Journal of Cancer Treatment and Research
2022; 10(1): 1-7
http://www.sciencepublishinggroup.com/j/jctr
doi: 10.11648/j.jctr.20221001.11
ISSN: 2376-7782 (Print); ISSN: 2376-7790 (Online)

An Evaluation of Pain Response Between Single Fraction Radiotherapy Versus 10 Fractions RT in Metastatic Vertebral Bone Disease: A Quasi Experimental Study

Bhaskar Chakraborty[1], Tarim Mahmood[2, *], Maksud Hassan Binoy[3]

[1]Oncology, Ahsania Cancer Mission Hospital, Dhaka, Bangladesh

[2]Department of Maternal and Child Health, NIPSOM, Dhaka, Bangladesh

[3]Biotech, Beacon Pharmaceuticals Ltd, Dhaka, Bangladesh

Email address:

bchakraborty383@gmail.com (B. Chakraborty), drtarim-onco@beaconpharma.com.bd (T. Mahmood), maksudbinoy@gmail.com (M. H. Binoy)

[*]Corresponding author

To cite this article:

Bhaskar Chakraborty, Tarim Mahmood, Maksud Hassan Binoy. An Evaluation of Pain Response Between Single Fraction Radiotherapy Versus 10 Fractions RT in Metastatic Vertebral Bone Disease: A Quasi Experimental Study. *Journal of Cancer Treatment and Research*. Vol. 10, No. 1, 2022, pp. 1-7. doi: 10.11648/j.jctr.20221001.11

Received: February 15, 2022; **Accepted**: March 4, 2022; **Published**: March 15, 2022

Abstract: The prognosis of bone metastasis is poor, with median survival measured in months, not years. Treatment remains an important issue to alleviate the complications and sufferings of the patients. This study was aimed to evaluate the pain response between single versus multiple fraction radiotherapy in metastatic vertebral bone disease. In this prospective quasi experimental study, the sample consisted of 60 patients of Oncology Dept., KYAMCH. Purposive sampling method was used. The respondents were divided into 2 arms, Arm A consisted of 30 patients, receiving 800 cGy single fraction RT, and Arm B consisted 30 patients who received 3000 cGy multiple fractions RT. The data were collected using a semi-structured questionnaire, which was constructed in line with the reviewed literature along with RECIST (Response Evaluation in Solid Tumor) criteria, VAS (Visual Analogue Scale) after 4 weeks of RT completion and Radiation Therapy Oncology Group (RTOG) criteria. Mean age of Arm A was 43.73 years, and Arm B was 46.8 years. Lung cancer was the leading cancer in both arms, 43.3% and 36.6% respectively. Adenocarcinoma was the commonest histopathological type of cancer found in both arms, 39.9% and 36.6% respectively. To determine associations, Chi-Square tests were done. For Arm A, 66.6% initially presented with severe pain, 23.31% with moderate and 10% with mild pain. In arm B 59.94%, 33.3% and 6.66% patients presented with severe, moderate and mild pain respectively. One month after completion of RT, pain significantly reduced in patients of both arms with a p value of $< .001$. No significant difference was observed between 8 Gy in single fraction versus 30 Gy in 10 fractions radiotherapy in the management of secondary bone tumour. It was found, both the radiation fractionation schedule for the management of secondary bone tumour are equally effective. More patients can be provided with the desired treatment with shorter period of time. It will certainly ease the economic burden on the patients as well as on the country.

Keywords: Pain Response, Radiotherapy, Metastatic Vertebral Bone Disease, Cancer

1. Introduction

Cancer that begins in an organ and then spreads to bone is called metastatic bone disease. This is a very commonly encountered problem in oncology practice as bone metastasis is a common cause of mild to severe grade of pain and other significant symptoms that are detrimental to quality of life of patients. Sometimes bone metastasis is a common manifestation of distant relapse from many types of solid malignancies especially from cancers of the lung, breast and prostate. The exact incidence of bone metastases is difficult to determine, but evidence suggests that more than 100,000 people in the United States develop osseous metastatic disease annually. The incidence of bone metastases varies significantly, depending on the primary site. Common

cancers that frequently metastasize to bone include prostate, lung, liver, thyroid, kidney, breast, testis, ovary etc. with breast, prostate and lung cancers accounting for up to 70% of all patients. On the other hand, gastrointestinal sites of primary malignancy give rise to bone metastasis in only 3% to 15% of patients with metastatic disease [26].

