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Single fraction image guided radiation therapy for management of bone metastases during the COVID-19 pandemic

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ABSTRACT

Aim: Radiation therapy (RT) plays a major role in management of bone metastases, however, various dose-fractionation schemes are utilized taking into account patient, tumor, and treatment characteristics. The aim of this study was to assess Image Guided Single Fraction Radiation Therapy (IG-SFRT) for management of painful bone metastases during the COVID-19 pandemic.

Material and Method: Patients receiving IG-SFRT for painful bone metastases were assessed for age, gender, primary cancer diagnosis, location of metastases, performance status, analgesic intake, pain relief, and overall treatment efficacy in this study.

Results: Out of the total 65 patients treated with IG-SFRT during the course of COVID-19 pandemic at our department, 54 patients were evaluable for overall treatment efficacy analysis. Based on the international consensus on palliative RT endpoints, rates of complete response (CR), partial response (PR), pain progression (PP), and indeterminate response (IR) were 16.67%, 59.26%, 9.26%, 14.81%, respectively corresponding to an overall response rate of 75.93%. IG-SFRT was well tolerated by all patients without toxicity.

Conclusion: For patients with bone metastases, pain palliation is a critical aspect of management. In view of the high rate of overall treatment efficacy achieved with IG-SFRT in our study, we suggest routine utilization of this image guided radiotherapeutic approach for management of painful bone metastases which additionally allows for minimization of treatment visits thereby improving patient and treatment facility convenience under the special circumstances of the recent COVID-19 pandemic.

Keywords: Radiation therapy (RT), image guided radiation therapy (IGRT), bone metastasis, COVID-19 pandemic

INTRODUCTION

Pain is the most common symptom of bone metastasis which leads to quality of life impairment in affected patients. Along with pain, bone metastases may also lead to several deteriorating consequences including pathological fractures, spinal cord compression, bone marrow aplasia and hypercalcemia which may be severe and fatal (1). Bone metastases constitute a frequent complication of systemic cancer and a leading cause of pain in affected patients (2). Various factors may be involved in occurrence bone metastasis, nevertheless, it is considered that osteoclasts play a critical role in pathophysiology of pain by several mechanisms including damage of bone and nerve fibers along with acidotic stimulation of pH-sensitive receptors (3-5).

A considerable proportion of patients with cancer suffer from bone metastases during the course of their disease, and prompt management may be required to provide symptomatic relief. Radiation therapy (RT) plays a major role in treatment of bone metastases with satisfactory results (6,7). Nevertheless, patterns of RT practice in terms of dose-fractionation schemes vary widely among treatment centers. Management of patients using single fraction radiation therapy (SFRT) has not been considered as the standard irradiation strategy for palliative treatment of painful bone metastases in several centers despite high level of evidence suggesting comparable efficacy of SFRT for pain relief (6-11). Selection of fractionation pattern for RT of bone

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metastases may be affected by many factors including patient, tumor, and treatment characteristics (7). Affected patients' life expectancy, compliance with treatment, and performance status are important considerations. Primary tumor histology, time interval between primary diagnosis and bone metastasis, location of metastasis, perceived risk of pathological fracture, presence or absence of accompanying neurological deficits, soft tissue involvement and spinal cord compression are among the critical tumor related factors. Logistical issues including source availability, distance to treatment center, facility workload, and reimbursement may be considered among different aspects of palliative management of bone metastases with RT (7,8). While multifraction RT of bone metastases has been common practice in majority of private and public RT centers in different parts of the world, utility of single fraction treatments may be justified for management of selected patients taking into account the comparable efficacy in pain relief along with other factors including source availability, patient convenience and compliance, treatment cost, staff and facility workload (6-11). Palliative irradiation of bone metastasis comprises a large proportion of the total workload in RT centers given its high frequency. From another standpoint, the recent coronavirus disease 2019 (COVID-19) pandemic has resulted in incorporation of certain administrative measures along with modification of treatment facility practice patterns accordingly (12,13). Since high dose of radiation is delivered in a single session with SFRT, incorporation of contemporary RT technologies such as Image Guided Radiation Therapy (IGRT) may be considered to improve the accuracy and precision of treatments. IGRT refers to use of advanced imaging techniques at several steps of the treatment process including RT simulation and data acquisition, radiation treatment planning (RTP), setup verification and precise target localization. This advanced technology allows for minimizing setup margins which may reduce exposure of normal tissues and radiation induced toxicity. We adopted IG-SFRT for prompt management of bone metastases during the critical course of the COVID-19 pandemic and report our treatment results in this study.

MATERIAL AND METHOD

The study was carried out with the permission of Selçuk University Hospital Clinical Research Ethics Committee (Date: 15.03.2022, Decision No: 2022/135). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients receiving IG-SFRT for management of pain due to bone metastases during the course of COVID-19 pandemic were assessed for age, gender, primary cancer diagnosis, location of metastases, performance status, analgesic intake, pain relief, and overall treatment efficacy. Written informed consents of all patients were acquired prior to treatment, and this retrospective study was performed in compliance with the Declaration of Helsinki principles and its later amendments. All patients had histologically proven cancer diagnosis with radiologically confirmed bone metastases causing a pain score of 5 or more on the Brief Pain Inventory (BPI) scale (14). Patients who did not receive hormone therapy at least 9 months before RT were included to assess the effect of IG-SFRT, concurrent hormone therapy was not used.

