

WJCO 5<sup>th</sup> Anniversary Special Issues (1): Lung cancer**Palliative radiotherapy for bone metastases from lung cancer: Evidence-based medicine?**

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Author contributions: Fairchild A solely contributed to this paper.

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Received: December 31, 2013 Revised: April 28, 2014

Accepted: July 17, 2014

Published online: December 10, 2014

**Abstract**

To review current recommendations for palliative radiotherapy for bone metastases secondary to lung cancer, and to analyze surveys to examine whether global practice is evidence-based, English language publications related to best practice palliative external beam radiotherapy (EBRT) for bone metastases (BM) from lung cancer were sought *via* literature search (2003-2013). Additional clinical practice guidelines and consensus documents were obtained from the online Standards and Guidelines Evidence Directory. Eligible survey studies contained hypothetical case scenarios which required participants to declare whether or not they would administer palliative EBRT and if so, to specify what dose fractionation schedule they would use. There is no convincing evidence of differential outcomes based on histology or for spine *vs* non-spine uncomplicated BM. For uncomplicated BM, 8Gy/1 is widely recommended as current best practice; this schedule would be used by up to 39.6% of respondents to treat a painful spinal lesion. Either 8Gy/1 or 20Gy/5 could be considered standard palliative RT for BM-related neuropathic pain; 0%-13.2% would use the former and 5.8%-52.8% of respondents the latter (range 3Gy/1-45Gy/18). A multifraction schedule is the approach of choice for irradiation of impending

pathologic fracture or spinal cord compression and 54% would use either 20Gy/5 or 30Gy/10. Survey results regarding management of complicated and uncomplicated BM secondary to lung cancer continue to show a large discrepancy between published literature and patterns of practice.

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**Key words:** Bone metastases; Lung cancer; Survey; Evidence-based practice; Radiotherapy

**Core tip:** Palliative radiotherapy (PRT) remains the gold standard for treatment of painful bone metastases from lung cancer. While PRT should be appropriately customized to patients, prescription should also be based on robust evidence. Depending on the clinical scenario, between 4%-66% of survey respondents would use dose-fractionation schedules considered congruent with best available current evidence. These results show a large discrepancy between treatment guidelines and international patterns of practice. It is not completely clear why level 1 data supporting specific dose schedules continues to be overlooked, although reasons for reticence in following these recommendations are reviewed.

Fairchild A. Palliative radiotherapy for bone metastases from lung cancer: Evidence-based medicine? *World J Clin Oncol* 2014; 5(5): 845-857 Available from: URL: <http://www.wjgnet.com/2218-4333/full/v5/i5/845.htm> DOI: <http://dx.doi.org/10.5306/wjco.v5.i5.845>

**INTRODUCTION**

Lung cancer causes bone metastases (BM) in a large proportion of patients, up to 40%-80%<sup>[1]</sup>. With improvements

in systemic therapy, median survival of patients with advanced lung cancer is now approximately 12 mo; as such, the prevalence of BM has significantly increased. BM can be described as complicated or uncomplicated, where uncomplicated generally refers to the absence of: impending or established pathological fracture (PF), surgical fixation, impending or established spinal cord compression (SCC), impending or established cauda equina or nerve root compression, neuropathic pain, previous RT, or associated soft tissue mass.

By definition, all patients with lung cancer and BM have stage IV disease and treatment is palliative. Goals for the treatment of BM are pain relief, preservation of mobility and function, prevention of future complications, optimized quality of life (QoL), maintenance of skeletal integrity, and minimization of hospitalization. About half of all patients with stage IV non-small cell lung cancer (NSCLC) receive at least one course of palliative external beam radiotherapy (EBRT) within 15 mo of diagnosis<sup>[2]</sup>.

A prospective observational multicenter study recently documented treatment costs of BM in patients with pathologically-proven lung cancer during the first year after BM diagnosis<sup>[3]</sup>. Five hundred and fifty-four patients with radiologically-proven BM were enrolled. A mean monthly cost was calculated using a Markov approach, taking into account direct costs only (hospitalization, drug purchases, medical and transport costs). Indirect costs such as lost income and intangible costs such as pain and suffering were not assessed. 76.5% were male, with a mean age of 62 years, 9% with small cell lung cancer, 69.3% with PS 0-1, and 64.6% had metastases other than to bone. At some point during follow-up, 89.9% had analgesic treatment (77.7% with opioids) and 42.1% had RT. Median survival was 5.8 mo and 1 year OS was 22%. Factors predictive of better OS were adenocarcinoma, performance status (PS) 0-1, and female. Monthly costs for asymptomatic and symptomatic BM were €190 and €374 respectively. Mean disease management costs during the first year after BM diagnosis were €3999 +/- €4135 (95% confidence interval €374-15886)<sup>[3]</sup>.

EBRT remains the gold standard for treatment of BM<sup>[4]</sup>, and comprises the largest single component of palliative RT practice<sup>[5]</sup>, approximately 40%<sup>[6]</sup>. The number of lung cancer patients requiring palliative EBRT for BM is continuing to grow, increasing pressure on clinicians, simulators, and treatment units, in addition to health care costs.

Both the limited survival of most patients with advanced lung cancer and a requirement for the judicious use of resources argue for use of the shortest dose fractionation schedule which is effective<sup>[7]</sup>. Single fraction (SF) EBRT for palliation of painful BM has many advantages: the risk of acute side effects is minimized which increases patient QoL and acceptance of treatment; RT can be delivered over as little as one day, which decreases transportation and hospital admission requirements; it is more convenient; decreased discomfort with positioning

and travel increases tolerance for those with poor PS; and it frees resources for others. SFRT is cost-effective, and is easier to schedule amongst systemic therapy and other appointments, resulting in increased accessibility and decreased waiting times<sup>[7,17]</sup>.

Previous patterns of practice surveys focusing on EBRT for BM, including a large international study from 2009, have suggested that considerable controversy over the optimal treatment schedule still exists<sup>[9]</sup>. The objectives of this review were to (1) examine the literature supporting current treatment recommendations for BM secondary to lung cancer, to determine for which clinical scenarios SFRT is appropriate; and (2) analyze published surveys to examine evolution in practice and degree to which it can be considered evidence-based.

## LITERATURE SEARCH

Publications related to best practice palliative EBRT for complicated and uncomplicated BM from lung cancer were sought *via* literature search (Table 1). Medline and Embase were searched for English language articles published in full between 2003 and 2013. Eligible studies were also identified from reference lists of retrieved papers and review articles. Additional clinical practice guidelines and consensus documents were obtained from searching the online SAGE (Standards and Guidelines Evidence) Directory compiled by the Canadian Partnership Against Cancer ([www.cancerview.ca](http://www.cancerview.ca)). Eligible survey studies contained hypothetical case scenarios which required participants to declare whether or not they would administer palliative EBRT and if so, to specify what dose fractionation schedule they would use. Retrospective reviews and practice audits which did not include hypothetical patient cases<sup>[18-25]</sup> as well as surveys which did not include lung cancer cases<sup>[26-31]</sup> were excluded.

## RESEARCH

### **Evidence summary-uncomplicated bone metastases**

Four meta-analyses of more than 20 randomized controlled trials [level I evidence, according to the Oxford Centre for Evidence-Based Medicine ([www.cebm.net](http://www.cebm.net))] have shown that for uncomplicated bone lesions, there is no advantage in degree of pain relief, analgesic use, time to first improvement in pain, time to complete pain relief, time to pain progression, duration of response, rates of PF or SCC, acute toxicity, QoL, or overall survival from protracted fractionation *vs* SFRT above 4Gy<sup>[8,12,13,15]</sup>. The randomized trials accrued patients with various histologies; selected studies published since 2000 included up to 26% of patients with lung cancer. The most recent meta-analysis evaluated 25 studies comprising 2818 randomizations to SF and 2799 to MF arms, respectively<sup>[8]</sup>. On an intent-to-treat basis, the overall response rate to SF RT was 60%, and complete response (CR) rate was 23%, which was not significantly different from the 61% and 24% rates of patients randomized to MF RT. The overall

