Radiotherapy in bone metastasis : the Dutch bone metastasis study

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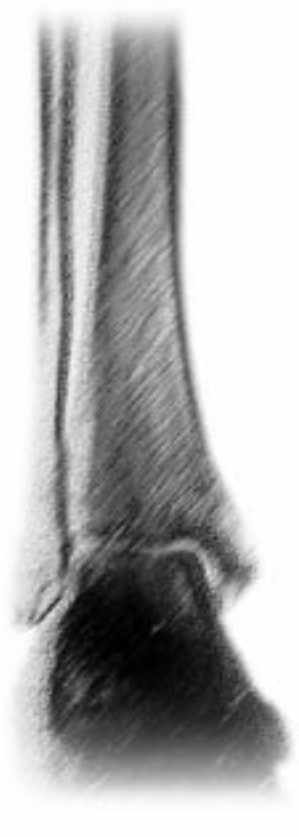

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Patients with a favorable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study

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Abstract

Introduction: In the prospectively randomized Dutch Bone Metastasis Study on the effect of a single fraction of 8 Gy versus 24 Gy in six fractions on painful bone metastases, 28% of the patients survived for more than one year. Purpose of the present study was to analyze the palliative effect of radiotherapy in long-term surviving patients, and to identify prognostic factors for survival.

Material and Methods: Response rates were compared in all patients surviving > 52 weeks. The Cox proportional hazards model stratified by primary tumor was used for multivariate (MV) analyses of prognostic factors for survival.

Results: In 320 patients surviving > 52 weeks, responses were 87% after 8 Gy and 85% after 24 Gy (P= 0.54). Duration of response and progression rates were similar. For all primary tumors, prognostic factors for survival were a good Karnofsky Performance Score, a solitary bone metastasis, no visceral metastases, and non-opoid analgesics intake (all factors, MV P< 0.001).

Conclusions: Single fraction radiotherapy should be the standard dose schedule for patients with painful bone metastases including patients with an expected favorable survival. General prognosticators as the Karnofsky Performance Score and metastatic tumor load are useful in predicting survival.

Introduction

The treatment of patients with painful bone metastases comprises a substantial part of the daily workload of the average radiotherapy department. Since a large number of retrospective and prospectively randomized studies reported that single fraction radiotherapy provides equal palliation when compared to multiple fraction regimens, [1-17] this treatment has more and more become the standard therapy. While in the past the value of a single fraction has been criticized,[18-20] recent reviews [21-24] and a meta-analysis [25] reported equal overall response percentages of 60% to 70% in evaluable patients. Of course, for the patient, the advantage of a single fraction instead of multiple fractions is evident: fewer tiring and painful visits to the hospital. For the radiotherapy department the use of a single fraction means a more economic use of limited resources. Although most patients with painful bone metastases have a limited median overall survival of 7 to 9 months, [5,7,20] some patients live longer. There is concern among radiation oncologists that in these patients a single fraction might not be beneficial. Pain may well be controlled more adequately if they receive multiple fractions with a higher total dose, leading to a reduced tumor load at the site of the metastasis.

To answer this question, the prospectively randomized Dutch Bone Metastasis Study (DBMS) on the palliative effect of a single fraction of 8 Gy versus 24 Gy in 6 fractions stratified patients into two groups: expected favorable prognosis, and expected less favorable prognosis. [5] We reported earlier the equality between the two treatment schedules for treating pain, [5,6] both in the group of 1157 patients as a whole, as in the expected favorable group that consisted of 92 patients. Surprisingly, observed survival in these 92 patients was less positive than anticipated. From the 320 patients who survived for more than 1 year after randomization, only 15% were with an expected favorable prognosis.

In the present paper, we focus on the palliative effect of single fraction and multiple fraction radiotherapy in DBMS patients with an observed favorable prognosis, i.e. all 320 patients surviving for more than 1 year after randomization. In addition, prognostic factors for survival in the DBMS were studied.

