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Pain and quality of life in patients with metastatic bone disease treated with palliative radiotherapy at Ocean Road Cancer Institute, Tanzania

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Abstract

Introduction: Palliative radiotherapy is a frequently prescribed treatment for pain control in advanced cancer patients presenting with painful bone metastasis. Treatment using a single fraction of radiotherapy is widely recommended since it is as effective in pain control as multiple fraction treatments but also reduces cost and travel burdens. Studies have documented the late adoption of single fraction schedules globally despite the known advantages of this treatment option.

Objectives: This study aimed to evaluate the effectiveness of palliative radiotherapy in controlling pain in patients presenting with metastatic bone disease at Ocean Road Cancer Institute (ORCI) and assess the role of fractionation in pain control and quality of life. This understanding can provide insight into current practices and recommendations on possible practice changes in prescribing palliative radiotherapy.

Methods: A prospective study was conducted involving patients presenting with metastatic bone disease due to various primary cancers who were scheduled for palliative radiotherapy. Consenting patients were evaluated for pain intensity before and 4 weeks after treatment. Clinical data on diagnosis, metastatic site, and prescribed treatments were recorded. Quality of life before and after treatment was assessed using the Short Form Survey (SF-36).

Results: Forty-eight patients with complete follow-up results were included in the final analysis. The mean age was 56.7 years, and 52.1% were females. Prostate cancer was the most frequent primary diagnosis (31.3%), followed by breast and cervix (18.8% each). The spine was the most affected metastatic site (90%). Only 27% of patients received single-fraction radiotherapy treatments, with a 5-fraction treatment being the most prescribed schedule. More than 80% of patients had improvement in pain after treatment, and there was no difference in pain improvement across the different treatment schedules. Quality of life improved in 6 out of 8 dimensions after treatment.

Conclusion: Cancer patients receiving palliative radiotherapy for bone metastasis at ORCI have similar clinical features as those in other parts of the world. Radiotherapy is an effective treatment for pain relief, with similar analgesic effects regardless of the fractionation schedule, and contributes to improving quality of life. There is a preference for prescribing multiple fraction regimens for radiotherapy; this has implications for educating clinicians to change practice to single fraction schedules, which are equally effective and can reduce patient cost and burden.

Keywords: Metastatic bone disease, Palliative radiotherapy, pain, Quality of Life

Introduction

Metastatic bone disease is a common manifestation of advanced cancers. Primary tumors that metastasize to the bone include breast, lung, prostate, thyroid, kidney, and myelomas, with

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breast, prostate, and lung accounting for over 85% of such patients (Kang & Formenti, 2017)(De Felice, Piccioli, Musio, & Tombolini, 2017). Fifty to seventy-five percent of patients with bone metastasis experience severe pain (S. Lutz et al., 2012), which results in a compromise in their quality of life.

Despite being a heterogenous group with differing clinical outcomes, most patients with bone metastasis require active treatment. Palliative radiotherapy (PRT) is often given since it is highly effective in providing symptom relief, and the toxicity associated with it is typically mild, making it suitable for relatively sick patients (Gutt et al., n.d.). External beam radiotherapy (EBRT) can provide significant palliation of pain in bone metastasis in 50-80% of patients, with complete pain relief in up to one-third of patients (Y. Zhu, 2012).

PRT may be given to improve quality of life (QOL), reduce analgesic requirement and maintain or ameliorate skeletal function(De Felice et al., 2017). PRT given to relieve pain can be offered through different regimens such as a single fraction (SF) of 8 Gray (Gy) delivered in 1 treatment, and multiple fractions (MF) regimens including 20 Gy in 5 fractions delivered daily over 1 week, and 30 Gy in 10 fractions delivered over 2 weeks. Other less commonly prescribed regimens also exist. Several clinical trials have demonstrated that SF and MF provide equivalence in pain relief. However, there has been a worldwide reluctance among radiation oncologists to adopt SF as a standard practice (Chow, Harris, Fan, Tsao, & Sze, 2007). It is known that MF regimens involving longer PRT schedules are cumbersome and require patients to make several visits, increasing costs and inconvenience. (Gutt et al., 2015).

