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Radiotherapy in bone metastasis : the Dutch bone metastasis study

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Uit kwaliteit van leven onderzoek bij patiënten met bijvoorbeeld darmkanker of hoofdhalsskanker is gebleken dat de huidige basislijst om de kwaliteit van leven te meten (EORTC QLQ-C30) hiervoor niet specifiek genoeg is om alle vragen te kunnen beantwoorden. Hoewel grondiger analyses over de kwaliteit van leven van de patiënten uit de Nederlandse Botstudie nog moeten worden verricht, veronderstellen we dat de gebruikte instrumenten ook in deze studie niet afdoende zijn geweest om een verschil in de behandeling aan te kunnen tonen. Lokale bestraling kan de dagelijkse activiteiten verbeteren die door pijn gehinderd worden, maar niet de algemene kwaliteit van leven van een patiënt met een uitgezaaide vorm van kanker. Daarom zal een speciale botmetastasen-module als aanvulling op de EORTC QLQ-C30 questionnaire ontwikkeld gaan worden zodat toekomstige studies naar botmetastasen de kwaliteit van leven gerichter kunnen onderzoeken.

Als laatste concluderen we dat de uitkomsten van de Nederlandse Botstudie aantonen dat een éénmalige bestraling van 8 Gy even effectief is als 24 Gy in 6 fracties. Een éénmalige bestraling van 8 Gy is dan ook de standaard behandeling voor het merendeel van de patiënten met pijnlijke botmetastasen.

Appendix 1

The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study

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Introduction

Since the early 1980s the optimal radiotherapy treatment schedule for the palliation of painful bone metastases has been under debate.¹⁻⁴ Several non-randomised and randomised studies indicated that one fraction or a few fractions could be as effective both in the incidence of pain relief and in the duration of response as the normally used multiple fractionated schedules.⁵⁻⁸ However, other investigators concluded that higher doses were more effective especially for patients with a relatively good prognosis.^{2,9-11} Because of this persisting controversy we embarked on a national study in which we compared the most frequently used treatment of 4 Gy x6 with one single fraction of 8 Gy. We aimed for a total number of 1200 randomised patients to ensure that all possibly important variables would be equally balanced between the two groups. We also decided to register the patients who were not included in the study to make sure that our sample was representative and our conclusions valid. We on purpose included patients considered to have a more favourable prognosis in order to judge the long term palliative effect of a single dose irradiation. Finally, we not only analysed the effect on pain but also the effect on quality of life. In addition, a cost-analysis was performed. In this large study 4084 patients were registered of whom 1171 were prospectively randomised between the two treatment arms. Although aspects of this study have to be analysed in more detail, the general conclusions are presented here.

Patients and methods

From 1st March 1996 until 1st September 1998 patients with painful bone metastases from a solid tumour were randomised into the study by 17 out of 21 radiotherapy institutes in The Netherlands. These patients had a pain score of at least 2 on an 11-point scale from 0 (no pain at all) to 10 (worst imaginable pain) at time of admission to the radiotherapy department. The painful bone metastases had to be treatable in one target volume. If these had previously been irradiated, or in the case of a pathological fracture that needed surgical fixation or a spinal cord compression, patients were excluded from randomisation. Patients with metastases of malignant melanoma or renal cell carcinoma were excluded because these were considered to express a different biological behaviour. Patients with metastases in the cervical spine were excluded because it was believed that large fractions might lead to a radiation induced myelopathy. Eight of the 17 participating institutes also included patients with favourable prognosis, that is patients with breast cancer with no visceral metastases in a long term complete remission (more than 1 year) due

Abstract

Purpose: To answer the question whether a single fraction of radiotherapy that is considered more convenient to the patient is as effective as a dose of multiple fractions for palliation of painful bone metastases.

Patients: 1171 patients were randomised to receive either 8 Gy x1 (n=585) or 4 Gy x6 (n=586). The primary tumour was in the breast in 39% of the patients, in the prostate in 23%, in the lung in 25% and in other locations in 13%. Bone metastases were located in the spine (30%), pelvis (36%), femur (10%), ribs (8%), humerus (6%) and other sites (10%).

Method: Questionnaires were mailed to collect information on pain, analgesics consumption, quality of life and side effects during treatment. The main endpoint was pain measured on a pain scale from 0 (no pain at all) to 10 (worst imaginable pain). Costs per treatment schedule were estimated.

