■ ONCOLOGY

The assessment of the risk of fracture in femora with metastatic lesions

COMPARING CASE-SPECIFIC FINITE ELEMENT ANALYSES WITH PREDICTIONS BY CLINICAL EXPERTS

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Previously, we showed that case-specific non-linear finite element (FE) models are better at predicting the load to failure of metastatic femora than experienced clinicians. In this study we improved our FE modelling and increased the number of femora and characteristics of the lesions. We retested the robustness of the FE predictions and assessed why clinicians have difficulty in estimating the load to failure of metastatic femora. A total of 20 femora with and without artificial metastases were mechanically loaded until failure. These experiments were simulated using case-specific FE models. Six clinicians ranked the femora on load to failure and reported their ranking strategies. The experimental load to failure for intact and metastatic femora was well predicted by the FE models ($R^2 = 0.90$ and $R^2 = 0.93$, respectively). Ranking metastatic femora on load to failure was well performed by the FE models ($\tau = 0.87$), but not by the clinicians ($0.11 < \tau < 0.42$). Both the FE models and the clinicians allowed for the characteristics of the lesions, but only the FE models incorporated the initial bone strength, which is essential for accurately predicting the risk of fracture. Accurate prediction of the risk of fracture should be made possible for clinicians by further developing FE models.

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doi:10.1302/0301-620X.94B8.28449 $2.00

J Bone Joint Surg Br 2012;94-B:1135–42.
Received 12 October 2011; Accepted after revision 26 April 2012

Patients with metastatic disease in the femur are at risk of pathological fracture. In some the risk is low, and pain can be managed with radio-[1] or systemic chemotherapy,[2] hormonal therapy[2] and/or bisphosphonates[1,3] for widespread disease. If the predicted risk of fracture is high, the bone is mechanically stabilised[3,4]; however, assessing the risk of fracture can be difficult. Among the predictive factors are the plain radiological features or those on CT scans, which are prone to error.[6] Overall there are no indicators that reliably predict impending pathological fractures.[5-9]

Additional aspects that play an important role in the assessment of the risk of fracture are the initial strength of the bone and the daily activity pattern of the patient.[6] These aspects can be analysed using patient-specific finite element (FE) models,[10-16] which are based on quantitative CT (QCT) scans, from which the bone geometry and quality is retrieved.[17] Mechanical properties are calculated from the distribution of the bone mineral density (BMD) and are then assigned to the FE model.[18,19] A loading pattern is applied and the load at which the femur fails is calculated. Although essentially an *in vitro* method of predicting the load at which the femur will fail, this method could have an important clinical application.

In a previous pilot study,[19] we ranked five paired femora with and without artificial metastases according to their load to failure. The data were retrieved from mechanical experiments, and compared with rankings predicted by the FE model and by clinical experts, respectively. Predictions using the FE model were considerably better than those made by the experts. However, due to the limited variety in the characteristics of the lesions in the femur we could not establish which determinants accounted for the differences in the accuracy of prediction. Moreover, in the pilot study we used FE models that provided numerical stability problems in about 20% of the simulations, meaning that in those cases the results were not fully reliable. Obviously, if this model is to be used to analyse femoral fracture risks in patients, numerical problems to this extent are not acceptable.

The aim of this study was to assess whether case-specific non-linear FE models could improve the prediction of the load at which the femur would fail as compared with the predictions of experienced physicians, using improved FE models with a non-voxel based element type and modelling an increased variety in lesion characteristics. We defined the following research questions: 1) is the current FE model able to predict case-specific fracture

Table I. Lesion characteristics and experimental results of the 20 femora in this study

Subject	Lesion site	Lesion size (mm)	Load to failure of control femur (N)	Load to failure of metastatic femur (N)	Reduction in load to failure (%)
1	Medial, proximal	40	4141	1237	70
2	Medial, shaft	40	5007	1853	63
3	Medial, proximal	22	5031	2181	57
4	Posterior, proximal	40	4728	2806	41
5	Medial, proximal	45	7852	3002	62
6	Lateral, proximal	40	4660	3960	15
7	Medial, proximal & shaft	2 × 22	11 034	3980	64
8	Anterior, proximal	40	7970	5985	25
9	Anterior, proximal	22	6821	6547	4
10	Anterior, proximal & shaft	2 × 30	10 470	8815	16

