Radiotherapy and Oncology 79 (2006) 278–284
www.thegreenjournal.com

Phase III randomised trial

Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy×1) versus multiple fractions (3 Gy×10) in the treatment of painful bone metastases

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Abstract

***Background and purpose*: To investigate whether single-fraction radiotherapy is equal to multiple fractions in the treatment of painful metastases.**

***Patients and methods*: The study planned to recruit 1000 patients with painful bone metastases from four Norwegian and six Swedish hospitals. Patients were randomized to single-fraction (8 Gy×1) or multiple-fraction (3 Gy×10) radiotherapy. The primary endpoint of the study was pain relief, with fatigue and global quality of life as the secondary endpoints.**

***Results*: The data monitoring committee recommended closure of the study after 376 patients had been recruited because interim analyses indicated that, as in two other recently published trials, the treatment groups had similar outcomes. Both groups experienced similar pain relief within the first 4 months, and this was maintained throughout the 28-week follow-up. No differences were found for fatigue and global quality of life. Survival was similar in both groups, with median survival of 8–9 months.**

***Conclusions*: Single-fraction 8 Gy and multiple-fraction radiotherapy provide similar pain benefit. These results, confirming those of other studies, indicate that single-fraction 8 Gy should be standard management policy for these patients.**

Keywords: Bone metastases; Radiotherapy; Single fraction

Radiotherapy of painful skeletal metastases consumes a considerable proportion of the resources available at most radiotherapy departments. A wide variety of dose schedules have been used, varying from one fraction of 6–10 Gy to multiple fractions—most often 30 Gy delivered in 10 fractions [20]. For more than two decades an ongoing discussion on the optimal radiotherapy regimen has taken place [4,15]. The first randomized study assessing the effect of one fraction of 8 Gy versus multiple fractions (3 Gy×10) was published in 1986 [18]. No difference was found between the regimens with regard to onset and/or duration of pain. Pain relief was independent of histology of the primary tumor. Patients receiving a single fraction were more likely to receive re-irradiation to the same site as compared to patients receiving multiple fractions. However, an increased analgesic consumption was seen in the latter group as compared to the single-fraction group. In a subsequent study it was found that a single fraction of 4 Gy was inferior to a single fraction of 8 Gy [10].

Between 1997 and 1999, four randomized studies comparing one fraction with multiple fractions were published. The first two studies in this series compared 10 Gy×1 versus 4,5 Gy×5 [7], and 8 Gy×1 versus 5 Gy×4 [14]. Both gave similar results when comparing treatment regimens with regard to the primary aim, pain control. However, these studies were criticised for low compliance in patient's pain assessments [7], and also for having too few patients for evaluating long-term effects (pain relief at around 10–14 weeks) or for demonstrating equivalence [7,14]. Two more recent larger studies were published after our trial had started in 1998 and confirmed the previous studies [1,22], supporting treatment equivalence and

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concluding that the single fraction is therefore preferred to the multi-fractionated regimen.

The present randomised trial was designed to have adequate sample size for testing treatment equivalence, and also has sufficient patients at 12 weeks to evaluate long-term pain control. Furthermore, it included rigorous evaluation of pain control and analgesic consumption. Thus, the primary aim of this trial was to test the treatment equivalence of 8 Gy×1 versus 3 Gy×10 in relieving pain caused by skeletal metastases. The primary endpoint was the degree and duration of pain relief over the first 28 weeks.

Patients and methods

Patients

From April 1998 to July 2000, patients from four centres in Norway and six centres in Sweden were included. Patients were eligible if they had bone metastases resulting in clinically important pain, judged by the physician and the patient. Inclusion criteria were biopsy- or cytology-proven malignant disease, bone metastasis (at any site) verified by bone X-ray, bone scan, computer tomagraph (CT) or magnetic resonance imaging (MRI), and Karnofsky Performance Status above 40. Patients who had received previous irradiation to the present symptom site were excluded, as were patients with manifest spinal cord compression, and those in need of bone surgery. Also excluded were patients unable to complete the quality of life assessment tools, and those with a life expectancy of less than 6 weeks.

Treatment and research schedule

Patients were randomised to receive either single fraction 8 Gy, or a total of 30 Gy in 10 fractions. Randomly permuted blocks were used, stratified by centre, primary diagnosis and anatomic localisation. Randomisation was by phone to St Olav's University Hospital, using a computer-generated randomisation.

