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Radiotherapy in bone metastasis : the Dutch bone metastasis study

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Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions

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Introduction

Metastases are the most frequent cause of malignant destructive lesions in the skeleton. The majority of bone metastases develop in patients with breast, prostate or lung cancer.^{35,37} Most lesions are located in the spine, pelvis and proximal part of the extremities. Besides local or generalized pain, patients can suffer from pathological fracturing, the loss of limb function, compression of nerves or spinal cord from bulging bone or tumor fragments, or systemic conditions such as hypercalcemia. Palliative treatment options are external beam radiotherapy, chemotherapy, hormonal therapy, surgery, systemic administration of radioisotopes, regular infusions with bisphosphonates and the use of analgesics. The choice for a specific type of treatment depends on the symptoms experienced by the patient and on the localization and number of metastases. In addition, the clinician has to consider the performance status and life expectancy of each individual patient. Treatment should be aimed at providing the patient with maximum palliation and minimum discomfort. For a patient with a metastasis in the femur, the occurrence of a pathological fracture can be most distressing and causes considerable morbidity. Therefore, prevention of a femoral fracture is an important palliative topic.

In the multicenter prospectively randomized Dutch Bone Metastasis Study (DBMS), the palliative effect of a single fraction (SF) of 8 Gy versus 6 fractions of 4 Gy on painful bone metastases was investigated in 1157 patients. No major differences were found between the treatment schedules in response to pain, treatment side effects, analgesic consumption or overall quality of life.³³ In a subgroup of 102 patients with femoral metastases, 14 fractures occurred during follow-up.

The purpose of the present study was to identify lesional risk factors for femoral fracturing and to evaluate the influence of the treatment schedule on the occurrence of a femoral fracture. Therefore, all femoral patients and femoral lesions within the DBMS were reviewed. The objective of the study was to define a practical guideline that can be used in a clinical setting, to decide which femoral lesions should be treated with radiotherapy and which with prophylactic surgery.

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 randomized between a SF of 8 Gy (n= 579) and 6 fractions (multiple fractions= MF) of 4 Gy (n= 578).³³ Purpose of

Abstract

Background and Purpose: In the randomized Dutch Bone Metastasis Study on the palliative effect of a single fraction (SF) of 8 Gy versus 6 fractions of 4 Gy on painful bone metastases, 14 fractures occurred in 102 patients with femoral metastases. Purpose of the present study was to identify lesional risk factors for fracturing and to evaluate the influence of the treatment schedule.

Material and Methods : Pretreatment radiographs of femoral metastases were collected. Three observers separately measured the lesions and scored radiographic characteristics.

Results: Ten fractures occurred after median 7 weeks in 44 SF patients (23%) and 4 after median 20 weeks in 58 multiple fraction patients (7%) (UV, P= 0.02). In 110 femoral metastases, an axial cortical involvement > 30 mm significantly predicted fracturing (MV, P= 0.02). Twelve out of 14 fractured lesions and 40 out of 96 non-fractured metastases had an axial cortical involvement > 30 mm (negative predictive value, 97%). When correcting for the axial cortical involvement, the treatment schedule was not predictive anymore (MV, P= 0.07).

Conclusions: Fracturing of the femur mostly depended on the amount of axial cortical involvement of the metastasis. We recommend to treat femoral metastases with an axial cortical involvement < 30 mm with an SF of 8 Gy for relief of pain. If the axial cortical involvement > 30 mm, prophylactic surgery should be performed to minimize the risk of pathological fracturing, or, if the patient's condition is limited, irradiation to a higher total dose.

the study was to prove the equal effectiveness of SF versus MF; endpoint of the study was response to pain. Seventeen out of 21 radiotherapy institutes in the Netherlands participated in the trial. Patients had a minimal pain score of 2 on an 11-point scale of 0 (no pain) to 10 (worst imaginable pain).¹⁹ Already fractured lesions and lesions that were suspected to have a high risk of fracturing by the treating physician were excluded from the trial. The Medical Ethics Committees of all participating institutions approved the study and all patients signed informed consent forms. Registration of patients who did not meet the entry criteria (n= 2927) was performed to identify the reasons for exclusion. After randomization, intensive follow-up with 13 weekly and afterwards monthly questionnaires on pain using the 11-point scale, treatment side effects, quality of life, and analgesic consumption was carried out to a maximum of two years or until death. Data managers in the participating hospitals collected data on all events, such as death, retreatment and occurrence of a fracture or spinal cord compression. In December 1998 the follow up on survival and fractures of all randomized patients was updated and the study was closed. For the present study all patients with a femoral metastasis within the DBMS were selected.

