70–7.
[10] Chow E, Hoskin P, Mitera G, Zeng L, Lutz S, Roos D, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. International Journal of Radiation Oncology, Biology, Physics 2012;82(5):1730–7.
[11] Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clinical Oncology (Royal College of Radiologists) 2012;24(2):112–24.
[12] Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. Journal of Clinical Oncology 2007;25(11):1423–36.
[13] Fairchild A, Barnes E, Ghosh S, Ben-Josef E, Roos D, Hartsell W, et al. International patterns of practice in palliative radiotherapy for painful bone metastases: evidence-based practice? International Journal of Radiation Oncology, Biology, Physics 2009;75(5):1501–10.
[14] Chow E, Danjoux C, Wong R, Szumacher E, Franssen E, Fung K, et al. Palliation of bone metastases: a survey of patterns of practice among Canadian radiation oncologists. Radiotherapy and Oncology 2000;56(3):305–14.
[15] Roos DE. Continuing reluctance to use single fractions of radiotherapy for metastatic bone pain: an Australian and New Zealand practice survey and literature review. Radiotherapy and Oncology 2000;56(3):315–22.
[16] Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. International Journal of Radiation Oncology, Biology, Physics 2011;79(4):965–76.
[17] van der Linden YM, Leer JW. Impact of randomized trial-outcome in the treatment of painful bone metastases; patterns of practice among radiation oncologists. A matter of believers vs. non-believers? Radiotherapy and Oncology 2000;56(3):279–81.
[18] Kachnic L, Berk L. Palliative single-fraction radiation therapy: how much more evidence is needed? Journal of National Cancer Institute 2005;97(11):786–8.
[19] Chow E, Hahn CA, Lutz ST. Global reluctance to practice evidence-based medicine continues in the treatment of uncomplicated painful bone metastases despite level 1 evidence and practice guidelines. International Journal of Radiation Oncology, Biology, Physics 2012;83(1):1–2.
[20] Hoskin PJ, Stratford MR, Folkes LK, Regan J, Yarnold JR. Effect of local radiotherapy for bone pain on urinary markers of osteoclast activity. Lancet 2000;355(9213):1428–9.
[21] Szumacher E, Llewellyn-Thomas H, Franssen E, Chow E, DeBoer G, Danjoux C, et al. Treatment of bone metastases with palliative radiotherapy: patients' treatment preferences. International Journal of Radiation Oncology, Biology, Physics 2005;61(5):1473–81.
[22] Zeng L, Chow E, Zhang L, Tseng LM, Hou MF, Fairchild A, et al. An international prospective study establishing minimal clinically important differences in the EORTC QLQ-BM22 and QLQ-C30 in cancer patients with bone metastases. Supportive Care in Cancer 2012;20(12):3307–13.
[23] Zhang L, Nguyen J, Hird A, Chow E. Shortening the bone metastases quality of life instrument tool. Journal of Pain Management 2009;2(4):465–74.
[24] Zeng L, Chow E, Bedard G, Zhang L, Fairchild A, Vassiliou V, et al. Quality of life after palliative radiation therapy for patients with painful bone metastases: results of an international study validating the EORTC QLQ-BM22. International Journal of Radiation Oncology, Biology, Physics 2012;84(3):e337–42.
[25] Chow E, Nguyen J, Zhang L, Tseng LM, Hou MF, Fairchild A, et al. International field testing of the reliability and validity of the EORTC QLQ-BM22 module to assess health-related quality of life in patients with bone metastases. Cancer 2012;118(5):1457–65.
[26] Chow E, Bottomley A. Understanding the EORTC QLQ-BM22, the module for patients with bone metastases. Expert Review of Pharmacoeconomics and Outcomes Research 2009;9(5):461–5.
[27] Harris K, Chow E, Zhang L, Velikova G, Bezjak A, Wu J, et al. Patients' and health care professionals' evaluation of health-related quality of life issues in bone metastases. European Journal of Cancer 2009;45(14):2510–8.
[28] Hird A, Chow E, Zhang L, Wong R, Wu J, Sinclair E, et al. Determining the incidence of pain flare following palliative radiotherapy for symptomatic bone metastases: results from three canadian cancer centers. International Journal of Radiation Oncology, Biology, Physics 2009;75(1):193–7.
[29] Chow E, Loblaw A, Harris K, Doyle M, Goh P, Chiu H, et al. Dexamethasone for the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases: a pilot study. Supportive Care in Cancer 2007;15(6):643–7.
[30] Hird A, Zhang L, Holt T, Fairchild A, DeAngelis C, Loblaw A, et al. Dexamethasone for the prophylaxis of radiation-induced pain flare after palliative radiotherapy for symptomatic bone metastases: a phase II study. Clinical Oncology (Royal College Radiology) 2009;21(4):329–35.
[31] Dennis K, Nguyen J, Presutti R, DeAngelis C, Tsao M, Danjoux C, et al. Prophylaxis of radiotherapy-induced nausea and vomiting in the palliative treatment of bone metastases. Supportive Care in Cancer 2012;20(8):1673–8.
[32] Sohn S, Chung CK. The role of stereotactic radiosurgery in metastasis to the spine. Journal of Korean Neurosurgical Society 2012;51(1):1–7.
[33] Cunha MV, Al-Omair A, Atenafu EG, Masucci GL, Letourneau D, Korol R, et al. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. International Journal of Radiation Oncology, Biology, Physics 2012;84(3):e343–9.
[34] Rose PS, Laufer I, Boland PJ, Hanover A, Bilsky MH, Yamada J, et al. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. Journal of Clinical Oncology 2009;27(30):5075–9.
[35] Abstracts of the 2012 International MASCC/ISOO (Multiple association of supportive care in cancer/international society for oral oncology) Symposium. New York City, New York, USA. June 28–30, 2012. Supportive Care in Cancer 2012 Jun;20 Suppl. 1:S1–283.
[36] Kennedy JE. High-intensity focused ultrasound in the treatment of solid tumours. Nature Reviews Cancer 2005;5(4):321–7.
[37] Revay V. New use of ultrasound to enhance cancer radiation therapy. Global News 2012.
[38] Nofiele JT, Karshafian R, Furukawa M, Al Mahrouki A, Giles A, Wong S, et al. Ultrasound-activated microbubble cancer therapy: ceramide production leading to enhanced radiation effect in vitro. Technology in Cancer Research and Treatment 2013;12(1):53–60.
[39] Schroeder A, Heller DA, Winslow MM, Dahlman JE, Pratt GW, Langer R, et al. Treating metastatic cancer with nanotechnology. Nature Reviews Cancer 2011;12(1):39–50.
[40] Lewington V, Parker C. Radium 223 chloride and improved survival in castration resistant prostate cancer patients with bone metastases. American Society of Clinical Oncology. 2012 Genitourinary Cancers Symposium. (abstr).