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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 aimes 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 schmerzhafte 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.

KARGER

Fax +49 761 4 52 07 14
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Prof. Dr. med. Dirk Rades
Klinik für Strahlentherapie (Radioonkologie)
Universitätsklinikum Schleswig-Holstein, Campus Lübeck
Ratzeburger Allee 160, 23538 Lübeck, Germany
Tel. +49 451 500-6661, Fax -3324
rades.dirk@gmx.net

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 recurrent 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)

[a]2% 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 radionucleotides 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.

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