Dose-Fractionation Schedules for Radiotherapy of Bone Metastases

Dirk Rades

Department of Radiation Oncology, University of Lübeck, Germany

Key Words

Bone metastases · Radiotherapy · Bone pain · Pathological fractures · Metastatic spinal cord compression

Summary

Background: Bone metastases are common in breast cancer patients. Radiotherapy is safe and effective. This review aims to contribute to the definition of the appropriate radiation regimens for different endpoints. **Material and Methods:** Information was compiled by searching PubMed and MEDLINE databases including early-release publications. When possible, primary sources were quoted. Full articles were obtained. References were checked for additional material when appropriate. **Results:** Randomized trials and meta-analyses demonstrated that single-fraction radiotherapy with 1×8 Gy is as effective for pain relief as multi-fraction regimens such as 5×4 Gy or 10×3 Gy. Re-irradiation for recurrent pain is required more often after single-fraction radiotherapy. Re-irradiation with another single fraction is safe and effective. Multi-fraction long-course radiotherapy such as 10×3 Gy leads to better re-calcification and better local control of metastatic spinal cord compression (MSCC). Because both re-calcification and MSCC recurrences occur only several months after radiotherapy, long-course radiotherapy is particularly appropriate for patients with a favorable survival prognosis. **Conclusions:** For uncomplicated painful bone metastases, single-fraction radiotherapy with 1×8 Gy may be considered the standard regimen. If re-calcification is a major goal, longer-course radiotherapy (i.e. 10×3 Gy) should be used. For MSCC, 10×3 Gy is preferable for patients with a favorable survival prognosis.

Schlüsselwörter

Knochenmetastasen · Strahlentherapie · Knochenschmerzen · Frakturen, pathologische · Rückenmarkskompression, metastatisch bedingte

Zusammenfassung

Hintergrund: Knochenmetastasen kommen bei Brustkrebspatientinnen häufig vor. Die Strahlentherapie stellt eine sichere und wirksame Behandlung dar. Diese Übersichtsarbeit soll zur Definition geeigneter Strahlentherapie-Regime bei verschiedenen Endpunkten beitragen. **Material und Methoden:** Die Daten wurden durch eine Recherche der Datenbanken von PubMed und MEDLINE inklusive sogenannter „Early-Release Publications“ gewonnen. Wann immer möglich, wurden primäre Quellen zitiert. Vollpublikationen wurden berücksichtigt, und deren Literaturanhang wurde nach weiteren relevanten Quellen durchsucht. **Ergebnisse:** Randomisierte Studien und Metaanalysen haben gezeigt, dass eine Einzeit-Bestrahlung mit 1×8 Gy ähnlich wirksam hinsichtlich des Endpunkts Schmerzerleichterung ist wie die fraktionierten Regime 5×4 Gy oder 10×3 Gy. Nach einer Einzeit-Bestrahlung ist häufiger eine Re-Bestrahlung erforderlich. Eine erneute Einzeit-Bestrahlung derselben Region ist sicher und wirksam. Eine fraktionierte Langzeit-Bestrahlung z.B. mit 10×3 Gy führt zu einer besseren Remineralisierung und zu einer besseren lokalen Kontrolle einer metastatisch bedingten Rückenmarkskompression (MSCC). Da eine Remineralisierung und Rezidive einer MSCC zumeist erst Monate nach Bestrahlung auftreten, ist die Langzeit-Bestrahlung besonders für Patienten mit einer vergleichsweise guten Überlebensprognose geeignet. **Schlussfolgerungen:** Für unkomplizierte schmerzhaftes Knochenmetastasen kann die Einzeit-Bestrahlung mit 1×8 Gy als Standard-Regime angesehen werden. Wird eine Remineralisierung angestrebt, sollte eine Langzeit-Bestrahlung (z.B. 10×3 Gy) erfolgen. Bei der MSCC ist 10×3 Gy bei Patienten mit besserer Überlebensprognose zu bevorzugen.

