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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