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Pathological fracture prediction in patients with metastatic lesions can be improved with quantitative computed tomography based computer models

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ABSTRACT

Purpose: In clinical practice, there is an urgent need to improve the prediction of fracture risk for cancer patients with bone metastases. The methods that are currently used to estimate fracture risk are dissatisfying, hence affecting the quality of life of patients with a limited life expectancy. The purpose of this study was to assess if non-linear finite element (FE) computer models, which are based on Quantitative Computer Tomography (QCT), are better than clinical experts in predicting bone strength.
Materials and methods: Ten human cadaver femurs were scanned using QCT. In one femur of each pair a hole (size 22, 40, or 45 mm diameter) was drilled at the anterior or medial side to simulate a metastatic lesion. All femurs were mechanically tested to failure under single-limb stance-type loading. The failure force was calculated using non-linear FE-models, and six clinical experts were asked to rank the femurs from weak to strong based on X-rays, gender, age, and the loading protocol. Kendall Tau correlation coefficients were calculated to compare the predictions of the FE-model with the predictions of the clinicians.
Results: The FE-failure predictions correlated strongly with the experimental failure force ($r^2 = 0.92$, $p < 0.001$). For the clinical experts, the Kendall Tau coefficient between the experimental ranking and predicted ranking ranged between $\tau = 0.39$ and $\tau = 0.72$, whereas this coefficient was considerably higher ($\tau = 0.78$) for the FE-model.
Conclusion: This study showed that the use of a non-linear FE-model can improve the prediction of bone strength compared to the prediction by clinical experts.

Introduction

The skeleton is the most common organ to be affected by metastatic cancer [1,2]. Most bone metastases arise from the breast, prostate, lung, or kidney, and occur in about 15% of all cancer cases. An important complication of metastatic lesions is a pathological fracture, due to weakening of the bone. These fractures cause significant morbidity in advanced cancer patients and occur in 71% of the cases in the proximal femur or femoral diaphysis [3]. Patients with metastatic lesions most often fracture the femur by simple movements like starting to walk, standing, raising from a chair, and stair climbing. Metastatic lesions with a high fracture risk are surgically treated using prophylactic osteosynthesis or prosthetic replacement [4], whereas low-risk lesions are treated conservatively using radiotherapy [5], chemotherapy, hormonal therapy [6], or bisphosphonates [6,7]. However, it is difficult to discriminate between low- and high-risk lesions based on the available radiographic imaging material, even for experienced physicians.

Attempts have been made to define objective risk factors in order to decide which lesions need surgery or can be treated conservatively [8–11]. Risk factors include increasing local pain, size of the lesion, radiographic osteolytic appearance, and percentage of circumferential cortical involvement. Mirels [8] proposed a scoring system that combined clinical and radiographic factors into one score. If Mirels' score had been applied to patients from The Dutch Bone Metastasis Study Group, who were conservatively treated, 87% of these patients would have been surgically over-treated [9]. Surgical over-treatment has large impact on a patient's quality of life with considerable post-operative morbidity and mortality as a result. Therefore, they [9,11] developed an improved score to predict fracture risk. When the axial cortical involvement of the lesion with a threshold of 30 mm was used

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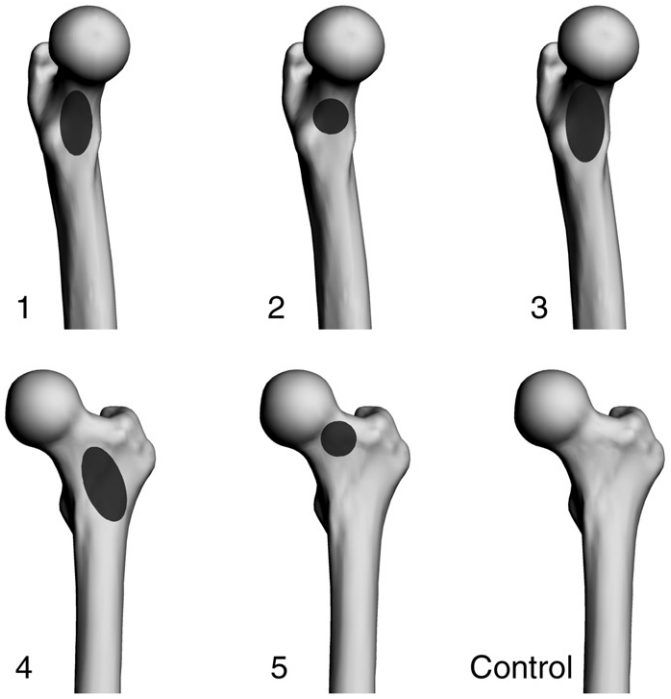

