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Towards clinical application of biomechanical tools for the prediction of fracture risk in metastatic bone disease

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ABSTRACT

Current clinical practice lacks an accurate predictor for the pathological fracture risk in metastatic bone disease, but biomechanical tools are under development to improve these predictions. In this paper we explain the limitations of currently used clinical guidelines and provide an overview of more objective and quantitative approaches that have been proposed for fracture risk assessment in metastatic bone disease. Currently, such mechanical models are as sensitive and specific as clinical guidelines, but there are a number of opportunities to further improve their predictive capacity. Hence, they are a promising tool to decrease the numbers of over- and undertreated patients.

1. Introduction

Bone is a preferred organ for primary tumour cell seeding in common cancer types such as breast, prostate, lung, kidney and thyroid cancer (Coleman, 1997, 2006; Gralow et al., 2013; Laitinen et al., 2012). Particularly skeletal parts that contain bone marrow (*e.g.* the skull, ribs, spine, and long bones of the axial skeleton) provide a fertile environment for seeding and are therefore commonly invaded by tumour cells (Johnson and Knobf, 2008; Laitinen et al., 2012; Mavrogenis et al., 2012). In more progressive states bone metastases can, amongst others, cause pathological fractures (Coleman, 1997; Laitinen et al., 2012; Mantyh, 2013), in which case patients lose their full mobility and may develop severe complications (Mavrogenis et al., 2012; Ruggieri et al., 2010). Pathological fractures are treated with complex surgical procedures. Surgeons have to weigh the impact of the operation and rehabilitation against the physical status and expected survival of the patient (Attar et al., 2012). In addition, they must be convinced that the load capacity of the reinforced bone will sustain the daily loads for the life expectancy of the patient (Attar et al., 2012). In current clinical practice, metastatic lesions identified with an impending fracture are treated with preventive surgery. This treatment is less complex and has better survival rates than surgical treatment of actual pathological fractures (Laitinen et al., 2012; Mavrogenis et al., 2012; Ratasvuori et al., 2013). Lesions that do not jeopardise the mechanical integrity of the bone are treated conservatively with (a combination of) radiation therapy, analgesics, chemotherapy, hormonal therapy or bisphosphonates, with the aim to relieve pain (Van der Linden, 2005). However, it turns out to be extremely difficult, if not impossible, to assess clinical fracture risks based on conventional X-rays or CT images. Hence, even for experienced clinicians, it is impossible to make accurate predictions. This was well demonstrated in a study by Hipp et al. (1995). They used 10 paired cadaver femurs, with an artificial lesion drilled in one of the femurs of the pair. The failure load for each bone and the strength reduction within a pair was determined based on a mechanical axial loading experiment. Using CT-scans and roentgenograms of the bones, three orthopaedic surgeons were asked to report on the lesion size, the femoral failure load and the strength reduction within a femoral pair. There was moderate agreement in defining the lesion size (mean difference 11%, range 2–47%), but there was no relationship between the failure load measured in the experiments and the failure load estimated by the surgeons. The same disappointing result was found for the strength reduction in the femoral pairs. In a comparable experiment we showed very similar results. Clinical experts were asked to rank femurs with and without artificial lesions on bone strength; the rank correlations between experimental bone strength and predictions by clinical experts ranged only between 0.45 and 0.53 (Fig. 2) (Derikx et al., 2012). This demonstrates that a more quantitative measure of bone strength in patients with metastatic bone disease is urgently needed.

In this paper we provide an overview of more objective and quantitative approaches that have been proposed for fracture risk

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assessment in metastatic bone disease. We discuss their efficacy and the potential challenges that may come in with the clinical implementation of such tools.

2. Clinical methods for fracture risk assessment in metastatic bone disease

Finding an objective measure for fracture risk assessment of bones with metastases has been under study for several decades. By evaluating roentgenograms of patients who sustained a pathological fracture, the size of the lesion (Beals et al., 1971; Cheng et al., 1980; Harrington et al., 1976; Keene et al., 1986; Miller and Whitehill, 1984; Snell and Beals, 1964; Van der Linden et al., 2004; Zickel and Mouradian, 1976), the extent to which cortical bone was disrupted by the lesion (Van der Linden et al., 2004) and the radiographic appearance of the lesion (Beals et al., 1971; Bunting et al., 1985; Keene et al., 1986; Miller and Whitehill, 1984; Mirels, 1989; Snell and Beals, 1964; Van der Linden et al., 2004; Yazawa et al., 1990; Zickel and Mouradian, 1976) have been studied as potential predictors for the fracture risk. Pain has been included as well in these studies (Beals et al., 1971; Fidler, 1973; Harrington et al., 1976; Keene et al., 1986; Mirels, 1989; Parrish and Murray, 1970; Van der Linden et al., 2004), as it was hypothesised to be a measure for loss of mechanical strength (Mirels, 1989), or an indicator of excessive deformation (Fidler, 1973). Despite these documented efforts, none of the studies identified a powerful predictor for the fracture risk. The most recent clinical study in this field compared, amongst others, two guidelines: Mirels' scoring system and a threshold for cortical disruption (Van der Linden et al., 2004). Mirels' system scores the location of the lesion, pain and the appearance and size of the lesion. Patients with high scores need immediate surgery, while patients with low scores can be treated conservatively. Had Mirels' scoring system been applied to the patients in the study of van der Linden et al., none of the impending fractures would have been missed but a large number of patients would have undergone unnecessary surgery (sensitivity=1.0, specificity=0.13). Alternatively, a threshold of 3 cm cortical disruption was proposed to identify impending pathological fractures. Had this method been used in Van der Linden's work, some of the impending fractures would have been missed (sensitivity=0.86), but the power to identify non-fracture patients would have increased (specificity=0.58). Thus, the latter guideline improved upon Mirels' scoring system but remained to have difficulties preventing unnecessary surgeries.