Introduction

On autopsy, bone metastases are detected in up to 70% of breast cancer patients [1]. If (impending) pathological fractures or spinal cord compression occur, the metastases are defined as ‘complicated’. Without such complications, the metastases are defined as ‘uncomplicated’. Bone metastases are the most common cause of cancer-related pain [2]. With radiotherapy alone, significant pain relief can be achieved in up to 90% of patients, and complete freedom from pain can be expected in up to 50% of patients (tables 1–3) [3–18].

In addition to pain relief, the need for re-irradiation for re-current pain and pathological fractures following radiotherapy are important endpoints for radiotherapy of painful bone metastases. The presence of bone metastases generally is a palliative situation. Patients with a poor survival prognosis may benefit from a radiation regimen with a short overall treatment time in order to avoid that these patients will have to spend much of their limited life span with treatment. However, such a short course of radiotherapy can only be recommended if it is as effective as longer radiotherapy programs. The major goal of this review was to contribute to the definition of the appropriate radiation regimen for different endpoints such as pain relief, pathological fractures, re-calcification, and metastatic spinal cord compression (MSCC).

Table 1. Randomized trials that compared single-fraction to multi-fraction short-course radiotherapy

Trial	Overall pain response	Complete pain relief	Re-irradiation rate	Pathological fracture rate
Cole 1989 (n = 29) [17]				
1 × 8 Gy	88%	not stated	25%	not stated
6 × 4 Gy	85%	not stated	0%	not stated
Breast cancer patients: not stated	(p > 0.05)		(p < 0.05)	
Gaze et al., 1997 (n = 265) [5]				
1 × 10 Gy	84%	39%	not stated	not stated
5 × 4.5 Gy	89% (p > 0.05)	42% (p > 0.05)	not stated	not stated
Breast cancer patients: n = 117 (44%)				
Nielsen et al., 1998 (n = 241) [8]				
1 × 8 Gy	62%	not stated	21%	5%
5 × 4 Gy	71%	not stated	12%	5%
Breast cancer patients: n = 94 (39%)	(p > 0.05)		(p > 0.05)	(p > 0.05)
BPTWP 1999 (n = 761) [3]				
1 × 8 Gy	72%	52%	23%	2%
5 × 4 Gy ^a	68%	51%	10%	<1%
Breast cancer patients: n = 273 (36%)	(p > 0.05)	(p > 0.05)	(p < 0.001)	(p = 0.2)
Steenland et al., 1999 (n = 1171) [12]				
1 × 8 Gy	72%	37%	25%	4%
6 × 4 Gy	69%	33%	7%	2%
Breast cancer patients: n = 451 (39%)	(p = 0.24)	(p > 0.05)	(p < 0.001)	(p < 0.05)
Roos et al., 2005 (n = 272) [11]				
1 × 8 Gy	53%	26%	29%	4%
5 × 4 Gy	61%	27%	24%	4%
Breast cancer patients: n = 23 (8%)	(p = 0.18)	(p = 0.89)	(p = 0.41)	(p > 0.05)

^a2% of patients received 10 × 3 Gy.

Table 2. Randomized trials that compared single-fraction to long-course radiotherapy

Trial	Overall pain response	Complete pain relief	Re-irradiation rate	Pathological fracture rate
Price et al., 1986 (n = 288) [16]				
1 × 8 Gy	21%	9%	11%	not stated
10 × 3 Gy	23%	9%	3%	not stated
Breast cancer patients: n = 107 (37%)				
Koswig and Budach 1999 (n = 107) [7]				
1 × 8 Gy	79%	31%	not stated	not stated
10 × 3 Gy	82%	33%	not stated	not stated
Breast cancer patients: n = 23 (8%)	(p > 0.05)	(p > 0.05)		
Hartsell et al., 2005 (n = 888) [6]				
1 × 8 Gy	65%	15%	18%	5%
10 × 3 Gy	66%	18%	9%	4%
Breast cancer patients: n = ? (~ 50%)	(p = 0.6)	(p > 0.05)	(p < 0.001)	(p > 0.05)
Foro Arnalot et al., 2008 (n = 160) [4]				
1 × 8 Gy	75%	15%	28%	not stated
10 × 3 Gy	86%	13%	2%	not stated
Breast cancer patients: n = 40 (25%)	(p > 0.05)	(p > 0.05)	(p = 0.001)	

