Original Article

Prophylactic single fraction radiotherapy for the prevention of pathologic femoral fractures

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Background: Femoral metastases increase the risk of pathologic fracture. While multiple studies exist discussing the efficacy of single fraction radiotherapy in control of metastatic bone pain, little data exists confirming the efficacy of single fraction radiotherapy for fracture prevention. The objective of this study is to investigate the utility of single fraction radiotherapy to prevent pathologic femoral fractures.

Methods: Retrospective study of femoral metastases treated with 8 Gy in 1 fraction (fx). Relevant images and pain scores were reviewed for bony stability and assigned a Mirels bone score (MBS). Surgical consultation/intervention, prospectively acquired pain scores/toxicity assessments, and in-field fracture rate as reported on follow-up imaging were assessed.

Results: A total of 27 patients with 34 bone metastases were identified. For single fraction radiation, 28 bone lesions were included. In all patients treated with single fraction radiotherapy for femoral fracture prevention, the median time to first clinical and radiographic follow-up was 1.40 and 1.82 months, respectively. Thirteen patients died with a median overall survival (OS) post completion of therapy of 3.20 months (0.33–9.40 months). Specific site of disease of the 28 lesions receiving single fraction radiation included: femoral neck 39.29%, femoral shaft 32.14%, femoral head 17.86%, and other femoral locations 10.71%. Median MBS for the lesions was 8.5 (range, 6–12) with 39.00% of bone metastases evaluated by orthopedic surgery. Five fractures occurred prior to radiation therapy. Six lesions received a surgical intervention with a median time interval of 4.00 months from orthopedic intervention to radiation completion (0.37–18.73 months). All irradiated bony sites had no subsequent fractures. Median pre- and post-treatment pain were 6.5 and 0 on a 10-point pain scale.

Conclusions: Femoral Single fraction radiotherapy is effective in reducing metastatic bone pain with a trend towards pathologic fracture prevention. Further studies with longer follow up duration are needed to explore the efficacy of single fraction palliative radiation in preventing pathologic fracture and compare against multifractionated palliative radiation as an effective means of delivering therapeutic treatment in metastatic patients.

Keywords: Bone; metastasis; palliative; single fraction; multi fraction radiotherapy

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Introduction

Metastases are one of the most common causes of cancer related deaths accounting for 90% deaths of cancer patients (1). The bone is a common site of metastatic disease, and a bone metastasis is associated with significant cancer-related morbidity and mortality. Though all cancers have a propensity to metastasize to the bone, breast, and lung, prostate cancers tend to be the most common histology (1-3). The spine, pelvis, and ribs are the commonly involved bony sites of metastases with the femur being less involved. However, the femur is the most common long bone site for metastases with an incidence of roughly 5–25% (4). The anatomic distribution of metastatic disease of the femur is variable with 50% of lesions involving the femoral neck, 30% the subtrochanteric site and 20% the intertrochanteric site (1). The femoral bone can be a morbid site of metastases, causing pain, impaired function, increased risk of morbidity, and increased risk of pathologic fracture.

A multidisciplinary approach which may include surgery, chemotherapy, hormonal therapy, radionuclides, and/or radiotherapy (RT) is usually recommended for management of painful bone metastases (5,6). Surgery alone, RT alone, or surgery followed by RT are some of the commonly used local treatment options available (4). Many of the patients treated for femoral metastases are near the end of life, and practitioners consider single fraction RT (SFRT) to be convenient and effective therapy for reducing pain, making this a preferable regimen especially for patients with a poor prognosis.

The goals of RT in management of bone metastases are to reduce pain, maintain function, and prevent further deterioration of bone in affected areas. RT has been shown to provide significant reduction in metastatic bone pain with minimal adverse effects (7,8). Typically, 50–80% of patients report at least partial pain reduction following external beam RT, and up to one-third endorse complete relief (9). Multiple randomized controlled trials and retrospective studies have compared the efficacy of 8 Gy in 1 fraction (fx) with multifractionated RT regimens (MFRT, 20 Gy in 5 fractions, 24 Gy in 6 fractions, 30 Gy in 10 fractions) in previously un-irradiated bone metastases (8-11). These studies have shown similar rates in pain relief ranging from 50–85% but higher retreatments rates with SFRT (20% *vs.* 8%) (8-16). Both arms have been shown to have similar rates of adverse effects with possibly lower rates in the SFRT arm (8). Pathologic fracture incidence has been higher in single fx groups in some retrospective studies (13,14,17), whereas others show no difference (11). These findings contribute to the lack of a standardization in palliative RT dosing and fractionation schedule for management of bone metastases.

