

# Clinical Cancer Research



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

Brian D. Snyder, Marsha A. Cordio, Ara Nazarian, et al.

*Clin Cancer Res* 2009;15:7676-7683. Published OnlineFirst December 8, 2009.

**Updated Version** Access the most recent version of this article at:  
doi:[10.1158/1078-0432.CCR-09-0420](https://doi.org/10.1158/1078-0432.CCR-09-0420)

**Cited Articles** This article cites 41 articles, 8 of which you can access for free at:  
<http://clincancerres.aacrjournals.org/content/15/24/7676.full.html#ref-list-1>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, contact the AACR Publications Department at [permissions@aacr.org](mailto:permissions@aacr.org).

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

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

**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

**Authors' Affiliations:** <sup>1</sup>Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center, <sup>2</sup>Departments of Anesthesia and Orthopaedic Surgery, Boston Children's Hospital, and <sup>3</sup>Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts  
Received 2/20/09; revised 9/14/09; accepted 9/15/09; published OnlineFirst 12/8/09.

**Grant support:** NIH grant CA40211 and Susan Komen Foundation.  
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

**Requests for reprints:** Brian D. Snyder, Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, RN115, Boston, MA 02215. Phone: 617-667-2940; Fax: 617-667-7175; E-mail: bsnyder@bidmc.harvard.edu.

© 2009 American Association for Cancer Research.  
doi:10.1158/1078-0432.CCR-09-0420

## Translational Relevance

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 chemotherapy  $\pm$  radiation therapy, and patients at 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  $\pm$  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.

fracture risk based on the size and geometry of an osteolytic lesion (16). However, 30% to 75% of the bone must be destroyed before an osteolytic lesion is detectable on a plain radiograph (17, 18), and because bone strength varies as the square of bone density (19), the strength of the affected bone is already reduced 50% to 90% by the time the metastasis is evident radiographically. The relative size of the lesion is also most often used to predict vertebral fracture risk, but this has been shown to account for only 50% of the variation in vertebral body strength (20, 21).

Fracture predictions have been established empirically based on retrospective review of patients with spinal metastases that fractured using multivariate logistic regression analysis to estimate the risk of a vertebral fracture as a function of the size and the location of the lesion within the vertebra. After retrospective review of 100 breast cancer patients with vertebral metastases that fractured, Taneichi et al. (22) used transaxial computed tomography (CT) images through affected vertebrae to establish the probability that a vertebra containing an osteolytic metastasis involving at least 25% to 45% of its cross-section would fracture depending on the type of vertebra (thoracic versus lumbar), percent tumor occupancy, and the location of the osteolytic lesion within the vertebra relative to the anatomic structures that conferred the mechanical properties of the vertebra.

The risk that a vertebra will fracture depends on the reduction in the LBC of the bone as a consequence of metastatic cancer, the "quality" of the host bone, and the loads applied to the bone (23). The LBC of a vertebra depends on its structural properties, which are determined by the geometry, location,