Table 1 Search strategy

Step	String	Results
1	Exp Bone Neoplasms/sc OR Bone Neoplasms/rt OR [(boneCarcinoma/sc OR exp Neoplasm Metastasis/rt) AND exp 26956 "Bone and Bones"/] OR [(osseous OR skeletal) ADJ3 metastasis\$] OR (bone ADJ3 metastasis\$)	
2	Exp *Lung Neoplasms/OR exp Lung Neoplasms/pa OR lung cancer.mp	188189
3	Exp Radiotherapy/OR exp Dose Fractionation/OR exp Radiotherapy Dosage/	133052
4	Exp Palliative Care/OR exp Pain/RT OR Pain Management/mt OR (palliative OR palliation).mp OR painful adj3 metastasis\$ OR (palliative\$ ADJ3 radiotherapy).mp	94404
5	1 AND 2 AND 3 AND 4	88
		Limit 10 yr: 28
6	1 AND 3 AND 4	608
	Exclusion criteria: non-lung primary site cancers	Limit 10 yr: 256
7	(1 AND 4 AND radiotherapy.mp AND combined modality therapy/OR analgesics/OR treatment outcome/OR quality of life/OR exp Antineoplastic Combined Chemotherapy Protocols) NOT 6	129
		Limit 10 yr: 50
8	Total	156

pain response proportion increases by about 10% if per-protocol patients only are analyzed<sup>[15]</sup>. Median time to onset of pain relief is 1-4 wk and median duration of response is 12-24 wk. After SF, 3.3% of patients fractured *vs* 3.0% after MF ( $P = 0.72$ ). Two point eight percent of patients receiving SF and 1.9% of patients receiving MF experienced SCC ( $n = 6$  trials;  $P = 0.13$ ). There were significantly more retreatment episodes in the SF arms (20%) *vs* MF arms (8%) ( $P < 0.00001$ ). Re-analysis of assessable patients did not alter conclusions. There is a trend for greater acute toxicity after MF which is not statistically significant, and which was not a primary endpoint for any of the source trials<sup>[8]</sup>.

In view of mounting evidence, 8Gy/1 has been repeatedly recommended as standard of care for uncomplicated BM in the practice guidelines of many international bodies, including specifically for lung cancer (see Table 2 for references; level 5 evidence). A secondary analysis of the Dutch trial reported that in patients with spine BM, SF and MF EBRT result in equivalent pain relief (level 1 evidence)<sup>[32]</sup>. In general, neither anatomic location treated nor RT dose is predictive of degree of functional improvement after RT (level 4 evidence)<sup>[33,34]</sup>. No subgroups of patients with uncomplicated painful BM have been identified that clearly benefit from a higher total dose (level 5 evidence)<sup>[11]</sup>. Additionally, it is not standard practice to prophylactically irradiate an asymptomatic uncomplicated BM (to avoid toxicity).

### Evidence summary - does histology influence outcome?

The most detailed data on outcomes in relation to histology were reported in a secondary analysis of the Dutch Bone Metastases trial related to reirradiation (level 1 evidence)<sup>[35]</sup>. In the original trial, between 03/1996 and 09/1998, 1157 Dutch patients with painful BM were randomized between 8Gy/1 ( $n = 579$ ) and 24Gy/6 ( $n = 578$ ); 287 lung patients were accrued<sup>[16]</sup>. Patients had a minimum pain score of 2/10. Eligibility criteria included BM treatable in one RT target volume, no previous RT, no fracture or impending PF needing surgery, no SCC, and no BM within the cervical spine. Participants completed weekly questionnaires  $\times$  13 wk, then monthly to

a maximum of 2 years, reporting maximum pain at the treated site, analgesic use and acute side effects. No major differences were reported between SF and MF in overall response rates, duration of response or progression rates<sup>[16]</sup>.

267/287 lung patients were assessable for response to initial EBRT: 107 (39.8%) were non-responders and 162 (60.2%) were responders<sup>[35]</sup>. Fifty-eight percent responded after initial SF and 62% after initial MF. Mean time to initial response was 3 wk and mean duration of remission was 11 wk. Overall there was no correlation between histology and initial response ( $P = 0.69$ ). Of the 267, 78 experienced pain progression (29.2%).

Within the first year after randomization, 49 patients with lung cancer were retreated. Of initial nonresponders, 22% were retreated at a mean time of 10 wk and mean pain score of 7.7/10. Of initial responders, 7% were retreated at a mean time of 11 wk and mean pain score of 3.8/10. Of those who had progressed, 19% were retreated at a mean time of 5 wk and mean pain score of 7.2/10. Progressive patients with lung cancer were retreated most often and earliest after randomization of any histology<sup>[35]</sup>.

Response to retreatment could be ascertained for 40/49<sup>[35]</sup>. Of those who did not respond to initial RT, 50% (8/16) responded to repeat treatment at a mean time to response of 7 wk. Of those responding to initial treatment, 67% (16/24) also responded to repeat treatment at a mean time of 5 wk. After progression, 12/14 (86%) responded to a second course of RT at a mean time of 4 wk. The mean duration of response in initial non-responders, responders and those with progressive pain was 8 wk, 12 wk and 6 wk, respectively. Including the effects of retreatment, overall response rates in lung cancer patients receiving SF increased from 58% to 62%, but did not change post-MF. This is likely because SF patients were retreated earlier than were MF patients. Almost three times more lung patients were retreated than breast patients (HR = 2.6; 95%CI: 1.7-3.8;  $P < 0.001$ ), probably because they were less likely to both respond to initial RT and to receive systemic therapy. In multivariate analysis corrected for early death, primary tumour, PS and randomization arm remained predictive for retreat-

**Table 2 Evidence supporting recommended dose-fractionation schedules**

Indication	Recommended schedule	Selected references	Level of evidence
Uncomplicated bone metastases (spine, non-spine)	8Gy/1	[15]	1
Neuropathic pain	8Gy/1 or 20Gy/5	[10,32,39,41,60,61]	5
Impending SCC, RT alone	Multifraction	[38]	1
		[41]	5
		[36]	4
Impending pathologic fracture, RT alone	20-40Gy/5-20	[45]	1

RT: Radiotherapy; SCC: Spinal cord compression.

ment ( $P = 0.01$ ,  $P = 0.001$  and  $P < 0.001$  respectively)<sup>[35]</sup>.

Results of other studies are contradictory: in one, lung cancer patients were less likely to experience an early pain response to EBRT [only 27% had responded by month two, *vs* 70% of breast and prostate cancer patients (level 4 evidence)<sup>[34]</sup>], and in another, lung cancer patients had the highest response rate (level 4 evidence)<sup>[36]</sup> (see below). Overall there is no convincing evidence that outcomes differ based on primary site as reported in the dose-finding randomized trials [reviewed by reference 6 (level 4 evidence)]. Similarly, none of the meta-analyses separated out treatment effects by histology (level 1 evidence)<sup>[8,12,13,15]</sup>.

#### **Evidence summary - complicated bone metastases**

Although neuropathic pain secondary to BM is not as predictively responsive to standard analgesics<sup>[37]</sup>, it does respond to RT<sup>[38]</sup>. Roos *et al*<sup>[38]</sup> compared a single 8 Gy *vs* 20 Gy/5 for 245 per-protocol patients with any primary site with BM causing neuropathic pain; 31% had lung cancer (level 1 evidence). Eligible patients had no other metastases along the distribution of the neuropathic pain, no cauda equina or SCC. Pain relief was seen in 53% of SF and 61% of MF patients (intent-to-treat) with 26%-27% experiencing CR at two months. Median time to treatment failure was longer in the fractionated arm (3.7 mo *vs* 2.4 mo), but, like the response rates, the difference did not reach statistical significance within the confidence limits set by this non-inferiority trial. Rates of SCC, PF and reirradiation were not significantly different. Therefore, for BM causing neuropathic pain, either 8Gy/1 or 20Gy/5 may be considered standard. The authors recommended the latter; however, patients with decreased PS, shorter expected survival or comorbidities, who would not be amenable to multiple hospital visits should receive SF<sup>[38]</sup> (Table 2).

The treatment of an asymptomatic BM may be deferred unless the patient has a serious impending condition such as SCC or PF. Diagnosis of impending SCC requires radiologic evidence of indentation of the thecal sac at the level of local or radicular pain, without associated neurologic signs or symptoms<sup>[39]</sup>. RT may prevent neurologic dysfunction in impending SCC<sup>[40]</sup> although these patients were excluded from the vast majority of the clinical trials investigating RT doses for uncomplicated BM. There is insufficient evidence at present to

guide practice on the optimal dose schedule, although definitive EBRT for epidural tumour without neurological impairment, mechanical pain, or spinal instability should be fractionated (level 5 evidence)<sup>[41]</sup>. Based on data from established SCC, MFRT may have advantages in terms of local control and/or in-field recurrence (level 1 evidence)<sup>[8,42,43]</sup>, and there is likely no advantage in offering more than 30Gy/10 (level 1 evidence)<sup>[42]</sup> (Table 2).

