Evaluation of Serial MRI / MRSI of the Prostate in Prostate Cancer Patients Receiving Dutasteride, an Antiandrogen Therapy

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Introduction Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopic Imaging (MRSI) are increasingly being used to evaluate prostate cancer therapy. It has been shown that after androgen deprivation therapy (ADT) there were time dependent changes in prostate metabolism (1). However, in that work, the data were not aligned to baseline and subjective assessments were made to identify healthy and cancer post therapy, without any established criteria. In the current study, established criteria (2) were used to identify healthy and cancerous tissue in the pretreatment baseline. These regions were then translated to the aligned, serial studies during dutasteride treatment. Dutasteride is a form of ADT (5-α-reductase inhibitor) that has less side effects (hot flashes, impotence) than conventional ADT. Dutasteride is currently being used for the treatment of benign prostatic hyperplasia but may have a role in prostate cancer treatment. The goal of this study was to develop an approach that reduces qualitative input and provides a quantitative assessment of serial metabolic changes in patients receiving Dutasteride therapy.

Methods MRI and MRSI were performed in 6 patients with biopsy confirmed prostate cancer. The subjects had early stage disease, a Gleason score of 6 (=3+3), and a mean age of 64 (range: 58-78). For this study, the subjects took 3.5mg of dutasteride daily, two times the usual dosage used to reduce effects of BPH. Subjects were scanned at baseline and at 1, 3, and 6 months. MR imaging included FSE T2-weighted imaging with TR/TE=6000/102ms FOV=140, with 3mm slices. MRSI used a 3D PRESS CSI acquisition with 12x8x8 phase encodes per direction. Five subjects were scanned at 3T with an MRSI resolution of 0.16 cc while one subject was scanned at 1.5T with an MRSI resolution of 0.343cc.

Images were automatically aligned to the baseline images using VTK software (www.vtk.org), allowing translations in R/L and A/P and rotations about the S/I axis. In one case, the data were initially rotated about the R/L axis. Based on a visual identification of corresponding points at the urethra in the midgland, the images were then further translated. To assess volume change, regions of interest were manually drawn on the aligned images of the prostate from the apex to the base by one experienced prostate MR spectroscopist.

The total translations and rotations were then applied to the MRSI data and spectra were reconstructed at the same locations as on the baseline image. Spectra were automatically Fourier transformed, frequency aligned and baseline corrected and were manually phased. In the baseline dataset, peripheral zone spectra were labeled as healthy, cancerous or unusable. These labels were applied to successive, aligned examinations. If labeled spectra were outside the acquisition grid, or off the prostate at any timepoint, they were deemed unusable. Healthy spectra adjacent to cancerous spectra were not used to avoid any partial voluming with cancer. Thus, a final set of healthy spectra and of cancerous spectra were found that could be applied to all timepoints. The healthy and cancerous spectra were then averaged for each timepoint. The peak areas of the composite (choline + polyamines + creatine) and of citrate resonances were normalized to the standard deviation of the spectral noise. Receiver gains were set the same for all timepoints and positions relative to the coils were very similar across timepoints. These S/N measures and the prostate volumes were compared across timepoints and among patients, once normalized to the baseline. Dunnett's test was used to determine significant differences with baseline.