Scoring of radiographic aspects and measurements of the lesions

The pretreatment radiographic imaging material and the radiotherapy simulation films of patients with a femoral metastasis were collected. Radiographs taken no more than 2 weeks prior to randomization were considered suitable for evaluation. Without knowledge of the treatment schedule or outcome after treatment (i.e. a fracture yes or no), all femoral lesions were separately analyzed by three experienced observers (a radiologist, an orthopedic surgeon and a radiation oncologist).

The following radiographic aspects were scored: appearance (predominantly osteolytic or predominantly osteoblastic), feature (solitary lesion, multiple lesions, diffuse lesions in the femur), pattern of bone destruction (geographic, moth-eaten, permeative pattern^{21,25}), axial localization (proximal femur, shaft, distal femur) and transverse localization (mostly medial, mostly central, mostly lateral, or a combination of medial, central and/or lateral). In case of discrepant scoring between the observers they re-evaluated the radiographs and reached a consensus.

The observers measured on the available conventional radiographs the sizes of the lesions in mm (figure 1): largest axial length of the entire lesion (L-lesion), largest transverse extension of the lesion (W-lesion) and largest axial cortical involvement of the lesion (L-cort). They also measured the largest transverse width of the bone (W-tot), the maximal thickness of the cortex without lesional involvement (C-tot) and the maximal thickness of the cortex with

lesional involvement (C-lesion). The measurements were summarized and a mean score for the three observers was calculated. In the analysis cut-off points of measurements were chosen to detect differences in fracture risk.

In order to compare the lesional measurements correctly, only conventional radiographs were measured. If a lesion was only visible on a CT scan, MRI scan and/or bone scintigram, no measurements were taken, but only the radiographic aspects were scored. In case of lesions with a permeative or moth-eaten pattern of bone destruction, the observers carefully measured the entire lesion. In case of more than one lesion within the radiation field, only the lesion considered at risk of fracturing was measured and scored. In patients with more than 1 lesion considered at risk of fracturing, both lesions were separately analyzed only if their localizations were at a minimal distance of 50 mm.

Statistical analysis

The database was analyzed using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA). Spearman's rank correlation tests were used to analyze the interobserver variability of separate measurements. Fisher's Exact tests were used to compare proportions for baseline characteristics and baseline scored radiographic aspects. Mann-Whitney tests were used to compare quantitative and ordered variables for baseline characteristics and baseline lesional measurements. Student's t-tests were used to analyze differences in normally distributed data for baseline characteristics. Predictive values of risk factors were calculated. Kaplan-Meier curves and log rank tests were used for survival analyses (figure 2). Log rank tests were used to determine differences in time to fracture with end of follow-up or death considered as censored. Because the endpoint of this study was prevention of fractures, patients who died without a fracture were regarded as being successfully palliated. Therefore, to get a good estimate of the probability of fracture before death for each new patient presenting with a femoral lesion, patients who died without a fracture were not censored but were considered to have an uneventful follow-up until December 1998 (figure 3 and 4). A Cox proportional hazards model was used for uni- and multivariate analyses. All reported p-values are based on two-sided tests with P< 0.05 taken to be significant.