Fig. 1. Schematic overview of the locations and sizes of the simulated metastatic lesions. At the medial site, the lesions were 40 mm (1), 22 mm (2), and 45 mm (3); at the anterior site, the lesions were 40 mm (4) and 22 mm (5). The contra-lateral site of each subject served as control (6).

as predictor, the percentage of over-treatment reduced to 42%, which is a significant improvement but still unacceptable. Conversely, using this method, 14% of the patients, who were defined to be at low risk, would fracture their bones.

Due to recent technical developments, the prediction of fracture risk can be improved. Micro-CT has been used to improve the insight in fracture risk [12,13]. However, it is not yet possible to scan a patient's femur *in vivo* using micro-CT. Several researchers have shown that finite element (FE) computer models could be used to simulate the mechanical behavior of bones under loading [14–21]. FE-models consist of the 3D geometry of a bone, including the location and size of a possible metastasis, and the bone density distribution, as obtained using Quantitative Computer Tomography (QCT) scans. To these models, loads can be applied and mechanical calculations performed. These types of FE-models were able to give an indication of the failure mode as well as an estimation of the failure load in the proximal femur under compressive force, which was often more predictive than the methods based on just QCT and dual energy X-ray absorptiometry (DXA) [14,15]. In most FE-studies, the mechanical behavior of the model was assumed to be linear elastic [16,17,19,22]. However, bone failure is a non-linear phenomenon by definition. It is therefore not surprising that the highest correlations between predicted and measured failure load under compression, up to $r^2 = 0.96$, were found using non-linear FE-models [18,21]. Whether these rather complex, non-linear FE-models are actually better in predicting the failure load than the clinical experts, however, has never been proven.

The purpose of this study was to assess if a non-linear finite element model could improve the prediction of bone strength as compared to a strength prediction by clinical experts. For this purpose, laboratory experiments on human cadaver femurs were performed and simulated by non-linear femur-specific finite element models. Subsequently, the predictions of the FE-simulations were compared to the predictions of the clinical experts. In addition, the laboratory experiments were used to acquire more insight in the effect of lesion location and lesion size on the fracture strength of the proximal femur.

Materials and methods

Five pairs of fresh-frozen cadaveric human proximal femurs (aged 63–96, 2 female and 3 male) were used for the evaluation of femoral strength in stance loading. The femurs were obtained from the Department of Anatomy. For each femur pair, a hole was drilled in one of the two bones to simulate a metastatic lesion (Fig. 1). The location (anterior or medial) and size (22, 40 and 45 mm diameter) of each hole varied amongst the bones and were based on realistic examples of metastatic lesions found in patients, as discussed with our orthopedic oncologists. With this variation in artificial lesions, femurs with both high and low risk scores according to the 30 mm system [11], which is a recommended method in hospitals in The Netherlands, were included in the study (Table 1).

The femurs were cleaned from soft tissue and cut at 25 cm from the proximal end. The distal 5 cm was embedded in PMMA (polymethylmethacrylate bone cement) for fixation of the bone during testing. Twenty-four tantalum markers (ø 0.8 mm) for Rontgen Stereophotogrammatical Analysis (RSA) were inserted in the medial and lateral cortices of the bone and another four (ø 1.0 mm) in the anterior and posterior side. All markers were visible on X-rays and CT scans, hence providing detailed 3D coordinate information of the orientation of the femur [23]. The RSA picture was taken initially to the loading process.