An impending PF is defined as a BM that has a significant likelihood of fracture under normal physiological loads. In patients with lung cancer who have a painful BM affecting a weight-bearing bone, especially a solitary lytic lesion involving > 50% of the cortex circumferentially, an expected survival > 4 wk, and satisfactory health otherwise, surgical fixation is recommended (level 5 evidence)<sup>[39]</sup>. Although at least one group has reported a marked increase in surgical involvement for metastatic bone lesions in recent years (level 4 evidence)<sup>[44]</sup>, a proportion of patients will not be candidates for operative intervention, or will decline. In that circumstance, multifraction RT should be delivered (level 1 evidence)<sup>[45]</sup> (Table 2).

Harada *et al*<sup>[36]</sup> reviewed results from a single institution to clarify the outcomes of RT for femoral BM (level 4 evidence). 72 consecutive patients (20.8% with a lung primary) with 84 femoral lesions (77/84 symptomatic) were treated (2002-2005). 39/84 lesions were lytic and 43/84 were considered impending PF. Median RT dose was 30Gy/10 (range 20-40Gy/5-20) and peri-RT systemic therapy was allowed. No reirradiation was performed. Median follow-up was five months (range 1-28 mo). Overall post-RT, 8 lesions achieved a radiological CR and 27 a radiological partial response (PR) on plain X-ray assessed independently by a radiologist and orthopedic oncologist. The best overall response rate (CR + PR) was 42% (35/84), with 30 lesions considered stable and 19 showing progressive disease. Of impending PF lesions, 15/43 showed a radiological response. Median interval from the start of RT to radiologic CR/PR was 3 mo and median duration was 10 mo. Administration of chemotherapy, hormone therapy or bisphosphonates significantly correlated with a favourable radiological response; RT dose and impending PF status did not. Response rates differed significantly based on primary site: lung cancer had the highest (65%) in comparison to breast (47%), prostate (42%) and other (28%) ( $P =$



0.03). Eleven lesions eventually required surgery at a median of 3 mo of which 8 had actually fractured; seven of these had been classified initially as impending PF. Eventual fracture rate in the impending PF group (7/43; 16%) was significantly higher than in the no impending PF group (1/41; 2%) ( $P = 0.03$ ). In the 77 symptomatic lesions at baseline, pain was classified as improved in 36, stable in 36 and as progressive in 5. There was no correlation between radiological response and pain relief ( $P = 0.17$ ). Overall median survival was 7 mo (95%CI: 4-9 mo)<sup>[36]</sup>.

### Results of survey studies

Since 1998, 12 hypothetical cases involving patients with lung cancer and BM have been reported in one abstract and five full publications<sup>[6,9,46-49]</sup> (Table 3). Case histories included patients of both genders, ranging in age from 45-78 years, PS 1-2, previously treated with radical surgery +/- adjuvant chemotherapy or curative chemRT, or metastatic at diagnosis. Histologic subtype of lung cancer was usually unspecified. Investigations diagnosing BM varied as did extent of non-osseous metastases. One publication described current pain score and response to analgesics<sup>[47]</sup>. Overall, eight cases were of uncomplicated BM (one non-spine, seven spine), and four were complicated (three neuropathic pain, one impending SCC and impending PF). Fairchild Case 3 and Chow Case 2 were identical except for the patient's age, while Chow Case 2 and Hartsell Case 2 are presumed identical given that the Chow survey was designed based on Hartsell's questionnaire. Overall response rates ranged from 15.7% to 63.3% ( $n = 5$  studies); response rate of the Nakamura survey was provided as a proportion of institutions rather than practitioners (Table 3).

Radiation Oncologists living in Japan, Italy, the United States, Canada, Australia, and New Zealand along with members of the American, Canadian, Australian and New Zealand Radiation Oncology professional groups were surveyed by mail<sup>[48,49]</sup>, internet<sup>[9,46]</sup> or during attendance at national meetings<sup>[6,47]</sup>. Responses to three surveys were anonymous<sup>[6,9,47]</sup>. Trainees were included in the sampling frame<sup>[6,47]</sup>, excluded<sup>[9]</sup>, or not specified but likely excluded<sup>[46,48,49]</sup>. A prespecified list of dose fractionation schedules was provided only by De Bari. Factors influencing dose prescribed were sought on the basis of case<sup>[6,46,47]</sup>, overall<sup>[9]</sup>, or not explored<sup>[48,49]</sup>.

Table 4 indicates the proportion of respondents who would deliver EBRT in each case and the specified dose fractionations, with shading indicating practice that would currently be considered evidence-based. For uncomplicated bone BM, 8Gy/1 would be used by 13.7% of Japanese respondents to treat a right shoulder, and between 5.9% and 39.6% of respondents internationally to treat a painful spinal lesion. Range of doses suggested for an uncomplicated spine metastasis was 3Gy/1 to 55Gy/22 with up to 78.4% using 30Gy/10; this was also the most common dose suggested by respondents in Hartsell and in the Nakamura survey. For a BM associated with neu-

ropathic pain, 0%-13.2% would use 8Gy/1 and 5.8% to 52.8% would use 20Gy/5 (range 3Gy/1-45Gy/18). Finally, for the patient with impending SCC and PF, 54% would use a multifraction schedule of either 20Gy/5 or 30Gy/10; the respondents using a dose in the 'other' category could also be considered to have evidence-based practice although the specific additional proportion cannot be differentiated from missing values.

In the four publications which explored factors influencing choice of dose fractionation based on direct questioning of respondents, the most commonly cited factors impacting treatment decisions were wish to minimize risk of neurologic progression/SCC, prognosis, literature results and wish to minimize the chance of recurrent pain. Among those factors impacting treatment decisions the least were waiting list, personal habits and financial aspects (Table 5). In the only study to explore it, 36.4% (uncomplicated BM) and 30.6% (complicated BM) of respondents were influenced in their decision to deliver RT by analgesic response<sup>[47]</sup>.

Statistical predictors of characteristics of respondents likely to use SF schedules were reported by Fairchild, Chow, and Roos; Hartsell reported predictors of use of <30 Gy (Table 6). For use of SF in uncomplicated spinal BM, time in practice was associated with use of < 30 Gy by Hartsell but not associated in the Chow or Roos publications. University/academic practice was associated with use of SF<sup>[9]</sup>, and private practice with less use of SF<sup>[9]</sup>, while no differences were found by Roos. Fairchild *et al*<sup>[9]</sup> found that those trained in the United States tended to use SF less often while Chow found no correlation. Radiation Oncologists practicing in the Southwest United States, New Zealand and Australia tended to use lower doses more often<sup>[49]</sup>, with no differences between Australia and New Zealand or between Australian states<sup>[6]</sup>. No trends were observed for treatment of neuropathic pain in the two surveys reporting statistical predictors (Table 6).

## DISCUSSION

Treatment decisions regarding palliative EBRT for BM should be based on individualized considerations of symptom burden, extent of disease, life expectancy, PS, comorbidities, toxicity, prior treatment and patient wishes. A retrospective study of 33 patients dying within 30 d of hospital admission, 39.4% of whom had lung cancer and 94% with metastatic disease, reported planned *vs* actual EBRT treatment; sites were not specified<sup>[50]</sup>. 90% were planned for  $\geq 30$ Gy but only 58.1% completed it; almost 25% died during treatment. Half of patients spent > 60% of their remaining life on therapy with the median treatment time equivalent to the cohort's median survival (15 d)<sup>[50]</sup>. However, while palliative EBRT should be appropriately customized to patients, the choice of dose schedule should have a robust evidence base.

