Integrated Diagnostic and Interventional MRI for the Molecular Characterization of Prostate Cancer

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Rationale

Emerging diagnostic MRI techniques, such as dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), hold promise for the delineation and molecular characterization of prostate cancer. Spatial heterogeneity in the kinetics of contrast transit is thought to reflect variations in tissue perfusion and microvascular permeability. Kinetic analysis of DCE-MRI is thus hypothesized to create an image reflecting the underlying vasculature of an individual patient’s prostate gland. Imaging has the potential to provide more complete information on a tumor’s microvascular biology, in contrast to information obtained from a biopsy, which may be subject to sampling error. However, data elucidating the molecular processes that underlie DCE-MRI and establishing its validity as a surrogate are lacking. Notable intraprostatic and intratumoral heterogeneity mandates millimeter co-localization accuracy between tissue samples and their corresponding image pixels. When prostate MR imaging and tissue acquisition procedures are performed at separate times and settings, clinical co-registration is fraught with error. To address this key issue, we developed a technique for MRI-guided needle biopsy of the prostate to be performed concurrently with a diagnostic MRI procedure inside a cylindrical 1.5T MRI scanner.

Methods

For the integrated procedure, the patient is positioned prone and a custom-designed interventional endorectal imaging coil is inserted and secured to the scanner table. A needle guide inside the stationary imaging coil contains MR tracking microcoils allowing for spatial registration of the device. A continuous series of DCE-MRI images of the prostate (3D spoiled GRE, scan time 5.1s, Fig. 1a) are acquired before and during the injection of intravenous contrast (gadolinium chelate, 0.2mmol/kg, 3cc/s). The needle guide is translated and rotated within the endorectal coil until its trajectory, computed from the tracking coils, coincides with a biopsy target location defined on the MR images. A 14G core biopsy needle is then inserted, its location is verified by repeat MR imaging, and tissue is collected. (Fig. 1b and c) This can be repeated for additional biopsy target sites within the prostate gland. To analyze DCE-MRI data, pixel data are submitted to a general kinetic model (GKM) fitting routine, which corrects the data for arterial input kinetics and implements a curve-fitting solution to a GKM convolution integral. In this fashion, regions of interest (ROIs- red and blue) encompassing those MR image pixels that correspond to the biopsy locations can be defined, and their corresponding time-intensity profiles and summary kinetic parameters computed. (Fig. 1e) To characterize the biological processes underlying the image data, needle biopsy specimens are subjected to comprehensive histopathological, genomic, and proteomic analysis. In this example, mRNA was isolated and amplified from snap frozen cores. The amplified mRNA was co-hybridized to a cDNA microarray with a reference standard (g,k). In turn, whole cell protein lysates from ethanol-fixed and paraffin-embedded tissue sections of twin cores obtained at the same biopsy sites were analyzed using reverse phase protein arrays (h,l-array probed with STAT3 antibody shown).

Results: We demonstrate the ability to perform prostate DCE-MRI data acquisition with simultaneous co-located biopsy sampling and subsequent sample analysis. The overall imaging and procedure time is
approximately 90 minutes depending on the number of biopsies. For the molecular analysis, we focused on signaling pathways known to be associated with angiogenesis. Results show differing levels of protein and gene expression at sites with distinct contrast enhancement kinetics on DCE-MRI. (Fig. 1) The level of hypoxia inducible factor HIF-1α mRNA and protein was lower at the site of higher contrast enhancement, while a number of other genes involved in angiogenesis signaling were upregulated.

Conclusion: Our results show that the technical challenges of integrating needle-based prostate interventions with diagnostic MRI in a cylindrical clinical scanner can be overcome. Tissue of interest can be precisely sampled, providing a research platform well suited for the correlation of MR imaging, histology, and molecular analysis. As we gain knowledge in the molecular biology underlying cancer and DCE-MRI, a more valid interpretation of an individual patients' tumor biology may ensue.