Risk of Fracture After Single Fraction Image-Guided Intensity-Modulated Radiation Therapy to Spinal Metastases

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ABSTRACT

Purpose

Single-fraction image-guided intensity-modulated radiation therapy (IG-IMRT) allows for tumoricidal treatment of traditionally radioresistant cancers while sparing critical adjacent structures. Risk of vertebral fracture after IG-IMRT for spinal metastases has not been defined.

Patients and Methods

We evaluated 62 consecutive patients undergoing single fraction IG-IMRT at 71 sites for solid organ metastases. A neuroradiologist and three spine surgeons evaluated prospectively obtained magnetic resonance/computed tomography (CT) imaging studies for post-treatment fracture development and tumor recurrence.

Results

Fracture progression was noted in 27 vertebrae (39%). Multivariate logistic regression analysis showed that CT appearance, lesion location, and percent vertebral body involvement independently predicted fracture progression. Lesions located between T10 and the sacrum were 4.6 times more likely to fracture than were lesions above T10 (95% CI, 1.1 to 19.7). Lytic lesions were 6.8 times more likely to fracture than were sclerotic and mixed lesions (95% CI, 1.4 to 33.3). As percent vertebral body involvement increased, odds of fracture also increased. Patients with fracture progression had significantly higher narcotic use, change in Karnofsky performance score, and a strong trend toward higher pain scores. Local tumor progression occurred in seven patients and contributed to one fracture. Obesity, posterior element involvement, bisphosphonate use, and local kyphosis did not confer increased risk.

Conclusion

Vertebral fracture is common after single fraction IG-IMRT for metastatic spine lesions. Lytic disease involving more than 40% of the vertebral body and location at or below T10 confer a high risk of fracture, the presence of which yields significantly poorer clinical outcomes. These results may help clinicians identify high-risk patients who would benefit from prophylactic vertebro- or kyphoplasty.

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INTRODUCTION

The majority of patients who die from cancer have skeletal metastases; the spine remains the most common site of bony metastases in patients with disseminated disease and is a source of significant morbidity for patients.¹⁻³ With improving therapies and increasing life expectancies for patients with metastatic disease, effective palliative treatment of spinal metastases is an important clinical issue.

Local control of metastatic spine lesions is usually accomplished with radiation therapy, surgery, or a combination of both. Image-guided intensity-modulated radiation therapy (IG-IMRT) is a recently developed technique for delivery of radiation therapy.⁴ Using inverse planning algorithms and

micro-multileaf beam collimation, clinicians can deliver treatment in a stereotactic manner with a precision of ≤ 2 mm. The use of single-dose fractionation schemes can deliver tumoricidal doses to traditionally radioresistant cancers; recent results have demonstrated actuarial local control rates of $\geq 90\%$ using single-fraction IG-IMRT protocols to treat solid tumor metastases, without significant neural or systemic toxicity.⁵

The risk of vertebral fracture from metastatic disease is difficult to predict. A number of authors have performed biomechanical and clinical studies to estimate fracture risk from metastatic spine disease.^{2,6-10} However, we are unaware of any studies investigating the risk of vertebral fracture after either conventional or intensity-modulated radiotherapy. After observing

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Fig 1. A 66-year-old man with metastatic cholangiocarcinoma underwent 24 Gy single-fraction image-guided intensity-modulated radiation therapy (IG-IMRT) to a lytic lesion of T11 involving 40% of the vertebral body. (A) Pre-treatment computed tomography myelogram; (B) IG-IMRT treatment plan; (C) subsequent compression fracture imaged 12 months post-treatment.

several fractures after IG-IMRT treatment of spinal metastases in our practice, we sought to define the incidence and risk factors for vertebral fracture in a cohort of patients prospectively followed after undergoing single fraction IG-IMRT for solid organ metastases to the spine (Fig 1).

PATIENTS AND METHODS

This study was approved by the institutional review board at our institution. We identified all patients who had undergone single-fraction IG-IMRT for histologically confirmed solid tumor metastases. Patients with prior surgery or radiation therapy to the region of interest or high-grade epidural compression were excluded from this analysis. Decisions to treat with IG-IMRT were made by a multidisciplinary tumor board consisting of orthopedic and neurologic spine surgeons, neuroradiologists, physiatrists, and radiation oncologists. IG-IMRT treatment and delivery were carried out according to standard techniques as described in the literature.⁵ Treatment planning was carried out on in-house software with the planning treatment volume (PTV) receiving prescribed doses ranging from 18 to 24 Gy. The PTV never included the spinal cord and the maximal allowable spinal cord dose was limited to 12 to 14 Gy. Doses were prescribed to the 100% isodose line and the treatment plan was normalized to the 100% isodense line to maximize the percentage of the PTV that received 100% of the prescribed dose without exceeding the maximal allowable dose to the spinal cord or cauda equina.

