

20 Gy in five fractions versus 8 Gy in one fraction in palliative radiotherapy of bone metastases. A multicenter randomized study

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Introduction. Bone is the most common site of cancer dissemination and 70% of patients with bone lesions present with pain requiring therapy. Radiotherapy plays a major role in the treatment of painful bone metastases, but optimal dose and fractionation regime remain debatable.

Material and methods. To address this issue a randomized trial comparing a single dose of 8 Gy vs. 20 Gy in 5 fractions was performed and enrolled 115 patients with 146 metastatic lesions. Pain relief was assessed longitudinally based on a pain questionnaire, in which patients were supposed to record their pain intensity using a 4-point scale (none, mild, moderate, severe), as well as doses and types of analgesic drugs taken. Questionnaires were collected prior to treatment, 2, 4 and 8 weeks after treatment completion and every 4 weeks thereafter.

Results. Complete pain relief was achieved in 23 patients (36%) treated with one fraction of 8 Gy and in 24 patients (39%) who received 20 Gy in 5 fractions ($p=0.96$). Remarkable pain relief after one fraction and 5 fractions was achieved in 21 patients (33%) and 18 patients (29%), respectively ($p=0.89$) and moderate pain relief in 9 patients (14%) and 10 patients (16%), respectively ($p=0.94$). There was also no difference between the two treatment regimes according to duration of pain relief (medians of 8 and 10 months, respectively).

Conclusions. Single fraction of 8 Gy is equally effective to a fractionated schedule in the treatment of painful bone metastases, and should be recommended as standard care in the majority of patients.

20 Gy w pięciu frakcjach w porównaniu z 8 Gy w jednej frakcji w paliatywnej radioterapii przerzutów do kości – wielośrodkowe badanie randomizowane

Uzasadnienie. Kości stanowią najczęstszą lokalizację przerzutów nowotworów złośliwych, a w 70% przypadków zmianom tym towarzyszą dolegliwości bólowe, wymagające leczenia. Radioterapia odgrywa istotną rolę w leczeniu bolesnych przerzutów do kości, ale optymalna dawka i sposób frakcjonowania są nadal przedmiotem dyskusji.

Materiał i metody. Celem oceny skuteczności leczenia jednorazową dawką 8 Gy przeprowadzono wielośrodkowe badanie randomizowane, w którym porównywano efekt paliatywny napromieniania jednorazową dawką 8 Gy i dawką 20 Gy w 5 frakcjach. Do badania włączono 115 chorych, u których poddano napromienianiu łącznie 146 ognisk przerzutowych. Nasilenie bólu oceniane było na podstawie kwestionariusza wypełnianego przez chorego przed leczeniem oraz w 2, 4 i 8 tygodniu po leczeniu, a następnie co 4 tygodnie.

Wyniki. Całkowite ustąpienie bólu osiągnięto u 23 chorych (36%) leczonych jedną frakcją i u 24 (39%) leczonych dawką 20 Gy w 5 frakcjach ($p=0,96$). Znaczne ustąpienie dolegliwości bólowych przy użyciu jednej frakcji i 5 frakcji osiągnięto odpowiednio u 21 chorych (33%) i 18 chorych (29%; $p=0,89$), a częściowe – odpowiednio u 9 chorych (14%) i 10 chorych (16%) ($p=0,94$). Czas utrzymywania się efektu przeciwbólowego był podobny w porównywanych grupach (mediany odpowiednio 8 i 10 miesięcy).

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Wnio s ki. Efekt przeciwbólowy napromieniania pojedynczą dawką 8 Gy i wyższą dawką podaną w kilku frakcjach jest podobny. Napromienianie jedną frakcją może być zatem zalecane u większości chorych.

Key words: bone metastases, palliative radiotherapy, single fraction irradiation, randomized study

Słowa kluczowe: przerzuty do kości, paliatywna radioterapia, napromienianie pojedynczą frakcją, badanie randomizowane

Introduction

Bone is the most common site of cancer dissemination and 80% of patients dying with cancer have bone metastases [1]. Up to 70% of patients with bone lesions suffer from pain requiring therapy. External beam radiotherapy plays a major role in the treatment of painful bone metastases, but the optimal dose schedule remains a matter of debate. A series of randomized trials has evaluated pain relief in patients irradiated with a single 8 Gy fraction or with fractionated schedules and no significant differences were found [2-4]. Although these publications have suggested that a single fraction of radiotherapy is more cost-effective and as good as fractionated schedules in terms of pain relief, many radiation oncologists still use multiple fractions. This is probably a result of tradition, past teaching and reimbursement criteria [5]. This study was performed in order to confirm previous results and to convince radiation oncologists in Poland to more frequent use of single-fraction irradiation.

