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The insufficiencies of risk analysis of impending pathological fractures in patients with femoral metastases: A literature review☆

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ABSTRACT

Purpose: Pathologic fractures in patients with bone metastases are a common problem in clinical orthopaedic routine. On one hand recognition of metastatic lesions, which are at a high risk of fracture, is essential for timely prophylactic fixation, while on the other hand patients with a low risk of pathologic fractures should be spared from overtreatment.
The purpose of this review is to identify all methods for fracture risk evaluation in patients with femoral metastases in the literature and to evaluate their predictive values in clinical applications.
Methods: A MEDLINE database literature research was conducted in order to identify clinical scoring systems, conclusions from prospective and retrospective radiologic and/or clinical studies, as well as data from biomechanical experiments, numerical computational methods, and computer simulations.
Results: The search identified 441 articles of which 18 articles met the inclusion criteria; 4 more articles were identified from citations of the primarily found studies. In principle there are two distinct methodologies, namely fracture risk prediction factors based on clinical and radiological data such as the most deployed the Mirels' score and fracture risk prediction based on engineering methods. Fracture risk prediction using Mirels' score, based on pure clinical data, shows a negative predictive value between 86 and 100%, but moderate to poor results in predicting non-impending fractures with a positive predictive value between 23 and 70%. Engineering methods provide a high accuracy (correlation coefficient between ex vivo and results from numerical calculations: $0.68 < r^2 < 0.96$) in biomechanical lab experiments, but have not been applied to clinical routine yet.
Conclusion: This review clearly points out a lack of adequate clinical methods for fracture risk prediction in patients with femoral metastases. Today's golden standard, the Mirels' score leads to an overtreatment. Whereas, engineering methods showed high potential but require a clinical validation. In future definition of patient-specific, quantitative risk factor based modelling methods could serve as useful decision support for individualized treatment strategies in patients with a metastatic lesion.

1. Introduction

Pathologic fractures in patients with metastatic cancer of the breast, prostate, lung, multiple myeloma, bladder, thyroid, kidney and other primary carcinomas with skeletal involvement are a common problem in clinical orthopaedic routine (Fig. 1) (Cheal et al., 1993; Dijstra et al., 1994; Fidler, 1981; Menck et al., 1988). In a study with nearly 700 patients with breast cancer, almost one third (29%) of patients with femoral metastases experienced a pathologic fracture (Oda and Schurman, 1983). Metastatic lesions can be lytic, blastic or of a mixed type, whereas the majority of all metastatic lesions are lytic and these lesions have the highest impact on bone strength, which causes pathologic fractures. Pathologic fractures of the femur mostly occur during everyday activities, such as starting to walk, standing, raising from a chair or bed or stair climbing. Pathologic fractures often require surgical interventions due to poor healing of the affected bone (Cheal et al., 1993; Mirels, 1989) and include need of fixation devices and endoprostheses (Dijstra et al., 1994; Keyak et al., 2007; Palumbo et al., 2014) that are often augmented with polymethyl methacrylate (Dijstra et al., 1994; Palumbo et al., 2014; Keene et al., 1986). Prophylactic fixation is generally preferable to the trauma of fracture and its subsequent treatment

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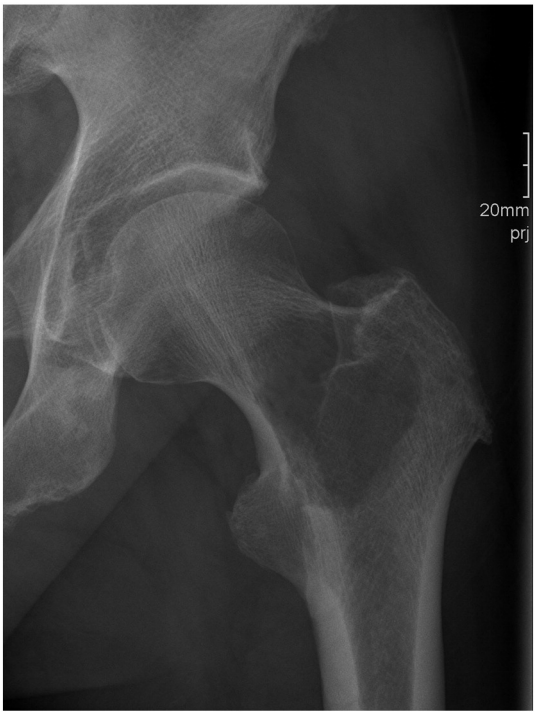

Fig. 1. Conventional radiograph of the left proximal femur of a 73 yr old man diagnosed with renal cell cancer. Image demonstrates a large lytic lesion involving the femoral neck and the intertrochanteric regions.