Before treatment, all patients had spinal magnetic resonance imaging or computed tomography (CT) myelogram studies. Patients were examined clinically and radiographically 8 weeks post-treatment and at 3- to 4-month intervals thereafter on an institutional review board–approved treatment protocol until hospice admission or death. Imaging studies were reviewed in concert by three spine surgeons and one neuroradiologist using a digital computer workstation for image analysis. Percent vertebral body involvement was estimated using digital volume measurements. Percent vertebral body collapse was estimated by comparing the height of the body of interest after fracture to its pretreatment height or to the mean height of the bodies directly cephalad and caudal to the body of interest for those levels with fractures present at baseline. Lesions were classified as lytic, sclerotic, or mixed by their appearance on bone windows of CT scans. Vertebral body collapse, tumor volumes, and lesion classification were all agreed on by the four reviewers. Obesity was defined as a body mass index of ≥ 30 kg/m². Local kyphosis was measured using the Cobb angle between the levels directly cephalad and caudal to the area of interest. Bisphosphonate use within 6 months of treatment was recorded.

The primary outcome measure was development of a new fracture or progression of an existing fracture at the site of treatment (henceforth, fracture progression) obtained from prospectively obtained imaging. As an example, if a patient at the time of IG-IMRT had a vertebral body collapse deformity or end-plate infraction, the degree of this was recorded. On follow-up if the fracture or endplate infraction got any worse, it was then recorded as fracture progression. If no fracture was present at the time of IG-IMRT and an endplate infraction or collapse deformity subsequently developed, this was recorded as a new fracture. For tumor progression or local failure there was always un-

equivocal evidence by magnetic resonance imaging; worsening epidural or paraspinal disease and all cases of tumor progression were agreed on by the spine surgeons and neuroradiologist.

Secondary outcome measures, clinical details for which were obtained from the medical record, included pain (as measured on a 10-point scale); American Spinal Injury Association impairment scale (ASIA) assessment of neurologic function; Karnofsky performance score (KPS); and narcotic use and tumor recurrence.^{11,12}

Patient Population

The study included 71 treated lesions in 62 patients (24 women, 38 men). The mean patient age was 62 years and overall median follow-up was 13 months. At the time of analysis, 28 patients had died with a median interval of 10 months between treatment and death. The median follow-up time among patients who were alive at the time of analysis was 19 months. The median IG-IMRT dose was 24 Gy. Twenty-eight of 62 patients received bisphosphonate therapy within 6 months of vertebral IG-IMRT.

Review of CT scans showed that 46 disease sites were lytic (65%), 13 were sclerotic (18%), and 12 were mixed (17%). Six lesions were located in the cervical spine (9%), 47 in the thoracic spine (66%), and 18 in the lumbosacral spine (25%). Twenty-six lesions (37%) occupied 0% to 20% of the vertebral body, 18 lesions (25%) occupied 21% to 40%, 10 lesions (14%) occupied 41% to 60%, seven lesions (10%) occupied 61% to 80%, and 10 lesions (14%) occupied more than 80%. Common primary tumors included renal cell ($n = 14$), melanoma ($n = 9$), prostate ($n = 9$), and sarcoma ($n = 7$; Table 1).

Statistical Analysis

Two-sample comparisons were carried out using the Wilcoxon rank sum test for continuous and ordinal data and Fisher's exact test for binary data. In patients with at least 3 months of follow-up, hypothesis-driven multivariate logistic regression modeling was used to determine which factors were associated with fracture progression. The Hosmer and Lemeshow goodness-of-fit test was used to check the linearity assumption of the final model. Time-to-event analysis, which included all lesions, was carried out using the Kaplan-Meier estimation method of fracture probability. Stratified probability

Table 1. Primary Tumor Histologies

Tumor Histology	No.
Renal cell	14
Melanoma	9
Prostate	9
Sarcoma	7
Colorectal	6
Cholangiocarcinoma	5
Thyroid	5
Non small cell lung	5
Breast	4
Other	7

functions were compared using the log-rank test. Multivariate proportionate hazards regression modeling was used to determine which variables significantly altered time-dependent fracture probability. The proportional hazards assumption of the final model was tested quantitatively by rejecting the significance of time-varying coefficients and graphically by ensuring that the functions are parallel on the log-minus-log scale. In all statistical comparisons and models *P* values lower than .05 were considered significant.