Table 3. Randomized trials that compared multi-fraction short-course to long-course radiotherapy

Trial	Overall pain response	Complete pain relief	Re-irradiation rate	Pathological fracture rate
Tong et al., 1982 (n = 146) [13]				
[single metastasis]	82%	53%	not stated	4%
5 × 4 Gy	85%	61%	not stated	18%
15 × 2.7 Gy	(p = 0.82)	(p = 0.42)		(p = 0.02)
Breast cancer patients: not stated				
Tong et al., 1982 (n = 613) [13]				
[multiple metastases]	85%	49%	not stated	5%
5 × 3 Gy	83%	56%	not stated	7%
5 × 4 Gy	78%	49%	not stated	9%
5 × 5 Gy	87%	57%	not stated	8%
10 × 3 Gy	(p = 0.16)	(p = 0.26)		(p > 0.05)
Breast cancer patients: not stated				
Okawa et al., 1988 (n = 80) [15]				
5 × 4.5 Gy	75%	40%	not stated	not stated
10 × 2 Gy	78%	37%	not stated	not stated
15 × 2 Gy	76%	41%	not stated	not stated
Breast cancer patients: n = 17 (21%)	(p > 0.05)	(p > 0.05)		
Rasmusson et al., 1995 (n = 217) [10]				
3 × 5 Gy	69%	not stated	not stated	not stated
10 × 3 Gy	66%	not stated	not stated	not stated
Breast cancer patients: n = 217 (100%)	(p > 0.05)			
Niewald et al., 1996 (n = 100) [9]				
5 × 4 Gy	77%	33%	2%	8%
15 × 2 Gy	86%	31%	2%	12%
Breast cancer patients: n = 43 (43%)	(p > 0.05)	(p > 0.05)	(p > 0.05)	(p > 0.05)

Material and Methods

Review Criteria

The information for this review was compiled by searching the PubMed and MEDLINE databases. Electronic early-release publications were also included. The search terms used included ‘bone metastases’, ‘bone metastasis’, ‘metastatic spinal cord compression’, ‘malignant spinal cord compression’, ‘metastatic epidural spinal cord compression’, ‘malignant epidural spinal cord compression’, ‘pathological fracture’, and ‘skeletal related event’. When possible, primary sources were quoted. Full articles were obtained and references were checked for additional material when appropriate.

Pain Relief

Single-fraction radiotherapy with 8 Gy was not inferior to multi-fraction regimens with respect to pain relief. These results have been confirmed in 3 meta-analyses. The most-important studies are summarized in tables 1–3. Wu et al. [19] compared single-fraction radiotherapy with 1 × 8 Gy to multi-fraction regimens ranging from 5 × 4 Gy to 10 × 3 Gy in 3260 patients from 8 trials. In the per-protocol analysis, 39% of patients after 1 × 8 Gy and 50% of patients after multi-fraction radiotherapy achieved complete pain relief (relative risk (RR) 0.98; 95% confidence interval (CI) 0.89–1.07; p = 0.6). The overall response rates (intention-to-treat analysis) were 73 and 73%, respectively (RR 1.00; 95% CI 0.95–1.04; p = 0.9). Similar results have been demonstrated in the meta-analysis of Sze et al. [20], who included 3621 patients from 12 trials. The complete response rates were 34% after single- and 32% after multi-fraction radiotherapy (odds ratio (OR) 1.10; 95% CI 0.94–1.30, p > 0.05). Overall response rates were

60 and 59%, respectively (OR 1.03; 95% CI 0.90–1.19; p > 0.05). The meta-analysis of Chow et al. [21] included 5000 patients from 16 trials. The overall response rates (intention-to-treat analysis) were 58% after single- (mostly 1 × 8 Gy) and 59% after multi-fraction radiotherapy, mostly with 5 × 4 Gy or 10 × 3 Gy (OR 0.99; 95% CI 0.95–1.03; p = 0.60). Complete pain relief was achieved in 23 and 24% (558/2351) of patients, respectively (OR 0.97; 95% CI 0.88–1.06; p = 0.51).