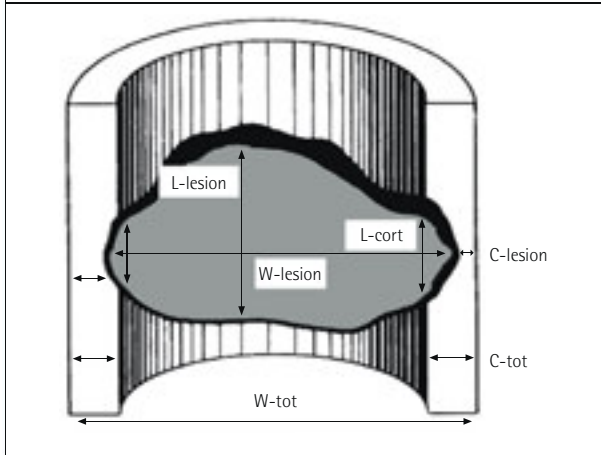
Results

Registered and randomized patients

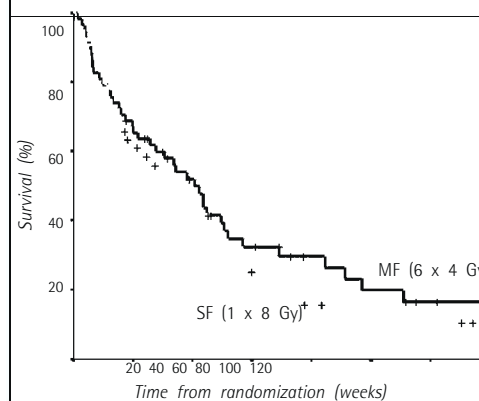
Of 2927 registered patients who did not meet the entry criteria, 8% (n= 234) were excluded because of impending or actual fractures. More than 50% of

FIGURE 1

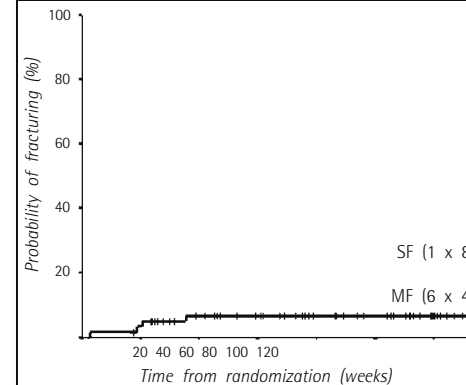
Measurements of metastatic lesions in the femur (in mm): largest axial length of the entire lesion (L-lesion), largest transverse extension of the lesion (W-lesion), largest axial cortical involvement (L-cort). Measurements of the femur (in mm): largest transverse width of the bone (W-tot), maximal thickness of cortex without lesional involvement (C-tot) and maximal thickness of cortex with lesional involvement (C-lesion)

**FIGURE 2**

Survival in 102 patients with femoral metastases treated within the Dutch Bone Metastasis Study for the treatment schedule single fraction of 8 Gy (SF) versus 6 fractions of 4 Gy (MF)

**FIGURE 3**

Probability of fracturing in 110 femoral metastases for the treatment schedule single fraction of 8 Gy (SF) versus 6 fractions of 4 Gy (MF) in patients treated within the Dutch Bone Metastasis Study



these patients (n= 121) had femoral metastases. The patient characteristics of the registered patients have been reported elsewhere.³³ In short, no major differences were noted between registered and randomized patients for sex, age, Karnofsky Performance Scale, initial pain score, primary tumor or treatment site. Of the 1157 randomized patients, 110 patients were entered into the trial with a femoral metastasis. When the radiographs were evaluated, 8 patients turned out to have an acetabular metastasis and were therefore not included in this analysis. Of the remaining 102 patients, 44 patients (43%) received a SF and 58 patients (57%) received MF.

Availability of radiographs and number of femoral lesions

From the 102 patients with a femoral lesion all available radiographs were collected in hospitals throughout the Netherlands. The radiographs of 2 MF patients were missing and could therefore not be evaluated. From the remaining 100 patients the following imaging films were available: 91 radiotherapy simulation films (AP direction), 100 conventional radiographs (51 AP radiographs, 49 multidirectional radiographs), 6 CT-, or MRI scans and 9 bone scintigrams. The radiotherapy simulation films were checked for geographical misses: all lesions were adequately treated within the radiation fields. In 10 patients the lesion was only visible on a CT scan, MRI scan or bone scintigram. Five SF patients and 3 MF patients had two lesions considered at risk of fracturing, 1 MF patient had three lesions. In these 9 patients, the lesions were located in different parts of the femur with a minimal distance of 50 mm. All lesions

were included in the analysis. In total, in 100 patients with available radiographs, 110 lesions were scored on radiographic aspects and 100 lesions were measured.