Results: On average, patients participated in the study for 4 months. Median survival was 7 months. Response was defined as a decrease of at least two points as compared to the initial pain score. The difference in response between the two treatment groups proved not significant and stayed well within the margin of 10%. Overall, 71% experienced a response at some time during the first year. An analysis of repeated measures confirmed that the two treatment schedules were equivalent in terms of palliation. With regard to pain medication, quality of life and side effects no differences between the two treatment groups were found. The total number of retreatments was 188 (16%). This number was 147 (25%) in the 8 Gy x1 irradiation group and 41 (7%) in the 4 Gy x6 group. It was shown that the level of pain was an important reason to retreat. There were also indications that doctors were more willing to retreat patients in the single fraction group because time to retreatment was substantially shorter in this group and the preceding pain score was lower. Unexpectedly, more pathological fractures were observed in the single fraction group, but the absolute percentage was low. In a cost-analysis, the costs of the 4 Gy x6 and the 8 Gy x1 treatment schedules were calculated at 2305 and 1734 Euro respectively. Including the costs of retreatment reduced this 25% cost difference to only 8%. The saving of radiotherapy capacity, however, was considered the major economic advantage of the single dose schedule.

Conclusion: The global analysis of the Dutch study indicates the equality of a single fraction as compared to a 6 fraction treatment in patients with painful bone metastases provided that 4 times more retreatments are accepted in the single dose group. This equality is also shown in long term survivors. A more detailed analysis of the study is in progress.

to first line systemic treatment and patients with a diagnosis of prostate cancer, a Karnofsky index of 60% or more, who had not been treated by hormonal treatment yet. These patients were separately randomised to be able to answer the question whether patients with a longer life expectancy would also benefit from a single dose of irradiation. To evaluate whether or not the selection of randomised patients was representative, all patients with painful bone metastases were registered.

Treatment schedules

Patients were randomised to receive either a single dose of 8 Gy or a total dose of 24 Gy given in 6 fractions. No guidelines or restrictions were formulated with respect to the radiation technique. It was expected that the sample size would guarantee an equal balance of possible differences. Single or parallel opposing fields were documented only in the case when bone metastases in the spine were treated.

Pre-treatment evaluations

For all patients primary tumour site, initial pain score, Karnofsky index and site of the bone metastases were registered. For patients who were randomised also the site of other metastases and the need for systemic treatment were recorded. A first questionnaire at time of randomisation was filled out by the patients without interference of their doctor. An 11-point scale¹² was used to assess the worst pain they had experienced in the previous week with scale endpoints from 0 (no pain at all) to 10 (worst imaginable pain). The patients were also asked to write down their pain medication. This medication was divided in phase 1 (NSAIDs: non-opioids and paracetamol), phase 2 (weak opioids and combinations with codeine) and phase 3 (strong opioids like morphine) according to the analgesic ladder.¹³ The Rotterdam Symptom Checklist (RSCL)¹⁴ was used to assess quality of life and adapted to measure acute side effects on a four point scale from 1 (not at all) to 4 (very much).

Post-treatment evaluations

The first 12 follow-up questionnaires for self-assessment of pain at treatment site, analgesics consumption, quality of life and side effects were filled out every week up to 3 months; the next 23 questionnaires were filled out every 4 weeks up to 2 years. Data collection stopped when the patient notified the Data Centre that filling out questionnaires had become too strenuous and at death. Data on the number of fractions and total dosage given, the need for re-irradiation, the occurrence of spinal cord compression and/or fractures along with data on systemic treatment were collected at three-monthly intervals at the institutes.

Response definitions

Response was defined as a decrease in the initial pain score by at least two points. A subsequent increase with return to the initial pain score or higher was considered progression. Time to response and time to progression were calculated from the date of randomisation until the date of response and date of progression respectively. Patients were considered complete responders if they lowered their pain scores to 0 or 1, independent of analgesics consumption.

Statistical considerations

To determine a difference in response rate of 10% in a two-sided analysis with alpha 0.05 and the power as 85%, a total of 900 evaluable patients were needed. To compensate for an early retrieval, the inclusion of 1200 patients was aimed for. If no significant difference would be found within a margin of 10%, the two treatment regimens would be considered equivalent. Statistical analysis used Kaplan–Meier survival curves and the log-rank test to determine differences in time to response and time to progression. An analysis of repeated measures was included to estimate mean differences taking into account missing data. The intention-to-treat principle was used in this study. This meant that analysis was performed on the data of all patients that met the inclusion criteria irrespective of abnormalities during their study period.