The axial skeleton is the most common site of bone metastasis, with metastasis most frequently occurring in the spine, pelvis, and ribs. Among them, spinal metastasis contributes upto 65% and the lumber spine is the most frequent site of spinal metastasis. In the appendicular skeleton, the proximal femurs are the most common site of metastatic disease, and humeral lesions also occur frequently. The acral sites (feet and hands) are rarely involved. The ultimate prognosis for patients with bone metastases is poor, with median survival typically measured in months rather than years. Overall survival depends on the primary site and the presence or absence of visceral metastases. Patients with bone metastases from lung cancer have short median survival with a duration of 6 months. However, patients with bone metastases from breast or prostate primary sites may have significantly longer survival times. In patients with bone-only metastatic prostate or breast cancer, median survivals of 2 to 4 years have been reported.

After lungs and liver, bone is the most important site of metastasis. Metastasis to lungs and liver are often not detected until late in the course of disease because patients experience no symptoms [6]. In contrast different metastatic foci to bone especially vertebral bone metastasis cause severe debilitating effects such as severe pain (due to pressure over periosteum and nerve roots), pathological fracture, spinal cord compression, bowel and bladder incontinence etc. at initial presentation which are together referred to as skeletal related events. That is why, whether the survival time is only a few months or extends to multiple years, treatment of bone metastasis is an important issue to alleviate such symptoms especially vertebral bone metastasis.

Multiple modalities of treatments are available for optimal management of metastatic bone disease which includes medical treatment like chemotherapy and hormone therapy, surgical treatment, bone targeted treatment with bisphosphonates and radiotherapy. The main goal of all of the treatment approaches for bone metastases is pain control. Other objectives include prevention and treatment of fractures, maintenance of patients, function and local tumor control [7].

The World Health Organization's pain ladder was designed for the management of cancer-associated pain and mainly involves various strength of opioids. Mild pain or breakthrough pain may be treated with nonsteroidal anti-inflammatory drugs but these give short term pain relief. [1]. Other treatments include bisphosphonates, corticosteroids, radiotherapy, radionucleotides and percutaneous osteoplasty which involves the use of bone cement to reduce pain and improve mobility but not significantly [31]. That is why Radiotherapy (RT) is considered as a powerful modality most frequently used for bone metastasis which can be delivered either by conventional 3000 cGy in 10 fractions or 2000 cGy in 5 fractions or 800 Gy in single fraction. [15].

However, conventional RT requires daily hospital attendance at a specialized center that may be of some distance from the patient's home. As part of that protracted course of RT may also cause considerable problems for patients, especially for those with poor performance status and limited life expectancy. Sometimes the cost becomes burden enough for the patient party to stop the treatment in the midway. It also increases the workload of the treatment center. So, this study is aimed to evaluate pain response in between 800 cGy in single fraction RT versus conventional 3000 cGy in 10 fractions RT in metastatic vertebral bone disease.

2. Materials and Methods

2.1. Methods

This prospective quasi experimental study was conducted at Khwaja Yunus Ali Medical College and Hospital, Enayetpur, Shirajganj. The study was done from July 2016 to December 2016. The ethical committee approval from KYAMCH was obtained. The respondents were selected by purposive sampling technique. 60 patients suffering from metastatic vertebral bone disease were the respondents of this study. The objectives of the study along with its procedure, alternative methods, risks and benefits of this study were explained to the patients in easily understandable local language and then informed written consent from the patients was obtained. A semi structured questionnaire was prepared after pre-testing containing patient profile. This was used for collection of information by interviewing & examining patients & their reports. An interview usually lasted for an hour. Following procedures were followed to evaluate the patients' condition before treatment:

1) Complete clinical history and physical examination
2) General and systemic examination
3) Radiological studies
4) Whole body bone scan
5) Metastasis present over
   a) Cervical vertebrae
   b) Dorsal vertebrae
   c) Lumber vertebrae
   d) Sacral vertebrae

Others:

1) X-ray dorsal spine
2) Lumbo sacral spine
3) Chest X-ray P/A view
4) USG of W/A
5) C. T. Scan or MRI of the site

Laboratory studies

   a) Complete blood picture
   b) Liver function test
   c) Renal function test
   d) Serum electrolytes

All of the enrolled patients were grouped in two arms, arm A and arm B.

In arm A patients were treated with 800 cGy single fraction RT and in arm B patients were treated with 3000 cGy, 10 fractions RT.

One month after completion of radiotherapy response was evaluated.

Treatment response was assessed in the light of RECIST (Response Evaluation in Solid Tumor) version 2.0 (2010) criteria, by VAS (Visual Analogue Scale) after 4 weeks of RT completion and toxicities were evaluated by RECIST (Response Evaluation Criteria in Solid Tumor) and RTOG acute radiation morbidity criteria.

Patients were managed symptomatically with different analgesics, steroids on the basis of degree of pain. Sometimes antihistamines, anti-emetics, vitamins, IV fluids and blood transfusion were also given on need basis.

Every patient of both arms was monitored routinely by CBC, platelet count and serum creatinine during treatment and one month after completion of treatment. Size of the tumor was measured by CT scan with contrast before starting radiotherapy and 1 month after completion of treatment. Oral mucositis, radiation dermatitis, oesophagitis etc. were evaluated weekly during treatment according to "RTOG" toxicity criteria.

2.2. Inclusion Criteria

1) Adult patients
2) Patients having Karnofsky Performance Status (KPS) ≥ 40
3) Patients with painful radiologically proven bone metastases
4) All patients with histopathologically proven primary malignancy
5) Patients who will be on WHO analgesic ladder II [Non-Steroidal Anti-Inflammatory Drugs (NSAID) combined with opioids].
6) Patients having minimum laboratory criteria-
   a. Hb% > 10 gm/dl
   b. Total WBC count > 4000cells/cu mm
   c. Total Platelet count > 1,50,000 cells/cu mm.

2.3. Exclusion Criteria

1) patients with wide area of multiple spinal metastases;
2) patients with existing bone disease;
3) patients previously treated with radiation to spine or any site overlapping the treatment site;
4) P/S below 40 in Karnofsky scale;
5) Pregnant women;
6) Patients with uncontrolled DM, HTN.

2.4. Operational Definitions

Conventional radiotherapy: Conventional or fractionated radiotherapy is a form of external beam radiation where a complete radiation dose is delivered over many treatment sessions to shrink or destroy tumours. This fractionated radiotherapy allows normal cells to repair themselves in between treatments and protect themselves from permanent cellular injury or death.

Single fraction radiotherapy: It is a type of radiotherapy where high dose of radiation is delivered to the tumour in single treatment session.

The visual analogue scale (VAS): Visual analogue scale (VAS) is a measurement instrument for subjective characteristics or attitudes like pain that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points.

2.5. Data Collection and Analysis

Data were collected from 60 patients. After cleaning and editing, all the relevant data were compiled on a master chart. Statistical analysis of the results was obtained by Statistical Package for Social Science (SPSS) version 19.0. Continuous data were expressed as mean ± SD and were compared by Student "t" test. Categorical data were expressed as number and percentage and were compared via the Chi-square test and Fisher's exact tests. Two tailed $p<0.05$ was considered as significant.

3. Results

This quasi-experimental study was carried out to compare the pain response in between 800 cGy single fraction radiotherapy (RT) versus 3000 cGy in 10 fractions RT in patients with painful vertebral bone metastasis at Khwaja Yunus Ali Medical College and Hospital, Sirajgonj. Total study population was 60 among which 30 were in the intervention arm (arm A, 800 cGy single fraction RT) and 30 were in the control arm (arm B, conventional 3000 cGy in 10 fractions RT).