(Cheal et al., 1993; Mirels, 1989; Dijkstra et al., 1997). Furthermore, a prophylactic surgery can also play a role in pain reduction, functional improvement and an increased quality of life (Dijkstra et al., 1997; Malawer and Sugarbaker, 2001), while surgery of an established fracture increases the perioperative morbidity in patients with often non ideal to poor general condition. While patients with a limited life expectancy and with impending pathologic fractures can benefit from a surgical intervention, others can be spared from unnecessary procedures if fracture risk of identified lesions could be clearly defined.

Current guidelines for the prediction of fracture risk in patients with bone metastases are based on retrospective studies with small sample size designed to identify radiographic and clinical factors that are unique to examined patients who sustained a fracture. Experts seem to agree that there are no proven and established clinical or radiological guidelines for fracture risk prediction in metastatic bones (Keyak et al., 2007; Keene et al., 1986; Hipp et al., 1995; Michaeli et al., 1999; Hong et al., 2004; Van der Linden et al., 2004; Snyder et al., 2006; Spruijt et al., 2006; Lee, 2007; Tanck et al., 2009; Derikx et al., 2012).

The aim of this article is to review and evaluate existing clinical and radiologic risk factors as well as prediction methods for pathologic fractures in patients with femoral metastases from the literature.

2. Methods

A MEDLINE (Medical Literature Analysis and Retrieval System Online) database literature research via PubMed and also a research using Google Scholar were conducted for all articles published prior January 12th, 2016. Keywords for the MEDLINE search included '(pathologic OR pathological) AND (fracture OR fractures) AND (bone OR hip OR femur OR femoral OR subtrochanteric) AND (lesion OR lesions OR metastases OR metastasis OR metastatic OR defect) AND (risk OR size OR predict OR predicts OR predicting OR prediction OR parameter OR parameters)' in the field Title or Abstract. Our keywords were chosen based on a careful evaluation of abstracts of studies, authors were familiar with.

The initial search suggested 441 articles. The abstracts of these articles were reviewed by two independent reviewers, and 27 were identified as relevant articles, published between 1986 (Harrington, 1986) and 2015. After full review of the articles, as well as additional citations from these articles, 18 original articles met our final inclusion criteria: full text was available, studies with prospective and retrospective clinical and/or radiological data, studies on engineering methods in fracture risk assessment, biomechanical studies conducted on human, animal or artificial bone (Cheal et al., 1993; Mirels, 1989; Keyak et al., 2007; Keene et al., 1986; Dijkstra et al., 1997; Michaeli et al., 1999; Hong et al., 2004; Van der Linden et al., 2004; Spruijt et al., 2006; Lee, 2007; Tanck et al., 2009; van der Linden et al., 2003; Keyak et al., 2005; Alexander Iii et al., 2013; Sivasundaram et al., 2013; Amanatullah et al., 2014; Anez-Bustillos et al., 2014; Yosibash et al.). Articles were excluded from the review as per the following exclusion criteria: unrelated articles, review articles, case studies, and non-English articles. Four additional articles (Fidler, 1981; Menck et al., 1988; Derikx et al., 2012; Snyder et al., 2004) either familiar to the authors from past surveys or derived from the citations of the included articles, were included in the review (Fig. 2). Seventeen of these 22 articles were published in either the United States (10) or the Netherlands (7). One article was published by authors from each of the following countries: Republic of South Africa, Denmark, Republic of Singapore and Israel.

The finally selected articles were divided into four categories: radiologic and clinical reviews, clinical scoring systems, biomechanical studies, and finite element analyses.

3. Results

3.1. Radiological and clinical reviews

Fractures in femora occur predominantly in the diaphysis and the subtrochanteric region followed by the neck and trochanteric regions (Menck et al., 1988). Lesions vary greatly in size and shape. Most authors describe the length and width of the lesion as well as the percentage of axial cortical involvement of the lesion (Table 1).