Material and Methods

Patient selection and follow-up

Between March 1996 and September 1998, 1157 Dutch patients with painful bone metastases from solid tumors were randomly assigned to a single fraction (SF) of 8 Gy (n= 579) or 6 fractions (multiple fractions= MF) of 4 Gy (n= 578). [5,6]

Purpose of the study was to prove the equal effectiveness of SF versus MF; endpoint of the study was response to pain. The criteria for randomization are listed in Table 1. In eight participating institutes, patients were stratifi ed according to expected favorable or less favorable prognosis. Patients were eligible for the favorable prognosis subgroup if they had breast cancer without visceral metastases with a long-term remission (more than 1 year) due to fi rst line systemic treatment, or prostate cancer with a Karnofsky Performance Score of 60% or more, and had not been treated with hormone therapy yet. A total of 92 patients was randomized into the favorable subgroup: 75 breast cancer patients, and 17 prostate cancer patients. [5] In the other nine participating institutions, patients who met the criteria for expected favorable prognosis were excluded from participation and received a multiple fraction regimen outside the study. The study protocol did not enclose guidelines for retreatment during follow-up, therefore, retreatment was given at the discretion of the treating physician. The Medical Ethics Committees of all participating institutions approved the study and all patients gave their informed consent. At randomization age, sex, Karnofsky Performance Score (KPS), [26] initial pain score on an 11-point scale from 0 (no pain) to 10 (worst imaginable pain), date of pathology diagnosis of the primary tumor, primary tumor site, treatment site, presence of other bone metastases and/or visceral metastases, concomitant systemic treatment, and analgesics intake were registered. After randomization, intensive follow-up by mail with 13 weekly and afterwards monthly questionnaires on pain, treatment side effects, quality of life, and analgesic intake was carried out to a maximum of two years or until death. Datamanagers in the participating hospitals collected data on all events, such as retreatment, occurrence of fractures or spinal cord compressions, and death. In December 1998, the follow up on survival of all randomized patients was updated and the study was closed.

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

Randomization criteria	
Inclusion	**Exclusion**
Informed consent Metastases of solid tumors Pain score minimum 2 on 11-point scale (0= no pain to 10= worst imaginable pain) Metastases treatable in one radiotherapy target volume No previous radiotherapy to same metastases	No informed consent Pathological fracture or impending fracture needing surgical fi xation Spinal cord compression Metastases of renal cell carcinoma or melanoma* Metastases in cervical spine† For some institutions: patients with an expected favorable prognosis‡

* *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 ra myelopathy.*

‡ *Patients with breast cancer without visceral metastases with a long term remission (more than 1 year) due to systemic treatment, and patients with prostate cancer, a Karnofsky Performance Score of 60% or more, who had treated with hormone therapy yet.*

Response definitions

Response was calculated in alignment with the International Bone Metastases Consensus Working Party Guidelines, [6,27] taking into account changes in the administration of analgesics. A change from phase 1 (non-opoid analgesics: paracetamol and non-steroid anti-infl ammatory drugs) or phase 2 (non-opoid analgesic combinations with weak opoids) to phase 3 (strong opoids like morphine) or phase 4 (non-oral administration of opoids) was noted as an analgesic increase. If the patient stopped using phase 3 or 4 analgesics, this was noted as an analgesic decrease.

Response was defi ned as a) a decrease in the initial pain score by at least two points on the pain scale, without analgesic increase, or b) a change in analgesics from phase 3 or 4 to a lower phase 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. 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) an increase in analgesics from a lower phase to phase 3 or 4 irrespective of the pain score.