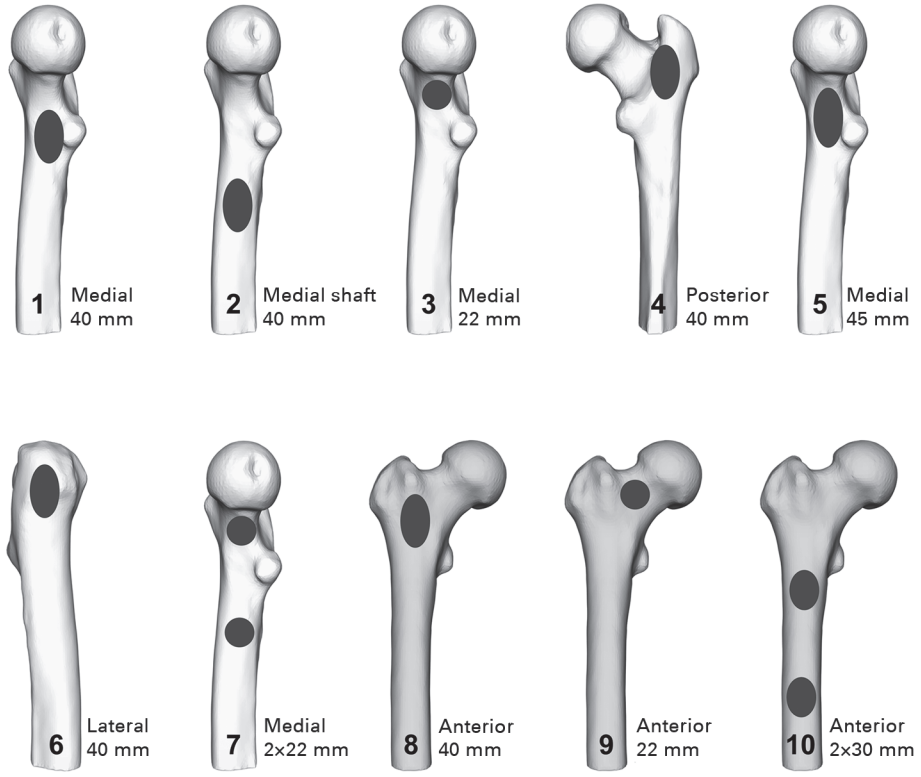

Fig. 1

Diagrams showing the varying size and location of the artificial lytic lesions created in the ten femora.

risks under uni-axial loading in terms of load to failure and location of the failure? 2) is this FE model better at predicting the risk of fracture than clinical experts when a large set of metastatic and control femora are tested? 3) which characteristics of the lesion, such as size or location, are important in predicting the risk of fracture, and how are these scored by clinical experts?

Materials and Methods

Ten paired fresh-frozen human cadaveric femora aged between 63 and 96 years (mean 81.7 years), seven male and three female, were mechanically tested to failure. Five of these pairs were tested previously.[19] The specimens were obtained from the Department of Anatomy with institutional approval. After removing the soft tissues, one of each pair of femora was left intact and assigned to the control group. In the contralateral femur, one or more artificial lytic metastases were created by drilling holes through one cortex only. The location, size and number of these lesions varied between the specimens and resembled the clinical appearance of metastases in bone, as previously discussed with orthopaedic oncologists (Table I, Fig. 1). All femora were embedded distally in polymethylmethacrylate (PMMA). Before starting the experiments, anterior-posterior and mediolateral radiographs were taken. For alignment purposes, the femora were subsequently equipped

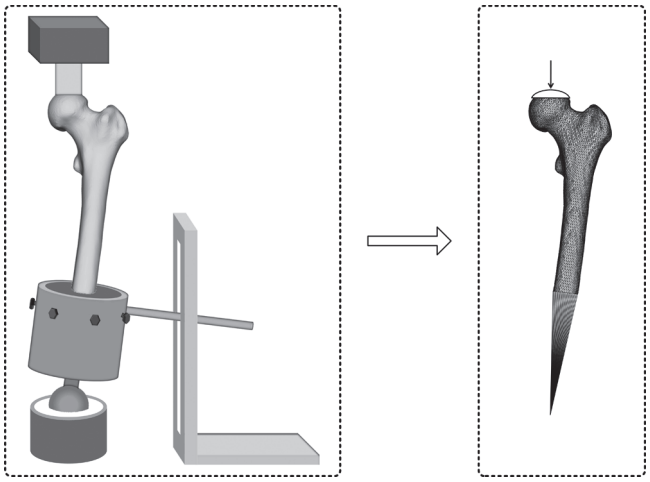

Fig. 2

Diagrams showing the experimental set-up (left) and the same conditions mimicked in the finite element model (right).