Mirels bone score (MBS) was developed to predict metastatic bony disease with impending pathologic fractures. The scoring system focuses on four main categories: site of the lesion, nature of the lesion, size of the lesion, and pain with scores of 1 to 3 assigned to each variable (17). It includes radiographic and clinical features such as cortical involvement, weight bearing bone involvement, pain level, and lytic versus blastic bony changes (18). Subsequent studies validated the utility of MBS in determining which subset of patients would benefit from prophylactic internal fixation prior to radiation (19,20). An MBS of 8 or greater indicated possible recommendation for prophylactic surgery prior to RT. Patients with an MBS of ≤7 may be safely irradiated without significant risk of fracture (0–4%) (17,18). Although there are multiple studies that depict the efficacy of SFRT for relieving metastatic bone pain, there are very few studies that have shown its effectiveness in preventing femoral fractures.

The goal of our study is to evaluate the use of SFRT

Highlight box

Key findings

- Single fraction radiotherapy is effective in reducing metastatic bone pain with a trend towards prevention of pathologic fracture. Prospective study with longer duration follow up is needed to confirm this finding.

What is known and what is new?

- Metastatic bone disease in weight bearing bones increases the risk of pathologic fracture. Studies comparing single and multi-fraction radiotherapy have shown similar efficacy in prevention of pathologic bone metastases. However, there is little data on the utilization of SFRT for prevention of pathologic fracture prevention.
- This manuscript confirms the known benefits of single fraction radiation in pain control. While the primary endpoint was not met due to the short follow up duration, there were no reported fractures in this cohort at time of median follow up. This trend towards pathologic fracture prevention could be useful in patients with limited life expectancy.

What is the implication, and what should change now?

- There is a potential benefit of single fraction radiotherapy for the prevention of pathologic long bone fractures. However, further prospective randomized studies are needed to establish long term outcomes especially in patients with limited life expectancy

in preventing pathologic fracture and reducing pain in patients with femoral metastases. We present this article in accordance with the STROBE reporting checklist (available at https://tro.amegroups.com/article/view/10.21037/tro-22-40/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and ethical approval and informed consent were exempt by Institutional Review Board given this is a retrospective study with deidentified patient data. This retrospective study evaluated patients treated with palliative intent RT. Analysis of 472 charts from July 2012 through June 2016 was conducted with the following inclusion criteria: histologically confirmed diagnosis of malignancy other than lymphoma, multiple myeloma or small cell lung cancer; femoral metastases of any histology treated with 8 Gy in 1 fx; availability of radiographic imaging before and after treatment suitable for MBS calculation; at least 18 years of age.

Patients and lesions

A total of 27 patients with 34 bone metastases were identified, however for SFRT, 28 metastatic bone lesions were included in 22 patients for the study.

Radiation treatments

Relevant radiographic images pre- and post-RT were reviewed for bony stability with each metastatic lesion receiving a MBS based on site, pain, lesion type, and size. Orthopedic surgery consultation was ordered at the physician's discretion with interventions reported. Pain scores were collected using the Numerical Rating Scale (NRS) on a scale of 0–10 as well as the common terminology criteria for adverse events (CTCAE) v4.0 toxicity criteria. Narcotic and bisphosphonate/RANK-L usage during RT were also recorded. kV or MV imaging was conducted at the time of treatment delivery to confirm accurate targeting and treatment plans were reviewed if two areas were treated in proximity of each other to confirm lack of overlap and retreatment.

