Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

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

Lucia Gutiérrez Bayard[a,*], *María del Carmen Salas Buzón*[a], *Esther Angulo Paín*[b], *Lourdes de Ingunza Barón*[a]

[a] *RadiotherapyOncology Department, UCG Atención Integral al Cáncer, H.U.Puerta del Mar, Cádiz, Spain*
[b] *Radiophysics and Radioprotection Department, Spain*

ARTICLE INFO

Article history:
Received 30 May 2013
Received in revised form
31 January 2014
Accepted 10 April 2014

Keywords:
Bone metastases
Palliation painful bone metastases
Radiotherapy fractionation
Palliative radiotherapy

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.

* *Corresponding author at*: H.U. Puerta del Mar, Av. Ana de Viya n° 21, 11009 Cádiz, Spain. Tel.: +34 616 270158; fax: +34 956003077.
E-mail address: guillermoylucia@gmail.com (L. Gutiérrez Bayard).
http://dx.doi.org/10.1016/j.rpor.2014.04.009

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

Table 1 – Baseline characteristics of the patients.

	8 Gy 1×	3 Gy 10×	Total	p
Number of patients	45 (50%)	45 (50%)	90 (100%)	
Age mean	62.6	61.8	62.2	
Gender				0.830
Male	28 (62.2%)	26 (57.7%)	54 (60%)	
Female	17 (37.8%)	19 (42.3%)	36 (40%)	
Karnofsky performance	74.2%	72.4%	73.3%	0.136
Diagnosis				
Lung cancer	5 (11.1%)	9 (20%)	14 (15.6%)	0.9
Prostate cancer	14 (31.1%)	17 (37.8%)	31 (34.4%)	0.178
Breast cancer	18 (40%)	9 (20%)	27 (30%)	0.870
Other types of cancer	8 (17.8%)	10 (22.2%)	18 (20%)	0.9
Differentiated grade 1/2/3	3/29/13	1/33/11	4/62/24	0.635
Primary treatment site				
Limbs	7 (15.6%)	3 (6.7%)	10 (11.1%)	
Axial skeletal bones	28 (62.2%)	33 (73.3%)	61 (67.8%)	
Limbs + axial bones	6 (13.3%)	3 (6.7%)	9 (10%)	
Cranial bones	3 (6.7%)	1 (2.2%)	4 (4.4%)	
Axial + cranial bones	0	1 (2.2%)	1 (1.1%)	
Limbs + cranial bones	1 (2.2%)	4 (8.9%)	5 (5.6%)	
Number metastases				0.662
Single/multiple	15 (33.4%)/30 (66.6%)	18 (40%)/27 (60%)	33 (36.7%)/57 (63.3%)	
Soft tissue mass associated				
Yes/No	27 (60%)/18 (40%)	26 (57.8%)/19 (42.3%)	37 (41.2%)/53 (58.8%)	1.0
Visceral metastases				
Yes/No	8 (17.8%)/37 (82.2%)	12 (26.7%)/33 (73.3%)	20 (22.2%)/70 (77.8%)	0.447
Pretreatment pain (1–10)	7.84 95%CI 7.44–8.24	7.76 95%CI 7.35–8.16	7.8	0.753
Time pretreatment pain (month)	2.84 95%CI 2.34–3.34	2.99 95%CI 2.33–3.65	2.92 m	0.892
Function pretreatment				
Grade 1/2/3/4%patient)	0/28.8/62.3/8.9	2.2/20/62.3/15.5	1.1/24.4/62.2/12.2	0.546

type anti-inflammatory medication, poor or slight: required analgesics morphine type, null: no relief despite medication). Monitoring of patients was also performed at 15, 30, 60, 90 days of treatment completion, 6 months to a year, performing the same evaluations as that at the end of radiotherapy treatment.

Patients who died during the study or failed to follow, did not attend the review, were assessed until they remained in the study. Data were collected by the authors from the patients' records; we registered the following parameters during five years: data of inclusion, date of death or date of last record if alive, irradiation regimen received, anatomical treatment site, pathological fractures (fracture in previously irradiated area confirmed by X-ray), pain, function, re-calcification (in lytic bone metastases studied by X-ray 3, 6 and 12 months post-treatment) and re-irradiation (irradiation administered to the same anatomical site, if more than one such re-irradiation had been given, the first one was the one registered, to allow comparison in time to the first re-irradiation).