Recurrent Bone Pain

A comparison of single- and multi-fraction radiotherapy for re-irradiation of recurrent bone pain in the previously irradiated region was performed in 6 trials (tables 1 and 2) [3, 4, 6, 8, 11, 12]. In 4 trials, the re-irradiation rate was significantly higher after single- than after multi-fraction radiotherapy. In the meta-analysis of Wu et al. [19], pooled data were not presented for this endpoint. In the meta-analysis of Sze et al. [20], re-irradiation rates were 22% after single- and 7% after multi-fraction radiotherapy (OR 3.44; 95% CI 2.67–4.43; p < 0.05). In the meta-analysis of Chow et al. [21], re-irradiation rates were 20% after single- and 8% after multi-fraction radiotherapy (OR 2.50; 95% CI 1.76–3.56; p < 0.0001). Whether the need for re-irradiation is really greater with a single-fraction regimen is still unclear. Re-irradiation after single-fraction radiotherapy is safe and effective [22, 23]. Acute toxicity does not exceed grade 2. The response rates after re-irradiation are similar (74–87%) to those after primary radiotherapy. If re-irradiation is required after primary long-course radiotherapy with total doses of ≥ 30 Gy, re-irra-

diation should be preferably delivered using high-precision techniques to better spare healthy tissues and reduce potential late toxicity. High-precision radiotherapy techniques include stereotactic body radiation therapy (SBRT), radiosurgery, and intensity-modulated radiotherapy (IMRT).

Pathological Fractures after Radiotherapy

4 of the 5 trials that investigated the pathological fracture rate in the irradiated region following radiotherapy did not demonstrate a significant difference between single- and multi-fraction radiotherapy (tables 1 and 2) [3, 6, 8, 11]. In the 5th study, more pathological fractures occurred after single-fraction radiotherapy with 1×8 Gy than after 6×4 Gy [12]. In the meta-analysis of Wu et al. [19], pathological fracture rates were not stated. In the meta-analysis of Sze et al. [20], pathological fracture rates were 3.0% after single- and 1.6% after multi-fraction radiotherapy, respectively (OR 1.82; 95% CI 1.06–3.11; $p < 0.05$). In contrast, the more recent and larger meta-analysis of Chow et al. [21] did not demonstrate a significant difference. Pathological fracture rates were 3.2% after single- and 2.8% after multi-fraction radiotherapy (OR 1.10; 95% CI 0.61–1.99; $p = 0.75$). It remains unclear whether single-fraction radiotherapy is associated with a higher rate of pathological fractures than multi-fraction regimens. Regarding the assessment of pathological fractures following radiotherapy, it sometimes may be difficult to distinguish between fractures due to progression/recurrence of osteolytic bone metastases and radiation-induced fractures. However, the biologically effective radiation doses for the treatment of bone metastases are generally far below the tolerance dose of 55 Gy for bone damage.

Toxicity of Radiotherapy

The most common acute side effects are skin reactions. Gastrointestinal toxicity such as nausea/vomiting and diarrhea may occur if the irradiated bone metastases are close to stomach or bowels. There was a trend towards a higher acute toxicity rate with multi-fraction radiotherapy. Foro Arnalot et al. [4] reported 5% grade 2–4 toxicity with 10×3 Gy versus 2% with 1×8 Gy. In another study, acute toxicity rates were 26% in the 5×4.5 Gy group and 22% in the 1×10 Gy group [6]. In the Radiation Therapy Oncology Group (RTOG) 97–02 trial, the acute toxicity rate was significantly higher with 10×3 Gy than with 1×8 Gy (17% versus 10%, $p = 0.002$) [6]. An intermittent aggravation of bone pain ('pain flare') may occur during radiotherapy. Pain flare rates range from 14 to 44% and can be reduced to 3% by prophylactic administration of 8 mg dexamethasone [24–26].