Patient characteristics, survival and occurrence of fractures: SF versus MF

Between the 44 SF patients and 58 MF patients no major differences in age, sex, pain score at time of randomization, Karnofsky Performance Scale, or primary tumor were found (table 1). Median follow-up was 21 months in both groups (range 4 - 36 months). Median time from randomization to the start of radiotherapy was 3 days in SF patients (range 0-22 days) versus 6 days in MF patients (range 0-26 days). In total, 9 SF and 5 MF patients received a second irradiation because of continuing or recurring pain (20% vs. 9%, respectively, $P=0.14$).

Figure 2 shows the overall survival of the treatment groups. SF and MF patients had a median survival of 33 weeks (95% CI 15-51 weeks) and 41 weeks (95% CI 30-51 weeks), respectively ($P=0.31$).

During follow-up, 10 fractures (23%) occurred in 44 SF patients vs. 4 fractures (7%) in 58 MF patients ($P=0.02$). Figure 3 shows the probability of a fracture before death in both treatment groups, demonstrating that SF patients had a higher chance to experience a pathological fracture than MF patients. Median time to fracturing after randomization was 7 weeks in 10 SF patients (range 2-29 weeks) and 20 weeks in 4 MF patients (range 3-36 weeks). Because SF patients were treated sooner after randomization than MF patients, the median time to fracturing from the start of radiotherapy was studied

TABLE 1 CHARACTERISTICS AT TIME OF RANDOMISATION OF 102 PATIENTS WITH A METASTATIC FEMORAL BONE LESION PER TREATMENT SCHEDULE (SINGLE FRACTION VS. MULTIPLE FRACTIONS)					
	1 x 8 Gy (N= 44)	SD*	6 x 4 Gy (N= 58)	SD	P-value
Gender					0.84
Male	48%		45%		
Female	52%		55%		
Age					0.92
Mean	63.5	10	63	14	
Pain score[†]					0.88
Mean	6.3	2	6.3	2	
Karnofsky[‡]					0.53
Mean	68%	17	70%	16	
Primary tumour					0.97
Breast	43%		45%		
Lung	25%		26%		
Prostate	16%		17%		
Other	16%		12%		
* SD= standard deviation † Pain score at randomisation, minimal score of 2 on an 11-point score from 0 (no pain) to 10 (worst imaginable pain) ‡ Karnofsky Performance Scale= conditional score, ranging from 100% (normal situation, no complaints) to 0% (death)					

additionally: 10 SF patients experienced a fracture at a median of 6 weeks from the day the radiation was delivered (range 2-29 weeks) compared to median 17 weeks for 4 MF patients (range 2-35 weeks). These results suggest that MF postponed the occurrence of a pathological fracture.

Lesional characteristics and measurements: SF versus MF

To evaluate the variability between the observers, Spearman’s rank correlation coefficients for the separate measurements were calculated, ranging from 0.64-0.70 for L-lesion, 0.52-0.57 for L-cort, 0.65-0.74 for W-lesion, 0.71-0.75 for W-tot, 0.46-0.65 for C-tot and 0.58-0.80 for C-lesion. Variability of measuring was acceptable and justified combining the measurements into one outcome. Table 2 lists the lesional characteristics and measurements for SF versus MF lesions. Between the randomization groups no significant differences in radiographic feature, appearance, pattern of destruction or axial localization of the lesions were noted. The SF lesions were more often a combination of a medial, central and/or lateral located lesion than MF lesions (54% vs. 29%, respectively, P= 0.005), suggesting that SF lesions were larger in the transverse plane than MF lesions. The transverse width of both bone and lesion were indeed larger in SF lesions compared to MF lesions (median W-tot 45 mm vs. 33 mm respectively (P= 0.01), median W-lesion 31 mm vs. 21 mm respectively (P= 0.003)). SF lesions were located more often proximally in the femur than MF lesions (71% and 62%, respectively) and this perhaps caused the significantly larger W-tot and W-lesion. The axial measurements L-lesion and L-cort and the cortical

