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Pathological fracture risk assessment in patients with femoral metastases using CT-based finite element methods. A retrospective clinical study

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ABSTRACT

Physician recommendation for prophylactic surgical fixation of a femur with metastatic bone disease (MBD) is usually based on Mirels' criteria and clinical experience, both of which suffer from poor specificity. This may result in a significant number of these health compromised patients undergoing unnecessary surgery. CT-based finite element analyses (CTFEA) have been shown to accurately predict strength in femurs with metastatic tumors in an ex-vivo study. In order to assess the utility of CTFEA as a clinical tool to determine the need for fixation of patients with MBD of the femur, an ad hoc CTFEA was performed on a retrospective cohort of fifty patients.

Patients with CT scans appropriate for CTFEA analysis were analyzed. Group 1 was composed of 5 MBD patients who presented with a pathologic femoral fracture and had a scan of their femurs just prior to fracture. Group 2 was composed of 45 MBD patients who were scheduled for a prophylactic surgery because of an impending femoral fracture. CTFEA models were constructed for both femurs for all patients, loaded with a hip contact force representing stance position loading accounting for the patient's weight and femur anatomy. CTFEA analysis of Group 1 patients revealed that they all had higher tumor associated strains compared to typical non-diseased femur bone strains at the same region (>45%).

Based on analysis of the 5 patients in Group 1, the ratio between the absolute maximum principal strain in the vicinity of the tumor and the typical median strain in the region of the tumor of healthy bones (typical strain fold ratio) was found to be the 1.48. This was considered to be the predictive threshold for a pathological femoral fracture. Based on this typical strain fold ratio, twenty patients (44.4%) in Group 2 were at low risk of fracture and twenty-five patients (55.5%) high risk of fracture. Eleven patients in Group 2 choose not to have surgery and none fractured in the 5 month follow-up period. CTFEA predicted that seven of these patients were below the pathological fracture threshold and four above, for a specificity of 63%

Based on CTFEA, 39% of the patients with femoral MBD who were referred and underwent prophylactic stabilization may not have needed surgery. These results indicate that a prospective randomized clinical trial evaluating CTFEA as a criterion for determining the need for surgical stabilization in patients with MBD of the femur may be warranted.

1. Introduction

Between one third to one half of all cancers metastasize to bones [1]. In 30–50% of the cases metastatic bone disease (MBD) weakens the bone's structure and may lead to pathologic fractures under daily physiological loading or pain symptoms severe enough to require treatment [2]. As a result of new immuno-oncological and chemotherapy treatments, patients with MBD are living longer [3]. >280,000 new cases of long bone skeletal metastases are reported in the United States every year [4]. Weight bearing bones, specifically the femur, are at highest risk of pathologic fracture. For suspected impending femoral fractures, prophylactic fixation is the recommended treatment because it has less morbidity and mortality than actual fracture surgery which occurs after the trauma triggers a cascade of adverse hemodynamic, metabolic and neuro-endocrine events [3,5]. The cost of prophylatic femoral fixation is $78,000/patient [7]. Economic impact studies have shown that

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the cost of prophylactic femoral fixation for a MBD patient is $21,000 less than if treatment is given post fracture [6]. On the other hand, unnecessary prophylactic surgery can cause morbidity and require a lengthy patient rehabilitation period. Effective management of patients with MBD depends on patient-specific accurate assessment of the risk of fracture.

Using clinical judgment to predict pathologic fracture risk is in many ways a learned art. Orthopedic surgeons are often expected to assess this risk in the setting of disseminated metastatic disease with bone involvement. They have to identifying those who are at high risk of fracture and those who are not. Although clinical judgment has been shown to be a suboptimal tool, its strength is in its ability to account for change in pain over time. A patient with increasing pain over time is considered to have an increasing probability of fracture. Plain radiographs are not sensitive or specific enough to make this prediction [8,9]. Based on radiographs, experts tend to overestimate fracture risk [10]. Fracture prediction based on radiographs is further complicated in patients with permeative or diffuse lesions without clear margins. Dijkstra et al. were not able to perform an accurate measurement in such cases in 50% of patients (27 out of 54 patients) [11].

Mirels' system [12] classifies the risk of pathologic fractures related to MBD based on pain, location of lesion, size of cortical destruction, and the appearance of the lesion (lytic vs. blastic). Each feature is assigned progressive scores ranging from 1 to 3 and the scores are summated. Patients with a score above 8 are considered to be at high fracture risk and in need of prophylactic fixation. Mirels' classification has been shown to be reproducible, valid and more sensitive than clinical judgment, but its low specificity (35%) may result in unnecessary surgery in two thirds of the patients [2,13,14]. In a cohort of 102 patents with painful femoral metastases, Mirels' score correctly predicted fracture in all 14 patients who fractured, but also predicted fracture in 84 out of 88 patients who did not fracture [10]. Mirels' classification is therefore more valid as a screening tool given its sensitivity [2].

