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Rapid *ex vivo* imaging of PAIII prostate to bone tumor with SWIFT-MRI

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Abstract

Introduction—The limiting factor for MRI of skeletal/mineralized tissue is fast transverse relaxation. A recent advancement in MRI technology, SWIFT (Sweep Imaging with Fourier Transform), is emerging as a new approach to overcome this difficulty. Among other techniques like UTE, ZTE and WASPI, the application of SWIFT technology has the strong potential to impact preclinical and clinical imaging, particularly in the context of primary or metastatic bone cancers since it has the added advantage of imaging water in mineralized tissues of bone allowing MRI images to be obtained of tissues previously visible only with modalities such as CT. The goal of the current study is to examine the feasibility of SWIFT for the assessment of the prostate cancer induced changes in bone formation (osteogenesis) and destruction (osteolysis) in *ex vivo* specimens.

Methods—A luciferase expressing prostate cancer cell line (PAIII) or saline control was inoculated directly into the tibia of 6-week old immunocompromised male mice. Tumor growth was assessed weekly for three weeks prior to euthanasia and dissection of the tumor bearing and sham tibias. The *ex vivo* mouse tibia specimens were imaged with a 9.4T and 7T MRI systems. SWIFT images are compared with traditional gradient-echo and spin-echo MRI images as well as CT and histological sections.

Results—SWIFT images with nominal resolution of 78 μ m are obtained with the tumor and different bone structures identified. Prostate cancer induced changes in the bone microstructure are visible in SWIFT images, which is supported by spin-echo, high resolution CT and histological analysis.

Conclusions—SWIFT MRI is capable of high-quality high-resolution *ex vivo* imaging of bone tumor and surrounding bone and soft tissues. Furthermore, SWIFT MRI shows promise for *in vivo* bone tumor imaging, with the added benefits of non-exposure to ionizing radiation, quietness and speed.

Keywords

SWIFT; MRI; Cancer; imaging; bone; CT

Introduction

Prostate cancer will claim the lives of approximately 30,000 men in the US alone in 2013 [<http://www.cancer.org>]. Of the men that succumb to the disease, studies have shown that up to 90% will have evidence of bone metastasis [1]. Prostate to bone metastases are hallmarked by areas of extensive osteogenesis and osteolysis. Common side effects include hypercalcemia, pain and pathological fractures that greatly impact the patient's quality of life. Despite knowledge of the molecular mechanisms underlying the disease, little is known in terms of determining which patients will relapse with metastatic bone cancer [2]. Furthermore, treatment for these patients is limited (radiation/bisphosphonate), mainly palliative, and as a result their prognosis is poor [3]. Early detection of metastases can be advantageous in terms of treatment and long term survival. Currently, patients with advanced prostate cancer undergo screening for bone metastases with radionuclides such as ^{18}F FDG and ^{99}Tc -MDP or magnetic resonance imaging (MRI) [3,4].

MRI has become a critical non-invasive and non-ionizing tool for the imaging of soft tissue disease. It relies mostly on magnetic resonance signal from hydrogen nuclei of water molecules, which is abundantly present in biological tissues. There are numerous tissue contrast mechanisms based on longitudinal (T_1) and transverse (T_2) relaxation time differences in different tissues. While most of the biological tissues are easy to visualize with conventional MRI, some tissues like teeth and bone are not. Bone substance consists of collagen matrix intermixed with apatite-like mineral crystals and water. Water can be bound to collagen matrix, tightly bound to minerals and free in microscopic pores [5]. Short and very short T_2 's of bound and tightly bound water make it invisible to conventional MRI. What can be imaged, however, is marrow that fills trabecular spaces with bone appearing as void signal [5,6]. The last decade has seen the emergence of new methods [7–10] to image water protons or other NMR visible components associated with solid bone itself. These methods use various acquisition schemes to capture short T_2 content and preparation pulses to saturate signal from marrow that masks signal from bone. Marrow can also be physically removed in ex vivo studies. The important applications include quantitative MRI of human cortical bone [11], measuring mineralization and water content in response to treatment [12] and direct depiction of trabecular bone [10]. High requirements are often imposed on hardware to capture short T_2 components and acquisition from several hours to several days is used to get high resolution.

The emerging MRI method Sweep Imaging with Fourier Transformation or SWIFT can detect MR-signals with a broad range of T_2 relaxation times, including extremely short T_2 's [13]. SWIFT uses a swept RF excitation and simultaneous signal acquisition in a time-shared mode in the presence of field gradients. It has already shown very promising results in detection of mandibular invasion by squamous cell carcinoma [14] and in dental imaging [15].