Follow-up

Patients were seen at approximately 1-month follow-up with further post-RT visits scheduled as needed. All subsequent relevant imaging was reviewed for bony stability, new pathologic fracture, or new instrumentation. The rate of post radiation pathologic fracture was evaluated for SFRT. Overall survival (OS) was calculated from the time of treatment completion to the time of last recorded contact with patient (including clinic, imaging, or telephone communication) or date of death. Enrollment in hospice was noted and elapsed time from consultation date to date of hospice enrollment was calculated.

Statistical analysis

Statistical analysis was performed by Microsoft Excel (Microsoft Office 2016, Redmond, Washington, United States). Categorical data was described as numbers and percentages. Continuous data was described as median and normal range.

Results

Patient characteristics

Of the 22 patients reviewed, 14 were male with a median age of 64 (range, 34–84 years). These patients had primary gastrointestinal cancers [8], prostate [5], lung [4], breast [4]. Other tumors included GIST [2], Yolk Sac [1], neuroendocrine [1], thyroid [1], renal cell [1], and melanoma [1].

Lesion characteristics

Of the 28 lesions eligible for review, femoral neck comprised of 39.29% (11 lesions), followed by femoral shaft 32.14% [9], femoral head 17.86% [5], and other femoral locations 10.71% [3]. The median MBS for the SFRT cohort was 8.5 (range 6–12). There were 13 lesions that had MBS scores >8 (1 MBS of 12; 3 MBS of 11; 5 MBS of 10; 4 MBS of 9). *Table 1* describes both patient and lesion characteristics.

Surgical consultation and intervention

Orthopedic surgery consults were requested for 10 patients (45.45%) with 11 lesions (39.00%). Ninety percent of orthopedic surgery consults were for patients with MBS greater than or equal to 8, with a median score of 10 (range, 6–12). Of the 10 patients with surgical consults, 6 patients underwent surgical intervention, and these patients had a

Table 1 Patient and lesion characteristics

Characteristics	Value
Median age (years)	64
Sex, n (%)	
Male	14 (63.63)
Female	8 (36.36)
Primary histology, n (%)	
Breast	4 (14.29)
Gastrointestinal	8 (28.57)
Gastrointestinal stromal tumor	2 (7.14)
Lung	4 (14.29)
Melanoma	1 (3.57)
Neuroendocrine	1 (3.57)
Prostate	5 (17.86)
Renal cell	1 (3.57)
Thyroid	1 (3.57)
Yolk Sac	1 (3.57)
Metastasis, n (%)	
Femur	28 (100.00)
Neck	11 (39.29)
Shaft	9 (32.14)
Head	5 (17.86)
Other	3 (10.71)
Median MBS	8.5

MBS, Mirels bone score.

median MBS of 10.5. Orthopedic consults were prior to RT. The median time from most recent surgical intervention to completion of RT was 4.00 months (0.37–18.73 months).

Adverse effects

SFRT was generally well-tolerated by patients included in the study with a median grade for acute toxicity of 0 (range, 0–3). The most frequently noted treatment-related adverse effects were pain at the treatment site (n=4), fatigue (n=3), and nausea (n=2). There were 5 observed pathologic fractures prior to SFRT (17.85%) and no pathologic fractures or radiographically observed instability at the time of SFRT completion. Narcotic pain medication was utilized by 54.55% of patients prior to RT initiation with a median pre-treatment pain level of 6.5, on a 10-point pain scale (range, 0–10). Median post-treatment pain was 0 on a 10-point pain scale for patients with site-specific pain follow-up data. Maximum pain relief (defined as >5 point change in pain scores) was seen for lesions in the femur with MBS scores >8 (range, 8–10). Performance status data was not collected.

Table 2 Interventions used for pain and/or fractures

Characteristics	Value
Narcotic use (n = patients), n	12
Bone growth stimulant use (RANK-L or bisphosphonate, or vitamin D) (n = patients), n	9
Median pain score (10-point scale)	
Pre-treatment	6.5
Post-treatment	0
Orthopedics involvement, n (%)	
Consult (n = lesions)	11 (39.00)
Intervention (n = patients)	6 (21.42)

RANK-Ls & bisphosphonates

The use of RANK-Ls and bisphosphonates as adjunctive/supplemental therapy during SFRT was variable. Of the 22 patients, 9 (40.91%) received supplemental therapy including: denosumab/Xgeva (RANK-Ls), zoledronic acid/Zometa (bisphosphonates) or vitamin D/calcium supplementation either prior or after RT. *Table 2* includes information on interventions used for pain and/or fractures.