In summary, clinical studies so far have mainly focussed on lesion characteristics and pain, while the bone strength of the femur was largely ignored. In order to estimate the fracture risk, however, it is important to assess the reduction in bone strength caused by the lesion with respect to the initial bone strength.

3. Mechanical models to assess femoral bone strength

More recently, the focus has shifted towards mechanical models for fracture risk assessment. The most commonly proposed ones are computed tomography based rigidity analysis (CTRA) and patient-specific finite element (FE) modelling.

The use of composite beam theory in the context of fracture risk assessment has been extensively investigated over the last two decades (Leong et al., 2010; Snyder et al., 2009; Snyder et al., 2006; Windhagen et al., 1997). Starting in the spine, Windhagen et al. (1997) generated quantitative CT (QCT) scans from vertebral segments with artificial and actual metastatic lesions and mechanically loaded them until fracture. Using a calibration phantom, the grey values in the CT scans were converted to ash densities and Young's moduli, respectively, and the axial rigidity for every CT slice was subsequently calculated based on composite beam theory. High correlations were found between the experimental failure load and axial rigidity (R^2 ranging from 0.79 to 0.85). No correlation was found between defect size and failure load, which confirms earlier findings showing that lesion characteristics alone cannot accurately predict fracture risk in metastatic bone. Additionally, CTRA was applied in the femur in a clinical setting. Snyder et al. (2006) included 36 patients with benign femoral lesions, 18 of which had sustained a fracture. Axial, torsional and bending rigidities were calculated for the affected bone and the intact contralateral bone, respectively (Fig. 1). Statistical analysis revealed no difference in lesion characteristics between the two groups, but the relative reduction in rigidity (*i.e.* the difference in rigidity between the intact and the affected bone) was significantly larger in the fracture group than in the non-fracture group. Thus, in the fracture group the lesions had weakened the bone to a larger extent than in the non-fracture group. This was the case for axial, bending and torsional rigidity. Based on these results, cut-off values were defined, on the

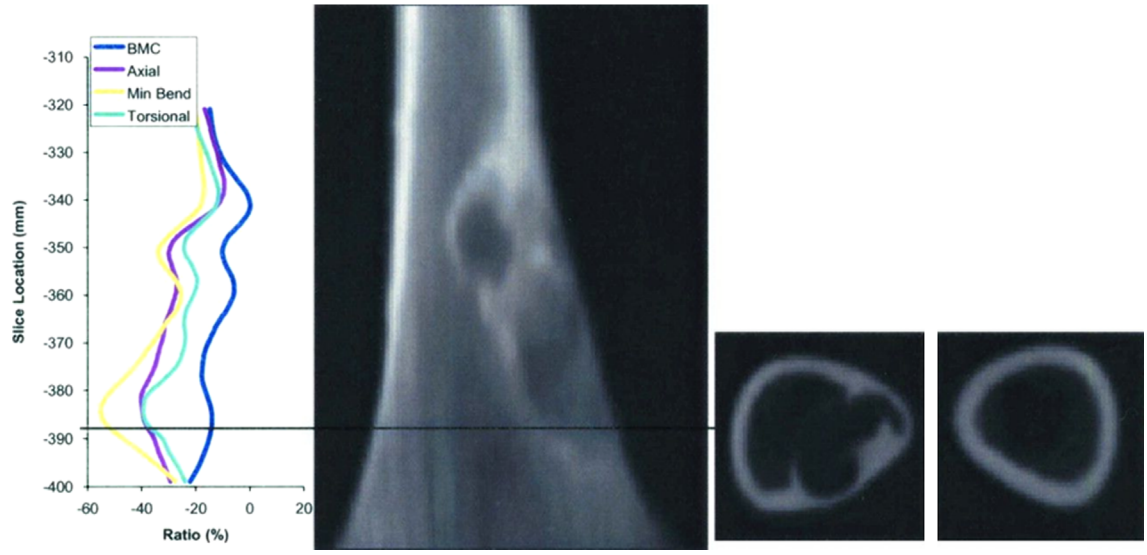

Fig. 1. The left panel shows the relative reduction in bone mineral content (BMC), axial rigidity (axial), minimum bending rigidity (min bend) and torsional rigidity (torsional) for every CT slice. This reduction is largest in the slice at location −385 mm (> 50% for minimum bending rigidity) and indicated with the black line in the lateral plane (middle panel). In the right panel, the affected and unaffected femurs at this specific level are shown. Reprinted from (Snyder et al., 2006) with permission.