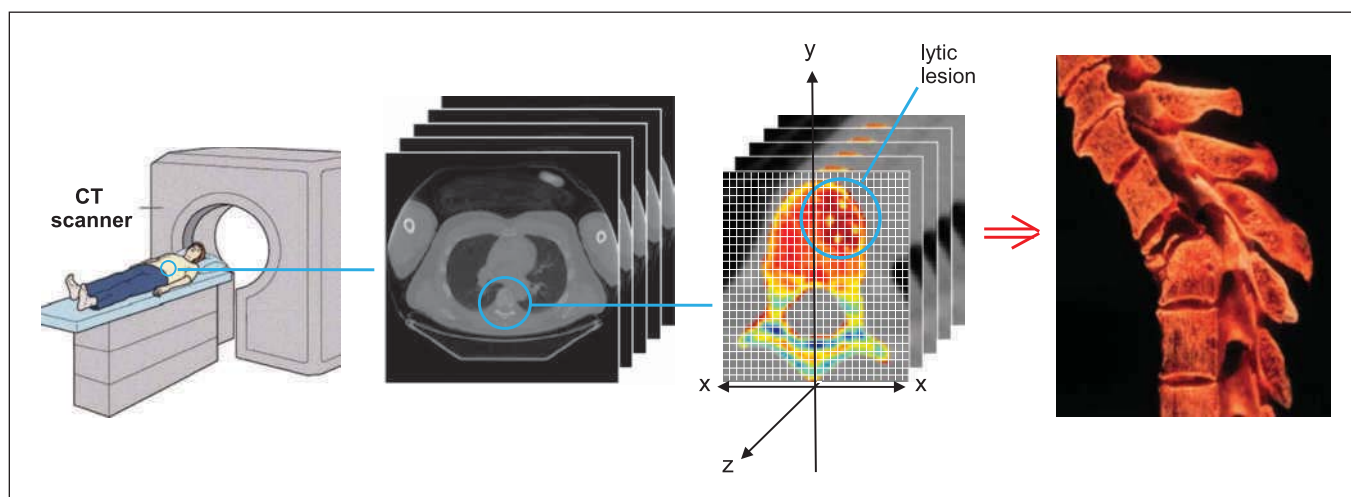
and biological activity of the tumor and the geometry and material properties of the host bone. Metabolic bone diseases such as osteoporosis (which can be coexistent) and metastatic cancer alter both bone tissue material and geometric properties; failure to account for changes in both of these parameters limits the accuracy of fracture risk predictions. The increased fragility associated with osteolytic metastases suggests that the strength of the tissue comprising the tumor and surrounding bone is degraded and/or the stresses within the bone under applied loads are increased because of changes in bone geometry. Thus, any method that predicts fracture risk must be able to measure both changes in bone material behavior (by monitoring bone density) and changes in bone structural geometry (by monitoring cross-sectional area and moment of inertia). Rigidity, the product of bone tissue modulus and geometry, is the structural property that reflects the resistance of the vertebra to axial (EA), bending (EI), or torsional loads (24).

Therefore, we have developed and validated a CT-based method to predict the fracture risk associated with osteolytic vertebral lesions by calculating the cross-sectional structural rigidity of affected bones (Fig. 1; ref. 25). In a series of *ex vivo* studies, we previously showed that the force required to fracture a bone with a simulated lytic lesion was proportional to the structural rigidity of the "weakest" cross-section through the affected bone (26, 27). Subsequently, we used our CT-based, structural rigidity analysis *in vivo* to evaluate fracture risk in children and young adults with a variety of benign skeletal neoplasms. In this pediatric cohort, the reduction in EI and torsional rigidity calculated from transaxial CT images through affected bones was significantly more accurate (97%) for predicting pathologic fracture compared with fracture predictions based on the relative size of the lesion measured on plain radiographs (42-61%; ref. 28).

The objective of this study was to test the hypothesis that CT-based structural rigidity analysis (CTRA) is as sensitive as, and significantly more specific for predicting vertebral fractures in breast cancer patients with spinal metastases than, the currently used empirically derived fracture risk predictions based on the size and location of the lesion.

## Materials and Methods

**Study design.** This prospective observational study compared the diagnostic performance of CTRA for predicting the occurrence of a new vertebral fracture in patients with metastatic breast cancer to an empirically derived logistic regression analysis based on the size and location of vertebral metastases observed on transaxial CT images of the spine. After receiving Investigational Review Board approval, the medical records of breast cancer patients from Dana-Farber Cancer Institute (Boston, MA) were screened to identify female patients with skeletal metastasis and no prior history of a spine fracture. The Investigational Review Board allowed us to evaluate serial transaxial CT scans of the torso in women with metastatic breast cancer obtained as part of routine screening for lung and liver metastases for the presence of spinal metastases. These CT scans included thoracic and lumbar vertebrae from at least T8 to L5. A hydroxyapatite phantom (CIRS, Norfolk, VA) was included with each scan to convert X-ray attenuation (Hounsfield units) to equivalent bone mineral ash density ( $\text{g cm}^{-3}$ ; Fig. 2). The density-weighted centroid and moment of inertia was calculated for each of the serial transaxial cross-sections through the vertebra and the minimal EA and EI rigidities determined for that vertebra. The LBC of the vertebra in combined axial compression and forward bending was derived from the minimal EA and EI rigidities using composite beam theory. All cases in which the simulated



**Fig. 1.** A schematic diagram highlighting the steps from patient CT imaging to structural rigidity analysis to assess fracture risk. The CTRA method has several important clinical implications. The LBC of a patient with metastatic disease to the spine can be used to determine if a patient is at risk for fracture during specific activities. If a patient is determined to be at high fracture risk, surgery can be considered to stabilize the spine. If the fracture risk is borderline, the clinician might advise the patient to alter his/her activity level. The analysis can be repeated on a periodic basis to determine if the vertebra is responding to various treatment modalities.