The frequencies of endpoints were compared between the two groups using the chi-square test (χ^2). Two-sided p-values <0.05 were considered significant. Baseline characteristics between groups were tested by chi-square and binomial tests. The overall survival in the groups was estimated using Kaplan–Meyer analyses and significant difference was evaluated using Log-Rank test, like actuarial analysis of time to re-irradiation by tumor site. Mann–Whitney U-test was used to estimate the difference between the two arms in the time elapsed before the first re-irradiation. The statistical software SPSS for Windows version 13.0 was employed. The study was done in accordance with the Helsinki Declaration.

4. Results

A total of 90 patients were included in the study, 60% men ($n = 54$) and 40% women ($n = 36$). Baseline characteristics of patients in the two groups are shown in Table 1. There were no major differences between the two arms. The most prevalent diagnoses were cancer of the prostate (34.4%), breast (30%) and lung (15.6%). Histological grade were moderately differentiated in 62 patients and poorly in 24; only 4 patients were well differentiated.

The most common primary treatment sites were the axial skeletal bones (pelvis and column) $n = 61$. 57 patients (63.3%) had multiple bone metastases, and 20 (22.2%) had synchronous visceral metastases. There were soft tissue masses associated in 37 patients. Mean intensity of pretreatment pain using VAS was 7.8 regardless of gender and age and mean time pretreatment pain was 2.92 months. We found no significant differences in analgesia applied to patients in both groups, in each of the reviews. The following values of significance (p-value) were obtained: First follow-up (f-u): 0.673, second f-u: 0.816, third f-u: 0.281, fourth f-u: 0.480, fifth f-u: 0.083, and sixth f-u: 0.560.

There was no difference between the two groups in total reduction of analgesic treatment ($p = 0.934$) (Fig. 1). Karnofsky Performance ($p = 0.011$) and recalcification ($p = 0.007$) were influenced significantly. Less significant was the influence on

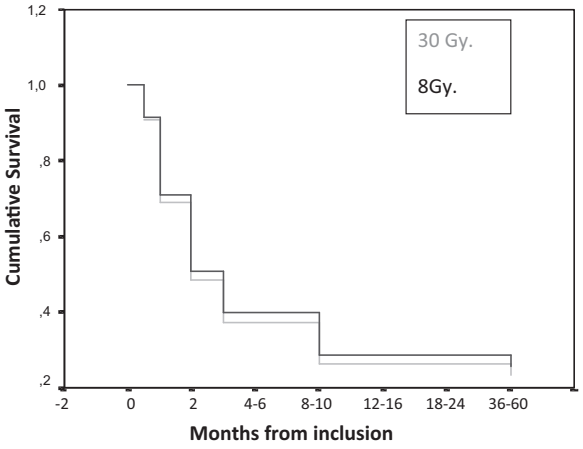

Fig. 1 – Survival functions and total reduction of analgesic treatment.

functionality ($p = 0.038$) and initial size of the bone metastases ($p = 0.089$), if soft tissue was affected ($p = 0.078$) and if there is more than one bone metastasis ($p = 0.093$).

There was no difference when we analyzed time to reduce one analgesic's level ($p = 0.781$) between the two treatments groups.

Response study to review and review between the first and last reviews there were no significant differences in pain response, relative to declining levels of analgesia, between the first and last reviews or between successive reviews: reduction of analgesia between visits 1 and 2 ($p = 0.736$), between visits 2 and 3 ($p = 0.715$), between 3 and 4 follow up ($p = 1.0$), between visits 4 and 5 ($p = 0.317$), between 5 and 6 follow-up ($p = 1.0$) and reduction of analgesia between visits 1 and 6 ($p = 0.794$). A complete response at 4 weeks was observed in 17% and partial response in 62% (overall response (OR) rate of 79%) of patients in the 8-Gy arm, and in patients in the 30-Gy arm, the complete response (CR) and partial response (PR) rates were 18% and 70%, respectively (OR rate 88%). At 3 months CR, PR and OR were 13%, 53%, and 66% for 8 Gy, and 15%, 59%, and 74% for 30 Gy. No significant differences were observed between the two arms. In patients who achieved response (OR), the mean of response duration was 26 weeks for the 30-Gy schedule and 23 weeks for the 8-Gy schedule. These differences are not statistically significant and the same resulted in patients who achieved a CR with a mean response of 29 and 26 weeks for the 30-Gy and the 8-Gy schedules, respectively.

