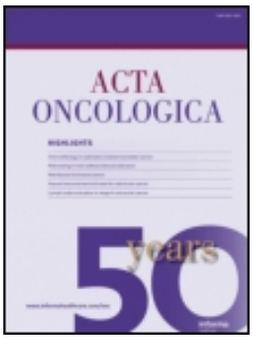

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ORIGINAL ARTICLE

Half body irradiation of patients with multiple bone metastases: A phase II trial

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Abstract

Aim of study. The primary aim of this study was to evaluate the effect of half-body irradiation (HBI) on pain and quality of life in cancer patients with multiple bone metastases. The secondary aim was to evaluate side effects of the treatment. *Patients and methods.* A total of 44 patients received lower (n = 37), upper (n = 5), or sequential HBI (n = 2). The dose for lower HBI was 8 Gy in one fraction and for upper HBI 7 Gy in one fraction, with reduction of the lung dose to 6 Gy in one fraction by partial shielding. The majority of patients (n = 41) were males with prostate cancers (93%). Outcome and side effects were measured by the EORTC Quality of Life Questionnaire C30 (QLQ-C30), and by the doctors′ toxicity scores in the medical record. Pain relief was defined as a reduction of more than 10 points on the QLQ-C30 scale. Evaluations were performed before and 2, 4, 8, 16, and 24 weeks after treatment. *Results.* Relief of pain was observed in 76% of the patients receiving HBI with 8.8% of the patients experiencing complete pain relief with no residual pain in the treated field. For most patients, the pain relief was lasting throughout the follow-up period. About one third of the patients were able to reduce their intake of analgesics. Grade 1–2 diarrhoea was the most common side effect observed in 49% of the patients two weeks after treatment. Mild pulmonary symptoms (grade 1–2) were observed in four of seven patients receiving upper HBI. No clear effect was observed on the patients' global quality of life.*Conclusion.* Single fraction HBI is safe and effective providing long lasting pain reduction in 76% of patients with multiple bone metastases.

Bone metastases are common in patients with advanced cancers of the lung, breast and prostate [1–3]. Bone metastases usually indicate incurable disease and may be associated with severe pain [4]. Localized radiotherapy (RT) is an effective treatment of painful bone metastases [4,5]. However, patients with bone metastases often have multiple areas involved and often require additional treatment. Half-body irradiation (HBI) has the advantage of treating many sites simultaneously and has been suggested to prevent or delay further development of subclinical disease [6–8]. Previous studies have shown a good pain relieving effect of HBI given either as a single dose or by fractionated treatment, with pain relief reported in up to 80% of the patients treated, mainly in patients with prostate and breast cancers [6,9–11]. Still, some reluctance persists in using HBI, because radiotherapy to a greater field increases the risk of toxicity. The most common known side effects to lower HBI are nausea, vomiting and diarrhoea. A more serious side effect of upper HBI is pneumonitis. Most of the literature on HBI is retrospective [11,12].

Here we report the results of a prospective phase II study designed to evaluate the effects and side effects of HBI, given as one fraction, to cancer patients with multiple bone metastases.

Patients and methods

Patient population

Between December 1996 and April 2004 a total of 44 patients were enrolled. The study aimed to include 100 patients but due to local logistic problems recruitment was so slow that it was decided to close the study in April 2004. Inclusion criteria were: a histologically confirmed malignant

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disease, performance status ≤ 3, and pain caused by multiple bone metastases. Bone metastases should be verified by bone scintigraphy and at least one metastasis verified by x-ray. The exclusion criteria were: pathological fractures, suspicion of spinal cord compression, bone marrow depression, and for upper HBI significant heart and lung diseases. Previous localized RT was allowed, providing the maximum tolerable doses in the specific area was not exceeded. Ongoing endocrine treatment was allowed, but changes during the follow-up period were registered. Patients were evaluable if they had completed at least one follow-up visit.

Patient characteristics

Patient characteristics are shown in Table I. The study included 43 men (41 with prostate cancer, one with lung cancer, and one with primary tumour of unknown origin) and one woman with breast cancer. All but three patients had received antineoplastic treatment previously. Median performance status was 2 (range 0–3). The survival from treatment to death ranged from 3 weeks to 54 months with a median survival of 6 months. A total of 15 patients lived to be evaluated at 24 weeks.

