

# Palliative Radiotherapy to Asymptomatic Bone Metastasis: Is It Beneficial or Not? Single Institution Experience

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## Abstract

**Background:** Bone metastases are believed to be the complications of cancer occurring in 20-75% of patients with advanced tumors. External beam radiation therapy (EBRT) is recommended in case of symptomatic bone metastases. Preventing skeletal-related events (SREs) and pain through early treatment of bone metastases is to be studied. We conducted the present study to investigate EBRT in asymptomatic bone metastases.

**Method:** A retrospective cohort study for patients with bone metastases without symptoms, who were treated with EBRT, formed group A. Group B comprised the patients who did not receive EBRT. The time from diagnosis to onset of the 1<sup>st</sup> SRE was recorded for both groups. The follow-up period was three years. Pain was moderate to severe when rated as 5/10.

**Results:** Asymptomatic bone metastases were found in 200 patients. They were free from pain or pathological fractures. They were divided into two groups of A and B. The overall demographics and disease characteristics were well-balanced for the two groups. The two groups were more or less similar concerning the mean age and sex, with no statistically significant differences; the mean age in groups A and B was 57 years. For both groups, the mean time from the occurrence of asymptomatic bony metastases to the onset of SRE were about 33 and 19 months for groups A and B, respectively, which is statistically significant.

**Conclusion:** Prophylactic EBRT of metastatic breast and prostate cancer patients should be considered in order to delay the onset of SREs and improve the quality of life.

**Keywords:** Palliative radiotherapy, SREs, Bone metastasis, Bisphosphonates

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## Introduction

Bone metastases are complications of cancer that are

potentially debilitating or life-limiting. They occur in about 20%-75% of advanced solid tumor

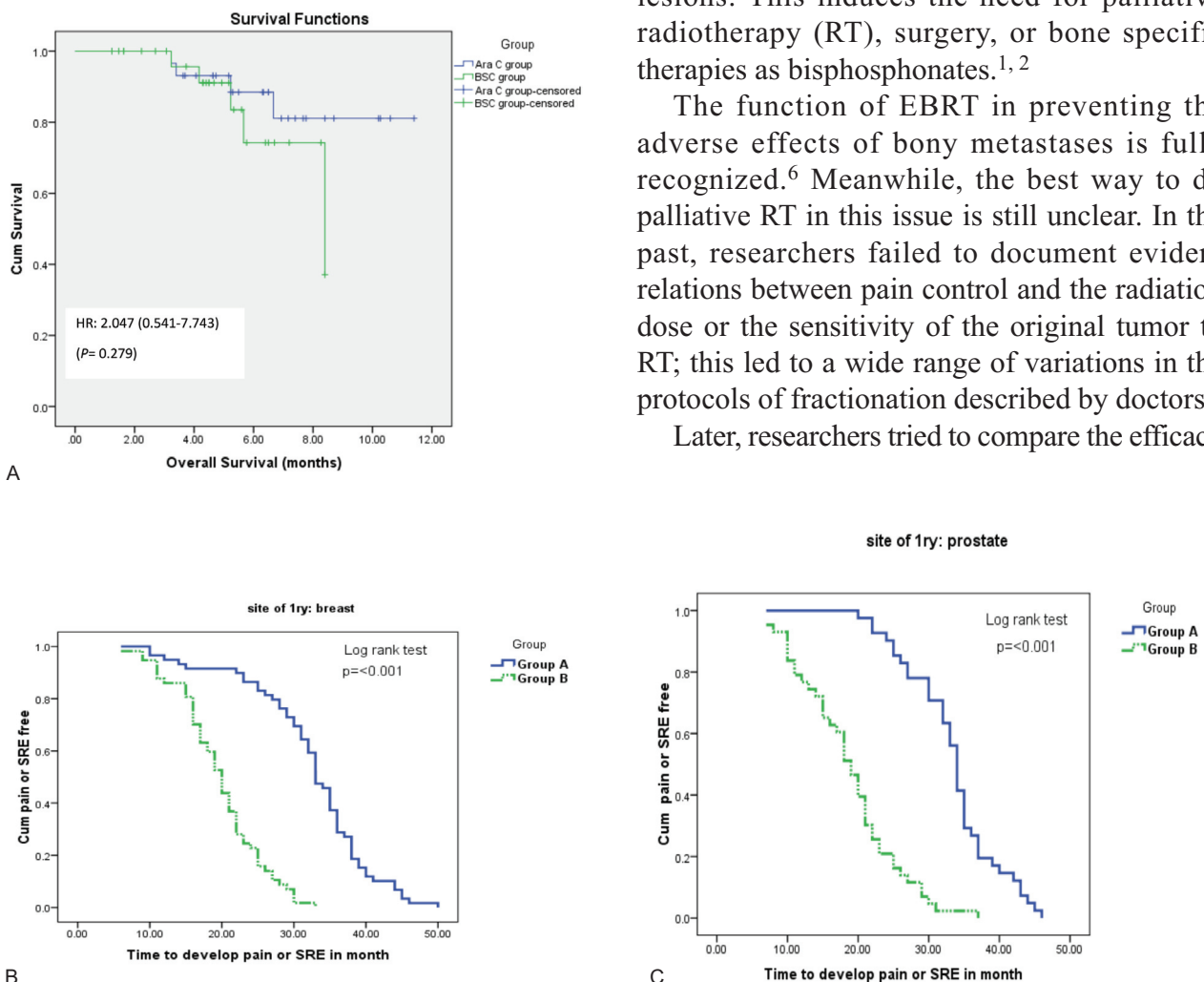
patients. The incidence increases in patients with advanced stages of breast cancer (BC) or prostate cancer (PC) occurring in nearly 65-75 % of them.<sup>1, 2</sup> Bone metastases usually occur after the treatment of the original tumor. Approximately 20% of cases present the associated symptoms at the initial diagnosis.<sup>3</sup> Once symptomatic bone metastases are diagnosed, external beam radiation therapy (EBRT) is normally the prescribed.<sup>4</sup>

