

Dose Fractionation Schemes for Palliative External Beam Radiotherapy on Painful Bone Metastasis from Breast Cancer

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ABSTRACT

Background: The efficacy of palliative external beam radiotherapy (PRT) for relief of metastatic bone pain had been well established, a single fraction is as effective as multiple fractions in relieving bone pain, but variation exist among the radiation oncologist in our environment on the ideal dose per fraction regimen. **Methods:** We retrospectively reviewed data from breast cancer patients treated with PRT using linear accelerator for metastatic bone pain in University College Hospital Ibadan between 2005 and 2009. The extracted information includes bio-data, presenting symptoms, metastatic sites, and bone pain assessment before and after four weeks of PRT using visual analogue pain scale (VAS), radiation doses, fractionation numbers and number of re-irradiation. **Results:** There were 161 eligible breast cancer patients who were treated with PRT secondary to painful bone metastases between 1st January 2005 and 31st December 2009. Majority were females with only 1.2% male patients (Figure 1). Table 1 showed demographic characteristics of treated patients with mean age of 45.2 years, pain was the major presenting complaint (92.5%) and multiple bony metastases constituted the highest metastatic presentation (52.2%). Table 2 shows patient's responses to PRT treatment for pain relief (complete responses of 88.8% and 11.2% partial responses). No significant association between patient's responses to PRT and magnitude of radiation doses delivered. However, fractionation sizes were significantly associated with re-irradiation p-value < 0.05. **Conclusion:** No differences exist between various dose fractionation schemes in terms of relief from painful bony metastases. However, shorter dose fractionation schemes are associated with re-irradiation of previously irradiated sites.

Keywords: Palliative radiotherapy; doses fractionations; bone metastases; breast cancer

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Introduction

Most breast cancer patients present very late in Nigeria due to ill-informed perceptions concerning the disease, gap in cancer knowledge among health care providers, less friendly hospital environment and fear of mastectomy.¹⁻³ These factors contributed to more number of metastatic breast carcinoma than early and locally advanced disease in our tertiary institutions.⁴ Despite the lack of accurate estimates of metastatic sites, it is generally believed that 27% of patients who die of carcinomas will have bone metastases and in most cases bone metastases are multiple.^{5,6} Patanaphan et al. found the commonest site of distant metastasis to be in

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the bone by 51%, the sites include the spine, pelvis, femur, ribs, humerus, and skull.^{7,8} The most frequent consequence of bone metastases is pain.⁸ It was estimated that fifty percent of all cancer pain is due to bone metastases.⁹ Bone pain most frequently affects the spine and the chest, although pain in the hip and shoulder girdle are also common.⁹ The mechanism of bone pain aroused from the periosteum, a thick membrane covering the bones, which contains many receptors that are highly sensitive to mechanical or chemical stimulation. Increasing pressure from an expanding tumor, cytokine release, the formation of micro fractures, and pathological fracture may all trigger the pain signal via the receptors, and produce pain sensation.⁸ Bone pain is generally a dull aching pain that may be interspersed with a stabbing discomfort. Pain is often worsened by movement, and this debilitation is associated with a reduction in quality of life.⁸ When treatment intent is towards cure, curative external beam radiotherapy is delivered using large total dose of 60-70 Gy spread out over many fractions (20-30),¹⁰ whereas palliative external beam radiotherapy (PRT) is aimed to improve quality of life by using lower radiation doses between 20-30 Gy spread out over fewer fractions (≤ 10)¹⁰ to avoid acute side effects that are undesirable, as this can seriously diminish the quality of life in patients with a limited life span. The overall effectiveness of PRT for bone pain relief has been consistently demonstrated by numerous randomized controlled trials.^{6,11-13} Majority of these trials have examined the effectiveness of RT for complete or partial pain relief.¹¹⁻¹⁵ Adenipekun et al in Ibadan reviewed the

response of 92 patients to the analgesic effect of radiotherapy for bony metastases. The results showed a total response of about 90% (67% complete response and 23% partial response) within 4 weeks of treatment.¹⁶ Similarly, another review by Wu et al. reported that 60 to 80% of patients experienced partial pain relief, and 15-40% of patients experienced complete pain relief.¹⁷ Mc. Quay et al. also conducted a systematic review that synthesized the results of twenty trials which examined the use of PRT for bone pain relief.¹⁵ Their findings indicated that at least 50% of patients undergoing PRT achieved complete or partial pain relief.¹⁵ No doubt about the fact that efficacy of PRT for bone pain relief had been well established, but the ideal dose/fraction regimen remains controversial among radiation oncologist all over the globe. Since the early 80's, large randomized trials have demonstrated that one single fraction of PRT is as effective at relieving bone pain as multiple fractions,^{11,18} suggesting the absence of a dose response relationship with respect to pain relief. A meta-analysis by the Cancer Care Ontario group similarly demonstrated similar result with no differences.^{19,17} Countries that are advanced in the use of PRT for symptoms relief in cancer patients also share contrary views with regards to ideal dose per fraction regiment. The United Kingdom (U.K) uses 20Gy in 5 fractions and the United State of America (U.S) uses 30Gy in 10 fractions, respectively.^{20,21} However, in our environment, the commonly prescribed dose/fractionation as at the time of this study was 25Gy in 6 fractions usually using simple noncomplex fields such as directly applied fields e.g AP/PA portals. The reasons for the variation in practice patterns are not fully