To obtain data for the FE-models, all femurs were CT scanned (ACQsim, Philips, Eindhoven, The Netherlands). The following settings were used: 120 kVp, 220 mAs, slice thickness 3 mm, pitch 1.5, spiral, and standard reconstruction. The in-plane resolution was 0.9375 mm. Each femur was placed horizontally in a water basin and scanned simultaneously on top of a solid calibration phantom (0, 50, 100, and 200 mg/ml calcium hydroxyapatite, Image Analysis, Columbia, KY, USA). The calibration phantom was used to translate the CT-values (Hounsfield Units, HU) to calcium equivalent densities (ρ_{CHA}, g/cm^3).

Mechanical loading experiments

To simulate single-limb stance-type loading conditions in the proximal femur, the femur was placed in a hydraulic MTS testing

Table 1
Characteristics and results of the experiments and simulations.

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Experimental failure force					
Intact (*N*)/metastatic (*N*)	4141/1237	5031/2181	7852/3002	7970/5985	9821/6547
Simulated failure force					
Intact (*N*)/metastatic (*N*)	3333/1436	5250[a]/3433	7447/4166[a]	7418/6069	7144/7266
Decreased strength (%) (experimental)	70.1	56.7	61.7	33.2	4.01
Metastasis (mm, location)	40 medial	22 medial	45 medial	40 anterior	22 anterior
Risk prediction					
30 mm system	High risk	Low risk	High risk	High risk	Low risk

[a] Last calculated reaction force.

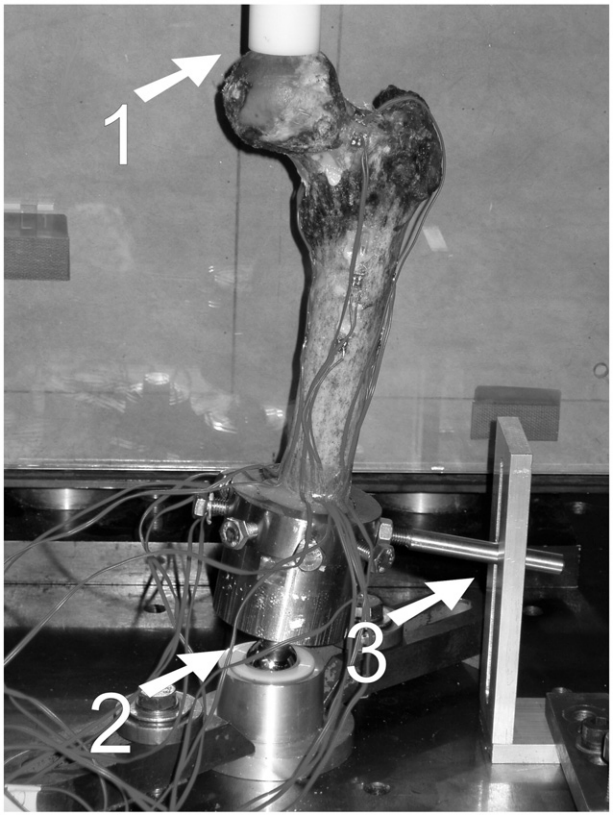

Fig. 2. Setup for mechanical experiments: (1) the plastic cup to apply load, (2) the rotation point and (3) the mechanism to restrain all rotations except the rotation around the AP-axis.

machine. All movements except for rotation around the antero-posterior (AP) axis were mechanically restrained using a distal ball bearing and a lateral sliding hinge (Fig. 2). The distal rotational point was located along the femoral axis distal to the femoral resection (Fig. 2).