Results

Patients accrual

A total of 4084 patients with painful bone metastases were registered into the study by 17 radiotherapy institutes in The Netherlands of whom 1171 patients (29%) met the inclusion criteria and were randomised to receive either 4 Gy x6 (n=586) or 8 Gy x1 (n=585). The reasons for non-randomisation were: no informed consent (22%), pain score less than 2 (8%), no solid tumour (1%), no single target volume possible (24%), fractured bones that needed surgery (8%), spinal cord compression (13%), previous irradiation (8%), cervical bone metastases (6%), melanoma or renal cell carcinoma (6%), and for some institutes favourable diagnosis of breast cancer (3%) or prostate cancer (1%). In Table 1 the characteristics of the non-randomised and randomised patients are given. There are no differences between the two groups except in the number of males and females. Table 2 shows the characteristics of the randomised patients by treatment group. There exists a good balance between the two randomisation groups. In retrospect 14 patients of the 1171 randomised patients did not meet the inclusion criteria: 6 because of the presence of multiple painful bone metastases that could not be encompassed in one

TABEL 1 CHARACTERISTICS OF PATIENTS IN THE NON-RANDOMISED AND RANDOMISED GROUPS		
Characteristic	non-randomised (N=2913)	randomised (N=1171)
Sex	47% (1359) 53% (1554)	54% (630) 46% (541)
Age	21 - 95 65 66	32 - 89 65 66
Karnofsky	10 -100 70	20 -100 70
Score at admission, and 1 excluded	6.30	6.30
Primary Tumour, carcinoma and renal cell carcinoma excluded	42% 20% 19% 19%	39% 23% 25% 13%
Treatment Site, cervical excluded		
Thoracic/Lumbar Spine	37%	30%
Pelvis	29%	36%
Femur	16%	10%
Ribs	5%	8%
Humerus	4%	6%
Other	9%	10%

volume; 3 because of previous irradiation; 3 because of the occurrence of fractures that needed surgical fixation at time of randomisation and 2 because of diagnoses that appeared to be non-Hodgkin lymphoma and osteoporosis respectively. Eventually the data of 1157, that is 578 in the 4 Gy x6 treatment group and 579 in the 8 Gy x1 group, were analysed.

Compliance

We analysed the data of 1157 patients. These data came from 16 130 questionnaires. On average, patients filled out 14 questionnaires. Twenty-five per cent of the patients completed less than 4 questionnaires. Overall, 37% of the patients stopped filling out questionnaires due to death, only 13% stopped due to closure of the study and 50% due to, mostly, ill health. From the latter group,

TABEL 2 CHARACTERISTICS OF PATIENTS IN THE TWO TREATMENT GROUPS AT TIME OF RANDOMISATION*		
Characteristic	4Gyx6 (N=578)	8Gyx6 (N=579)
Sex		
Male	55% (317)	53% (307)
Female	45% (261)	47% (272)
Age		
Range	32 - 89	33 - 89
Mean	65	65
Median	66	67
Karnofsky		
Range	20 -100	20 -100
Median	70	70
Primary Tumour		
Breast	38%	40%
Prostate	24%	22%
Lung	25%	25%
Other	13%	13%
Treatment Site		
Thoracic/Lumbar Spine	30%	29%
Pelvis	39%	34%
Femur	11%	9%
Ribs	8%	9%
Humerus	5%	6%
Other	7%	13%
Other Metastases		
Lung	5%	4%
Liver	5%	5%
Bone (non-painful)	67%	68%
Lymph nodes	8%	10%
Other	15%	13%
Systemic Treatment	53%	54%
Pain Medication		
None	12%	13%
Phase 1	39%	38%
Phase 2	7%	10%
Phase 3	42%	39%

* The characteristics of the patients with favourable prognosis are included in Table 2. This group consisted of 92 patients, 75 with breast cancer and 17 with prostate cancer.