known. It may be from expectation that patients who were treated with single fractions are more likely to be re-treated from subsequent episodes of pain that lead physicians to choose a multi-fractionated regimen.²²

Other treatment modalities for bone metastases were also recommended; among them are oral analgesics, corticosteroids, radiopharmaceuticals and biphosphonates, but cost, side-effects, lack of availability and sometimes poor response have always been the problem. Palliative radiotherapy is well effective and tolerated, side-effects are mainly related to total dose and fraction size, and depend largely on the body region irradiated,²³ only one third of patients treated will experience pain flare-up, which can be prevented or treated with corticosteroids.²⁴

Materials and methods

Patients

We retrospectively collected data on breast cancer patients treated with palliative radiotherapy (PRT) using Elekta precise linear accelerator for bone metastasis from breast cancer between 1st of January, 2005 and 31st December, 2009. The extracted information included bio-data, presenting symptoms, metastatic sites, assessment of bone pain before and four weeks after radiotherapy using visual analogue pain scale (VAS) that is graded 0 to 10, where 0 stand for no pain and 10 as the worse pain ever experienced by the patient, radiation doses and fractionation numbers, responses to radiotherapy four weeks after PRT and records of patients that were re-irradiated on the same site after six months of initial radiotherapy treatment.

Statistical methods

A statistical analysis was performed using Statistical Package for Social Sciences version 20.0, using an alpha value of 5%, a pearson correlation was conducted between radiation doses and responses to symptoms relief. Similarly, correlation between fractionation sizes and re-irradiation was also conducted to test for any relationship between the two variables at 5% α level of significant. Results obtained were presented in tables and charts.

Results

There were 161 eligible patients with advanced breast cancer who were treated with PRT secondary to painful bone metastases between January 2005 and December 2009. Female patients constituted 98.8% of 161 patients, only 1.2% were males (Figure 1). Table 1 showed the mean age of the patients as 45.2 yrs with SD \pm 11 and age range of 21-85 years. Pain alone accounted for 92.5% of presenting complaints, pain and sensory deficit in 3.1% of patients, followed by pain sensory and motor deficit in 4.3%. Multiple bony metastases constituted the highest metastases (52.2%) followed by uncomplicated vertebral metastases of 13%, ribs (11.8%), long bones (9.9%), spinal cord compression (5.6%), impending fracture (2.5%), clavicle (1.9%), skull (1.9%) and mandible of 1.2%. Figure 2 shows range of radiation doses that were used for PRT treatment, 11-20Gy were the common radiation doses used for PRT (60.3%) followed by 21-30Gy (36.7%) and then 1-10Gy of 3%. Similarly, fractionation numbers ranged between 4-6 fractions were the commonest fractionation sizes used for PRT which accounted for 75.8% of all the fractionations, followed by 1-3 fractions (14.3%) and > 6 fractions which accounted for



9.9% (Figure 3). Table 2 showed a complete response by all the five patients treated with radiation doses between 1-10Gy, 88.7% of 97 patients treated with radiation doses ranged 11-20Gy had a complete response and only 6.8% of them had a partial response. This was followed by a complete response rate of 88.1% of those treated with 21-30Gy and partial response of 11.9%. No significant association seen between patient's responses and various radiation doses delivered ($p=0.353$), however,

a significant association was observed between fractionation sizes and re-irradiation ($p<0.05$). Patients who were treated with fractionation sizes ranged between 1-3 fractions (23 patients) had about 96% of them being re-irradiated and those treated with 4-6 fractionation numbers have only 9.8% of patients that were re-treated. Similarly only 6.7% of those treated with fractionation range > 6 fractions were re-irradiated.