For the calculation of response, no fi xed time interval from the date of randomization was applied. Response to treatment was calculated if at least two successive follow-up pain scores were available. Time to response and time to progression were calculated from the date of randomization. Duration of remission was calculated subtracting time to response from time to progression. Response to initial treatment was calculated including and excluding the effect of a possible retreatment during follow up. [6,27] When a patient was retreated during follow-up, the response status (either no response, in res - ponse, or with progression) the week before retreatment was labeled to identify reasons for retreatment. In addition, the direct effect of retreatment, i.e. changes in pain score compared to the pain score the week before retreatment, was studied.

Baseline characteristics and response to treatment in patients with an observed favorable prognosis (N= 320)

In order to perform subgroup analyses, we analyzed per treatment schedule the baseline characteristics of all patients who survived for more than 1 year after randomization: age, sex, KPS, primary tumor, treatment site, presence of other bone metastases, presence of visceral metastases, analgesics intake, concomitant systemic treatment, and pain score at randomization.

Response to initial treatment, time to response, duration of response, number of retreatments, and response to retreatment were studied up to 52 weeks after randomization. After 52 weeks, few patients returned questionnaires making comparison of pain scores beyond 52 weeks unreliable. Analysis of

response to initial treatment was possible in 97% of the 320 patients with a survival > 52 weeks. Calculation of the direct effect of retreatment, i.e. changes in pain score compared to the pain score the week before retreatment, was possible in 60% of the retreated patients with a survival > 52 weeks.

Survival and prognostic factors for survival (N= 1157)

For the survival analyses, patients were divided into 4 primary tumor groups: breast (39%), prostate (23%), lung (25%), and other types of cancer (13%). Overall survival (OS) was studied from randomization, and from the date of diagnosis of the primary tumor. In addition, the interval between the date of diagnosis of the primary tumor and entry into the trial was analyzed. Prognostic factors for survival studied were age, sex, KPS, primary tumor, treatment site, presence of other bone metastases, presence of visceral metastases, analgesics intake, concomitant systemic treatment, pain score at randomization, and treatment schedule.

Statistical analysis

The database was analyzed using SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA). Kaplan-Meier statistics were used for survival curves. Because survival was highly infl uenced by the primary tumor site, a Cox proportional hazards model stratifying for the primary tumor was used for univariate and multivariate (MV) analyses of prognostic factors for survival. Interactions were studied within the Cox proportional hazards model. Chi-Square and Fisher's Exact tests were used to compare proportions for baseline characteristics. Mann-Whitney tests were used to compare quantitative and ordered variables for baseline characteristics. All reported P-values are based on two-sided tests with P< 0.05 taken to be signifi cant.

Results

Expected favorable prognosis (N= 92) versus expected less favorable prognosis (N= 1065)

Three hundred-and-twenty patients survived for > 52 weeks after randomi zation. Of the 92 separately randomized patients with an expected favorable prognosis, only 53.3% survived for more than 1 year. These were 40 patients with breast cancer and 9 patients with prostate cancer. Of the remaining 1065 patients who did not meet the randomization criteria for favorable prognosis, nonetheless 25.4% survived for more than one year. We conclude that the DBMS criteria for separate randomization of patients into the expected favorable prognosis group were not adequate.

TABLE 2 BASELINE CHARACTERISTICS PER TREATMENT SCHEDULE IN 320 PATIENTS SURVIVING > 52 WEEKS FROM RANDOMIZATION TREATED WITHIN THE DUTCH BONE METASTASIS STUDY (SINGLE FRACTION VERSUS MULTIPLE FRACTIONS)