Breast and prostate cancer are among the top 5 cancers seen at Ocean Road Cancer Institute (ORCI), Tanzania's National Cancer Referral Centre, and a significant proportion of such patients present with painful metastatic bone disease. PRT and bisphosphonates are routinely offered to patients as measures to control pain and prevent complications however many patients are still prescribed MF regimes that increase travel costs and burden to patients (Patel et al., 2023)Most patients are discharged home after treatment, and an objective assessment of the treatment's impact is rarely done until the next follow-up visit. As a result, little is known about the impact of PRT and the various fractionation schemes prescribed to control pain in this population.

Understanding the differences in the outcomes of the different radiotherapy regimens in these patients would help inform the choice of regimen when prescribing PRT. The impact of shorter Vs more extended treatment regimens on pain and quality of life would also provide insights into this important element when choosing regimens, thereby preventing unnecessary costs and delays in delivering treatments and reducing the treatment burden on already crowded radiotherapy services.

Therefore, this study aimed to evaluate the effectiveness of palliative radiotherapy in controlling pain in patients presenting with metastatic bone disease at Ocean Road Cancer Institute and assess the role of fractionation in pain control and quality of life.

Materials and Methods

A prospective cohort study was conducted at ORCI involving patients presenting with metastatic bone disease due to various primary cancers. Patients with bone metastasis resulting from recurrence and those presenting with up-front bone metastasis who had been prescribed PRT for pain were identified from clinics, radiology, and nuclear medicine over three months. Consenting participants were assessed for pain intensity using a numerical scale ranging from 1-10, categorized into no pain, mild pain, and moderate and severe pain (scores of 0, 1-4, 5-6 and 7-10, respectively). Data on clinical and pathological variables (ECOG score, cancer diagnosis and sites of bone metastasis, use of analgesics) were documented from medical records. Treatment-related information was also documented. The Short Form (SF-36) survey, a standardized 36-item

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questionnaire, assessed QOL (Lins & Carvalho, 2016). Patients were followed up and interviewed 4 weeks after completion of PRT and re-assessed for pain and QOL.
Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23. Demographic and clinical data were summarized using descriptive statistics. Pain intensity improvements were assessed by comparing mean scores before and after treatment. A bivariate analysis explored the effect of fractionation and bisphosphonates on pain improvement.

The SF-36 questionnaire consisting of 36 items was used to calculate eight subscales: physical functioning (PF), role limitations due to physical health (RP), role limitations due to emotional problems (RE), energy/fatigue (EF), emotional well-being (EW), social functioning (SF), bodily pain (BP) and general health (GH). The composite scores for PF, RP, RE, EF, EW, SF, BP and GH were calculated by taking the average of 10 questions (3 to 12), four questions (13 to 16), three questions (17 to 19), four questions (23, 27, 29, 31), five questions (24, 25, 26, 28, 30), two questions (20, 32), two questions (21, 22) and five questions (1, 33, 34, 35, 36) respectively. Scores for the SF-36 scales range between 0 and 100, with higher scores indicating a better quality of life ('36-Item Short Form Survey (SF-36) Scoring Instructions | RAND', n.d.). Differences in mean scores were compared before and after treatment using paired sample t-tests.

Results

Fifty-two patients who met the inclusion criteria and consented were recruited over the study period; 4 died during follow-up. Of the 48 patients whose results were analyzed, 25 (52.1%) were female. The mean age of patients was 56.73 years (standard deviation = 13.876). The majority (58.3%) had attended primary education, and 56.3% were peasants (Table 1).

