Noninvasive Prediction of Fracture Risk in Patients with Metastatic Cancer to the Spine

Brian D. Snyder,1,2, Marsha A. Cordio,1, Ara Nazarian,1,3 S. Daniel Kwak,1 David J. Chang,1, Vahid Entezari,1 David Zurakowski,2 and Leroy M. Parker3

Abstract  
Purpose: Skeletal metastases affect up to 85% of breast cancer patients by the time of their death. This prospective in vivo study evaluated the diagnostic performance of computed tomography–based structural rigidity analysis (CTRA) to predict vertebral fracture risk in breast cancer patients with skeletal metastasis and in comparison with the current standard of care.

Experimental Design: Torso CT scans of 94 women with vertebral metastatic breast cancer were obtained as part of routine screening for lung and liver metastases. The load-bearing capacity (LBC) and axial (EA) and bending (EI) rigidities of vertebrae T8 to L5 were calculated from CT images. The LBC was normalized by patient body mass index (BMI) to account for height and mass variations. Vertebral fracture risk was also calculated using the current radiographic-based criteria based on lesion size and location. The actual occurrence of a new vertebral fracture was assessed radiographically over the ensuing 4 months.

Results: Eleven vertebral fractures occurred in 10 patients. The structural parameters EA, EI, LBC, and LBC/BMI were all 100% sensitive and 55%, 53%, 44%, and 70% specific to predict fracture risk, respectively. Although radiographic criteria correctly predicted all fracture cases (100% sensitive), only 48 of the 236 spinal segments that did not have a fracture were correctly predicted not to fracture (20% specific).

Conclusions: CTRA, using CT scans as part of routine screening for lung and liver metastasis, is shown to be as sensitive as, and significantly more specific than, the current radiographic criteria for predicting vertebral fracture in breast cancer patients with skeletal metastasis. (Clin Cancer Res 2009;15(24):7676–83)

Skeletal metastases occur in 65% of patients with breast cancer due to the overall high incidence and the relatively long clinical course of the disease (1). The spine is the most common site for skeletal metastasis in breast cancer patients (2). Of these patients, 17% to 50% sustain a vertebral fracture, resulting in pain, deformity, loss of mobility, and/or paralysis (3, 4). Although much has been learned about the mechanisms of metastasis of cancer to the spine, little headway has been made in the past 25 years to establish guidelines to estimate fracture risk associated with spinal metastasis or monitor the response of a specific bone defect to treatment (5). Currently, clinicians make subjective assessments about fracture risk on plain radiographs using guidelines now recognized to be inaccurate (6).

Systemic treatment with cytotoxic agents, hormone manipulation, bisphosphonates, and/or local treatment with radiation and/or surgical stabilization constitutes the range of therapies available to breast cancer patients with skeletal metastases (7–10). However, there are no objective methods for selecting which treatment will best reduce the patient’s risk for sustaining a pathologic fracture and for monitoring the patient’s response to therapy. Our goal is to establish objective criteria for evaluating the load-bearing capacity (LBC) of involved vertebrae that can be used both to monitor changes in the bone structure that reflect the interaction of the tumor with the host bone and to guide treatment for fracture prevention.

Anatomic site, lesion type (lytic, blastic, or mixed), size, geometry, presence of pain, patient age, and activity level have all been shown to be predictors of fracture risk in retrospective clinical studies (11–13). However, although pain is the most common presenting symptom of a skeletal metastasis, it is not always present (14), may be unrelated to the metastatic cancer (e.g., degenerative disc disease and facet arthropathy), and is not a reliable indicator of imminent vertebral fracture (15).

