Radiotherapy in bone metastasis : the Dutch bone metastasis study

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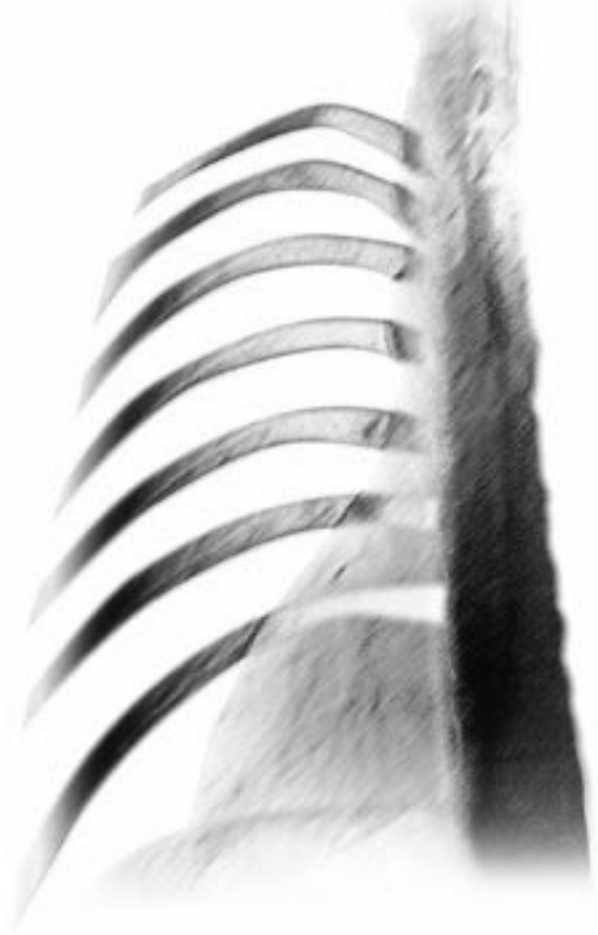

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Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment

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Abstract

Purpose: The Dutch Bone Metastasis Study on the effect on painful bone metastases of 8 Gy single fraction (SF) vs. 24 Gy in multiple fractions (MF) showed 24% retreatment after SF vs. 6% after MF (P< 0.001). Purpose of the present study was to evaluate factors influencing retreatment and its effect on response.

Methods & Materials: The database on all randomized patients was re-analyzed with separately calculated responses to initial treatment and retreatment.

Results: Response to initial treatment was 71% after SF vs. 73% after MF (P= 0.84). Retreatment raised response to 75% for SF; MF remained unaltered (P= 0.54). The response status after initial treatment did not predict occurrence of retreatment: 35% SF vs. 8% MF non-responders, and 22% SF vs. 10% MF patients with progressive pain were retreated. Logistic regression analyses showed the randomization arm and the pain score before retreatment to significantly predict retreatment (P< 0.001). Retreatment for non-responders was successful in 66% SF vs. 33% MF patients (P= 0.13). Retreatment for progression was successful in 70% SF vs. 57% MF patients (P= 0.24).

Conclusions: With or without the effect of retreatment, single and multiple fraction radiotherapy provided equal palliation for painful bone metastases. Irrespective of response to initial treatment, physicians were more willing to retreat after SF. Overall, retreatment was effective in 63% of retreated patients.

Introduction

Radiotherapy is a well-accepted and effective local treatment modality for patients with painful bone metastases. Various retrospective and prospectively randomized studies have focused on the effect of different dose schedules, studying both single fraction (SF) and multiple fraction (MF) regimens.[1-17] The majority of these studies concluded that SF radiotherapy was equally effective to MFs for most patients. Although one review concluded the opposite,[18] 3 systematic reviews and a recently published meta-analysis also concluded that no significant differences in pain relief could be detected between single and multiple fraction regimens.[19-22] However, the authors of the meta-analysis commented that additional data were required to evaluate the role of retreatment during follow-up,[22] because the randomized trials used various definitions with regard to the calculation of response and the means by which a possible retreatment during follow-up was reported. In this respect, in 2002 already an international consensus agreement was published on endpoint definitions for future clinical trials in order to achieve more uniformity in bone metastases research.[23]

In the largest study to date, the Dutch Bone Metastasis Study (DBMS) on the effect of 8 Gy SF vs. 24 Gy in 6 fractions, responses were calculated including the effect of a possible retreatment during follow-up.[5] Retreatment was given at the discretion of the treating physician. Within the first year after randomization, significantly more patients were retreated after SF (24%) as compared with MFs (6%) (P< 0.001). No major differences were reported in overall response rates (72% after SF vs. 69% after MFs), duration of response or progression rates. Therefore, the global analysis of the DBMS concluded a SF to be as effective as MFs, provided that 4 times more retreatment were accepted to reach the same response percentages.[5]

In order to evaluate whether SF radiotherapy would remain successful with the effect of retreatment excluded from the response calculations, we re-analyzed the database of the DBMS. Separate responses to initial treatment and retreatment were calculated in alignment with the international consensus agreement on endpoint definitions.[23] In addition, the response status of retreated patients before retreatment was labeled to identify factors influencing retreatment. Lastly, the efficacy of retreatment was studied.