	1 x 8 Gy (N= 163)	SD*	6 x 4 Gy (N= 157)	SD	*P-value*
Age					
Mean (range)	64 yrs (33-89)	12	64 yrs (32-89)	12	*0.74*
Sex					
male	34%		35%		*0.91*
female	66%		65%		
KPS†					*0.66*
Mean (range)	76% (20-100)	14	76% (20-100)	14	
Primary tumor					
Breast	63%		63%		*0.27*
Prostate	22%		27%		
Lung	10%		5%		
Other	4%		5%		
Treatment site					*0.04*
Spine	26%		31%		
Pelvis	39%		44%		
Femur	7%		10%		
Ribs	8%		7%		
Humerus	6%		5%		
Other	14%		3%		
Number of bone metastases					*0.82*
Solitary	37%		38%		
Multiple	63%		62%		
Visceral metastases					
Absent	87%		87%		*1.00*
Present	13%		13%		
Pain medication phase 3-4‡					
No	69%		72%		*0.54*
Yes	31%		28%		
Systemic treatment					*0.70*
No	26%		24%		
Yes	74%		76%		
Pain score§					*0.98*
Mean (range)	6 (2-10)	2	6 (2-10)	2	

* *SD= standard deviation*

† *KPS= Karnofsky Performance Score, a conditional score ranging from 0% (= death) to 100% (normal situation, no complaints)*

‡ *Pain medication phase 3 = strong opoids like morphine, phase 4= non-oral administration of opoids*

§ *Pain score at randomization: 11-point pain score ranging from 0 (no pain) to 10 (worst imaginable pain).*

TABLE 3 RESPONSE TO RADIOTHERAPY PER TREATMENT SCHEDULE IN 320 PATIENTS SURVIVING > 52 WEEKS FROM RANDOMIZATION TREATED WITHIN THE DUTCH BONE METASTASIS STUDY

	1 x 8 Gy		6 x 4 Gy		P-value*	HR (95% CI)
	N	Response	N	Response		
Breast cancer	102	90%	94	89%	0.58	0.9 (0.7-1.2)
Prostate cancer	34	85%	40	90%	0.11	1.5 (0.9-2.5)
Lung cancer	17	77%	7	43%	0.38	0.6 (0.2-2.1)
Other types	7	71%	8	50%	0.61	0.7 (0.2-2.7)

* *P-value = univariate analysis, HR = hazard ratio calculated with Cox proportional hazards model (95% CI) = 95% confi dence intervals.*

Baseline characteristics in patients with an observed favorable prognosis (N= 320)

Of the 320 observed long-term survivors, the primary tumor was in the breast in 63%, in the prostate in 24%, in the lung in 8%, and at other sites in 5%. Fifty-one percent was randomized into the SF group and 49% into the MF group. Between SF and MF long term surviving patients no major differences in age, sex, KPS, primary tumor site, presence of other bone metastases, presence of visceral metastases, analgesics intake, concomitant systemic treatment, or pain score at randomization were found *(Table 2)*. Only treatment site differed between the two regimens (P= 0.04), but the clinical implication of this outcome is considered minor.

Response to treatment in patients with an observed favorable prognosis (N= 320)

Of all patients with a survival > 52 weeks, 87% responded to SF and 85% to MF (P= 0.54, HR 0.9,95% CI 0.7-1.2). Five percent of all responses were caused by a decrease in analgesic intake. Complete response was noted in 62% after SF and 48% after MF (P= 0.07, HR 0.8, 95% CI 0.6-1.0). Mean time to response was 4 weeks in both treatment groups. Mean duration of response was 29 weeks after a SF (median duration 35 weeks) and 30 weeks after MF (median duration 42 weeks). Progressive pain was reported in 55% of SF responders and in 53% of MF responders. For patients who experienced progressive pain, mean time to progression after response was reached was 17 weeks for SF patients and 18 weeks for MF patients.

For the primary tumor groups response to treatment is listed in table 3: again, no differences between the single fraction and multiple fraction regimen were seen. Patients with breast cancer or prostate cancer had 85% to 90% response after both regimens (P= 0.58 and P= 0.11, respectively). Although patients with lung cancer reached 77% response to SF, compared to only 43% to MF, due to small numbers these outcomes were not statistically signifi cantly different (P= 0.38, HR 0.6,95% CI 0.2-2.1).

