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Original research article

Radiation therapy for the management of painful bone metastases: Results from a randomized trial

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ABSTRACT

Aim: The aim of this study was to compare the effectiveness of two radiotherapy schedules in patients with bone metastases.
Background: We analyzed the need for re-irradiation, rates of pain control, pathological fractures, and functionality in patients randomized to single-fraction (8 Gy 1×) or multiple-fraction radiotherapy (3 Gy 10×) with at least 12 months follow-up, during five years. The hypothesis was that the two radiotherapy schedules are equally effective.
Materials and methods: Ninety patients with painful skeletal metastases were randomized to receive single fraction (8 Gy) or multiple fraction (3 Gy 10×) radiotherapy.
Results: In the single-fraction group, seven pathological fractures occurred (15.5%) versus two (4.4%) in the multiple-fraction group. There was no statistically significant difference between the time it took to suffer a pathological fracture in both groups ($p = 0.099$). Patients in the single-fraction group received twelve re-irradiations (26.6%), four in the multiple-fraction group (8.8%), with no significant difference between time elapsed before the first re-irradiation ($p = 0.438$).
Conclusion: This study shows no difference between the two groups for the majority of patients with painful bone metastases. Patients were followed up during five years, and the trial showed no disadvantage for 8 Gy 1× compared to 3 Gy 10×. Despite the fact that the pathological fracture rate is 3.75 times higher in the single-fraction group, this schedule is considered more convenient for patients and more cost-effective for radiotherapy departments.

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1. Background

Bone metastases are a common manifestation of distant relapse for many types of solid cancer, especially those arising in the lung, breast and prostate. This condition is associated with significant and debilitating pain, compression of the spinal cord, reduced physical function and pathological fractures.

Almost 80% of patients with solid tumors will develop painful bone metastases to the spine, pelvis and extremities during the course of their illness.[1] The goals of palliative treatment of bone metastases are pain relief, preservation of function, and maintenance of skeletal integrity. When bone pain is limited to a single or a limited number of sites, local field external beam radiation therapy (EBRT) to the painful sites can provide pain relief in 80–90% of cases,[2,3] with complete pain response obtained in 50–60%.[3–5]

There is strong evidence that pain relief lasts for at least 6 months in at least 50% of the patients.[2] Although treatment can be effective for patients with mild, moderate and severe pain, early interventions may be useful in maintaining the quality of life and minimizing side effects of analgesic medications.[6] In addition to relieving pain, radiotherapy may prevent pathological fractures, maintain activity and mobility, and, rarely, prolong survival. Although almost all the patients eventually die of their disease, some survive for several years. So, finding the optimal palliative treatment both with a short and long-term perspective is crucial.

Several systematic reviews and randomized studies have compared 8 Gy single-fraction radiotherapy with a multifraction schedule. These two regimens are now considered equivalent regarding pain control and the need for analgesics is similar whether a single or multiple fractions are received, without significant difference in the incidence of spinal cord compression.[7–9] On the other hand, some reports indicate that patients receiving a single-fraction experience more pathological fractures and are more likely to be treated with re-irradiation to the same site compared to patients receiving multiple fractions.[7–11] Some authors argued that for patients with a relatively long live expectancy, a fractionated regimen may be considered.[7]

2. Aim

The aim of this study was a global assessment of the results in the control of pain, duration of response and retreatment rate comparing patients who received a single-fraction radiotherapy (8 Gy 1×) and a multiple-fraction therapy (3 Gy 10×) in a prospective-randomized study with five years of follow-up. Secondary objectives were: assessment of the functional response of the patient; evaluation of the rate of recalcification and evaluation of the incidence of pathologic fractures.

3. Materials and methods

We performed a prospective randomized study of 98 patients diagnosed with metastatic disease to the bone level, treated in the Radiation Oncology Department in Puerta del Mar Universitary Hospital in Cádiz, Spain, who were treated between January 2005 and December 2006. Follow-up had been discontinued for four patients because of aggravated conditions and another four patients were excluded because of incomplete records. Thus, a total of 90 patients with painful bone metastases were included in the present analysis (Table 1).

Considered for inclusion in this study were valid patients with histologically proven malignant primary tumor (biopsy, cytology) or radiological confirmation of metastatic bone lesion (verified either by bone X-ray, bone scan, computer tomography (CT) or magnetic resonance imaging (MRI)). There were no restrictions regarding the site of bone metastases. We excluded patients with Karnofsky Performance below 50%, those who had large bony lesions on the spine or pelvis that required orthopedic surgery (before or after a pathological fracture) and those who manifested spinal cord compression, patients with poor prognosis with life expectancy less than 6 weeks. We did not include patients that had previously undergone radiotherapy to the actual symptom site, and those unable to complete the quality of life assessment tools. The study pre-treatment of patients included in this study was to conduct a thorough history and physical examination usually with blood count and biochemistry. Assessment of pain was done according to visual analogue scale (VAS) (0–10 with 0: absent pain, and 10: maximum pain imaginable).[12] We assessed the state of functionality, such as degree of impairment of mobility and quality of life,[13] according to the following scale based on Barthel index of activities of daily living: 1 – normal use without pain (100 total independence (90 being high if the patient uses a wheelchair)); 2 – normal use with pain (60 small dependence); 3 – use is significantly limited (35–55 moderate dependence); 4 – no functionality (<35 severe dependence). Also, we made an assessment of the analgesia-requirements. Clinical and radiological findings determined the target volume. If the patient had more than one index site, all targets were treated at the same time. In the case of lesions in the long bones or pelvis, we took a 4 cm margin of apparently normal bone, or above the articular surface, encompassing the wide-spread bone lesion, and lesions of the spine; patients were treated with a single field, with calculation of dose to the depth of 6 cm, involving the affected vertebra and two vertebrae above and below, following the protocol of the RTOG 74-02. The radiation therapy was delivered using a linear accelerator with 6 or 15 MV photon energy, with three-dimensional conformal techniques. 45 patients (50%) received a traditional scheme of 30 Gy in 10 fractions 3 Gy per fraction, 5 fractions per week. The remaining patients (50%) received a single-fraction radiotherapy (8 Gy 1×). Patients were evaluated weekly during treatment for acute toxicity, need of analgesic treatment or modification of other concurrent medications, in addition to the response to treatment. After radiation treatment, the following assessments were made: pain, following the VAS, and the response to pain (complete: without pain, good: two or more levels down the pain, poor or slight: only decreases the pain level, null: remains unchanged); state of functionality: the degree of disruption and, following the same scale as in the initial study prior to treatment; requirements for analgesia (measuring the response as: complete: no pain without analgesia, good or partial: precise