**Phase III randomised trial**

Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction

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**Abstract**

**Background and purpose:** The aim was to demonstrate similar pain relief with two schedules of radiotherapy for painful bone metastases.

**Materials and methods:** A total of 160 patients were assigned to receive a single 8-Gy fraction or 30 Gy in 10 fractions. Pain intensity was measured on an ordinal pain scale of 0–10. Partial response was defined as a pain reduction of two points or more and complete response as a pain score of zero at the treated area. Response follow-up was at 3, 12, 24 and 48 weeks.

**Results:** The overall response was 75% in the 8-Gy arm and 86% in the 30-Gy arm. Complete response and partial response rates were 15% and 60% in the 8-Gy arm, 13% and 73% in the 30-Gy arm. Acute toxicity was of 18% in the 30-Gy arm and of 12% in the 8-Gy arm. These differences were not statistically significant. The re-treatment rate was 28% vs 2% in the 8-Gy and 30-Gy arms, respectively, these were statistically significant.

**Conclusions:** A single-fraction regimen of 8 Gy was as safe and effective as a multifraction regimen of 30 Gy for painful bone metastases in terms of pain relief.


**Keywords:** Bone metastases; Radiotherapy; Fractionation

Pain is the most common symptom in cancer patients with bone metastases, radiation therapy provides significant pain relief of symptomatic bone metastases. Between 50% and 80% of patients will have significant improvement in pain after radiotherapy. Almost 50% of patients with bone metastases will require radiotherapy to control their pain representing about 30–40% daily practice of a radiotherapy department. In our experience, of 4600 treatments made in our department between 1990 and 1997, 30% were with palliative intent [23].

For pain control, different radiotherapy schedules had been employed: 40 Gy in 20 fractions, 30 Gy in 10 fractions and single fractions of 8 Gy, 6 Gy or 4 Gy. Several randomized prospective trials and meta-analyses have been reported showing the same results in pain relief when comparing single doses vs protracted treatments [5, 6, 8–13, 15–17, 19–22, 24]. Despite clinical evidence supporting single-fraction regimens, fractionated treatments remain the choice for pain treatment in many institutions and this also occurs in our country. In Spain there are few published randomized reports on palliative radiation. In 1999 we published a study that compared three schedules and observed no differences [8]. Thus, we decided to undergo a single institution randomized trial to compare 8 Gy in a single fraction as compared to 30 Gy in 10 fractions. The aim was to demonstrate similar pain relief with these two schedules frequently used in daily practice to assess effectiveness.

**Materials and methods**

From July 1999 to December 2001 a randomized clinical trial was conducted in 160 patients with painful bone metas-
The inclusion criteria were age of 18 years or older, presence of a painful multiple bone metastases but only one site of pain, estimated life expectancy of at least 1 month, and a signed informed consent. Patients were ineligible who reported pain due to a pathological fracture or impending fracture following Mirels’ criteria [14]; as was the practice in our Hospital, in patients with a score of 9 were referred for a prophylactic surgical fixation. Also were excluded patients with clinical or radiographic evidence of spinal cord compression, patients with pain at more than one site, patients who had received prior radiotherapy at the same site, and patients whose pain could not be assessed either because of an overall poor state of health or due to difficulties in applying the ordinal pain scale (OS).

Patients were randomised using a computerized randomization table to receive either a 30 Gy delivered in 10 fractions over 2 weeks or a 8 Gy delivered in one fraction. The following procedure before randomization was history and physical examination, pain severity according to the OS as recommended by a reported consensus [3]. The OS assesses pain severity as ranging from 0 to 10, where 0 equals no pain and 10 equals maximum pain intensity. Data on analgesics received by the patient according to WHO recommendations were also registered as well as the Karnofsky Performance Status (KPS), and also radiographically documented bone metastases. The severity of pain was assessed prior to and following radiotherapy at weeks 3, 12, 24 and 48 or until death.

The primary endpoints were complete response (CR) defined as the absence of pain without the need for increasing analgesia, and partial response (PR) which was defined as an improvement $\geq 2$ on the ordinal scale with no need for increasing analgesia, and overall response (OR). Response was assessed by follow-up or with telephone interviews. Response was evaluated at 3 and 12 weeks. Patients with same or worse pain level at 3 weeks were considered to have no response. The results presented are both the actuarial and crude response rates.