Patients and methods

A total of 115 patients from five radiation oncology centers in Poland were enrolled in the study over 4 years. Altogether 146 metastatic lesions diagnosed in these patients were randomized to receive either 20 Gy in 5 fractions or 8 Gy in one fraction. Because randomization included metastatic sites, patients with more than one metastatic lesion might have been irradiated with 8 Gy in one fraction to one site and 20 Gy in five fractions to the other.

Inclusion criteria covered cytological or histopathological evidence of malignant disease, painful bone metastases confirmed by x-ray, and patient compliance. Patients with pathological fracture or previous irradiation to the metastatic sites were excluded. Randomization was performed by a dedicated computer program after telephone contact with the coordinating center. Data was stratified based on the type of malignancy, site of metastatic bone lesion and type of equipment used for irradiation.

Choice of radiotherapy technique was left to discretion of the treating physician; both single-field and two parallel-opposed field techniques were allowed. For single-field irradiation, the dose was specified on the lesion depth, whereas for parallel-opposed fields the dose was specified in the mid-plane. No restrictions were made for machine or photon energy used for irradiation. A majority of the patients were treated with orthovoltage units (63%), some with cobalt units (31%) and very few with linear accelerators (5%). The single-field technique was used more frequently (76%), than the two parallel-opposed fields technique (24%).

Pain relief was assessed basing on a pain questionnaire, in which patients were requested to record their pain intensity using a 4-point scale (none, mild, moderate, severe), as well as

doses and types of analgesic drugs taken. Patients were asked to complete the questionnaire immediately before treatment, 2, 4, 8 weeks after the irradiation and every 4 weeks thereafter. An additional questionnaire was completed by the treating physician at each follow-up visit. Pain relief was defined as a decrease in pain score recorded by the patient, by at least one category, or significant decrease in doses of analgesic drugs taken with stable pain level. Complete response was defined as complete disappearance of pain and withdrawal of all analgesic drugs taken by the patient.

In order to compare categorical data we used the Chisquared test and Fisher's exact test. Response duration time distribution was assessed according to the Kaplan-Meier method, for comparisons between subgroups we used the log-rank test.

Results

We included 115 patients in whom 146 metastatic bone lesions were treated. The most common localization of metastatic sites was the spine, followed by the pelvis, limbs and ribs. The most frequent primary tumor was breast cancer, followed by kidney, lung and prostate cancers. A total of 74 metastatic lesions were randomized to receive 20 Gy in 5 fractions and 72 – to 8 Gy in one fraction. Both groups were well balanced in regard to age, sex, performance status, primary tumor location, metastatic site location and treatment technique used (Tables I and II).

Table I. Patient characteristics

Variable	20 Gy/5 fr.	8 Gy/1 fr.
Age		
range	33-78	23-80
mean	57.6	55.7
Sex		
male	18 (31%)	16 (28%)
female	40 (69%)	41 (72%)
PS		
0	9 (16%)	9 (16%)
1	15 (26%)	18 (32%)
2	26 (44%)	21 (37%)
3	4 (7%)	7 (12%)
Primary tumor		
Breast	28 (48%)	28 (49%)
Kidney	4 (7%)	6 (11%)
Lung	6 (10%)	8 (14%)
Prostate	4 (7%)	3 (5%)
Other	16 (28%)	12 (21%)

Table II. Treatment characteristics

Characteristics	20 Gy/5 fr.	8 Gy/1 fr.
Unit		
Orthovoltage	37 (64%)	36 (63%)
⁶⁰ Co	20 (34%)	16 (28%)
Linear accelerator	1 (2%)	5 (9%)
Technique		
Single-field technique	42 (78%)	42 (76%)
Two parallel opposed fields	12 (22%)	13 (24%)

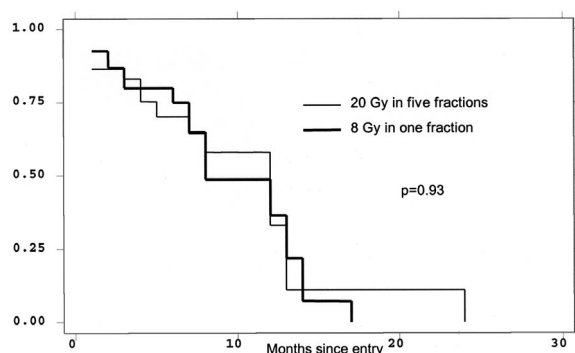
Response to treatment was assessed in 104 patients in whom 126 metastatic lesions were treated. The remaining 11 patients were lost to follow up or died before the first assessment. Of those 126 lesions, 64 were randomized to receive 8 Gy in one fraction and 62 to receive 20 Gy in 5 fractions. Complete pain relief was achieved in 23 patients (36%) treated with one 8 Gy fraction and in 24 patients (39%) who received 20 Gy in 5 fractions ($p=0.96$). Remarkable pain relief was achieved in 21 patients (33%) and 18 patients (29%; $p=0.89$) and moderate pain relief in 9 patients (14%) and 10 patients (16%), respectively ($p=0.94$). In 11 (17%) and 10 patients (16%), respectively, no pain relief was achieved ($p=0.92$; Table III). No significant difference in the response rates was seen among tumors of different histopathology.