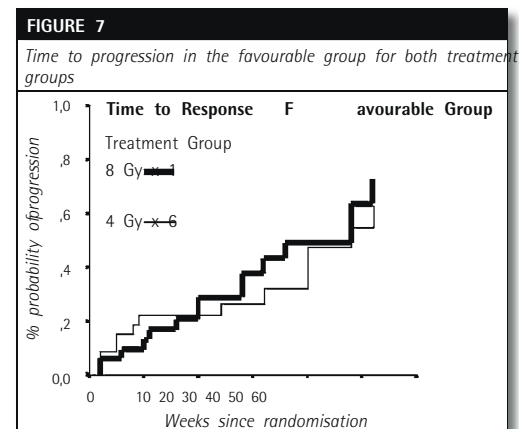
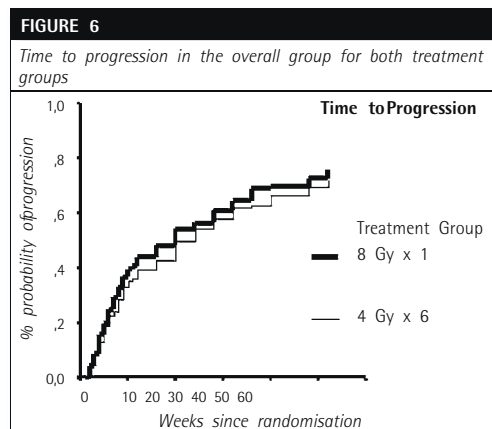
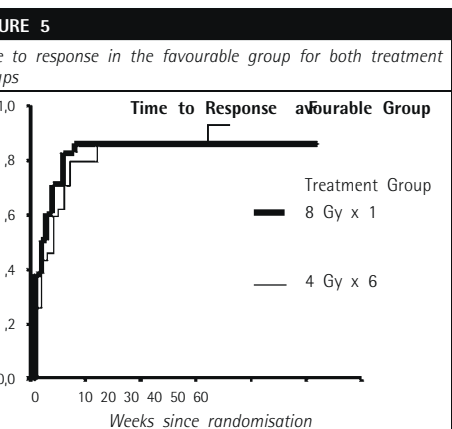
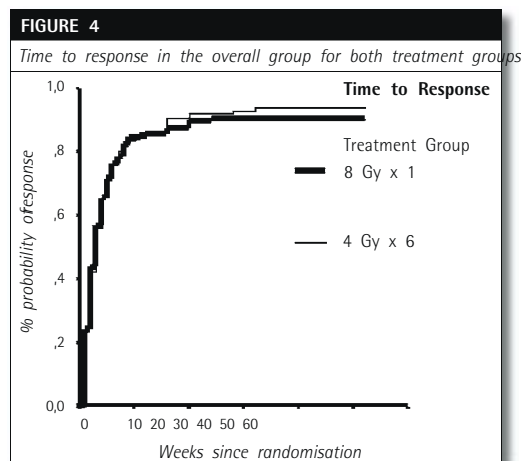
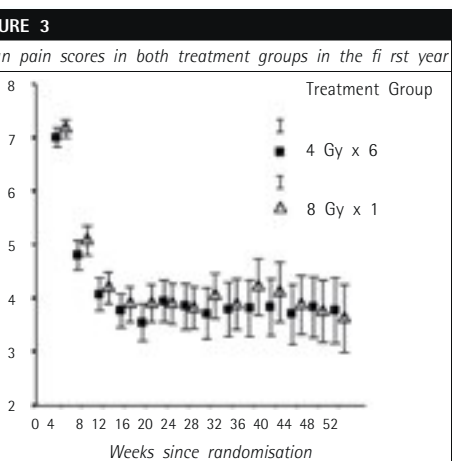
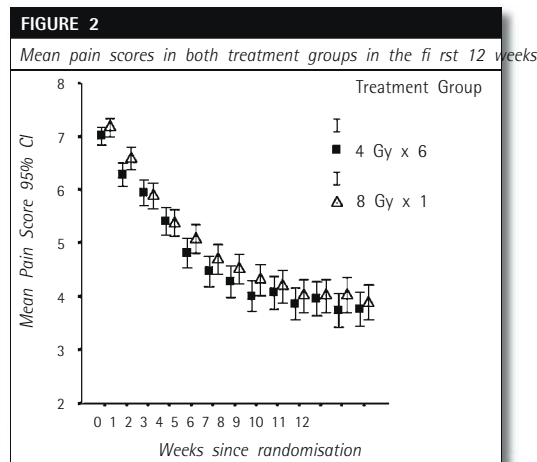
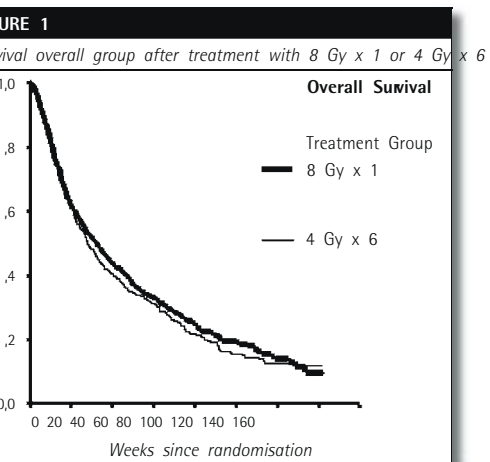
we documented that 75% died within the closing time of the study and shortly after sending the last questionnaire in. In the analysis, we chose to use the answers to the first 23 questionnaires. At that time, 1 year after randomisation, the number of participants was still 98 in the 4 Gy x6 group and 107 in the 8 Gy x1 group. These numbers were considered large enough to obtain reliable results, also for long term survivors.

