

Radiotherapy of Bone Metastasis in Breast Cancer Patients – Current Approaches

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Keywords

Bone metastasis · Radiotherapy · Breast cancer, metastatic

Summary

Bone metastases (BM) represent the most frequent indication for palliative radiotherapy in patients with breast cancer. BM increase the risk of skeletal-related events defined as pathological fractures, spinal cord compression, and, most frequently, bone pain. The therapeutic goals of palliative radiotherapy for BM are pain relief, recalcification, and stabilization, reducing spinal cord compression and minimizing the risk of paraplegia. In advanced tumor stages radiotherapy may also be used to alleviate symptoms of generalized bone metastasis. This requires an individual approach including factors, such as life expectancy and tumor progression at different sites. Side effects of radiation therapy of the middle and lower spine may include nausea and emesis requiring adequate antiemetic prophylaxis. Irradiation of large bone marrow areas may cause myelotoxicity making monitoring of blood cell counts mandatory. Radiotherapy is an effective tool in palliation treatment of BM and is part of an interdisciplinary approach. Preferred technique, targeting, and different dose schedules are described in the guidelines of the German Society for Radiooncology (DEGRO) which are also integrated in 2012 recommendations of the Working Group Gynecologic Oncology (AGO).

Schlüsselwörter

Ossäre Metastasen · Radiotherapie · Mammakarzinom, metastasiertes

Zusammenfassung

Knochenmetastasen (KM) stellen die häufigste Indikation für eine palliative Therapie bei Patienten mit Mammakarzinom dar. Sie erhöhen das Risiko skelettbezogener Ereignisse, definiert als pathologische Frakturen, Rückenmarkskompression und die am häufigsten auftretenden Knochenschmerzen. Die therapeutischen Ziele einer Radiotherapie bei KM sind sowohl Schmerzreduktion, Rekalzifizierung und Stabilisierung des Knochens als auch eine Reduktion der Rückenmarkskompression und die Minimierung des Risikos für die Entwicklung neurologischer Symptome. Dies erfordert eine differenzierte Herangehensweise, die individuelle Faktoren wie Lebenserwartung und Tumorprogression an den verschiedenen Manifestationsorten einbezieht. Dosierungskonzept und Fraktionierung einer palliativen Radiotherapie sollten entsprechend adaptiert werden. Als Nebenwirkungen einer Strahlentherapie der mittleren und unteren Wirbelsäule können Nausea und Emesis auftreten, die eine adäquate antiemetische Prophylaxe erfordern. Die Bestrahlung von größeren Knochenmarkabschnitten kann myelotoxisch wirken, regelmäßige Blutbildkontrollen sind obligatorisch. Die Radiotherapie ist eine effektive palliative Therapie und ist Bestandteil des interdisziplinären Vorgehens. Bevorzugte Techniken, Zielstrukturen und Dosierungskonzepte werden in den Leitlinien der Deutschen Gesellschaft für Radioonkologie (DEGRO) beschrieben, die auch in den Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)-Leitlinien 2012 integriert sind.

Introduction

Bone metastasis represents the most frequent indication for palliative radiotherapy in patients with breast cancer. About 70% of the patients with bone metastases suffer from pain [1, 2]. Osteolytic, osteoplastic, and mixed forms of metastasis are observed. Irrespective of the type and depending upon site, skeletal metastasis may lead to complications such as pain, stability endangerment, or the risk of spinal cord compression. In the interest of the patient a rapid introduction of treatment is advisable. The additional application of anti-resorptive agents (e.g., bisphosphonates or the receptor activator of nuclear factor- κ B (RANK) ligand inhibitor denosumab) has proven successful [3–5].

Indication

Bone pain, fracture risk, movement limitations after surgery of fractures due to bone metastasis, and the risk of spinal cord compression are indications for palliative radiotherapy [6]. Radiotherapy is also recommended for asymptomatic patients with favorable prognostic factors. The updated Working Group Gynecologic Oncology (AGO) breast cancer guidelines focus in detail on the treatment of bone metastases in breast cancer patients [7, 8] (table 1).

The goals of palliative radiotherapy are pain alleviation, recalcification and stabilization of the bone as well as minimizing the risk of paraplegia. In singular or oligometastasis, further disease progression with the expected complications is stopped by high-dose radiotherapy of the affected skeletal manifestation. While pain relief is generally observed within a few days after the start of radiotherapy, radiologically detectable recalcification and stabilization are to be expected at the earliest within 6–12 weeks after termination of radiotherapy.