Despite multiple randomized trials and four meta-analyses showing efficacy of SF irradiation for uncom-

Table 3 Hypothetical cases utilized by previous surveys

Ref.	Case history	Methodology	Response rate
Nakamura <i>et al</i> <sup>[46]</sup> Case 1 (Japan, 2012)	A 65 yr old man was diagnosed with squamous cell lung cancer one year earlier and was treated by radical surgery. He now has pain in his right shoulder. Radiologic examinations detected osteolytic bone metastasis at the right scapula and multiple lung metastases. ECOG 1	Radiation Oncologist members of JROSG completed an internet-based survey Presumed trainees were excluded Not anonymous	NR
Nakamura <i>et al</i> <sup>[46]</sup> Case 2 (Japan, 2012)	A 65 yr old man was diagnosed with squamous cell lung cancer one year earlier and was treated by radical surgery. He now has back pain. Radiologic examinations detected osteolytic bone metastasis at L1 and multiple lung metastases. There is no evidence of vertebral collapse or spinal or thecal sac compression. ECOG 1		
Nakamura <i>et al</i> <sup>[46]</sup> Case 3 (Japan, 2012)	Same setting as in case 2 with the addition of paresthesias in a distribution consistent with the L1 dermatome, compatible with neuropathic pain		
De Bari <i>et al</i> <sup>[47]</sup> Case 2 <sup>1</sup> (Italy, 2011)	68yo woman ECOG 1, right lung cancer in 2005, pT2N1M0 underwent lobectomy -> adjuvant chemotherapy. No previous RT. Negative F/U to today. Lumbar pain (L2-L3) underwent bone scan and spinal MRI, total body CT and CT brain. 3 new liver lesions. Bone scan: multiple sites of pathological uptake. MRI: multiple osteolytic spinal metastases including at symptomatic sites. No clinical or radiologic evidence of SCC and no risk of immediate fracture. VAS: 8 without analgesics, 3 after regular weak opioids	Questionnaires given to ROs attending the national congress at the time of registration and collected at the end of the congress Trainees included Anonymous Prespecified list of dose fractionation schedules provided as answer choices, or 'other'	122/300 (40.6%) <sup>3</sup>
De Bari <i>et al</i> <sup>[47]</sup> Case 4 <sup>1</sup> (Italy, 2011)	78yo man ECOG 2, left lung cancer in 2007, pT3N0M0 post left pneumonectomy -> adjuvant chemo x6. Negative f/u until today. Sudden thoracic (D5/D6, D10) and lumbar (L4) pain. No clinical signs of cord compression. No other symptomatic sites. MRI spine: multiple spinal secondary lytic lesions. Radiological signs of D10 spinal cord compression. Risk of pathologic fracture at C3. CT body: multiple liver and lung metastases. VAS: 9 without analgesics, 3 after regular opioids analgesics (transdermal fentanyl 50 ug) and prn NSAIDs	Factors influencing dose were sought for each case	
Fairchild <i>et al</i> <sup>[9]</sup> Case 3 (Intl, 2009)	A 55-year-old male was diagnosed with stage IIIA (T3N2) non-small cell lung cancer one year ago, and was treated radically with chemotherapy and thoracic radiotherapy. He now has pain in the lower back, and a bone scan shows a lesion at L3. His pain localizes to an area consistent with L3, and motor and sensory exams are unremarkable. There is a lytic lesion present and evidence of mild vertebral collapse, but no cauda equina or thecal sac compression on MRI scan	Web-based survey distributed to Radiation Oncologist members of ASTRO, CARO and RANZCR Anonymous Trainees, retirees excluded No prespecified list of dose fractionation schedules provided	962/6110 (15.7%)
Fairchild <i>et al</i> <sup>[9]</sup> Case 4 (Intl, 2009)	Same setting as in case above, with the addition of paresthesias in a distribution consistent with the L3 dermatome, compatible with neuropathic pain	General factors influencing dose were sought (not case-by-case) Bonferroni used	
Chow <i>et al</i> <sup>[48]</sup> Case 2 (Canada, 2000)	A 45 yr old male was diagnosed with stage IIIA (T3N2) large cell carcinoma of the lung one year ago, and was treated with chemotherapy and thoracic irradiation. He now has pain in his lower back, and a bone scan shows a lesion in the third lumbar vertebra. His pain localizes to an area consistent with L3, and does not radiate. Motor and sensory examinations are unremarkable. A CT scan of this area shows a lytic lesion, but no evidence of compression of the cauda equina or thecal sac	Survey mailed to all ROs in active practice in Canada Excluded retirees or those practicing outside of Canada No mention of including trainees Did not specify whether anonymous No prespecified list of dose fractionation schedules provided	172/300 (57.3%)
Chow <i>et al</i> <sup>[48]</sup> Case 3 (Canada, 2000)	Same setting as above, but instead of L3, the lesion is at L1 with no evidence of cord compression. Assume the external beam irradiation to the painful site in L1 would not overlap the previous radiation field	Factors influencing dose not explored	
Roos <i>et al</i> <sup>[6]</sup> Case 3 (Aust/NZ, 2000)	Male, age 63 with disseminated large cell lung cancer and bone scan positive L1-L3, several ribs and skull. There is pain in the upper lumbar spine only and no neurologic dysfunction	Survey distributed to delegates at 1998 Royal ANZ College of Radiologists Annual Scientific Meeting and returned before a presentation on bone pain Anonymous Trainees included Presumed no prespecified list of dose fractionation schedules were provided since cases were designed based on previous surveys	53/114 (46.5%) <sup>3</sup>
Roos <i>et al</i> <sup>[6]</sup> Case 4 (Aust/NZ, 2000)	Male, age 63 with disseminated large cell lung cancer and bone scan positive L1-L3, several ribs and skull. There is pain in the upper lumbar spine as well as pain and tingling in the right L2 distribution consistent with neuropathic pain	Factors influencing dose sought for each case Used Bonferroni correction	

Hartsell <i>et al</i> <sup>[49]</sup> Case 2 <sup>2</sup> (United States, 1998)	A 45 yr old male was diagnosed with stage IIIA (T3N2) large cell carcinoma of the lung one year ago, and was treated with chemotherapy and thoracic irradiation. He now has pain in his lower back, and a bone scan shows a lesion in the third lumbar vertebra. His pain localizes to an area consistent with L3, and does not radiate. Motor and sensory examinations are unremarkable. A CT scan of this area shows a lytic lesion, but no evidence of compression of the cauda equina or thecal sac	Survey mailed to randomly selected radiation oncologists in United States Factors influencing dose not reported Did not specify whether prespecified list of doses was given Presumed trainees excluded Did not report whether anonymized	229/362 (63.3%)
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<sup>1</sup>Only surveys containing all the answers for at least 3 of the 4 clinical cases in the wider survey were analyzed; <sup>2</sup>Few case details provided in abstract but Chow *et al*<sup>[49]</sup> reports using the same case so clinical history is as described by Chow *et al*; <sup>3</sup>Including trainees. NR: Not reported; CT: Computed tomography; MRI: Magnetic resonance imaging; SCC: Spinal cord compression; Intl: International; ECOG: Eastern Cooperative Oncology Group.

**Table 4 Grey shading indicates dose-fractionation schedules which would be supported by current evidence**

Case	N treating with EBRT	8Gy/1	20Gy/5	30Gy/10	Other	Median (Range)
Uncomplicated-non-spine						
Nakamura case 1 (Japan, 2012)	51	13.70%	9.80%	66.70%	9.80%	NR (NR)
Uncomplicated-spine						
Hartsell case 2 (United States, 1998)	229	4% recommended < 30Gy		76% recommended 30-35Gy 20% recommended > 35Gy		NR (15Gy/5 - 47.5Gy/25)
Nakamura case 2 (Japan 2012)	51	5.90%	3.90%	78.40%	11.80%	NR (NR)
Chow case 3 (Canada, 2000)	171	15.80%	66.10%	8.80%	9.4% <sup>3</sup>	NR (8Gy/1 - 30Gy/10)
Chow case 2 (Canada, 2000)	170	15.90%	64.70%	8.20%	11.2% <sup>3</sup>	NR (8Gy/1 - 30Gy/10)
Fairchild case 3 (Intl, 2009)	867	18.3% <sup>2</sup>	19.8% <sup>2</sup>	41.9% <sup>2</sup>	20.00%	30Gy/10 (3Gy/1 - 55Gy/22)
De Bari case 2 (Italy, 2011)	107€	22.20%	50.10%	26.80%	0.90%	NR (NR)
Roos case 3 (Aust/NZ, 2000)	53€	39.6%€	35.8%€	15.1%€	9.4%€	NR (8Gy/1 - 40Gy/18)
Complicated-neuropathic pain						
Nakamura case 3 (Japan, 2012)	52	0%	5.80%	78.80%	15.40%	NR (NR)
Fairchild case 4 (Intl, 2009)	844	6.6% <sup>2</sup>	29.0% <sup>2</sup>	42.8% <sup>2</sup>	21.60%	30Gy/10 (3Gy/1 - 45Gy/18)
Roos case 4 (Aust/NZ, 2000)	53€	13.2%€	52.8%€	24.5%€	9.4%€	NR (8Gy/1 - 40Gy/20)
Complicated-impending spinal cord compression and impending pathologic fracture						
De Bari case 4 (Italy, 2011)	113€	30.60%	25.80%	28.20%	15.4% <sup>3</sup>	NR (NR)

<sup>1</sup>41 specialists/12 trainees; <sup>2</sup>Takes into account multiple dose fractionation schemes listed per respondent; <sup>3</sup>Includes unknown/missing responses; €: Extrapolated from data reported or from figure. EBRT: External beam radiotherapy; Intl: International; NR: Not reported.

plicated BM and BM associated with neuropathic pain in patients with lung cancer, its use as reported by respondents to hypothetical case scenarios remains low. Most common practice internationally and over time continues to be a 30Gy/10 schedule, representing significant divergence from multiple clinical practice recommendations and consensus guidelines (Table 2). The consequences in terms of increased departmental workload, health care costs and patient burden are significant<sup>[6]</sup>.