Table III. Response to treatment

Response	20 Gy/5 fr.	8 Gy/1fr.
Complete relief	24 (39%)	23 (36%)
Remarkable relief	18 (29%)	21 (33%)
Moderate relief	10 (16%)	9 (14%)
No effect	10 (16%)	11 (17%)

$p=0.956$

Response duration was similar in patients treated with 1 fraction and 5 fractions (medians of 8 months and 10 months, respectively; $p=0.93$) (Figure 1). In patients who achieved complete pain relief the median time to pain reappearance with 1 fraction and 5 fractions was 10 months and 11 months, respectively ($p=0.87$). In patients with remarkable improvement median duration

**Figure 1. Pain relief duration**

of pain relief was 8 months and 7.5 months, respectively ($p=0.64$).

Discussion

This study did not demonstrate any difference between treatment effects achieved by palliative irradiation with 8 Gy in 1 fraction and 20 Gy in 5 fractions. The percentage of patients with complete, remarkable and moderate pain relief, as well as the duration of pain relief were not significantly different in both the study arms. Similar results were demonstrated in other randomized studies comparing single fraction of 8 Gy with various fractionation schedules [3, 4, 6, 7], although in one study the retreatment rate was somewhat higher in patients who had received a single fraction of 8 Gy [7]. In the light of similar efficacy of both methods in terms of pain control and relief duration, the higher retreatment rate in patients receiving single fraction can probably be explained by physicians' preferences.

The largest trial comparing treatment effects of different radiotherapy schedules in palliation of bone metastases was performed by the Radiation Therapy Oncology Group [2]. A total of 759 metastatic sites were evaluated for pain relief produced by the 5 different fractionated schedules: 40 Gy in 15 fractions, 20 Gy in 5 fractions, 30 Gy in 3 fractions, 27 Gy in 5 fractions and 25 Gy in 5 fractions. None of the regimens was significantly superior over the others in terms of response rates and pain relief duration. Subsequent reanalysis of this data with different statistical methods and different endpoints found relationship between higher doses in more fractions and improved pain control [8]. This reanalysis was criticized on methodological grounds and because the authors did not use original data from the RTOG study (which were lost) [9-11]. The factor which may considerably influence results is the endpoint definition chosen in particular studies. By combining pain score, analgesic drugs taken by patient and retreatment rate in various ways, different conclusions could be drawn in the course of the same study. For this reason, despite published results of randomized studies, the optimal treatment regime for palliation of painful bone metastases still remains debatable. A recent consensus meeting on the palliative radiotherapy endpoints developed guidelines for the future studies to ensure consistency of reporting [12].

Doses lower than 8 Gy were investigated in some studies. One trial compared a single fraction treatment using 4 Gy and 8 Gy and found significantly better effect in patients treated with higher doses (pain relief rate for 8 Gy and 4 Gy was 69% and 44%, respectively; $p<0.001$) [13]. Another study comparing 3 single fraction doses: 8 Gy, 6 Gy and 4 Gy demonstrated similar results for the two former regimes, whereas the dose of 4 Gy was significantly less effective [14]. Thus, doses lower than 8 Gy should only be used in case of reduced tolerance.

Analogous to the results published by other authors [2, 13], in the present study no significant difference in

treatment effect was found between primary tumors of different types. These findings suggest that tumor regression is not necessary for pain reduction, as treatment effects are similar in radioresistant and radio-sensitive tumors. The palliative effect of irradiation for bone metastases probably results from killing the radiosensitive cells – macrophages secreting various cytokines and osteoclasts responsible for bone destruction. The levels of osteoclast activity markers were shown to stabilize after the irradiation for bone metastases and raise in not irradiated patients [15]. In patients with a single metastatic lesion and relatively good prognosis recalcification of osteolytic lesions may be another goal of treatment. In such cases higher doses may be needed for cell killing sufficient for recalcification and bone stabilization [16].

In conclusion, our results indicate that single-fraction irradiation of 8 Gy is as effective as a fractionated schedule in the treatment of painful bone metastases. Further carefully designed studies may be needed to optimize radiotherapy delivery in particular categories of patients and to find most effective means of combining radiotherapy with other treatments of bone metastases.

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