Patient specific CT-based finite element analysis: a new tool to assess fracture risk in benign bone lesions of the femur

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Abstract (233 words)

Background: Most benign active and latent lesions of proximal femur often do not predispose a patient to a pathologic fracture. Nonetheless, internal fixation may be performed unnecessarily due to the lack of accurate clinical tools that may determine the patients at low risk of pathologic fracture. The percentage of unnecessary surgeries is estimated to be more than 30%. A patient-specific CT-based finite element analysis (CTFEA) may quantify bone strength and risk of fracture under normal weight-bearing conditions.

Methods: Clinical relevance of such CTFEAs is investigated herein in a retrospective study on a cohort of 17 patients. CTFEA results (high risk = indication for surgery, low or moderate risk = follow-up) were compared to actual clinical decisions (surgery vs follow-up): all patients predicted by the CTFEA as high risk underwent internal fixation and had good outcomes (n=6).

Findings: Among the low- and moderate-risk CTFEA patients (n=11), four (36%) were operated immediately, and seven (64%) were either operated after a delay of at least 6 months or were never operated. None sustained a pathologic fracture. Patients predicted as low fracture risk by CTFEA remained fracture-free for a minimal period of 6 months. Prediction of high risk of pathologic fracture by CTFEA was in complete agreement with the conventional clinical evaluation.

Interpretation: We consider that CTFEA is a promising decision support system for management of patients with benign tumors of femur, which may reliably back-up the decision to withhold surgery.

Keywords: benign bone tumors, femur, pathologic fracture, fracture risk, bone strength, finite element analysis
Introduction (2965 words)

Benign bone lesions of the femur include fibrous dysplasia (FD, 42%), giant cell tumor (GCT, 23%), chondroblastoma (14%), aneurysmal bone cyst (ABC, 9%), and others (11%). Although benign, these lesions disrupt the normal bone anatomy and may predispose patients to pathologic fractures, with as high as 30% of patients with such tumors having been reported to present with a pathologic fracture \(^1\). Benign aggressive (e.g., GCT or ABC) and some benign active (e.g., chondroblastoma) lesions are most often operated upon, given the natural course of the disease, which includes significant tumor-related pain and local bone destruction. However, fractures are less frequent among other benign active and latent lesions (e.g., FD, simple bone cyst or non-ossifying fibroma (NOF)). These latter patients present a clinical dilemma: whether their management should be preventive fixation or follow-up and watchful waiting. The decision to perform surgery mostly depends upon the risk of pathologic fracture, although it is also influenced by other considerations, including the extent of the patient's pain and discomfort. The outcome of preventive fixation with the primary goal to treat the latter symptoms may, however be disappointing by failure to solve the complaints on pain, and a validated estimation of fracture risk is therefore necessary to guide in choosing a successful treatment option.

Clinical decision-making support tools that would identify patients with benign tumors who are at higher risk of pathologic fractures are limited. Imaging does not always adequately present the destructive effect of the lesion on normal bone anatomy. Radiographic exams are of very limited value given their variance in opacity and lack of size calibration. Cross-sectional imaging is valuable, since only a computerized tomographic (CT) scan clearly shows cortical bone with enough resolution and detail to subjectively provide a guess on the strength of the bone, although this feature does not account for the material properties of the bone. Additionally, the decision to perform surgery depends on the location of the lesion, its size, the amount of cortical bone destruction, the presence of mechanical pain, and progression of the lesion over time on repeated imaging studies. Application of Mirels’ score \(^2\), which estimates the risk of a pathologic fracture and the need for preventive fixation in the case of metastatic bone lesions, may not be appropriate for patients with benign tumors of the proximal femur, nor has it been validated in this setting. Mirels’ score gives considerable weight to the subjective symptoms of pain (three points) that, together with the peritrochanteric location of the lesion (three points) and the minimum one-point score in two other parameters (type and size of the lesion), provide a total score of eight points,
which is the accepted cut-off point to proceed with surgery and preventive fixation of the involved bone. Shin et al. have recently suggested the following alternative criteria for surgery in patients diagnosed with non-aggressive lesions of the proximal femur: pain on initiating hip movement, progressively worsening pain, cortical thinning, and the absence of a sclerotic margin. Thirty-nine of their patients lacking these criteria were followed for at least twelve months without sustaining a pathologic fracture. Despite this encouraging evidence, the use of qualitative clinical tools is inferior to quantitative estimates of fracture risk due to selection bias and inter-rater variability.

