MRI Guidance and Monitoring of Injected Therapeutic Agents

R. C. Susil[1], S. L. Chowning[1], A. Krieger[2], G. Fichtinger[3], L. L. Whitcomb[4], E. Atalar[2]

[1]Biomedical Engineering, Johns Hopkins University, Baltimore, MD, United States, [2]Radiology, Johns Hopkins University, Baltimore, MD, United States, [3]Computer Science, Johns Hopkins University, Baltimore, MD, United States, [4]Mechanical Engineering, Johns Hopkins University, Baltimore, MD, United States

Synopsis: Through its excellent soft-tissue contrast and ability to visualize liquid agents, MRI can be used for targeting and monitoring of focal injections into soft tissue. In this study, a series of intraprostatic injections were performed using a transrectal system that allows for accurate MR-guided needle placement concurrent with imaging in a standard, 1.5T MR scanner. Eleven intraprostatic injections were performed in-vivo in canines; one injection was performed in an excised human cadaveric prostate. Without MR guidance, injection patterns can be difficult to predict; in particular, the injected agent leaked away from the target tissue in eight of the eleven cases. Tissue structure is shown to have a very strong impact on injection distribution patterns. MR visualization of injected agents may allow for prediction and monitoring of drug distributions, improving efficacy and reducing treatment side effects.

Introduction: Novel strategies for prostate cancer therapy are increasingly focused on the use of immunomodulatory (1), viral (2,3), genetic (4), and radiosensitizing agents (5). Some of these agents can be delivered systemically; however, many require focal injection in order to maximize local drug concentration while minimizing systemic exposure and unwanted side-effects (6). A minimally-invasive system for local therapeutic injections should include five steps: (a) identification of the target tissue, (b) placement of a needle at the target site, (c) prediction of the agent's distribution pattern, (d) injection of the therapeutic agent, and (e) confirmation of the agent's actual distribution. Accurate prediction of the distribution pattern is important to avoid accidental delivery of an injected agent to the incorrect tissue, where it may cause unintended damage or simply be wasted. Confirmation is necessary to ensure that the agent actually reaches the target site. This is particularly true for therapeutic trials, where an agent could be falsely labeled as ineffective simply because it never actually reached the desired target tissue. Here, we investigate the potential role of MRI for performing minimally invasive therapeutic injections in the prostate.

Methods: A system that allows for precise needle placement based upon MR image data was employed for this study (7). Central to the system is a stationary endorectal sheath, which includes an integrated imaging coil, that provides access to the prostate through the anterior rectal wall and minimizes soft-tissue motion during the procedure (Figure 1A). Using a microcoil tracking method, the position and orientation of a needle guide, which fits inside of the endorectal sheath (Figure 1B), can be tracked in realtime (60 msec per localization). Using a mechanical positioning mechanism and extended control rods (Figure 1C), the needle guide can be translated and rotated while the subject is being imaged, allowing for precise needle targeting within the prostate based on MR image data. In a prior study, consistent needle placement accuracy within 2 mm was demonstrated with this system (7). All studies were performed in a GE Signa CV/i 1.5T MR scanner.

In the canine studies, a 30mM solution of Gd-DTPA in normal saline was injected at eight sites within the prostate gland. Different volumes of contrast solution (0.15, 0.3, or 0.6 ml) as well as different injection rates (0.6 to 6 ml/min) were utilized. During injection, the flow of the contrast solution was monitored using a high flip-angle, RF-spoiled, gradient echo imaging sequence (FSPGR, TE 1.5 msec, TR 6 msec, FA 90°, BW +/-62.5KHz, FOV 16cm, no slice-selection, 256x160, 0.96 sec/image). The location of the injected solution was determined by comparing gradient echo axial images acquired both before and after the injection (FSPGR, TE 2.0 msec, TR 80 msec, FA 60°, BW +/-31.25KHz, FOV 16cm, slice thickness 3mm, interslice spacing 0.5mm, 256x256, NEX 4, scan time 1:20). In the excised human cadaveric prostate, a single 0.3 ml injection was performed through the 0.018 inch diameter nitinol needle (injection rate 0.6 ml/min). Because this prostate was excised, the needle was simply placed by hand and confirmed in axial MR images. The distribution of the injected solution was visualized by comparing T1-weighted FSE images acquired before and after the injection and also by using a high flip-angle, RF-spoiled, gradient-echo imaging sequence during the injection (as described for the canine experiments). Following the imaging experiment, the prostate was fixed in formalin for 24 hours, sectioned axially into 3 mm slices, and photographed.