All patients underwent computed tomography (CT)-simulation at the CT-simulator (Siemens Somatom Emotion, Siemens Healthcare, Germany) at our department. Acquired planning CT images were transferred to the delineation workstation (MonacoSim, Elekta, UK) for contouring of treatment volumes and critical structures. A margin of 5 to 10 milimeters was used to generate the planning target volume. Delineation data sets were sent to the Elekta Monaco treatment planning system (Elekta, UK) for RTP. IGRT was routinely utilized for setup verification of each patient. Radiation dose was 8 Gray for IG-SFRT and all treatments were delivered by VersaHD (Elekta, UK) Linear Accelerator (LINAC) using 6 MV photons.

Primary endpoint of the study was overall treatment efficacy assessed by the pain response with BPI at baseline before IG-SFRT and 1 month after treatment. Briefly, a score of 0 refers to no pain and a score of 10 refers to the worst possible pain on the BPI scale. Response categories based on the international consensus on palliative RT endpoints are shown on **Table 1** (15).

Table 1. Response categories based on the international consensus on palliative radiation therapy endpoints

Category	Definition
Complete response	A pain score of zero without any increase in analgesic intake 1 month after single fraction radiation therapy
Partial response	A decrease of at least 2 points on the Brief Pain Inventory pain score without any increase in analgesic intake, or at least a 25% reduction in analgesic intake without an increase in pain score
Pain progression	An increase of 2 points or more in pain score without reduction in analgesic use, or as at least a 25% increase in analgesic use without accompanying decrease in pain score
Indeterminate response	A response which does not reflect the definitions of complete response, partial response, and pain progression

Complete response (CR) was categorized as a pain score of zero without any increase in analgesic intake 1 month after IG-SFRT. Partial response (PR) was categorized as a decrease of at least 2 points on the BPI pain score without

any increase in analgesic intake, or as at least a 25% reduction in analgesic intake without an increase in pain score. Pain progression (PP) was defined as an increase of 2 points or more in pain score without reduction in analgesic use, or as at least a 25% increase in analgesic use without accompanying decrease in pain score. A response which did not reflect the definitions of CR, PR, or PP was categorized as indeterminate response (IR).

Overall treatment efficacy was determined based on the rate of responding patients with CR or PR. Any adverse effects occurring as treatment toxicity were recorded.

Statistical Analysis

Data analysis was performed by using Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc., Chicago, IL) software with the level of significance set at $p < 0.05$. Descriptive analysis was performed for quantitative variables, mean and median values were calculated along with the range. Qualitative variables including CR, PR, PP, and IR indicating the overall treatment efficacy were presented as percentages. Paired t-test was used for comparison between BPI scores before and after IG-SFRT.

RESULTS

Patient, disease, and treatment characteristics are shown on **Table 2**. All patients suffered from multiple metastases in lungs, liver, skeleton and other regions. However, bone metastases were uncomplicated without clinical or radiological findings suggestive of spinal cord compression, pathological fracture, or imminent fracture requiring surgical fixation. Number of metastases was 6 in 30 patients (55.56%), 7 in 11 patients (20.37%), 8 in 7 patients (12.96%), and 9 in 6 patients (11.11%). Out of the total 65 patients treated with IG-SFRT at our department, 54 patients were evaluable for overall treatment efficacy analysis using the BPI pain scores acquired at baseline before IG-SFRT and 1 month after IG-SFRT. Median age was 65 years (range: 38-84 years). Thirty one patients (57.41%) were male and 23 patients (42.59%) were female. Primary diagnosis was prostate cancer, breast cancer, lung cancer, and other for 20 patients (37.04%), 16 patients (29.63%), 11 patients (20.37%), and 7 patients (12.96%), respectively. Hormone therapy was utilized for 30 patients (55.56%) at least 9 months before RT and bisphosphonate therapy was used for 50 patients (92.59%).

Site of metastatic involvement included the hips and pelvis in 21 patients (38.89%), lumbar spine in 10 patients (18.52), thoracic spine in 9 patients (16.67%), lower limbs in 7 patients (12.96%), and other locations in 7 patients (12.96%). Type of bone metastasis was osteolytic in 16 patients (29.63%), osteosclerotic in 20 patients (37.04%), and mixed in 18 patients (33.33%). Median Karnofsky Performance Status was 60 (range: 40-90).