Therapy Strategies for Pain Relief

The Canadian working group of Wu and colleagues suggested guidelines for the radiotherapy of bone metastasis based on a comprehensive literature search [9]. For painful bone metastasis in not previously irradiated areas without stability endangerment, without an extraskeletal proportion, and without

Table 1. Guidelines for the treatment of bone metastases [8]

Therapeutic goal: pain reduction
Single-dose RT 1 \times 8 Gy (cave: >8 Gy to the myelon may cause paresis) (LoE 3)
Therapeutic goal: stabilization, good prognosis
Fractionated regimen preferable, e.g. 10–12 \times 3 Gy (LoE 2b)
Oligometastases
Full dose fractionated regimen recommended, e.g. 20–25 \times 2 Gy to 40–50 Gy (LoE 2b)

RT = Radiotherapy, LoE = level of evidence.

risk of spinal cord compression one single fraction with 8 Gy is recommended. Dose intensification or fractionated irradiation does not result in a better analgesic effect in these patients. The advantage for the patient is the short duration of radiation therapy. As far as we know today, acute side effects as well as late toxicities are not increased.

In a Cochrane review on radiotherapy for bone metastasis 11 studies were pooled for metaanalysis and 3,487 painful metastatic lesions were examined. Pain alleviation amounted to 59–60%, with a complete pain recovery in 32–34% of patients, independent of the fractionation [10]. The analgesic effect of radiotherapy after high single doses is achieved earlier but is of shorter duration. Patients who received a one-time irradiation of 8 Gy showed a higher rate of pain recurrence and more frequently needed re-irradiation (21.5 vs. 7.4% with fractionated irradiation). The rate of pathological fractures was slightly increased after one-time irradiation (3 vs. 1.6% after fractionated irradiation). The risk of spinal cord compression due to metastatic progression was similar with both procedures. The conclusion was drawn that a single fraction of 8 Gy is equally effective as an alternative fractionating for pain relief, but the risk for re-irradiation and pathological fractures is increased.

After publication of the Cochrane review the Dutch Bone Study Group published their results with re-irradiation [11]. If an increase of pain occurred in the pre-irradiated area, a comparable palliative effect by re-irradiation was observed in 63% of patients. The long-term results concerning pain relief after re-irradiation were thus comparable in both arms, with a palliative effect of more than 70% [11].

Patients prefer different therapy patterns regarding fractionation. Patients in a good general health status would rather select fractionated irradiation. This decision is justified with a smaller re-irradiation rate and smaller fracture rate as both parameters significantly affect quality of life [12]. Therefore, the decision should be taken in agreement of radiotherapist and patient.

Based on the data of a prospective randomized study including 342 patients with symptomatic bone metastasis, the Dutch Bone Metastasis Study Group compiled a score to estimate survival. Significant prognostic factors for survival with bone metastasis were Karnofsky index, type of the primary tumor, and visceral metastasis. Female patients with breast cancer in good general health and without visceral metastasis had the best prognosis with a median survival of 18.7 months [13]. Rades et al. showed that dose escalation improves local control and survival in patients with favorable prognostic factors [14].

Therapy Results for Recalcification and Stabilization

If the goal of therapy is recalcification, radiotherapy should be fractionated. Also with extraskeletal tumor proportions or

large irradiation volumes a fractionated radiotherapy with an adapted dosage of 5×4 Gy or 10×3 Gy should be used. In case of favorable prognostic factors, the dose can be escalated.

Recalcification is accelerated by concomitant bisphosphonate therapy. It is achieved in more than 80% of patients [15]. Results regarding the simultaneous application of denosumab are still outstanding. Recalcification and stabilization of the bone are detectable with X-ray after 6 weeks at the earliest, usually after 10–12 weeks after radiotherapy. Up to this time, the risk of fracture still exists. Therapy of patients with acute risk of fracture by expanded bone metastasis should be discussed by multiprofessional teams. It must be estimated whether stabilization surgery is necessary before radiotherapy.

Therapy Results for Spinal Cord Compression

Spinal cord compression can be induced by tumor infiltration of the spinal space or by intraspinal metastases. On suspicion of metastatic spinal cord compression, magnetic resonance imaging (MRI) should be performed [16]. For the evaluation of stability or risk of fracture with spine metastasis, an additional computed tomography (CT) scan is helpful [17].