The purpose of this study is to assess the feasibility of SWIFT to visualize prostate-to-bone tumor in *ex vivo* specimens derived from pre-clinical animal models as well as to compare SWIFT images with CT, traditional MRI and histological sections. The additional goal is also to highlight the potential of SWIFT for *in vivo* bone cancer applications. SWIFT is a quiet and fast MRI method, which makes it very attractive for a clinical use. At the same time, its ability to detect signals with broad range of T_2 makes it possible to image soft tissue and bone lesions/metastases in a single scan.

Methods

Luciferase expressing prostate cancer cells (PAIII) [16] were injected (1×10^5 in 10 μ l volume) into the tibia of an anesthetized immunocompromized mouse while contralateral limbs received sham injections of saline. Tumor growth was imaged using bioluminescence imaging system IVIS 200 (Caliper Life Science, Hopkinton, MA) [17] and after two and three weeks, the animals were euthanized. The tumor bearing and control limbs were carefully excised and soft tissue removed. The bones were then fixed overnight in 10% buffered formalin prior to imaging procedures. Although formalin fixing is known to change magnetization transfer characteristics [18], the sham and tumor bearing samples were both fixed, and hence, the potential effect of fixing on their comparative behavior to detect abnormalities should be minimized. All experiments were done with IACUC approval. Subsequent to imaging, bones were decalcified in 14% EDTA at pH 7.4 for two weeks, processed and sectioned for histology. Initially tibia with three weeks old tumor was imaged, but later for methodological improvement and reproducibility another one with two weeks old tumor was also studied. Images were co-registered manually to 3D SWIFT and/or gradient echo (GRE) data..

MRI experiments

SWIFT experiments were performed in a 31-cm, 9.4-T magnet (Magnex Scientific, Abingdon, UK) equipped with a Varian Direct Drive console (Agilent, Santa Clara, CA). Sequence and reconstruction software were from the CMRRpack DJ SWIFT version 0.4e-f packages [<http://www.cmrr.umn.edu/swift/>]. RF transmission and reception were performed with a home built, single loop, 17 mm- diameter coil. In the SWIFT sequence, RF excitation was performed with a hyperbolic secant pulse [19] having a time-bandwidth product of 256, an excitation bandwidth of 100 kHz, and a nominal flip angle of 14° . The pulse was oversampled by a factor of 16 [20]. Data were collected in 256 gaps of 6 microseconds each, when radio-frequency transmitter was off. The repetition time TR, including 2.56 milliseconds pulse length, was 3.16 milliseconds. Data in 3D k-space consisted of 128,000 spokes for high resolution images. The terminus of the k-space vectors described the isotropically distributed points on a sphere located in up to 16 interleaved spirals [21]. The total acquisition time was equal to about 19 minutes for the first and 10 minutes for the second tumor/sham pair. Field of view was 20^3 mm^3 with the nominal resolution of 78 μm . Besides regular SWIFT, additional SWIFT experiments were conducted, in which MR-signals from fat and portion of water with long T_2 were suppressed. Because the degree of suppression achieved is usually diminished by B_0 -inhomogeneity, samples were placed in proton-free, susceptibility matching fluid (Fluorinert FC-77, 3M Corp., St Paul, MN) for

improving shimming in all MRI experiments. Agilent ge3dshim autoshimming technique based on 3D GRE was used. The suppression was achieved by applying an 8 ms, 90 degree flip angle, double banded Gaussian pulse (focused on water and fat resonances) after each 8th SWIFT readout. According to simulated spin evolution based on Bloch equations, application of such a pulse effectively saturates all signals with T_2 's exceeding 400 microseconds [22,23]. In addition, conventional gradient-echo and spin-echo images were collected. For the first sample with three weeks old tumor all experiments except spin-echo were performed on the 9.4-T magnet described above. Spin-echo imaging was done as an additional experiment on a 7-T magnet (Magnex Scientific, Abingdon, UK) equipped with a Varian Direct Drive console (Agilent, Santa Clara, CA) using a home built, single loop 17mm- diameter coil. For the second sample (two week old tumor) and for more appropriate comparison, all the sequences were done in one experiment on the 9.4-T scanner. GRE parameters for the first/second sample pair were: 10 degree flip angle, 2.9/3.1 ms echo time, 8 ms repetition time, 100 kHz bandwidth, 20³ mm³ FOV with 256³ resolution. To capture spin-echo images at different echo times, a 2D Multiple Echo Multi Shot (MEMS) sequence was used. For the first/second sample pair, image acquisition used 227kHz bandwidth, FOV of 20² mm² with 256² resolution, a repetition time of 2 sec, while the echo time varied from 5/8 ms to 40 ms. For presentation, the spin-echo images for the first sham/tumor pair were filtered with a directionally selective bandpass filter to remove horizontal interference lines utilizing ImageJ software [<http://rsbweb.nih.gov/ij/>].