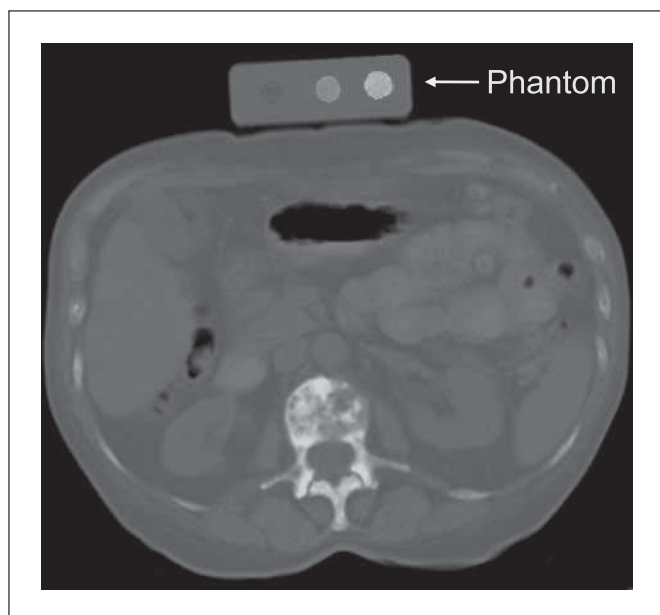
applied load for the vertebra with metastatic lesion exceeded the CTRA-generated failure load were considered at high risk for fracture. Vertebral fracture risk was also estimated from the size, location, and spine level of the metastatic lesion assessed on transaxial CT images of the spine using Taneichi 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.

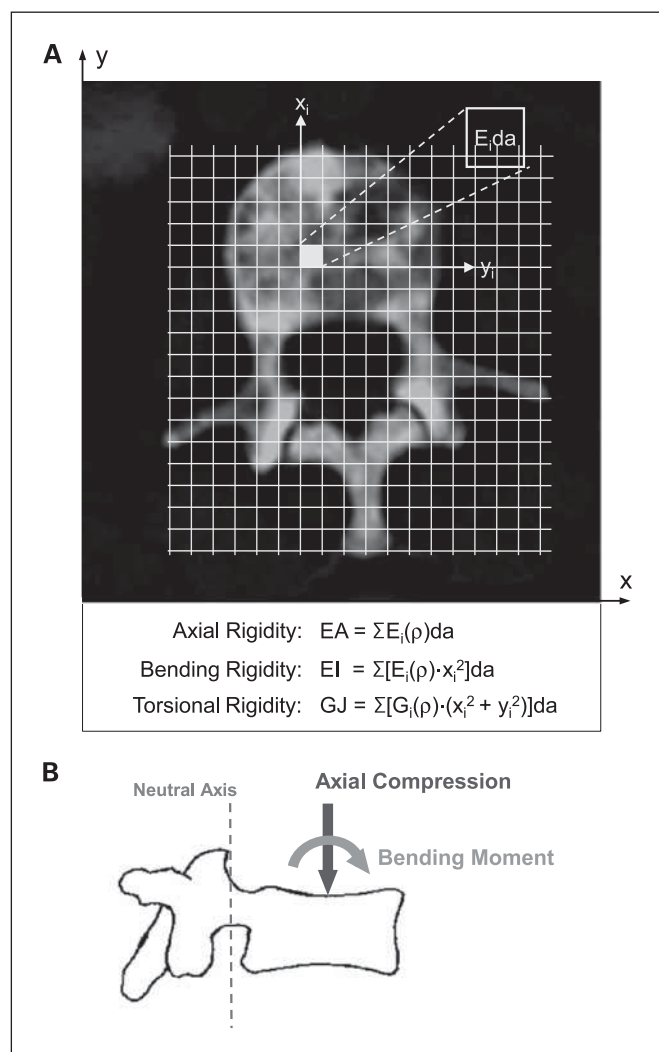
**Clinical assessment of vertebral fracture.** To assess the accuracy of the current standard of care and the proposed methods for predicting vertebral fracture, it was necessary to determine the prevalence of vertebral fractures in patients over a 4-mo surveillance period. Because pain is not considered 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



**Fig. 2.** CT slice of a torso with density conversion phantoms.





**Fig. 3.** A, a schematic overview of composite beam theory used in CTRA to assess EA, EI, and torsional rigidities. B, modeling of a vertebra as a beam loaded in axial compression and forward bending.