TABLE 2 RADIOGRAPHIC ASPECTS AND LESIONAL MEASUREMENTS OF THE FEMORAL LESIONS FOR THE TREATMENT SCHEDULES SINGLE FRACTION VERSUS MULTIPLE FRACTIONS			
	1 x 8 Gy (N= 49 lesions)	6 x 4 Gy (N= 61 lesions)	P-value
Radiographic feature			0.44
Solitary	54%	42%	
Multiple	27%	37%	
Diffuse	19%	21%	
Radiographic appearance			0.21
Osteoblastic	14%	7%	
Osteolytic	86%	93%	
Radiographic pattern			0.24
Geographic	23%	37%	
Moth-eaten	70%	52%	
Permeative	6%	11%	
Axial localization			0.19
Proximal	71%	62%	
Shaft	23%	36%	
Distal	6%	2%	
Transverse localization			0.005
Medial	23%	18%	
Central	19%	26%	
Lateral	4%	26%	
Combination	54%	29%	
Length (median and range in mm)*			
L-lesion	53 (17-251)	46 (14-232)	0.12
L-cort	35 (7-155)	31 (0-94)	0.37
Width (median and range in mm)*			
W-tot	45 (25-81)	33 (22-68)	0.01
W-lesion	31 (7-59)	21 (7-54)	0.003
Cortex (median and range in mm)*			
C-tot	6 (1-18)	6 (1-10)	0.44
C-lesion	2 (0-9)	2 (0-9)	0.82
Radiographic aspects were scored in 110 lesions in 100 patients of whom radiographs could be collected (conventional radiographs, CT scans, MRI scans and/or bone scintigrams) * Lesional measurements on only conventional radiographs of 100 lesions (in mm) (see Figure 1): largest axial length of entire lesion (L-lesion), largest transverse extension of the lesion (W-lesion) and largest axial cortical involvement (L-cort). Measurements of the femur (in mm): largest transverse width of the bone (W-tot), maximal thickness of cortex without lesional involvement (C-tot) and maximal thickness of cortex with lesional involvement (C-lesion)			

measurements C-tot and C-lesion were not significantly different between lesions in the two treatment groups.

Patient characteristics and survival: fractures versus no fractures

Between the 14 patients that experienced a fracture and the 88 patients that remained free from fracturing no major differences existed for age, sex, pain score at time of randomization, Karnofsky Performance Scale or primary tumor. Six fractures were reported in a total of 45 patients with breast cancer (13%), 3 in 17 patients with prostate cancer (18%), 2 in 26 patients with lung cancer (8%) and 3 in 14 patients with other primary cancers (21%) (P= 0.93). Median follow-up was 21 months for patients with or without a pathological fracture. Median overall survival for patients with a fracture was 44 weeks (95% CI 16-71 weeks) and 38 weeks for patients without a fracture (95% CI 25-51

TABLE 3 RADIOGRAPHIC ASPECTS AND LESIONAL MEASUREMENTS OF FEMORAL LESIONS FOR THE OUTCOME FRACTURE YES OR NO				
	Fracture no (N= 96 lesions)	Fracture yes (N= 14 lesions)	P-value	UV [†] HR (95%CI)
Radiographic feature				
Solitary	43%	83%	0.18	1
Multiple	34%	17%		0.2 (0.1 – 1.1)
Permeative	23%	0%		0.0 (0.0 – 7.3)
Radiographic appearance				
Osteoblastic	12%	0%	0.44	1
Osteolytic	88%	100%		29 (0.0 – > 100)
Radiographic pattern				
Radiographic	34%	22%	0.13	1
Eaten	60%	57%		1.6 (0.4 – 6.1)
Permeative	6%	21%		4.9 (0.9 – 24.5)
Axial localization				
Medial	64%	86%	0.18	1
Lateral	33%	7%		0.1 (0.0 – 1.5)
Combination	3%	7%		2.4 (0.3 – 18.9)
Transverse localization				
Medial	19%	29%	0.36	1
Central	25%	7%		0.2 (0.02 – 1.8)
Lateral	17%	7%		0.3 (0.04 – 2.8)
Combination	37%	57%		1.0 (0.3 – 3.3)
Length (median and range in mm)*				
Entire lesion	48 (14-251)	58 (31-229)	0.13	
Cortical	29 (0-120)	42 (27-155)		
Width (median and range in mm)*				
Total	39 (22-81)	40 (26-74)	0.53	
Lesion	23 (7-59)	31 (15-52)	0.22	
Cortex (median and range in mm)*				
Total	6 (1-11)	6 (2-18)	0.11	
Lesion	2 (0-9)	1 (0-6)	0.29	

Radiographic aspects were scored in 110 lesions in 100 patients of whom radiographs could be collected (conventional radiographs, CT scans, MRI scans and/or bone scintigrams)