Computed Tomography

Each sample was placed in a small eppendorf tube with 10%-solution of formalin and imaged on InveonTM preclinical multimodality scanner (Siemens medical, Knoxville, Tennessee). The x-ray source voltage and current were 60kV and 200 microamperes respectively. X-ray source and detector were used in high magnification mode with binning factor 1. The exposure time was 9 sec. The number of CT views was 420 with the total rotation angle of 210 degrees. The number of light and dark calibrations for this high resolution scan was 100. All this made a scan time around 100 minutes. The reconstruction protocol used a downsample factor of 1, bilinear interpolation, a Shepp-Logan reconstruction filter, and beam hardening correction. The data were calibrated in Hounsfield Units.

Histology

After imaging analyses, specimens were decalcified for 2 weeks in 14% EDTA (pH 7.6) with changes of EDTA every 2 days. The specimens were then dehydrated through ethanol and xylene prior to being paraffin embedded. Tissue sections (5 um) at multiple points throughout the specimen were generated. The sections were processed (rehydration through ethanol series 100% to 50% and then H₂O) and stained with hematoxylin and eosin.

RESULTS

2D Spin Echo images for the first sham/tumor pair are shown in figure 1. The signal is strongest at 5 ms and diminished at 30 ms echo time for the sham sample. For the tumor sample the signal from tumor remains strong and tumor shows better contrast for longer

echo time. Increasing T_2 in the presence of developing tumor for a prostate to bone tumor model has been previously observed [24]. It can be explained by increased water reorientation and displacement in tumor disrupted tissue.

Representative SWIFT, CT and gross histology images for sham injected and PAIII prostate tumor bearing tibia are illustrated in figure 2. The resolution for SWIFT and CT images is 78 and 15 μm respectively. For sham tibia, regular SWIFT shows relatively uniform signal from the medullary cavity and hypointense (dark) signal from the surrounding cortical bone. Cortical bone appears brighter on the long T_2 saturated SWIFT image, while upper medullary cavity appears darker, than on the regular SWIFT image. At the same time, the resolution is not sufficient to resolve trabecular bone structure, due to its small size of $\sim 20 \mu\text{m}$ for mice. Normal uniform marrow and trabecular bone patterns can be identified in histological sections and high resolution CT respectively. Overall, as expected, all sham tibia images are quite uniform.

In contrast to the sham tibia, the tumor bearing tibia displayed areas of cancer induced bone formation and resorption on the short T_2 SWIFT image. For this sample, CT analysis identified irregular bone growth as opposed to the regular lattice-like trabecular bone pattern observed in sham tibia. In tissue sections, prostate cancer is clearly visible in the upper medullary cavity as more opaque area comparative to the remaining darker colored bone marrow. This happens due to the bone content depletion of marrow cells. While seen as a brighter region on spin echo images with 30 ms echo time, the long T_2 signal is completely absent on long T_2 saturated SWIFT, where tumor appears as dark area and shows negative contrast with surrounding regions. In addition, tumor induced bone formation, a characteristic commonly associated with prostate to bone metastases, was identified in the same image by comparison with CT. Results for the second experiment are shown in figure 3. Some GRE signal loss seen in figure 2 (probably, due to water and fat being out of phase) was fixed by choosing a different echo time. Since the sham sample demonstrated the same uniform behavior as the sham sample in figure 2, only the second tumor bearing sample is shown. Just like in the first case, the tumor exhibits longer T_2 on spin echo, although with a weaker signal than that on figure 1. This can be attributed to the much smaller acquisition time and less developed tumor. The GRE image appears to have a dark region that can be osteogenesis by looking at the CT image, but the other osteogenic CT regions are not seen, and it is hard to make a judgment. SWIFT imaging as shown in figure 2 were repeated, although using a 2-week old animal (instead of the 3-week old animal in the first case). Shorter acquisition time was also used. Still the same dark and white tumor/osteogenesis pattern is seen and in good agreement with CT and histology.