Computational methods for patient-specific evaluation of fracture risk based on diagnostic CT imaging may offer the benefits of precision, validity, and the ability to accurately track changes in fracture risk if the lesion progresses. CT-based finite element analysis (CTFEA) can assess the risk of fracture by creating a patient-specific finite element model of the bone with the lesion, load the bone model with physiological loads typical to daily activity, and compute the femur's mechanical response. It accounts for the patient's weight, the accurate geometry and inhomogeneous material properties of the femur, the geometry and location of the tumor, and, importantly, these computational methods have been validated ex-vivo on normal femurs and on femurs with real metastatic tumors. The analysis outcome is the tensile and compressive strains (in microstrain) at any location along the femur, which are used to determine the risk of fracture when compared to the typical values in a healthy femur. These results are also compared to ones in the healthy contralateral bone that is universally present on CT scans. The algorithm used to generate the FE model from the CT scan stage until the results stage is shown in Fig. 1. This method has been validated against the experimental mechanical loading of twelve femurs in a double blind study and on fourteen fresh-frozen femurs with real metastatic tumors, with a high correlation between the predicted and the observed yield load. One retrospective clinical study on metastatic bone lesions of the femur demonstrated that about 39% of patients who underwent operative fixation based on clinical evaluation and application of Mirel’s criteria may not have required surgery.

The evidence supporting the use of CTFEA in clinical practice instead of clinical scoring systems in the decision of whether or not to operate on benign tumors of the femur in order to avoid a pathological fracture is still under investigation. In this retrospective study, we analyzed bone strength and evaluated the fracture risk in patients with benign bone lesions of the femur.
hypothesized that CTFEA analyses would add valuable information to the decision-making process of whether or not to operate on these patients, and support the conducting of a randomized interventional study.

Fig. 1. Schematic algorithm for generating the patient-specific FE model of the femur. a) CT scan of the two femurs (arrow point at the tumor location), b) The 3-D segmented femurs and a cross section showing the E-modulus within the femurs, c) FE mesh and application of stance position loading conditions, d) Compressive maximum principal strains.
Methods

Study population

The study is a retrospective case series of patients with a benign bone lesion of the proximal femur treated at the National Unit of Orthopedic Oncology in the Tel Aviv Sourasky Medical Center between 2014 and 2018. Permission to review patient files was given by the local IRB. Patients were included in this study if they had a painful lesion in the proximal femur that resulted in significant changes in bone structure on imaging studies that were deemed to be sufficient to warrant prophylactic fixation of the involved bone by the surgeons of the multidisciplinary team. Requirements for study entry were a CT scan of the involved femur and being sixteen years of age or older (the latter since CTFEA has not been validated in the pediatric population before achieving skeletal maturity). Patients who did not undergo a CT scan as part of their work-up were excluded, as were those who had been diagnosed with a benign aggressive bone tumor (e.g., GCT, ABC and chondroblastoma), since surgery is dictated in these cases.

Data on demographics (gender, age, weight, and height), type of lesion, CT findings, CTFEA results, the details of treatment management, and the postoperative follow-up course were collected for each patient. Decisions regarding surgery were approved by four surgeons and a musculoskeletal radiologist who are an integral part of the hospital's tumor board, with decisions based on clinical and radiographic judgement. Due to the retrospective nature of this study, CTFEA results did not influence the tumor board’s clinical decision-making process regarding surgery.