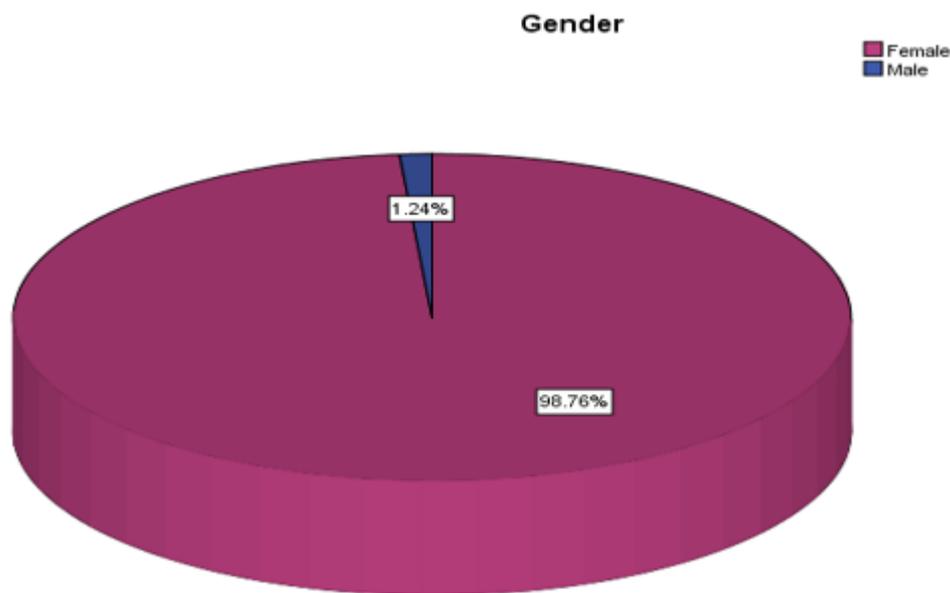


Figure 1: Sex distribution of 161 patients treated with palliative radiotherapy

Table 1: Demographic characteristics of 161 patients treated with palliative radiotherapy

Characteristics of patients	Number of patients	Percentage
Age group		
20-29	8	5
30-39	41	25.5
40-49	62	38.5
50-59	27	16.8
60-69	20	12.4
70-79	1	0.6
≥80	2	1.2
Symptoms		
Pain	149	92.5
Pain and sensory deficit	5	3.1
Pain-sensory and motor deficit	7	4.3
Sites of metastases		
Multiple bony metastasis	84	52.2
Uncomplicated vertebral metastasis	21	13
Ribs	19	11.8
Long bones	16	9.9
Spinal cord compression	9	5.6
Impending fracture of long bones	4	2.5
Others	8	5.0

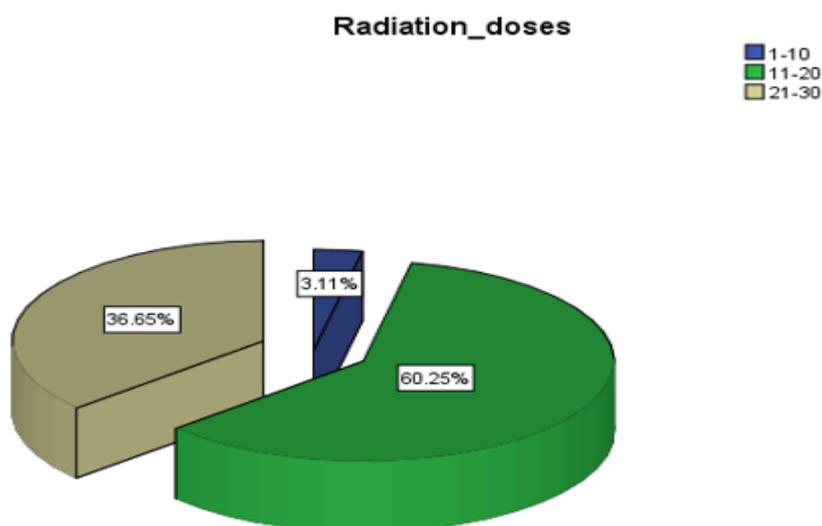


Figure 2: Range of radiation doses (in Gy) used for palliative treatment of 161 patients with bone metastases