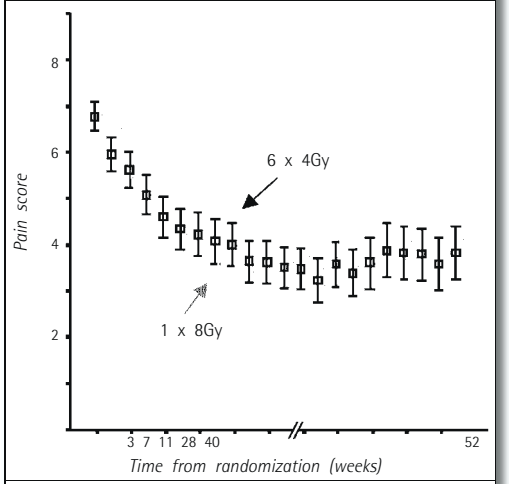
Figure 1 shows the fi rst year pain scores of the 320 SF and MF patients. Again, mean pain scores overlap consistently throughout the year showing the equality of response to both treatment schedules.

In total, 24% of the 320 patients received a second radiotherapy treatment: 61 patients within the fi rst year, and 15 patients within the following year. More SF patients than MF patients were retreated: 58 SF patients (36%) versus 18 MF patients (11%). The higher retreatment percentage after initial SF did not signifi cantly alter the response percentages for the two treatment schedules: when excluding the effect of retreatment from the response percen tages to initial treatment, 80% responded to SF and 85% to MF (P= 0.95, HR 1.0,95% CI 0.8-1.3). Mean time to retreatment was 25 weeks in SF patients (range 2-78 weeks) and 39 weeks in MF patients (range 5-83 weeks). At retreatment, 54% of the patients were responders to initial treatment. Of these responders, 61% had progressive pain before retreatment. Thirty-fi ve patients were non - res ponder. When the additional effect of retreatment on the pain score reported at randomization was studied, 69% of initial non-responders responded yet: an additional 32% increase of response to 86%.

When calculating the direct effect of retreatment, i.e. changes in pain score compared to the pain score the week before retreatment, 84% of SF patients responded, and 64% of MF patients (P=0.44, HR 1.3, 95% CI 0.7-2.7).

FIGURE 1

Pain scores during the fi rst year after randomization for patients surviving > 52 weeks within the Dutch Bone Metastasis Study per treatment schedule



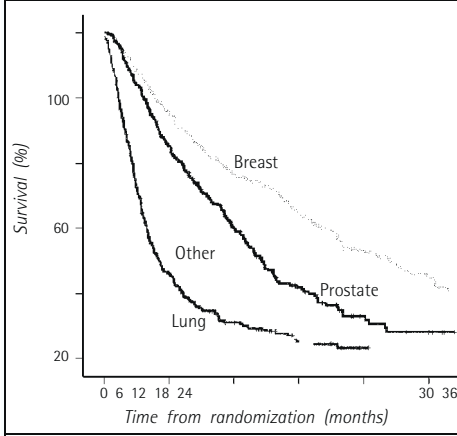
Pain was scored on an 11-point pain scale ranging from 0 (= no pain) to 10 (= worst imaginable pain).

Pain scores of 320 patients with a survival > 52 weeks treated with 1x 8 Gy (grey lines with 95% confi dence intervals, N=163) versus 6 x 4 Gy (black lines with 95% confi dence intervals, N =157) are presented.

// = Time from randomization in weeks: after 13 weekly questionnaires follow up was altered into monthly questionnaires to a maximum of two years or until death.

FIGURE 2

Survival in 1157 patients treated within the Dutch Bone Metastasis Study per primary tumor



Number of patients 'at risk'

Breast	451	320	209	123	66	19
Prostate	267	165	81	34	9	-
Lung	287	74	26	6	-	-
Other primaries	152	46	17	6	-	-

Survival (N= 1157)

From randomization, patients with breast cancer had the best median overall survival (16.4 months, 95% CI 14.2 – 18.5 months), followed by prostate cancer (median OS 9.5 months, 95% CI 7.8 – 11.1), and other types of cancer (median OS 3.9 months, 95% CI 3.4 – 4.4) (P< 0.001) *(Figure 2)*. Patients with lung cancer suffered the worst median overall survival: 3.2 months only (95% CI 2.8 – 3.5 months).