Linear accelerator therapy was delivered, using 6 or 15 MV photon energy for spinal, pelvic and long bone lesions and 8–18 MeV electron energies for lesions in ribs or sternum. The target volume was based on clinical and radiological judgement. Fields were planned to include known skeletal manifestations with an additional 2–3 cm margin. For spinal lesions the fields included at least one vertebral body above and below the painful vertebrae. For spinal bone metastases, all doses were prescribed to the posterior edge of the vertebral corpora. For long bone and pelvic lesions, mid-plane prescribed doses were delivered by two opposing fields. Electron field doses were prescribed to the deep limitation of the target. Fields delivered to the pelvic region were not to exceed a size of 400 cm^2, excluding shielding. Several targets could be treated simultaneously. Analgesics were given according to local guidelines. Prophylactic treatment with cortico-steroids was not given routinely; if cortico-steroids were given, indications and doses were recorded.

Evaluation schedule

Pre-study clinical examination was according to local routines. As a minimum, the following were recorded: Karnofsky Performance Status, previous and ongoing tumour-directed treatment including previous radiotherapy and chemotherapy, use of steroids, and patients' pain intensity on a 5-point numerical rating scale.

Patients completed health-related quality of life (HRQOL) questionnaires, including the EORTC QLQ-C30 [2], the fatigue questionnaire [17], a pain assessment chart that included pain location, and a 5-point numerical rating scale with intensity ranging from no pain to extreme pain. The HRQOL package was completed before randomisation, and at 4, 8, 12, 20 and 28 weeks.

Pain medication was accessed using diaries completed daily for 6 weeks, reporting pain intensity, pain localisation, nausea, diarrhoea, and analgesic usage. Opioid analgesics were converted to the mean morphine-equivalent dose per week [8]. Provided opioid dosage was reported on at least 4 days of the week, missing data were estimated using the mean of the reported days. When more than 3 days were unreported in 1 week, data for the whole week were considered missing.

Outcomes and statistical considerations

This trial was designed as an equivalence study. The primary outcome was defined as pain relief, based upon the pain scale in the EORTC QLQ-C30 supplemented by estimates from the pain charts. Reduction of pain intensity and duration of effect were the primary outcomes. The other scales and single items of the EORTC QLQ-C30 and fatigue questionnaire were considered as secondary endpoints.

In equivalence studies it is more important to aim for a high power than a small type 1 error (P-value) [13]. Thus the trial was designed to have 90% power to detect a difference in pain at 12 weeks, using a one-sided t-test with $P<0.10$. From past experience, the standard deviation of the QLQ-C30 pain score in similar patients was known to be approximately 30, and an effect size of 0.20 standard deviations (equivalent to approximately six units on the 100-point pain scale) was taken to be a small effect in terms of its clinical importance [16]. Power calculations showed that a total study size of 700 patients suffices to exclude such a difference and hence confirm equivalence [13]. To compensate for deaths and poor patient compliance, it was therefore planned to recruit a total of 1000 patients; that is, 500 per treatment arm.

It was pre-specified in the protocol that a single interim analysis would be carried out after approximately 50% of patients had been recruited. As described in the results, the trial was terminated earlier than planned. In view of this early termination, and bearing in mind that this is an equivalence trial, the consequent lack of power would support the study hypothesis by making it more likely that no significant differences are found and thus equivalence declared. In this situation, confidence intervals (CIs) are more statistically informative than significance tests and P-values, since CIs reflect the degree of uncertainty in the estimates of treatment effect. Hence, two-sided 95% confidence intervals are presented.

Table 1
Baseline characteristics in 376 patients randomised to single or multiple fractions radiotherapy for painful bone metastases

	Treatment					
	3 Gy×10		8 Gy×1		Total	
Total patients	190		186		376	
Age mean (SD)	67.0	(11.1)	66.7 (10.2)		66.9 (10.7)	
Gender						
Male	98	52%	112	60%	210	56%
Female	92	48%	74	40%	166	44%
Diagnosis						
Prostate	69	36%	70	38%	139	38%
Breast	60	32%	53	28%	113	30%
Lung	20	11%	20	11%	40	11%
Other	41	22%	43	23%	84	22%
Karnofsky mean (SD)	74	(17)	73 (16)		74 (16)	
Metastatic site						
Spine	70	37%	73	39%	143	38%
Pelvis	66	35%	66	35%	132	35%
Upper/lower extremity	37	19%	38	20%	75	20%
Other	17	9%	9	5%	26	7%