CT-based finite element analysis (CTFEA)

Using the individual CT-scan a CTFEA was performed following the procedure documented in $^6,^9$ and briefly described herein. Femur’s mechanical response to physiological loads can be well predicted by solving the equations of the linear theory of elasticity in the inhomogeneous femur domain. The analysis starts by processing the individual DICoM (Digital Imaging and Communication in Medicine) format quantitative CT scans: The two femurs are segmented and aligned with the z axis, retaining only these pixels that belong to the femur and discarding the surrounding soft tissue pixels. The Hounsfield Units (HUs) of each pixel includes information on the local bone density, that is correlated to the Young modulus using relationships
between Young’s modulus and ash density for cortical \(^{10}\) and trabecular bone \(^{11}\), validated in \(^7\). The following relations were used to determine Young’s modulus in the femur:

\[ \rho_{K2HPO4} = 10^3 (a \times HU + b) \quad [\text{g/m}^3] \quad (1) \]
\[ \rho_{ash} = 0.877 \times 1.21 \times \rho_{K2HPO4} + 0.08 \quad [\text{g/m}^3] \quad (2) \]
\[ E_{cort} = 10200 \times \rho_{ash}^{2.01} \quad [\text{MPa}], \quad \rho_{ash} \geq 0.486 \quad [\text{g/m}^3] \quad (3) \]
\[ E_{trab} = 2398 \quad [\text{MPa}], \quad 0.3 < \rho_{ash} < 0.486 \quad [\text{g/m}^3] \quad (4) \]
\[ E_{trab} = 33900 \times \rho_{ash}^{2.2} \quad [\text{MPa}], \quad \rho_{ash} \leq 0.3 \quad [\text{g/m}^3] \quad (5) \]

The Poisson ratio was set to the constant value of \( \nu = 0.3 \).\(^7,9\)

A tetrahedral FE mesh is created automatically for each femur that divides each it into approximately 100,000 finite elements. A physiological load of a magnitude of 2.5 body weight, that mimics the contact hip force, was applied to femur’s head that mimics a stance position loading.\(^{12}\) The hip contact force is applied on the femur’s head directed along the line connecting the center of the femoral head to the intercondylar region of the distal femur. The load was applied at an angle approximately 7° to the shaft axis for patients whose CT scans had included only the proximal part of the femur.

A linear elastic analysis was then performed by solving the system of generated equations obtaining strains at any location of interest in the femur, particularly in the regions adjacent to the tumor lesions. These quantitative strain measures are compared to typical values in a healthy bone and compared to the values at the same locations in the contralateral healthy bone enables the determination of the risk of fracture.

**Estimation of femur strength and fracture risk**

The relative bone strength at tumor surroundings compared to non-diseased femurs is based on the CTFEA predicted principal strains. The median tensile or compressive principal strains at 4 regions of the femur (neck, proximal shaft, middle shaft, distal shaft) of disease free femurs were computed based on 12 femurs as shown in Table 1.\(^6\) The ratio between the absolute maximum principal strain in the vicinity of the benign tumor and the typical median strain in the same anatomical region of the disease free femurs was calculated and denoted typical strain fold ratio. As another measure of the femur strength at the tumor region we calculated the ratio between the...
tensile and compressive strains at the tumor surroundings and the strain in the same region in the contralateral disease free femur denoted by contralateral strain fold ratio.

<table>
<thead>
<tr>
<th>Femur region</th>
<th>Tensile strain (µstrain)</th>
<th>Compressive strain (µstrain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>2850</td>
<td>2750</td>
</tr>
<tr>
<td>Proximal shaft</td>
<td>1375</td>
<td>2100</td>
</tr>
<tr>
<td>Middle shaft</td>
<td>1325</td>
<td>1850</td>
</tr>
<tr>
<td>Distal shaft</td>
<td>625</td>
<td>1100</td>
</tr>
</tbody>
</table>

The 1.5 typical strain fold ratio value was used as the determinant of the threshold for pathological femoral fracture. A typical strain fold ratio of 1.4-1.5 was used to determine a moderate risk of fracture. For patients who demonstrated a low or moderate fracture risk, an additional analysis of torsional load was performed, with fracture risk defined according to the difference between the diseased and healthy femur.