Survival

The median survival of patients is 30 weeks. There is no significant difference between the two treatment arms ($P= 0.24$) with in the 4 Gy x6 group a median survival of 28 weeks and in the 8 Gy x1 group a median survival of 33 weeks. In Fig. 1 the survival curves are shown. Differences exist for primary tumour type ($P< 0.0001$) with a median survival of 69 weeks for breast cancer patients, 40 weeks for prostate cancer patients, 13 weeks for lung cancer patients and 16 weeks for patients with other types of cancer. As expected, patients stratified in the favourable group lived longer with a median survival of 83 weeks as compared to 27 weeks in the rest of the group ($P< 0.0001$).

Pain

Fig. 2 shows the mean pain scores in both treatment groups in the first 12 weeks after randomisation. Pain reduction is clearly shown in the first 4–6 weeks. In Fig. 3 the mean pain scores are shown in the first year after randomisation. In both figures the 95% confidence intervals overlap considerably and differences between the two treatment groups seem small even towards the end of the year. In an analysis of repeated measures, it is confirmed that no significant differences between the two groups exist ($P= 0.24$) and that the mean difference between the pain scores in the two treatment arms is no more than half a score. Next, a response analysis was performed. Fig. 4 shows the time to response in the overall group. No significant difference is found between the two treatment arms. Median time to response is 3 weeks in both treatment groups. In Fig. 5 the time to response is shown for the favourable group. Again, no effect of treatment schedule could be detected. Moreover, it was shown that the confidence intervals of the differences in response between the two treatment arms stayed well within the margin of 10%. After 1 year this difference was 1% with a margin of about 6%. These results mean that the two treatment schedules can safely be considered equivalent. Time to progression was analysed only for responders and progression defined as a return to the initial pain score or higher. Fig. 6 shows the time to progression in the overall group. The time to progression for the favourable group is shown in Fig. 7. There are no significant differences in time to progression between the two treatment schedules nor in the overall group neither in the favourable group. Median time to progression is 24 weeks



in the 4 Gy x6 arm and 20 weeks in the 8 Gy x1 arm in the overall group whereas in the favourable group 48 weeks are observed irrespective of treatment schedule. There is, however, an effect of primary tumour type ($P < 0.0001$). Breast cancer patients do better than prostate, lung or other cancer patients with median times to progression of 36 weeks, 20 weeks, 10 weeks and 8 weeks respectively. The percentages of patients in response at any time during the first year are given in Table 3. Overall, 71% ($n = 753$) reached a response with 35% ($n = 374$) experiencing a complete response. Progression is shown in 49% ($n = 369$) of the responders later in the year. These percentages of progression are also presented in Table 3. In summary then, there are no significant differences in response rates neither in complete response nor in progression between the two treatment groups. Moreover, there was no indication that the treatment effect depended on tumour type or localisation of bone metastases.

Pain medication

At time of randomisation 88% in the 4 Gy x6 and 87% in the 8 Gy x1 group used analgesics (Table 2). This medication was divided in phase 1 to 3. Analogously to the mean pain scores (Fig. 2 and Fig. 3), we looked at the percentages of patients using pain medication in the first year and more specifically at the percentages of those patients using only phase 3 analgesics. For both percentages, the 95% confidence intervals overlapped suggesting that there are no differences between the two treatment groups. A more advanced analysis is needed and will be performed.

Retreatments

Overall 188 (16%) retreatments took place which reflects that for the majority of patients an acceptable pain relief was achieved. There is a significant difference

TABLE 3 PERCENTAGES OF RESPONSE, COMPLETE RESPONSE AND RESPONSE RELATED PROGRESSION IN THE TWO TREATMENT GROUPS*				
	4 Gy x 6		8 Gy x 1	
	Total			
Response				
Favourable Group	79%	(34/43)	77%	(34/44)
Overall	69%	(361/520)	72%	(392/542)
Breast	75%	(152/203)	78%	(169/218)
Prostate	77%	(96/124)	78%	(95/121)
Lung	58%	(72/125)	62%	(83/133)
Other	60%	(41/68)	64%	(45/70)
Complete response				
Favourable Group	53%	(24/45)	50%	(22/44)
Overall	33%	(175/528)	37%	(199/545)
Breast	39%	(81/206)	49%	(108/219)
Prostate	44%	(55/125)	38%	(46/122)
Lung	19%	(24/127)	28%	(37/133)
Other	21%	(15/70)	11%	(8/71)
Progression				
Favourable Group	38%	(13/34)	44%	(15/34)
Overall	46%	(166/361)	52%	(203/392)
Breast	36%	(55/152)	41%	(70/169)
Prostate	53%	(51/96)	61%	(58/95)
Lung	46%	(33/72)	55%	(46/83)
Other	66%	(27/41)	64%	(29/45)
* Due to early retrieval and missing data, less than 1157 patients are included in the response percentages presented in Table 3				