Results

It was noted at the end of 1999 that patient recruitment was tailing off. This was thought due to the increasing belief amongst participating physicians that the single fraction was preferable. This view was encouraged by the publication of the two large trials in 1999 [1,22], both supporting the equivalence of single and multi-fractionated regimens. Thus, it was decided to carry out an ad-hoc interim analysis, before the one that was due when 50% of the patients had been recruited, and convene an independent trial-monitoring and review committee. At that time a total of 376 patients had been randomised. After examining the results in the context of the accruing external evidence from other studies, it was decided to terminate the trial. This paper reports data on these 376 patients and the ensuing 18-month follow up.

Patients were included from Norway (53%) and Sweden (47%), with four hospitals recruiting 73% of the patients. The most frequent diagnoses were cancer of the prostate (38%), breast (30%) and lung (11%) (Table 1).

Of the randomised patients, 190 received 10 fractions, while 186 received one fraction. The following sites were irradiated: columna (41%), pelvis (39%), arms and legs (26%) and others (12%). Cortico-steroids were given prior to and during radiotherapy in 92 patients, with 49 in the single-fraction, and 43 in the multiple-fraction arm.

The median survival times were 9.6 months (8 Gy) and 7.9 months (3 Gy×10), with a suggestion of a short-term advantage to the single fraction although this disappears by 1 year. Overall, there was no significant difference in survival between the two groups (Fig. 1). However, as expected, there were major differences in survival according to site (Fig. 2). A stratified analysis using both log-rank tests and Cox survival models was used to confirm that there was no significant difference between the two treatment arms within any of these cohorts.

The patients' compliance in returning pain assessment charts and HRQOL questionnaires was high during the entire study period, ranging from 94 to 82% of the patients alive (Table 2). The baseline results are shown in Table 3. As expected, there were no differences in pain at study entry.

The patterns of pain scores over time are shown in Fig. 3. The plots are, respectively: The two QLQ-C30 pain items q9 ('Have you had pain?') and q19 ('Did pain interfere with your daily activities?'), QLQ-C30 pain scale and the pain intensity verbal rating scale (VRS). Further more, overall quality of life (QLQ-C30), QLQ-C30 fatigue scale, and the fatigue questionnaire total, physical and mental fatigue scores were analysed. No significant differences were seen at any time. The levels over time were very similar in the two groups, and the (narrow) confidence intervals support treatment equivalence.

Supplementary analyses, not presented here, examined change from baseline and also area under the curve (AUC) analyses. These confirmed the lack of any observable difference between the treatment groups.

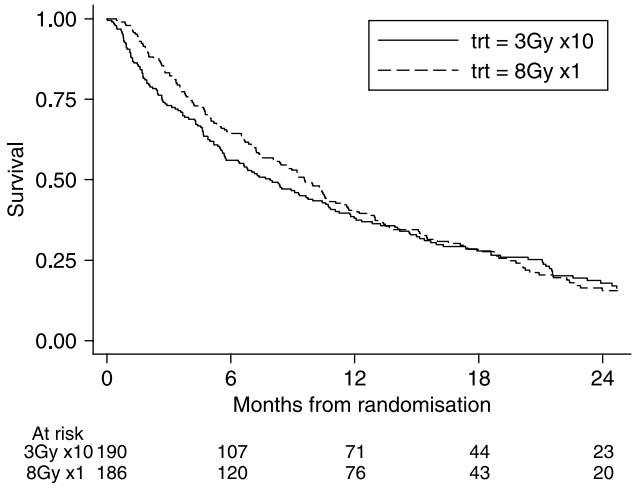

Fig. 1. Overall survival in 376 patients treated with single or multiple fraction radiotherapy for painful bone metastases.