Re-Calcification

In case of an (impending) pathological fracture, surgical stabilization should be performed. Postoperative long-course radiotherapy is required to avoid slackening or dislocation of the osteosynthetic material. Re-calcification of the osteolytic bone, which is best after long-course radiotherapy, can only be expected several months after radiotherapy and is therefore particularly important for patients with a relatively favorable survival prognosis [7]. The survival prognosis of patients with bone metastases can be estimated with the help of a specific scoring system reported by Van der Linden et al. [27]. However, this scoring system was developed in patients with metastases of the vertebral column, and may therefore not be generalized to patients with bone metastases at other locations.

Metastatic Spinal Cord Compression

Radiotherapy alone is effective in the treatment of MSCC in breast cancer patients. In a prospective study of 56 patients, back pain disappeared or lessened in 89% of patients [28]. 4 of 6 patients with urinary dysfunction responded to radiation therapy. Of 35 non-ambulatory patients, 21 patients regained the ability to walk. All 21 patients without motor deficits before treatment maintained good motor performance after radiation therapy. According to a retrospective study of 1304 MSCC patients, single-fraction radiotherapy, multi-fraction short-course radiotherapy, and long-course radiotherapy provided similar functional outcomes [29]. Overall response (improvement or no further progression) was about 85%. Similar results were observed for 335 breast cancer patients [30]. 91% of these patients responded to single fraction/short-course radiotherapy with 1×8 Gy or 5×4 Gy, and 88% of patients responded to long-course radiotherapy with 10×3 Gy, 15×2.5 Gy, or 20×2 Gy ($p = 0.31$). Recurrences of MSCC in the irradiated spinal region (in-field recurrences) are more common after single-fraction and short-course multi-fraction radiotherapy than after long-course radiotherapy. In a retrospective series of 1852 patients, the local control rates at 2 years were 74 and 90%, respectively ($p < 0.001$) [31]. Similar results were described for the subset of breast cancer patients [31]. The local control rates at 2 years were 80 and 90%, respectively ($p = 0.008$). A recent prospective study including various primary tumors also demonstrated long-course radiotherapy to be associated with fewer in-field recurrences [32]. Because patients with a favorable survival prognosis may live long enough to develop a recurrence, these patients should receive long-course radiotherapy. This applies in particular to patients with MSCC from breast cancer, for whom a median survival of 20 months was reported [30]. Survival of patients with MSCC can be estimated with a new scoring system [33]. Patients with a favorable survival prognosis may be consid-

ered candidates for decompressive surgery preceding radiotherapy or for high-precision radiotherapy. Selected patients treated with decompressive surgery followed by long-course radiotherapy had a better post-treatment ambulatory status (84% versus 57%, $p < 0.001$) than patients treated with radiotherapy alone in a small randomized trial of 101 patients [34]. High-precision radiotherapy techniques may be considered to reduce the risk of potential late toxicity.

Radionuclide Therapy

Pain relief from radionuclides is best in osteoblastic lesions, and likely arises from inhibition of pain mediators from normal bone cells, not from a direct effect on the tumor. Strontium-89 and samarium-153 are effective for bone metastases from solid tumors [35–37]. Up to 80% of patients with osteoblastic bone metastases from breast cancer may experience pain relief following strontium-89 administration [35]. Duration of clinical response usually lasts for several months. However, platelet and leukocyte counts usually fall by 25–40%. Samarium is less myelosuppressive than strontium but similarly effective. Because radionuclide therapy is myelosuppressive, chemotherapy can only be safely administered about 6 weeks later.