with 28 tantalum markers, which were glued along the femoral cortex in the sagittal plane. QCT images (ACQSim; Philips, Eindhoven, The Netherlands) with the following settings were acquired: 120 kVp, 220 mAs, slice thickness 3 mm, pitch 1.5, spiral and standard reconstruction, in-plane resolution 0.9375 mm. The femora were scanned in a water basin, positioned on top of a solid calibration phantom containing four tubes with 0, 50, 100 and 200 mg/ml calcium hydroxyapatite (Image Analysis, Columbia, Kentucky), respectively. A stereo radiograph was then taken of the femora in order to calculate the three-dimensional (3D) position of the tantalum markers.

Mechanical experiments. In line with our pilot study,[19] the femora were fixed using a distal ball-bearing and a sliding hinge, allowing only rotation around the dorsoventral axis (Fig. 2). Using a hydraulic MTS machine, an axial load was applied on the femoral head, via a plastic cup (diameter 30 mm, polyoxymethylene, Delrin) with 10 N/s from 0 N until failure. During these load controlled experiments the force and displacement of the plunger were registered. The course of failure of each femur was recorded with a conventional digital camera.

Finite element model. Geometric information for the FE models was retrieved by segmenting the QCT images and converting them to a solid mesh consisting of four-noded tetrahedral elements (mean edge length approximately 2 mm). Calibration of the CT data and material property assignment was performed using software developed in our lab. Subsequently, we adopted non-linear isotropic material behaviour according to Keyak et al.[18] The position of the tantalum markers in the stereo radiographs and in the CT scans was used to orient the FE model in the experimental configuration. The experimental boundary conditions were exactly mimicked in the FE simulations (Fig. 2); the distal fixation of the femora was accomplished by adding two bundles of high-stiffness springs.[19]

In the FE simulations we used a displacement-controlled loading condition. Loads were applied via a cup (diameter 30 mm) that displaced with 0.1 mm per increment. In order to prevent artefacts as a result of the loading configuration, post-yield material behaviour[18] was not implemented in the surface elements underneath the cup. The FE simulations were performed with MSC Marc (MSC.MARC2007r1; MSC Software Corporation, Santa Ana, California). The total time expenditure for generating a case-specific FE model and running the simulation was approximately eight hours. The incremental displacement was registered via a reference node underneath the cup. The total reaction force in the loading direction was defined as the sum of the contact normal forces of all the nodes in the model. Structural fracture was assumed to occur when the maximum total reaction force was reached. The location of the failure was defined by elements that plastically deformed[18] when the maximal total reaction force was reached.

Clinical assessment. Clinicians often rely on conventional radiographs when assessing the risk of femoral fracture due to metastases.[7,9] Moreover, current clinical guidelines such as Mirels' score[7] or the degree of cortical destruction[9] are based on radiological assessment. Furthermore, it has been shown by Hipp et al[6] that the estimation by clinical experts of the femoral load to failure does not improve when they are provided with CT scans in addition to conventional radiographs. Therefore, six experts (three orthopaedic surgeons, two oncologists (one of whom an author: AS) and one radiologist) were provided with the baseline anteroposterior (AP) and mediolateral (ML) radiographs of the femora and information on gender, age and experimental set-up. The radiographs of one of the controls were missing; this femur was therefore excluded from the clinical assessment. The clinicians ranked the 19 remaining femora on load to failure, starting with the weakest femur. We did not prescribe any rules or guidelines for ranking, as it appeared from clinical practice that clinicians use a combination of techniques, depending on their professional background. Subsequently, a short survey was conducted among them in which they reported their strategies for assessing the load to failure. They indicated the five most relevant factors they used to predict the load to failure. Five points were assigned to the most important factor, while the least important factor received one point and the redundant factors zero points. The scores per factor were then summed for all clinicians.