between the two groups, 147 retreatments (25%) in the 8 Gy x1 group and 41 (7%) in the 4 Gy x6 group. In a logistic regression analysis, it is subsequently shown that retreatment depends on the preceding pain score (P< 0.0001), which means that the higher the pain score, the higher the chance on retreatment. It is shown next that pain is not the only reason to retreat as chances on retreatment still depend on treatment schedule (P< 0.0001) with pain cancelled out. Furthermore, retreatment is shown to take place at an earlier stage in the 8 Gy x1 group (P< 0.0001). With respect to time to retreatment, an average of 14 weeks in the single fraction group is found as compared to 23 weeks in the multi-fraction group. The preceding pain score happens to be 7.52 in the 4 Gy x6 group and 6.82 in the 8 Gy x1 group. A difference that may suggest that a higher pain score is awaited for in the 4 Gy x6 group before re-irradiation is decided on. Table 4 shows the percentages of retreatments related to tumour type and treatment site. It is shown that breast cancer patients are less frequently retreated.

Fractures and spinal cord compression

Overall 34 fractures and 23 spinal cord compressions were observed. Signifi- cantly more fractures were found in the 8 Gy x1 group than in the multiple fraction group, 24 (4%) compared to 10 (2%) (P< 0.05). The mean time to occur- rence was 21 weeks in the single fraction group and 17 weeks in the multifrac- tion group. In Table 5 the percentages of fractures are given by tumour type

TABLE 4 PERCENTAGES OF RETREATMENTS BY PRIMARY TUMOUR TYPE AND TREATMENT SITE				
	4 Gy x 6		8 Gy x 1	
	Total			
Primary Tumour				
Breast	6%	(12/218)	22%	(51/233)
Prostate	11%	(15/138)	22%	(29/129)
Lung	5%	(7/147)	32%	(45/140)
Other	9%	(7/75)	29%	(22/77)
Treatment Site				
Thoracic/Lumbar Spine	4%	(7/177)	18%	(31/165)
Pelvis	9%	(20/224)	27%	(53/199)
Femur	8%	(5/61)	25%	(12/48)
Ribs	11%	(5/44)	23%	(12/53)
Humerus	11%	(3/27)	32%	(11/34)
Other	2%	(1/45)	35%	(28/79)
Total	7%	(41/578)	25%	(147/579)

TABLE 5 PERCENTAGES OF FRACTURES BY PRIMARY TUMOUR TYPE AND TREATMENT SITE				
	4 Gy x 6		8 Gy x 1	
	Total			
Primary Tumour				
Breast	1%	(2/218)	4%	(9/233)
Prostate	2%	(3/138)	5%	(7/129)
Lung	2%	(3/147)	4%	(5/140)
Other	3%	(2/75)	4%	(3/77)
Treatment Site				
Thoracic/Lumbar Spine	1%	(1/177)	2%	(4/165)
Pelvis	2%	(4/224)	3%	(6/199)
Femur	7%	(4/61)	2%	(8/48)
Ribs		(0/44)		(0/53)
Humerus		(0/27)	3%	(1/34)
Other	2%	(1/45)	6%	(5/79)
Total	2%	(10/578)	4%	(24/579)

and treatment site. The difference in the number of spinal cord compressions, 13 (2%) in the 8 Gy x1 and 10 (2%) in the 4 Gy x6 group was not signifi cant.

Quality of life

The analysis of repeated measures showed that no signifi cant differences were observed between the two treatment groups in overall quality of life (P= 0.22).

Side effects

The occurrence of nausea, vomiting, tiredness, itching and painful skin as acute side effects were analysed in the fi rst 4 weeks. For all fi ve, no signifi cant differences were found between the two treatment groups.

Two adverse side effects were reported, a small bowel ileus in the 4 Gy x6 group and a radiation enteritis in reaction to retreatment in the 8 Gy x1 group.

Cost analysis

In the cost analysis, only the medical costs for radiation therapy were consid- ered. In the cost model, a radiotherapy department is thought to produce three