We evaluated functionality pretreatment according to the functionality scale: 1: one patient; 2: 22 patients, 3: 56 patients, and 4 (no functionality): 11 patients. There was no difference in time to improve a grade of functionality between the two treatment groups ($p = 0.339$). In the single-fraction group, half of the patients experienced improvement with this treatment at least 2 months after the treatment ended (CI (1.1–2.9), with a mean of 4.8 months (CI (3.3–6.4). In the multiple-fraction group, the median value is 2 months (CI (1.3–2.7), and the mean is 5.4 months (CI (3.9–6.9).

No differences were found in time to obtain normal use without pain (Barthel index 1 ($p = 0.549$)). In the single-fraction group, the mean value was 7 months (CI: 5–9), and the median was of 6 m. In the multiple-fraction group, the mean value was 5, (CI: 4–7), and the median was of 2 m, and the influenced variables were recalcification ($p = 0.000$), soft tissue mass present ($p = 0.037$) and pathological fracture ($p = 0.094$). Study of the response with respect to obtaining reduction of at least one level in functionality, revision to revision showed: follow-up 1 and 2. p: 0.281, 2 and 3 follow-up p: 0.383, follow-up 3 and 4 p: 0.674, follow-up 4 and 5 p: 1.000.

No significant differences were found between the two groups in recalcification. The ratio of difference between recalcification rates was 0.881. None of the variables studied appears to affect decisively the rate of recalcification.

In the single-fraction group, seven pathological fractures occurred (15.5%) versus two (4.4%) in the multiple-fraction group. Pathological fracture rate is 3.75 times higher for individuals with single fractionation than for those receiving multiple-fraction treatments. There was no statistically significant difference between the time it takes to suffer pathological fracture in both groups ($p = 0.099$) (see Table 2).

Patients in the single-fraction group received six re-irradiations (13.3%) compared to four in the multiple-fraction group (8.8%), and most of them (65%) were given within the first 8 months (see Table 2). However, there was no significant difference between the time elapsed before the first re-irradiation between the two groups ($p = 0.438$). The most affected variables or those that best describe the retreat time are total reduction in analgesia ($p = 0.0209$), Karnofsky performance status ($p = 0.088$), and the fact of reducing in at least one level of analgesia ($p = 0.047$).

Actuarial analysis to compare the two treatment arms according to metastatic bone site and the presence of skeletal-related events was performed, but the numbers were too small for a valid statistical comparison. Of re-irradiations, 5 (50%) were delivered to the spinal column, 3 (30%) to pelvic bones, and 2 (20%) to lower limbs. There were a total of 9 pathological fractures, five (55.5%) in the pelvis, 3(33.3%) in the lower limbs, and one (11.1%) in the upper limbs. In relation to the type of cancer, rate of re-irradiation and time-interval to re-irradiation, actuarial analysis was performed, but all the numbers were too small for a valid statistical comparison between the two schedules.

The estimated median survival, and follow-up time according to treatment was 7.9 months in the hypo-fractionated group (8 Gy) and 8.73 months in the multi-fractionated group (30 Gy), and no statistically significant difference in overall survival was demonstrated ($p = 0.495$). Despite the fact that death rate for the single-fraction is 1.23 times higher than for the multi-fraction treatment (Fig. 2).

The variables that best describe overall survival are: primary cancer diagnosis ($p = 0.000$), Karnofsky performance status ($p = 0.001$), presence of visceral metastases ($p = 0.000$), and histological differentiated grade ($p = 0.034$). There were major differences according to primary cancer diagnosis. Breast cancer patients (median survival: 12.4 months) had significantly longer survival than lung cancer ($p = 0.000$) with 2.3 months median survival and prostate cancer ($p = 0.048$) with 8.6 months median survival.

Table 2 – Pathological fractures and re-irradiations according to primary treatment regimen ($n = 90$).

	8 Gy	30 Gy	p-value	Total
Pathological fracture	7 (5%[a])	2 (4.4%)	0.099	9 (10%[b])
Re-irradiation	6 (13.3%)	4 (8.8%)	0.043	12 (13.3%)
Skeletal-related events[c]	13 (28.8%)	6 (13.3%)		21 (23.3%)
Total	45 (100%)	45 (100%)		90 (100%)

[a] Percent within treatment arms.
[b] Percent within the total number of patients.
[c] Includes at least one event of re-irradiation or pathological fracture following irradiation for bone metastases.