Results

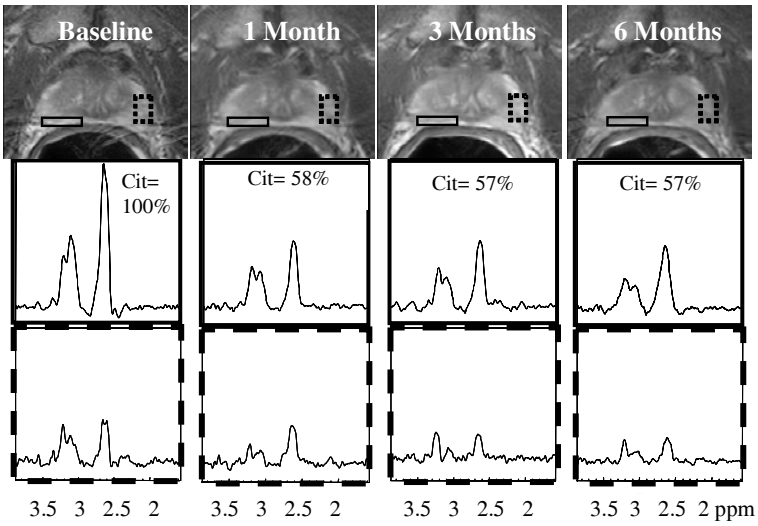

Figure 1 - Aligned T2-weighted images (top), averaged healthy spectra (middle) and averaged cancerous spectra (bottom) for one subject. The averaged spectra shown are in part from the regions marked in the images and in part from locations on other slices. (healthy – solid line, cancer – dashed line) (Cit = citrate)

Figure 1 shows representative aligned images and averaged spectra from the prostate of a patient at baseline, 1, 3, and 6 months. It is visually clear that citrate dramatically decreases in healthy tissue by 1 month after therapy whereas cancer shows a slower decrease in metabolites. All patients studied demonstrated an early decrease in citrate (64±17%, $p<0.003$ vs. baseline). Both volume ($p<0.001$) and citrate ($p<0.003$) were significantly lower than baseline at points 1, 3, and 6 months. A graph of the average changes with time is in Figure 2. The decrease in citrate after 1 month of therapy (36±17%) was more dramatic that the decrease in volume at this point (11±5%). Citrate levels tended to stabilize after one month whereas volume continued to decrease for the length of time subjects were studied. Metabolites decreased in the cancerous regions. Choline+polyamines+creatine significantly decreased to a minimum at 3 months (48±28%, $p<0.006$). The metabolites then increased at 6 months, with citrate to near baseline, and choline+polyamines+creatine to 81±34% of baseline (Figure 2B).

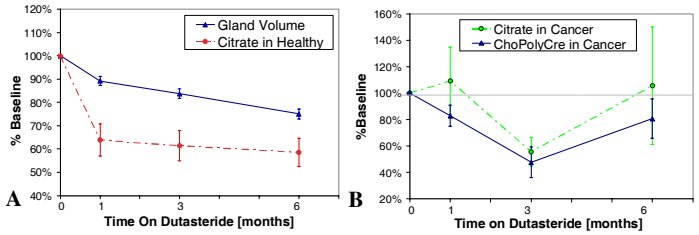

Figure 2 – Graphs vs. time: **A.** Volume and citrate in healthy tissue. **B.** Citrate and choline+polyamines+creatine in cancerous tissues.

Discussion The shrinkage of the prostate that occurs after all prostate cancer therapies, the complex zonal anatomy and often small multifocal nature of prostate cancer, and the large number of spectra obtained per MRSI exam complicates interpretation of serial prostate MRI/MRSI data. In this work we developed an approach that involves aligning serial MRI/MRSI data, and propagating regions of interest that encompassed the same anatomic region of tissue containing a single tissue type through all serial studies. From these regions of interest, summary spectra were generated yielding a visual and numerical assessment of time dependent metabolic changes after therapy. Using this approach, we demonstrated that by one month after Dutasteride therapy there was a significant decrease in both 1)citrate metabolism in regions of healthy tissue and 2) total prostate volume. The citrate reduction was more dramatic than the volume change. Establishing the spectral patterns in healthy tissue is very important for evaluating patients who are on androgen deprivation therapies. Regarding cancerous regions, metabolism significantly decreased to a minimum at 3 months. Malignant measures were more variable due to the smaller cancer size and the consequent greater potential for partial voluming. A study involving a larger number of patients on dutasteride therapy, with larger initial cancers and with longer follow-up times is necessary to determine the significance of early metabolic changes after Dutasteride therapy. However, the current study demonstrates an approach that reduces the qualitative input of the reader and provides a quantitative assessment of serial metabolic changes after therapy. Future improvements in this approach will involve correcting for changes in non-rigid deformations that can occur due to non-uniform shrinkage of the prostate and slight differences in the placement of the endorectal coil.

References: (1) Mueller-Lisse, *MRM* 2001, 46:49-57. (2) Jung JA. *Radiology*. 2004; 233701-708.