Results: In the canine studies, a total of ten transrectal intraprostatic needle placements and injections were performed. During each injection, a high-flip-angle, RF-spoiled, gradient-echo acquisition was run to visualize the agent's distribution. In the majority of cases, much of the solution does not stay within the tissue but rather, leaks into surrounding structures. Dynamic images acquired during one injection are shown in Figure 2. During this injection, the solution penetrated to the middle of the prostate and then tracked up the urethra towards the bladder. In the cadaveric prostate study, a 0.018 inch diameter needle made from nitinol hypotubing was placed in the right posterior lobe of the prostate and a volume of T1-weighted gradient echo images were collected (Figure 3, first column). Following injection of 0.3 ml of Trypan blue tissue dye mixed with 30 mM Gd-DTPA, a second set of axial T1-weighted images was acquired, allowing for clear visualization of the injected solution (Figure 3, second column), which shows a complicated distribution within and around the prostate. Tissue sections corresponding to the imaged planes are shown in Figure 3, third column. The blue stained tissue correlates well with the gadolinium enhanced tissue.

Discussion: MRI may be useful for improving the efficacy and safety of therapeutic injections. First, through the use of dynamic imaging (Figure 2), it is possible to determine *during the injection* whether the agent is staying localized at the target or rather, if it is leaking into nearby tissue structures (such as the urethra). Therefore, failed injections could be stopped early, conserving drug and preventing damage to surrounding tissues. Second, if more precise visualization of the injected agent is desired, T1-weighted images can be collected to visualize the three-dimensional distribution of the injected solution within and around the target tissue (Figure 3).

Intraprostatic injections, using dehydrated ethanol, are currently being investigated as a minimally invasive treatment for benign prostatic hypertrophy (BPH). However, side effects that have plagued this treatment include inadvertent damage to the external urethral sphincter and stricture of the urethra (8). Given the leakage pattern seen in Figure 2, these side effects are not surprising. MR imaging during the injection procedure could allow for the detection of these potentially dangerous leaks before the ethanol is delivered. With the advent of local genetic, viral, and immunomodulatory therapy for cancer treatment, proper targeting and monitoring of injections using MRI may become increasingly important.

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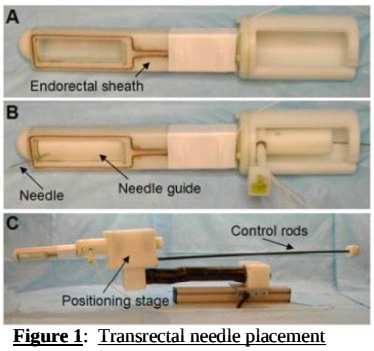

Figure 1: Transrectal needle placement device. **Panel A**: Stationary endorectal sheath with integrated imaging coil. **Panel B**: Sheath with cylindrical needle guide. **Panel C**: Positioning stage with control rods, allowing for positioning of the needle guide during imaging.

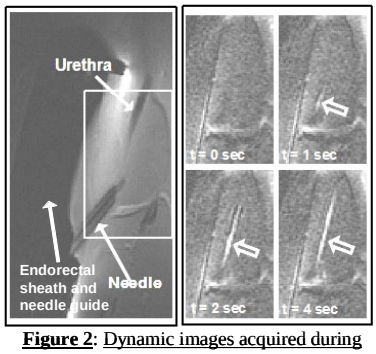

Figure 2: Dynamic images acquired during injection of 30 mM gadolinium-DTPA solution. The location of the dynamic images (right 4 frames) is given by the white box on the sagittal scout image (left). The injected solution can be seen tracking up the urethra (open arrows).

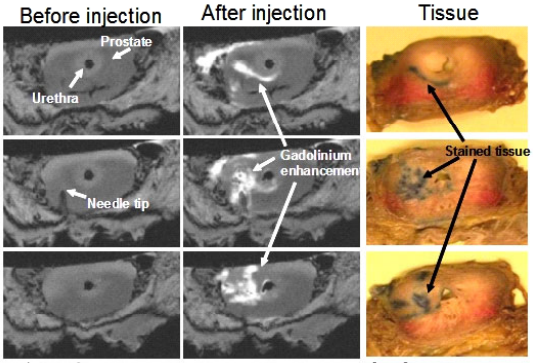

Figure 3: Intraprostatic injection in an excised cadaveric human prostate. By comparing axial T1-weighted images acquired before (first column) and after (second column) the injection, the distribution of the injected solution can be clearly visualized. Enhancement correlates well with stained tissue seen on gross tissue slices (third column).