Material and Methods

Patient selection and follow-up

Between March 1996 and September 1998, 1157 Dutch patients with painful bone metastases were randomized between a single fraction of 8 Gy (n= 579)

TABLE 1 INCLUSION- AND EXCLUSION CRITERIA OF THE DUTCH BONE METASTASIS STUDY

Randomization criteria

Inclusion	Exclusion
Informed consent	No informed consent
Metastases of solid tumors	Pathological fracture or impending fracture needing surgical fi xation
Pain score minimum 2 on 11-pointscale (0= no pain to 10= worst imaginable pain)	Spinal cord compression
Metastases treatable in one radiotherapy target volume	Metastases of renal cell carcinoma or melanoma*
No previous radiotherapy to same metastases	Metastases in cervical spine†

* *Metastases of renal cell carcinoma or melanoma were excluded because of expected different biological behavior*

† *Metastases in the cervical spine were excluded because it was believed that large fractions might lead to a radiation-induced myelopathy*

FIGURE 1

Time scales for analysis of response to initial treatment and retreatment in patients with painful bone metastases treated within the Dutch Bone Metastasis Study

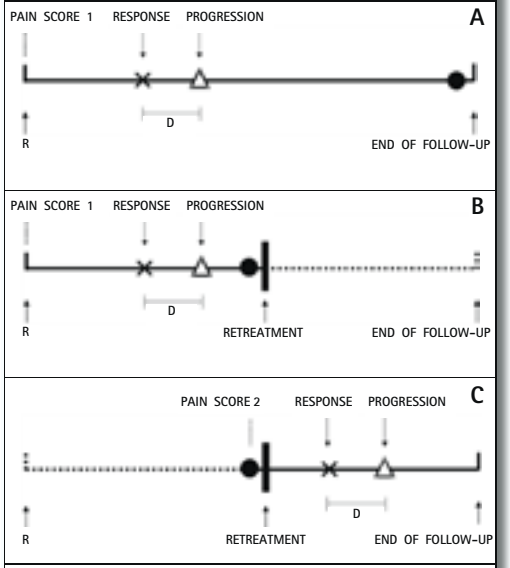


Figure legends

Time scale A refers to patients who were not retreated during follow-up. Time scales B and C refer to patients who were retreated during follow-up. For (B) effect of initial treatment, change in pain score compared to randomization pain score, ior (C) effect of retreatment: change in pain score compared to pain score week prior to retreatment

R = *Randomization*
Pain score 1 = *randomization pain score*
Pain score 2 = *pain score week prior to retreatment*
● = *Response status of the patient after initial treatment: non-responder, responder, or responder with subsequent progression*
D = *Duration of remission*
····· = *For time scale B: time period after retreatment until end of follow-up. For time scale C: time period from randomization until retreatment*

and 6 fractions of 4 Gy (n= 578). [5] Seventeen out of 21 Dutch radiotherapy in stitutes participated in the trial. Patients had a minimal pain score of 2 on an 11-point scale from 0 (no pain) to 10 (worst imaginable pain). [24] The rando - mi zation criteria are listed in table 1. At randomization and during follow-up, patients fi lled out 13 weekly questionnaires by mail and continued with monthly questionnaires to a maximum of 2 years or until death. The patients reported the maximum pain they experienced at the treatment site during the preceding week using the 11-point scale. Concomitant use of analgesics was noted, divided into phase 1 (non-opoid analgesics: paracetamol and non- steroid anti-infl ammatory drugs), phase 2 (non-opoid analgesic combinations with weak opoids), phase 3 (strong opoids, like morphine) and phase 4 (non-oral administration of opoids). The Rotterdam Symptom Checklist (RSCL) was adapted to measure acute treatment side effects[25]: nausea, vomiting, itching, painful skin and tiredness were reported on a 4 point scale from 1 (not at all) to 4 (very much). In the study protocol no guidelines for the application of retreatment were prescribed. In December 1998 the survival status of all patients was updated and the study was closed. For the current analysis, all patients were re-evaluated for their response to initial treatment, with a focus on the 173 patients who were retreated within the fi rst year after randomization. Patients were clustered according to their primary tumor into four groups: breast cancer, prostate cancer, lung cancer and other primary tumors.

Response definitions

Response to treatment was calculated taking into account changes in the administration of opoids. A change from phase 1 or 2 to phase 3 or 4 was noted as an analgesic increase. If the patient stopped using phase 3 or 4 analgesics, this was noted as an analgesic decrease. Partial response (PR) was defi ned as (1) a decrease in the initial pain score by at least two points on the 11-point pain scale, without analgesic increase, or (2) analgesic decrease without an increase in pain. Complete response (CR) was defi ned as a decrease in the initial pain score to zero on the pain scale, without concomitant analgesic increase. When pain scores remained unaltered or when they increased the patient was considered to be a non-responder (NR).
Progression after response was defi ned as (a) an increase in pain with return to the initial pain score or higher, without analgesic increase, or (b) analgesic increase irrespective of the pain score.

Response calculations

Response to treatment was calculated excluding and including the effect of a possible retreatment during follow-up. Figure 1 shows 3 different time scales in order to interpret the possible events during follow-up.

