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A phase I feasibility study of multi-modality imaging assessing rapid expansion of marrow fat and decreased bone mineral density in cancer patients ☆

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ABSTRACT

Purpose: Cancer survivors are at an increased risk for fractures, but lack of effective and economical biomarkers limits quantitative assessments of marrow fat (MF), bone mineral density (BMD) and their relation in response to cytotoxic cancer treatment. We report dual energy CT (DECT) imaging, commonly used for cancer diagnosis, treatment and surveillance, as a novel biomarker of MF and BMD.
Methods: We validated DECT in pre-clinical and phase I clinical trials and verified with water–fat MRI (WF-MRI), quantitative CT (QCT) and dual-energy X-ray absorptiometry (DXA). Basis material composition framework was validated using water and small-chain alcohols simulating different components of bone marrow. Histologic validation was achieved by measuring percent adipocyte in the cadaver vertebrae and compared with DECT and WF-MRI. For a phase I trial, sixteen patients with gynecologic malignancies (treated with oophorectomy, radiotherapy or chemotherapy) underwent DECT, QCT, WF-MRI and DXA before and 12 months after treatment. BMD and MF percent and distribution were quantified in the lumbar vertebrae and the right femoral neck.
Results: Measured precision (3 mg/cm^3) was sufficient to distinguish test solutions. Adiposity in cadaver bone histology was highly correlated with MF measured using DECT and WF-MRI ($r = 0.80$ and 0.77, respectively). In the clinical trial, DECT showed high overall correlation ($r = 0.77$, 95% CI: 0.69, 0.83) with WF-MRI. MF increased significantly after treatment ($p < 0.002$). Chemotherapy and radiation caused greater increases in MF than oophorectomy ($p < 0.032$). L4 BMD decreased 14% by DECT, 20% by QCT, but only 5% by DXA ($p < 0.002$ for all). At baseline, we observed a statistically significant inverse association between MF and BMD which was dramatically attenuated after treatment.
Conclusion: Our study demonstrated that DECT, similar to WF-MRI, can accurately measure marrow adiposity. Both imaging modalities show rapid increase in MF following cancer treatment. Our results suggest that MF and BMD cannot be used interchangeably to monitor skeletal health following cancer therapy.

Introduction

Cancer survivors experience a greater risk of fracture compared to the general population [1–6]. However, the effect of cancer treatment, especially the relationship between marrow fat (MF) and bone mineral

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density (BMD), is not well known. Mesenchymal stem cells (MSCs) are non-hematopoietic, pluripotent marrow progenitor cells which give rise primarily to osteoblasts and adipocytes. Bone and marrow (B&M) represent a functional biological entity, with evidence of bi-directional co-regulation of bone and marrow components [7,8]. Under the influence of radiotherapy or chemotherapy, MSCs demonstrate enhanced commitment to adipogenesis [9,10], resulting in reduced osteogenic potential [11] and increased MF, one source of circulating adiponectin [12]. Bone marrow fat was associated with vertebral fracture in older adults and postmenopausal women [13]. The rapid increase in marrow fat after cytotoxic cancer therapy in pre-clinical studies [14,15] and a recent retrospective clinical study revealing post treatment early fracture events [16] emphasize the need to assess MF along with the bone in cancer patients. However, changes in MF are not readily detected by a traditional dual-energy X-ray absorptiometry (DXA) scan, since DXA only calculates average BMD by superimposing cortical and cancellous BMD. Indeed, we demonstrated that radiation-induced increases in MF were not reflected in equivalent loss of cancellous bone in ovariectomized compared with intact mice [14].

Increased MF could also affect the BMD since the physical density of fat/yellow marrow (YM) and red marrow (RM) is different [17,18]. The BMD could be lowered by up to 10.8 mg/cm^3 in the presence of 10% marrow fat. The apparent BMD of red marrow is approximately 50 mg/cm^3 higher than the BMD of yellow marrow [19,20]. Since cancellous bone is composed mostly of marrow (70% at the age of 25) [21], change in marrow composition may confound true change in trabecular bone density if they are not distinguished. Dual energy CT (DECT) uses differential attenuation from two energies for marrow correction [22], but has never been translated into osteoporosis clinical care. This may be due to the high radiation dose exposure from multiple CT scans using older scanners, or because age-related osteoporosis typically results in only modest changes in marrow composition. In contrast, cancer treatment induces large changes in marrow composition [23–25]. Moreover, water–fat MRI (WF-MRI) could also measure volumetric marrow composition [26]. However, MRI use is limited in cancer patients after diagnosis, perhaps due to its high cost. Furthermore, MRI alone cannot accurately measure bone mineral density and therefore assess risk. In contrast, CT scan is part of routine cancer diagnosis, radiotherapy treatment planning and disease surveillance. DECT could provide multiple time points of measurement without requiring additional CT scans and the additional cost or radiation burden. Furthermore newly developed iterative reconstruction technology has significantly reduced the radiation dose to patients and improved imaging quality of DECT [27]. Thus DECT is economically viable and advantageous. However, DECT has never been used to measure marrow fat and it is also unknown if the DECT-predicted MF will be equivalent to MF measured using WF-MRI. In this trial, we hypothesized that DECT and WF-MRI could reliably measure changes in MF associated with cancer treatments.