The oldest study found on this topic included 66 patients with 100 metastases in long bones with 40 fractures (Fidler, 1981). Based on plain radiographs the author estimated the percentage of metastatic circumferential involvement dividing them roughly into four categories of cortex involved: <25%, 20–50%, 50–75% and >75%. It was concluded, upon the finding of 39 fractures to have a cortical involvement in the latter groups that metastatic long bones involving 50–75% and especially over 75% of the cortex are likely to fracture and should be considered for prophylactic fixation (Table 1) (Fidler, 1981).

Keene at al. evaluated radiographic and clinical documentation of 203 patients and a total of 220 measurable metastatic lesions on the proximal femur and femoral shaft in patients with breast cancer. Twelve of these metastases resulted in a pathological fracture. The authors were unable to identify either a specific percent involvement of the bone or a critical diameter for metastases that fractured. Despite the average involvement of bone in fractured femora was higher, the range of percent involvement was similar to the non-fractured group and it was concluded that radiographic measurements were of little, if any, predictive value. A further analysis of other variables, such as age height and weight did not show a significant difference between patients who suffered a fracture and the ones who did not (Keene et al., 1986).

In 69 pathologic femoral fractures Menck at el. described the geometry of the bone and the metastatic lesion and found the following metastasis sizes to be critical: axial expansion of cortical destruction zone in the neck region ≥13 mm and in other parts of the femur ≥30 mm, the ratio between width of the metastasis and bone ≥0.60, and cortical destruction of the circumference ≥50% (Menck et al., 1988). Another study examined retrospectively a total of 54 lesions with 24 pathologic fractures. Out of 27 measurable lesions, there were only 9 reported fractures. Still risk factors were defined in maximal

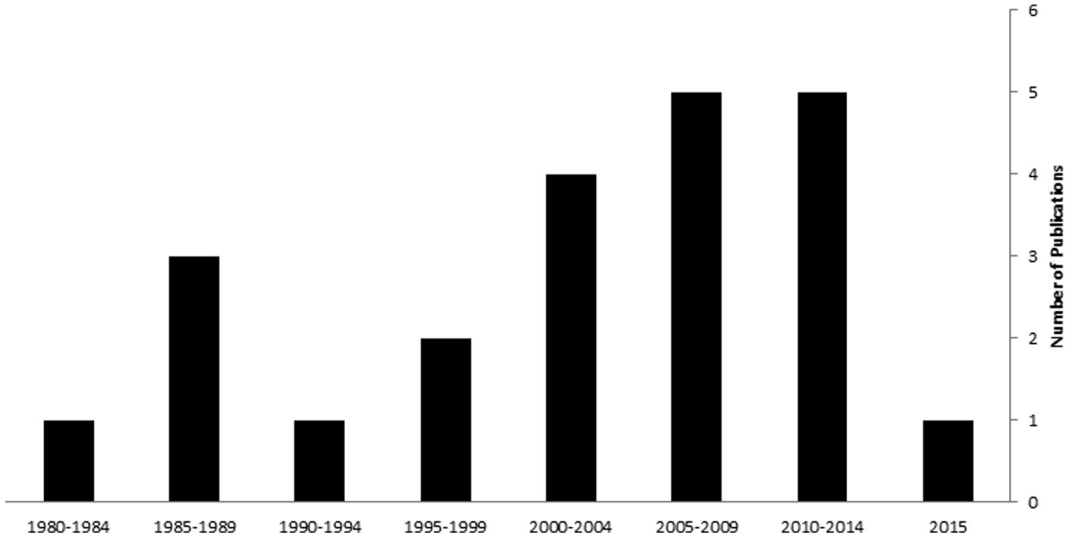

Fig. 2. Number of studies published for each year since 1986 on fracture risk prediction in patients with femral metastatic lesion.

axial cortical involvement to be ≥38 mm, width metastases to width of the bone ratio ≥0.9 and maximal width of the lesion >30 mm (Dijkstra et al., 1997). In the same study pain was not found to be a risk factor, however the authors suggest to regard increasing local pain as an indication for a lesion with growing fracture risk (Dijkstra et al., 1997). A prospective trial found only axial cortical involvement >30 mm and circumferential cortical involvement >50% to be predictive parameter in 102 patients with 14 pathologic fractures (van der Linden et al., 2003).