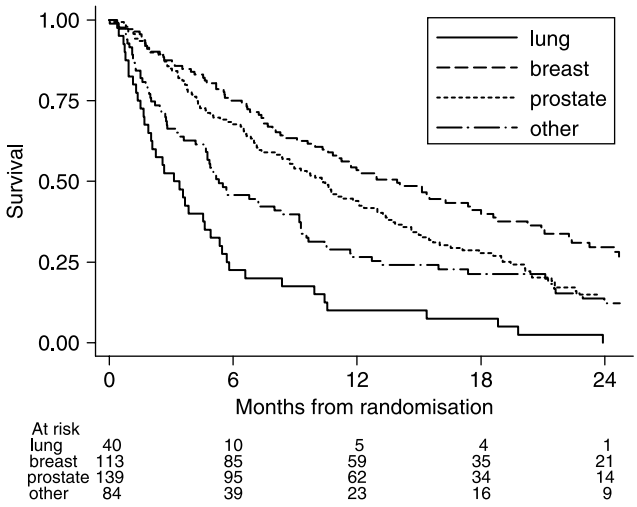

Fig. 2. Survival by diagnosis in 376 patients treated with single or multiple fraction radiotherapy for painful bone metastases.

In order to investigate possible differences between treatment schedules in relation to survival, patients were grouped into three subcohorts: those alive less than 1 year ($n=227$), between one and 2 years ($n=70$), and more than 2 years ($n=79$). No significant differences were found between treatment arms in any of these subcohorts.

Types of additional treatments were recorded (Table 4). More patients in the single-fraction group received retreatment of the previous volume, but more patients in the multiple-fraction group had treatment for pathological fracture or bone surgery. In the first 4 weeks, fewer patients in the single-fraction arm experienced nausea and diarrhoea compared to the multiple-fraction arm.

Pain medication

Compliance in returning diaries fell from 85% during the first 2 weeks, to 73% during weeks 5 and 6. Across treatments, more patients treated with 8 Gy× returned their diaries ($P<0.005$ for all time periods).

The number of patients medicated with paracetamol fell from 115 during the first 2 weeks to 93 during weeks 5 and 6 in the single-fraction group, and from 105 to 73 patients over the same time periods for the multiple-fraction group. The number of patients consuming non-steroid anti-inflammatory drugs (NSAID) changed from 48 patients during weeks one and two to 41 during weeks 5 and 6 in the single-fraction group, while in the multiple-fraction group, the number of patients consuming NSAID dropped from 52 to 37. Less than five patients in each group used fenazon+coffeine. The consumption of non-opioid analgesics was similar in both groups, and none of the differences were statistically significant.

The converted mean opioid doses are displayed in Fig. 4. No differences were found between groups over time. For patients in the single-fraction arm, the mean daily opioid doses during weeks 1–6 were 100 mg (95% CI 83–118), while in the multiple-fraction patients the mean daily opioid doses were 115 mg (95% CI 66–164). The confidence intervals were overlapping, implying no evidence of difference. Similar results were found when analyzing opioid amounts for the patients that returned all their diaries throughout the observation period. The amount of opioids used was stable throughout the observation period.

Discussion

The results of this study support the hypothesis that single fraction 8 Gy compared to multiple-fraction radiotherapy provides the same degree of pain relief, and that the impact on fatigue and overall quality of life is equivalent. These findings are in accordance with several studies published after this study had been initiated [1,14,22], several systematic reviews [6,24,26,27], and reports from earlier studies [7,18,19]. We showed that, in both groups, there was a clinically and statistically significant reduction in pain score assessed by the pain scale of the EORTC QLQ-C30 and a five point Likert scale. This reduction was maintained throughout the 28 weeks follow up.

This study was terminated early, based on the results from an interim analysis and the recommendations of an independent panel of international experts in radiotherapy and statistics. This took into account the published studies that consistently pointed towards one single fraction of 8 Gy being as effective for relief of pain due to bone metastasis as multiple-fraction regimes [1,7,14,18,19,22]. Due to its much lower cost and greater convenience to the patients, one single fraction should now be regarded as the standard treatment.