LE 2 RETREATED PATIENTS IN THE DUTCH BONE METASTASIS STUDY ACCORDING TO THE PRIMARY TUMOR A THE RESPONSE STATUS AFTER INITIAL TREATMENT

	Non-responder (N = 310)				Responder (N = 789)				Progression (N = 387)			
	N	%	Pain* †	Time †	N	%	Pain †	Time †	N	%	Pain	Time ‡
st	92	27	8 6		342 4	5.5 18			142	14	7.8	*5*
tate	56 11 7.8 21				197 7 4.1 21				111 16 7.4			*11*
g	107 22 7.7 10				162 7 3.8 11				78 19 7.2			*5*
er	55 24 7.4 10				88 5 6.5 8				56 18 8.3			*9*

number of patients, 1099 patients were labeled into non-responders or responders. In addition, responders with progressive pain are listed rately in the third column
Mean pain score the week prior to retreatment
Mean time to retreatment from randomization in weeks
Mean time to retreatment from date of progression in weeks

LE 3 RETREATMENT PERCENTAGES ACCORDING TO THE PATIENT CHARACTERISTICS AT TIME OF RANDOMIZATION INTO THE DUTCH BONE METASTASIS STUDY

	Total N = 1157	Not retreated N = 984	Retreated N = 173	UV* *P-value*	HR (95%CI)	MV* *P-value*
ale	533	87%	13%	0.001	1	0.71
e	624	83%	17%		1.7 (1.2-2.3)	
n (range)		65 (32-89)	65 (33-86)	0.09		
score†						
n (range)		6.3 (2-10)	6.4 (2-10)	0.05		
‡						
n (range)		70% (20-100)	77% (40-100)	0.003		0.001
nary tumor						
st	451	87%	13%		1	0.01
tate	267	86%	14%	0.46		
g	287	83%	17%	<0.001	2.6 (1.7-3.8)	
er	152	82%	18%	<0.001	2.3 (1.4-3.6)	
alization						
e	342	89%	11%		1	
s	432	84%	16%	0.04	1.5 (1.0-2.3)	
ur	109	87%	13%	0.42		
nerus	61	79%	21%	0.01	2.3 (1.2-4.3)	
	97	84%	16%	0.06		
er	123	79%	21%	0.001	2.3 (1.4-3.8)	
mber of metastases						
ciple	675	87%	13%	0.02	1	0.18
ary	482	83%	17%		1.4 (1.1-1.9)	
medication						
e	136	81%	19%		1	
se 1/2	531	82%	18%	0.99		
se 3/4	490	89%	11%	0.32		
emic therapy						
	626	86%	14%	<0.001	1	0.37
	531	84%	16%		1.7 (1.3-2.3)	
domization arm						
4 Gy	578	94%	6%	<0.001	1	<0.001
8 Gy	579	76%	24%		4.3 (2.9-6.1)	

numbers of patients, percentages add up horizontally
UV= univariate analysis, HR= hazard ratio calculated with Cox proportional hazards model, 95% CI= 95% confi dence intervals, MV=multivariate analysis
Pain score at randomization
Karnofsky Performance Score= physical score, ranging from 100% (=normal situation, no complaints) to 0% (= death)

For patients who were not retreated during the fi rst year of follow-up time scale A is applicable (N= 984).

Time scale A

Time scale A starts at the date of randomization and ends at the end of follow-up. During follow-up, patients either responded to initial treatment or not. At that moment, the response status of the patient was marked as non-responder or responder. In addition, if the patient had responded and progressive pain was noted, he or she was also marked as having progression. Time to response and time to subsequent progression were calculated from the date of randomization. Duration of remission was calculated subtracting time to response from time to progression or end of follow-up.

For patients who were retreated during the fi rst year of follow-up (N = 173), time scales B and C are applicable. Their follow-up time was split into the period before retreatment (= B) and the period after retreatment (= C) in order to study the effect of the initial treatment, the additional effect of retreatment on initial response, and the changes in pain scores after retreatment compared with the painscore that was reported the week before retreatment.

Time scale B

Time scale B starts at the date of randomization and ends at the date of the retreatment. The response status of the patient the week before retreatment was labeled to calculate response rates excluding the effect of retreatment. The patient was either a non-responder or a responder to initial treatment. In addition, if the patient responded, and progressive pain was noted before retreatment, the patient was also marked as having progression. Time to response and time to subsequent progression were calculated from the date of randomization. Duration of remission was calculated subtracting time to response from time to progression or the date of retreatment.

Time scale C

Time scale C starts at the date of retreatment and ends at the end of follow-up. The response status of the patient and the reported pain score the week before retreatment (= pain score 2) were used as reference points in order to study the effi cacy of retreatment. Response after retreatment was calculated for non- responders and responders. In addition, for responders who already experienced progressive pain before retreatment, response after retreatment was reported separately. Time to response and time to subsequent progression after retreatment were calculated from the date of retreatment. Duration of remission was calculated subtracting time to response after retreatment from time to progression or end of follow-up.

For the calculation of response no fi xed time interval from the date of randomization or the date of retreatment was applied. Response to treatment was

calculated if at least two successive follow-up pain scores were available. Because 58 patients (5%) did not return enough questionnaires to determine response, analysis of response to initial treatment was possible in 1099 patients. Of the 173 first year retreated patients, 21 did not return a pain score the week before retreatment. Six patients returned questionnaires the following weeks and were included in the response analysis. For these patients, the pain score reported the week in which the retreatment was given was used. In addition, 13 patients returned no further pain scores after retreatment was given. Thus, in 145 patients (84%) enough pain scores were available to calculate response to retreatment.