In the retrospective study from 1981 metastases were approximately drawn based on a radiograph on a rolled paper tube, representing the affected bone. The paper was then unrolled and the size of the metastasis was measured in order to find the critical size of affected cortex, which will cause a fracture (Fidler, 1981). One must assume a high measurement error rate in this presented assessment technique compared to today's available digital imaging and image processing techniques. Furthermore the authors did not distinguish between different extremities and bones. A high number of patients, who were considered at risk for a fracture, did not sustain a pathological fracture and would have been overtreated, if surgically treated. Still this article has been cited nearly two-hundred times providing a clinical decision aid in orthopaedic oncology. Such and similar guidelines, based on plain radiographs are used by most clinicians in fracture risk assessment. Radiological evaluations using X-ray images are difficult when standardized criteria for patient positioning are not used. Van der Linden found that a difference of the largest axial cortical involvement for anterior–posterior (AP) radiographs versus multidirectional radiographs was 1 mm ($p = 0.15$) (van der Linden et al., 2003). Fracture prediction based on radiographs is not possible in case of permeative or diffuse lesions without clear boundaries. One study reported 12 out 96 (13%) metastases as permeative (Menck et al., 1988), while Dijkstra et al. (1997)were not able to perform an accurate measurement on 27 out of 54 patients (50%). Keene et al. (1986) reported 296 out of 516 (57%) metastases as unmeasurable due to unidentifiable margins on radiographs.

Also, subjective evaluations of plain radiographs should be performed with high cautiousness. In the absence of CT (computed tomography) scans three different observers (a radiologist, an orthopaedic surgeon and a radiation oncologist) estimated the percentage of circumferential cortical involvement on plain radiographs using a two (≤50%, >50%) and a three-tiered approach (≤33%, 33% < × ≤ 66%, >66%). The separate scores of the observers were combined and in the case of scoring discrepancies, the majority opinion was taken as to the final outcome. The finer, three-tiered approach considered more lesions to have a >50% cortical involvement irrespective of fracture (Van der Linden et al., 2004), proving subjective assessments to be inaccurate and simply inadequate for fracture risk prediction in bones with metastatic lesions.

Prediction of fracture risk based on radiographs and clinical data was the subject of most studies found on the given topic. Several authors identified possible risk factors, which appears to be a mixed blessing. While predictive values such as a specific cortical involvement have a high negative predictive value (NPV), their positive predictive value (PPV) is very low (Van der Linden et al., 2004), suggesting many, up to two thirds of the patients without an impending fracture for preventive surgery (Keene et al., 1986) (Table 2).

3.2. Clinical scoring systems

Dr. Hilton Mirels, a South-African orthopaedic surgeon introduced in 1989 a weighted scoring system to quantify the risk of sustaining a pathologic fracture in long bones with a metastatic lesion (Mirels, 1989). Mirels included 78 patients in the study and found a high incidence of fractures in patients with pain aggravated by function, patients with metastases occupying more than two-thirds of the bone diameter and patients with lytic lesions compared to the ones with blastic lesions (Mirels, 1989). The Mirels' score combined four radiographic and clinical risk factors: degree of pain, lesional size or its cortical involvement, lytic versus blastic nature, and anatomic location. Each of the four variables is given a score between 1 and 3 depending on the characteristics found and a total score is derived by summing the individual scores. Therefore, scores range from 4 to 12 points (Table 2), whereas a total score of 7 or lower indicates a low chance of fracture; a total score of 8 is regarded as a borderline case, suggestive of an impending fracture and the total score of 9 or higher indicates a high chance of fracture and a necessity for prophylactic stabilisation (Mirels, 1989; Damron et al., 2003).

The Mirels' score was found insufficiently specific to predict pathologic fractures in 102 patients with femoral metastases, of whom only 13% of lesions without fracture were low-risk (Van der Linden et al., 2004). The positive predictive value was 14% in the same study underlying the weakness on fracture risk prediction based purely on clinical data (Van der Linden et al., 2004).

3.3. Experimental biomechanical studies

The use of bone mineral content (BMC) and bone mineral density (BMD) from DXA (dual energy X-ray absorptiometry) scans for prediction of pathologic fractures was examined in a biomechanical ex-vivo study (Michaeli et al., 1999). Thirty-two fresh-frozen human femora

Table 1
Size of metastatic lesions measured from radiographs and pathologic fracture risk factors defined in the literature based on radiological and clinical data and their positive and negative predictive value (PPV and NPV). All Values are given as median (MIN-MAX); values marked with an asterisk (*) are given as the arithmetic mean.