Table 1. *Baseline demographic and clinical characteristics of the study population.*

Characteristics	Arm A (Intervention Group) n=30		Arm B (Control Group) n=30	
	N	%	N	%
Sex				
Male	16	53.33	17	56.66
Female	14	46.66	13	43.33
Age				
Mean (±SD)	43.73 (7.741)		46.8 (7.513)	
Range	30-75		31-59	
Primary malignancy				
Lung	13	43.33	11	36.66
Breast	7	23.33	6	19.98
Prostate	5	16.66	4	13.32
Thyroid	3	10.00	3	10.00
Kidney	1	3.33	2	6.66
Others (Testis, Ovary, Cervix, Liver)	1	3.33	4	13.32
Involved vertebral sites after metastasis				

Characteristics	Arm A (Intervention Group) n=30		Arm B (Control Group) n=30	
	N	%	N	%
Lumbar	13	43.29	11	36.63
Thoracic	12	39.96	14	46.62
Cervical	5	16.65	3	10.00
Sacral	0	0	2	6.66

*SD=Standard Deviation.

This table shows baseline demographic and clinical characteristics of the respondents. Baseline patient characteristics were comparable in both the arms. Mean age was 43.73 years (range 30-75) and 46.8 years (range 31-59) in arm A and arm B, respectively. Male patients were predominant in both arms (53.33% in Arm A and 56.66% in Arm B). Majority of the patients had primary site of malignancy from lungs (43.33% in arm A and 36.66% in arm B). Most common metastatic sites were lumbar and thoracic spines in both the arms.

Table 2. *Distribution of patients by pre and post radiotherapy performance status (KPS).*

KPS	Arm A				Chi-square test	Arm B				Chi-square test
	Before RT		After RT			Before RT		After RT		
	N	%	N	%		N	%	N	%	
80	1	3.33	8	26.64		2	6.66	9	29.97	
70	3	10.00	10	33.3	χ^2=14.373	5	16.65	13	43.29	χ^2=15.33
60	15	49.95	7	23.31	df=3	16	53.28	6	19.98	df=3
50	11	36.63	5	16.65	p=0.002^s	7	23.31	2	6.66	p=0.002^s
TOTAL	n=30	100	n=30	100		n=30	100	n=30	100	

*KPS=Karnofsky Performance Status
*Chi-square test was performed to see the association between two groups, s=significant.

This table shows the pre and post radiotherapy performance status (measured by KPS) of all of the enrolled patients of this study. In both arms after radiotherapy, the improvement of performance status of patients was significant with a p value.002.

Table 3. *Grading of pain before and after radiotherapy in patients of both arms.*

Grading of pain	Arm A				Chi-square test	Arm B				Chi-square test
	Before RT		After RT			Before RT		After RT		
	N	%	N	%		N	%	N	%	
Severe pain (75-100mm)	20	66.6	0	0		18	59.94	0	0	
Moderate pain (45-74 mm)	7	23.31	6	19.98	χ^2=36.9	10	33.3	3	10	χ^2=43.61
Mild pain (5-44mm)	3	10	16	53.28	df=3	2	6.66	17	56.61	df=3
No pain (0-4mm)	0	0	8	26.64	p<0.001^s	0	0	10	33.3	p<0.001^s
TOTAL	n=30	100%	n=30	100%		n=30	100%	n=30	100%	

*RT=Radiotherapy
*Chi-square test was performed to see the association between two groups, s=significant.

This table shows the measured grading of pain before radiotherapy (by VAS) and response evaluation after radiotherapy. In arm A, 20 patients (66.6%) initially presented with severe pain, 7 patients (23.31%) with moderate and 3 patients (10%) with mild pain. In arm B, 18 (59.94%), 10 (33.3%) and 2 (6.66%) patients presented with severe, moderate and mild pain respectively. One month after completion of radiotherapy, pain significantly reduced in patients of both arms with a p value of < .001. 8 patients of arm A and 10 patients of arm B did not have any pain during response evaluation which goes in favour of excellent response of radiotherapy in both of the arms.