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:

$$\text{Prob}(T) = \exp^{(\lambda T)} / \{1 + \exp^{(\lambda T)}\} \quad (\text{A})$$

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:

$$\text{Prob}(L) = \exp^{(\lambda L)} / \{1 + \exp^{(\lambda L)}\} \quad (\text{B})$$

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 from one another for each question ( $P > 0.05$  for all cases). Here, exp denotes the base of the natural logarithm,  $\sim 2.71$ .

**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 [group 1 = thoracic vertebrae proximal to T8 forming the thoracic kyphosis; group 2 = the transitional thoracolumbar 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 (L5)].

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:

$$\varepsilon = \frac{F_z}{EA} + \frac{M_y c}{EI} \quad (\text{C})$$

where  $\varepsilon$  is the strain at the anterior vertebral body, LBC is the axial compressive load, EA is the EA rigidity,  $M_y$  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):

$$EA = \int E(\rho) da \quad (\text{D})$$

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

$$E(\rho) = 21.91 * \rho - 23.5 \quad (\text{E})$$

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

$$EA = \int E(\rho) da \quad (\text{F})$$

and

$$EI = \int E(\rho) x^2 da - EAX^2 \quad (\text{G})$$

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,  $M_y$ , was assumed to be a function of LBC and therefore was described as follows:

$$M_y = F_z a \quad (\text{H})$$

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:

$$F_z = \frac{.01}{\frac{ca}{EI} + \frac{1}{EA}} \quad (\text{I})$$

**Table 1.** Distribution of spinal segments included in the study

Group	Vertebral level	No. involved	No. fractured	Percentage fractured
1	T8	33	0	0
2	T9-L1	93	10	11
3	L2-L5	82	1	1
4	L5	39	0	0
Total	T8-L5	247	11	4

**Data and statistical analysis.** The EA and EI rigidities and flexion-compression LBC represent the ability of the vertebra to remain intact during specific loading conditions. Therefore, these variables were considered as potential predictors of fracture in these patients. LBC, EA, EI, and the flexion-compression LBC normalized by body mass index (LBC/BMI) were calculated for each spinal segment, and the maximum value of each variable among fracture cases was considered as the threshold value for predicting fracture risk. Values less than the threshold were considered to fracture and values greater than the threshold were predicted not to fracture. Sensitivity (ability of the model to correctly classify vertebrae that will fracture) of each model was set at 100%. These predictions were compared with the clinical occurrence of fracture at 4 mo, and sensitivity and specificity of the two models were compared. Sensitivity and specificity were calculated for EA, EI, LBC, LBC/BMI, and the Taneichi fracture criteria using standard formulas for decision making (34). Fisher's exact test was used to compare sensitivity and specificity results between the radiographic fracture criteria and other predictive variables, such as LBC/BMI. Receiver operating characteristic curve methodology using a binormal model was applied to determine the area under the curve for predicting spinal fracture based on radiographic criteria, EA, EI, LBC, and LBC/BMI, which provided the optimal diagnostic performance among the predictor variables analyzed (35). We chose to use a binormal model because it has the advantage of incorporating covariates into the analysis and provides a more precise estimation of the area under the curve (36). Logistic regression analysis with generalized estimating equations strategy was used to establish the probability of fracture with a 95% confidence interval according to LBC/BMI to take into account the multiple spinal segments from the same individual patient (i.e., correlated data) with significance assessed by the Wald  $\chi^2$  test (37).

Statistical analysis was done using the Statistical Package for the Social Sciences software package (version 16.0; SPSS, Inc.). Two-tailed values of  $P < 0.05$  were considered statistically significant. Power analysis indicated that a minimum of 10 fractures among the study patients would provide 80% power to detect odds ratio of 2.5 using radiographic and quantitative CT-based variables between patients who fractured based on logistic regression analysis (version 7.0; nQuery Advisor, Statistical Solutions).