Skeletal metastases are most often diagnosed using plain radiographs of the spine. Investigators have estimated vertebral
Lesion size has most often been used as a predictor of vertebral fracture risk in patients with osteolytic metastases to the spine, but this parameter only accounts for 50% of the variation in vertebral body strength. A method for predicting fracture risk in breast cancer patients with spinal metastases has been developed using structural rigidity load-bearing capacity, which uses computed tomography scans of the torso obtained as part of routine screening for lung and liver metastases. We have shown in an in vivo study that this approach is as sensitive and more specific than the current empirically derived fracture risk predictions based on lesion. Improved specificity is clinically important because patients who are not at imminent risk of fracture might be safely treated noninvasively by chemotheraphy alone, and those with moderate fracture risk might be treated using minimally invasive stabilization techniques such as vertebroplasty, whereas patients at high fracture risk might require extensive surgical stabilization with instrumentation or intercalary replacement. Therefore, an accurate, cost-effective, noninvasive, and objective method to assess fracture risk in patients with spinal metastases will allow clinicians to select the most appropriate treatment for a particular patient and monitor their treatment response with confidence.
applied load for the vertebra with metastatic lesion exceeded the CTRA-generated failure load were considered at high risk for fracture. Vertebral fracture risk was also estimated from the size, location, and spine level of the metastatic lesion assessed on transaxial CT images of the spine using Taneichi et al. (22) empirically derived multivariate logistic regression analysis. The occurrence of a new vertebral fracture was assessed radiographically over the ensuing 4 mo based on the consensus opinion among orthopedic oncologists at the Harvard affiliated hospitals (Drs. Henry Mankin, Mark Gebhardt, Dempsey Springfield, and John Ready) that tumor-host bone interactions change significantly after 4 mo. The sensitivity and specificity of CTRA and the empirically derived fracture risk predictions for the occurrence of a new vertebral fracture were compared.

Patient cohort. Medical records of 1,024 female breast cancer patients (age, 28-77 y) at Dana-Farber Cancer Institute were reviewed to identify patients who met the study eligibility criteria. The general exclusion criteria consisted of (a) neural compromise due to metastasis in the brain or spinal cord; (b) patient withdrawal, relocation, or death; (c) history of previous fracture at the site of metastasis or adjacent vertebrae; (d) surgical treatment for impending fracture; and (e) fractured bones due to significant trauma (traffic accident or fall from height >0.5 m). Because this study was observational, the oncologists were unaware of our analysis and could not use the information to influence their treatment. Patients continued their medical treatment and were not asked to modify their activity level. Several oncologists instructed their patients with significant osteolytic lesions to restrict their activity based on their own clinical interpretation of the CT scans to minimize the risk of a pathologic spine fracture. All patients were asked to complete the standard outcomes instrument Short Form 36 and the Oswestry back pain disability questionnaire to provide information on how patients were affected by the presence of spinal metastases.

Clinical assessment of vertebral fracture. To assess the accuracy of the current standard of care and the proposed methods for predicting vertebral fracture, it was necessary to determine the prevalence of vertebral fractures in patients over a 4-mo surveillance period. Because pain is not considered a good surrogate for vertebral metastasis and subsequent fracture risk (29), fracture occurrence was defined according to commonly used criteria for osteoporotic vertebral fractures (30). Vertebral heights were measured on all patients from plain radiographs and/or magnetic resonance imaging scans that included part or all of the spinal column. Wedge fractures were diagnosed by detection of a 15% loss of height from one side of the vertebrae compared with the other in either the frontal or sagittal planes. Axial compression fractures were diagnosed by detection of a 15% loss of vertebral height compared with adjacent vertebrae. An independent radiologist, unaware of the fracture risk predictions of the patients and blinded to the clinical outcomes, reviewed all plain radiographs and magnetic resonance imaging scans.