Discussion

For this study, we utilized the rat adenocarcinoma cell line, PAIII. The cell line induces robust osteolytic and osteoblastic lesions upon inoculation into the tibia over a three week period that recapitulate the lesions commonly found in human patients with prostate to bone metastases.

Negative tumor contrast seen on short T_2 SWIFT images is a consequence of the sharp difference between long T_2 of tumor and short T_2 of surrounding bone, which allows one to see tumor and associated bone formation at the same time. As compared to the fine, uniform, marrow-filled trabecular network of the sham, we have highly contrasting, large areas of tumor and osteogenesis that can be spatially resolved with SWIFT.

Due to broad lines of short T_2 components the long T_2 saturated images are naturally blurred. All sharp transitions between voxels in this case are related to noise and can be filtered out without loss of information. For clarity of presentation filtered images were not included in figures 2 and 3.

Preclinical studies using prostate to bone tumor models would greatly benefit from a robust *in vivo* imaging method to monitor and possibly quantify tumor progression. Traditional micro CT, like one performed in this study, delivers images of exceptional resolution but with associated high radiation dose that may affect the animal and interfere with the rate of tumor progression. CT imaging within dose, allowed by animal protocol, on the other hand, has greatly reduced quantification accuracy, with the radiation effect on the tumor and animal still unclear. T_2 weighted spin-echo images show tumor at 20–40 milliseconds echo time, but completely miss the very informative signal from trabecular bone, since its T_2 is less than the shortest available 3–5ms echo time typical for preclinical systems. SWIFT, in contrast, captures both tumor and associated trabecular bone changes and would have very little effect on animal, since it is nonionizing, fast and quite. The *ex vivo* results obtained in the current study give us initial evidence that SWIFT could become an effective *in vivo* method for monitoring prostate to bone tumor progression in preclinical models and eventually in the clinic.

For this application we suspect one can use any sequence sensitive to T_2 less than 400 microseconds, not only SWIFT. Other comparable sequences include UTE [7] or BLAST/ZTE [25–27]. We chose SWIFT for this project due to our familiarity with the method, availability on our MRI scanner, and the robustness of the SWIFT method to field gradient timing/accuracy in comparison with the UTE sequence [28,29]. In addition SWIFT has reduced requirements for RF peak power relative to the ZTE sequence. Because all methods, SWIFT, ZTE and UTE are not widely available on pre-clinical or clinical scanners it is not known which is optimal. It is also hard to do a comparison, because not all are supported and available simultaneously. It is possible that SWIFT will have some advantages over ZTE for in-vivo clinical scanning, due to requiring less peak power for a given flip angle.

The most logical continuation of this work is an *in vivo* study, in which earlier stages of the disease could be assessed. The latter will be challenging, however, since it is difficult to achieve the same level of shimming and some optimization schemes [30,31] for saturation pulses may be necessary. Another possibility is to measure T_2 of osteoblastic bone, which may differ from that of normal trabecular bone [10]. At the moment we can only say that osteoblastic bone signal most likely comes from water in the collagen matrix, since other components are nondetectable due to broad spectral lines. Knowledge of tumor induced

abnormal bone microstructure in this mouse model may allow one to make more definite statements about the origin of its MRI signal.

Conclusion

In this preliminary study SWIFT was able to identify prostate to bone tumor and associated bone formation in agreement with spin echo, CT and histology. This makes it very attractive for potential preclinical and clinical applications. Unlike CT, SWIFT is non-ionizing and unlike spin echo SWIFT is capable of showing very informative short T_2 content like new bone formation. It also has better tumor contrast for the samples measured.

A limitation of our study is that we studied only two tumor bearing samples. The goal was just to investigate initial feasibility of SWIFT for imaging prostate to bone tumors. At the same time the high quality of the images and the fact that SWIFT findings were in good agreement with typical CT and histology findings makes us optimistic about the use of SWIFT for *in vivo* imaging of prostate to bone tumor progression.

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Figure 1.
2D Spin Echo images of bone with sham (A) and tumor (B). The echo time increasing from 5 (left) to 30 ms (right).

Figure 2.
Regular SWIFT (1), short T_2 SWIFT (2), gradient echo (3), histology (4), CT (5) images of bone with sham (A) and tumor (B)

Figure 3.
Second sample with tumor. Top: 2D Spin Echo images. The echo time increasing from 8 (left) to 40 ms (right). Bottom: Regular SWIFT (1), short T_2 SWIFT (2), gradient echo (3), histology (4), CT (5)