External-Beam Radiotherapy for Generalized Bone Metastases

External-beam radiotherapy for pain relief may also be administered for carefully selected patients with generalized bone metastases, in particular if they are not candidates for radionuclide therapy. In some countries, hemibody irradiation (HBI) is used [38–40]. HBI is generally administered either as upper HBI (above the umbilicus) or lower HBI (below the umbilicus). In many cases there is overlap between upper and lower HBI as it may be required to include the thoracic-lumbar vertebral column and the pelvic bone in one field. So, instead of HBI, one may use large-field irradiation. The maximum field size achieved with a modern linear accelerator is 40 cm × 40 cm (source-skin distance 100 cm). Lungs are the critical dose-limiting organs. As the pneumonitis rate increases beyond 1×6 Gy, the recommended dose for upper HBI or large-field irradiation above the diaphragm is 1×6 Gy. Below the diaphragm, 1×8 Gy is possible. Splitting the dose into 2 fractions did not show any benefit [39]. Large-

field irradiation is associated with increased acute toxicity compared to local irradiation. Prophylactic administration of antiemetic drugs and dexamethasone is recommended. Bone marrow depression is common and may last up to 6 weeks like after radionuclide therapy. Significant pain relief was observed in 70% of patients after HBI or large-field irradiation [38, 40].

Bisphosphonates

Particularly in patients with a favorable survival prognosis, radiotherapy should be supplemented by bisphosphonates to further enhance re-calcification and to reduce the risk of an in-field recurrence of MSCC following radiotherapy. Studies demonstrated the efficacy of bisphosphonates in reducing the rates of pathological fractures and MSCC [41–42]. Zoledronic acid demonstrated the broadest clinical activity [42]. In a randomized trial of 1130 breast cancer patients, it was superior to pamidronate [43]. Zoledronic acid can cause well-manageable flu-like symptoms. Renal monitoring is recommended, with dose reductions for patients with renal dysfunction. Long-term use of bisphosphonates is associated with a risk of osteonecrosis of the jaw [44]. Other agents such as the RANK-ligand inhibitor denosumab may also reduce the risk of skeletal-related events such as pathological fractures and MSCC [45].

Conclusions

For uncomplicated painful bone metastases, single-fraction radiotherapy with 1×8 Gy may be considered the standard regimen. If re-calcification of the osteolytic bone is a major goal of treatment, longer-course radiotherapy with 10×3 Gy should be used. In case of an (impending) fracture, mechanical stabilization should be performed, followed by 10×3 Gy of radiotherapy. For MSCC, 10×3 Gy is superior to 1×8 Gy and 5×4 Gy. Because both re-calcification of the osteolytic bone and in-field recurrences of MSCC generally occur only several months following radiotherapy, 10×3 Gy is preferable in patients with a relatively favorable survival prognosis.

Conflict of Interest

Amgen: advisory board, honoraria for presentations. Novartis Oncology: research grant, honoraria for presentations.

References

- 1 Coleman RE: Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006;12(suppl):6243s–6249s.
- 2 Coleman RE, Rubens R: The clinical course of bone metastases in breast cancer. *Br J Cancer* 1987;77:336–340.
- 3 Bone Pain Trial Working Party: 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain (randomised comparison with a multifraction schedule over 12 months of patient follow-up). *Radiother Oncol* 1999;52:111–121.
- 4 Foro Arnalot P, Fontanals AV, Galcerán JC, Lynd F, Latiesas XS, de Dios NR, Castillejo AR, Bassols ML, Galán JL, Conejo IM, López MA: Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. *Radiother Oncol* 2008;89:150–155.