Calculation of fracture risk using standard of care radiographic criteria. Vertebral fracture risk was estimated from the size and location of the lesion and the vertebral level using Taneichi et al. (22) empirically derived multivariate logistic regression analysis. All serial transaxial CT images were reviewed by an orthopedic surgeon, a resident orthopaedic physician, and a biomedical engineer trained in application of a semi-automated segmentation algorithm to define the extent of the osteolytic defect relative to the host bone and the location of the defect within the vertebra. Four factors were combined to assess the risk of a vertebral
Fracture Risk Prediction in Patients

Fracture: (a) percentage of tumor occupancy in the vertebral body, (b) destruction of the pedicle, (c) destruction of posterior elements excluding the pedicles, and (d) destruction of the costovertebral joint (thoracic vertebrae T1-T10 only). The probability of fracture for T1 to T10 spine segments was calculated as follows:

\[
\text{Prob} (T) = \frac{\exp(\lambda T)}{1 + \exp(\lambda T)}
\]  

where \(\lambda T = 0.089x_1 + 0.546x_2 + 0.161x_3 + 2.319x_4 - 4.597\), and for spine segments T11 to L5 as follows:

\[
\text{Prob} (L) = \frac{\exp(\lambda L)}{1 + \exp(\lambda L)}
\]  

where \(\lambda L = 0.147x_1 + 5.694x_2 - 3.609x_3 - 5.492\), \(x_1 = \) percentage of tumor occupancy in the vertebral body, \(x_2 = \) destruction of the pedicle (0 = intact, 1 = involved), \(x_3 = \) destruction of the posterior elements except the pedicle (0 = intact, 1 = involved), and \(x_4 = \) destruction of the costovertebral joint (0 = intact, 1 = involved; ref. 22). The assignment of values to the binary questions above was operator dependent; however, the operators' responses were not different form one another for each question (\(P > 0.05\) for all cases). Here, \(\exp\) denotes the base of the natural logarithm, \(\approx 2.71\).

Calculation of fracture risk using structural rigidity analysis. The EA and EI rigidities for each vertebra were calculated on each transaxial CT image through the vertebra using CTRA (Fig. 3A) by a trained biomedical engineer. Assuming that the vertebra will fracture at its weakest cross-section, the capacity of each vertebra to support combined flexion and compression (the most common mechanism of pathologic vertebral fractures; ref. 31) was determined from the minimal EA and EI calculated for each vertebra using composite beam theory where the spine was modeled as a beam loaded in combined axial compression and forward bending (Fig. 3B). To simplify the analysis, the vertebral CT images for each patient were segmented into four groups according to biomechanical loading zones (4): group 1 = thoracic vertebrae proximal to T8 forming the thoracic kyphosis; group 2 = the transitional thoraco-lumbar region spanning T9-L1, where the rib cage provides less anterior structural support; group 3 = the straight lumbar region spanning L2-L4; and group 4 = the lordotic lumbosacral region (15).

The failure analysis using composite beam theory with CT-derived measures of structural rigidity to determine the LBC of a vertebra has previously been validated in vitro using cadaver spines with simulated lytic defects (26). Assuming that each vertebra behaves mechanically as a short beam subjected to combined axial compression and forward bending, the LBC of the vertebra can be derived as follows.

The resultant strain at the anterior vertebral body as a result of an applied axial compressive load in combination with a flexural bending moment is given by the following equation:

\[
\varepsilon = \frac{F_a}{E_A} + \frac{M_c}{E_I}
\]  

where \(\varepsilon\) is the strain at the anterior vertebral body, LBC is the axial compressive load, EA is the EA rigidity, \(M_c\) is the applied bending moment, \(c\) is the radial distance of the anterior vertebral body from the neutral bending axis of the vertebra, and EI is the EI rigidity. A strain-based failure criterion was used to estimate the LBC of each vertebra. Because bone fails at a constant strain of 1% independent of bone density, it was assumed that \(\varepsilon = 1\%\) in Eq. C.

The density \((\rho)\) of each pixel corresponding to bone was calculated from the CT images using the hydroxyapatite calibration phantom to convert CT Hounsfield units to equivalent bone density. The modulus of elasticity for trabecular bone was derived (32):

\[
E_A = \int E(\rho)\,da
\]  

and the modulus for cortical bone was derived (33):

\[
E(\rho) = 21.91 \times \rho - 23.5
\]  

where the transition from trabecular bone to cortical bone was assumed to occur at an apparent density of 1.1 g cm\(^{-3}\). EA and EI rigidities were calculated using the following equations:

\[
E_A = \int E(\rho)\,da
\]  

and

\[
E_I = \int E(\rho)\,x^2\,da - EAX^2
\]  

where \(x\) = distance to neutral axis, \(da\) = pixel area, and \(X\) = coordinate of the modulus weighted centroid, which is also assumed to be the location of the neutral bending axis of the vertebra.