Table 1: Social-demographic characteristics of patients with metastatic bone disease (n = 48)

Characteristics		**n**	**%**
Gender	Male	23	47.9%
	Female	25	52.1%
Age	Mean	56.73	
	Standard deviation	13.876	
Level of education	Primary	28	58.3%
	Secondary	11	22.9%
	College/University	9	18.8%
Occupation	Peasant	27	56.3%
	Employed	4	8.3%
	Business	7	14.6%
	Housewife	3	6.3%
	Retired	6	12.5%
	Student	1	2.1%

Clinical and treatment parameters

Table 2 summarizes the clinical and treatment characteristics. Prostate cancer was the most common primary (31.3%) followed by breast and cervix (18.8% each). Half of the patients were assigned a performance score (ECOG) of 3, meaning they were confined to the bed or chair for more than 50% of their waking time, and another 40% had a score of 2 (capable of limited self-care). The most affected site was the spine (90%), with 4 (8%) of patients presenting with widespread bone metastasis involving multiple sites. All patients were prescribed opioid analgesics (liquid morphine), with about two-thirds using the stronger (10 mg/ml) strength.
The preferred fractionation scheme for PRT was 20 Gy in 5 fractions (40%), followed by 30 Gy in 10 fractions (33%). Only 13 patients (27%) were treated using SF.

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Table 2: Clinical and treatment parameters (n = 48)

Variables		n	%
Primary cancer site	Breast	9	18.8%
	Prostate	15	31.3%
	Lung	1	2.1%
	Thyroid	2	4.2%
	Cervix	9	18.8%
	Others	11	22.9%
ECOG Performance status	1 (Ambulatory, can carry out light work)	2	4.2%
	2 (Capable of limited self-care)	19	39.6%
	3 (Confined to bed/chair >50% of waking hrs	24	50%
	4 (Completely disabled, totally confined to bed/chair)	3	6.3%
Site of bone metastasis	Spine	43	89.6%
	Widespread bone metastasis	4	8.3%
	Proximal humerus	1	2.1%
Analgesics given	Weak opioids	16	33.3%
	Strong opioids	32	66.7%
Prescribed Radiation dose/scheme	Single fraction, 8 Gy	13	27.1%
	20 Gy in 5 fractions	19	39.6%
	30 Gy in 10 fractions	16	33.3%

Pain control after palliative Radiotherapy

The majority (71%) of patients experienced severe pain before beginning radiotherapy, with 25% experiencing moderate pain. Following PRT, no patients had severe pain, and 7 (15%) had no pain (Table 3).

Table 3: Comparison of pain intensity before and after palliative radiotherapy (n=48)

Pain intensity	Before Palliative Radiotherapy		After Palliative Radiotherapy	
	N	%	n	%
No pain	0	0	7	14.6
Mild pain	2	4.2	33	68.8
Moderate pain	12	25	8	16.7
Severe pain	34	70.8	0	0

Table 4 summarizes the bivariate analysis of prescribed radiation dose vs. pain intensity after palliative radiotherapy. The analysis shows no difference in pain relief between the prescribed radiation schemes (Single fraction 8 Gy vs. 20 Gy in 5 fractions vs. 30 Gy in 10 fractions) (P-value 0.596).

Table 4: Bivariate analysis of fractionation regimen in controlling pain (n=48)

Variable	Intensity of pain after treatment			P-value
	No pain n (%)	Mild pain n (%)	Moderate n (%)	
Prescribed radiation dose				*0.596*
Single fraction 8 Gy (n=13)	1 (7.7%)	11 (84.6%)	1 (7.7%)	
20 Gy in 5 fractions (n=19)	3 (15.8%)	13 (68.4%)	3 (15.8%)	
30 Gy in 10 fractions (n=16)	3 (18.8%)	9 (56.3%)	4 (25.0%)	

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Quality of life after palliative radiotherapy

Table 5 summarizes the quality of life of metastatic bone disease patients before and after palliative radiotherapy. There were significant improvements in six of the QOL composite scores after PRT: Physical functioning, Energy/fatigue, Emotional well-being, Social functioning, Pain and General health (84.38, 86.67, 130.42, 29.17, 30.83 and 93.23 vs. 167.71, 110.83, 157.92, 36.98, 76.88 and 108.33), $p<0.05$. There was no difference in the mean scores for Role functioning (Physical) and Role functioning (emotional) before and after palliative radiotherapy.