cost carriers: series, fractions and grays. A 4 Gy x6 radiation treatment consists of one series, 6 fractions and 24 grays. Therefore, the costs are estimated as once the costs per series, plus 6 times the costs per fraction, plus 24 times the costs per gray. Similarly, the costs of the 8 Gy x1 radiation treatment are estimated as once the costs per series, plus once the costs per fraction, plus eight times the costs per gray. The costs per retreatment are estimated as the average of the costs of the 4 Gy x6 and the 8 Gy x1 treatment schedules. The costs per cost carrier were calculated in 3 out of 21 Dutch radiotherapy institutes: 1 academic hospital (out of 7), 1 general hospital (out of 8) and 1 independent radiotherapy institute (out of 6). In each institute the costs of different types of staff, equipment, material, housing and overheads for 1997 were calculated. Costs were converted to 1998 Euro using the standard conversion rate (2.20 Dfl =1 Euro ≈ 1 US \$). Each cost item separately was then assigned to the three cost carriers. For example, costs for radiotherapists were mostly assigned to series whereas the costs of linear accelerators were partly assigned to fractions (because equipment wears out by turning it on and off) and partly assigned to grays (because the duration of the on-period wears out equipment). The results of the three institutes were aggregated into a typical radiotherapy department, and weighted relative to the number of each type of institute. For this typical radiotherapy department, the yearly costs assigned to the cost carriers are divided by the yearly number of cost carriers to obtain the costs per series, fraction, and gray. The two treatment schedules are compared based on these assumptions. Table 6 shows the costs for both treatment schedules. The costs for the 4 Gy x6 and the 8 Gy x1 schedules are 2305 and 1734 Euro, leading to a difference of 571 Euro for the first radiation treatment. Including the costs of retreatment reduces the cost difference from 571 Euro to 207 Euro.

Discussion

The purpose of this study was to compare a multifractionated palliative treatment with a single fraction radiotherapy schedule for patients with painful bone metastases. Several studies ⁵⁻⁷ have shown that a single fraction could be as effective as a multiple fraction treatment with a higher total dose. However, others⁹⁻¹¹ indicated the superiority of the latter especially for patients with a more favourable prognosis and a longer survival time. As several of these observations were made in non-randomised or retrospective studies ⁸⁻¹⁰ and the existing prospective studies ^{7,15} were only small with a limited follow-up time, a large nationwide study in which 17 of the 21 Dutch radiotherapy departments participated, was started in 1996. A total of 1171 patients were randomised and a total of 4084 patients registered. The comparison showed that

TABLE 6 COSTS PER COST CARRIER AND TREATMENT SCHEDULE IN EURO			
	Cost carrier	4 Gy x 6	8 Gy x 1
Costs of series	1583	1583	1583
Costs of fractions	90.50	543	91
Costs of grays	7.47	179	60
First radiation treatment		2305	1734
Retreatment		141	505
Costs per treatment schedule		2446	2239

the randomised patients could indeed be considered a representative sample. Of particular interest was a relatively large group of 92 patients with a favourable prognosis. Overall, a total number of 205 patients completed questionnaires up to year. Using weekly questionnaires to be filled out by the patients at home for the first 12 weeks of follow-up and monthly thereafter, we obtained data on the pain profiles of the patients, the results of which can only be discussed globally in this paper with an emphasis on the comparison of the two groups. The composition of the two randomisation groups was well balanced and as could be expected from the literature with respect to tumour type and site of the bone metastases. The use of analgesics both in type and frequency was the same for both groups and there were no initial differences in systemic treatment. The compliance of the participating patients was better than expected. Most patients sent in their forms in time and only stopped because of imminent death or deterioration of their general condition.

The repeated measures analysis showed that the incidence of pain relief including retreatments was the same in both arms. This was also true with respect to time to response and time to progression, for the overall group as well as for the favourable group with long term survivors. Chances to receive retreatments, however, were clearly higher in the single dose treatment group than in the multifraction group. We were able to show that the level of the pain scores at time of decision to retreat justified re-irradiation. The results of the analysis indicated that the level of preceding pain was not the only reason to retreat. Regardless of pain, patients in the single fraction group experienced more retreatments. The preceding pain score appeared to be slightly higher in the multifraction group, which might indicate a greater readiness to prescribe another series of radiation in patients treated with one fraction only. Moreover, the interval until retreatment was substantially shorter in the single fraction group which might indicate that the duration of pain relief in this group is less good or again indicate the greater willingness to retreat. Regarding the duration of response, time to progression appeared to be shorter in the single fraction group but not significantly. Our results on retreatment with more retreatments in the single fraction group are in accordance with other studies^{3,11,15} and were recently demonstrated in a study by Nielsen et al. ⁶ where retreatment was given in 12% in the multi-

fraction group (5 Gy x4) and 21% in the single fraction group (8 Gy x1). The reasons for retreatment remain often unclear. Hoskin et al. suggested that a lower threshold in the single fraction group may play a role. Our results point in the same direction and will be subjected to further study. Nevertheless, with a 25% retreatment in the single dose group and a 7% in the multiple fractionated group, the overall efficacy of the two treatment schedules is equal, also in the long run. A 25% retreatment which can safely be applied still means that 75% of the patients are optimally palliated with one single fraction.