The applied bending moment at yield, \(M_p\), was assumed to be a function of LBC and therefore was described as follows:

\[
M_p = F_2\,a
\]  

where \(a\) = the distance from the neutral axis to the point of load application at the center of the vertebral body (Fig. 2).

The LBC of the spine to support combined axial compression and forward bending was then determined:

\[
F_2 = \frac{0.01}{B + 0.5}\]
Results

Ninety-four patients (mean age, 55 years) with radiographically evident spinal metastasis met inclusion criteria. Serial transaxial CT scans of their spine provided 247 vertebrae that were analyzed to determine fracture risk. Fifty-one percent of the patients included in this cohort were postmenopausal, many exhibiting coexistent osteopenia that could potentially influence the risk of a vertebral fracture independent of the size and location of the osteolytic lesion. Eleven new vertebral fractures were diagnosed over the 4-month follow-up period in 10 separate patients (~11% of patients). All fractures occurred in the thoracolumbar spinal segment T9 to L1 (Table 1).

All 11 new vertebral fractures were correctly predicted to fracture (100% sensitive) using the Taneichi fracture criteria. Because semiautomated segmentation algorithms were used, there was little variability among reviewers on percentage lesion occupancy or the location of the osteolytic lesion (100% concordance). However, the Taneichi probability models predicted fracture in 188 of the 236 nonfractured vertebrae (80% false positive). Only 48 of the 236 vertebrae that did not fracture were correctly predicted not to fracture (20% specific). These two ratios (11 of 11 versus 188 of 236) were not significantly different based on a two-sample Fisher's exact test (P = 0.13), underscoring the lack of predictive discrimination for the Taneichi probability models.

All 11 vertebral fractures were correctly predicted (100% sensitive) using each of the CTRA-derived variables: EA, EI, LBC, and LBC/BMI. However, of the 236 vertebrae that did not fracture, 129, 125, 103, and 162 were correctly predicted not to fracture using each of the CTRA-derived variables: EA (55% specific), EI (53% specific), LBC (44% specific), and LBC/BMI (70% specific), respectively. The specificity of all the CTRA-derived variables was significantly better (P < 0.001) than the specificity of the Taneichi probability models (Table 2) using Fisher's exact test. Moreover, vertebral fracture risk predictions using the Taneichi probability models were not different from chance (P = 0.25), whereas fracture risk predictions for each of the CTRA-derived variables were significantly different (P < 0.002) from chance (Fig. 4A).

The estimated probability of sustaining a vertebral fracture was inversely related to LBC/BMI (Fig. 4B). Specifically, the lower the normalized vertebral LBC, the higher the vertebral fracture risk. For instance, a woman with BMI of 22 and a vertebral LBC of 132 N (30 lbs) has a 50% risk of sustaining a vertebra fracture (LBC/BMI = 132/22 = 6), whereas a woman with BMI of 22 and a vertebral LBC of 440 N (99 lbs) has a 25% risk of sustaining a vertebral fracture (LBC/BMI = 440/22 = 20). The

Table 1. Distribution of spinal segments included in the study

<table>
<thead>
<tr>
<th>Group</th>
<th>Vertebral level</th>
<th>No. involved</th>
<th>No. fractured</th>
<th>Percentage fractured</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T8</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>T9-L1</td>
<td>93</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>L2-L5</td>
<td>82</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>L5</td>
<td>39</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>T8-L5</td>
<td>247</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2. Sensitivity and specificity details for all fracture prediction models used in this study