Two studies [3,20] and one recent editorial [21] have questioned some aspects related to the recommendation of one single fraction being the standard treatment for all patients with uncomplicated bone metastasis. Are there subgroups of patients who will benefit from a multiple fraction? In four recently published studies, with patient samples of 765 [1], 1171 [22], 241 [14] and 898 [9],

Table 2
Compliance of returning HRQOL questionnaire in 376 patients treated with radiotherapy for painful bone metastases

Time (week)	3 Gy×10				8 Gy×1			
	Dead	At risk	QLQ	%	Dead	At risk	QLQ	%
0	2	188	171	91	0	186	174	94
4	25	165	144	87	7	179	163	91
8	39	151	123	82	21	165	149	90
12	52	138	111	80	33	153	136	89
20	71	119	97	82	55	131	112	86
28	88	102	84	82	71	115	94	82

Table 3
Baseline pain scores—patient self-assessment in 336 patients planned for palliative radiotherapy for painful bone metastases

	Treatment					
	3 Gy×10		8 Gy×1		Total	
QLQ-C30 pain score						
Mean (SD)	67 (25)		69 (26)		68 (25)	
Baseline QLQ-C30 pain (q9)						
Not at all	3	2%	5	3%	8	2%
A little	34	20%	28	16%	62	18%
Quite a bit	84	49%	82	47%	166	48%
Very much	50	29%	58	34%	108	31%
Total	171		173		344	
Visual rating scale—pain intensity						
No pain	2	1%	4	2%	6	2%
Slight pain	20	12%	26	15%	46	14%
Moderate	85	52%	73	42%	158	47%
Strong pain	44	27%	51	30%	95	28%
Very strong pain	13	8%	18	11%	31	9%
Total	164		172		336	

respectively, more patients in the hypofractionated arm were retreated. Numbers were ranging from 16 to 23% in the single-fraction arm and from 7 to 12% in the multiple-fraction arm. This is in accordance with the findings in the present study. The reasons for retreatment are often unclear [12,22]. It has been suggested that a lower threshold is used for retreatment in the single-fraction arm [10], and it is noted that results from the largest study support this [22]. Furthermore, regardless of retreatment, equivalence of a single and multiple fractions of radiotherapy can be maintained [25].

In our study, more patients experienced pathological fractures in the multiple-fraction arm (11%) as compared to the hypofractionated arm (4%). However, in other studies more fracturing has been found in the single-fraction group [24,27]. The higher proportion of pathological fractures in the multiple-fraction arm of our study needs to be interpreted with caution, due to the relatively small

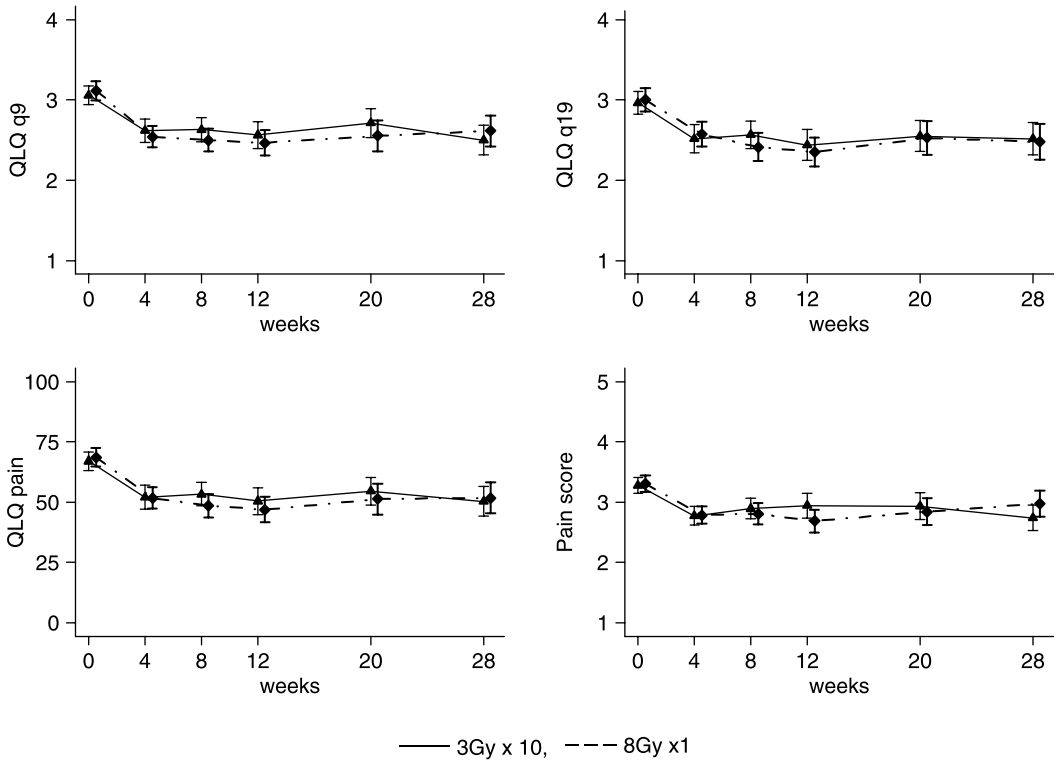

Fig. 3. Pain in patients randomised to single or multiple fractions radiotherapy for painful bone metastases. QLQ q9 = 'Have you had pain?' QLQ q19 = 'Did pain interfere with your daily activities?'.