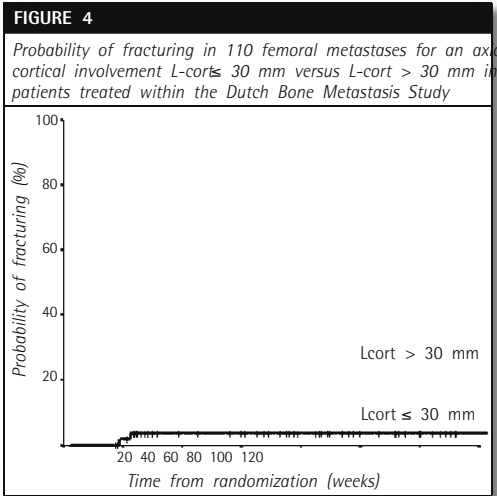
Lesional measurements on only conventional radiographs of 100 lesions (in mm) (see Figure 1): largest axial length of the entire lesion (L-tot), largest transverse extension of the lesion (W-lesion) and largest axial cortical involvement (L-cort). Measurements of the femur (in mm): largest transverse width of the bone (W-tot), maximal thickness of cortex without lesional involvement (C-tot) and maximal thickness of cortex with lesional involvement (C-lesion)

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

weeks) (P= 0.93). Patients who remained free from fracturing during follow-up were not retreated more often than patients who developed a fracture (15% vs. 21%, respectively, P= 0.44). Therefore, a higher total dose of irradiation due to more retreatment was not a valid explanation for non fracturing of lesions.

Lesional characteristics and measurements: fractures versus no fractures

In table 3 the radiographic aspects and lesional measurements are listed for fractured vs. non-fractured lesions. Radiographic feature, appearance, pattern of destruction, axial or transverse localization of the lesions was not different between fractured and non-fractured lesions. Most fractured and non-fractured lesions were solitary, osteolytic lesions, located proximally in the femur. Although fractured lesions more often had a permeative radiographic pattern,



this was not predictive for fracturing (P= 0.13). Most fractured lesions were located medially (29%) or were a combination of medial, central and/or lateral (57%) (P= 0.36). The largest axial length of the entire lesion, the transverse measurements W-tot and W-lesion and the cortical measurements C-tot and C-lesion were not significantly different between fractured and non-fractured lesions. The axial cortical involvement L-cort was the only parameter in the univariate analysis significantly predictive for fracturing (P= 0.001). Median L-cort for fractured lesions was 42 mm vs. 29 mm for non-fractured lesions.

Cut-off points for the axial cortical involvement were chosen to determine a more objective predictor for fracturing. A cut-off point of 30 mm significantly predicted fracturing (P= 0.01, HR 7 (95% CI 1.6 - 31.4)). Twelve fractured lesions had L-cort > 30 mm. Figure 4 shows the probability of fracture for each patient presenting with a lesion with L-cort ≤ 30 mm versus L-cort > 30 mm. In total, 52 lesions had L-cort > 30 mm of which 12 fractured: the positive predictive value of L-cort > 30 mm was limited (23%). No fractures occurred in the 10 lesions that were only visible on a CT-scan, MRI-scan or bone scintigram. If we consider those 10 lesions to have an L-cort ≤ 30 mm, a total of 58 lesions had L-cort ≤ 30 mm. Only 2 lesions with L-cort ≤ 30 mm eventually fractured (1 SF and 1 MF lesion). The negative predictive value of L-cort ≤ 30 mm was high (97%).

Because 51% AP and only 49% multidirectional radiographs were available for review, we evaluated whether underestimation of L-cort occurred if measured only on AP radiographs. Of the 52 lesions with L-cort > 30 mm, 46% were measured on AP radiographs only. Of the 48 lesions with L-cort ≤ 30 mm, 50% were measured on AP radiographs. The median L-cort was not significantly

smaller (32 mm vs. 33 mm for AP vs. multidirectional respectively, $P=0.15$), demonstrating that AP films could be used reliably to measure L-cort.