Analysis of data. The accuracy of the FE predictions was determined by regressing the predicted load to failure on the experimental failure load. Furthermore, we ranked the femora on experimental load to failure and on the failure load predicted by the FE model. These rankings were then compared using the Kendall rank correlation coefficient (τ), which defines the degree of similarity between two rankings.[20] In the same vein, the rankings by the clinicians were compared to the experimental ranking, to the ranking by

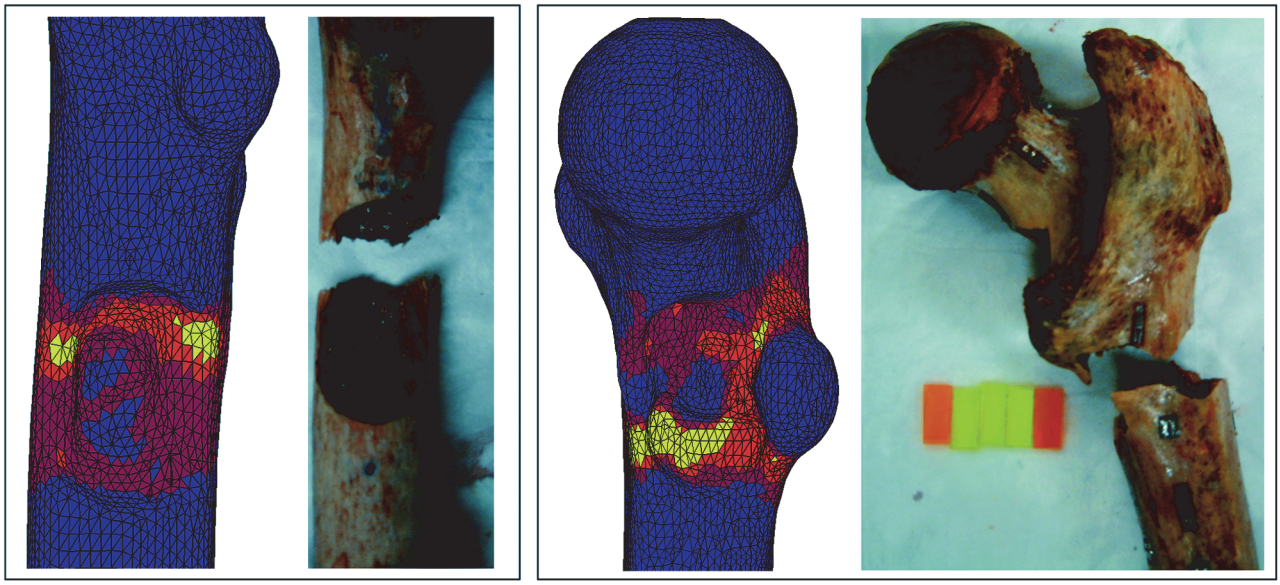

Fig. 3

Finite element images predicting two representative fracture locations, showing areas of plastic deformity (indicated in red/orange/yellow), with experimental photographs showing fracture sites corresponding to those predicted by the FE model.