Interpretation of findings

A mixed method approach was applied for analysis and presentation of the study results. The patients were divided into groups of high or moderate/low risk of fracture based on the CTFEA analysis findings. Continuous variables (age, weight, height) were presented with standard distribution parameters (mean ± SD), and they were compared between the two groups using the t-test. Frequency of nominal variables (gender, type of lesion) was presented as percentages and compared between groups using the chi-square test. Alpha and beta parameters were set at 0.05 and 0.2, respectively. The p-value was used for convenient reporting of statistical significance. In the qualitative analysis, the agreement between CTFEA results (low vs high risk of fracture) and the eventual clinical decision (preventive fixation vs conservative follow-up) was described as six possible outcome groups arranged in a standard 2X2 table (high- vs moderate- or low-risk patients...
who underwent surgery and high- vs moderate- or low-risk patients who were either operated after a period of at least 6 months or were never operated).

The focus was treatment decisions and treatment outcomes of patients with a CTFEA-based low risk of fracture and the necessity of surgical fixation in that group. Since many of these patients were eventually operated on, the duration of fracture-free follow-up between the CTFEA result and the operation was regarded as an indicator of the CTFEA assessment of safety. Therefore, patients with low CTFEA risk who were operated on six or more months after the first analysis and did not fracture were assigned to the “nonoperative treatment” group. Representative figures of CTFEA of the femurs of a patient with a high and a patient with a low CTFEA-predicted fracture risk are presented by Figs, 2 and 3, respectively.

**Fig. 2.** Patient 12: a male aged 36 years at the time of diagnosis who developed a benign-appearing lesion in the region of the lesser trochanter and femoral neck and pain on weight bearing. Biopsy demonstrated an epithelioid hemangioma. Definitive surgery included extensive curettage, cryoablation, and internal fixation. **A** The appearance of the lesion in the neck of the left femur on CT (four images in the axial plane). **B** A 3D reconstruction of the CT scan. **C** The CTFEA strains on compression during stance position load (2.5 times the body weight). High strains are demonstrated in the left femur at the tumor region (lesser trochanter and femoral neck) compared to the healthy right femur. According to these findings, the risk for hip fracture in the left femur is very high.
Fig. 3. Patient 14: a female aged 21 years at the time of diagnosis of an enchondroma located in
the superolateral neck of the left femur. The patient was followed for ~33 months and eventually
underwent surgery (curettage+burring+cryoablation+cemented internal fixation). A The
appearance of the lesion in neck of the left femur on CT. B A 3D reconstruction of the CT scan. C-
D The CTFEA showing bone strain with tension C and compression D during stance position
loading (2.5 times the body weight). The tension strain in the superior neck area of the impaired
left femur is only 9% larger than the equivalent strain in the healthy right femur. The differences
between the right and left femurs are no more than 17% in all other strains. These findings
suggest a low risk of fracture.

Results
Seventeen heretofore unreported patients were included in this retrospective case series. Their
baseline characteristics and treatment courses are outlined in the Table in the Appendix.
Examination of the differences between subjects with high vs moderate/low CTFEA fracture risk
revealed that the groups were generally similar except for differences in type and location of their
respective lesions. Some of the high-risk lesions occupied more than one region of the involved
femur (e.g., head and neck, neck and proximal shaft, etc.) (see Appendix).

The result of the CTFEA and the decision to offer surgical treatment based on the clinical
assumption that the involved bone was at risk of a fracture were in agreement in most cases
(13/17, 76.5%). The group of subjects who had a high risk for CTFEA and underwent surgery (n =
6, 35.3%) and the group who had a low or moderate risk for CTFEA and did not undergo surgery (n = 7, 41.2%) were the two largest groups (Table 2).