Bone metastases weaken the bone and affect its structural continuity. Bone pain is mostly the first and the most prevalent bone metastases-associated symptom. Bone pain is often the factor that promotes a patient's first diagnostic bone scan. Accordingly, bone-specific treatment usually

starts following the onset of bone tenderness, which may not be the optimum treatment of metastatic bony lesions.<sup>1</sup> This pain has devastating effects on the patient mobility causing difficulty with movement and social relations, on top of lowering the quality of life; in certain cases, it may speed their death. Bone metastases is mostly characterized with pathological fractures of bone, the spinal cord compression, or compression of nerve roots due to vertebral damage, collapse, and hypercalcemia of malignancy. The patient survival decreases following the skeletal-related events (SREs).<sup>4, 5</sup> The aim of maintaining patients' functional ability by preventing SREs and controlling bone pain might be best achieved through the rapid management of metastatic bony lesions. This induces the need for palliative radiotherapy (RT), surgery, or bone specific therapies as bisphosphonates.<sup>1, 2</sup>

The function of EBRT in preventing the adverse effects of bony metastases is fully recognized.<sup>6</sup> Meanwhile, the best way to do palliative RT in this issue is still unclear. In the past, researchers failed to document evident relations between pain control and the radiation dose or the sensitivity of the original tumor to RT; this led to a wide range of variations in the protocols of fractionation described by doctors.<sup>2</sup>

Later, researchers tried to compare the efficacy



**Figure 1.** Time to pain or SRE in treated and untreated patients. A: Time to SRE for treated and untreated patients in all cancer groups; B: time to SRE for treated and untreated patients with breast cancer; C: time to SRE for treated and untreated patients with prostate cancer.