Table 4. *Assessment of symptomatic improvement after radiotherapy.*

Symptoms After RT	Arm A (n=30)		Arm B (n=30)		Chi-square test
	N	%	N	%	
1. Muscle weakness	3	10	3	10	
2. Paraplegia	2	6.66	2	6.66	
3. Loss of sensation (both upper and lower limb)	1	3.33	1	3.33	χ^2=0.356
4. Bowel and bladder dysfunction	0	0	0	0	df=4
5. Loss of gait	2	6.66	1	3.33	p=0.986^{ns}
6. No neurological deficit	22	73.26	23	76.59	
Total	n=30	100%	n=30	100%	

*RT=Radiotherapy
*Chi-square test was performed to see the association between two groups, ns=not significant.

This table shows the symptomatic improvement after one month of completion of radiotherapy. About 10 patients (33.30%) in arm A and 12 patients (39.96%) in arm B initially presented with muscle weakness which dropped down to 10% in both arms after radiotherapy. Symptoms like paraplegia, sensory loss, bowel and bladder dysfunction, loss of gait also improved significantly after radiotherapy. 22 patients (73.26%) of arm A and 23 patients (76.59%) of arm B had no neurological deficit in that visit.

Table 5. *Assessment of toxicities after radiotherapy (according to RTOG acute radiation morbidity criteria).*

Toxicities after RT	Arm A (n=30)		Arm B (n=30)		Chi-square test
	N	%	N	%	
Pulmonary toxicities	4	13.32	3	10	
Cardiac toxicities	1	3.33	0	0	
Gastro intestinal toxicities	3	10	1	3.33	
Genito urinary toxicities	1	3.33	1	3.33	χ^2=3.019
Haematological toxicities	3	10	2	6.66	df=6
Skin toxicities	2	6.66	2	6.66	p=0.806 ^{ns}
No toxicities	16	53.28	21	69.93	
Total	n=30	100%	n=30	100%	

*RT=Radiotherapy

*Chi-square test was performed to see the association between two groups, ns=not significant.

This table shows the evaluation of radiotherapy induced toxicities in both arms. Pulmonary (13.32%), gastrointestinal (10%) and haematological (10%) toxicities were more commonly found in arm A. In arm B pulmonary (10%), haematological (6.66%) and skin (6.66%) toxicities were more commonly found. 21 patients (69.93%) of arm B and 16 patients (53.28%) of arm A did not develop any radiotherapy induced toxicities with a p value of.806 which was not significant.

4. Discussion

In this study, both arms A and B had more males than female patients, that is 53.33% males and 46.66% females and 56.66% and 43.33% respectively. In terms of age, mean age of Arm A was 43.73 and Arm B was 46.8. The findings revealed, among the primary malignancy sites, lung was most common in both arms, 43.33% and 36.66%, followed by breast, being 23.33% and 19.98% in Arm A and B respectively. It was seen that, among the involved vertebral sites after metastasis, lumbar and thoracic were spines were commonest, 43.29% and 39.96% in Arm A and 46.62% and 36.63% in Arm B. Similar study reported that, median age was 58 years (range 55-64) and 60 years (range 56-63) in arm A and arm B, respectively. Male patients were predominant in both the arms (84.8% in arm A, 80.6% in arm B). Most of the patients had primary site of malignancy from prostate (81.8% in arm A and 77.4% in arm B). Most common metastatic sites were thoracic and lumbar spine in both the arms [41].