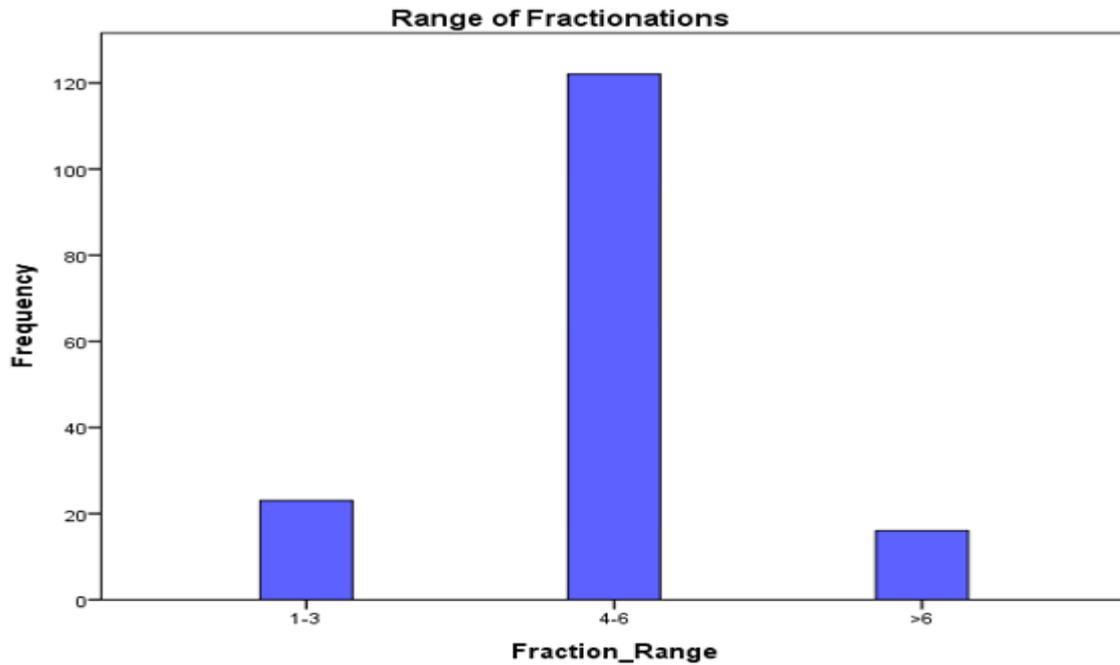


Figure 3: Range of fractionations used for palliative radiotherapy treatment of bone metastases

Table 2: A pearson correlation of symptoms relief from radiation doses and re-irradiation from fractionations schemes

Radiation doses / fractionations	N	Symptoms relief / Re-irradiations		P-value
Radiation doses (Gy)		Complete	Partial	
1-10	5	5	0	
11-20	97	86	11	0.353
21-30	59	52	7	
Range of fractionations		Re-irradiated	Not re-irradiated	
1-3	23	22	1	0.000
4-6	122	12	110	
>6	16	1	15	

N- Number of Fractionation Schemes for Palliative External Beam Radiotherapy

Discussions



This study had confirmed the effectiveness of PRT in breast cancer patients with painful bony metastases, 88.8% of patient had complete pain relief and only 12.2% experienced partial pain relief. This had been supported by numerous trials that examined the similar effect of PRT for complete or partial pain relief in bony metastases from different primary diseases.¹¹⁻¹⁵ Adenipekun et al. also supported our findings by reviewing the response rates of 92 patients to the analgesic effect of radiotherapy for bony metastasis. The results showed a total response of about 90% (67% complete response and 23% partial response) within 4 weeks of treatment.¹⁶ Differences in the response rate might be attributed to criteria for patient's selections and differences in sample sizes, we carefully selected only patients with complete follow up records of four weeks post PRT.

The results of this study supported the hypothesis of equivalent effect of shorter dose fractionation schemes to that of multiple-fraction radiotherapy in degree of pain relief,²⁵ both gave similar results when comparing treatment regimens with regard to the primary aim of pain control, suggesting no dose response relationship with respect to pain relief.^{11,25-28} Despite numerous evidences that demonstrated comparable pain relief of single fractionation treatment and its preference over multiple fractionations by

some scholars, only 14.3% of patients in this study were treated with shorter fractionation schemes (1-3 fractions). Some scholars had questioned and criticized the recommendations of shorter fractionations as being the standard treatment for all patients with uncomplicated bone metastasis^{29,30} because of re-treatment

findings associated with shorter dose fractionation schemes in many conducted studies.^{27,31,25,32} Similar result was recorded in this study with about 97% of our patients who were treated with shorter fractionations (1-3 fractions) being re-irradiated due to subsequent pain from previously radiated areas. Variation concerning fractionation schemes for bone metastases is an unresolved issue among radiation oncologist globally.^{20,21} The reasons for different practice patterns remain unknown,^{31,32,33} but concern for re-irradiation or expectations of inability of a single fraction to prevent other serious latent bone related complications in future, such as pathological fracture and spinal cord compressions might be responsible for the choice of multi-fractionated regimen among radiation oncologist.²²

Conclusion

Different dose fractionation schemes have the same response to painful bony metastasis. However, shorter fractions schemes are associated with re-irradiations of previously radiated areas. Hence, longer fraction schemes are recommended in patients whom were supposedly expected to survive longer so as to avoid re-treatments and other serious latent bone related complications in future such as pathological fractures and spinal cord compressions.

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