<table>
<thead>
<tr>
<th>Model</th>
<th>Cutoff value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>CI of AUC (m²)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC</td>
<td>—</td>
<td>100</td>
<td>20</td>
<td>0.60</td>
<td>0.46</td>
<td>0.74</td>
</tr>
<tr>
<td>LBC (N)</td>
<td>1,607.5</td>
<td>100</td>
<td>44</td>
<td>0.82</td>
<td>0.73</td>
<td>0.91</td>
</tr>
<tr>
<td>EI (N·m²)</td>
<td>154,640.5</td>
<td>100</td>
<td>53</td>
<td>0.80</td>
<td>0.72</td>
<td>0.89</td>
</tr>
<tr>
<td>EA (N)</td>
<td>726.0</td>
<td>100</td>
<td>55</td>
<td>0.77</td>
<td>0.68</td>
<td>0.87</td>
</tr>
<tr>
<td>LBC/BMI (N·kg·m⁻²)</td>
<td>46.5</td>
<td>100</td>
<td>70</td>
<td>0.84</td>
<td>0.78</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; CI, confidence interval; RC, radiographic criteria.
wide 95% confidence interval at the lower range of the LBC/BMI values is due to the small number of patients in the study who actually suffered a vertebral fracture.

**Discussion**

The skeleton is the third most common site of metastatic cancer, and a third to half of all cancers metastasize to the skeleton (38). Clinicians make subjective assessments about fracture risk based on clinical and radiographic guidelines now recognized to be inaccurate (6). Lesion size has most often been used as a predictor of vertebral fracture risk in patients with osteolytic metastases to the spine, but this parameter only accounts for 50% of the variation in vertebral strength (20, 21, 39). The risk that a vertebra will fracture depends on the reduction in the LBC of the vertebra as a consequence of metastatic cancer, the "quality" of the host bone, and the loads applied to the spine. Many cancer patients with spinal metastases are postmenopausal women with coexistent osteoporosis (40, 41) or premenopausal women who develop osteoporosis as a consequence of hormone manipulation and chemotherapy used to treat their cancer (42). The osteoporotic bone comprising the vertebra put these patients at an increased risk for sustaining a vertebral fracture independent of the size and/or location of the osteolytic lesion. A smaller metastatic lesion may have greater potential for precipitating a fracture in the vertebra of an osteoporotic female compared with the same-sized lesion in a non-osteo- porous patient (42). Further complicating the relationship between lesion size and material properties is that metastatic tumors can also form mixed osteoblastic-lytic lesions.

Preventing fragility fractures due to skeletal metastasis depends on objective criteria for evaluating changes in bone structure that reflect the interaction of the tumor with the host bone. The LBC of a bone depends on the geometry, location, and biological activity of the metastatic tumor and the geometry and material properties of the host bone. To this end, we developed a method to predict the fracture risk associated with vertebral metastases by calculating the cross-sectional structural rigidity and LBC of affected vertebrae from serial transaxial CT images that incorporate both the bone tissue material and the geometric properties of the metastatic tumor and host bone. We showed that predicting vertebral fractures in breast cancer patients with spinal metastases using structural engineering analysis to calculate the LBC of affected vertebrae from CT scans of the torso obtained as part of routine screening for lung and liver metastases was as sensitive as an empirically derived logistic regression model based on the size and location of spinal metastases in breast cancer patients with a pathologic spine fracture but was significantly more specific as to which patients would not sustain a spine fracture. Whereas both CT-based methods were 100% sensitive for predicting a pathologic vertebral fracture, the normalized vertebral LBC was 70% specific compared with the Taneichi fracture probability model, which was only 20% specific. Improved specificity is clinically important because patients not at imminent fracture risk might be safely treated by chemotherapy and/or radiation therapy, whereas patients at moderate fracture risk might be treated using minimally invasive stabilization techniques such as vertebroplasty, and patients at high fracture risk might require extensive surgical stabilization with instrumentation and intercalary replacement. Therefore, our CT-based analysis provides an accurate, objective, accessible, and cost-effective method to assess fracture risk in patients with spinal metastases that will allow clinicians to select the most appropriate treatment for a particular patient and to monitor the response to treatment with confidence.