The findings showed, after evaluation of pre and post radiotherapy status by Karnofsky Performance Status, 60 score was commonest (49.95%) before radiotherapy and 70 score after radiotherapy (33.3%) in Arm A. When association was seen by doing Chi-Square test, P value was 0.002 which suggests statistical significance. In terms of Arm B, again 60 score was commonest (53.28%) before radiotherapy and 70 score after radiotherapy (43.29%). Chi-Square test revealed a P value of 0.002 which means statistically significant association. On the contrary, previous study showed, patients with KPS score 40 and 50 were predominant in both the arms [41].

Grading of pain by Visual Analogue Scale (VAS) before and after radiotherapy showed, for Arm A, which is our intervention group, maximum patients reported severe pain (66.6%), before radiotherapy, whereas after radiotherapy, 53.28% patients reported mild pain. On doing Chi-Square test to view association, the result was statistically significant (P value<0.001). Even in terms of Arm B, which is our control group, maximum patients, that is 59.94% reported severe pain before radiotherapy, whereas 56.61%, meaning maximum patients reported mild pain after completion of radiotherapy. Chi-Square test revealed statistically significant association between the two groups (P value > 0.001). Kapoor et al. took 250 consecutive patients of bone metastasis for a study. 62% of the patients received a single fraction while the remaining received 10 fractions. In the 10-fraction group, overall response was present in 60% of the patients. Stable pain was present in 23% of the patients while 9% patients had progressive pain. In the single-fraction arm, overall response was seen in 58%, stable pain in 27% and progressive pain in 7% of the patients [29].

The study revealed, when symptomatic improvement after radiotherapy was assessed, both arms, Arm A and Arm B, had the greatest number of patients with no neurologic deficit, that is 73.26% and 76.59% respectively. On doing Chi-Square test for seeing associations, the result was not statistically significant (P value=0.986).

The findings demonstrated that, on assessment of toxicities after completion of radiotherapy, in both A and B Arms, maximum number of patients, that is 53.28% and 69.93% reported no toxicities. Chi-Square test was performed, and there was no significant association between the two groups (P=0.806). Another study showed

that, all patients finished their scheduled course of RT without incident. Side effects included only mild gastrointestinal disturbances. Eight patients (12.1%) suffered from grade 2 toxicities while only two (3%) faced grade 3 G-I adverse effects. Differences in two arms were not statistically significant (P=0.49) [41].

5. Limitations

This single-center study has several limitations. The follow up time was very limited. Sample size was also very narrow, which could hamper the generalizability of the study. Randomization was absent, so it is difficult to establish causal association between an intervention and outcome. Study design was quasi-experimental. It is very difficult to eliminate confounding bias.

6. Recommendations

Considering the small sample size and shorter follow-up time it will not be logical to come to a definite conclusion about the advantage of hypo-fractionated radiotherapy over the conventional radiotherapy in the management of secondary bone tumour. As far as we observed both the radiation fractionation schedules for the management of secondary bone tumour were equally effective in terms of final response and toxicity, hypo-fractionated radiotherapy schedule has its own inherent benefits. More patients can be provided with the desired treatment with shorter period of time with fewer complications. It will certainly ease the economic burden on the patients as well as on the country. However, further studies with better design and longer duration of follow up are required to reach a conclusive decision.

Declaration of Interest

The authors report no conflict of interest.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Ethical Consideration

The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained.

Acknowledgements

The author would like to express earnest gratitude to the ethical committee for considering the approval to conduct the study, also heartfelt respect to all the patients without whom the study would not be completed.

References

[1] Asdourian PL, Weidenbaum MA, DeWald RL, Hammerberg KW, Ramsey RG. The pattern of vertebral involvement in metastatic vertebral breast cancer. Clinical orthopaedics and related research. 1990 Jan 1 (250): 164-70.

[2] Beals RK, Lawton GD, Snell WE. Prophylactic internal fixation of the femur in metastatic breast cancer. Cancer. 1971; 28 (5): 1350-4.

[3] Cheal EJ, Hipp JA, Hayes WC. Evaluation of finite element analysis for prediction of the strength reduction due to metastatic lesions in the femoral neck. Journal of biomechanics. 1993 Mar 1; 26 (3): 251-64.