## 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.

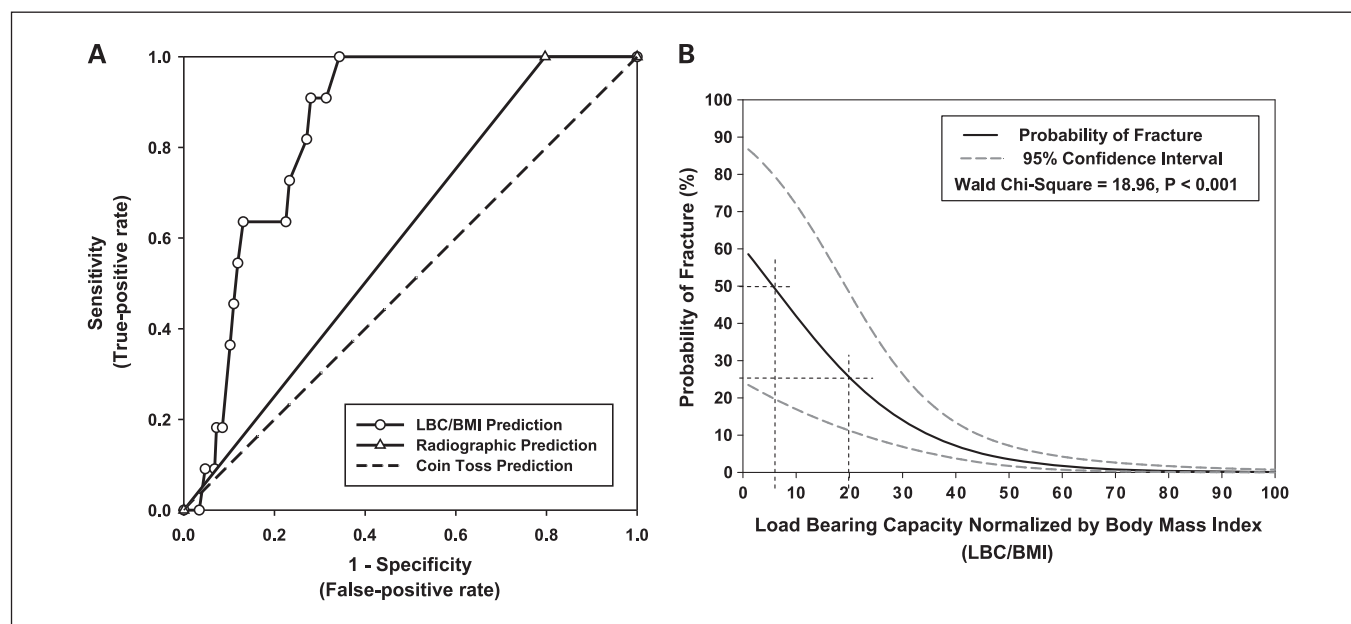
All 11 vertebral fractures were correctly predicted (100% sensitive) using each of the CTRA-derived variables: EA, EI, LBC, and LBC/BMI. However, of the 236 vertebrae that did not fracture, 129, 125, 103, and 162 were correctly predicted not to fracture using each of the CTRA-derived variables: EA (55% 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 vertebral fracture ( $\text{LBC/BMI} = 132/22 = 6$ ), 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 ( $\text{LBC/BMI} = 440/22 = 20$ ). The

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

Model	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	CI of AUC ( $\text{m}^2$ )		P
					Lower bound	Upper bound	
RC	—	100	20	0.60	0.46	0.74	0.25
LBC (N)	1,607.5	100	44	0.82	0.73	0.91	0.001
EI ( $\text{N}\cdot\text{m}^2$ )	154,640.5	100	53	0.80	0.72	0.89	0.001
EA (N)	726.0	100	55	0.77	0.68	0.87	0.002
LBC/BMI ( $\text{N}\cdot\text{kg}\cdot\text{m}^{-2}$ )	46.5	100	70	0.84	0.78	0.93	<0.001

Abbreviations: AUC, area under the curve; CI, confidence interval; RC, radiographic criteria.



**Fig. 4.** A, receiver operating characteristic curves for LBC/BMI, radiographic criteria, and chance (dashed line). B, estimated probability of fracture for a range of LBC normalized by BMI values. Logistic regression analysis using a generalized estimating equations approach established that LBC/BMI is a highly significant predictor of fracture (Wald  $\chi^2 = 18.96$ ,  $P < 0.001$ ).

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 nonosteoporotic 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 bi-

ological 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 fracture 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 oncologists instructed their patients with significant osteolytic lesions to restrict their activity based on their own clinical interpretation 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; however, 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 structural 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 patients 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) techniques. Although voxel-based models are technically easier to generate, errors in the integrity of the reconstructed bone surface 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 research studies are also limited in that the bone models use simulated 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 finite element models. In comparison, CTRA requires no subjective 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 decide whether a metastatic tumor has weakened the bone sufficiently 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 structural 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.