In recent years more accurate methods based on either rigidity analysis or finite element models generated from computed tomography (CT) scans have been suggested as a means to predict bone strength that account for both patient specific geometrical structure and spatial distribution of material properties in bones with metastases [15–18]. A patient-specific CT-based finite element analysis (CTFEA) has been validated in double-blinded ex-vivo experiments using fresh-frozen femurs [19]. Employing the same CTFEA method, CTFEA predictions were compared to experimental mechanical tests in 14 fresh frozen femurs with real metastatic tumors [15]. The study showed that CTFEA predicts the mechanical response of femurs with metastases with a linear regression slope of 0.95 and a coefficient of linear regression $R^2 = 0.967$. A good correlation was demonstrated between the predicted yield load and experimental observed yield, with a linear regression slope of 0.80 and a coefficient of linear regression $R^2 = 0.78$ [17].

A recent systematic review [14] addressed the different methods for fracture risk evaluation in patients with femoral metastases. It concludes that "*Fracture risk prediction using Mirels' score, based on pure clinical data, shows moderate to poor results in predicting non-impending fractures with a positive predictive value between 23 and 70%. Engineering methods provide high accuracy in biomechanical lab experiments, but have not been applied to clinical routine yet...*".

Given that Mirels' classification combined with clinical judgment has a low specificity rate, and the successful correlation between CTFEA and ex-vivo experiments, we hypothesize that personalized CTFEA may be significantly more specific at predicting the need for prophylactic surgery in patients with femoral MBD. To clinically validate the hypothesis we performed an ad hoc CTFEA retrospectively on a cohort of 50 patients with femoral MBD compared to Mirels' scores and clinical outcome data.

2. Materials and methods

2.1. Patients

Records of 157 patients with metastatic tumors of their femurs referred to the National Unit of Orthopedic Oncology Center at Tel-Aviv Medical Center during March 2013–March 2017 were reviewed. Institutional review board approval (# 0530-15-TLV) to retrospectively perform a review of patient clinical records was received. Weight, gender, type of primary cancer and CT date were collected for each patient. To be included in the study patients were required to have a CT extending from the femoral head to at least 1 cm below the femoral less trochanter, with a tube current of 120 kVp, with a pitch <1.5 mm and an appropriate filter. Decisions regarding surgery were approved by hospital's tumor board consisting of 4 surgeons and a musculoskeletal radiologist, based on clinical and radiographic judgment.

Fifty-seven patients were referred after already experiencing a pathological fracture. Five of these patients had an appropriate CT scan within a month prior to the fracture. All 5 sustained spontaneous fractures. These 5 patients form Group 1. In four of the five patients their CT scan included the entire femur and their contralateral, non-fractured femur was judged to be disease free.

One hundred patients were recommended prophylactic fixation because of high risk of impending pathologic fractures based on Mirels' scoring done by two orthopedic surgeon and their clinical judgment. Forty-five of these had an appropriate CT scan. These patients form study Group 2. Twelve of the 45 patients chose not to have the recommended surgery. One of the twelve was confined to bed rest from the time of the surgical recommendation until his death three months later and therefore was excluded from study calculations. Eight of the 45 patients in Group 2 and four of the five patients in Group 1 had CT scans which included the entire femurs and their contralateral non symptomatic femur was judged to be disease free. These twelve disease free femurs were used to determine biomechanical properties of healthy femurs.

There was no statistically significant difference ($p = 0.9$) between subjects years of age in Group 1 (63.6 ± 7.3) and Group 2 (62.7 ± 15) or between subject weight ($p = 0.65$) in Group 1 (72.4 ± 9.7 kg) and Group 2 (78 ± 26.7 kg). 3/5 of the patients in Group 1 and 28/45 in Group 2 were females ($p = 0.36$) . Details of the tumor origin for the two groups are presented in Table 1.

Two orthopedic oncology surgeons independently scored the patients based on Mirels' criteria for this study. The summary of all cases including gender, age, weight, cancer type, Mirels' score and whether the patient had a prophylactic surgery is presented in Appendix A. All tumors in Groups 1 and 2 were either lytic or permeative. All patients were treated in the same orthopedic oncology unit and had a minimum follow-up five months post CT scan unless marked by an *.

Table 1
Number of patients and tumor origin of metastasis in each group.

			Number of patients
Group one	Tumor origin of metastasis	Multiple myeloma	3
		Lung	1
		Adenocarcinoma intrauterine	1
		Total	5
Group two	Tumor origin of metastasis	Breast	14
		Multiple myeloma	9
		Lung	6
		Renal cell cancer	6
		Prostate	2
		Other	8
		Total	45