Three-dimensional MR Tracking of Convective Therapy Distribution in Prostate

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Abstract

This research investigates the feasibility of using MRI to non-invasively assess the distribution of a convectively delivered therapy in an *in vivo* prostate model, using a surrogate solution meant to simulate the distribution of gene therapy vectors, in order to correlate the distribution of injectate between MRI and pathology photographs.

Introduction

Convective delivery of therapy is a minimally invasive alternative for systemic delivery of chemotherapy and other cancer treatments, such as gene therapy, for localized tumor sites. Convective delivery of gene therapy in prostate may help maximize gene transfection of the prostate. Prostate cancer is currently the most frequently diagnosed malignancy and the second leading cause of cancer death in American men (1). Altered gene expression in cancer leads to increased proliferation and metastasis (2). Current research indicates intraprostatic administration of adenoviral vector results in the highest transfection rates for gene therapy delivery with the least systemic adenoviral dissemination of all delivery methods (3). To verify adequate delivery of the treatment to the gland, an imaging technique is needed capable of verifying that the vector is appropriately distributed throughout the target volume. The purpose of our study was to build upon our previous ex vivo experience (4) to determine the feasibility of using MR imaging to track the distribution of a convectively delivered gene therapy solution distribution in the canine prostate *in vivo*.

Methods

The prostates of 12 adult male dogs were exposed by laparotomy. A standard volume (3 ml) of injectable solution composed of a 1:10 dilution of Gadolinium-DTPA (Magnevist, Berlex Laboratories, Wayne, NJ) and a 1:10 dilution of 1% methylene blue were injected into the prostate using either a 3-core, 10-core or 20-core injection schema. Previous experiments have indicated that the distribution of methylene blue (mol. wt. 319.86 Daltons) seen on pathology slices, closely correlated with the observed areas of gene transduction, making methylene blue a reasonable surrogate marker for the distribution of gene therapy injectate (5). Ex vivo studies performed at 1.5T in our laboratory demonstrated that the signal intensity distribution due to convective delivery of Gadolinium-DTPA (Gd-DTPA, mol. wt. 938 Daltons) seen on three-dimensional T1-weighted gradient-echo images was highly correlated with the distribution of methylene blue in canine prostates, strongly indicating its potential use as a surrogate model for in vivo work. All imaging was performed on a 1.5 T scanner (*Signa EchoSpeed*, GE Healthcare, Milwaukee, WI). A three-dimensional fast spoiled gradient-recalled echo sequence was used with TR/TE =13.4 ms/4.2 ms, flip angle = 20°, NEX = 6, and bandwidth = +/- 16 kHz. After imaging, the animals were exsanguinated under deep anesthesia and their prostates resected and sectioned (3- 10 mm slices) axially along the urethra in a manner congruent to the MR acquisitions. The methylene blue distribution on gross photos was compared with the gadolinium distribution on the MR images. To overcome the inconsistencies in prostate sectioning, some of the MR images were reformatted slightly to provide better visualization of the correlation to the gross specimens. Statistical analyses were performed using the Pearson's correlation test and paired t-test.
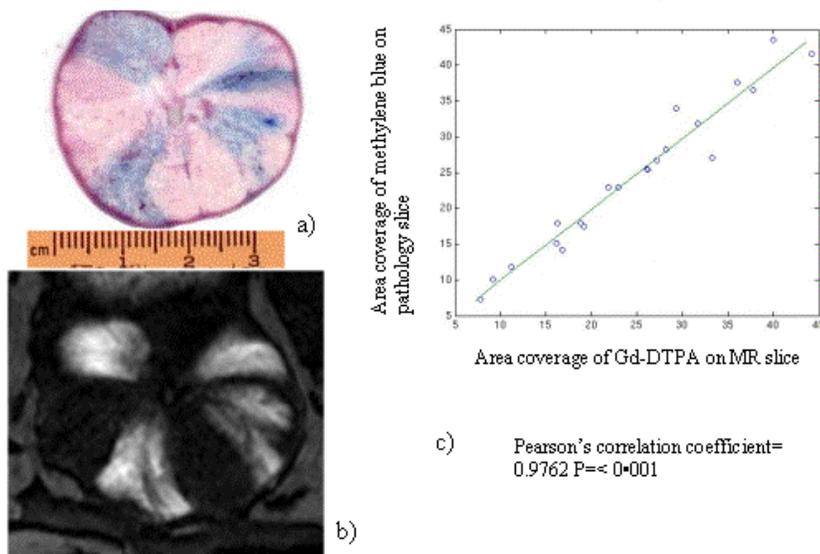
Results

The methylene blue distribution correlated well with the enhanced signal regions on MR images, with a Pearson's coefficient of 0.9762 ($p<0.001$). The mean proportion of the prostate to which gadolinium was distributed in the 3-core, 10-core, and 20-core injection schema was $10.2\% \pm 0.743$, $28.5\% \pm 4.103$ and $30.1\% \pm 4.309$, respectively. The 10-core and 20-core injection schema covered significantly more area than the 3-core ($p<0.002$), but there was no statistically significant difference in coverage between the 20-core and 10-core injection schema ($p< 0.524$).

Conclusion

For the time point investigated in this study, 3D MRI demonstrated excellent correlation with the volume of tissue containing methylene blue (mimicking the distribution of the vectors) in an *in vivo* prostate model. In addition to gene therapy, this technique could be adapted to noninvasively monitor other convective cancer therapies such as drug delivery, vaccinations and nanoparticle-mediated local thermal treatments, by tailoring the properties of the surrogate marker used. While this demonstrates that MRI has the potential for verifying the distribution of injectate immediately after therapy, longitudinal studies are needed to see if this is predictive of the actual pattern of transfection, which occurs over a longer period. Higher molecular wt contrast agents may be better suited for this purpose. Investigation of such techniques using longitudinal MRI T1 measurements is planned with an adenoviral vector system. The knowledge gained would generate useful tools for the clinician like visualization of anatomical vector distribution and, ultimately develop a more quantitative model of dosimetry feedback for verification of treatment delivery and prediction of outcome.

Figure 1: **a)** methylene blue area coverage on pathology slice (40%)   **b)** Gd-DTPA area coverage on corresponding MR slice (43.6%)   **c)** correlation data of Gd-DTPA and methylene blue distribution.

References

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