5. Discussion

The high incidence of cancer patients, as well as greater control rates, lead to a higher proportion of patients with painful bone metastases to radiation treatment. Bone metastases can cause severe and debilitating effects, including pain, spinal cord compression, hypercalcemia, and pathologic fracture. EBRT provides successful palliation of painful bone metastases that is time efficient and has been associated with very few side effects.[12–14] External beam radiotherapy can provide significant palliation of painful bone metastases in 50–80% patients, with up to one-third of patients achieving complete pain relief at the treated site.[15] Widespread variation exists in worldwide practice patterns for palliative radiation dose fractionation schedules.[16]

Multiple prospective randomized trials have shown pain relief equivalence for dosing schema, including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction for patients with previously unirradiated painful bone metastases.[6,8,10–13,18] Several meta-analyses[9,15,19] have compared different radiotherapy schedules and have concluded that single-fraction radiotherapy is as effective as multifraction radiotherapy in terms of pain relief. However, for neuropathic pain, Roos et al.[20] compared 8 Gy vs. 20 Gy and concluded that a single fraction was not so effective as multifractionated and they recommended 20 Gy for those patients. Fractionated radiotherapy courses have been associated with an 8% repeat treatment rate to the same anatomic site because of recurrent pain vs. 20% after a single fraction; however, the single fraction treatment approach optimizes patient and caregiver convenience.[6,15] In addition it is more cost-effective for radiotherapy departments.[7,9,17–19,21–22]

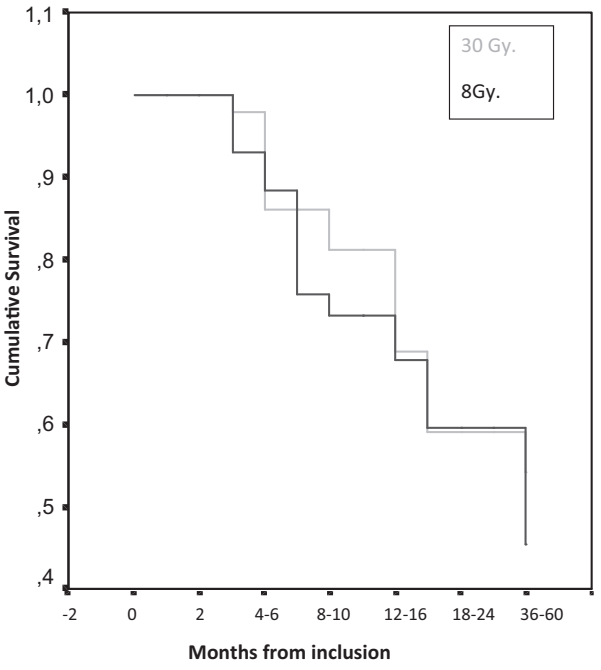

Fig. 2 – Survival functions and overall survival in 90 patients treated with single or multiple-fraction radiotherapy.

The mean of response duration was 26 weeks for the 30 Gy schedule and 23 weeks for the 8 Gy schedule, this difference is not statistically significant. The results are similar to those in other series published, which range from 11 to 24 weeks. In the study by Niewald,[13] response duration was the same for both treatment arms, whereas Gaze et al.[23] reports a 13.5 week response duration for the single fraction course vs. 14 weeks for the multifraction course in his series. In the study of van der Linden et al.,[17] the duration of response was 18 weeks for a single fraction and 19 weeks for a multifraction with no significant differences between the schemes.

Patients in the single-fraction group receive significantly more re-irradiations (13.3%) as compared to patients receiving multiple-fractions (8.8%). Consequently, there was also a significant difference in skeletal-related events. This difference is significant, as in the case of the study of Hartsell et al.[11] where 18% of the patients in the 8 Gy arm received re-irradiation vs. 9% in the 30 Gy arm ($p < 0.001$). These results are observed in almost all reported randomized trials. Steenland et al.[7] observed 25% re-treatments in the 8 Gy group and 7% in the 24 Gy group and confirmed by Chow's metaanalysis[15] that shows that in single dose treatments reirradiation is 2.5 times higher than in protracted schedules. The percentage of re-irradiation ranges from 11% to 42% according to the literature.[7,9,15,19] The meta-analyses carried out by Wu et al.[19] and Sze et al.[9] also show a higher incidence of re-irradiation for the single fraction arm compared with the multifraction arm. Specifically, Sze's meta-analysis[9] shows that in patients receiving the single-fraction course, the incidence of re-irradiation was 21.5% compared with 7.4% in the multifraction arm. It has been suggested that it reflects prior uncertainty concerning the long-term effect of single-fraction therapy.[10] Another possibility is that pain response following 8 Gy is less durable, resulting in more frequent re-irradiation, but some studies have concluded that this is unlikely.[7,24] Several authors have suggested that this reflects a tendency of many oncologists to have a lower threshold for re-irradiation

after single-fraction treatment compared to multiple-fraction schedule.[7–11,18]