Table 2. Patient, tumor and treatment characteristics

Characteristic	Number	%
Number of patients with pain response assessment	54	
Median age (range)	59 (38-84) years	
Median Karnofsky Performance Status (range)	60 (40-100)	
Radiation dose	8 Gray	100
Gender		
Man	31	57.41
Woman	23	42.59
Primary tumor histology		
Prostate Cancer	20	37.04
Breast Cancer	16	29.63
Lung Cancer	11	20.37
Other	7	12.96
Site of metastatic involvement		
Hips and pelvis	21	38.89
Lumbar spine	10	18.52
Thoracic spine	9	16.67
Lower limbs	7	12.96
Other	7	12.96

Treatment outcomes with IG-SFRT are summarized in **Table 3**. Median BPI pain score was 7 (range: 5-10) before IG-SFRT at baseline, and median BPI pain score was 4.5 (range: 0-10) 1 month after IG-SFRT. There was a median decrease of 40.18% (range: 0%- 100%) in BPI pain scores 1 month after IG-SFRT, which was statistically significant ($p < 0.05$). Based on the international consensus on palliative RT endpoints, rates of CR, PR, PP, and IR were 16.67%, 59.26%, 9.26%, 14.81%, respectively corresponding to an overall response rate of 75.93%. Treatment requirement rate was 37.04%. IG-SFRT was well tolerated by all patients without toxicity.

Table 3. Summary of treatment outcomes with IG-SFRT

Characteristic	
Median BPI score (range)	7 (5-10) before IG-SFRT 4.5 (0-10) one month after IG-SFRT
Median decrease in BPI score one month after IG-SFRT	40.18% (range: 0%-100%)
Rate of Complete Response	16.67%
Rate of Partial Response	59.26%
Rate of Pain Progression	9.26%
Rate of Indeterminate Response	14.81%
Overall response rate based on BPI scores before and one month after IG-SFRT	75.93%

DISCUSSION

Bone metastases constitute a major health concern as a frequent complication of systemic cancer resulting in considerable morbidity and even mortality. Radiotherapeutic management of pain due to bone metastasis is still a matter of debate in terms of optimal dose and fractionation schemes. Despite the

accumulating high level evidence, there appears to be underutilization of SFRT for palliative management of bone metastases (16). Although there may be plausible justifications in favor of multifaction RT for selected patient subgroups, emerging pertinent and important aspects of radiotherapeutic management under the special circumstances of the recent COVID-19 pandemic should include minimization of treatment visits thereby improving patient and treatment facility convenience through prioritization of expedited irradiation protocols such as single fraction RT regimens.

In a recent study by McDonald et al. (17) assessing the effect of RT on painful bone metastases, pain reduction and improved quality of life indices were achieved as early as 10 days after SFRT, justifying the utility of this approach for management of all patients regardless of performance status and life expectancy. Although there may be controversies regarding the incorporation of patients in the decision-making process for their management, a study by Szumacher et al. (18) about palliative RT of bone metastases revealed that a higher proportion of patients favored SFRT particularly due to the convenience of the treatment plan. Focusing on a less addressed perspective, Saito et al. (19) investigated the influence of RT schedule on decisions of physicians from various specialties to refer their patients suffering from bone metastases for palliative irradiation. The study underscored that referring physicians preferably considered SFRT particularly for management of patients with poor performance status and prognosis, which may have implications for increased utilization of palliative irradiation with wider adoption of SFRT (19). From a different standpoint, cost-utility analysis based on the large randomized Dutch bone metastasis study revealed that SFRT provided equivalent palliation and quality of life compared to multiple fraction RT with lower medical and societal costs (20,21).

In our study, three-quarters of the 54 evaluable patients had an overall pain response 1 month after 8 Gray IG-SFRT with one-sixth of patients being completely free of pain. A satisfactory rate of overall treatment efficacy has been achieved by use of SFRT, which is consistent with the literatüre (6-11, 21-23). SFRT dose was 8 Gy as suggested by the IAEA randomised trial (23) investigating the optimal SFRT dose for management of pain due to bone metastases.

Our study may add to the existing literature in the context of routine IGRT utilization as a viable radiotherapeutic approach for irradiation of bone metastases, which is a poorly addressed treatment concept in palliative RT setting. A critical objective to consider in SFRT is avoidance of geographical miss and excessive toxicity which may be more relevant given the high dose of radiation delivered in a single session. IGRT is a contemporary technique to achieve this goal since it allows for precise treatment delivery with volumetric imaging guidance for accurate setup verification and reduced setup margins for decreased exposure of normal tissues. Incorporation of IGRT in RT of bone metastases may improve the accuracy, precision, and toxicity profile of RT without extending the overall treatment time (24-26).

CONCLUSION

In conclusion, pain palliation is a critical aspect of management for patients with bone metastases. In view of the high rate of overall treatment efficacy achieved with IG-SFRT in our study, we suggest utilization of this image guided radiotherapeutic approach for management of pain due to bone metastases which additionally allows for minimization of treatment visits thereby improving patient and treatment facility convenience under the special circumstances of the recent COVID-19 pandemic.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Hospital Clinical Research Ethics Committee (Date: 15.03.2022, Decision No: 2022/135).

Informed Consent: Written informed consents of all patients were acquired prior to treatment.

Referee Evaluation Process: Externally peer-reviewed.

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