### Acknowledgments

We thank the patients who graciously consented to participate in this study.

### References

- Coleman RE. Bisphosphonates: clinical experience. *Oncologist* 2004;9 Suppl 4:14–27.
- Asdourian PL, Weidenbaum M, DeWald RL, Hammerberg KW, Ramsey RG. The pattern of vertebral involvement in metastatic vertebral breast cancer. *Clin Orthop Relat Res* 1990;164–70.
- Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol* 1998;16:2038–44.
- Hortobagyi GN. The status of breast cancer management: challenges and opportunities. *Breast Cancer Res Treat* 2002;75:S61–5; discussion S57–9.
- Damron TA, Ward WG. Risk of pathologic fracture: assessment. *Clin Orthop Relat Res* 2003; S208–11.
- Hipp JA, Springfield DS, Hayes WC. Predicting pathologic fracture risk in the management of metastatic bone defects. *Clin Orthop Relat Res* 1995;312:120–35.
- Scheid V, Buzdar AU, Smith TL, Hortobagyi GN. Clinical course of breast cancer patients with osseous metastasis treated with combination chemotherapy. *Cancer* 1986;58:2589–93.
- Garmatis CJ, Chu FC. The effectiveness of radiation therapy in the treatment of bone metastases from breast cancer. *Radiology* 1978;126:235–7.
- Cobleigh MA. Hormone replacement therapy and nonhormonal control of menopausal symptoms in breast cancer survivors. *Cancer Treat Res* 1998;94:209–30.
- Tanaka M, Fushimi H, Fuji T, Ford JM. Sclerosis of lytic metastatic bone lesions during treatment with pamidronate in a patient with adenocarcinoma of unknown primary site. *Eur Spine J* 1996;5:198–200.
- Bunting R. Pathologic fracture risk in rehabilitation of patients with bony metastases. *Clin Orthop Relat Res* 1985;192:222–7.
- Cheng D, Seitz C, Eyre H. Nonoperative management of femoral, humeral, and acetabular metastases in patients with breast carcinoma. *Cancer* 1980;45:1533–7.
- Harrington KD. New trends in management of lower extremity metastases. *Clin Orthop Relat Res* 1982;169:53–61.
- Front D, Schneck SO, Frankel A, Robinson E. Bone metastases and bone pain in breast cancer. Are they closely associated? *JAMA* 1979; 242:1747–8.
- Winchester DP, Sener SF, Khandekar JD. Symptomatology as an indicator of recurrent or metastatic breast cancer. *Cancer* 1979;43:956–60.
- DeWald RL, Bridwell KH, Prodromas C, Rodts MF. Reconstructive spinal surgery as palliation for metastatic malignancies of the spine. *Spine* 1985;10:21–6.
- Tubiana-Hulin M. Incidence, prevalence and distribution of bone metastases. *Bone* 1991;12:S9–10.