Study	Number of patients	Number of femoral lesions	Number of pathologic fractures	Imaging method	Length of the lesion	Width of the lesion	Length of cortical involvement	Width of cortical involvement	Risk factor	PPV	NPV
Fidler, (1981)	66	100 (lesions in all long bones)	40	Radiographs	N/A	N/A	N/A	N/A	Percentage of cortex involved >50%	68%	98%
Keene et al. (1986)	203	222 on proximal femur (79 measurable)	11	Radiographs	Fracture: 75.2%* (13–90) No fracture: 46.3%* (17–99)	Fracture: 59.0%* (24–99) No fracture: 50.0* (17–99)	N/A	N/A	risk of fracture canot be identified from standard radiographs	–	–
		294 on femoral shaft (141 measurable)	1	Radiographs	N/A	N/A	N/A	No fracture: 41.2% (10–99) Fracture: 29%			
Mirels, (1989)	38	61	23	Radiographs	N/A	N/A	N/A	N/A	Mirels Score > 7	70%	98%
Menck et al. (1988)	69	N/A	69	Radiographs	Fracture: 35 mm (30–40)	Fracture 30 mm (14–40)	Fracture: 40 mm (10–149)	N/A	Ratio width lesion/width bone ≥0.60 and/or axial cortical involvement ≥13 mm in the neck and ≥30 mm in other parts of the femur, or circumferential cortical involvement ≥50%	N/A	N/A
Dijkstra et al. (1997)	54	54 (27 measurable)	9	Radiographs	Fracture: 100 mm (42–200) No fracture: 65 mm (25–150)	Fracture: 33 mm (21–48) No fracture: 28 mm (17–50)	Fracture: 54 mm (38–100) No fracture: 38 mm (7–125)	Fracture: 88% (50–100) No fracture: 79% (20—100)	Axial cortical destruction ≥38 mm ratio width lesion/width bone ≥0.9 width lesion >30 mm	50% 58% 50%	100% 86% 91%
van der Linden et al. (2003, 2004)	102	110	14	Radiographs	Fracture: 58 mm (31–229) No fracture: 48 mm (14–251)	Fracture: 31 mm (15–52) No fracture: 23 mm (7–59)	Fracture: 42 mm (27–155) No fracture: 29 mm (0—120)	Fracture: 1 mm (0–6) No fracture: 2 mm (0–9)	Axial cortical involvement >30 mm circumferential cortical involvement >50%	23% 26%	97% 91%

were loaded simulating two different loading scenarios: stair ascent and external rotation with simulated circular 5 mm lytic defects between the lesser trochanter and the neck of the femur. The setup allowed horizontal movement of the specimens using bearings in order to eliminate uncontrolled forces and torques, while the load was applied vertically on the specimens. The authors could determine a linear correlation between BMC and BMD of the total proximal femur and resultant failure load for the stair ascent and external rotation configuration ($r^2 = 0.78$ and $r^2 = 0.69$). However the BMC was reduced by simulated defects by <1% in over a third of all specimens of proximal femora. The size and geometry of defects varied from specimen to specimen, not specified by the authors. Also no intact femora were included in the study as a healthy control group. Nevertheless the authors suggest investigating different loading scenarios for different daily activities to estimate the risk of fracture (Michaeli et al., 1999).

Sivasundaram et al. (2013) used synthetic femora to evaluate different tumour defect locations on the proximal femur and found the medial location to have a statistically lower stiffness values compared with intact femora and have lower strength than femora with anterior and posterior defects in axial load scenarios. In another study with synthetic bones there was a high correlation between the defect size and torsional stiffness (Amanatullah et al., 2014). However synthetic bones have a different failure behaviour from real bone and should be used only to enhance biomechanical test set-up accuracy or to study elastic properties (Hausmann, 2006).

In order to simulate lytic defects in trabecular bone, Hong and colleagues harvested cylindrical cores of trabecular bone from the vertebral bodies of whale spines, created symmetric through-hole defect groups with circular-hole diameter to specimen diameter ratios of 28%, 47% and 56% and subjected the specimen to uniaxial tension, four-point bending or torsion until failure (Hong et al., 2004). They found the load bearing capacities of the trabecular bone to be directly proportional to the axial, bending, or torsional rigidity at the weakest cross-section through the core containing the defect and concluded that QCT (quantitative computed tomography), DXA and MRI (magnetic resonance imaging) images of bones containing lytic defects can be used to determine the structural rigidity of the cross-sectional geometric data and predict the load bearing capacity of the involved bone (Hong et al., 2004). The results point out the importance of accuracy in lesion geometry for fracture prediction.