LE 4 PROGNOSTIC FACTORS FOR SURVIVAL IN 1157 PATIENTS WITH PAINFUL BONE METASTASES TREATED WITHIN THE DUTCH BONE METASTASIS STUDY

	%	Overall Survival (months)			UV†			MV
		Mean	(95% CI)*	Median	P-value	HR	(95% CI)	P-value
50 yrs	14	13.7	(11.8-15.6)	10.1	0.45	1		-
89 yrs	86	11.0	(10.3-11.8)	6.5		1.1		
ale	46	15.1	(14.1-16.2)	11.6	0.85	1		-
e	54	8.0	(7.3-8.7)	4.8		1		
‡								
100	47	14.6	(13.5-15.6)	11.6	< 0.001	1		< 0.001
70	46	9.1	(8.2-9.9)	5.0		1.9	(1.6-2.2)	
40	7	5.4	(3.9-6.8)	2.6		3.3	(2.6-4.3)	
atment site								
ne	30	11.2	(10.0-12.4)	7.0		1		
is	37	12.0	(10.9-13.1)	7.2	0.3	0.9		
ur	9	11.1	(9.0-13.2)	8.0	0.7	1		
	8	10.2	(8.2-12.3)	6.0	0.2	0.9		
nerus	5	11.6	(8.8-14.4)	6.7	0.5	0.9		
er	11	10.2	(8.3-12.1)	7.3	0.6	0.9		
mber of bone metastases								
tary	42	10.5	(9.5-11.5)	6.0	0.009	1		< 0.001
tiple	58	12.1	(11.2-12.9)	7.9		0.8	(0.7-1.0)	
ceral metastases								
ent	76	12.6	(11.8-13.4)	8.2	< 0.001	1		< 0.001
ent	24	7.5	(6.4-8.5)	4.3		1.6	(1.4-1.9)	
n medication phase 3-4§								
	58	14.0	(13.1-13.9)	10.4	< 0.001	1		< 0.001
	42	7.9	(7.1-8.7)	4.1		1.8	(1.6-2.1)	
temic treatment								
	46	7.6	(6.8-8.4)	4.0	0.02	1		-
	54	14.6	(13.6-15.5)	11.6		0.8	(0.7-1.0)	
n score‖								
	20	13.8	(12.2-15.3)	9.6		1		
	48	10.9	(10.0-11.8)	7.3	0.01	1.3	(1.1-1.5)	-
0	32	10.3	(9.2-11.5)	5.6	< 0.001	1.4	(1.2-1.7)	-
domization arm¶								
	50	11.7	(10.8-12.7)	7.6	0.27	1		-
	50	11.0	(10.1-11.9)	6.5		1.1		

95% CI)= 95% confi dence interval

UV= univariate analysis with stratifi cation by primary tumor, HR= hazard ratio calculated with Cox proportional hazards model, (95% CI)= 95% confi dence intervals, MV=multivariate analysis with stratifi cation by primary tumor.

KPS= Karnofsky Performance Score, a conditional score ranging from 0% (death) to 100% (normal situation, no complaints)

Pain medication phase 3 = strong opoids like morphine, phase 4= non-oral administration of opoids

Pain score at randomization: 11-point pain score ranging from 0 (no pain) to 10 (worst imaginable pain).