<table>
<thead>
<tr>
<th></th>
<th>High risk of fracture (n=6)</th>
<th>Low risk of fracture (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Operated</strong></td>
<td>P2 - normal</td>
<td>P4 – limping and a new-onset back pain</td>
</tr>
<tr>
<td></td>
<td>P6 – intraoperative fracture, continued trochanteric bursitis and pain postoperatively</td>
<td>P5 – normal</td>
</tr>
<tr>
<td></td>
<td>P9 – postoperative infection, series of surgeries ending with girdlestone procedure</td>
<td>P7 - normal</td>
</tr>
<tr>
<td></td>
<td>P10 - normal</td>
<td>P14 - normal</td>
</tr>
<tr>
<td></td>
<td>P12 – high intraoperative blood loss, reoperation to extend currettage, postoperative normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P17 – normal</td>
<td></td>
</tr>
<tr>
<td><strong>Not operated/operated after &gt; 6 months</strong></td>
<td>none</td>
<td>P1 – after surgery had persistent pain and reoperation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P3 – after surgery developed weakness of quadriceps, difficulty climbing stairs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P8 – normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P11 - persistent pain with nonoperative treatment, no fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P13 – normal</td>
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<tr>
<td></td>
<td></td>
<td>P15 - normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P16 - normal</td>
</tr>
</tbody>
</table>

Patient 13 is an interesting example of a patient who was scheduled for surgery but showed clinical and radiographic improvement on follow-up analysis of a repeat CT scan that showed that
the patient was no longer at an increased risk of fracture and thus the decision to intervene surgically was overturned (Fig. 4).

![Fig. 4](image)

**Fig. 4.** Patient 13: a male aged 20-year-old when he initially presented with a painful lesion of the left proximal femur (A-B, white arrows), which was classified as "high risk". The patient was scheduled for surgery, but the symptoms started to improve, and the lesion appeared sclerotic on a follow-up CT five months later (C-D, white dotted arrows). The decision to operate was overturned, and a repeat CTFEA confirmed a low fracture risk.

In the low-risk group, two patients (patient 1 = intraosseous lipoma and patient 3 = NOF) were referred to non-operative treatment but eventually underwent surgery after a mean follow-up of 18.5 months (minimum 10 months), during which they did not sustain a fracture. There were additional patients in this group (4 - FD and 14 – atypical cartilaginous tumor), whose surgery was initially postponed by 3 to 5 months and who did not sustain a fracture either. Although intervention was not initially indicated by neither the surgeon nor by the CTFEA results, the above
four patients strongly favored surgical treatment as a possible solution for their pain and related symptoms. For example, one of the patients (patient 1) underwent curettage and cementation in a private practice facility for which he had no insurance coverage after having undergone 18 months of conservative treatment. On follow-up, 15 months after the operation, he explained that his decision to proceed with surgery was guided by unrelenting pain and the concern about the possibility of malignancy, which he wished to be ruled out by excisional biopsy. Unfortunately, the operation did not relieve his pain, and he was scheduled for additional surgery, i.e. internal fixation, at the time of the interview.

The six patients who comprised the “high risk with surgery” group included two cases of fibrous dysplasia, one simple bone cyst, one epithelioid hemangioma, one unicameral bone cyst and one non-ossifying fibroma (Table 3). There were no high-risk patients who were not operated. All six patients had good immediate and long-term outcomes. Three of them deserve special mention. One subject (patient 6) had an intraoperative pathologic fracture, which may be regarded as proof of the bone fragility. She continued experiencing hip pain postoperatively. Another subject (patient 2) had a relatively large benign lesion in the neck proximal to the lesser trochanter, which however was considered amenable to conservative treatment by some members of the management board (Fig. 5). CTFEA analysis showed high risk of fracture supporting those members of the management board who proposed operative treatment. The third subject (patient 12) had an aggressive epithelioid hemangioma, which progressed soon after undergoing a surgical biopsy and curettage and required a repeated and more aggressive surgical intervention. Since then, the patient has been disease free with full function. Patient 9 was a 70-year-old female who had a fibrous dysplasia lesion of femoral neck and lesser trochanter that was followed conservatively for several years. The most recent CT analysis showed a high risk of fracture. The patient underwent partial hip replacement that was complicated with infection. A series of
operations and prolonged intravenous antibiotic course failed to control infection, ending with Girdlestone procedure.