A plastic (Delrin®: polyoxymethylene) cup, with a diameter of 30 mm and a concave surface that fitted to the head, was used to apply the force during the compression experiments. The cartilage on the head was removed with a circular rasp to apply the external force directly on the subchondral bone. The midpoint of this cup was axially aligned with the distal ball bearing. The load was increased with 10 N/s from 0 N until failure. The applied force and the displacement of the load application point were recorded during the whole experiment.

FE-modeling: calculation of failure force and failure location

To automatically generate three dimensional FE-models from the CT scan data, a specific software package was developed within the lab. With this software, the calcium equivalent density (ρ_{CHA}, mg/ml) of each voxel in the CT scan was calculated using the calibration phantom [24]. Subsequently, all voxels with a ρ_{CHA} above 30 mg/ml, that were mutually connected, were selected. The threshold value was based on a sensitivity study. With this information the FE-model was generated with $0.9375 \times 0.9375 \times 3$ mm brick elements corresponding with the selected voxels of the CT scan. The bone density (ash density, ρ_{ash}, g/cm^3) of each element was computed from the calibrated CT scan data using the relationship: $\rho_{ash} = 0.0633 + 0.887\rho_{CHA}$ [18]. The non-linear isotropic mechanical properties, such as the elastic modulus (E, MPa), the ultimate strength (S, MPa) and the post failure behavior were based on the relationships with the bone density (ρ_{ash}) as described by Keyak et al. [18].

Each model was rotated to the exact orientation of the femur in the mechanical tests, using the RSA information, to apply the exact boundary conditions of the experiment. Boundary conditions were imitated in the model using high stiffness springs. The high stiffness springs were used to obtain a distributed load to the femoral head. At the distal part, the springs were fixed at the rotation axis (Fig. 3). For stability reasons, the FE-simulation was displacement driven while the experiments were performed force driven. In a pilot study we found that the failure force for both load applications, i.e. force driven and displacement driven, was identical. The load was applied incrementally (0.025 mm/s) at one top node, which was connected to the surface area of the femoral head by the springs. The diameter of the contact area was 30 mm, similar to the experiment. Plastic behavior

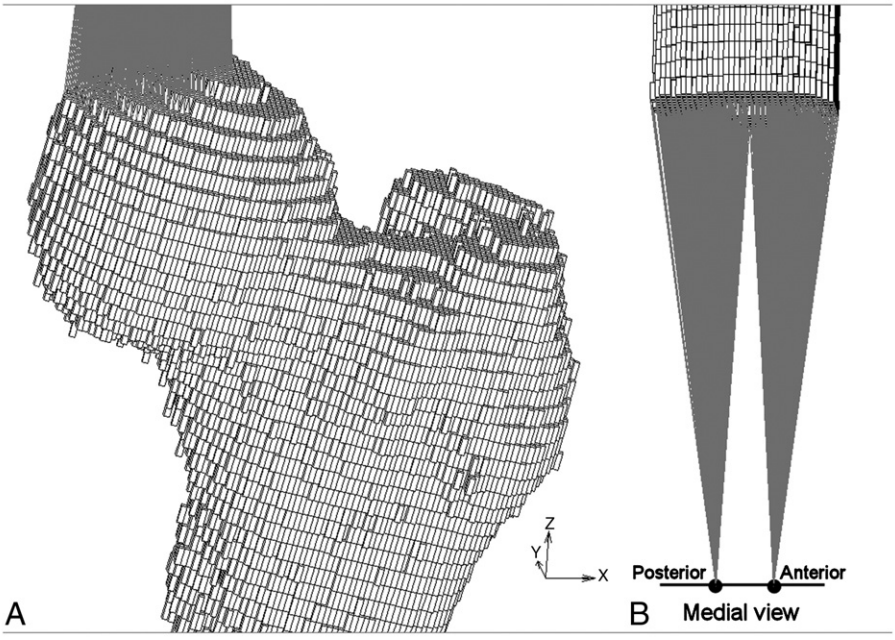

Fig. 3. Anterior and medial view of the FE-model, generated from a CT scan. The distal springs were fixated on two extra nodes allowing rotation around the AP-axis. Load was applied to proximal femur by springs attached to the surface.