Symptomatic patients should immediately receive a bolus injection of dexamethasone, followed by dexamethasone maintenance therapy. The pre-therapeutic degree of function restriction and the interval between onset of neurological symptoms and the beginning of therapy is of prognostic importance for neurological function. The therapeutic decision must be taken by an interdisciplinary team. An interval longer than 24 h between the development of paresis and the start of therapy is prognostically unfavorable, the chance of symptom recovery small. Spinal cord compression requires immediate emergency therapy [18–20]. Patients able to walk to the radiation unit have a chance of 80% to remain mobile. For already existing paraparesis, a chance of around 40% for improvement and to regain the ability to walk is described, for patients with paraplegia there is only a chance of 7%. Therefore, these patients have to be treated as emergency patients [15]. Radiation therapy is initiated with high single doses of 3–4 Gy and cortisone protection. Doses between 12 and 20 mg of dexamethasone are recommended. An advantage of a higher steroid dose has not been clearly confirmed. Surgical decompression is the therapy of choice for instability and in case of neurological symptoms. In a prospective randomized trial surgical decompression followed by radiotherapy showed significantly improved neurological results compared to radiotherapy alone, in particular regarding walking ability [22, 23].

Due to the high recurrence risk because of incomplete tumor resection a postoperative palliative radiotherapy is usually indicated [16]. For patients without neurological symptoms radiotherapy is the treatment of choice, with frac-

tionation (short-term therapy with 1×8 Gy or 5×4 Gy vs. 10×3 Gy or 20×2 Gy) depending on the overall prognosis of the patient [24, 25]. Upon occurrence or deterioration of neurological symptoms during radiotherapy and steroid application a laminectomy has to be considered, taking in consideration the overall prognosis of the patient.

Rades et al. examined the prognostic factors for spinal cord compression due to metastasis [26] and developed a prognosis score for function preservation after therapy. 2,096 patients were analyzed retrospectively; the score was prospectively tested in 653 patients. In particular a long interval from first diagnosis until metastasis (>15 vs. <15 months), additional visceral metastasis (prognostically unfavorable), motoric function before beginning of radiotherapy (able to walk vs. paraplegia), and the time interval of the development of the neurological deficits until beginning of radiotherapy (1 day vs. 14 days) are prognostically relevant. Patients with a high score (unfavorable prognosis) do not profit from radiotherapy concerning the re-establishing or improvement of function. However, in order to avoid further loss of function and to alleviate pain, these patients should still receive irradiation. They should be irradiated only; additional surgery is not of advantage. Patients with a medium prognostic score should undergo combined treatment (laminectomy with stabilization and radiotherapy).

Several randomized clinical trials investigated the dosage and fractionation of radiotherapy. The results show that dosage should depend on the prognosis of the patient. Rades et al. examined the influence of the fractionation schedule on neurological function and local control. [27]. In this randomized study including 265 patients a short-term irradiation pattern with 1×8 Gy or 5×4 Gy was compared to a long-term pattern 10×3 Gy or 15×2.5 Gy. After 1 year, local control in the long-term arm was definitely superior to the short-term arm (61 vs. 81%). However, function improvement between the two application schedules was not significantly different (37 vs. 39%). Also, the 1-year survival rate was not significantly different. In conclusion, in patients with unfavorable prognostic factors a short-term pattern is to be preferred, for patients with a prognosis of at least 6 months a long-term pattern is recommended.

Rades et al. [28] evaluated if patients with favorable survival prognosis benefit from a dose escalation beyond 30 Gy. Data from 191 patients treated with 30 Gy in 10 fractions were matched to 191 patients (1:1) receiving higher doses (37.5 Gy in 15 fractions or 40 Gy in 20 fractions). All patients had favorable survival prognoses based on a validated scoring system and were matched for age, gender, tumor type, performance status, number of involved vertebrae, visceral or other bone metastases, interval from tumor diagnosis to radiotherapy, ambulatory status, and time to developing motor deficits. Both groups were compared for local control, progression-free survival, overall survival, and functional outcome. Local control rates at 2 years were 71% after 30 Gy and

92% after higher doses ($p = 0.012$). 2-year progression-free survival rates were 68 and 90%, respectively ($p = 0.013$); 2-year overall survival rates were 53 and 68%, respectively ($p = 0.032$). Results maintained significance in multivariate analyses (Cox proportional hazards model; stratified model) with respect to local control ($p = 0.011$; $p = 0.012$), progression-free survival ($p = 0.010$; $p = 0.018$), and overall survival ($p = 0.014$; $p = 0.015$). Functional outcome was similar in both groups. Motoric function improved in 40% of patients after 30 Gy and in 41% after higher doses ($p = 0.98$). In conclusion, escalation of the radiation dose beyond 30 Gy resulted in significantly better local control, progression-free survival, and overall survival in patients with favorable survival prognoses. On the other hand, patients with limited prognosis and reduced performance status can benefit from single irradiation with 6–8 Gy.