The ultimate goal is to develop clinically useful biomarkers to predict, measure, and monitor cancer-therapy induced bone loss, thereby individualizing therapy to decrease bone morbidity and ultimately enhancing quality of life for cancer survivors. The aims of this pilot translational study consisted of two steps: reporting pre-clinical validation of DECT predicting MF simulating in physical space with basis material composition and correlating imaging modalities with histology in cadavers. With these results, a clinical feasibility study was conducted with Aim 1) to assess the possibility of DECT as a biomarker to quantify the effects of cancer treatments on MF by comparing with the simultaneously measured and previously established WF-MRI method. Secondary aims of this study were to assess the effects of cancer treatment modalities (oophorectomy, chemotherapy and radiation) on MF expansion and mapping of MF distribution, and Aim 2) to test if commonly known inverse correlations between MF and BMD hold true in patients undergoing cancer treatment [14]. Secondary aim was to measure sensitivity of BMD comparing DECT, QCT and DXA.

Methods

Pre-clinical validation of DECT

Somatom Definition Flash (Siemens, Germany) is used for DECT (at 140 and 80 kVp) scan and 80 kVp energy in single energy or QCT scan. For pre-clinical validation of DECT, basis material composition estimates for bone regions were derived relative to the manufacturer-reported basis material compositions for the CT calibration phantom. XCOM, an X-ray attenuation database, was used to estimate basis material composition calculations for the following series of five compounds: water, methanol (50%), ethanol (95%), 2-propanol (70%) and 1-butanol (100%) [28,29]. Basis material compositions were also estimated for yellow marrow and red marrow using average atomic compositions from International Commission on Radiation Units & Measurements (ICRU)-46 report in XCOM for these marrow types with assumed physical densities of 0.93 g/cm^3 and 1.03 g/cm^3, respectively [30]. Basis material density estimates were observed to have a precision on the order of 3 mg/cm^3. Measurement precision was sufficient to distinguish the series of test solutions in the two dimensional basis material spaces. More details are in the supplement section.

Pre-clinical correlation between DECT and WF-MRI

Detailed methodology of physiological verification is communicated separately [31]. Briefly, five female donors (mean age of 56.8 ± 8.2 years) were scanned by DECT (1 mm slice thickness at 140 and 80 kVp energy in single scan) and WF-MRI (3 T MRI scanner, Tim TRIO, Siemens Medical Solutions, Malvern, PA, USA) imaging sequentially, within 24 h postmortem. Seventeen lumber vertebrae samples were then removed, decalcified, paraffin embedded, and stained with hematoxylin and eosin (H&E). The ratio of adipocyte volume per tissue volume (AV/TV) was extracted from the histology sample and a correlation between DECT and WF-MRI MF calculation was obtained. Taking a histologic section from the center of the vertebral body ensured that the AV/TV was taken from a representative section of the imaging ROI. In order to test intra-sample variability, histologic examinations were also performed at 0.5 cm superior and 0.5 cm inferior to the middle in three vertebral bodies and the average coefficient of variation between the sections was found to be 0.08. Inter-user variability between the two users as seen by an intraclass correlation coefficient of $r = 0.984$.

Clinical feasibility trial

Women >18 years old with newly diagnosed ovarian and endometrial cancer who planned to receive chemotherapy or radiation therapy following oophorectomy were considered eligible for the study. We excluded women with osteoporosis and hyperparathyroidism and those who had received chemotherapy, radiation or hormonal therapy within the prior year.

The study was approved by the University of Minnesota Institutional Review Board and subjects provided written consent. Thirty one patients were recruited for this study.

Twelve women with early stage ovarian or endometrial cancer who underwent surgical oophorectomy but not adjuvant chemotherapy or radiation therapy served as the control group.

Ovarian cancer patients ($n = 13$) were treated with carboplatin and paclitaxel 175 mg/m^2 every 21 days for ≥6 cycles. Endometrial cancer patients ($n = 6$) were primarily treated using external beam radiation therapy (EBRT) to the pelvis (median dose, 45–50 cGy in 25–28 fractions) and additional radiation at the vaginal surface using high dose rate (HDR) brachytherapy. The radiation window encompassed the pelvis up to ~L5. Though radiation fields covered up to L5 with a dose of 45 Gy, L4 and L3 fell in a dose gradient region. Thus, to include the radiation dose gradient, we chose to include the L3–L5 spine for this study.