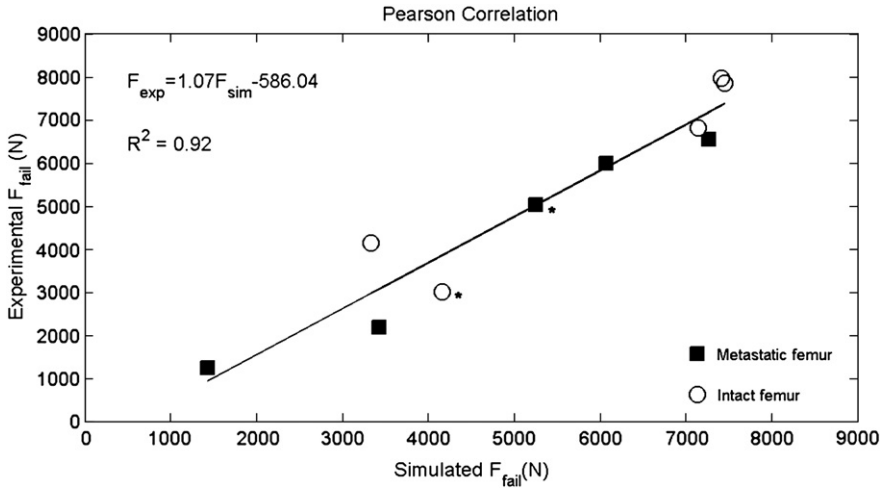

Fig. 4. A Pearson's correlation of $r^2 = 0.92$ was found between the experiment failure force and the simulated failure force.

was prevented in the surface elements of the contact area to prevent severe distortion. The FE analyses were performed using MARC2005 release 3 (MSC Software Cooperation, Palo Alto CA, USA). For each incremental displacement the reaction force was computed at the tip of the proximal spring cone. The calculated failure force of the model was defined as the maximal reaction force in the loading direction.

Clinical assessment

Six clinical experts, with experience in evaluating X-rays of patients with bone metastases (three orthopedic surgeons, two radiation oncologists and one radiologist), were asked to rank the tested femurs from weak to strong. For each femur, the physicians received two X-rays which were taken just before mechanical testing, one in medial–lateral direction and the other in anterior–posterior direction, similar to the clinical situation. Of one of the femurs the X-rays were missing; this femur was excluded from the clinical assessment. Additional information was given about gender, age, and the mechanical experiment. Posture and body weight of the subjects were unknown. The experts were asked to use the same methods as in their clinical routine to analyze the X-rays meaning that they were left free to use their usual method. Hence, their method was primarily based on their own intuitive clinical experience including consideration of lesion size and age.

Analyses

The Pearson correlation coefficient was used to compare the failure strength of the mechanical experiments and the FE-simulations. Failure location was compared qualitatively. In addition, the decrease in strength, due to the lesion was calculated for each femur pair. To compare the prediction of the FE-simulation with the prediction of the clinical experts, the Kendall Tau correlation coefficients were computed. If the ranking by a clinician or by the FE-simulation agreed perfectly with the experiment, the Kendall Tau coefficient would have a value of $\tau = 1$, whereas a total disagreement results in $\tau = -1$. A Kendall Tau coefficient of $\tau = 0.5$, means 75% agreement and 25% disagreement.

Results

Mechanical experiments

All mechanical tests were successfully performed. Most of the femurs (6 out of 10) fractured from the transition of femoral head and neck in the longitudinal direction (Fig. 4). Three out of five femurs with an artificial metastasis started at the proximal tip of the greater trochanter, one fractured in the neck, and one in the shaft. These femurs all fractured through the artificial lesion.