Between SF and MF patients the percentage of lesions with L-cort > 30 mm was not different (53% vs. 43%, respectively, $P=0.34$). Subsequently, we performed a multivariate analysis with the variables that predicted fracturing in the univariate analysis: randomization treatment schedule and L-cort > 30 mm. When correcting for L-cort > 30 mm, we could not demonstrate the treatment schedule to be a significant predictor for fracturing ($P=0.07$, HR 2.9 (95% CI 0.9 – 9.4)). An axial cortical involvement > 30 mm remained predictive for fracturing in the multivariate analysis ($P=0.02$, HR 6 (95% CI 1.3 – 27)).

Discussion

In this study on fracture risks in femoral metastatic lesions, we demonstrated the axial cortical involvement of the lesion to be significantly predictive for fracturing (L-cort > 30 mm, MV-analysis, $P=0.02$). Although more fractures occurred after a single dose of 8 Gy, we could not prove the treatment schedule to be predictive in the multivariate analysis when correcting for L-cort ($P=0.07$).

Treatments with a palliative intent comprise a large proportion of the total care that is delivered to cancer patients every day.¹⁸ It is therefore necessary that all involved professionals are informed on issues relating to palliative care. However, Barnes et al showed recently that only 1.3% of all abstracts presented at the annual meetings of the American Society for Therapeutic Radiology and Oncology (ASTRO) during the period 1993-2000 were devoted to symptom control and palliation.² One of the major problems in palliative care is the management of bone metastases. In the treatment of femoral metastases, one has to consider on the one hand prevention of pathological fractures with considerable morbidity, and on the other prevention of unnecessary surgical procedures. Elective surgery on patients with a relatively good performance status has been recommended because it is easier to perform than after pathological fracturing.³² In addition, it has been reported that pain is often reduced to a minimum directly after surgery and the ability to walk is usually regained within a few days.¹¹ Some physicians even advocate preventive osteosynthesis in all patients with proximally located femoral metastases, irrespective of the estimated risk of fracturing. However, we believe it is better to spare a patient with a limited life expectancy an operation with associated morbidity and mortality. Therefore, it is necessary to formulate good criteria for the correct application of surgical and non-surgical treatments for femoral metastases.

In the literature, several authors have studied femoral lesions and formulated risk factors for fracturing.^{4,6-8,10-13,15,16,20,22-24,28,31,32,38,39} Most often mentioned are the size of a lesion > 25 mm, increasing pain, and a circumferential cortical involvement > 50%. However, the majority of these studies was retrospective and used mostly surgical data. Patients in these studies already presented with a femoral fracture or underwent prophylactic fixations. Therefore, no information on the natural course of these lesions without fixation was available. Because most patients have limited life expectancies, it is possible that a large proportion of the lesions would have never progressed into a fracture. The present study has the major advantage that all reviewed femoral patients were randomized into a prospective radiotherapy trial with adequate follow-up on survival and development of fractures. Fourteen of the 102 randomized patients with a femoral lesion developed a pathological fracture during follow-up. We demonstrated the axial cortical involvement of the lesion to be significantly predictive for fracturing (L-cort > 30 mm, MV-analysis, $P=0.02$). These results are in line with Menck et al, who studied 69 pathological femoral fractures and concluded that 90% of the fractured lesions had an L-cort > 30 mm.²² Dijkstra et al noted a median L-cort of 54 mm in 9 actual subtrochanteric fractures (range 38 mm-100 mm).¹⁰ In our study, all other lesional measurements and radiographic aspects, such as the size of the lesion, the amount of transverse cortical involvement or a proximally located, solitary, osteolytic lesion were not predictive for fracturing. The strength of our study lies in the high negative predictive value of L-cort (97%), although the positive predictive power of L-cort was limited (23%). Of all 58 lesions with L-cort ≤ 30 mm, only 1 SF lesion and 1 MF lesion progressed into a fracture (3%). The use of L-cort pointed out that, as long as L-cort < 30 mm, even large lesions could be safely treated with radiotherapy. Although more fractures occurred after a single dose of 8 Gy, we could not prove the treatment schedule to be predictive for fracturing, when correcting for L-cort in the multivariate analysis ($P=0.07$). This outcome was probably due to the limited number of events. However, we showed that 6 fractions of 4 Gy seemed to postpone the occurrence of a fracture.