Table I. Baseline characteristics of 44 Danish patients receiving HBI

	(n)	(%)
Gender		
Male	43	97.7
Female	1	2.3
Age (years)*	66 (50; 80)	
Site of primary tumor		
Prostate	41	93.2
Breast	1	2.3
Lung	1	2.3
Unknown	1	2.3
Previous cancer treatment		
None	3	6.8
Radiotherapy	2	4.5
Hormone (including orchiectomy)	25	56.8
Surgery	1	2.3
Combined	13	29.5
Ongoing cancer therapy		
Hormone	17	38.6
None	27	61.4
Performance status		
0	2	4.5
1	14	31.8
2	21	47.7
3	7	15.9
Morphine/equivalent (mg p.o)	120 (0;640)	
HBI		
Upper	5	11.4
Lower	37	84.1
Both	2	4.5

*median (range)

Thirty-seven patients received lower HBI, 5 received upper HBI, and two patients received sequential lower and upper HBI with 8 to 12 weeks between the two treatments. The baseline characteristics were similar for patients receiving upper, lower and sequential treatment.

HBI

HBI was given with a linear accelerator with 8 MV photons. The patients received either an upper or a lower HBI depending on the site of their pain. When both upper and lower HBI was required, the patient was treated in the most painful area first and an additional treatment was given after no less than 6 weeks to allow the bone marrow to regenerate between the two treatments. Upper HBI was defined as a field extending from 2nd cervical vertebra to the iliac crests and was treated with two anterior-posterior opposing fields. The lower HBI was defined as a field extending from the iliac crests and down below the knee. Laterally, the field borders extended into free air. The lower HBI was given in two pairs of anterior-posterior opposing fields joined together at the femoral shaft. The central dose for an upper HBI was 7 Gy in one fraction. The dose to the lungs and kidneys was reduced to 6 Gy by partial shielding and the bowels were protected by shielding 3 cm below the ribs. The radiation dose for a lower HBI was 8 Gy in one fraction. The radiation dose was prescribed centrally; for the upper HBI at the level of carina. The patients were hospitalized and treated on day one prior to treatment with prednisolone 100 mg $\times 1$, metopimazin 30 mg $\times 4$, ondansetron 8 mg i.v. During the first 12 hours following HBI the patients received 1 000 ml isotonic saline and 1 000 ml glucose i.v. On day two medication included prednisolone 50 mg, metopimazin 30 mg $\times 4$ and lorazepam 1 – 2 mg p.n.

Follow-up

The patients were seen at weeks 2, 4, 8, 16 and 24 following treatment or until death. The follow-up visits included assessments of QoL, performance status, intake of analgesics, and toxicity scoring and blood tests for haematological toxicity. Serum calcium was not measured as a part of the protocol but symptomatic hypercalcaemia was treated according to local guidelines. All doses of opioid were converted into equivalent doses of morphine in mg for oral intake. Toxicity was scored according to the WHO toxicity grading scale ranging from one as

being mild side effects to four as being life threatening.

Quality of life assessment

For assessment of the quality of life we used the EORTC QLQ-C30 version 1.0. The QLQ-C30 is composed of multi-item scales as well as single-item measures. Given scores were transformed linearly to a scale ranging from 0–100. A high score in any of the functional scales represents a high level of functioning, a high score in the global health status a high global health status, and a high score in any of the symptom scales a high level of symptoms. A change of 10 or more points was considered to be of clinical significance [13]. In addition to the QLQ-C30, the patients were asked to describe their pains in the treated field on a 7 point scale. As for the QLQ-C30, the scores were linearly transformed to a scale from 0–100 to ensure comparability with other studies. The patients were asked to fill in the questionnaires alone without receiving any help.

Ethics

This trial was performed in accordance to the Helsinki Declaration and approved by the local ethical committee. Appropriate informed consent was obtained from all patients.

Statistical analysis

McNemar's test for matched samples with Yates correction was used to detect significant changes in the frequencies of patients experiencing side effects at baseline and at follow-up visits. All p-values are two-sided.

Results

Pain relief after treatment

Maximal pain relief in the treated area was observed four weeks after treatment (Table II), where 26 patients (76%) reported partial or complete pain relief. Three of these (8.8%) reported complete pain relief. In most patients, the pain relief lasted throughout the follow-up period. The pain score at baseline was relatively high with a median of 67 points (range 17–100). Two weeks after treatment, the median symptom score was reduced to 50 points (range 0–100) and the lowest symptom score was observed in week four with a median of 33 points (range 0–100).

About a third of the patients were able to reduce their use of analgesics (Table II). The maximum reduction was observed four weeks after treatment, where more than a third of the patients (n = 13) were able to reduce their intake of analgesics compared to baseline. The effect did not last beyond week 16 after treatment.