Table 4
Additional treatment in patients having received radiotherapy for painful bone metastases

Type of treatment	3 Gy×10 (M) 8 Gy×1 (*n*)	8 Gy×1 (*n*)
Radiotherapy to new painful sites	61	78
Re-treatment of previous volume	7	29
Treatment for pathological fractures[a]	21	8
Treatment for spinal cord compression[a]	5	10
Chemotherapy	32	22
Surgery	15	9

[a] Not referable to treatment site only.

numbers. Overall, our data support the hypothesis that a single fraction for bone metastasis is biologically similar to multiple-fraction regimes.

There was high compliance in completing HRQOL questionnaires during the 28-week follow up (range 94–82%). This is similar to or higher than what is achieved in most studies when HRQOL is assessed in curative or palliative settings [5,11,23]. However, there was slightly higher compliance in the single-fraction arm. Since, the non-compliers appeared to be patients with worse health, any bias caused by non-compliance is likely to result in relative underestimation of pain and fatigue in (i.e. favour) the multiple-fraction arm, and overestimation of overall quality of life. Thus, we believe our findings are secure.

The compliance of patients in completing the pain diaries was also excellent, varying form 85 to 73% during the six-week period. There was a higher compliance in the single-fraction group, again possibly resulting in bias in favour of the multiple-fraction group. The consumption of non-opioid analgesics was similar in the two treatment arms. Mean opioid doses in the two treatment regimens did not differ during the 6-week observation period, and the consumption of opioids was stable in both groups. Reported pain, did, however, fall during the first 6 weeks. This may reflect the immediate effect of radiotherapy.

It has been suggested that there might be a subgroup of patients with longer survival who may benefit from receiving multiple fractions [14,22]. To evaluate this assumption, we analysed our data in three subgroups according to survival (analyses not reported here). Within these subgroups, no differences in pain, fatigue or overall quality of life were found between the two treatment regimes.

In this study more patients in the single-fraction arm ($n=10$) experienced spinal cord compression as compared to the multiple-fraction arm ($n=5$). In the other major reports, the results are inconclusive regarding spinal cord compression [20,24].

In conclusion, the present study endorses the adoption of single-fraction radiotherapy as standard. However, there remain some uncertainties regarding possibly higher frequency of spinal cord compression, pathological fractures and need for re-irradiation in the single-fraction regimen.

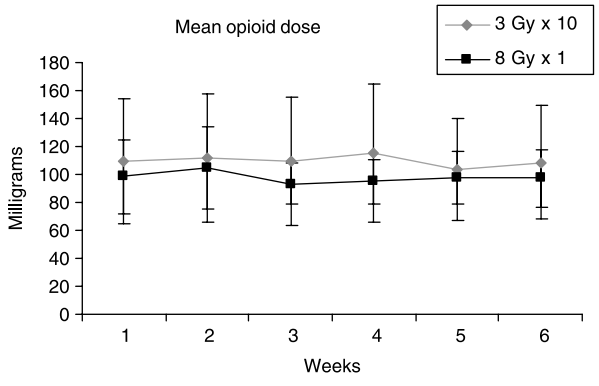

Fig. 4. Mean opioid dose in 376 patients treated with radiotherapy for painful bone metastases.

Acknowledgements

We thank Ingegerd Carlberg, Norrlands Hospital, Umea; Christina Lindemalm, Jan Fagerberg, Ingemar Näslund, Radiumhemmet, Karolinska Hospital, Stockholm; Roy Bremnes, Tromso University Hospital, Tromso; Anders Ask, Jacob Engellau, Lunds Hospital, Lund; Steinar Hagen, Ulleval University Hospital, Oslo and Mikael Kälkner, Uppsala University Hospital, Uppsala for recruiting patients to this study.

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Received 14 April 2005; received in revised form 2 May 2006; accepted 8 May 2006

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