18. Edlstyn GA, Gillespie PJ, Gvebbel FS. The radiological demonstration of osseous metastases: experimental observations. *Clin Radiol* 1967;18:158-62.
19. Keller T. Predicting the compressive mechanical behavior of bone. *J Biomech* 1984;27:1159-68.
20. Silva MJ, Hipp JA, McGowan DP, Takeuchi T, Hayes WC. Strength reductions of thoracic vertebrae in the presence of transcortical osseous defects: effects of defect location, pedicle disruption and defect size. *Eur Spine J* 1993;2:118-25.
21. McGowan D, Hipp J, Takeuchi T, White A, Hayes W. Strength reductions from trabecular destruction within thoracic vertebrae. *J Spinal Disord Tech* 1993;6:130-6.
22. Taneichi H, Kaneda K, Takeda N, Abumi K, Satoh S. Risk factors and probability of vertebral body collapse in metastases of the thoracic and lumbar spine. *Spine* 1997;22:239-45.
23. Hayes WC, Bouxsein ML. Biomechanics of cortical and trabecular bone: implication for assessment of fracture risk. In: Mow VC, Hayes WC, editors. *Basic orthopaedic biomechanics*. Philadelphia: Lippincott-Raven; 1997, p. 69-112.
24. Lai W, Rubin D. Introduction to continuum mechanics. 3rd ed. Boston: Butterworth-Heinemann; 1993.
25. Eliceiri KW, Fan CH, Lyons GE, White JG. Analysis of histology specimens using lifetime multiphoton microscopy. *J Biomed Opt* 2003;8:376-80.
26. Whealan KM, Kwak SD, Tedrow JR, Inoue K, Snyder BD. Noninvasive imaging predicts failure load of the spine with simulated osteolytic defects. *J Bone Joint Surg Am* 2000;82:1240-51.
27. Hong J, Cabe GD, Tedrow JR, Hipp JA, Snyder BD. Failure of trabecular bone with simulated lytic defects can be predicted non-invasively by structural analysis. *J Orthop Res* 2004;22:479-86.
28. Snyder BD, Hauser-Kara DA, Hipp JA, et al. Predicting fracture through benign skeletal lesions with quantitative computed tomography. *J Bone Joint Surg Am* 2006;88:55-70.
29. Clohisy DR, Mantyh PW. Bone cancer pain and the role of RANKL/OPG. *J Musculoskelet Neural Interact* 2004;4:293-300.
30. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semi-quantitative technique. *J Bone Miner Res* 1993;8:1137-48.
31. Windhagen HJ, Hipp JA, Silva MJ, Lipson SJ, Hayes WC. Predicting failure of thoracic vertebrae with simulated and actual metastatic defects. *Clin Orthop Relat Res* 1997;313-9.
32. Rice JC, Cowin SC, Bowman JA. On the dependence of the elasticity and strength of cancellous bone on apparent density. *J Biomech* 1988;21:155-68.
33. Snyder S, Schneider E. Estimation of mechanical properties of cortical bone by computed tomography. *J Orthop Res* 1991;9:422-31.
34. Fletcher R, Fletcher S. *Clinical epidemiology: the essentials*. 4th ed. Baltimore (MD): Lippincott Williams & Wilkins; 2005.
35. Kleinman PL, Zurakowski D, Strauss KJ, et al. Detection of simulated inflicted metaphyseal fractures in a fetal pig model: image optimization and dose reduction with computed radiography. *Radiology* 2008;247:381-90.
36. Cai T, Moskowitz CS. Semi-parametric estimation of the binormal ROC curve for a continuous diagnostic test. *Biostatistics* 2004;5:573-86.
37. O'Brien L, Fitzmaurice G. Analysis of longitudinal multiple source binary data using generalized estimating equations. *Appl Stat* 2004;53:177-93.
38. Wong DA, Fornasier VL, MacNab I. Spinal metastases: the obvious, the occult, and the impostors. *Spine* 1990;15:1-4.
39. McGowan DP, Hipp JA, Takeuchi T, White AA, Hayes WC. Strength reductions from trabecular destruction within thoracic vertebrae. *J Spinal Disord* 1993;6:130-6.
40. Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet* 1993;341:72-5.
41. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;312:1254-9.
42. Mincey BA, Moraghan TJ, Perez EA. Prevention and treatment of osteoporosis in women with breast cancer. *Mayo Clin Proc* 2000;75:821-9.
43. Trout AT, Kallmes DF, Kaufmann TJ. New fractures after vertebroplasty: adjacent fractures occur significantly sooner. *AJNR Am J Neuroradiol* 2006;27:217-23.
44. Snyder B, Hecht AC, Tedrow JR, Hauser DL. Structural rigidity measured by CT accurately predicts fracture in children with benign tumors of the appendicular skeleton. 45th Annual Meeting of the Orthopedic Research Society, Orlando, FL 2000.
45. Rimnac CM. Commentary & Perspective on "Predicting fracture through benign skeletal lesions with quantitative computed tomography". *J Bone Joint Surg Am* 2006.
46. Keyak JH, Meagher JM, Skinner HB, Mote CD, Jr. Automated three-dimensional finite element modelling of bone: a new method. *J Biomed Eng* 1990;12:389-97.
47. Tschirhart CE, Nagpurkar A, Whyne CM. Effects of tumor location, shape and surface serration on burst fracture risk in the metastatic spine. *J Biomech* 2004;37:653-60.
48. Viceconti M, Bellingeri L, Cristofolini L, Toni A. A comparative study on different methods of automatic mesh generation of human femurs. *Med Eng Phys* 1998;20:1-10.
49. Imai K, Ohnishi I, Bessho M, Nakamura K. Nonlinear finite element model predicts vertebral bone strength and fracture site. *Spine* 2006;31:1789-94.