Statistical analysis

The database was analyzed using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA). Patient baseline characteristics were studied for their value of predicting retreatment. Fisher's Exact tests were used to compare proportions. Kaplan Meier and log rank statistics were used for survival analysis. A Cox proportional hazards model was used for univariate and multivariate analyses, with hazard ratio's correcting for the effect of early death of patients *(Tables 3 and 4)*. A logistic regression model was used to model the weekly hazard on retreatment as a function of the pain scores and the randomization treatment arm. All reported P-values are based on two-sided tests with $P< 0.05$ taken to be significant.

Results

Response to initial treatment and additive effect of retreatment

Without the effect of a retreatment, 71% of 556 SF patients and 73% of 543 MF patients responded (P= 0.84, HR 1.0 (95% CI 0.9-1.1)). Three percent of responders in both arms were due to a decrease in analgesics intake (n=18). In both treatment arms, 14% of the patients reached a complete response. Mean time to response was 3 weeks in both SF and MF patients. Mean duration of remission was 18 weeks for SF patients and 19 weeks for MF patients.

If the response percentages included the effect of retreatment on the randomization pain score, total response rates of SF patients increased with 4% to 75%. In addition, CR rates improved from 14% to 15%. In MF patients no additional benefit of the retreatment was seen, total response remained 73%. In summary, no significant differences were observed between MF and SF patients with the effect of retreatment included in the total response percentages (P= 0.54, HR 0.96 (95% CI 0.84-1.1)).

For the different primary tumors, patients with breast cancer or prostate cancer had the highest response rates after initial treatment (for breast, 78% after SF, 80% after MF: for prostate, 77% after SF, 78% after MF). Of patients with lung cancer, 58% responded after SF and 62% after MF, whereas patients with other primary tumors responded in 63% after SF and 60% after MF. Mean time to response was 3 weeks in all patients, except in patients with prostate cancer (mean time to response 4 weeks). Mean duration of remission was 24 weeks in breast cancer, 18 weeks in prostate cancer, and 11 weeks in lung cancer and other primary tumors. Apparantly, patients with breast- and prostate cancer benefitted most of the radiation therapy.

No additional effect of retreatment was seen in SF patients with prostate cancer, but response rates increased in SF patients with breast cancer, lung cancer or other primary tumors (for breast, from 78% to 84%: for lung, from 58% to 62%: for other primary tumors, from 63% to 68%). In MF patients, retreatment was additive only in patients with prostate cancer, from 78% to 79%.

Time to retreatment

Overall, mean time to retreatment was 13 weeks in SF patients vs. 21 weeks in MF patients *(Figure 2)*. The mean pain score the week before retreatment was 6.8 in SF patients vs. 7.5 in MF patients. For the different primary tumors, mean time to retreatment was 22 weeks for prostate cancer at a mean pain score of 6.3, 14 weeks for breast cancer at a mean pain score of 7.4, 11 weeks for lung cancer at a mean pain score of 6.5 and 13 weeks for other primary tumors at a mean pain score of 7.6. Apparently, a longer waiting period was observed in patients with prostate cancer to start retreatment as compared with the other 3 tumor groups. In addition, because SF patients with breast cancer, lung cancer and other primary tumors were retreated earlier than MF patients, retreatment raised the response percentages for these types of tumors, as was shown previously.

Factors influencing retreatment

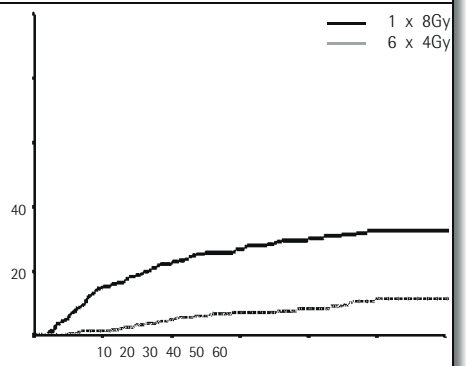
Response status after initial treatment: 3 possible reasons for retreatment

1. Non-responder

Figure 3 illustrates the percentages of retreated patients according to their response status before retreatment. After initial treatment, 161 SF and 149 MF patients were non-responder. Thirty-five percent of SF patients were subsequently retreated vs. only 8% of MF patients. Mean time to retreatment was 8 weeks for non-responding SF patients vs. 19 weeks for MF patients. The preceding mean pain score was 7.7 in SF patients and 8.3 in MF patients. Evidently, the threshold to give a retreatment was lower in a non-responding SF patient than in MF patients.