Lee hypothesized that fracture loads can be predicted using engineering beam structural analysis combined with QCT data. Lee used 20 fresh-frozen femora with oval-shaped lytic defects in the cortex (20%, 35% and 50% of the cortex) between lesser trochanter and the neck of the femur. The results for ultimate load were validated with ex-vivo tests and correlation values $r^2 < 0.87$ were found for different defect locations (Lee, 2007).

Data from biomechanical experiments show that guidelines, such as Mirels' score or specific critical geometry seem to oversimplify the problem. The strength of the bone depends on one hand on size and shape of the bone and its three-dimensional variation in density of the trabecular and cortical bone (Michaeli et al., 1999), its microarchitecture and on the other hand on size (Amanatullah et al., 2014) and shape (Kaneko et al., 2003), but also the type of the lesion (Mirels, 1989; Keene et al.,

Table 2
Mirels' scoring system (Mirels, 1989). It is based on four characteristics: site of lesion, pain, nature of lesion and size of lesion. All the features were assigned progressive scores ranging from 1 to 3.

	Score		
Variable	1	2	3
Site	Upper limb	Lower limb	Peritrochanter
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size	<1/3	1/3–2/3	>2/3

1986). The bearing demands of the bone (with lesion) depend on patient's size, weight, activity level (Mirels, 1989; Hipp et al., 1995; Bergmann et al., 1993) and loading regimen (Michaeli et al., 1999; Bergmann et al., 1993; Bergmann et al., 1989). Using engineering methods it was not possible to find any correlation between failure load and following single image parameters: cross-sectional bone density, axial and bending rigidity (both functions of bone geometry and density), defect size or geometry (Lee, 2007). On the other hand a correlation was found between failure loads from in-vitro tests and numerical calculations, which include geometric and data on mechanical properties.

A study group from the University of California (Kaneko et al.) could even show, in a carefully conducted study, that cortical bone harvested from patients with cancer generally can have degraded mechanical properties, the elastic modulus and compressive strength in comparison from specimens from donor without cancer (Kaneko et al., 2003). Other authors suspect different remodelling processes in metastatic bones (e.g. after radiation therapy) and therefore different behaviours in fatigue tests (Keyak et al., 2007). Other factors, which are likely to weaken the bone, could be besides radiation also chemotherapy, immobilisation, weight loss, sarcopenia and other (cancer-) related factors.

Provided data suggest that the specification of one or only few (geometrical) parameters cannot be regarded as a sufficient method to predict subject-specific impending fracture and furthermore to classify lesions as not critical, which seems to be a bigger issue. Based on reviewed literature, any method for predicting pathologic fracture risk must include geometric data of the lesion and the host bone and an adequate assessment of their material properties. The ultimate choice of radiological method in patients with bone metastases is governed by several parameters, such as accuracy, cost, radiation exposure, accessibility and availability. Routine use of QCT, as the only method able to discriminate changes in both the cortical and trabecular bone (Hong et al., 2004), to study the three-dimensional geometry of the bone and lesion would be most optimal.

High accuracy in pathologic fracture prediction was achieved using QCT data in a simple numerical method, such as the beam theory (Lee, 2007) or computed tomography rigidity analysis (Anez-Bustillos et al., 2014). Despite the relative simplicity and promising results, one must consider more complex models with more than just a compressive force to simulate physiological loading scenarios in the future studies.

3.4. Finite element analysis

The finite element method (FE) is a computer simulation method which has been recognised as a powerful tool for prediction of bone fragility especially structural stiffness, ultimate failure load, and local mechanical stresses (Pahr et al., 2012; Varga et al., 2011; Zysset et al., 2013; Dall'Ara et al., 2013; Keyak, 2001). FE models are based on CT scans, from which bone geometry and quality, is retrieved based on distribution of bone mineral density. Various loading patterns can be simulated by applying specific boundary conditions and external forces allowing a non-invasive prediction of resulting stresses and displacements including bone failure. Compared to other techniques, FE simulation models allow an image-based quantification of mechanical behaviour, are thus patient-friendly and relatively cost-effective, however underlying data assessment requires exposure to radiation; also patients have to be scanned with a calibration phantom lying underneath them in order to establish the reference between the BMD and mechanical properties for each element, which is crucial for accurate simulation.

