Doctoral Thesis

Relative interaction of material and structure in normal and pathologic bone

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RELATIVE INTERACTION OF MATERIAL AND STRUCTURE IN NORMAL AND PATHOLOGIC BONE

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RELATIVE INTERACTION OF MATERIAL AND STRUCTURE IN NORMAL AND PATHOLOGIC BONE

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SUMMARY

Skeletal metastases occur in a large population of breast cancer patients by the time of their death. Annually, 25-40% of breast cancer patients with skeletal metastases will require radiotherapy for bone pain, 30% will develop hypercalcaemia and 17-50% will sustain a vertebral fracture. As a result of new and aggressive treatments, breast cancer patients are living longer but skeletal metastases continue to be a feared complication. These complications manifest themselves as intractable pain, fracture after minimal trauma, paralysis due to spinal cord compression and hypercalcaemia. While much has been learned about the mechanisms of metastasis to bone, little headway has been made in establishing guidelines for estimating fracture risk associated with skeletal metastases or monitoring the response of a specific bone lesion to treatment.

On the cellular level, osteoclasts and osteoblasts change the host bone material and structure in response to local and systemic cytokines, growth factors and hormones. Therefore, if changes in bone material and structure are to reflect the interaction of the metastatic tumor with bone itself, then bone mechanical properties (which reflect the combined effect of bone material and structural properties) could be used to monitor the effects of modulators of tumor growth contributing to the deterioration and/or preservation of bone structure. This interaction is the foundation for the non-invasive computer tomography (CT) based cross-sectional analysis used to calculate the load bearing capacity of bone, and hence monitoring the response of bone to metastatic cancer and treatment options. However, neither the underlying interaction, nor the non-invasive CT-based assessment has been validated in a controlled environment. This body of work will aim to show that at continuum level, human trabecular bone (normal and pathologic) can be modeled analytically as rigid porous foam with a hierarchical relationship between its tissue material and structural properties (Aim I). Furthermore, whole bone mechanical behavior is governed by structural mechanics and can be predicted using composite beam theory.

The overall goal of this thesis was to develop and validate a non-invasive CT-based method to predict mechanical behavior of normal and pathologic bone in-vivo to quantify fracture risk, guide treatment and assess response to treatment. In Chapter 2, modelling human cancellous bone as rigid porous foam and invoking Castigliano’s second theorem, we demonstrated that the cross-section through the bone with the minimum bone volume fraction governed the mechanical behavior of the entire specimen for normal, osteoporotic and metastatic cancer to bone. The study was continued in an animal model of osteolytic defects, where more control over the study design parameters was maintained for ethical and logistic reasons than possible in a human study. In Chapter 3, we presented an in-depth analysis of the use of calibration phantoms to measure equivalent bone mineral density in high resolution µCT imaging. In Chapter 4, we demonstrated that ovariectomy induced changes in skeletal state are caused primarily by changes in trabecular microstructure, reflecting its greater surface area and remodeling potential in comparison to cortical bone, further verified by no changes observed in equivalent bone tissue density of OVX trabecular bones. This is in contrast to renal osteodystrophy, where equivalent tissue density and structural level changes are observed in the cortical bones but very little change observed in trabecular bone. Additionally, we introduced univariate relationships to describe the mechanical
properties of rat bone based on equivalent mineral density, bone volume fraction or apparent density. These relationships can describe the mechanical properties of both cortical and trabecular bone over a wide range of bone density and common skeletal pathologies, obviating the need for an arbitrary value to separate cortical bone from cancellous bone and the use of two separate relationships. The relationships reported in this study coupled with the structural rigidity technique provide a non-invasive method to assess fracture risk in bones affected by pathology and/or treatment options. In Chapter 5, we designed and validated a novel torsion testing system for non-homogeneous, orthotropic materials using the incremental step-wise application of torsion and simultaneous time-lapsed μCT imaging.

Using the tools designed and validated in this study, in Chapter 6, we demonstrate that quantitative micro computed tomography based structural rigidity analysis provided a more accurate method for to predict fracture risk in rodents with skeletal metastases and monitor the subsequent lesions in response to treatment, where neither X-ray nor Dual Energy X-ray Absorptiometry were able to discriminate between test groups as the structural rigidity analysis method could.