Great care was taken in designing this study to avoid biasing the results in our favor. Patients with a history of a previous vertebral fracture were eliminated because it is well known that...
the risk of these patients sustaining a subsequent vertebral frac-
ture is significantly increased (43). This was conducted as an
observational study; the treating oncologists were unaware of
our analysis and could not use the information to influence
their treatments. Patients continued their medical regimens
and were not asked to modify their activities. Several oncolo-
gists instructed their patients with significant osteolytic lesions
to restrict their activity based on their own clinical interpreta-
tion of the CT scans so as to minimize the risk of a pathologic
spine fracture. Therefore, patients abstained from activities such
as lifting a heavy object, which may have negatively biased our
analysis and decreased the number of vertebral fractures that
occurred. By way of comparison, in another in vivo study using
our CTRA, we correctly predicted the occurrence of long bone
fractures in children with benign tumors of the appendicular
skeleton (44), with 100% sensitivity and 94% specificity; how-
ever, none of these children were aware of the presence of their
tumor and as such did not alter their physical activities. Thus, in
spite of optimal medical management and activity restriction,
there was still a 10% vertebral fracture incidence over the
4-month observation period.

This was the first in vivo study of its kind using a robust struc-
tural engineering analysis that accounts for changes in both
bone geometry and bone material properties (45) to predict
noninvasively the occurrence of new vertebral fractures in pa-
tients with skeletal metastases. With the emergence of powerful
computers, it is now feasible to create patient-specific virtual
three-dimensional models of affected bones from CT images
and use finite element analysis to estimate the LBC of affected
bones for specific load configurations (44–48). The CT-based
finite element methods have the potential to directly account
for changes in bone quantity, the wide distribution in bone
material properties, and the wide range of loading conditions.
Typically affected bones are modeled from serial CT images
using either voxel-based (46) or surface meshing (47) techni-
ques. Although voxel-based models are technically easier to
generate, errors in the integrity of the reconstructed bone sur-
face affect calculated surface strains (48).

Most work to date has relied on comparing finite element
analysis with ex vivo experiments where the physical model
and loading conditions are well controlled (49). Previous re-
search studies are also limited in that the bone models use sim-
ulated defects that do not accurately represent tumor-induced
osteolysis. Osteolytic tumors are associated with considerable
trabecular bone loss before cortical bone loss; these situations
are difficult to simulate in cadaveric bone.

The wide spread use of this advanced analytic technique is
limited in the clinical setting by the requirement for sophisticated
operator input to generate and refine patient-specific virtual bone
models and evaluate resultant stresses and strains; the need for
special image analysis software to automatically generate the finite
element mesh used to model the bone; and the necessity for
powerful computers to run these computationally intensive fin-
ite element models. In comparison, CTRA requires no subject-
ive input from the operator; the analysis takes 2 to 4 hours per
patient to calculate the LBC of affected vertebrae (depending
on the number of lesions and alignment of the transaxial CT images
relative to the vertebral bone axis) and the program can be run on
any laptop computer.

Preventing fragility fractures is an important component of
managing patients with skeletal metastases. The dilemma for
the oncologist responsible for treating these patients is to de-
cide whether a metastatic tumor has weakened the bone suffi-
ciently such that a fragility fracture is imminent. The present
study constitutes a training set. The "cutoff values" established
in this study for the significant predictors of vertebral fracture
need to be validated in a new cohort of women with metastatic
breast cancer to the spine to determine if our CT-based struc-
tural engineering variables can accurately predict vertebral
fractures in another group of patients. To this end, the authors
are currently conducting a multicenter study at 10 centers
across the country to validate that CTRA can prospectively
predict the occurrence of a new vertebral fracture in patients
with spinal metastases. Completion of this prospective study
will then establish CTRA as an accurate, cost-effective, non-
invasive method to assess fracture risk, to select treatment
based on the relative fracture risk, and to monitor treatment
response.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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