Table 5: Comparison of quality of life before and after palliative radiotherapy (n=48)[a]

	Before Palliative Radiotherapy		**After Palliative Radiotherapy**		***P*-value**
	Mean	SD	Mean	SD	
Physical functioning	84.38	157.492	167.71	291.637	***0.022***
Role functioning (physical)	0.0	0.0	0.0	0.0	-
Role functioning (emotional)	2.08	14.434	2.08	14.434	-
Energy/fatigue	86.67	48.349	110.83	51.025	***0.000***
Emotional well-being	130.42	77.073	157.92	66.683	***0.003***
Social functioning	29.17	23.255	36.98	29.621	***0.01***
Pain	30.83	22.723	76.88	39.835	***0.000***
General health	93.23	67.189	108.33	68.869	***0.008***

[a]Paired-samples *t-test*

Discussion

Clinical characteristics

Bone metastasis is a common presentation in our region, where the majority of patients present with advanced cancer. Post-mortem studies have found bone metastasis in up to 75% of patients with advanced breast or prostate cancer(Chin & Kim, 2015). The patients in this study cohort formed a heterogenous group with different primaries; the mean age of 56.7 years reflects this since the age ranges of similar patients with metastatic disease in other studies ranged from 45 years (breast cancer), 57 years (cervical cancer) to 69 years (prostate cancer) (Mwakigonja, Lushina, & Mwanga, 2017)(Nabawanuka, Galukande, Nalwoga, & Gakwaya, 2013)(Zhou & Peng, 2020)(Cassell et al., 2019).

The most common primary diagnosis in this cohort was prostate cancer, followed by breast and cervical cancer. Tanzania has a high burden of these cancers, and prostate and breast cancer have a high predilection for metastasis to the bone (Kang & Formenti, 2017)(Y.-J. Zhu, 2012) (Chin & Kim, 2015)(Vieira, Fragoso, Pereira, & Medeiros, 2019) ('Metastatic Bone Disease: Practice Essentials, Pathophysiology and Etiology, Epidemiology', n.d.). The spine was the highest-represented site (89.6%) of bone metastasis in this cohort. This is in keeping with other studies which have shown that the axial skeleton is the most common area for bone metastasis, with the spine representing the most frequent site ('Metastatic Bone Disease: Practice Essentials, Pathophysiology and Etiology, Epidemiology', n.d.) (Kakhki, Anvari, Sadeghi, Mahmoudian, & Torabian-Kakhki, 2013) (M. Zhu et al., 2019).

Pain is one of the most common and debilitating symptoms of advanced cancer. A systematic review study entailing literature generated for over 40 years on this subject found a pooled prevalence of pain at 53%, with 64% of patients with advanced/metastatic disease complaining of pain, of whom 31% rated their pain as moderate to severe (van den Beuken-van Everdingen et al., 2007). All patients in this cohort of metastatic bone disease presented with pain, with 71% and 25% rating their pain as severe and moderate, respectively. Moderate to severe bone pain is a common indication of PRT, as shown in this group.

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Radiotherapy prescriptions and pain control

PRT is one of the most effective and frequently used treatments for bone pain, and its effectiveness in providing analgesia and relief has been widely explored. Studies have documented pain relief (no to mild pain) ranging from 40% to 67% of patients treated with PRT, with a median time to relief of around 4 weeks (Gutt et al., n.d.)(McDonald et al., 2017) (Spencer, Parrish, Barton, & Henry, 2018)(Velden et al., 2018). Our study confirmed these findings, with 83.4% of patients documenting no pain or mild pain and no patients remaining with severe pain after PRT (Table 3).