[4] Cleeland CS. The measurement of pain from metastatic bone disease: capturing the patient's experience. Clinical Cancer Research. 2006 Oct 15; 12 (20): 6236s-42s.

[5] Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. Pain and its treatment in outpatients with metastatic cancer. New England Journal of Medicine. 1994 Mar 3; 330 (9): 592-6.

[6] Coleman RE. Skeletal complications of malignancy. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1997 Oct 15; 80 (S8): 1588-94.

[7] Coleman RE, Rubens R. The clinical course of bone metastases from breast cancer. British journal of cancer. 1987 Jan; 55 (1): 61-6.

[8] Daldrup-Link HE, Franzius C, Link TM, Laukamp D, Sciuk J, Ju rgens H, Schober O, Rummeny EJ. Whole-body MR imaging for detection of bone metastases in children and young adults: comparison with skeletal scintigraphy and FDG PET. American Journal of Roentgenology. 2001 Jul; 177 (1): 229-36.

[9] Eriksen EF. Cellular mechanisms of bone remodeling. Reviews in Endocrine and Metabolic Disorders. 2010 Dec; 11 (4): 219-27.

[10] Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H, Leibovitch I. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single-and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. Journal of Nuclear Medicine. 2006 Feb 1; 47 (2): 287-97.

[11] Fidler M. Incidence of fracture through metastases in long bones. Acta Orthopaedica Scandinavica. 1981 Jan 1; 52 (6): 623-7.

[12] Flickinger FW, Sanal SM. Bone marrow MRI: techniques and accuracy for detecting breast cancer metastases. Magnetic resonance imaging. 1994 Jan 1; 12 (6): 829-35.

[13] Fujimoto R, Higashi T, Nakamoto Y, Hara T, Lyshchik A, Ishizu K, Kawashima H, Kawase S, Fujita T, Saga T, Togashi K. Diagnostic accuracy of bone metastases detection in cancer patients: comparison between bone scintigraphy and whole-body FDG-PET. Annals of nuclear medicine. 2006 Jul; 20 (6): 399-408.

[14] Goblirsch MJ, Zwolak PP, Clohisy DR. Biology of bone cancer pain. Clinical cancer research. 2006 Oct 15; 12 (20): 6231s-5s.

[15] Gurney H, Larcos G, McKay M, Kefford R, Langlands A. Bone metastases in hypernephroma. Frequency of scapular involvement. Cancer. 1989 Oct 1; 64 (7): 1429-31.

[16] Harrington KD. Orthopaedic management of extremity and pelvic lesions. Clinical orthopaedics and related research. 1995 Mar 1 (312): 136-47.

[17] Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT. Bone imaging in metastatic breast cancer. Journal of Clinical Oncology. 2004 Jul 15; 22 (14): 2942-53.

[18] Hoskin, P. J., Stratford, M. R. L., Folkes, L. K., Regan, J. and Yarnold, J. R., 2000. Effect of local radiotherapy for bone pain on urinary markers of osteoclast activity. *The Lancet*, *355* (9213), pp. 1428-1429.

[19] Hitchins RN, Philip PA, Wignall B, Newlands ES, Begent RH, Rustin GJ, Bagshawe KD. Bone disease in testicular and extragonadal germ cell tumours. British journal of cancer. 1988 Dec; 58 (6): 793-6.

[20] Khan L, Uy C, Nguyen J, Chow E, Zhang L, Zeng L, Salvo N, Culleton S, Jon F, Wong K, Danjoux C. Self-reported rates of sleep disturbance in patients with symptomatic bone metastases attending an outpatient radiotherapy clinic. Journal of palliative medicine. 2011 Jun 1; 14 (6): 708-14.

[21] Manolagas SC, Jilka RL. Bone marrow, cytokines, and bone remodeling—emerging insights into the pathophysiology of osteoporosis. New England journal of medicine. 1995 Feb 2; 332 (5): 305-11.

[22] Matsuyama T, Tsukamoto N, Imachi M, Nakano H. Bone metastasis from cervix cancer. Gynecologic oncology. 1989 Jan 1; 32 (1): 72-5.