Response duration was calculated from the first date evaluated at 3 weeks to the date of relapse, or in absence of relapse to the date of last assessment or death. Pain progression was defined as an increase in the pain $\geq 2$ OS after an initial response. Re-treatment was left to the physician’s choice. Therefore all patients who were retreated were considered relapse and the response before retreatment was not recorded. Net pain relief is obtained by dividing the period of pain relief by the period of survival in days and multiplying the result by 100, to measure the duration of benefit. It represents the length of time the patient is alive and responsive after receiving a given radiotherapy regimen. Gain permits the quantification of the degree of pain relief and is obtained by subtracting pain severity on the ordinal scale following therapy, from pain severity prior to radiotherapy. Therefore the positive results of the gain means a decrease in pain and negatives represent progression. Finally, toxicity was assessed using the Radiation Therapy Oncology Group (RTOG) criteria and was collected in the monitoring visits [7].

Statistical analysis
Sample size was calculated on the basis of a 0.05 alpha risk and a 0.20 beta risk for a two-tailed hypothesis test, assuming an 89% proportion to detect a difference of 15% with an estimated 10% rate of lost to follow-up patients. Based on this calculation, each treatment arm required 76 patients, thus the minimum sample size was 152 subjects. Double entry of the data was carried out with subsequent validation to guarantee their quality and consistency. Hypothesis tests were two-tailed and considered significant for a p value $<0.05$.

The following statistical tests were applied: Student’s t-test to compare continuous quantitative variables; non-parametric tests (Mann–Whitney U and Kolmogorov–Smirnov) to compare ordinal quantitative variables; Pearson’s chi-square test to compare qualitative variables with Fisher’s exact test when the frequency of different events required it. Survival and response durations were analysed calculating the corresponding curves by means of the actuarial method using the Wilcoxon test for hypothesis testing.

Results
From July 1999 to December 2001, 160 patients were enrolled with an intention-to-treat; 82 patients received a 30-Gy and 78 received an 8-Gy dose. Patient characteristics were well balanced between two arms (Table 1). Mean survival was 33 and 28 weeks for the 30-Gy and 8-Gy schemes, respectively ($p = ns$). There were no significant differences between schedules in terms of survival probability, as shown by the actuarial curve (Fig. 1).

A complete response at 3 weeks was observed in the 15% and partial response in 60% (OR rate of 75%) of patients in the 8-Gy arm, and patients in the 30-Gy arm the complete response and partial response rates were 13% and 73%, respectively (OR rate 86%). At 3 months CR, PR and OR were 13%, 52%, and 65% for 8 Gy and 11%, 51%, and 62% for 30 Gy. No significant differences were observed between two arms (see Tables 2–4).

As the response was evaluated at first at three weeks, the actuarial curve begins on this date. CR and OR estimate calculations did not reveal significant differences between the two schedules (Figs. 2 and 3). In patients who achieved response (OR), the mean of response duration was 23 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 25 and 28 weeks for the 30-Gy and the 8-Gy schedules, respectively.

Net pain relief did not show statistical differences between the two schedules (71% for the 30-Gy and 68% for the 8 Gy). The results for gain were 4 and 3.5 for single fraction and multifraction respectively. Treatment was well tolerated by patients: the most common acute toxicity was dermitis. It was observed in 15% (10% was grade I and 5% was grade II) of patients with protracted treatment and in 10% in the single-fraction arm (8% grade I and 2% grade II). Gastrointestinal toxicity occurred less frequently (2% and 2%), in both arms was grade I. There were no grades 3 and...
4 toxicity. Acute toxicity was greater in the 30-Gy arm than in the single-fraction arm (18% vs 12%), without significant differences (Table 5).

Pain progression was observed in 43% of the patients in the 30-Gy arm and in 28% in the single-fraction arm. Patients received re-treatment in 2% in protracted arm, and in 28% in single-fraction arm. This difference was statistically significant ($p < 0.001$) (Table 5). Decision to re-treatment was left to the physician’s choice.