For a complicated BM presentation where the literature is less robust but supports fractionation, a higher proportion of respondents' dose schedules are evidence-based. For a patient with good PS, a truly solitary BM and no visceral disease, multifractionated highly conformal treatment may be a reasonable option. In that circumstance, long term tumour control may be important<sup>[7]</sup>.

However most patients with lung cancer and complicated BM do not meet these criteria and palliation, not tumour control, is the goal<sup>[7]</sup>. Additionally, patients who are not likely to benefit from irradiation, especially those who are not likely to complete the prescribed course, should not be offered treatment. Those with extensive metastatic disease, a short life expectancy or very poor PS should be considered for SF radiotherapy regardless

of type of BM lesion, if they are treated at all<sup>[42]</sup>. Settings in which RT should be omitted entirely in favour of best supportive care are reviewed by Lutz *et al*<sup>[51]</sup>.

It is not completely clear why the results of literature confirming the equivalence of single to MF continue to be overlooked, although studies suggest that trial evidence is just one of the factors physicians use in determining dose fractionation schedules<sup>[9]</sup>. Patient-, institution- and training-related factors, along with individual physician beliefs, also play a role (Table 7).

#### Patient-related

The number of respondents employing SF for neuropathic pain, which in fact decreased after the publication of the TROG trial in 2005, may be due to the risk of occult spinal cord/cauda equina compression, the belief that tumour shrinkage is required to alleviate pressure on nerves or the general exclusion of these patients from trials examining efficacy of SF EBRT<sup>[6,38]</sup>. Half of respondents to Nakamura Case 2 were concerned about the possibility of SCC<sup>[46]</sup>. Concerns over toxicity and other QOL issues have not emerged as major factors<sup>[6,9]</sup>, likely because acute toxicity is typically mild and long term toxicity uncommon<sup>[7,8]</sup>. As many as 85% of respondents who

**Table 5 Factors influencing choice of dose fractionation scheme based on direct questioning of respondents**

Case	Most impact	Least impact
Uncomplicated-spine Nakamura Case 2 (Japan, 2012)	Factors influencing those who chose MF: Time until first increase in pain Incidence of spinal cord compression Incidence of pathologic fracture	NR
De Bari Case 2 <sup>1</sup> (Italy, 2011)	Prognosis Performance status Radiologic appearance of lesions	Financial aspects Personal habits Waiting list
Roos Case 3 <sup>2</sup> (Aust/NZ, 2000)	Factors influencing those who chose SF: Literature results Patient convenience Resource limitations Factors influencing those who chose MF: Minimize chance of recurrent pain Minimize risk of neurologic progression (tie) Optimize tumour regression Patient convenience	NR
Complicated-neuropathic pain Roos Case 4 <sup>2</sup> (Aust/NZ, 2000)	Factors influencing those who chose SF: Literature results Patient convenience Resource limitations Factors influencing those who chose MF: Minimize risk of neurologic progression Minimize chance of recurrent pain Optimize tumour regression	NR
Complicated – impending spinal cord compression and impending pathologic fracture De Bari Case 4 <sup>1</sup> (Italy, 2011)	Radiologic appearance of lesions Site of metastasis Prognosis	Financial aspects Personal habits (tie) Waiting list
Overall Fairchild (Intl, 2009)	Prognosis Risk of spinal cord compression Performance status Previous RT Published evidence	Departmental policy Waiting list Future retreatment Age Late toxicity

<sup>1</sup>Literature results were not one of the prespecified options; <sup>2</sup>Includes specialist and trainee responses. Intl: International; MF: Multiple fractions; NR: Not reported; SF: Single fractions.

recommended MFRT for Nakamura Case 2 regarded it as superior based on time until first increase in pain; participants in the Roos survey also cited this factor, which is not supported by level 1 evidence.

### Physician-related

Some international guidelines still recommend multifraction schedules for uncomplicated BM. NCCN suggests, but does not provide supporting evidence for, the range of 8-30Gy/1-20 for an uncomplicated BM secondary to NSCLC<sup>[52]</sup>. Japanese radiation oncologists prefer to learn from US resources resulting in similar patterns of practice<sup>[46]</sup>. Despite evidence to the contrary, radiation oncologists may continue to believe that higher total doses, which can now be delivered with minimal toxicity *via* highly conformal techniques, are preferred<sup>[2,53]</sup>. However, the mechanism of pain relief may be related to changes in the local microenvironment rather than direct tumour kill<sup>[7]</sup>. Suboptimal quality of early studies (heterogeneity of patients, differences in endpoint selection, inconsis-

tent follow-up practices) may have contributed to lack of confidence in their results<sup>[48]</sup>.

### Institution-related

SF is most frequently prescribed in university or government (*vs* private) centres and in large treatment facilities<sup>[6,7,9,26,49]</sup>.

### Health Care System-related

Reimbursement system is one part of the wider cultural and bureaucratic context of location of practice/institutional structure<sup>[24]</sup>. SF is more commonly used in countries using a budget or case-payment system (*e.g.*, Canada) compared to those with fee-for-service reimbursement, such as Japan<sup>[7,46]</sup>. In a survey of 23/25 Belgian RT centres after changes in the Belgian reimbursement system in 2001 from fee-for-service to case payment, there was an increase in use of SF in 86% of centres<sup>[11]</sup>. In Canada, where SF are used more often, the majority of departments are funded mostly by government while university



**Table 6** Statistical predictors of use of single fraction schedules

Case	Factor	OR for use of SF (95%CI)	P
Uncomplicated-spine Hartsell Case 2 (1998, United States)	Respondents recommending doses < 30Gy: Longer time in practice Academic practice Practice in the Southwest	NR	NR
Chow Case 2 (Canada, 2000)	No differences based on country of specialty training or year training completed	NR	NR
Chow Case 3 (Canada, 2000)			
Fairchild Case 3 (Intl, 2009)	University practice Private practice Trained in United States Practice in Aust/NZ	2.08 (1.35-3.19) 0.27 (0.12-0.61) 0.17 (0.10-0.28) 2.44 (1.43-4.18)	0.001 0.002 < 0.001 0.001
Roos Case 3 (Aust/NZ, 2000)	No difference based on trainees vs specialists, public vs private practice, years of experience, % workload palliative, between Aust vs NZ or between Aust states	NR	NR
Complicated-neuropathic pain Fairchild Case 4 (Intl, 2009)	University practice Trained in US	2.31 (1.33-4.00) 0.22 (0.11-0.43)	0.003 < 0.001
Roos Case 4 (Aust/NZ, 2000)	No difference based on trainees vs specialists, public vs private practice, years of experience, % workload palliative, between Aust vs NZ or between Aust states	NR	NR

Aust: Australia; Intl: International; NR: Not reported; NZ: New Zealand.

and other funds make up < 10% support<sup>[28]</sup>.

A recently published patterns of care study characterized palliative RT dose and fractionation in a large US cohort of metastatic NSCLC patients (stage IV at baseline or metastatic at recurrence) and explored factors influencing RT delivery<sup>[2]</sup>. The Cancer Care Outcomes Research and Surveillance Consortium prospectively enrolled 1574 patients (2003-2005) who participated in phone surveys and whose medical records were reviewed. 65% were male with a median age of 68. Eighty-seven point two percent had metastatic disease at diagnosis and the remainder was diagnosed with a distant first recurrence within 15 mo. Among 194 patients who received palliative EBRT to bone (218 courses), 50% received 6-10 fractions, 20% five fractions or fewer and 6% received SF. Among 206 patients with known dose, 49% received 21-30Gy. Patients younger than age 55, who had had surgery to a metastatic site and those receiving chemotherapy were more likely to receive RT to any site. Type of insurance was not predictive. Patients receiving RT to BM treated in integrated networks (HMOs, Veterans Administration) received on average 3.4 fewer fractions ( $P = 0.001$ ) and 4Gy less dose ( $P = 0.049$ ), although had similar rates of RT delivery<sup>[2]</sup>. No information was provided about whether BM were complicated or uncomplicated. The authors concluded that a substantial proportion of patients received higher doses and more fractions than clinical trial data supports, despite the fact that this cohort had a short median survival. Patients treated in integrated networks received lower total doses and fewer fractions suggesting that provider characteristics, organizational structures and processes or financial incentives influenced clinical practice<sup>[2]</sup>.