There are some remarks to be made. Firstly, the radiation doses used in the DBMS were chosen for treatment of pain due to metastatic involvement of the bone. Prevention of fracturing by inducing remineralization of the affected bone was not expected with these limited dose schedules. Therefore, the trial excluded all suspected high risk and already fractured lesions. The study protocol did not provide criteria on high risk lesions because it was believed that the existing risk factors in the literature were perhaps not very accurate in fracture prediction. Instead, only lesions which the treating physician expected to be high risk of fracturing were excluded. Although we did not review the radiographs of the 121 excluded patients, it is most likely

that these expected high risk and already fractured lesions were larger than or at least as large as the expected low risk lesions that were randomized into the DBMS. Therefore, we believe the use of L-cort as a guideline for treatment is applicable to all femoral lesions. Secondly, the scoring and measuring of three observers were combined into one outcome to simulate a multi-disciplinary setting in which clinicians join their individual experience. The interobserver variability of the measurements was reasonable and justified this approach. As a result, the length of the axial cortical involvement seemed to be a simple and objective parameter to predict femoral fracturing. Thirdly, only 49% multidirectional radiographs were available for review, as has been reported in earlier studies.³² One could question the reliability of studying AP radiographs only. We therefore analyzed if L-cort was smaller when measured on AP radiographs only. The difference in median L-cort for AP radiographs versus multidirectional radiographs was only 1 mm (P= 0.15). Nonetheless, we advocate the use of multidirectional radiographs to study femoral lesions because AP radiographs provide less detailed information on lesional sizes, extensions and characteristics. In addition, routine use of a CT scan to study the 3-dimensional anatomy of bone would be most optimal, but unfortunately, also least practical.

Many randomized prospective trials have reported the equal palliative effect of a single dose or short-term radiotherapy compared to more protracted regimens for the treatment of pain due to bone metastases,^{1,9,14,17,26,29,33} although some authors disagreed.^{5,30} The overall percentage of fracturing in the Dutch Bone Metastasis Study, 3% in 1157 eligible patients, was similar to what other radiotherapy trials report (1-8%).^{1,26,27,29,34,36} In the femoral subgroup, 14 fractures occurred. Two other trials also reported the percentage of fracturing in subgroups: Uppelschoten et al observed 8% fractures in pelvic and femoral lesions after a single dose of 6 Gy in a non-randomized prospective study of 170 patients, but they made no distinction between the two sites.³⁶ Tong et al studied 1016 patients in a randomized prospective trial with 5 different treatment schedules.³⁴ They reported 13% fractures in 96 patients with a metastasis in the long bones, but made no distinction between humeral or femoral sites. In case of a solitary lesion (n=164) they noticed 18% fracturing after 40.5 Gy and only 4% after a lower dose of 20 Gy (P= 0.02). No explanation was given for this remarkable difference, but it is likely that other factors play a role, such as lesion size.

Only a few studies focused on the role of radiotherapy in fracture prevention and mentioned percentages of reossification after radiotherapy.^{8,20,27} Cheng et al retrospectively studied 97 bone metastases in 59 breast cancer patients. For impending fracturing they took criteria that Beals and Harrington suggested for predicting fracturing^{4,15}: a lesion > 25 mm in diameter and/or any lesion

with a circumferential destruction of the cortex > 50%. Thirty-nine expected impending femoral lesions did not break during follow-up after a radiation dose of 30 to 40 Gy. In 11 patients evidence of reossification was visible on serial radiographs. Keene et al²⁰ discussed the follow-up radiographs of 35 patients with femoral metastases after average doses of 30 Gy (range 15-60 Gy). They noted progression in 26% of the lesions, no change in 57% and partial healing in 17%. We agree with Bates, who suggested in her review on bone metastases that adequate doses for fracture prevention still have to be found by carrying out prospective studies.³

In conclusion, we recommend the use of the simple radiographic parameter axial cortical involvement in deciding which treatment to apply on patients with metastases in the femur. In case of a painful femoral lesion with an axial cortical involvement ≤ 30 mm, a single fraction of 8 Gy can be safely applied. If the axial cortical involvement > 30 mm and the patient's condition is limited, radiotherapy using multiple fractions should be given to postpone the occurrence of a fracture. If the axial cortical involvement > 30 mm, prophylactic surgery should always be considered, accepting a relatively high percentage of surgical interventions to prevent disabling pathological fracturing of the femur.

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