SRE: Skeletal-related events; Cum: Cumulative

**Table 1.** Patients' characteristics among the studied groups

Patients characteristics	Group A (n=100)	Group B (n=100)	Test of significance	P-value
<b>Age/years</b>				
Mean ± SD	57.05±6.05	57.36±5.96	t=0.365	0.716
Min-Max	44-69	43-68		
<b>Gender</b>				
Male	41 (41%)	43 (43%)	$\chi^2 = 0.082$	0.774
Female	59 (59%)	57 (57%)		
<b>Performance status</b>				
0	48 (48%)	50 (50%)	$\chi^2 = 0.08$	0.777
1	52 (52%)	50 (50%)		
<b>Site of 1ry</b>				
Breast	59 (59%)	57 (57%)	$\chi^2 = 0.082$	0.774
Prostate	41 (41%)	43 (43%)		
<b>Site of metastasis</b>				
Axial	30 (30%)	31 (31%)	$\chi^2 = 0.083$	0.959
Appendicular	28 (28%)	29 (29%)		
A+p	42 (42%)	40 (40%)		
<b>Type of metastasis</b>				
Blastic	47 (47%)	47 (47%)	$\chi^2 = 0.046$	0.977
Lytic	16 (16%)	15 (15%)		
Mixed	37 (37%)	38 (38%)		
<b>Presence of visceral metastasis</b>				
Absent	78 (78%)	77 (77%)	$\chi^2 = 0.029$	0.866
Present	22 (22%)	23 (23%)		
<b>Time to develop pain or SREs in months</b>				
Mean ± SD	32.86±7.72	19.29±6.39	t=13.52	<0.001*
<b>Skeletal related events</b>				
Pain	75 (75%)	72 (72%)	$\chi^2 = 0.338$	0.844
Pathological fracture	18 (18%)	19 (19%)		
Cord compression	7 (7%)	9 (9%)		

t: student t-test,  $\chi^2$ : chi square test, \*significant  $P < 0.05$ ; SD: Standard deviation

of single-fraction versus multiple fractions. They found that both protocols reduced the risk of skeletal complications down to the same extent.<sup>7</sup> These researches on the dosing of radiation therapy did not resolve the question of when the treatment should be initiated. In the absence of data, clinicians rely on personal judgments and habits acquired during training. As a result, EBRT is not often prescribed until bone metastases leads to bone tenderness. This strategy reserves the treatment from the 60% of those who are asymptomatic at the time of diagnosis.<sup>8</sup>

Given the above-mentioned information, we aimed to analyze a retrospective comparative study in order to investigate EBRT as a treatment to asymptomatic bone metastases in a single

institution experience to clinically prove the answer to a question: Is it beneficial to perform palliative RT for asymptomatic bone metastasis.

## Patients and Methods

Our study was a retrospective comparative study conducted for patients with bone metastasis from breast or prostate cancer. All the patients were treated at Clinical Oncology and Nuclear Medicine department, Mansoura University Hospital from January 2015 to June 2016 inclusive. The patients with bony metastases were suitable for the study provided that they reported no pain and no history of SREs as pathological fracture of bone and/or cord compression. The covariates included in the analysis were age, sex,

**Table 2.** Patients' characteristics among the breast patients in both groups

Patients characteristics	Group A (n=59)	Breast Group B (n=57)	Test of significance	P-value
<b>Age/years</b>				
Mean ± SD	52.89±3.91	53.14±3.90	t=0.333	0.740
Min-Max	44.00-60.00	43.00-60.00		
<b>Performance status</b>				
0	28(47.5%)	27 (47.4%)	$\chi^2 =0.001$	0.992
1	31(52.5%)	30(52.6%)		
<b>Site of metastasis</b>				
Axial	22 (37.3%)	20 (35.1%)	$\chi^2 =0.116$	0.944
Appendicular	16 (27.1%)	15 (26.3%)		
A+p	21 (35.6%)	22 (38.6%)		
<b>Type of metastasis</b>				
Blastic	17 (28.8%)	16 (28.1%)	$\chi^2 =0.014$	0.993
Lytic	14 (23.7%)	14 (24.6%)		
Mixed	28 (47.5%)	27 (47.4%)		
<b>Presence of visceral metastasis</b>				
Absent	41 (69.5%)	39 (68.4%)	$\chi^2 =0.016$	0.901
Present	18 (30.5%)	18 (31.6%)		
<b>Time develop pain or SRE in months</b>				
Mean ± SD	32.45±8.55	19.73±5.89	t=9.29	<0.001*
<b>Skeletal related events</b>				
Pain	46 (78.0%)	42 (73.7%)	$\chi^2 =0.347$	0.841
Pathological fracture	9 (15.3%)	11 (19.3%)		
Cord compression	4 (6.8%)	4 (7.0%)		

t: student t-test,  $\chi^2$  : chi square test,\*significant  $P<0.05$ ; SD: Standard deviation

cancer type, Eastern Cooperative Oncology Group (ECOG) status, metastasis site (axial, appendicular, or both), metastasis type (lytic, blastic, and/or both), and the presence or absence of visceral metastasis.