Survival and follow up

At the time of study analysis, the median OS for the SFRT cohort was 4.52 months and 13 patients were deceased. Seven patients were enrolled in hospice care prior to their death, and there was a median of 3.00 months after RT completed to hospice enrollment (0.33–7.77 months). The median time from completion of SFRT to death for the 13 deceased patients was 3.20 months. The median time from completion of SFRT to death for the 7 hospice patients was 3.00 months. *Table 3* summarizes findings for SFRT.

The median first clinical follow-up was 1.40 months (range, 0.17–5.50 months) and median first radiographic follow-up 1.82 months (range, 0.10–15.60 months). The time

Table 3 Findings for single fraction radiation therapy

Outcomes	Value
Dose	8 Gy × 1 fx
Total no. of patients	22
Median MBS	8.5
RANK-L use, n	6
Narcotic use, n	12
No. of patients having surgery, n	6
Median pain score	
Pre-treatment (10-point scale)	6.5
Post-treatment (10-point scale)	0
Fracture rate after radiation (%)	0
Median OS (months)	4.52
Median timing of hospice enrollment (months)	3.00
Time from completion of treatment to death on hospice (months)	3.00
Time from completion of treatment to death (months)	3.20
Acute toxicity, n	
Pain	4
Fatigue	3
Nausea	2

Number (n = patients) unless otherwise specified. MBS, Mirels bone score; OS, overall survival.

from consultation in radiation oncology clinic to completion of treatment was a median of 10 days (0–57 days).

The cancer histology of patients alive at time of analysis included: prostate (n=3), breast (n=3), renal cell carcinoma (RCC) (n=1), lung (n=1), and esophagus (n=1). Seventeen of 22 patients had completed some form of imaging after SFRT completion (i.e., CT, bone scan, MRI or plain film).

Discussion

The use of RT in patients with pain from bone metastases has been extensively studied focusing on the effectiveness of RT in reducing metastasis-related bone pain, the appropriate dosing and fractionation schedules, and treatment related toxicity. Other studies have shown similar rates of pathologic fractures with use of SF and MFRT (10,15). Few studies have investigated the benefits of RT in preventing pathologic fractures, specifically in weight bearing bones. This retrospective analysis focused on the utility of SFRT (8 Gy in 1 fx) for the prevention of pathologic factures in patients with femoral metastases. The findings of this study show likely short-term benefits of SFRT in fracture prevention and confirm its efficacy in reduction of bone metastasis-related pain.

Prior studies have shown that patients with a high MBS (≥8) have an associated fracture risk of > 33% with recommendation for prophylactic fixation (18,19) in these patients. However, current standard of practice may delay referral to radiation oncologists for palliative cases. As subspecialists, radiation oncologists are typically not involved in palliation until other options have been exhausted (i.e., chemotherapy, surgical intervention) (21). The findings of this study showed that patients were most likely referred to orthopedic surgery for a median MBS of 10, whereas referrals to radiation oncology frequently occurred for a median MBS of 8.5. For the 13 deceased patients, median OS from completion of treatment to death was 3.20 months.

After completion of SFRT, there were no observed pathologic fractures for patients in this study. Interestingly, this study included 13 lesions that had MBS scores >8. This is in contrast to data from prior studies which report similar or higher rates of pathologic fractures with use of SFRT. For example, the Dutch Bone Metastases (DBM) study (16) showed higher rates of pathologic fracture (23% *vs.* 7%) after SFRT vs MFRT for bone metastases. Interestingly, the DBM randomized study did not include patients at high risk of metastases, impending fractures or actual fractures (10), whereas our retrospective study was inclusive of patients at high-risk of fracture as well as those with bone pain. Similarly, in a meta-analysis of randomized controlled trials comparing SFRT and MFRT, Sze *et al.* showed almost double the rate of pathological fracture with SFRT (3% *vs.* 1.6%) (13). In another study of 949 patients receiving 8 *vs.* 30 Gy RT for palliation of bone pain, there was no significant difference in the rates of pathologic fracture rates (5% *vs.* 4%) between both treatment groups (10). Compared to historical data, our study demonstrates possible clinical benefit of SFRT in reducing incidence of pathologic femur fracture. This favorable result may be a result of the short follow up period which we have acknowledged as a limitation of this study.