Full potential of this method has not been exploited yet in the field of metastatic bone lesions.

The earliest application of finite element analysis for prediction of the stability reduction was performed by (Cheal et al., 1993). The rather primitive finite element model in terms of number of isoparametric quadratic elements and nodes, was based on a single femur from a donor, nearly twenty years younger than the mean age of femora used in the in-vitro tests, but still underestimated the absolute fracture resistance of the femora by a factor of approximately three.

Several authors proved later the ability of linear (Keyak et al., 2007; Tanck et al., 2009; Keyak et al., 2005; Yosibash et al.) and non-linear (Hipp et al., 1995; Tanck et al., 2009; Derikx et al., 2012; Anez-Bustillos et al., 2014) FE models generated from clinical CT scans to predict pathological fracture with a high accuracy (Table 3), and superior accuracy over predication by clinical experts (Hipp et al., 1995; Tanck et al., 2009). However all data were based on a small number of anatomic specimens, mostly with one specimen per different defect groups in an easily reproducible loading scenario, which does not sufficiently reflect the spectrum physiological load bearing. Only one study performed tests on femora with real metastatic lesions (Yosibash et al.). Furthermore the lack of a healthy control group (contralateral femur) in some of the studies doesn't allow a calculation of reduction in stress and the actual risk of fracture (Keyak et al., 2007, 2005). Furthermore FE models are based on QCT data, which induces much higher radiation dose compared to 2D imaging, such as DXA. Also FE analysis needs to show its predictive supremacy over current methodology in clinical routine with non-idealized scanning and loading conditions. So far no prospective studies on use of FE analysis in prediction of fracture risk exist. Furthermore FE analysis requires rather sophisticated software for image processing and analysis and a certain technical background for the operators. It was estimated that generation and calculation of a FE simulation model take about 8 h for a single femur with a metastatic lesion (Anez-Bustillos et al., 2014). A certain level of automatization will be necessary in order to make this method time- and cost-effective before it can serve as a clinically useful decision support system routine.

4. Conclusion

A definition of a risk factor may provide a more objective guideline for determining an individualized treatment strategy for each patient with a metastatic lesion. Still only few research groups have dealt with this question, which is reflected in the very low number of publications.

Table 3
Summary of FEA studies on stability of femora with simulated metastatic lesions. r… Pearson product-moment correlation coefficient between data sets from FEA and biomechanical validation.

Study	Defect	Source data	FEA Type	Number of specimen	Healthy control group	Number of different defects	Biomechanical validation	r^2	Remarks
Cheal et al. (1993)	Simulated	N/A	Linear	1	No	17	No	–	Poor performance of the FEA
Keyak et al. (2005)	Simulated	QCT	Linear	12	No	12	Yes	0.84–0.96	Four-point bending test
Spruijt et al. (2006)	Simulated	QCT	Linear	11 pairs	No	1	Yes	0.68–0.72	Torsional loading
Keyak et al. (2007)	Simulated	QCT	Linear	12	No	12	Yes	N/A	
Tanck et al. (2009)	Simulated	QCT	Non-linear	5 pairs	Yes	5	Yes	0.92	
Derikx et al. (2012)	Simulated	QCT	Non-linear	10 pairs	Yes	10	Yes	0.90–0.93	
Alexander Iii et al. (2013)	Simulated	QCT	Linear	8 pairs	Yes	1	Yes	N/A	
Anez-Bustillos et al. (2014)	Simulated	QCT	Non-linear	10 pairs	Yes	10	Yes	0.89	
Yosibash et al. (2014)	Real	QCT	Linear	7 pairs	No	12	Yes	0.78	

Several published approaches were not able to prove sufficient validity in prospective or retrospective studies based on purely clinical and radiological data. Importantly, this review points out the lack of a gold standard method. Mirels' scoring system is accurate in prediction of impending fractures, but often fails to recognise non-impending fractures and spares patients from overtreatment. While fracture risk prediction based on pure clinical data shows poor results, engineering methods provide high accuracy, but in idealized biomechanical setups, which are difficult to adapt to the variable physiological and pathophysiological conditions found in clinical routine. A combination of accurate clinical assessment and biomechanical modelling could lead to improved fracture risk prediction tools for decision support in clinical environment. It will be essential to include exact anatomy, tissue density and individual biomechanical load conditions to come to valid individual prediction statements.

Conflict of interest statement

The authors declare no potential conflicts of interest.

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