However, arguments against SF have been almost entirely refuted by recent data, including multiple second-

ary analyses of the 1999 Dutch trial which randomized between 8Gy/1 and 24Gy/6, reporting no difference in outcomes<sup>[16]</sup>. In terms of reirradiation, although SF and MF patients experienced equivalent response and progression rates, SF patients were retreated more frequently, at an earlier time during follow-up and at a lower pain score. This was interpreted by the authors as evidence that the differences resulted from practitioner bias rather than true differences in efficacy<sup>[35]</sup>.

Several economic analyses have compared different schedules of EBRT. A cost-utility analysis was conducted prospectively within the Dutch trial<sup>[14]</sup>. SF RT provided an additional 1.7 quality-adjusted weeks and cost USD\$873 less than MF, including the effects of retreatment. When considering total societal including non-medical costs, the estimated savings was larger (USD\$1753) but not statistically significant<sup>[14]</sup>. In a cost-effectiveness analysis of the TROG neuropathic bone pain study<sup>[38]</sup> incorporating data to three months post-RT, although larger retreatment costs were associated with the SF arm, these were offset by savings in medication and hospital admission costs, as well as by the lower cost of initial RT<sup>[54]</sup>. Through the use of a Markov model, Konski estimated that SF RT was more cost-effective for painful BM than either multifraction RT, chemotherapy (mitoxantrone and prednisone) or analgesics (oxycontin with senokot bowel routine). MF RT had only slightly more quality-adjusted life months than SF but cost USD\$1300 more<sup>[55]</sup>.

van der Linden *et al*<sup>[56]</sup> compared patients with any histology accrued to the Dutch trial surviving > 52 wk from randomization. Responses were 87% after 8Gy and 85% after 24Gy, again including effects of retreatment ( $P = NS$ ). Duration of response, time to response, and progression rates were also similar, indicating that patients do not outlive the benefits of SF.

**Table 7** Reasons for reticence in use of single fractions

Factor	Ref.
Patient-related	
Neuropathic pain	[6]
Prevent or address neurologic symptoms	[46]
Maximize time to first increase in pain	[6]
Patient selection	[7]
Prognosis	[7]
Patient wishes	[7]
Fear of toxicity (acute/late)	[6]
Site of bone metastasis	[9]
Comorbidities	[9]
Physician-related	
Influence of global opinion leaders	[52]
Presumed dose-response	[7]
Professional membership affiliation	[9]
Country of training	[9]
Country of practice	[9]
Lack of experience with large fraction sizes	[9]
Lack of participation in related trials	[6]
Disbelief of early trial results due to quality	[48]
Institution-related	
Departmental policy	[9]
Longer wait times for RT delivery	[62]
Type of centre	[9]
Health care system-related	
Retreatment more often required	[35]
Increased costs due to retreatment	[14]
Reimbursement system	[24]

Two studies have examined the effect of palliative EBRT in patients during the last 12 wk of life<sup>[57,58]</sup>. In a secondary analysis of 274 patients treated within the Dutch study, the proportion showing a pain response did not differ between the SF and MF arms<sup>[57]</sup>. A retrospective review evaluated 232 patients dying within 3 mo of beginning treatment, 34% with lung cancer, 64% men, median KPS 60, median age 69, and 58% received SF. Overall response rates were 70% at one month and 63% at two months, controlling for analgesic usage. The authors concluded that despite limited lifespan, patients with painful BM with an estimated survival of three months should still be considered for RT<sup>[58]</sup>.

In terms of risk of pathologic fracture, 35% of the lesions classified as impending fracture in Harada *et al*<sup>[36]</sup> study responded to multifraction RT, and 81% did not require surgical intervention. Both the degree to which recalcification is dependent on dose, and helps to prevent future fracture, remain unclear, however<sup>[46]</sup>.

Finally, no significant differences have been found in responses rates of elderly ( $\geq 65$  years) compared to younger patients at one, two and three months after RT, when controlling for analgesic usage, supporting referral of patients regardless of age<sup>[59]</sup>.

Surveys are valuable in assessing practice when it diverges from published data, but have well-known limitations, reviewed in Fairchild *et al*<sup>[9]</sup>. Exploration of differences in attitude may provide a more realistic basis for the construction of international consensus, leading to increased ownership. The results might not be entirely representative because it is not possible to conclude

whether answers accurately reflect practice. When the questionnaires were completed in comparison to when practitioners became aware of results of new published data cannot be determined. When facts are being solicited about existing systems, such as reimbursement method, accuracy of the answers cannot be checked. Some studies included trainee respondents, some did not, and some did not specify. Multiple calculations for associations are often performed, but rarely taken into account in the statistical analysis (*i.e.*, lack of Bonferroni correction). Possible explanations for differences in practice include a lack of histology-specific data<sup>[19]</sup>, demographics of respondents, contradictory definitions of uncomplicated BM, and varying availability of alternative treatment modalities such as vertebroplasty, radiofrequency ablation, radiopharmaceuticals and speciality surgery teams<sup>[9]</sup>. Additionally, increasing use of systemic therapy in patients with advanced lung cancer may add local anti-tumour effects<sup>[36]</sup>, and case histories often did not describe planned or delivered systemic therapy. Overall, a survey is still a useful method of exploring attitudes, beliefs and practices, although it is not possible to extrapolate beyond the data reported.

## CONCLUSION

Palliative EBRT has an essential role as a well-tolerated, minimally toxic, cost conscious and effective treatment for symptom control in this setting. However, survey studies concerning hypothetical cases of patients with lung cancer and both complicated and uncomplicated bone metastases continue to show a large discrepancy between published literature and patterns of practice. From a common sense perspective, the shortest RT regimen which maximizes outcomes in an evidence-based manner seems preferable. Schedules prescribed as multifraction courses, when SF would be appropriate, disadvantage all patients and overextend many centres' already strained resources.

## REFERENCES

- 1 **Morikawa K**, Mineshita M, Nishine H, Furuya N, Obayashi J, Miyazawa T. A case of squamous cell lung carcinoma with bone metastasis responding to denosumab after zoledronic acid hydrate. *Jap J Lung Cancer* 2012; **52**: 1035-1040 [DOI: 10.2482/haigan.52.1035]
- 2 **Chen AB**, Cronin A, Weeks JC, Chrischilles EA, Malin J, Hayman JA, Schrag D. Palliative radiation therapy practice in patients with metastatic non-small-cell lung cancer: a Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) Study. *J Clin Oncol* 2013; **31**: 558-564 [PMID: 23295799 DOI: 10.1200/JCO.2012.43.7954]
- 3 **Decroisette C**, Monnet I, Berard H, Quere G, Le Caer H, Bota S, Audigier-Valette C, Geriniere L, Vernejoux JM, Chouaid C. Epidemiology and treatment costs of bone metastases from lung cancer: a French prospective, observational, multicenter study (GFPC 0601). *J Thorac Oncol* 2011; **6**: 576-582 [PMID: 21270669 DOI: 10.1097/JTO.0b013e318206a1e3]
- 4 **Bezjak A**. Palliative therapy for lung cancer. *Semin Surg Oncol* 2003; **21**: 138-147 [PMID: 14508864 DOI: 10.1002/ssu.10031]