[23] Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. Pain. 2001 Sep 1; 93 (3): 247-57.

[24] Mirels HI. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. Clinical orthopaedics and related research. 1989 Dec 1 (249): 256-64.

[25] Morris C. Survival in patients operated on for pathologic fracture: implications for end-of-life orthopedic care. J Clin Oncol. 2005; 23: 6072-82.

[26] Nielsen OS, Munro AJ, Tannock IF. Bone metastases: pathophysiology and management policy. Journal of Clinical Oncology. 1991 Mar; 9 (3): 509-24.

[27] Nguyen J, Cramarossa G, Bruner D, Chen E, Khan L, Leung A, Lutz S, Chow E. A literature review of symptom clusters in patients with breast cancer. Expert review of pharmacoeconomics & outcomes research. 2011 Oct 1; 11 (5): 533-9.

[28] Ohta M, Tokuda Y, Suzuki Y, Kubota M, Makuuchi H, Tajima T, Nasu S, Yasuda S, Shohtsu A. Whole body PET for the evaluation of bony metastases in patients with breast cancer: comparison with 99Tcm-MDP bone scintigraphy. Nuclear medicine communications. 2001 Aug 1; 22 (8): 875-9.

[29] Parmar A, Mehta M, Yadav R, Parikh A, Suryanarayana U. Single Fraction versus Multi Fraction Radiotherapy Treatment Schedules for Management of Painful Bone Metastasis.

[30] Perez C, Brady L. Principles and practice of radiation oncology. Journal of Pediatric Hematology/Oncology. 1999 Nov 1; 21 (6): 560.

[31] Ratanatharathorn V, Powers WE, Moss WT, Perez CA. Bone metastasis: review and critical analysis of random allocation trials of local field treatment. International Journal of Radiation Oncology Biology Physics. 1999 Apr 1; 44 (1): 1-8.

[32] Roodman GD. Mechanisms of bone metastasis. New England journal of medicine. 2004 Apr 15; 350 (16): 1655-64.

[33] Schmidt GP, Schoenberg SO, Reiser MF, Baur-Melnyk A. Whole-body MR imaging of bone marrow. European journal of radiology. 2005 Jul 1; 55 (1): 33-40.

[34] Sim FH, Frassica FJ, Chao EY. Orthopaedic management using new devices and prostheses. Clinical orthopaedics and related research. 1995 Mar 1 (312): 160-72.

[35] Singh D, Yi WS, Brasacchio RA, Muhs AG, Smudzin T, Williams JP, Messing E, Okunieff P. Is there a favorable subset of patients with prostate cancer who develop oligometastases? International Journal of Radiation Oncology Biology Physics. 2004 Jan 1; 58 (1): 3-10.

[36] Smith HS. Painful osseous metastases. Pain physician. 2011 Jul 1; 14 (4): E373-403.

[37] Steinmetz MP, Mekhail A, Benzel EC. Management of metastatic tumors of the spine: strategies and operative indications. Neurosurgical Focus. 2001 Dec 1; 11 (6): 1-6.

[38] Van der Linden YM, Dijkstra PD, Kroon HM, Lok JJ, Noordijk EM, Leer JW, Marijnen CA. Comparative analysis of risk factors for pathological fracture with femoral metastases: results based on a randomised trial of radiotherapy. The Journal of bone and joint surgery. British volume. 2004 May; 86 (4): 566-73.

[39] Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain. 1995 Oct 1; 63 (1): 65-76.

[40] Zetter BR. The cellular basis of site-specific tumor metastasis. New England Journal of Medicine. 1990 Mar 1; 322 (9): 605-12.

[41] Majumder D, Chatterjee D, Bandyopadhyay A, Mallick SK, Sarkar SK, Majumdar A. Single fraction versus multiple fraction radiotherapy for palliation of painful vertebral bone metastases: A prospective study. Indian Journal of Palliative Care. 2012 Sep; 18 (3): 202.