**Discussion**

The high incidence of cancer patients, as well as greater control rates, leads a higher proportion of patients with painful bone metastases to radiation treatment. Several studies [8–12] as well as meta-analyses [20,24], the most recent one published by Chow et al. [5], have compared different radiotherapy schedules and have concluded that single-fraction radiotherapy is as effective as multifraction

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>Rates %</th>
<th>30 Gy</th>
<th>n</th>
<th>Rates %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS&lt; 70</td>
<td>14</td>
<td>17</td>
<td>82</td>
<td>78</td>
<td>49</td>
<td>ns</td>
</tr>
<tr>
<td>KPS= 70</td>
<td>68</td>
<td>83</td>
<td>57</td>
<td>45</td>
<td>58</td>
<td>ns</td>
</tr>
<tr>
<td>Men</td>
<td>47</td>
<td>57</td>
<td>33</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>35</td>
<td>43</td>
<td>7.0 ± 1.6</td>
<td>71</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1**

Pretreatment characteristics of groups studied

<table>
<thead>
<tr>
<th>Pretreatment characteristics</th>
<th>30 Gy</th>
<th>8 Gy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>82</td>
<td>78</td>
<td>ns</td>
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<td>KPS&lt; 70</td>
<td>14</td>
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</tr>
<tr>
<td>KPS= 70</td>
<td>68</td>
<td>63</td>
<td>81</td>
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<tr>
<td>Men</td>
<td>47</td>
<td>45</td>
<td>58</td>
</tr>
<tr>
<td>Women</td>
<td>35</td>
<td>33</td>
<td>42</td>
</tr>
<tr>
<td>Mean age</td>
<td>63.4 ± 11.4</td>
<td>64.8 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td>Pain severity (OS)b</td>
<td>7.0 ± 1.6</td>
<td>7.1 ± 1.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Primary tumour**

- Breast cancer: 22, 21
- Lung cancer: 22, 21
- Prostate cancer: 21, 19
- Myeloma: 9, 3
- Digestive tract cancer: 6, 10
- Others: 2, 6

**Histology**

- Adenocarcinoma: 58, 61
- Squamous cell carcinoma: 8, 9
- Myeloma: 9, 3
- Others: 7, 5

**Location of radiation**

- Pelvis: 28, 35
- Spine: 29, 29
- Long bone: 15, 8
- Others: 10, 6

KPS: Karnofsky performance status.

OS: ordinal score.

**Table 2**

Overall response rates

<table>
<thead>
<tr>
<th>Weeks</th>
<th>30 Gy</th>
<th>Rates%</th>
<th>8 Gy</th>
<th>Rates%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>86</td>
<td>59</td>
<td>75</td>
<td>ns</td>
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<tr>
<td>12</td>
<td>51</td>
<td>62</td>
<td>51</td>
<td>65</td>
<td>ns</td>
</tr>
</tbody>
</table>

Fig. 1. Survival probability $p = 0.163$. 

Radiation for painful bone metastases
radiotherapy in terms of pain relief. However for neuropathic pain, Roos et al. [18] compared 8 Gy vs 20 Gy and concluded that a single fraction was not effective as multifraction and they recommended 20 Gy for those patients.

Randomized trials [4,6,9,17] show OR rates similar to our series, Van der linden et al. [22] observed OR rates of 68% vs 69% for single and multifraction, but in meta-analysis of Chow et al. [5] the percentage is smaller, 58% vs 59%, in both arms, as well in meta-analysis of Sze that shows 60% vs 59% for single and multifraction. The studies published show different response rates, to unify the different response criteria; in 2002 Chow et al. [5] published an International Consensus in which the complete response (CR) and the partial response (PR) criteria were defined. In our study we have applied the definition of CR and PR recommended by consensus, we report our results as recommended by Chow et al. [5] at 12 weeks. In our series the CR rates at 3 months were 13% vs 11% for 8-Gy and 30-Gy, respectively, and the PR was 51% vs 52% vs for 8-Gy and 30-Gy, respectively. The CR rates were similar in the study published recently by van der Linden et al. [22] in a reanalysis of Dutch Bone Metastases Study (DMBS) 13% vs 14% for single and multifraction. As well the CR obtained in our series is comparable to that the published by Hartsell et al. [11] when they used the international consensus end point for CR 10% vs 12% with 8 Gy and 30 Gy (Table 6). Studies where consensus definition was applied the CR and PR rates resulted smaller compared with the others trials where consensus definition was not applied.