Overall, pain relief did not differ between patients receiving an upper or a lower HBI. The two patients receiving both upper and lower HBI experienced good pain relief from both treatments.

Quality of life after HBI

The global health score changed during follow-up, but no clear trends were observed. The patients showed a relatively low median score at baseline of 42 points, ranging from 8 to 83 (data not shown). No significant changes were observed at later follow-up visits.

Vomiting after HBI

Vomiting measured by the QLQ-C30 scale was reported by 18 (42%) patients at baseline (Table III). A few more patients (21 or 50%) reported vomiting in week two and thereafter the frequency of vomiting decreased to 25 – 33% during the remaining follow-up visits. However, none of the changes were statistically significant. The frequency of patients experiencing nausea and vomiting reported by the doctors' toxicity scoring showed the same trend (data not shown). Most cases reported by the doctors were categorized as grade 1 and 2 toxicities. Two patients experienced grade 3 toxicity in week

Table II. Pain relief in the treated HBI-field

Weeks after treatment	Patients (n)	Partial[1] or complete pain relief n (%)	Complete pain relief n (%)	Patients (n)	Reduced dose of analgesics[2] n (%)
2	36	22 (61)	3 (8.3)	36	10 (28)
4	34	26 (76)	3 (8.8)	37	13 (35)
8	27	19 (70)	5 (19)	29	10 (34)
16	21	14 (67)	5 (24)	19	5 (26)
24	13	9 (69)	1 (7.7)	11	5 (45)

[1]Partial pain relief was defined as a change on the QLQ-C30 of more than 10 points.
[2]All doses of opioid were converted into an oral morphine equivalent dose in mg.

Table III. Side effects after HBI

Weeks after treatment	Patients (n)	Vomiting[1] (%)	Patients (n)	Diarrhoea[2] (%)	Patients (n)	Fatigue[3] (%)
0	43	42	42	14	43	40
2	42	50	41	49*	40	63
4	39	31	38	21	37	46
8	32	25	31	19	31	39
16	23	22	23	7.0	23	57
24	15	33	15	13	15	60

[1]Vomiting measured as a QLQ-C30 symptom score ≥ 33 points.
[2]Diarrhoea measured as a QLQ-C30 symptom score ≥ 66 points.
[3]Fatigue measured as a QLQ-C30 symptom score ≥ 50 points.
*$p < 0.001$ (McNemar's test for matched samples)

two and one patient grade 4 toxicity in weeks two and four after treatment.

Diarrhoea after HBI

Also measured by the QLQ-C30 scale, six (14%) patients reported diarrhoea at baseline (Table III). The frequency of patients reporting diarrhoea increased significantly at week two, where 20 patients (49%) reported diarrhoea ($p < 0.001$). The frequency of patients experiencing diarrhoea decreased in week four and reached baseline level at week 8.

The frequency of diarrhoea measured by the doctors' toxicity scoring showed the same trend (data not shown), but the actual number of patients scored with diarrhoea was somewhat lower. The doctors reported five patients (12%) to have diarrhoea at baseline and 15 patients (38%) at week two ($p < 0.03$). There was one patient with grade 3 diarrhoea, otherwise the diarrhoea was grade 1 and 2. All cases of diarrhoea were reported by patients receiving lower or sequential HBI, while none of the five patients receiving upper HBI experienced diarrhoea.

Fatigue after HBI

Since the study population represented patients with advanced disease, we chose to classify the patients as having pronounced fatigue when they scored 50 or above on the fatigue symptom scale. By the QLQ-C30 questionnaires, Table III shows that 40% of the patients suffered from pronounced fatigue at baseline, increasing to 63% at week two, then decreasing from week 4 to 8 and increasing again with further follow-up. However, these changes were not statistically significant.

Other toxicity after HBI

Of the seven patients receiving upper HBI alone or sequential to lower HBI, four patients experienced mild pulmonary symptoms graded as 1 or 2 after HBI. These were recorded between two days and two weeks after treatment and were temporary ($n = 1$) or persistent ($n = 3$) throughout the remaining follow-up period. No nephrotoxicity was observed for the patients receiving lower or upper HBI.

Many patients had abnormal haematology at baseline but there was no particular pattern of haematological toxicity in relation to the treatment.