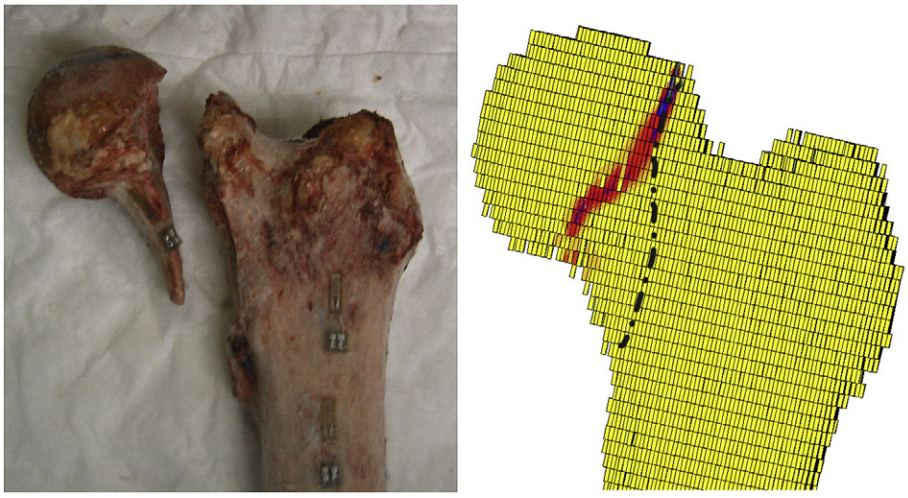

Fig. 5. A typical picture of the fracture side in the experiment and the predicted failure location in the FE-model. The dark red/blue area in the FE-model shows the plastic deformation after loading, simulating failure. The black dotted line shows the course of failure as was found in the experiment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The measured failure forces ranged from 1237 Newton (N) to 6547 N for the femurs with a lesion, and from 4141 N to 7970 N for the intact femurs (Table 1). In every femur pair, the femur with a lesion fractured at a lower force than its contra-lateral femur; the ultimate strength was decreased by the lesion with an average decrease of 45% (range 4%–70%, Table 1). The lesions at the medial side affected the strength more than those at the anterior side, whereas the size of the lesion was of less importance (Table 1).

FE-simulations

The FE-failure predictions correlated strongly ($r^2 = 0.92$, $p < 0.001$) with the experimental failure force (Fig. 4). Two of the FE-simulations showed instabilities and ended just before the ultimate reaction force was reached (Table 1). As the simulations were close to reaching the maximal reaction force, the last calculated reaction force was included in the statistical analysis of the results.

Initial failure location was correctly predicted in 8 out of 10 cases. The course of failure in the FE-simulations, visible by the plastic deformation, showed similarities with the fracture sides found in the experiments but were not identical (Fig. 5). The fractures predicted with the FE-models tended to go through the femoral head while in the experiments most fractures ended just above the minor trochanter.

FE-modeling and clinical assessment

The Kendall Tau coefficient between the experimental ranking and predicted ranking ranged between $\tau = 0.39$ and $\tau = 0.72$ for the physicians. For the FE-model this correlation was considerably higher ($\tau = 0.78$, Fig. 6). The weakest intact femur was predicted too strong by all physicians. Except for this communality, there was a rather poor mutual agreement between the rankings of the physicians. When focused purely on the metastatic femurs, there was a perfect agreement between the FE-models and the experiments but all physicians switched one or two metastatic femurs in their ranking.

Discussion

In the clinical practice, there is an urgent need to improve the prediction of fracture risk for cancer patients with bone metastases. Until now, prediction is mainly based on the individual judgment of clinicians using X-rays. However, it is hard to interpret the mechanical consequences of a lesion based on X-rays alone. The strength of a femur not only depends on the 2D size of the lesion but also on parameters like the bone geometry, the bone density distribution, the 3D size and location of the metastasis, and the loading condition of the femur. Hipp et al. [25] showed that orthopedic surgeons could not accurately estimate the strength reductions or load-bearing capacity for proximal femurs with intertrochanteric defects by using plane radiographs or computed tomography (CT). In this study, it was generally confirmed that the experienced orthopedic surgeons, radiation oncologists, and the radiologist had difficulties to predict bone strength. In addition, there was a large variation between the physicians in the way they ranked the femurs from weak to strong. The order of strength predicted by the FE-model was considerably better than the order of strength predicted by the clinical experts.