SF= single fraction, 1x 8 Gy, MF= multiple fractions, 6x 4 Gy

If survival was calculated from the date the primary tumor was diagnosed, breast cancer patients experienced by far the longest survival (median OS 7.6 years, 95% CI 6.5-8.6 years), followed by patients with prostate cancer (median OS 3.9 years, 95% CI 3.2-4.5 years), and other primary tumors (median OS 1.5 years, 95% CI 1.2-1.7 years). Lung cancer patients had a median OS from the primary diagnosis of only 9 months (95% CI 8-10 months).

Median time from the diagnosis of the primary tumor to randomization into the Dutch Bone Metastasis Study was 4.2 years in breast cancer patients (mean 5.7 years, range 0-34 years), 2.3 years in prostate cancer patients (mean 3.0 years, range 0-14 years), 9.6 months in patients with other primary tumors (mean 2 years, range 0-18 years), and only 4.8 months in patients with lung cancer (mean 9.6 months, range 0-18 years). These fi ndings point out the natural course of the different primary tumors: patients with lung carcinoma mostly develop bone metastases sooner in the course of their illness and have a worse prognosis than patients with breast or prostate carcinoma.

Prognostic factors for survival (N= 1157)

Because survival was highly infl uenced by the primary tumor type *(fi gure 2)*, the patient characteristics and their prognostic value for survival were analyzed stratifi ed by tumor type. Table 4 lists the outcome of this analysis. Age, sex, treatment site or randomization arm were not signifi cantly predictive for survival in any of the four tumor groups in the univariate analyses. Most predictive were a good performance, absence of visceral metastases and use of non-opoid analgesics (all factors, P< 0.001), followed by a solitary bone metastasis (P= 0.009), a low pain score (P= 0.01 and P< 0.001, respectively) and no concomitant systemic treatment (P= 0.02). In the multivariate analysis the KPS, absence of visceral metastases, a solitary bone metastasis, and use of non-opoid analgesics signifi cantly predicted survival in all four tumor groups (MV ana lysis, all factors P< 0.001). No intervening interactions were found in the analyses. A low pain score and no concomitant systemic treatment at randomization were not signifi cantly predictive anymore in the MV analysis.

Discussion

The present study shows that patients with painful bone metastases and a survival of > 52 weeks equally responded to 8 Gy single fraction and 24 Gy in six fractions: 87% and 85% response, respectively (P= 0.54). More patients reached a complete response after SF (62%) than MF (48%), but this was not statistically signifi cantly different (P= 0.07). Furthermore, median duration of response was similar for both treatment schedules: 29 weeks versus 30 weeks. Although SF

patients who survived > 52 weeks were retreated three times more than MF patients were, this did not alter the initial response percentages significantly. Responses excluding the effect of a retreatment were 80% to SF vs. 85% to MF, respectively (P= 0.95).

We demonstrated a strong relationship between the primary tumor and overall survival, and between the primary tumor and response to palliative radiotherapy. Most other studies also reported highest overall survival, response rates and duration of response in patients with breast cancer and prostate cancer [3,6,9,18,20] Probably, these patients experience the best overall survival due to the intrinsic nature of their cancer. Their tumors are also more responsive to systemic treatment, which adds to a more prolonged survival. In the present study, as expected, the majority of patients surviving for more than one year after randomization had breast cancer (63%) or prostate cancer (24%). When we calculated survival starting at the moment of diagnosis of the primary tumor, again patients with breast cancer had the best overall survival by far (median 7.6 years).