- 5 Gaze MN, Kelly CG, Kerr GR, Cull A, Cowie VJ, Gregor A, Howard GCW, Rodger A: Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. *Radiother Oncol* 1997;45:106–116.
- 6 Hartsell WF, Scott CB, Bruner DW, Scarantino CW, Ivker RA, Roach M 3rd, Suh JH, Demas WF, Movsas B, Petersen IA, Konski AA, Cleeland CS, Janjan NA, DeSilvio M: Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst* 2005;97:798–804.
- 7 Koswig S, Budach V: Remineralization and pain relief in bone metastases after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study. *Strahlenther Onkol* 1999;175:500–508.
- 8 Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR: Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiother Oncol* 1998;47:233–240.
- 9 Niewald M, Tkocz HJ, Abel U, Scheib T, Walter K, Nieder C, Schnabel K, Berberich W, Kubale R, Fuchs M: Rapid course radiation therapy vs. more standard treatment: a randomized trial for bone metastases. *Int J Radiat Oncol Biol Phys* 1996;36:1085–1089.
- 10 Rasmussen B, Vejborg I, Jensen AB, Andersson M, Banning AM, Hoffmann T, Pfeiffer P, Nielsen HK, Sjøgren P: Irradiation of bone metastases in breast cancer patients: a randomized study with 1 year follow-up. *Radiother Oncol* 1995;34:179–184.
- 11 Roos DE, Turner SL, O'Brien PC, Smith JG, Spry NA, Burmeister BH, Hoskin PJ, Ball DL; Trans-Tasman Radiation Oncology Group, TROG 96.05: 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.
- 12 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.
- 13 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;50:893–899.
- 14 Souchon R, Wenz F, Sedlmayer F, Budach W, Dunst J, Feyrer P, Haase W, Harms W, Sautter-Bühl ML, Sauer R: German Society of Radiation Oncology (DEGRO): DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: bone metastases and metastatic spinal cord compression (MSCC). *Strahlenther Onkol* 2009;185:417–424.
- 15 Okawa T, Kita M, Goto M, Nishijima H, Miyaji N: Randomized prospective clinical study of small, large and twice-a-day fraction radiotherapy for painful bone metastases. *Radiother Oncol* 1988;13:99–104.
- 16 Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR: Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986;6:247–255.
- 17 Cole DJ: A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Oncol (R Coll Radiol)* 1989;1:59–62.
- 18 Chow E, Wu JS, Hoskin P, Coia LR, Bentzen SM, Blitzer PH: International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Radiother Oncol* 2002;64:275–280.
- 19 Wu JS, Wong R, Johnston M, Bezjak A, Whelan T: Cancer Care Ontario Practice Guidelines Initiative Supportive Care Group: Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003;55:594–605.
- 20 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* 2003;15:345–352.
- 21 Chow E, Harris K, Fan G, Tsao MN, Sze WM: Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007;25:1423–1436.
- 22 Jeremic B, Shibamoto Y, Igrutinovic I: Single 4 Gy re-irradiation for painful bone metastases following single fraction radiotherapy. *Radiother Oncol* 1999;52:123–127.
- 23 Mithal N, Needham P, Hoskin P: Retreatment with radiotherapy for painful bone metastases. *Int J Radiat Oncol Biol Phys* 1994;29:1011–1014.
- 24 Chow E, Ling A, Davis L, Panzarella T, Danjoux C: Pain flare following external beam radiotherapy and meaningful change in pain scores in the treatment of bone metastases. *Radiother Oncol* 2005;75:64–69.
- 25 Chow E, Loblaw A, Harris K, Doyle M, Goh P, Chiu H, Panzarella T, Tsao M, Barnes EA, Sinclair E, Farhadian M, Danjoux C: Dexamethasone for the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases – a pilot study. *Support Care Cancer* 2008;15:643–647.
- 26 Loblaw DA, Wu JS, Kirkbride P, Panzarella T, Smith K, Aslanidis J, Warde P: Pain flare in patients with bone metastases after palliative radiotherapy – a nested randomized control trial. *Support Care Cancer* 2007;15:451–455.
- 27 Van der Linden YM, Dijkstra SP, Vonk EJ, Marijnen CA, Leer JW; Dutch Bone Metastasis Study Group: Prediction of survival in patients with metastases in the spinal column. Results based on a randomized trial of radiotherapy. *Cancer* 2005;103:320–328.