URE 2

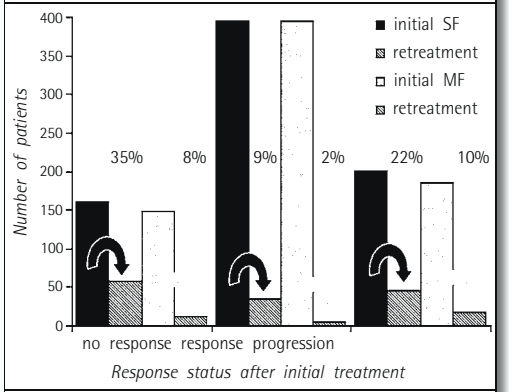
eatment for the randomization arms single fraction versus tiple fractions in patients with painful bone metastases ted within the Dutch Bone Metastasis Study



nber of patients 'at risk'
8 Gy 579 406 272 206 157 121
4 Gy 578 457 329 242 183 149

FIGURE 3

Retreatment percentages for patients with painful bone metastases in relation to the response status after initial treatment



SF= 1 x 8 Gy MF= 6 x 4 Gy

Table 2 shows the percentages of retreated patients according to their response status after initial treatment and primary tumor. Twenty-seven percent of non-responding breast cancer patients was retreated, at a mean time from randomization of 6 weeks. The mean pain score before retreatment was 8 in these patients. Non-responding patients with prostate cancer were least retreated, only 11%, at a mean time of 21 weeks after randomization.

2. Responder

Of 395 initial SF responders, 9% (n= 35) was retreated to further decrease their pain scores or to consolidate the status of remission *(Figure 3)*. Of 394 responding MF patients, only 2% (n= 6) was retreated while in remission. The mean pain score before retreatment was 4.4 for SF patients vs. 5.6 for MF patients. Mean time to retreatment was 14 weeks in SF patients and 26 weeks in MF patients. In conclusion, when a patient responded to initial treatment, SF patients were more frequently retreated to consolidate or further reduce the pain score, at a lower pain score and earlier during follow-up than MF patients. For the different primary tumors, retreatment rates for patients in remission were lowest in breast cancer patients, only 4% *(Table 2)*. Patients with primary tumors other than breast, prostate or lung were retreated earliest, at mean 8 weeks from randomization.

3. Progression

In total, 49% (n= 387) of the 789 responders to initial treatment experienced progressive pain: 51% (n= 201) of initial SF responders and 47% (n= 186) of initial MF responders (P= 0.73, HR 1.0 (95% CI 0.8-1.3)). Mean time to progression was 12 weeks in both groups. Mean duration of remission for progressive patients was 8 weeks in both groups. Of all patients with progressive pain, 22% (n= 45) were retreated after initial SF vs. only 10% (n= 18) after initial MF *(Figure 3)*. After progressive pain was observed, mean time to retreatment was 7 weeks in SF patients and 10 weeks in MF patients. The preceding mean pain score was 7.5 in SF patients and 7.8 in MF patients. In conclusion, it appeared that physicians were more reluctant to retreat initial MF patients with progression than initial SF patients.

For the different primary tumors, the percentage of responders with progressive pain was 42% (n= 142) for breast cancer, 56% (n= 111) for prostate cancer, 48% (n= 78) for lung cancer, and 64% (n=56) for other primary tumors. Mean duration of remission for progressive patients was 10 weeks in patien ts with breast- and prostate cancer, 5 weeks in patients with lung cancer, and 7 weeks in patients with other primary tumors. In summary, patients with breast cancer had the lowest progression rates and also the longest duration of remission before progression, irrespective of the treatment arm. Progressive patients with lung cancer were retreated most often (19%) and earliest after rando mization (5 weeks), at a mean pain score of 7.2 *(Table 2)*. If progressive pain was noted, time to retreatment was longest in patients with prostate cancer (11 weeks).

Altogether, although SF and MF patients experienced equivalent response rates and subsequent progression rates, SF patients were retreated more frequently, at an earlier time during follow-up, and at a lower pain score. Differences in response to initial treatment and subsequent progression did not explain the different retreatment rates between SF and MF patients.

Patient baseline characteristics

Patient characteristics at randomization were analyzed to evaluate which characteristics determined retreatment *(Table 3)*. Of all male patients, 17% was retreated vs. 13% of female patients (P= 0.001). Male patients more frequently suffered from lung cancer or other primary tumors, and because these tumor types had a higher chance of receiving retreatment than patients with breast or prostate cancer (P< 0.001), male patients were retreated more often. Patients with lung cancer had a higher chance to be retreated as compared with breast cancer patients (HR 2.6), probably because their response to initial radio - therapy was lower. In addition, most patients with breast or prostate cancer received some kind of systemic therapy, 79% and 81%, respectively, in contrast to patients with lung cancer (12%) or other primary tumors (14%). Concomittant use of systemic therapy perhaps made the physician decide to postpone giving another course of radiotherapy. Retreated patients had a better Karnofsky Performance Score (KPS) at baseline than those not retreated, mean 77%

vs. 70%, respectively (P= 0.003). This result is most likely caused by longevity. After initial SF, 24% of the patients were retreated vs. only 6% of MF patients (P< 0.001). In a multivariate analysis including all signifi cantly different risk factors from the univariate analyses, primary tumor, KPS and randomization arm remained predictive for retreatment (P= 0.01, P= 0.001 and P< 0.001, res - pectively). These fi ndings suggest that the randomization arm was the most important predictor for receiving a retreatment during follow-up.

Logistic regression analysis

A logistic regression analysis was performed to identify risk factors for retreatment. It showed that the chance of receiving a retreatment depended upon the randomization arm (P= 0.0001, HR 4.6 (95% CI 3.0-6.9)), but also on the pain score the week before retreatment (P= 0.0001, HR 1.4 (95% CI 1.4-1.6)). The pain scores for an individual patient in each follow-up week without retreatment were considerably lower (mean 4.7 for SF, mean 4.6 for MF) compared with the pain scores the week before the retreatment (mean 6.8 for SF, mean 7.5 for MF). In conclusion, the higher the reported pain, the higher the chance of receiving a retreatment.