The subjects with newly diagnosed asymptomatic bone metastases and treated with EBRT formed treated group A (100 patients) and those who did not receive EBRT were defined as group B (100 patients). The time from the diagnosis of asymptomatic bony metastases to either the start of moderate to severe pain or the first SRE was recorded for both groups. The period of follow-up was three years at least. Pain was recorded to be moderate to severe, if it was rated as 5/10 by the patient. The date assigned to an SRE was the date that a pathological fracture of bone or cord compression was primarily recorded. EBRT protocols with multiple fractionation doses were different and were not therefore included in the analysis of the current

study.

### Statistical analysis

The Statistical Package of Social Science program (SPSS version 21) was utilized for data analysis. The normality of data was primarily tested with one-sample Kolmogorov-Smirnov test.

The numbers and percentages were employed for qualitative data description. Chi-square test was used for testing the association between categorical variables.

Continuous variables were presented as mean±SD (standard deviation) for parametric data. Student t-test was used for the comparison between the two groups.

We utilized Kaplan- Meier test for SRE free and statistical significance of the differences among the curves which were determined with Log-Rank test.

### Level of significance

The threshold of significance was fixed at 5%

**Table 3.** Patients' characteristics among the prostate patients in both groups

Patients characteristics	Group A (n=41)	Prostate Group B (n=43)	Test of significance	P-value
<b>Age/years</b>				
Mean ± SD	63.02±2.57	62.95±2.71	t=0.123	0.903
Min-Max	58.00-69.00	59.00-68.00		
<b>Performance status</b>				
0	20(48.8%)	23(53.5%)	$\chi^2 =0.186$	0.666
1	21(51.2%)	20(46.5%)		
<b>Site of metastasis</b>				
Axial	8 (19.5%)	11 (25.6%)	$\chi^2 =0.811$	0.667
Appendicular	12 (29.3%)	14 (32.6%)		
A+p	21 (51.2%)	18 (41.9%)		
<b>Type of metastasis</b>				
Blastic	30 (73.2%)	31 (72.1%)	$\chi^2 =0.502$	0.778
Lytic	2 (4.9%)	1 (2.3%)		
Mixed	9 (22.0%)	11(25.6%)		
<b>Presence of visceral metastasis</b>				
Absent	37 (90.2%)	38 (88.4%)	$\chi^2 =0.077$	0.782
Present	4 (9.8%)	5 (11.6%)		
<b>Time develop pain or SRE in months</b>				
Mean ± SD	33.43±6.41	18.69±7.02	t=10.02	<0.001*
<b>Skeletal related events</b>				
Pain	29 (70.7%)	30 (69.8%)	$\chi^2 =0.528$	0.768
Pathological fracture	9 (22.0%)	8 (18.6%)		
Cord compression	3 (7.3%)	5 (11.6%)		

t: student t-test,  $\chi^2$ : chi square test, \*significant  $P<0.05$ ; SD: Standard deviation

level ( $P$ -value) for all the above-mentioned statistical tests. The results were considered to be:

\* statistically non-significant if the probability of error was over 5% ( $P>0.05$ ).

\* statistically significant if the probability of error was lower than 5% ( $P\leq 0.05$ ).

The smaller the obtained  $P$ -value was, the more significant were the results.

## Results

This was a retrospective comparative study conducted for patients with metastatic breast and prostate cancer to the bone. Asymptomatic bone metastases were identified in 200 patients totally for both groups. They did not report any pain, pathological fractures, and/or spinal cord compression. They were divided into two groups of A and B, each including 100 patients. Table 1 represents the geographic, clinical, and pathological data of both groups. The overall geographic and baseline disease characteristics were generally equal between the patients of the

two groups.

The two groups were more or less similar concerning the mean age and sex distribution with no statistically significant differences. The mean age of the patients receiving EBRT for asymptomatic bone lesions (group A) was 57 years old, which was equal to the mean age of the untreated group (group B). The patients in the two groups received systemic therapy in the form of chemotherapy and/or bone remodeling treatment as bisphosphonates.

Group A comprised 59 case with metastatic breast cancer and 41 patients with prostate cancer. Group B included 57 case with metastatic breast cancer and 43 patients with prostate cancer. These differences were not statistically significant between the two groups. The patients' distribution in both groups regarding the site of metastasis, type of metastasis, the presence of visceral metastasis, and SREs was nearly similar with no statistically significant differences between the two of them as described in table 1. Our results

showed a statistically significant difference between the groups concerning the mean time to develop pain or SREs; it was longer in group A ( $32.86 \pm 7.72$ ) compared to group B ( $19.29 \pm 6.39$ ) ( $P$  value  $< 0.05$ ) as mentioned in table 1.