There were no significant differences between the time elapsed before the first re-irradiation between the two groups ($p = 0.438$). This indicates that duration of pain relief was similar for the two regimens, as confirmed by other studies.[7,10,22,24] Single-fraction does not make it more likely for clinicians to admit the patients earlier for re-irradiation, so an oncologist does not have a lower threshold for re-irradiation after 8 Gy than after multiple-fraction therapy. The most affected variables or those that best describe the retreat time are: total reduction in analgesia ($p = 0.0209$), Karnofsky performance status ($p = 0.088$), and the fact of reducing in at least one level of analgesia ($p = 0.047$). Radiotherapy was repeated for symptomatic relapse in patients who were initially responders.

There were no significant differences between the time it took to suffer pathological fracture in both groups ($p = 0.099$), but pathological fracture rate was 3.75 times higher for individuals with single fractionation than for those receiving multiple-fraction treatments. The only included endpoints were those in the same anatomical site as the index lesion. Other studies have reported similar results[7,9–11]; however other authors show no difference with long term follow-up.[20,24] In assessing which factors influence the rate of pathologic fracture, the only one showing a significant value is the variable type of fractionation.

We analyzed intensity of pretreatment pain using the VAS (mean: 7.8) and time pretreatment pain (mean: 2.92 month). Like other studies, there was no difference between the two groups in total reduction of analgesic treatment ($p = 0.934$).[2,3,10,11,20,22,25] The influenced variables were Karnofsky Performance ($p = 0.011$) and recalcification ($p = 0.007$). There was no difference when we analyzed time to reduce one level of analgesics ($p = 0.781$) between the two groups. Other variables, such as functionality ($p = 0.038$), soft tissue involvement ($p = 0.078$), initial size of the metastatic bone lesion ($p = 0.089$), and multiple metastatic bone lesion ($p = 0.093$) were affected to a lesser degree. Secondly, we analyzed the response to pain reduction relative to some level of analgesia, without significant differences between the two groups. In our work, by analyzing the response in reducing pain at some level of analgesia, given in response to an improvement in pain by one level, there were no statistically significant differences between the two groups studied, ($p = 0.938$), with a ratio of the functions of 1.019.

We evaluated functionality pretreatment according to the functionality scale: 1: one patient; 2: 22 patients; 3: 56 patients; and 4: 11 patients. There was no difference in time to improve a grade of functionality between the two groups ($p = 0.339$). No differences were found in time to restore normal use without pain ($p = 0.549$), these results are similar to those reported by other trials,[17,19,20,21,24,25] and the influenced variables were recalcification ($p = 0.000$), soft tissue mass present ($p = 0.037$) and pathological fracture ($p = 0.094$).

It is important to note that the survival period after palliative radiotherapy usually was not related to the response of the metastases, but to the progression of other tumor process coexisting factors, altering the quality of life. At the study of survival between the two groups, it appears that the survival between 5 and 8 months is slightly higher in the daily fractionation scheme. Generally, the survival in 50% of patients is at least 12 months. In the single-fraction group this value is 11.67 months, which is slightly lower. The median survival time was 7.90, and 50% of patients survived more than 8 months. In the multiple-fraction treatment schedule, the mean survival time was 8.73 months; 50% of cases reached 11 months of life. Like Sande et al.,[24] in our study, no statistically significant difference in overall survival was demonstrated ($p = 0.495$) similar to results by other authors.[25] Despite the fact that death rate for the single-fraction was 1.23 times higher than for the multi-fraction treatment.

By analyzing which factors influenced survival, we found the following: location of the primary tumor, higher for breast, worse for lung ($p = 0.000$), presence of other non-bone metastatic location ($p = 0.000$); and performance status ($p = 0.001$).