The FE-simulations in this study were based on the work of Keyak et al. [18] but with two adjustments to further improve the accuracy. First, the elements in our model were an exact copy of the voxels of the CT scans, both in size and orientation. Secondly, an RSA system was used to accurately align the FE-model with the experimental orientation of the femur. The slope and intercept of the regression lines in this study were closer to 1.0 and 0.0, respectively as compared to the other studies [17,21,22,26], meaning a one-to-one prediction was approached, rather than having to correct the predicted values with systematic errors. The high correlation of $r^2 = 0.92$, between the predicted and the measured failure force, was comparable with the findings of other fail simulations in which the correlations ranged between $r^2 = 0.83$ [18] and $r^2 = 0.96$ [21].

The mechanical experiments and computer calculations showed that the lesions at the medial side affected the failure strength more

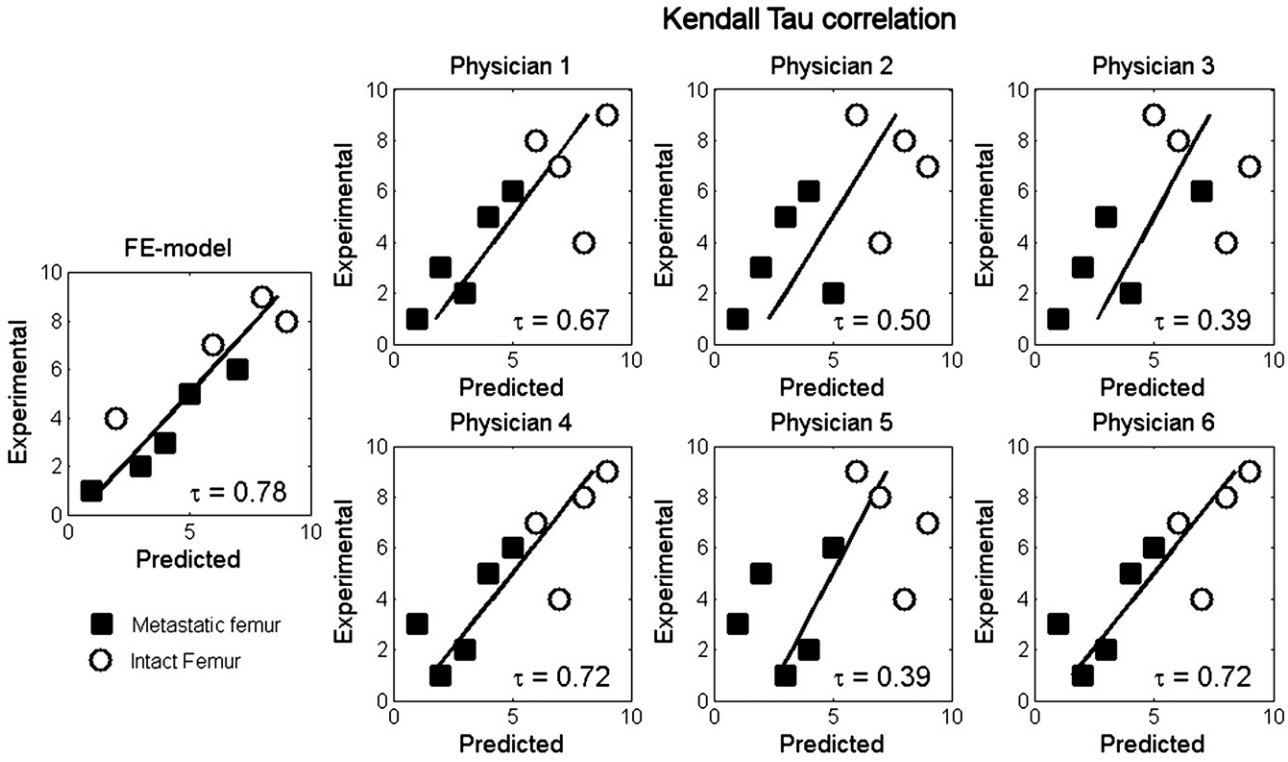

Fig. 6. The Kendall Tau correlation coefficients between the experimental and predicted ranking for both the FE-simulation (left) and the six clinical experts (right). On both *x*-axis and *y*-axis, 1 = weakest femur to 9 = strongest femur.

than lesions at the anterior side, whereas the size of the lesion seemed to be of less importance under compression. Under compression, the force transfer mainly goes through the femoral head and neck to the cortical bone of the diaphysis. Because the femoral head and the applied load are located medially from the diaphysis, the high stresses will primarily occur at the medial site of the femur. This may explain that a small lesion medially can cause a bigger loss of strength under axial loading conditions than a large lesion at the anterior site. These kinds of interactions between load-transfer, mechanical density, strength, and bone lesions (size and location) are difficult to judge for clinicians and could be made more tangible using patient specific computer models as proposed in this study.

There are a few limitations that should be considered. In this study, the metastatic lesions were artificially created and were limited to cortical lesions. It was practically impossible to simulate all types of lesions. Together with the clinical oncology team, cortical lesions were selected as these are affecting the strength to a large extend. In patients, the lesions may have an irregular shape and may be surrounded by compromised bone quality. Although these features were not included in this study, they would appear on a QCT scan and hence can be incorporated quite easily in the FE computer models. Even for the relatively simple configurations of metastatic lesions, the clinicians had great difficulties in predicting the strength values whereas the FE-model could predict the strength reasonably well. In future work, more complex configurations, such as multiple lesions, will be considered as well.