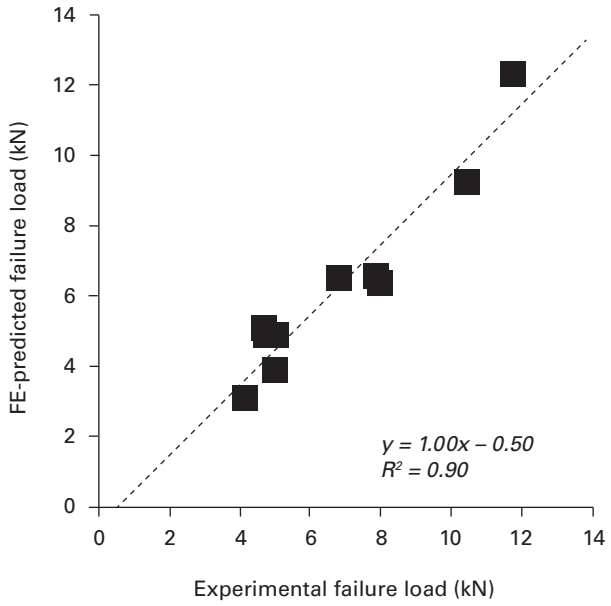

Fig. 4a

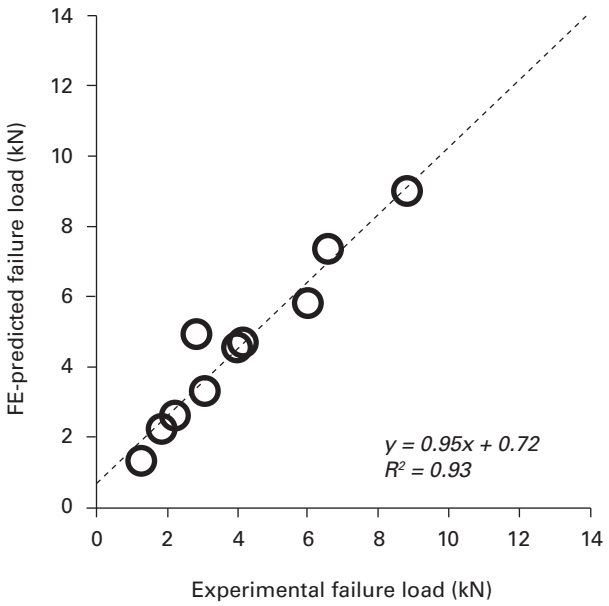

Fig. 4b

Graphs of the experimental load to failure *versus* the load to failure predicted by the finite element (FE) model for a) intact and b) metastatic femora showed a strong correlation for both (R^2 = 0.90 and 0.93, respectively).

the FE model, and to the rankings by the other clinicians, respectively. Studying consistencies and inconsistencies in the predictions among the clinicians could reveal which characteristics they did (or did not) take into account when ranking the femora with metastases. Finally, the reduction in load to failure as a result of the artificial metastatic lesions was defined as the difference in failure load between a pair of femora. We compared the reduction in load to failure measured in the experiments to the reductions predicted by the FE model.

Statistical analysis. Statistical analyses were performed in SPSS v16.02 (SPSS Inc., Chicago, Illinois). The fracture

Table II. Kendall rank correlations between experimental and predicted rankings on load to failure for metastatic femora. The asterisk indicates that the correlation is significant at the 0.05 level (two-tailed)

Experiment	Experiment	Finite element	Clinician 1	Clinician 2	Clinician 3	Clinician 4	Clinician 5	Clinician 6
Finite element	0.87*	-						
Clinician 1	0.33	0.47	-					
Clinician 2	0.24	0.29	0.64*	-				
Clinician 3	0.42	0.47	0.38	0.47	-			
Clinician 4	0.20	0.33	0.78*	0.60*	0.33	-		
Clinician 5	0.11	0.16	0.60*	0.60*	0.51*	0.56*	-	
Clinician 6	0.24	0.38	0.73*	0.64*	0.38	0.96*	0.51*	-

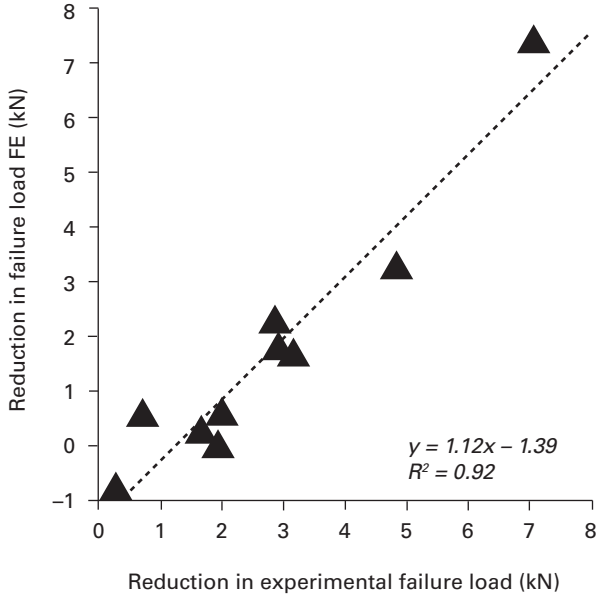

Fig. 5

Graph showing the failure load reduction in experiments *versus* that predicted by the finite element (FE) model, showing a strong correlation between the two ($R^2 = 0.92$).

locations in the experiments were qualitatively compared to the fracture lines predicted by the FE model. Results were considered statistically significant if $p < 0.05$.

Results

In all femoral loading experiments, the artificial lesions decreased the load to failure of the femora with metastases compared to the controls (Table I). The experiments were all simulated by the FE models, without numerical problems.