RESULTS

Fracture progression was noted in 27 vertebral bodies (39%). Multivariate logistic regression analysis showed that CT appearance, lesion location, and the amount of vertebral body occupied by tumor independently predicted fracture progression. Lesions located between T10 and the sacrum were 4.6 times more likely to fracture than were lesions above T10 (95% CI, 1.1 to 19.7). Lytic lesions were 6.8 times more likely to fracture than were sclerotic and mixed lesions (95% CI, 1.4 to 33.3). As the amount of vertebral body occupied by tumor increased, the odds of fracture increased as well, with the exception of the 80% to 100% group (Table 2). However, since only three patients had lytic disease involving more than 80% of the vertebral body, drawing conclusions from this subset is difficult.

Median time to fracture was 25 months (Fig 2). Stratification of the lesions according to CT appearance resulted in significantly different fracture probability functions ($P < .002$). The median time to fracture in lytic lesions was 19 months, while the median time in sclerotic and mixed lesions was 32 months ($P < .05$; Fig 3). Stratification of the lesions according to location also resulted in significantly different fracture functions ($P < .02$), with lesions between T10 and the sacrum having a median time to fracture of 20 months and lesions located higher in the spine fracturing at a median time of 35 months ($P < .05$). Stratification according to the amount of the vertebral body occupied by the lesion also resulted in significantly different fracture probability functions ($P < .02$). In the multivariate proportional hazards regression model, only lytic appearance (hazard ratio [HR], 3.8; 95% CI, 1.3 to 11.4) and lesions that occupied 41% to 60% of the vertebral body (HR, 3.9; 95% CI, 1.1 to 14.2) were associated with a statistically significant increase in the HR (Table 2).

In all models, obesity, local kyphosis, bisphosphonate use, and IG-IMRT radiation dose were not associated with fracture progres-

Fig 2. Kaplan-Meier function of fracture progression probability.

sion. At baseline, 12 patients had endplate fractures and eight had mild compression fractures. The presence of a baseline fracture was not associated with new fracture development or progression.

Among the 13 lesions that were lytic on CT and occupied 41% to 80% of the vertebral body, 11 showed evidence of fracture progression (Table 3). In this group, the median time for fracture progression was 13 months.

At initiation of treatment, 54 patients were ASIA E, seven ASIA D, and one was ASIA C. Two patients improved their ASIA status (D to E) at final follow-up, and 19 decreased their status. The decrease in their ASIA status was often secondary to disease progression elsewhere in the spine. Fracture progression was not correlated with change in ASIA status ($P < .8$).

The median KPS at the time of treatment was 90% and at final follow-up was 80%. The median change in KPS among patients with fracture progression was 10% and 0% among patients without fracture progression ($P < .03$).

The median pain score in patients with fracture progression was 5, while the median score was 2 for those without fracture progression. The difference in pain scores showed a strong trend toward a statistically significant difference ($P < .051$). At final follow-up, 32 of 62 patients were using narcotics for pain control. Patients with fracture progression were significantly more likely to use narcotics than patients without (70% v 41%; $P < .03$).

Local tumor progression occurred in seven patients (11%) as detected by contrast-enhanced MR scans. In one patient, a new fracture appeared to be related to tumor progression. Fracture progression led to surgery in two patients and kyphoplasty in one. There was no clear correlation between histology and risk of fracture.

Table 2. Fracture Progression Ratios: Results of Multivariate Logistic and Proportional Hazards Models

Imaging Characteristic	Model			
	Multivariate Logistic		Proportional Hazards	
	Progression Ratio	95% CI	Progression Ratio	95% CI
TL/lumbar	4.6*	1.1 to 19.7		
Lytic, %	6.8*	1.4 to 33.3	3.8*	1.2 to 11.4
21-40	14.1*†	2.3 to 85.7	1.5†	0.4 to 5.2
41-60	21.5*†	1.6 to 295.2	3.9*†	1.1 to 14.2
61-80	64.1*†	3.6 to > 999.9	2.8†	0.7 to > 10.3
81-100	5.0†	0.5 to 46.6	0.8†	0.1 to 4.6

Abbreviation: TL, thoracolumbar.

* $P < .05$.

†Compared with the 0% to 20% reference group.

Fig 3. Kaplan-Meier functions of fracture progression probability stratified by computed tomography appearance of lesions.