Three fractionation schemes are typically prescribed for PRT at ORCI. This cohort's most frequently prescribed scheme was 20 Gy in 5 fractions (39.6%). This was followed by 30 Gy in 10 fractions (33.3%) and 8 GY in a single fraction (27.1%). This is concerning, given the disadvantages of administering MF schedules in resource-limited settings. The choice of SF vs MF has been a question of extensive research, and multiple studies have confirmed the efficacy of SF vs MF in terms of pain control, with the only disadvantage being the increased rate of re-irradiation with the latter (S. T. Lutz, 2019)(Jones & Simone, 2014). Our study shows similar results, with no significant difference in analgesia achieved through SF compared to MF schedules (Table 4). SF schedules have been found safe and effective even in the elderly (Rühle et al., 2022), and a recent meta-analysis of evidence re-confirmed the effectiveness of SF for PRT and concluded no difference in rates of re-irradiation between SF and MF (Migliorini et al., 2021).

Despite the vast body of evidence regarding the equivalence of SF and MF regimens when treating uncomplicated bone metastasis palliatively, there is still reluctance among oncologists to prescribe single fractions. This trend has been repeatedly found across different countries. A review by Yu-jia Zhu documented significant differences in preferences for MF schemes for PRT, with several countries (USA, Iran) preferring 30 Gy in 10 fractions and others 20 Gy in 5 fractions (Y.-J. Zhu, 2012). Similar findings were found in Japan (Nakamura et al., 2012) and Korea (Chung et al., 2013). An international survey conducted among radiation oncologists in North America and Australia found 101 different daily dose schedules. However, SF schedules were notably the least often used in the United States. The authors concluded that there is a delay in the incorporation of evidence into practice for palliative radiotherapy for painful bone metastasis (Fairchild et al., 2009).

The justification for the choice of a single fraction lies not just in the reduced cost incurred for treatment but also in the reduction of indirect costs and burden to patients when coming for treatment. In an analysis of travel burdens for patients travelling for radiotherapy in Tanzania, Nigeria and South Africa, Saloni et al. showed that using hypofractionated schemes could result in significant savings in transportation costs and time (Patel et al., 2023). Indeed, hypofractionation schedules for palliative treatment is one of the recommendations reached by African practitioners themselves, as documented in the Choosing Wisely Africa guidelines (Rubagumya et al., 2020).

Quality of life

Since the primary goal of PRT is symptomatic relief, QOL is an important endpoint alongside pain control. There is a need for data on how PRT impacts overall QOL, as this has been less extensively studied than pain control. Our study used the 36-Item Short Form Survey (SF-36), which groups items into various dimensions of QOL, and found that 6 out of 8 items had significantly improved following PRT. The two items that did not show significant improvement were 'Role Functioning' on a physical and emotional level. In contrast, the Dutch Bone Metastasis Study found that QOL stabilized 1 month after PRT for patients with bone metastasis, but only the psychosocial dimension of QOL improved (Westhoff et al., 2016).

McDonald et al. reported in their NCIC Symptom Control Trial analysis that forty per cent of patients experienced pain reduction and better QOL on day 10 after PRT, with further improvements in QOL on day 42 (McDonald et al., 2017). Although improvement of QOL has been shown in some studies to differ between responding and non-responding patients following PRT, the factors that predict response to PRT are still unclear; hence, current recommendations stand at offering PRT to all patients with painful bone metastasis to decrease pain and improve QOL (Migliorini et al., 2021)(Westhoff et al., 2015).

Limitations

This was a small study with a limited number of patients and a short follow-up period. Exploring these results with a larger sample size and a longer follow-up would be helpful, as it may provide added insights into the effect on QOL after PRT.

Conclusion

Patients receiving PRT for bone metastasis at ORCI have similar clinical features as documented in other studies. Our study confirmed the effectiveness of PRT in providing pain relief and improvement of QOL for these patients, regardless of the fractionation scheme. We found that prescriptions for PRT follow similar trends as in other countries, with SF schemes being the least prescribed despite the evidence of their effectiveness and reduction in cost and time burden to the patients and treatment centres. Oncologists need to be reminded of this and reinforced in prescribing SF treatment schedules for PRT.

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