When we made the response actuarial curve, we noted that the two schedules have the same probability to remain

### Table 3
Complete response rates

<table>
<thead>
<tr>
<th>Weeks</th>
<th>30 Gy</th>
<th>8 Gy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rates %</td>
<td>n</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>9</td>
<td>11</td>
<td>10</td>
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</tbody>
</table>

### Table 4
Partial response rates

<table>
<thead>
<tr>
<th>Weeks</th>
<th>30 Gy</th>
<th>8 Gy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rates %</td>
<td>n</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>73</td>
<td>47</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>51</td>
<td>41</td>
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</table>

### Table 5
Gain and percentage of pain progression, net pain relief, toxicity, and re-treatment

<table>
<thead>
<tr>
<th>Gain</th>
<th>30 Gy</th>
<th>8 Gy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>3.5</td>
<td>ns</td>
</tr>
<tr>
<td>Pain progression %</td>
<td>43</td>
<td>28</td>
<td>ns</td>
</tr>
<tr>
<td>Net pain relief %</td>
<td>71</td>
<td>68</td>
<td>ns</td>
</tr>
<tr>
<td>Toxicity %</td>
<td>18</td>
<td>12</td>
<td>ns</td>
</tr>
<tr>
<td>Re-treatment %</td>
<td>2</td>
<td>28</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 6
Complete response rates in randomised trials where consensus definition is applied

<table>
<thead>
<tr>
<th>CR %</th>
<th>SF</th>
<th>MF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartsell et al. [11]</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Van der Linden et al. [22]</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Foro et al.</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

SF, single fraction; MF, multiple fraction; CR, complete response.
in response. No significant differences in overall response probability and complete response probability were achieved.

The mean of response duration was 23 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 [16], response duration was the same for both treatment arms, whereas Gaze et al. [9] 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. [22], the duration of response was 18 weeks for single fraction and 19 weeks for multifraction with no significant differences between schemes.

In our study we have made two supplemental analyses: net pain relief and gain. Net pain relief had been used by our team in a study of 78 hemibody irradiation procedures [1,2]. As explained in Material and methods, the net pain relief is obtained by dividing the period of pain relief by the period of survival in days and multiplying the result by 100. In this series, net pain relief was 71% and 68% for the 30-Gy and 8-Gy arms, respectively; these differences are not significant. Gain shows the quantification of the degree of pain relief and is obtained by subtracting pain severity on the ordinal scale following therapy, from pain severity prior to radiotherapy. Mean gain for the 30-Gy arm was 4, whereas for the 8-Gy arm it was 3.5, this difference is not statistically significant.

In our series there were no cases of severe toxicity. Overall, patients receiving 30 Gy showed more symptoms compared with those of 8 Gy: 18% vs 12%, but the differences were not significant. In the RTOG study [11] there were significant differences, and toxicity was higher in the 30-Gy arm compared with the 8-Gy arm: 17% vs 10%, respectively. Kaasa et al. [12] observed more toxicity in the 8-Gy arms than the 30-Gy arms. However there were no significant differences between patterns in most of the studies carried out, although the percentage varies with several studies [6,9,15,19].

After receiving treatment and during follow-up, 43% of patients in the 30-Gy arm and 28% of patients in the 8-Gy arm, experienced pain relapse, but once again this difference was not significant. Among the patients who experienced pain progression, 28% of those in the 8-Gy arm were retreated with radiotherapy, whereas only 2% of patients in the 30-Gy arm were re-irradiated. This difference is significant, as in the case of the study of Hartsell et al. [11] where 18% of 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. [19] observed 25% re-treatments in the 8-Gy group and 7% in the 24-Gy group and confirmed in Chow’s meta-analysis [5] that shows that in single dose treatments re-irradiation is 2.5 times higher than protracted schedules. The percentage of re-irradiation ranges from 11% to 42% according to the literature [5,24]. The meta-analyses carried out by Wu et al. [24] and Sze et al. [20] also show a higher incidence of re-irradiation for the single-fraction arm compared with the multifraction arm. Specifically, Sze’s meta-analysis [20] 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.

Conclusion

We can conclude that using the definition recommended by consensus to measure the pain relief in trials of bone metastases, a single fraction of 8 Gy for the treatment of bone metastases is as effective as a 30-Gy regimen in terms of complete, partial and overall response rates. Also, there are no significant differences between the two arms in response duration, pain progression, net pain relief, gain and toxicity. The percentage of re-irradiations is significantly higher for the single fraction vs the multifraction schedules, as is observed in other studies published.

Acknowledgement

We are grateful to Dr. Jose Maria Verdu Rotellar for his kind collaboration in statistical support.

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Received 20 August 2007; received in revised form 14 May 2008; accepted 17 May 2008; Available online 13 June 2008

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