In the control group, the fracture lines predicted by the FE model only moderately agreed with the experimental results. In most of the controls an intertrochanteric fracture was seen, yet the FE models mainly predicted subcapital fractures. However, in most of the metastatic femora, the model correctly predicted a fracture through the metastatic lesions, comparable to the experimental fracture lines (Fig. 3).

The FE model accurately predicted the load to failure as measured in the experiments, both for intact femora ($R^2 = 0.90$, $p < 0.001$; slope = 1.0, $p < 0.001$; intercept = -0.50 kN, $p = 0.576$) and for metastatic femora ($R^2 = 0.93$, $p < 0.001$; slope = 0.95, $p < 0.001$; intercept = 0.72 kN, $p = 0.119$) (Fig. 4). There were no significant differences between the regression lines in the two groups.

In the metastatic subset, the FE ranking of load to failure corresponded very well with the actual experimental ranking ($\tau = 0.87$; $p < 0.001$), whereas none of the clinical experts ranked the femora in agreement with the experimental results ($0.11 < \tau < 0.42$, $p \geq 0.089$) (Table II). Kendall tau rank correlations between clinicians and the FE model were not significant and ranged from 0.16 to 0.47 (Table II). The Kendall tau rank correlations among clinicians were quite variable and ranged from moderate ($\tau = 0.33$, $p = 0.180$) to good ($\tau = 0.96$, $p < 0.001$; Table II). Remarkably, the load to failure of the bone with the 40 mm posterior lesion in the proximal femur (Fig. 1) was largely overestimated by the FE model and by five of six clinical experts. Therefore, an outlier analysis was performed, but none of the femora could significantly be defined as such (Cook's distance[21] ≤ 0.83).

A more detailed analysis of the clinicians' predictions of load to failure revealed the following: the experimental results showed that three femora with lesions were stronger than five of the intact femora (Table I) and the FE model correctly ranked these three metastatic femora among the strongest femora (Fig. 4). However, five clinicians predicted that all metastatic femora were weaker than all the control bones, thus clearly penalising the presence of lesions in the bones, irrespective of the initial strength of the femur. Furthermore, the load to failure of the femur with a 22 mm medial lesion (number 3) was overestimated by all clinicians, but not by the model. The femur with a 45 mm medial lesion and the femur with a double lesion (30 mm) on the anterior side, respectively, were stronger than estimated by five clinicians (numbers 5 and 10). Two femora, with a 40 mm medial lesion and a 22 mm anterior lesion in the proximal femur, respectively, were correctly ranked by the model and all clinicians (numbers 1 and 9).

In the experiments, the relative reduction in failure load was largest (> 50%) for medial lesions, regardless of their size (Table I). Anterior lesions had a smaller effect on failure load (≤ 25%). The FE model adequately predicted the reduction in load to failure caused by the metastatic lesions ($R^2 = 0.92$, $p < 0.001$) (Fig. 5).