Retreatment dose schedule

In 137 retreated SF patients, 33% received a second SF and 67% received MFs. In 36 retreated initial MF patients, 25% received second MF and 75% received a SF. To evaluate whether response to initial treatment infl uenced the choice for the second treatment schedule, we studied the response status before retreatment. There was no correlation between the initial response status and the retreatment schedule (for initial SF, P= 0.90, for initial MF, P= 0.68).

Response to retreatment

Table 4 lis ts the effect of retreatment on the pain experienced the week be fore retreatment (see time scale C, Figure 1). In total, 63% of retreated patients responded to retreatment: 66% of retreated SF patients responded compared with 46% of MF patients (P= 0.12, HR 1.6 (0.9-3.0)). After retreatment, time to response was not different for initial SF and MF patients, but the mean duration of remission was substantially longer in initial SF patients, 16 weeks vs. only 8 weeks in initial MF patients. For SF patients, response to retreatment was irrespective of the initial response: 66%, 67%, and 70% of initial non- responders, responders, and progressive patients, respectively, responded to retreatment. Although more initial SF than MF non- responding patients responded to retreatment, due to small numbers this difference reached no signifi cance (66% vs. 33%, respectively, P= 0.13, HR 3.0 (0.7-12.7)).

TABLE 4 RESPONSE TO RETREATMENT FOR THE RANDOMIZATION TREATMENT ARMS

	SF (N=119)	MF (N=26)	UV* *P-value*	HR (95% CI)
Response retreatment †	66%	46%	0.12	1.6 (0.9-3.0)
Time to response ‡	5	6		
Duration of remission ‡	16	8		
Response retreatment §				
After SF	74% (29/39)	43% (9/21)		
After MF	63% (50/80)	60% (3/5)		
Response retreatment ||				
Non-responder	66% (31/47)	3% (2/6)	0.13	3.0 (0.7-12.7)
Responder	67% (48/72)	50% (10/20)	0.23	1.5 (0.8-3.0)
Progression	70% (30/43)	57% (8/14)	0.24	1.6 (0.7-3.5)

SF = 1 x 8 Gy, MF= 6 x 4 Gy, N= number of patients. Between brackets: number of responders/total number of retreated patients. Due to missing data, response to retreatment was calculated in 145 patients

* *UV= univariate analysis, HR= hazard ratio calculated with Cox proportional hazards model, 95% CI= 95% confi dence intervals*

† *Response to retreatment: changes in pain score after retreatment compared to pain score the week prior to retreatment*

‡ *Mean time to response after retreatment in weeks, mean duration of remission for responders in weeks*

§ *Response to retreatment according to the retreatment radiotherapy dose schedule*

|| *Response to retreatment according to the response status prior to retreatment. Responder= all responders to initial treatment. Progression= patients who experienced progressive pain prior to retreatment. Percentages add up exceeding 100%*

TABLE 5 RESPONSE TO RETREATMENT ACCORDING TO THE RESPONSE STATUS AFTER INITIAL TREATMENT AND THE RETREATMENT DOSE SCHEDULE

1st treatment	Response status	2nd treatment	Response 2nd*	Time†	2nd Remission
SF (137)	Non-responder 42% (57)	35% SF (20) 65% MF (37)	88% (15/17) 53% (16/30)	5 3	25 10
	Responder‡ 58% (80)	31% SF (25) 69% MF (55)	64% (14/22) 68% (34/50)	6 6	16 13
	Progression 32% (45)	35% SF (15) 65% MF (30)	64% (9/14) 75% (21/28)	4 6	16 12
MF (36)	Non-responder 33% (12)	83% SF (10) 17% MF (2)	4 0% (2/5) 0% (0/1)	8 -	4
	Responder‡ 67% (24)	71% SF (17) 29% MF (7)	44% (7/16) 75% (3/4)	6 6	8 8
	Progression 50% (18)	67% SF (12) 33% MF (6)	4 5% (5/11) 100% (3/3)	7 6	11 8

SF = 1 x 8 Gy, MF= 6 x 4 Gy, Numbers of patients are between brackets

* *Response to retreatment: changes in pain score after retreatment compared to pain score the week prior to retreatment. Due to missing data, response to second treatment was calculated in 145 patients. Between brackets: number of responders/total number of retreated patients*

† *Mean time to response after retreatment in weeks, mean duration of remission for responders in weeks*

‡ *Response to retreatment according to the response status prior to retreatment. Responder= all responders to initial treatment. Progression= patients who experienced progressive pain prior to retreatment. Percentages add up exceeding 100%*

Table 5 lists the response to retreatment with regard to the response status after initial treatment and the second treatment schedule. Of non-responders to initial SF, 88% responded to a second SF, and 53% to MF. Of the latter, 10% of responses were due to a decrease in analgesics intake. Overall, no major differences in mean time to response after retreatment were reported. Mean duration of remission ranged from 4 weeks in initial MF non-responders to 25 weeks in initial SF non-responders.