Table 3. Risk of Fracture in Patients With Lytic Metastases

Vertebral Body Involvement (%)	New or Progressive Fracture		New or Progressive Fracture (%)
	No	Yes	
0-20	14	4	22
21-40	5	7	58
41-60	1	6	86
61-80	1	5	83
81-100	2	1	33

DISCUSSION

With increasing life expectancies and improving therapies for patients with metastatic disease, the incidence of spinal metastases can be expected to increase. Recent results from Patchell et al's¹³ prospective randomized study have caused fresh enthusiasm for the surgical treatment of select patients with metastatic disease. However, radiation therapy remains the dominant treatment modality for most patients in whom spinal metastases are identified before neurologic compression.

Pathologic compression fractures remain a clinical problem in patients with metastatic disease. Several authors have proposed clinical parameters that suggest impending fracture.^{2,6-10} For example, Taneichi and colleagues⁹ examined 100 untreated vertebrae in 53 patients by CT to identify factors associated with collapse. However, these patients were not observed clinically over time to ascertain the risk of fracture in a clinical context.

Radiation therapy is known to increase the risk of fracture in other areas of the skeleton. The risk of rib fracture is increased after radiation therapy for breast cancer, and a high risk of femur fracture has been identified after certain soft tissue resections in the thigh treated with adjuvant radiotherapy.^{14,15} Similarly, Ewing's sarcoma of bone treated with radiation rather than surgical resection has a significant risk of subsequent fracture.¹⁶

Little data exists on the risk of vertebral fracture after radiation therapy to the spine, however. In a prospective trial of conventional radiation therapy, Maranzano and Latini¹⁷ report that 31% of their patients had vertebral collapse. However, they do not report what percentage of patients had baseline fractures; the time to fracture development; or risk factors for or the clinical effect of these fractures. We are unaware of any study that has directly analyzed fracture risk in patients after either conventional or IMRT for spinal lesions.

This study is limited in that it involves a selected group of patients without prior surgical or radiation treatment to the region of interest. IG-IMRT doses varied from 18 to 24 Gy as part of a deliberate dose escalation scheme as our facility gained experience delivering single-fraction IG-IMRT. However, the risk of fracture progression was not associated with dose within this range. In addition, although imaging studies in this study were obtained per a defined protocol (eliminating the risk of selection bias inherent in imaging only clinically symptomatic lesions), data on pain scores, narcotic use, and KPS were obtained from the medical record. Our study lacks a direct control group, as we have no comparable population of

patients prospectively imaged who underwent either no treatment or conventional fractionated radiotherapy.

Despite these limitations, our study identifies a high risk of vertebral fracture after single-fraction IG-IMRT to spinal metastases. Excellent local tumor control was achieved despite a large number of patients with unfavorable histologies, and local failure appeared responsible for only one fracture event. Determining disease progression in the presence of fracture can sometimes be difficult though in our study only one patient had disease progression that was associated with a fracture. In this case, the increase in epidural and paraspinal soft tissue was greater than any changes related to just fracture; also follow-up imaging confirmed progression. Fracture progression in this series likely stemmed from the combined effects of local high-dose radiation delivery and the cumulative loading effect on structurally compromised bone. No patients reported discrete traumatic episodes related to their fractures. Variables such as obesity and increased kyphosis did not appear to increase the risk of fracture in these patients. Bisphosphonate use did not show any significance in our study group. However, dose and duration of bisphosphonates were not determined and the use of bisphosphonates in this patient population will have to be looked at more closely in the future.

The clinical outcome of patients without fracture progression was excellent. Although fewer than half were using any narcotic pain medicine, median pain score was two of 10. In contrast, patients with fracture progression were 1.7 times more likely to require narcotic pain medicine and had a strong trend toward higher pain scores (median, 5 of 10; $P < .051$). Patients with fracture progression also showed over twice as great a decrease in their KPS. Given that most palliative chemotherapy regimens require a minimum KPS for eligibility, this decrease can significantly affect patients' care. Fortunately, fracture progression did not portend a worse neurologic outcome.

Our data identify lytic disease, increasing involvement of the vertebral body, and location in the thoracolumbar or lumbar region as significant risk factors for fracture progression, similar to other authors'⁹ findings in static cross-sectional studies of untreated metastases. These findings have led to changes in our clinical practice in that we often intervene earlier with vertebral augmentation, kyphoplasty, or vertebroplasty with our group now planning a trial of prophylactic vertebral augmentation in high-risk patients undergoing single fraction IG-IMRT for vertebral metastasis from solid organ malignancies. Future studies of IG-IMRT may need to consider bone as a potential organ at risk for evaluating treatment toxicities.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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