Our data need to be further analysed to determine whether we can identify groups of patients for whom one single fraction treatment might not be the best approach. The response rate for instance was best in patients with breast and prostate cancer. These patients also had the highest complete response rate and consequently this was true for patients with a favourable prognosis. Progression was less frequently seen in breast cancer patients although their survival was longest. The opposite was true for lung cancer patients with more progression and a shorter life span. These differences indicate the importance of a closer look at duration of pain relief in relation to survival with respect to tumour type, localisation of bone metastases and treatment schedule.¹¹

Also with regard to number of fractures, we need a better analysis of the localisation involved, the actual size of the metastasis, field size, etc. From the literature it is still unclear what the effect of fractionation is on the incidence of fractured bones^{1,11,16} Both percentages in our study, however, including the 4% in the single dose group, are considered low and fall below the percentages of 5% and 8% mentioned in studies where similar treatment schedules in similar groups of patients are used.^{6,8} The analysis of the overall quality of life showed no differences for treatment schedule. Further details with respect to pain relief in relation to the more specific domains of quality of life will be discussed elsewhere. The medical costs of the 4 Gy x6 and the 8 Gy x1 treatment schedules are estimated at 2305 and 1734 Euro. Although the former has six fractions instead of one, the difference in costs is limited. Compared to other types of radiation therapy, both schedules have relatively few fractions. As a result, a large proportion of the costs is independent of the number of fractions and total dose. If retreatment is taken into account, the cost difference further reduces from 25% to only 8%. Furthermore, the saving of radiotherapy capacity is considered the major economic advantage of the single dose schedule.

In conclusion, the global analysis of our study indicates the equality of a single fraction as compared to a 6 fractions treatment in patients with painful bone metastases provided that 4 times more retreatments are accepted in the single dose group. This equality is also observed in patients with long term survival. Given this equality, our general conclusion is that a single fraction that is more convenient to the patient and more economic to the radiotherapy

department, is preferred in patients with painful bone metastases even at the expense of a higher chance on retreatment. Further analysis of our data is in progress to identify patients for whom one single fraction might not be advisable based on tumour, pain and other characteristics particularly in relation to durability of pain relief.

Reference List

1. Bates T. A review of local radiotherapy in the treatment of bone metastases and cord compression. *Int J Radiat Oncol Biol Phys* 1992; 23(1):217-221.
2. Blitzer PH. Reanalysis of the RTOG study of the palliation of symptomatic osseous metastasis. *Cancer* 1985; 55(7):1468-1472.
3. Nielsen OS. Palliative treatment of bone metastases. *Acta Oncol* 1996; 35:58-60.
4. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group. *Cancer* 1982; 50(5):893-899.
5. Gaze MN, Kelly CG, Kerr GR, Cull A, Cowie VJ, Gregor A et al. Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. *Radiother Oncol* 1997; 45(2):109-116.
6. Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiother Oncol* 1998; 47(3):233-240.
7. Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986; 6(4):247-255.
8. Uppelschoten JM, Wanders SL, de Jong JM. Single-dose radiotherapy (6 Gy): palliation in painful bone metastases. *Radiother Oncol* 1995; 36(3):198-202.
9. Arcangeli G, Micheli A, Arcangeli G, Giannarelli D, La Pasta O, Tollis A et al. The responsiveness of bone metastases to radiotherapy: the effect of site, histology and radiation dose on pain relief. *Radiother Oncol* 1989; 14(2):95-101.
10. Arcangeli G, Giovinozzo G, Saracino B, D'Angelo L, Giannarelli D, Arcangeli A et al. Radiation therapy in the management of symptomatic bone metastases: the effect of total dose and histology on pain relief and response duration. *Int J Radiat Oncol Biol Phys* 1998; 42(5):1119-1126.
11. Ratanatharathorn V, Powers WE, Moss WT, Perez CA. Bone metastasis: review and critical analysis of random allocation trials of local field treatment. *Int J Radiat Oncol Biol Phys* 1999; 44(1):1-18.
12. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain* 1986; 27(1):117-126.
13. World Health Organization. *Cancer Pain Relief*, Geneva. 1986.
14. de Haes H, Olschewski M, Fayers P, et al. Measuring the quality of life of cancer patients with the Rotterdam Symptom Checklist (RSCL): a manual, *Northern Centre for Healthcare Research*. 1996. Groningen, The Netherlands.
15. Hoskin PJ, Price P, Easton D, Regan J, Austin D, Palmer S et al. A prospective randomised trial of 4 Gy or 8 Gy single doses in the treatment of metastatic bone pain. *Radiother Oncol* 1992; 23(2):74-78.
16. Hoskin PJ. Scientific and clinical aspects of radiotherapy in the relief of bone pain. *Cancer Surv* 1988; 7(1):69-86

Appendix 2

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