Response to retreatment for the different primary tumors is listed in table 6. Patients with prostate cancer had the lowest success rate: 20% of initial non-responding patients responded, and only 19% of patients with progression responded again. Patients with breast cancer had the highest response percentages for non-responders and progressed patients (82% and 89%, respectively). Mean duration of remission was longest in initial non-responding breast cancer patients (23 weeks). In summary, retreatment was successful in a high percentage of patients with breast cancer, lung cancer and other primary tumors, but patients with prostate cancer experienced little benefi t of the retreatment.

Toxicity and adverse events

Toxicity 1 month after retreatment was scored in approximately 73% of the re-treated patients. No major differences in nausea, vomiting, itching, painful skin, or tiredness were reported between initial SF or MF patients. Most SF and MF patients reported no or only mild nausea and vomiting. Nausea score 4 (very bad) was reported in 12% of MF patients vs. 6% of SF patients (P= 0.39).

TABLE 6 RESPONSE TO RETREATMENT FOR THE PRIMARY TUMORS ACCORDING TO THE RESPONSE STATUS AFTER INITIAL TREATMENT

	Breast (N= 52)	Prostate (N= 33)	Lung (N= 40)	Other (N= 20)
Response to retreatment*				
Non-responder	82% (18/22)	20% (1/5)	50% (8/16)	60% (6/10)
Responder	80% (24/30)	43% (12/28)	67% (16/24)	60% (6/10)
Progression	89% (16/18)	19% (3/16)	86% (12/14)	75% (6/8)
Time to response†				
Non-responder	4	2	7	4
Responder	6	7	5	3
Progression	7	8	4	3
Duration of remission‡				
Non-responder	23	-	8	11
Responder	18	6	12	6
Progression	17	-	6	10

N = number of patients. Due to missing data, response to second treatment was calculated in 145 patients. Between brackets: number of responders/total number of retreated patients

* *Response to retreatment according to the response status prior to retreatment. Responder= all responders to initial treatment. Progression= patients who experienced progressive pain prior to retreatment. Percentages add up exceeding 100%. Changes in pain score after retreatment compared to pain score the week prior to retreatment*

† *Mean time to response after retreatment in weeks*

‡ *Mean duration of remission for responders in weeks*

Vomiting score 4 (very bad) was reported in 1 MF patient and 2 SF patients (P= 0.49). All MF and most SF patients reported no or only mild itching (P= 1.0). Itching score 4 (very bad) was seen in 2 SF patients. One SF patient reported a painful skin score 4 (very bad). Severe tiredness was reported in 18% of SF patients and 27% of MF patients (P= 0.41).

Discussion

In 2000, an International Bone Metastases Consensus Working Party was initiated in order to promote consistency in endpoint defi nitions in future clinical trials on the treatment of patients with painful bone metastases, and resulted in a written consensus.[23] Participants in the consensus works fi lled out surveys containing preferences on bone metastases related issues, and visited the consensus meeting in Boston, USA in October 2000 at the ASTRO Annual Conference. Besides other important issues, the consensus stated that retreatment should not be included in the primary outcome of the fi rst irradiation and response to retreatment should be separately analyzed. The present re-analysis of the DBMS followed the international guidelines as strict as possible, incorporating changes in analgesics intake into the response calculations and defi ning a complete response as a pain score lowering to zero. Some exceptions were made: response rates anywhere during follow-up were calculated, opposite to the consensus that formulated to determine response at 1, 2 and 3 months (supported by 30 out of 41 survey responders). In addition, decrease in analgesics intake was defi ned as a change from phase 3 or 4 to phase 1 or 2, instead of a 25% or more reduction in analgesics (supported by 35 of 43 survey responders). We were restricted by the structure of the DBMS database, and, since not all survey participants accorded with these issues, we believe the results presented here are satisfactory.

In this re-analysis of the DBMS database with altered response defi nitions, we showed that a single fraction of 8 Gy is equally effective to MFs, even with the effect of retreatment excluded from the response percentages. Without effect of retreatment, 71% responded to SF vs. 73% to MF. When the effect of retreatment was included, response increased to 75% in SF patients, and response for MF patients remained unaltered. The response percentages were higher compared with those published in the fi rst analysis of the DBMS.[5] With effect of retreatment included, Steenland et al noted 72% response to SF vs. 69% to MF. With complete response defi ned as pain score lowering to 0 or 1, Steenland et al reported 37% complete responders to SF vs. 33% to MF. However, with the adjusted defi nition for complete response in the re-analysis, we observed only 14% complete responders in both treatment arms. These new

results are in line with Gaze et al, who also defined complete response as pain score zero, and reported 15% CR after 10 Gy SF and 13.8% after 22.5 Gy MF. [2] In the present re-analysis, only 3% of all responders in both treatment arms were due to a decrease in analgesics intake. These patients stopped using phase 3 or 4 analgesics while their pain scores remained unaltered. These results underline that the largest contributor to response by far was the radiation treatment, as Wu et al already suggested in their recent meta-analysis on bone metastases trials.[22]