**Fig. 5.** Patient 2: a male aged 21 years at diagnosis of a benign fibrous dysplasia lesion of the femoral neck proximal to the lesser trochanter (A, plain films, black arrow). The MRI demonstrated almost complete occupation of the femoral neck by the lesion (B, white thick arrow). The standard CTFEA protocol showed only moderate strains on compression and tension, possibly indicating a false-negative result. However, the CTFEA torsional load simulation, which is always performed in such cases, showed a high fracture risk, in line with the clinical decision.

Four subjects who were referred to immediate surgery despite being considered low or moderate risk by the CTFEA had an unremarkable postoperative course (mean follow-up of 24.3 months). One of them (patient 5) was satisfied with the surgery and reported only minimal discomfort on postoperative follow-up. Another patient (patient 4) still had a limping gait, and reported no improvement in hip pain, with sensitivity to weather changes, as well as a new-onset backache.
### Table 3: Summary of patient characteristics (n=17)

<table>
<thead>
<tr>
<th></th>
<th>High risk (n=6)</th>
<th>Low/Moderate risk (n=11)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean, sd)</strong></td>
<td>31 (20.2)</td>
<td>24.5 (7.3)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Gender (male:female)</strong></td>
<td>2:4</td>
<td>5:6</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Tumor type (n, %)</strong></td>
<td>Fibrous dysplasia (2, 33.3%)</td>
<td>Fibrous dysplasia (6, 54.5%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Non-ossifying fibroma (1, 16.7%)</td>
<td>Non-ossifying fibroma (2, 18.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epithelioid hemangioma (1, 16.7%)</td>
<td>Atypical cartilaginous tumor (1,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simple bone cyst (1, 16.7%)</td>
<td>9.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unicameral bone cyst with secondary</td>
<td>Intraosseous lipoma (1, 9.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>aneurysmal bone cyst (1, 16.7%)</td>
<td>Simple bone cyst (1, 9.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Location (%)</strong></td>
<td>Head and neck (1, 16.7%)</td>
<td>Head (3, 27.3%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Neck (1, 16.7%)</td>
<td>Distal femur (2, 18.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neck and lesser trochanter (1, 16.7%)</td>
<td>Lesser trochanter (2, 18.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lesser trochanter (1, 16.7%)</td>
<td>Neck (2, 18.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Below lesser trochanter (1, 16.7%)</td>
<td>Below lesser trochanter (1, 9.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distal femur (1, 16.7%)</td>
<td>Close to greater trochanter (1, 9.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Preventive fixation surgery (%)</strong></td>
<td>100%</td>
<td>45%</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>SFR (mean, sd)</strong></td>
<td>2.4 (0.7)</td>
<td>1.2 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>FU until surgery, months (mean, sd)</strong></td>
<td>2.7 (1.9)</td>
<td>5.8 (7.5)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Discussion

The findings of this study demonstrate that the CTFEA assessment of femoral bone lesions showed complete agreement with clinical decision-making in the high-risk fracture group. Moreover, the eleven subjects with moderate- and low-risk CTFEA who were never operated on or whose operation was postponed were shown to be fracture-free for long periods of time (6 months or more). CTFEA therefore, would appear to have reliably predicted a low fracture risk for a minimal period of six months. A review of the postoperative outcomes of six moderate- or low-risk patients who underwent surgery revealed that three (50%) of them had adverse outcomes of various severity including continued pain or limp; one required a re-operation.