Therapy Recommendations for Patients with Generalized Bone Metastasis

In advanced tumor stages skeletal metastases with diffuse pain occur frequently. If pain is refractory to analgesic drug treatment there are 2 alternative procedures that can be used: radionuclide therapy or half-body irradiation.

Half-Body Irradiation

Upper or lower half-body irradiation is directed to the main manifestations of painful bone metastases. Adequate supportive therapy with antiemetics and control of blood cell count are mandatory [29]. For these patients hospital treatment is recommended. A Polish publication showed that pain recovery is observed in 75–91% of patients irradiated with this large-field technique [30, 31].

Salazar et al. recommend an accelerated irradiation with single doses of 3 Gy twice daily on 2 consecutive days (total dose: 12 Gy). Complete pain control was achieved in 91% and relief of pain in 45% of patients [32]. Comparable results can be obtained using radiation with 3 Gy in 5 consecutive fractions (total dose: 15 Gy). Alternatively, a single irradiation of the upper half of the body with 6 Gy or the lower half of the body with 8 Gy can be applied. The acute side effects, however, are slightly increased. Today half-body irradiation is used rarely because of potential side effects.

Radionuclide Therapy

Radionuclide therapy is recommended if osteoblastic skeletal metastases with pain symptoms are predominant and if increased tracer enrichment in the bone scintigram could be detected. Palliative pain therapy with a radionuclide is given as intravenous injection of soluble radioactive drugs (Sr-89-chloride, Re-186-HEDP, Sm-153-EDTMP). These radionuclides differ in their physical characteristics, i.e. energy and half-life

time. At present, samarium and rhenium with short half-lives are preferred.

A sufficient interval should be kept after a previous myelotoxic chemotherapy or half body irradiation (4–6 weeks). Re-treatment should only be performed after the regeneration of blood cell count. This also applies to a planned chemotherapy or radiotherapy after radionuclide therapy, since myelosuppression can occur with some delay. Heron et al. [33] did not see dose-limiting myelotoxicity in their patients even after repeated therapy with samarium. The analgesic effect occurs only after approximately 1–3 weeks. 60–80% of patients respond to this approach, 50% even with complete pain recovery [34]. Leondi et al. [35] achieved good pain relief after rhenium-186-HEDP-therapy in patients with skeletal carcinosis from lung cancer. At the beginning, 22 out of 24 patients had morphine requiring pain. After therapy with rhenium-186-HEDP pain relief was obtained in more than half of the patients, most patients could reduce and some of them terminate the morphine administration. Almost all patients described an improvement in quality of life. Myelotoxicity occurred in one patient only.

Side Effects of Radiation Therapy

Radiotherapy of skeletal metastases within the area of the middle and lower spine can lead to nausea, emesis, and diarrhea. These patients should receive antiemetic prophylaxis before irradiation with high single doses [36, 37]. If large bone marrow areas are irradiated, regular controls of blood cell counts are mandatory.

Conclusion

Radiotherapy is an effective treatment option in the therapy concept of bone metastases. It plays a central role in the interdisciplinary approach and can effectively control neurological pain symptoms. Prevention of skeletal events is one of the goals of palliative radiotherapy in patients with bone metastases. Dose fractionation and the type of radiotherapy must be tailored to each patient individually taking into account the patient's perspective, goals of treatment, and prognosis. Radiotherapy should be started as early as needed. The combination with bisphosphonates or RANK ligand inhibitors should be considered. Re-irradiation is possible in most of the cases due to modern irradiation techniques and planning methods. Irradiation should be performed with higher doses per fraction and short overall treatment time if the performance status of the patient is poor and the live expectancy is limited. Selection of an individual palliative treatment concept including radiotherapy should be performed in a multidisciplinary and multiprofessional team [38, 39].

Disclosure Statement

The authors confirm that there are no primary financial relationships with any companies.

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