The mean time from the occurrence of asymptomatic bony metastases to pain or an SRE was about 33 months for group A and 19 months for group B (Figure 1A,  $P < 0.001$ ). Once the patients were stratified according to cancer type (prostate and breast), EBRT was found to delay the onset of pain or an SRE for the patients of each tumor type in the treated group more than that in the untreated group with  $P < 0.001$  as represented in tables 2 and 3 and figures 1B and 1C.

## Discussion

Nowadays, researchers aim to treat the patients with metastatic bony lesions, so that they would maintain their functional ability and good quality of life throughout the course of their disease via prohibiting SREs like pathological bone fractures and/or cord or nerve roots compression as a result of vertebral body collapse or damage.

Rosen and colleagues reported in 2004 that in the absence of bone-specific treatments, nearly 50% of patients with metastatic bony lesions from breast and lung cancer would develop SREs. This could lead to considerable morbidity, painful bony lesions and reduced functional ability.<sup>9</sup>

RT is suggested to reduce pain, protect the bone from other metastases, and prevent pathological bone fractures, as well as spinal cord or nerve root compression. Moreover, radioisotopes could be used for more diffuse bone pain, yet it is not candidate for palliative radiation therapy. On the other hand, bisphosphonates are usually administered in multiple non-painful bone metastases.<sup>3</sup> RT intends to improve quality of life, reduce analgesic needs, and maintain skeletal function.<sup>3</sup>

The number of patients living with asymptomatic metastases increased owing to the improvements in cancer treatment. However, physicians are worried as these patients may have late complications from bony metastatic disease.<sup>2</sup>

Shulman and colleagues reported that asymptomatic bone metastases were diagnosed in 171 patients. The primary disease was prostate, lung, and breast cancer, respectively, in 87, 51, and 33 patients. 28 of them (16%) received EBRT, when they were discovered with asymptomatic bony metastases. The mean age of the patients was almost 66 years.<sup>2</sup> This age range is higher than our mean age. In the present work, the mean age of the subjects receiving EBRT was 57 years old in groups A and B; this may be attributed to different geographical and genetic backgrounds between the two populations.

Our results indicated that the difference concerning the mean time to develop pain (TTP) or SREs was statistically significant between the two groups; it was longer in group A ( $32.86 \pm 7.72$ ), which was found to be nearly three years, compared with group B ( $19.29 \pm 6.39$ ) with 1.5 years ( $P < 0.05$ ). This is in accordance with the results of Shulman and colleagues in 2018. Their median time from the diagnosis of asymptomatic bone metastases to pain or an SRE was longer in the treated group than the untreated one (81 and 25 months, respectively) (Figure 1A,  $P < 0.001$ ).<sup>2</sup>

Similar results were reported by Costa and colleagues in 2013 in a study comparing the effects of bisphosphonates as zoledronic acid and pamidronate. Once zoledronic acid was applied for asymptomatic bony metastases, it delayed the commencement of the patients' first SRE by 17.5 months.<sup>1</sup> Radiopharmaceuticals agents and monoclonal antibodies also have an enhanced trend toward the treatment of bony metastases to delay the onset of these complications. A prospective research on breast and lung cancer patients studied the efficacy of the radionuclide samarium-153 EDTMP on bone metastasis. It demonstrated a remarkable pain relief in 18/21 treated patients. The authors concluded that the treatment must begin prior to the establishment of severe pain.<sup>10</sup>

Ultimately, large, prospective, and randomized clinical trials are recommended to be conducted in order to include the location of the bone metastases and the efficacy of different radiation dosing schedules. The types of the patients who

could benefit mostly from EBRT treatment should be evaluated in future studies. The patients with metastatic lesions of different sizes and locations and variable radiation dosing schedules should be evaluated.

## Conclusion

The current study demonstrated that prophylactic EBRT of metastatic breast and prostate cancer patients should be considered to delay the onset of pain and SREs and improve the quality of life. Include the size and the location of the bone metastases, the violence of the patient's primary tumor, the patient comorbidities, and the effects of different RT dosing protocols could be considered as the key points considered in further studies. Furthermore, larger prospective randomized trials could help to identify the probable risks and choose the best candidates for early intervention.

## Conflict of Interest

None declared.

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