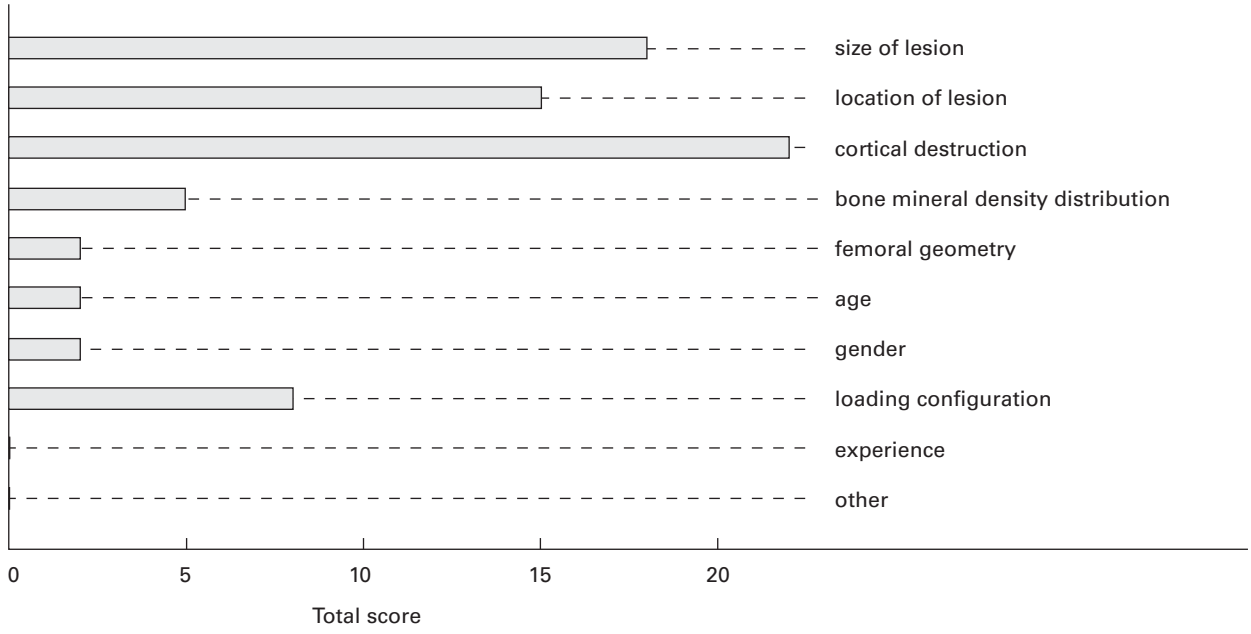

Fig. 6

Chart showing the results of a small survey into clinicians' strategies for assessing the load capacity of the femora. Five points were assigned to the most important factor, while the least important factor received one point and the redundant factors zero points. The scores per factor were then summed for all clinicians.

In the survey the clinicians indicated that the extent of cortical destruction is considered to be most important for the prediction of the risk of fracture, followed by the size of the lesion and their location (Fig. 6). The distribution of the BMD and the femoral geometry were considered by them to be of less importance in predicting the strength of the bone. Furthermore, they reported that their strategy in this study differed from clinical practice in that they normally also take into consideration the appearance of the lesion (lytic, blastic or mixed type) and the expected pattern of daily activity of the patient.

Discussion

Current clinical practice lacks an accurate predictor of the expected risk of fracture in patients with metastatic lesions in the femur. Yet, patient-specific FE models have been shown to be very promising in this field. In this study, we reassessed the robustness of our FE model and tried to link its predictions to clinical practice by focussing on the question as to why clinicians have difficulties in predicting load to failure of femora containing metastases.

As we found a moderate to good agreement in the predictions among our clinicians, we concluded that they more or less rely on the same determinants. However, their predictions neither corresponded to the experiments, nor to the FE predictions. On the contrary, there was a good correlation between the FE predictions and the experiments, from which we conclude that clinicians focussed on determinants that attributed less to the load to failure than those implemented by the FE model.

The FE model was shown to be sensitive to several characteristics of the lesions. Thus, the predicted fracture line often corresponded to the actual fracture line through the metastasis, suggesting that the model can incorporate cortical destruction. Furthermore, the FE models correctly predicted the relative reductions in load to failure, suggesting that they allow for the location of the metastasis. Most importantly, the FE models incorporated the initial bone strength, as they correctly ranked three metastatic femora among the strongest femora. In contrast, the clinicians could not incorporate the bone strength, but clearly focussed on the characteristics of the lesions as shown by the ranking results and the survey.

The relevance of accounting for initial bone strength or bone quality when assessing the femoral load capacity has previously been demonstrated, both by FE models and other methods. Michaeli et al[22] showed that the total bone mineral content and the BMD were both predictive of the load to failure of femora with artificial lytic metastases whilst climbing stairs and in external rotation. However, the total bone mineral content is not sensitive to the location of the lesion and potentially less predictive in the presence of blastic metastases. Another method of assessing the loading capacity of femora is to calculate structural rigidities on the basis of bone material properties retrieved from QCT scans. In this way, Lee et al.[23] found that the load to failure calculated on the basis of bending and axial rigidity was predictive for the experimental load to failure, whereas the characteristics of the lesions such as the size or relative width of the defect were not. The same conclusion was

drawn by Snyder et al,[24] who studied the accuracy of predicting fractures in patients with benign skeletal lesions. They showed that the sensitivity and specificity determined on the basis of bending and torsional rigidity were much higher than the sensitivity and specificity of any lesion characteristic. These results all emphasise that the initial strength and the biomechanical effect of metastatic lesions are very important for the assessment of the loading capacity of bone.