6. Conclusions

This study presents that radiotherapy with a single-fraction (8 Gy) and multi-fraction schedule (30 Gy) should be considered as equally efficient for the majority of patients with painful uncomplicated bone metastases. They were followed up during five years, without difference for 8 Gy compared to 30 Gy. Therefore, we recommended single-fraction therapy for two reasons: greater convenience for the patients and more cost-effective for radiotherapy departments.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Nielsen OS, Munro AJ, Tannock IF, et al. Palliative radiotherapy of bone metastases: there is now evidence for the use of single fractions. *Radiother Oncol* 1999;**52**:95–9.
2. Falkmer U, Jarhult L, Wersall P, Cavallin-Stahl E. A systematic overview of radiation therapy effects in skeletal metastases. *Acta Oncol* 2003;**42**:620–33.
3. Ratanatharathorn VMD, Powers WMD, Moss WTMD, et al. Bone metastases: a review and critical analysis of random allocation trials of local field treatment. *Int J Radiat Oncol Biol Phys* 1999;**44**(1):1–18.
4. Nielsen OS, Bentzen SM, Sandberg E, et al. Randomized trial of single doses versus fractionated palliative radiotherapy of bone metastases. *Radiother Oncol* 1998;**47**:233–40.
5. Kirou-Mauro A, Hird A, Wong J, et al. Is response to radiotherapy in patients related to the severity of pretreatment pain. *Int J Radiat Oncol Biol Phys* 2008;**71**:1208–11.
6. Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;**79**:965–71.
7. Steenland E, Leer JW, van Houwelingen H, et al. The effect of a single fraction compared to multiple fraction on painful

bone metastases: a global analysis of the Dutch Bone Metastases Study. *Radiother Oncol* 1999;**52**:101–9.
8. Badzio A, Jereczek-Fossa B, Senkus-Konefka E, et al. A multicenter randomized study of two regimens in palliative radiotherapy of bone metastases. *Rep Pract Oncol Radiother* 2001;**6**(1):43.
9. Sze WM, Shelley M, Held I, Wilt TJ, Mason M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy – a systematic review of randomized trials. *Cochrane Dtabase Syst Rev* 2004;(2):CD004721.
10. Bone Pain Trial Working Party. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomized comparison with a multifraction schedule over 12 months of patients follow up. *Radiother Oncol* 1999;**52**:111–21.
11. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short-versus long course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst* 2005;**97**:798–804.
12. Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Orthop* 1989;**1**:59–63.
13. Niewald M, Tkocz HJ, Abel U, et al. Rapid course radiation therapy versus more standard treatment. A randomized trial for metastases. *Int J Radiat Oncol Biol Phys* 1996;**36**:1085–9.
14. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *Int Disabil Stud* 1988;**10**(2):61–3.
15. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007;**25**:1432–6.
16. Faichild A, Barnes E, Ghosh S, et al. International patterns of practice in palliative radiotherapy for painful bone metastases: evidence-based practice. *Int J Radiat Oncol Biol Phys* 2009;**75**:1281–628.
17. van der Linden Y, Lokk JJ, Steenland E. 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**: 528–37.
18. Kaasa S, Brenne E, Lund JA, et al. Prospective randomised multicentre trial on single fraction radiotherapy (8 Gy × 1) versus multiple fractions (3 Gy × 10) in the treatment of painful bone metastases. *Radiother Oncol* 2006;**79**:278–84.
19. 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.
20. Roos DE, Turner SL, O'Brien PC, et al. 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.
21. Szostakiewicz B, Dziadziuszko R, Wełnicka-Jaśkiewicz M, Jassem J. Palliative irradiation of bone metastases: patterns of care with focus on single fraction treatment. *Rep Pract Oncol Radiother* 2004;**9**(1):9–12.
22. Chow E, Davis L, Holden L, et al. A comparison of radiotherapy outcomes of bone metastases employing international consensus endpoints and traditional endpoints. *Support Cancer Ther* 2004;**1**:173–8.
23. Gaze MN, Kelly CG, Kerr GR, et al. Pain relief and quality of life following radiotherapy for bone metastases: a randomized trial of two fractionation schedules. *Radiother Oncol* 1997;**45**:109–16.
24. Sande TA, Ruenes R, Lund JA, et al. Long term follow-up of cancer patients receiving radiotherapy for bone metastases: results from a randomized multicentre trial. *Radiother Oncol* 2009;**91**:261–6.
25. Zhu Y-J. Palliative radiotherapy for painful bone metastases: short-course or long-course? *Ann Palliat Med* 2012;**1**(1): 78–80.