Apparently, because the DBMS protocol provided no criteria on minimum pain score or time interval between randomization and retreatment, the choice to retreat was made individually, and was therefore biased. We labeled the response status of the patients after their initial treatment, and were able to show that, despite equal responses to initial treatment and equal progression after equal mean duration of remission, substantially more patients were retreated during follow-up after the 'new' treatment schedule SF (24%) compared with the 'accepted' schedule MF (6%). This suggests that physicians' expected effectiveness of the treatment schedule seemed of great influence on the percentages of retreated patients. Obviously, physicians were more willing to retreat patients after an initial single fraction of 8 Gy because the sum of both treatments was still considered within the limits of radiation tolerance. Also, after initial 24 Gy physicians probably reasoned that if MFs were not effective, it was unlikely for the patient to respond to even higher total doses. Hoskin et al carried out a prospectively randomized study on the palliative effect of 4 Gy vs. 8 Gy in 270 patients.[13] They found 20% retreatment after initial 4 Gy vs. only 9% after initial 8 Gy. The response status after initial therapy of retreated patients was similar, therefore the authors suggested that the clinicians who participated in the trial might simply have had a lower threshold for retreating patients after initial 4 Gy. Other studies reported on the unequal distribution of retreatment between SF and MFs regimens, with retreatment rates varying from 11-42% after SF to 0-24% after MFs. [1,3,4,6,8,9,12]

A few studies reported on the effectiveness of retreatment in patients with painful bone metastases. Mithal et al conducted a retrospective study of 105 patients, in which 57 sites with progressive pain were retreated in 35 patients.[26] They saw 84% response to the second treatment, with no statistical differences between SF and MF as retreatment dose. No relation to radiation dose, primary tumor type or tumor site in responders after retreatment was observed. Jeremic et al reported on 135 retreated patients after initial 4, 6, or 8 Gy.[27] In 26 non-responding patients, 46% responded to retreatment. In 109 patients with progressive pain, 73% responded again. In a successive study, Jeremic et al investigated the effect of a second retreatment in the same patient population as described above.[28] Second retreatment was effective in 80% of 25 patients, of whom 6 patients had been non-responders to 2 prior single fractions. In a prospectively randomized trial, Price et al studied the effect of a single fraction of 8 Gy vs. 30 Gy in 10 fractions in 288 patients. [3] No significant differences in response after 8 weeks were seen, with 73% response to SF compared with 64% after MF. Fifteen SF patients and 4 MF patients were retreated, but no details on the effect of retreatment are given. Price et al also conducted a pilot study on the efficacy of a single fraction of 4 Gy in 26 patients[14]. Response was seen in 43% evaluable patients. Seven patients were retreated for non-responding pain, but no effect of the retreatment was seen after either SF or MF. Lastly, Uppelschoten et al studied the effect of a single fraction of 6 Gy in 170 patients, with 88% responders. In 18 patients a second SF of 6 Gy was applied for recurring pain, and 72% experienced reduction of pain. [15] In the present study, we observed response to retreatment in 66% initial SF patients and 46% initial MF patients (P= 0.12), with longer mean duration of remission in initial SF patients (16 weeks for initial SF patients, 8 weeks for initial MF patients). An explanation for this difference could be that SF patients were retreated sooner after randomization and at a lower pain score. Therefore, they were more likely to survive longer, and as a consequence, have a longer duration of remission. The response percentages in initial non-responding or progressive patients were higher for SF patients than for MF patients (66% vs. 33%, and 70% vs. 57%, resp.), but, due to small numbers, these differences did not reach significance (P= 0.13, P=0.24, resp.).

To our surprise, we observed the lowest percentage of responders to retreatment in patients with prostate cancer. Although primarily 78% of these patients had responded to initial treatment, only 19% of progressive patients responded again. In patients with prostate cancer who were considered a non-responder to initial treatment, 20% response was observed. In contrast, 89% of breast cancer patients with progressive pain responded again, and 82% of non-responding patients with breast cancer responded. A possible explanation for the discrepancy between prostate cancer patients and breast cancer patients is the difference in time to start the retreatment. After randomization, time to retreatment was 6 weeks in non-responding breast cancer patients compared with 21 weeks in non-responding prostate cancer patients. In patients with progressive pain, retreatment was applied 5 weeks after progression was noted in breast cancer patients vs. 11 weeks in prostate cancer patients. Possibly, apart from intrinsic tumor sensitivity to radiotherapy, best results are achieved if retreatment is not postponed for too long. However, because retreatment was given at the discretion of the treating physician incorporating bias, these results must be interpreted with care.

In order to answer all outstanding questions relating to the effectivity of retreatment in a non biased manner, the National Cancer Institute of Canada

(NCIC) in collaboration with the United Kingdom, the Trans-tasman Radiation Oncology Group (TROG) and the DBMS will embark on a prospectively randomized trial on the effectiveness of retreatment in painful bone metastases using different retreatment dose schedules. In this trial, stratification for initial treatment dose and response status after initial treatment will be applied. Also, a minimum time interval between randomization and retreatment of 4 weeks will be used.

In conclusion, even with the effect of retreatment excluded from the response calculations, a single fraction of 8 Gy provided equal palliation for painful bone metastases when compared with 24 Gy in 6 fractions. In addition, SF radiotherapy was an effective retreatment schedule, for both initial non-responding and responding patients. Because SF radiotherapy reduces for patients the number of journeys to the hospital and is considered easier to implement into the radiotherapy department, SF radiotherapy should be the standard palliative treatment for patients with painful bone metastases.

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