An important limitation that is often mentioned in this type of study is that these complex and comprehensive methods are not ready for clinical implementation, as specific technical knowledge is needed in order to perform such simulations or calculations. Furthermore, in order to prove the clinical relevance of implementing such complicated methods to predict the risk of fracture, prospective studies should be performed. In this way, the true predictive value of these methods can be shown, and it will then become clearer how their output can be translated into a concrete advice for clinicians when planning treatment. Griffith and Genant[25] recently reported that imaging modalities such as FE models are gradually making their way into clinical practice. For example, they refer to the work of Keaveny et al[26-29] who have extensively used FE modelling to study osteoporosis in a clinical setting. In one of the first prospective case-cohort studies, they studied 250 men over 65 years of age and showed that the femoral strength calculated by FE models was more strongly associated with femoral fracture than the bone mineral density.[29] Such prospective studies with this number of participants that are analysed using patient-specific FE techniques indicate that clinical implementation of FE modelling will become possible in the near future.

This study has some limitations. Although the accuracy of our FE model was in line with other studies,[10,18] the case-specific under- or overestimation of the load to failure could still be quite large. Obviously, these aberrant predictions need to be improved in order to predict patient-specific fracture risks on which diagnoses and treatments can be based.

Although the location of the fracture was correctly predicted in the femora with metastatic lesions, in intact femora there was a difference between the predicted and actual location of the fractures. In line with previous studies,[10,11,13,18,19] our FE model mainly predicted subcapital fractures in intact femora under axial loading, whereas in the experiments mostly intertrochanteric femoral fractures were seen. This discrepancy may be reduced by using parameters describing more realistic behaviour of bone such as an asymmetric yield criterion[10,30-32] or mechanical anisotropy.[17]

Moreover, the simplified laboratory conditions and the artificial lytic metastases might have been quite different from those seen in clinical practice. However, the loading configuration was simple and clearly explained to the clinicians. The geometrical appearance of the lesions was simplified as compared to bone metastases in patients with cancer. If these simplified conditions were difficult for the clinicians to imagine, they would have had even more difficulty in predicting the risk of fracture *in vivo*. Additionally, bone metastases often have an osteoblastic component, which cannot be mimicked in healthy femora. Incorporating blastic metastases in FE models is challenging, since it has not been definitively determined how best to represent the structural contribution of this radio-dense but potentially weak mineralised tissue.

Finally, the axial loading condition in this study eliminated torsional components that are important for predicting the risk of femoral fracture. However, in this validation stage, the essence is that the loading condition from the experiment is copied in the FE simulations, and that the FE results agree with the experimental results. After implementing a more complex and more realistic loading scenario, the load cases will have closer agreement with the patterns of daily activity of the patients and clinicians therefore may be better at assessing the risk of fracture in these situations. As a result, they might come closer to the FE results. On the other hand, the loading condition is more complex, and therefore more difficult to comprehend, which might lead to even worse predictions by the clinicians.

In this study, we validated an improved, numerically stable, case-specific non-linear FE model against experiments. The superior predictions of the FE model relative to the predictions of clinicians enabled us to disentangle determinants that are important for achieving more accurate predictions of load to failure. We showed that the FE model was sensitive for cortical destruction, the location of the lesions and the initial strength of the femur. It appeared that clinicians relied heavily on the cortical destruction, the size and location of the lesion, but not on the initial bone strength.

We conclude that the assessment of initial bone strength is essential for the accurate clinical prediction of the risk of fracture in patients with femoral metastases. Obviously, for clinicians it is hard to glean this information from conventional imaging data, and to combine it with detailed characteristics of the lesion and the patients' medical history. In this study, we showed that FE models can accommodate these multi-factorial aspects. We therefore feel that FE models should be further developed into a clinical tool to clinicians to assess the risk of pathological fracture in patients with metastatic bone disease.

Supplementary material

Figures showing the Kendall rank correlations between experimental and finite element (FE)-predicted rankings on load to failure for metastatic femora and for the total sets of metastatic and intact femora are available with the electronic version of this article on our website www.bjj.boneandjoint.org.uk

The authors would like to thank the clinical experts who were involved in the clinical assessment of the femora. Furthermore, we thank MSc students J. Kalisvaart and H. van den Boomen, technical staff of the Orthopaedic Research Laboratory and the Department of Anatomy for their assistance.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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