- 28 Maranzano E, Latini P, Checchini F, Perrucci E, Aristei C, Panizza BM, Ricci S: Radiation therapy of spinal cord compression caused by breast cancer: report of a prospective trial. *Int J Radiat Oncol Biol Phys* 1992;24:301–306.
- 29 Rades D, Stalpers LJ, Veninga T, Schulte R, Hoskin PJ, Obralic N, Bajrovic A, Rudat V, Schwarz R, Hulshof MC, Poortmans P, Schild SE: Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *J Clin Oncol* 2005;23:3366–3375.
- 30 Rades D, Veninga T, Stalpers LJA, Schulte R, Hoskin PJ, Poortmans P, Schild SE, Rudat V: Prognostic factors predicting functional outcome, recurrence-free survival, and overall survival after radiotherapy of metastatic spinal cord compression in breast cancer patients. *Int J Radiat Oncol Biol Phys* 2006;64:182–188.
- 31 Rades D, Fehlauer F, Schulte R, Veninga T, Stalpers LJ, Basic H, Bajrovic A, Hoskin PJ, Tribius S, Wildfang I, Rudat V, Engenhart-Cabill R, Karstens JH, Alberti W, Dunst J, Schild SE: Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. *J Clin Oncol* 2006;24:3388–3393.
- 32 Rades D, Lange M, Veninga T, Stalpers LJ, Bajrovic A, Adamietz IA, Rudat V, Schild SE: Final results of a study comparing short-course and long-course radiotherapy (RT) for local control of metastatic spinal cord compression (MSCC). *J Clin Oncol* 2009;27(suppl):abstr 9522.
- 33 Rades D, Dunst J, Schild SE: The first score predicting overall survival in patients with metastatic spinal cord compression. *Cancer* 2007;112:157–161.
- 34 Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, Mohiuddin M, Young B: Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* 2005;366:643–648.
- 35 Robinson RG, Preston DF, Baxter KG, Dusing RW, Spicer JA: Clinical experience with strontium-89 in prostatic and breast cancer patients. *Semin Oncol* 1993;20:44–48.
- 36 Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Ell PJ, Bertrand A, Ahmann FR, Orihuela E, Reid RH, Lerski RA, Collier BD, McKillop JH, Purnell GL, Pecking AP, Thomas FD, Harrison KA: Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: A double-blind placebo-controlled trial. *J Clin Oncol* 1998;16:1574–1581.
- 37 Kraeber-Bodéré F: Treatment of bone metastases of prostate cancer with strontium-89 chloride: efficacy in relation to the degree of bone involvement. *Eur J Nucl Med* 2000;27:1487–1493.
- 38 Hoskin PJ, Ford HT, Harmer CI: Hemibody irradiation (HBI) for metastatic bone pain in two histological distinct groups of patients. *Clin Oncol* 1989;1:67–69.
- 39 Salazar OM, Sandhu T, da Motta NW, Escutia MA, Lanzós-Gonzales E, Mouelle-Sone A, Moscol A, Zaharia M, Zaman S: Fractionated half-body irradiation (HBI) for the rapid palliation of widespread, symptomatic, metastatic bone disease: a randomized phase III trial of the International Atomic Energy Agency (IAEA). *Int J Radiat Oncol Biol Phys* 2001;50:765–775.
- 40 Salazar OM, Rubin P, Hendrickson FR, Komaki R, Poulter C, Newall J, Asbell SO, Mohiuddin M, Van Ess J: Single-dose half-body irradiation for palliation of multiple bone metastases from solid tumors. Final Radiation Therapy Oncology Group report. *Cancer* 1986;58:29–36.
- 41 Berenson JR, Hillner BE, Kyle RA, Anderson K, Lipton A, Yee GC, Biermann JS; American Society of Clinical Oncology Bisphosphonates Expert Panel: American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2002;20:3719–3736.
- 42 Santini D, Fratto ME, Vincenzi B, Galluzzo S, Tonini G: Zoledronic acid in the management of metastatic bone disease. *Expert Opin Biol Ther* 2006;6:1333–1348.
- 43 Rosen LS, Gordon DH, Dugan W Jr, Major P, Eisenberg PD, Provencher L, Kaminski M, Simeone J, Seaman J, Chen BL, Coleman RE: Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004;100:36–43.
- 44 Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL: Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. *J Oral Maxillofac Surg* 2004;62:527–534.
- 45 Body JJ, Lipton A, Gralow J, Steger GG, Gao G, Yeh H, Fizazi K: Effects of denosumab in patients with bone metastases, with and without previous bisphosphonate exposure. *J Bone Miner Res* 2010;25:440–446.