- 5 **Hoegler D.** Radiotherapy for palliation of symptoms in incurable cancer. *Curr Probl Cancer* 1997; **21**: 129-183 [PMID: 9202888 DOI: 10.1016/S0147-0272(97)80004-9]
- 6 **Roos DE.** Continuing reluctance to use single fractions of radiotherapy for metastatic bone pain: an Australian and New Zealand practice survey and literature review. *Radiother Oncol* 2000; **56**: 315-322 [PMID: 10974380 DOI: 10.1016/S0167-8140(00)00250-4]
- 7 **Hartsell WF,** Konski AA, Lo SS, Hayman JA. Single fraction radiotherapy for bone metastases: clinically effective, time efficient, cost conscious and still underutilized in the United States? *Clin Oncol (R Coll Radiol)* 2009; **21**: 652-654 [PMID: 19744843 DOI: 10.1016/j.clon.2009.08.003]
- 8 **Chow E,** Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. *Clin Oncol (R Coll Radiol)* 2012; **24**: 112-124 [PMID: 22130630 DOI: 10.1016/j.clon.2011.11.004]
- 9 **Fairchild A,** Barnes E, Ghosh S, Ben-Josef E, Roos D, Hartsell W, Holt T, Wu J, Janjan N, Chow E. International patterns of practice in palliative radiotherapy for painful bone metastases: evidence-based practice? *Int J Radiat Oncol Biol Phys* 2009; **75**: 1501-1510 [PMID: 19464820 DOI: 10.1016/j.ijrobp.2008.12.084]
- 10 **Janjan N,** Lutz ST, Bedwinek JM, Hartsell WF, Ng A, Pieters RS, Ratanatharathorn V, Silberstein EB, Taub RJ, Yasko AW, Rettenmaier A. Therapeutic guidelines for the treatment of bone metastasis: a report from the American College of Radiology Appropriateness Criteria Expert Panel on Radiation Oncology. *J Palliat Med* 2009; **12**: 417-426 [PMID: 19416037 DOI: 10.1089/jpm.2009.9632]
- 11 **van der Linden Y,** Roos D, Lutz S, Fairchild A. International variations in radiotherapy fractionation for bone metastases: geographic borders define practice patterns? *Clin Oncol (R Coll Radiol)* 2009; **21**: 655-658 [PMID: 19733039 DOI: 10.1016/j.clon.2009.08.004]
- 12 **Chow E,** Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007; **25**: 1423-1436 [PMID: 17416863 DOI: 10.1200/JCO.2006.09.5281]
- 13 **Sze WM,** Shelley MD, Held I, Wilt TJ, Mason MD. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy--a systematic review of randomised trials. *Clin Oncol (R Coll Radiol)* 2003; **15**: 345-352 [PMID: 14524489 DOI: 10.1016/S0936-6555(03)00113-4]
- 14 **van den Hout WB,** van der Linden YM, Steenland E, Wiggenraad RG, Kievit J, de Haes H, Leer JW. Single- versus multiple-fraction radiotherapy in patients with painful bone metastases: cost-utility analysis based on a randomized trial. *J Natl Cancer Inst* 2003; **95**: 222-229 [PMID: 12569144 DOI: 10.1093/jnci/95.3.222]
- 15 **Wu JS,** Wong R, Johnston M, Bezjak A, Whelan T. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003; **55**: 594-605 [PMID: 12573746 DOI: 10.1016/S0360-3016(02)04147-0]
- 16 **Steenland E,** Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J, de Haes H, Martijn H, Oei B, Vonk E, van der Steen-Banasik E, Wiggenraad RG, Hoogenhout J, Wárlám-Rodenhuis C, van Tienhoven G, Wanders R, Pomp J, van Reijn M, van Mierlo I, Rutten E. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999; **52**: 101-109 [PMID: 10577695 DOI: 10.1016/S0167-8140(99)00110-3]
- 17 **Booth M,** Summers J, Williams MV. Audit reduces the reluctance to use single fractions for painful bone metastases. *Clin Oncol (R Coll Radiol)* 1993; **5**: 15-18 [PMID: 7678748 DOI: 10.1016/S0936-6555(05)80687-9]
- 18 **Expósito J,** Jaén J, Alonso E, Tovar I. Use of palliative radiotherapy in brain and bone metastases (VARA II study). *Radiat Oncol* 2012; **7**: 131 [PMID: 22863023 DOI: 10.1186/1748-717X-7-131]
- 19 **Sharma V,** Gaye PM, Wahab SA, Ndlovu N, Ngoma T, Vanderpuye V, Sowunmi A, Kigula-Mugambe J, Jeremic B. Patterns of practice of palliative radiotherapy in Africa, Part 1: Bone and brain metastases. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1195-1201 [PMID: 17967515 DOI: 10.1016/j.ijrobp.2007.07.2381]
- 20 **Szostakiewicz B,** Dziadziuszko R, Welnicka-Jaskiewicz M, Jassem J. Palliative irradiation of bone metastases: Patterns of care with focus on single fraction treatment. *Rep Pract Oncol Radiother* 2004; **9**
- 21 **Gupta T,** Sarin R. Palliative radiation therapy for painful vertebral metastases: a practice survey. *Cancer* 2004; **101**: 2892-2896 [PMID: 15534882 DOI: 10.1002/cncr.20706]
- 22 **Barton R,** Robinson G, Gutierrez E, Kirkbride P, McLean M. Palliative radiation for vertebral metastases: the effect of variation in prescription parameters on the dose received at depth. *Int J Radiat Oncol Biol Phys* 2002; **52**: 1083-1091 [PMID: 11958905 DOI: 10.1016/S0360-3016(01)02738-9]
- 23 **Adamietz IA,** Schneider O, Müller RP. Results of a nationwide survey on radiotherapy of bone metastases in Germany. *Strahlenther Onkol* 2002; **178**: 531-536 [PMID: 12386783 DOI: 10.1007/s00066-002-0988-6]
- 24 **Lievens Y,** Van den Bogaert W, Rijnders A, Kutcher G, Kesteloot K. Palliative radiotherapy practice within Western European countries: impact of the radiotherapy financing system? *Radiother Oncol* 2000; **56**: 289-295 [PMID: 10974377 DOI: 10.1016/S0167-8140(00)00214-0]
- 25 **Lievens Y,** Kesteloot K, Rijnders A, Kutcher G, Van den Bogaert W. Differences in palliative radiotherapy for bone metastases within Western European countries. *Radiother Oncol* 2000; **56**: 297-303 [PMID: 10974378 DOI: 10.1016/S0167-8140(00)00215-2]
- 26 **Ben-Josef E,** Shamsa F, Williams AO, Porter AT. Radiotherapeutic management of osseous metastases: a survey of current patterns of care. *Int J Radiat Oncol Biol Phys* 1998; **40**: 915-921 [PMID: 9531377 DOI: 10.1016/S0360-3016(97)00927-9]
- 27 **Duncan G,** Duncan W, Maher EJ. Patterns of palliative radiotherapy in Canada. *Clin Oncol (R Coll Radiol)* 1993; **5**: 92-97 [PMID: 7683204 DOI: 10.1016/S0936-6555(05)80855-6]
- 28 **Maher EJ,** Coia L, Duncan G, Lawton PA. Treatment strategies in advanced and metastatic cancer: differences in attitude between the USA, Canada and Europe. *Int J Radiat Oncol Biol Phys* 1992; **23**: 239-244 [PMID: 1572821 DOI: 10.1016/0360-3016(92)90568-3]
- 29 **Lawton PA,** Maher EJ. Treatment strategies for advanced and metastatic cancer in Europe. *Radiother Oncol* 1991; **22**: 1-6 [PMID: 1947207 DOI: 10.1016/0167-8140(91)90062-L]
- 30 **Crellin AM,** Marks A, Maher EJ. Why don't British radiotherapists give single fractions of radiotherapy for bone metastases? *Clin Oncol (R Coll Radiol)* 1989; **1**: 63-66 [PMID: 2484790 DOI: 10.1016/S0936-6555(89)80036-6]
- 31 **Priestman TJ,** Bullimore JA, Godden TP, Deutsch GP. The Royal College of Radiologists' Fractionation Survey. *Clin Oncol (R Coll Radiol)* 1989; **1**: 39-46 [PMID: 2486473 DOI: 10.1016/S0936-6555(89)80010-X]
- 32 **van der Linden YM,** Dijkstra SP, Vonk EJ, Marijnen CA, Leer JW. Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. *Cancer* 2005; **103**: 320-328 [PMID: 15593360 DOI: 10.1002/cncr.20756]
- 33 **Zeng L,** Chow E, Zhang L, Culleton S, Holden L, Jon F, Khan L, Tsao M, Barnes E, Danjoux C, Sahgal A. Comparison of pain response and functional interference outcomes between spinal and non-spinal bone metastases treated with palliative radiotherapy. *Support Care Cancer* 2012; **20**:



- 633-639 [PMID: 21476118 DOI: 10.1007/s00520-011-1144-6]
- 34 **Nguyen J**, Chow E, Zeng L, Zhang L, Culleton S, Holden L, Mitera G, Tsao M, Barnes E, Danjoux C, Sahgal A. 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**: 485-491 [PMID: 21353506 DOI: 10.1016/j.clon.2011.01.507]
  - 35 **van der Linden YM**, Lok JJ, Steenland E, Martijn H, van Houwelingen H, Marijnen CA, Leer JW. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *Int J Radiat Oncol Biol Phys* 2004; **59**: 528-537 [PMID: 15145173 DOI: 10.1016/j.ijrobp.2003.10.006]
  - 36 **Harada H**, Katagiri H, Kamata M, Yoshioka Y, Asakura H, Hashimoto T, Furutani K, Takahashi M, Sakahara H, Nishimura T. Radiological response and clinical outcome in patients with femoral bone metastases after radiotherapy. *J Radiat Res* 2010; **51**: 131-136 [PMID: 19934590 DOI: 10.1269/jrr.09096]
  - 37 **Grond S**, Radbruch L, Meuser T, Sabatowski R, Loick G, Lehmann KA. Assessment and treatment of neuropathic cancer pain following WHO guidelines. *Pain* 1999; **79**: 15-20 [PMID: 9928771 DOI: 10.1016/S0304-3959(98)00138-9]
  - 38 **Roos DE**, Turner SL, O'Brien PC, Smith JG, Spry NA, Burmeister BH, Hoskin PJ, Ball DL. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). *Radiother Oncol* 2005; **75**: 54-63 [PMID: 15878101 DOI: 10.1016/j.radonc.2004.09.017]
  - 39 **Kvale PA**, Selecky PA, Prakash UB. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; **132**: 368S-403S [PMID: 17873181 DOI: 10.1378/chest.07-1391]
  - 40 **Venkitaraman R**, Barbachano Y, Dearnaley DP, Parker CC, Khoo V, Huddart RA, Eeles R, Horwich A, Sohaib SA. Outcome of early detection and radiotherapy for occult spinal cord compression. *Radiother Oncol* 2007; **85**: 469-472 [PMID: 18036691 DOI: 10.1016/j.radonc.2007.10.043]
  - 41 **National Institute for Health and Clinical Excellence (NICE)**. Metastatic spinal cord compression. Diagnosis and management of adults at risk of and with metastatic spinal cord compression. London (UK): NICE, 2008
  - 42 **Prewett S**, Venkitaraman R. Metastatic spinal cord compression: review of the evidence for a radiotherapy dose fractionation schedule. *Clin Oncol (R Coll Radiol)* 2010; **22**: 222-230 [PMID: 20138487 DOI: 10.1016/j.clon.2010.01.006]
  - 43 **Rades D**, Abraham JL. The role of radiotherapy for metastatic epidural spinal cord compression. *Nat Rev Clin Oncol* 2010; **7**: 590-598 [PMID: 20808299 DOI: 10.1038/nrclinonc.2010.137]
  - 44 **Manabe J**, Kawaguchi N, Matsumoto S, Tanizawa T. Surgical treatment of bone metastasis: indications and outcomes. *Int J Clin Oncol* 2005; **10**: 103-111 [PMID: 15864695 DOI: 10.1007/s10147-005-0478-9]
  - 45 **Agarawal JP**, Swangsilpa T, van der Linden Y, Rades D, Jeremic B, Hoskin PJ. The role of external beam radiotherapy in the management of bone metastases. *Clin Oncol (R Coll Radiol)* 2006; **18**: 747-760 [PMID: 17168210 DOI: 10.1016/j.clon.2006.09.007]
  - 46 **Nakamura N**, Shikama N, Wada H, Harada H, Nozaki M, Nagakura H, Tago M, Oguchi M, Uchida N. Patterns of practice in palliative radiotherapy for painful bone metastases: a survey in Japan. *Int J Radiat Oncol Biol Phys* 2012; **83**: e117-e120 [PMID: 22381902 DOI: 10.1016/j.ijrobp.2011.11.075]
  - 47 **De Bari B**, Chiesa S, Filippi AR, Gambacorta MA, D'Emilio V, Murino P, Livi L. The INTER-ROMA project--a survey among Italian radiation oncologists on their approach to the treatment of bone metastases. *Tumori* 2011; **97**: 177-184 [PMID: 21617712]
  - 48 **Chow E**, Danjoux C, Wong R, Szumacher E, Franssen E, Fung K, Finkelstein J, Andersson L, Connolly R. Palliation of bone metastases: a survey of patterns of practice among Canadian radiation oncologists. *Radiother Oncol* 2000; **56**: 305-314 [PMID: 10974379 DOI: 10.1016/S0167-8140(00)00238-3]
  - 49 **Hartsell W**, Shah A, Graney M, Kun L. Palliation of bone metastases in the USA: A survey of patterns of practice. *Support Care Cancer* 1998; **6**: 175 [Abstr 45]
  - 50 **Grippy S**, Mjartan S, Boelke E, Willers R. Palliative radiotherapy tailored to life expectancy in end-stage cancer patients: reality or myth? *Cancer* 2010; **116**: 3251-3256 [PMID: 20564632 DOI: 10.1002/cncr.25112]
  - 51 **Lutz S**, Korytko T, Nguyen J, Khan L, Chow E, Corn B. Palliative radiotherapy: when is it worth it and when is it not? *Cancer J* 2010; **16**: 473-482 [PMID: 20890143 DOI: 10.1097/PP0.0b013e3181f28b4d]
  - 52 **National Comprehensive Cancer Network**. NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer, v2 2013. Available from: URL: [http://www.nccn.org/professionals/physician\\_gls/pdf/nscl.pdf](http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf)
  - 53 **Ben-Josef E**, Shamsa F, Youssef R, Porter AT. External beam radiotherapy for painful osseous metastases: pooled data dose response analysis. *Int J Radiat Oncol Biol Phys* 1999; **45**: 715-719 [PMID: 10524427 DOI: 10.1016/S0360-3016(99)00231-X]
  - 54 **Pollicino CA**, Turner SL, Roos DE, O'Brien PC. Costing the components of pain management: analysis of Trans-Tasman Radiation Oncology Group trial (TROG 96.05): one versus five fractions for neuropathic bone pain. *Radiother Oncol* 2005; **76**: 264-269 [PMID: 16153729 DOI: 10.1016/j.radonc.2005.07.003]
  - 55 **Konski A**. Radiotherapy is a cost-effective palliative treatment for patients with bone metastasis from prostate cancer. *Int J Radiat Oncol Biol Phys* 2004; **60**: 1373-1378 [PMID: 15590167 DOI: 10.1016/j.ijrobp.2004.05.053]
  - 56 **van der Linden YM**, Steenland E, van Houwelingen HC, Post WJ, Oei B, Marijnen CA, Leer JW. Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study. *Radiother Oncol* 2006; **78**: 245-253 [PMID: 16545474 DOI: 10.1016/j.radonc.2006.02.007]
  - 57 **Meeuse JJ**, van der Linden YM, van Tienhoven G, Gans RO, Leer JW, Reyners AK. Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: results from the Dutch Bone Metastasis Study. *Cancer* 2010; **116**: 2716-2725 [PMID: 20225326 DOI: 10.1002/cncr.25062]
  - 58 **Dennis K**, Nguyen J, Presutti R, DeAngelis C, Tsao M, Danjoux C, Barnes E, Sahgal A, Holden L, Jon F, Wong S, Chow E. Prophylaxis of radiotherapy-induced nausea and vomiting in the palliative treatment of bone metastases. *Support Care Cancer* 2012; **20**: 1673-1678 [PMID: 21901298 DOI: 10.1007/s00520-011-1258-x]
  - 59 **Campos S**, Presutti R, Zhang L, Salvo N, Hird A, Tsao M, Barnes EA, Danjoux C, Sahgal A, Mitera G, Sinclair E, DeAngelis C, Nguyen J, Napolskikh J, Chow E. Elderly patients with painful bone metastases should be offered palliative radiotherapy. *Int J Radiat Oncol Biol Phys* 2010; **76**: 1500-1506 [PMID: 19540056 DOI: 10.1016/j.ijrobp.2009.03.019]
  - 60 **Lutz S**, Berk L, Chang E, Chow E, Hahn C, Hoskin P, Howell D, Konski A, Kachnic L, Lo S, Sahgal A, Silverman L, von Gunten C, Mendel E, Vassil A, Bruner DW, Hartsell W. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011; **79**: 965-976 [PMID: 21277118 DOI: 10.1016/j.ijrobp.2010.11.026]
  - 61 **Macbeth FR**, Abratt RP, Cho KH, Stephens RJ, Jeremic B. Lung cancer management in limited resource settings: guidelines for appropriate good care. *Radiother Oncol* 2007; **82**: 123-131 [PMID: 17239979 DOI: 10.1016/j.radonc.2006.12.006]
  - 62 **Kong W**, Zhang-Salomons J, Hanna TP, Mackillop WJ. A



Fairchild A. RT for lung cancer bone metastases

population-based study of the fractionation of palliative radiotherapy for bone metastasis in Ontario. *Int J Radiat Oncol*

*Biol Phys* 2007; **69**: 1209-1217 [PMID: 17967310 DOI: 10.1016/j.ijrobp.2007.04.048]

**P- Reviewer:** Chen XL, Garfield D, Hattori N, Quattrocchi CC  
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