Our results may be attributed to a short follow-up period without time lapsed to allow for the incidence of

post-RT fractures. The lack of a longer follow-up period is largely due to the poor prognosis of the primary histology in the majority of our patients, and as a result, shorter life expectancy (4.52 *vs.* 11 months in DBM) over which to experience secondary fractures. For these patients with more aggressive disease and shorter OS, SFRT may be beneficial in preventing further bony destruction, therefore improving quality of life (QOL) and functional status prior to death. It is important to note that though previous randomized trials have shown higher re-treatment rates for recurrent pain with the use of SFRT, none of our patients reported recurrent pain in the immediate duration after SFRT. Our study showed median pre- and post-treatment pain was 6.5 and 0 on a 10-point pain scale. The findings of this study illustrate that in poor prognosis patients, SFRT may be beneficial in providing effective pain relief and potentially prevent fractures from femoral bone metastases. While walking and functional status was not directly assessed, we extrapolate from historical data that suggest less patient reported functional interference in patients with painful bone metastases that respond to palliative radiation (22). Due to the limited life expectancy in this cohort, the QOL associated with SFRT may be taken into consideration at the time of oncologic consultation. The median time from radiation oncology consultation to completion of SFRT was 10 days. This short duration of treatment likely reduced social demands on the patient with daily treatments, increased likelihood of completion (100%), and allowed quicker procession to the next phase of care such as chemotherapy or hospice (median 3.00 months after completion of treatment to hospice enrollment. Therefore, this study shows that in patients with limited life expectancy, SFRT can potentially be effective in preventing fractures and reducing pain at the end of life, thereby improving patient-related outcomes. For these patients, SFRT should be considered earlier in the treatment course, particularly for non-breast, non-prostate patients.

The limitations of our study include the size of our patient cohort and the short life expectancy of the patients included, which resulted in the inability for long-term follow-up data. Despite the shorter follow-up time, the findings of this study show potential clinical benefit with the use of RT in patients with femoral bone metastases. This short follow-up may also represent a more realistic treatment timeline and post treatment follow-up for patients with more aggressive cancers with shorter life expectancies. Another limitation of this study is that a subset of our patient underwent surgical fixation prior to RT (n=6), which could further dampen the actual effect of SFRT on pathologic fracture prevention. These patients all had high MBS scores (>10) and were at high risk for impending pathologic fracture. Elective fixation for impending pathologic fractures is generally preferred because it is less complex, reduces intense pain, and prevents loss of function (23). Lastly, the disproportionately higher number of patients with gastrointestinal malignancies compared to other malignancies like breast, prostate, RCC that may require more intensive therapies. The utilization and effectiveness of SFRT for fracture prevention should be explored further in patients with longer expected survival, possibly with a prospective or randomized trial.

Conclusions

Femoral bone metastases can be painful and can lead to bony instability if left untreated. Orthopedic surgery consultation should be initiated for MBS ≥8, however, a low percentage of poor prognosis patients undergo surgical intervention. The remainder subsequently present to the radiation oncology clinic where SFRT can be utilized even in patients with MBS of ≥8 based on our data. SFRT appears to potentially prevent femoral fractures and reduce pain in patients with short life expectancy with MBS ≥8. Further prospective, randomized studies are needed to establish long-term outcomes especially in patients with limited life expectancy and poor prognosis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tro.amegroups.com/article/view/10.21037/tro-22-40/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tro.amegroups.com/article/view/10.21037/tro-22-40/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board approval and informed consent was not required given this is a retrospective study with deidentified patient information.

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