Patients with low-risk CTFEA results can be safely followed for at least six months without expectations of their sustaining a fracture. This information is extremely valuable because it can be used in clinical practice to support a decision on non-intervention. The decision not to intervene for a surgeon is more difficult than the decision to proceed with surgery, possibly due to the surgeon’s wish to be “in control” of a perceived fracture risk. Another explanation for the overall trend for fixation is the patient’s expectations. Two major motives that guided patients to choose surgical intervention were the possibility to alleviate symptoms that could be caused by their respective bone lesions, and their need for histological proof that they did not have a malignant tumor. In such a setting, the surgeon needs a more solid basis to contend with patient preferences for intervention and justify the choice of the conservative treatment. Notably, clinical staging systems may not offer a reproducible basis for this purpose due to inter-rater variability. With CTFEA, however, fracture risk is measurable and reproducible, and the calculated fracture risk can be validated by clinical studies.

We view CTFEA as a decision-aiding tool, by providing quantitative insight to surgeons that has not been previously available to support their decision with regard to patient management. It must be borne in mind that CTFEA does not replace the need to take a complete history, a full physical examination, and referral to proper imaging studies before proposing a surgical plan. The example of patient 13, who had been scheduled for surgery but was not operated on due to an unexpected improvement of the lesion, well illustrates that history and physical examination remain important determinants of treatment. Like any other diagnostic measure, CTFEA quantifies bone strength and fracture risk at a given time and provides a prediction of outcome (fracture) with a certain degree of reliability. When input variables for the CTFEA change (tumor
growth or subsiding of growth), the results of the analysis will change as well. In the case of
patient 13, the analysis of the second CT scan showed a reduced risk of fracture, corresponding
with clinical improvement and radiographic appearance of the tumor.

Due to its high precision and the ability to reflect 3D changes in lesions and bone structures,
CTFEA can be especially useful for monitoring clinically progressing lesions. The analysis can
also direct the surgeon’s attention to the exact points of weakness in the bone. This is particularly
important in large benign lesions, and can help the surgeon choose the most appropriated implant
for surgical fixation. Currently, the analysis is performed automatically without any intervention
of an analysist, the CTFEA system is CE and ISO accredited and the results are available in the
hospital PACS system within 1 hour so that it does not delay the flow of the decision-making
process in terms of timing and type of surgery.

The limitations of this study include a small sample size and the lack of a gold standard for
comparison to CTFEA. In an ideal experimental design, patients who were clinically and
radiographically judged to have a low fracture risk and had a CTFEA that agreed with the
clinicians' judgment would not be candidates for surgery. None of the patients in our current
cohort, except for patient 13, underwent a repeat CT scan. Repeat CTFEA after a set time period
of follow-up (e.g., 6 months) would help to validate the original decision. In reality, four of the
eight patients who were deemed to have both a clinical and CTFEA low fracture risk nevertheless
underwent surgery; three of the latter did not report any improvement of their symptoms and even
developed surgery-related complications.

One possible limitation of the CTFEA analysis is that it does not fully account for the
fracture risk that results from trauma. CTFEA is carried out with loads of 2.5 times the body
weight of the patient which simulates stance and walking up and down stairs. These loads do not
simulate a fall. Therefore, a patient with a decrease in femoral strength due to a benign lesion,
who is resilient to physiological loads, may still suffer a fracture after a minor fall. This risk is
low, and no low-energy fractures were observed in seven of our patients who were not operated or
whose operations were postponed for long periods of time. However, we are aware that we may
encounter this problem in prospective studies or in clinical practice, as the percent of preventive
surgeries decreases.

In this study, CTFEA showed a high degree of agreement with clinical decisions on
preventive surgery: most patients with a high risk of fracture underwent surgery, and most patients
with a low or moderate risk of fracture did not. Patients with a low risk of fracture on CTFEA could be safely followed for more than 6 months (mean 20.6 months). Finally, many patients whose surgery was not indicated by CTFEA reported no improvement of their symptoms nor had they developed complications. Since nowadays the CTFEA is CE and ISO accredited and available as a fully automatic procedure for the surgeon with a report being automatically generated within 1 hour, we therefore recommend CTFEA as a valuable tool that supports clinical decision-making by providing a repeatable quantitative and objective estimate of fracture risk.

Conflicts of interests

HS, YG, YK, SD and AS have no conflicts of interest. NT and ZY have a financial interest in PerSimiO Ltd.

References