In deciding on treatment for patients with cancer, prediction of survival is often warranted to balance treatment side effects versus benefits. Chow et al already reported that the Karnofsky Performance Score is a useful tool in predicting survival. [28,29] Our data underline his findings, both KPS and a low metastatic tumor load, as demonstrated by a single bone metastasis and no visceral metastases, were important prognosticators in all four different primary tumor groups. Use of non-opoid analgesics for pain was an independent prognostic factor for survival as well. Possibly, need for strong medication is on ominous sign. Physicians and patients may also be reluctant to administer opoids in non-terminal situations. A low pain score at randomization was not significantly predictive for survival, nor was concomitant systemic therapy. Other predictive factors, such as weight loss, were not reported in our database. In the DBMS, 92 patients with an expected favorable prognosis were separately randomized to study the effect of the two treatment schedules. Steenland et al already reported that no differences in response after SF and MF were seen in these patients. [5] Eligible for favorable prognosis were patients with breast cancer without visceral metastases with a long-term remission due to first line systemic treatment, or patients with prostate cancer, a Karnofsky Performance Score of 60% or more, with no previous hormone therapy. These criteria turned out to be inadequate: only 53% of expected favorable patients survived for more than one year. For future palliative trials, prognosis should be based upon objective criteria such as the KPS and metastatic tumor load, as described above.

Unfortunately, more than 50% of the 320 DBMS patients surviving > 52 weeks experienced progressive pain, irrespective of the initial schedule SF or MF. This outcome is important: it directs us to the question if patients with an expected prolonged survival need even higher radiotherapy doses to increase the duration of response and decrease the percentage of patients with progressive pain. Or, have we reached the maximum palliative effect of radiotherapy in patients with painful bone metastases? In this manner, the outcome of the RTOG 97-14 trial on painful bone metastases by Hartsell et al is interesting. This trial compared a single dose of 8 Gy to 30 Gy in 10 fractions. [17] Early outcome showed no difference in response between the two schedules, 65% after 8 Gy versus 66% after 30 Gy, but duration of response and progression rates have not been reported yet. However, even if response durability after 30 Gy will turn out more beneficial than after 8 Gy single fraction, one still has to consider the benefit of single fraction radiotherapy to the patient compared to several weeks of treatment with concomitant side effects. Perhaps a more improved approach in order to prolong the effect of radiotherapy is not to raise the initial treatment dose, but to explore the benefit of a second radiotherapy treatment after the patient has experienced progressive pain. At least, 50% of the patients in our study did not experience progressive pain and were therefore adequately palliated with just one course of radiotherapy. In the published trials on bone metastases, retreatment rates ranged from 9% to 38% after single fraction radiotherapy and from 0% to 24% after multiple fractions. [1,3-7,9,13,18] In these trials, retreatment was given at the discretion of the treating physician and therefore these percentages are probably biased. In a recently published paper of our group on the effectiveness of retreatment we showed that the choice to retreat was highly subjective, mostly influenced by a disbelief of the treating physicians in the effectiveness of a single fraction. [6] We also showed that a second 8 Gy fraction for retreatment was as effective as multiple fractions: 74% response versus 63%, respectively. Two retrospective trials were published on the effectivity of retreatment. Jeremic et al showed 73% response after a second fraction of 4 Gy in 135 patients who were treated initially with 4, 6, or 8 Gy single fraction. [30,31] Mithal et al studied 105 patients and reported 87% response to retreatment. [32] Recently, the first international prospectively randomized trial on effectivity of different dose schedules for retreatment in bone metastases started, initiated by the National Cancer Institute of Canada Clinical Trialists Group. In this trial, patients are randomized between 8 Gy single fraction and 20 Gy in 5 to 8 fractions for retreatment dose. The interval has to be at least 4 weeks after initial treatment, and patients are stratified by initial dose and response to initial treatment. Hopefully, in a few years time this trial will provide us with useful information on the effectivity of different retreatment dose schedules and durability of response. A possible outcome could be that two subsequent single fractions will prove to be as effective as subsequent multiple fractions.

In conclusion, general prognostic factors as the Karnofsky Performance Score adequately predicted survival in patients with painful bone metastases. However, we demonstrated that long term surviving patients responded equal - ly to both the single treatment schedule as the multiple fraction schedule. Therefore, prediction of survival as a means to differentiate between palliative radiotherapy treatment schedules is unnecessary. Single fraction radiotherapy should be the standard palliative treatment for all patients with painful bone metastases, including patients with an expected favorable prognosis.

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