Patients with metastatic lesions most often fracture their femur by simple movements like starting to walk, standing, raising from a chair, and stair climbing. In this study we started with a simplified loading configuration, i.e. compression on the femoral head, comparable to other experiments reported in the literature [16,17,21,22]. The compressive force is important in daily life and its peak value varies between 2 and 4 times the body weight (BW) [27–30] during normal walking. However, for a patient specific risk prediction, the bone strength should be compared to the physiological loading of the femur in daily life. Physiological loading conditions are quite complex and involve the joint contact force as well as the forces generated by the muscles around the femur. When metastatic defects appear as transcortical holes in the femoral shaft, it has been found that especially torsional strength and torsional stiffness are reduced [19,31,32]. Torsional loading patterns can be found in activities such as sit-to-stand movements and climbing and ascending the stairs. Future research will, therefore, also include other loading modes than compression.

As the loading mode is an important parameter in the failure force estimates of the clinicians, the testing protocol of the laboratory experiments were given to them. The loading mode was very simple and easy to interpret and still the fracture prediction of the clinicians was not very good. It can be imagined that the prediction of failure force is even harder for the clinicians when more realistic, hence complex, loading modes are included. This would further emphasize the need for patient specific computer modeling to assist the clinicians in their judgments.

In conclusion, this study showed that the use of a non-linear finite element model can improve the prediction of bone strength in comparison to the strength prediction of experienced physicians. We found a very high correlation coefficient $r^2 = 0.92$ between the predicted and measured failure force and also the order of the strength prediction was considerably better than that of the physicians. Under compressive loading conditions we found that lesions at the medial side affected the failure strength more than those at the anterior side, whereas the size of the lesion seemed to be of less importance. The non-linear FE-model is currently being tested in a clinical setting to improve fracture risk prediction in patients with femoral metastases to distinguish patients with low-risk lesions, which can be treated with radiotherapy, and high risk lesions, which should be offered prophylactic surgery. Hence, the FE method may be helpful to positively affect the quality of life for cancer patients with bone metastases who have a limited life expectancy.

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