Discussion

This study shows that long lasting pain relief can be achieved for 76% of the patients following HBI. This is consistent with the findings in another prospective study by Salazar et al. [11] where pain relief was reported in up to 73% of the patients receiving HBI. Salazar et al. compared their findings with those of conventional localized RT [11,14] and reported that response rates were similar, but the pain relief with HBI was achieved sooner and with less evidence of recurrence of pain in the treated area compared to conventional RT. In other studies of HBI [9–11], pain was evaluated by a pooled pain score dependent on the severity of the pain as well as the use of analgesics. We chose to evaluate pain and use of analgesics separately. Though pain relief was observed in up to 73% of patients, only about a third were able to reduce their intake of analgetics. The relatively high median pain score at baseline (67 points) indicates that many of the patients were covered insufficiently by analgesics at baseline. This may contribute to the discrepancy between the number of patients experiencing pain relief in the treated area and the number of patients being able to reduce their intake of analgesics.

A previous study has documented a positive effect of HBI on Qol [15]. They used different approaches to assess quality of life such as pain relief, performance status and narcotic scores and concluded that an improvement in any of these represented an improvement in Qol. In the present study, we used the global health status from the QLQ-C30 questionnaire as an

effect measure of the Qol and found no effect of HBI on the global health status. The global health status may be a better effect measure, because it is the pooled score from two questions directly asking the patients about their Qol and about their physical condition. Patients with advanced cancer may suffer from low Qol for many reasons and one should be cautious when choosing one or more factors to predict Qol.

Diarrhoea is a well-known side effect of HBI and RT in general [9–11,15], but only few studies on HBI report the actual frequencies or grade. In our study, diarrhoea was observed in about half of the patients during the second week after treatment with lower HBI. Mostly, the diarrhoea was mild, being categorized as grade 1 and 2. Other studies have reported diarrhoea in between 20% of the patients treated with lower or mid-body HBI [11] and up to 73% of the patients receiving lower HBI [9] one to two weeks after treatment. These were mostly categorized as being mild or moderate, but two cases of life-threatening diarrhoea were reported. We found that the frequency of side effects reported by the patients was higher than that reported by the doctors. This may explain some of the discrepancy in the reported frequency of diarrhoea in the published reports.

Other known side effects of HBI include nausea and vomiting in the first few hours after treatment in up to 50% of the patients [9,11,12]. Since modern antiemetics were used in our study, we did not record these immediate side effects. Although we noted an increase in vomiting in week two after treatment compared with baseline, these changes were not statistically significant. Again, this result may reflect that most patients in our study received lower HBI.

Fatigue was present at baseline in 40% of the enrolled patients and varied over the study period which is compatible with the findings of other studies reporting HBI related fatigue to last 2 – 3 months after treatment [11,12]. In this study, we were not able to differentiate whether fatigue was caused by the treatment or related to progressive disease.

Of the seven patients treated with upper HBI alone or sequential to lower HBI, four patients experienced mild pulmonary symptoms. Pneumonitis is one of the more serious side effects of HBI and RT in general, and has previously been reported for about one third of the patients receiving upper HBI [12].

The major strength of this study was that it was conducted prospectively according to a specified protocol in two closely related radiotherapy departments. We are therefore reasonably sure that the treatment given and the follow-up of the patients adhered to the protocol. Another strength of this study is the use of the QLQ-C30 questionnaire, which has generally been accepted as a validated endpoint in cancer research.

The major limitation of this study is the size of our study population, which did not allow us to provide separate estimates of the effects and side effects for upper, lower or sequential HBI. We only measured pain in the HBI treated area and did not take into consideration that the patients were likely to develop painful metastases in other and untreated areas of the body resulting in a need to maintain a high intake or increase the dose of analgesics despite the pain relief in the treated area.

In addition, most patients were in a late stage of their disease as illustrated by the high baseline pain score and low baseline quality of life score. Since many patients died during follow-up, the study had limited power to estimate long-term effects of HBI. Though the trial was open for all patients with malignant disease, the doctors who treated prostate cancer were the most active to enrol patients. Since almost all of the patients enrolled in this trial had prostate cancer, we cannot be sure that the results can be generalised to patients with bone metastases from other cancers. A previous study suggests that response in terms of pain relief was higher when treating metastases from breast and prostate cancers than from lung cancer [11].

In summary, HBI given as 7 Gy in one fraction for the upper or 8 Gy in one fraction for the lower part of the body is effective to relieve pain in about 76% of patients mainly with prostate cancers with multiple bone metastases. The disadvantage of the treatment is diarrhoea at week two after treatment in about 50% of the patients.

Declaration of interest: The authors report no conflict of interest. The authors are responsible for the content and writing of the paper.

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