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RAPID COMMUNICATION

A NOVEL MRI MARKER FOR PROSTATE BRACHYTHERAPY

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Purpose: Magnetic resonance imaging (MRI) is the optimal imaging modality for the prostate and surrounding critical organ structures. However, on MRI, the titanium radioactive seeds used for brachytherapy appear as black holes (negative contrast) and cannot be accurately localized. We sought to develop an encapsulated contrast agent marker (ECAM) with high-signal intensity on MRI to permit accurate localization of radioactive seeds with MRI during and after prostate brachytherapy.
Methods and Materials: We investigated several agents with paramagnetic and superparamagnetic properties. The agents were injected into titanium, acrylic, and glass seeds, which were linked together in various combinations and imaged with MRI. The agent with the greatest T1-weighted signal was tested further in a canine prostate and agarose phantom. Studies were performed on a 1.5-T clinical MRI scanner.
Results: The cobalt-chloride complex contrast (C4) agent with stoichiometry $(CoCl_2)_{0.8}(C_2H_5NO_2)_{0.2}$ had the greatest T1-weighted signal (positive contrast) with a relaxivity ratio >1 ($r_2/r_1 = 1.21 \pm 0.29$). Acrylic-titanium and glass-titanium seed strands were clearly visualized with the encapsulated contrast agent marker.
Conclusion: We have developed a novel ECAM that permits positive identification of the radioactive seeds used for prostate brachytherapy on MRI. Preclinical *in vitro* phantom studies and *in vivo* canine studies are needed to further optimize MRI sequencing techniques to facilitate MRI-based dosimetry. © 2008 Elsevier Inc.

Prostate cancer, Brachytherapy, Magnetic resonance imaging, Contrast agent marker, Cobalt.

INTRODUCTION

The outcomes with high-quality prostate brachytherapy implants are good (1). However, while prostate brachytherapy prescription doses are uniform between institutions, significant variability exists in treatment length, planning treatment volume, seed strength, dose homogeneity, treatment margins, and extracapsular seed placement (2). Currently, the location of the titanium radioactive seeds with respect to the tumor and normal critical organ structures remains ill-defined with standard prostate imaging modalities such as ultrasonography and computed tomography (CT) (Fig. 1). While the importance of postimplant dosimetry cannot be overstated (3), the positive contrast of the titanium seeds on CT permits accurate localization of the seeds, the star/streak artifacts that the markers create make postimplant dosimetry highly subjective (4, 5).

Magnetic resonance imaging (MRI) is the optimal imaging modality for the prostate and surrounding critical organ structures (Fig. 1c) (6). However, with MRI, the titanium radioactive seeds, strands of seeds, and needle tracks appear as black holes (negative contrast) and cannot be accurately localized within the prostate and periprostatic tissue. Thus, MRI-based dosimetry is inaccurate, and MRI alone is not currently used in treatment planning, treatment delivery, or postimplant treatment quality evaluation for brachytherapy. MRI-CT fusion has been shown to improve postimplant quality assessment compared with CT alone (7, 8), but this combined imaging approach has not been translatable to the community setting owing to the inadequacies of fusing caused by imaging with different bladder and rectal filling, prostate volumetric differences between imaging modalities, and difficulties fusing the negative contrast of the seeds, strands of seeds, and needle tracks on MRI with the seeds visualized on CT.

We set out to develop a novel encapsulated contrast agent marker (ECAM) with high signal intensity (positive contrast) on MRI. Such an ECAM could permit accurate localization of the radioactive seeds with MRI both during prostate brachytherapy and on subsequent follow-up. In this report, we describe the construction and preliminary MRI evaluation of a novel ECAM.

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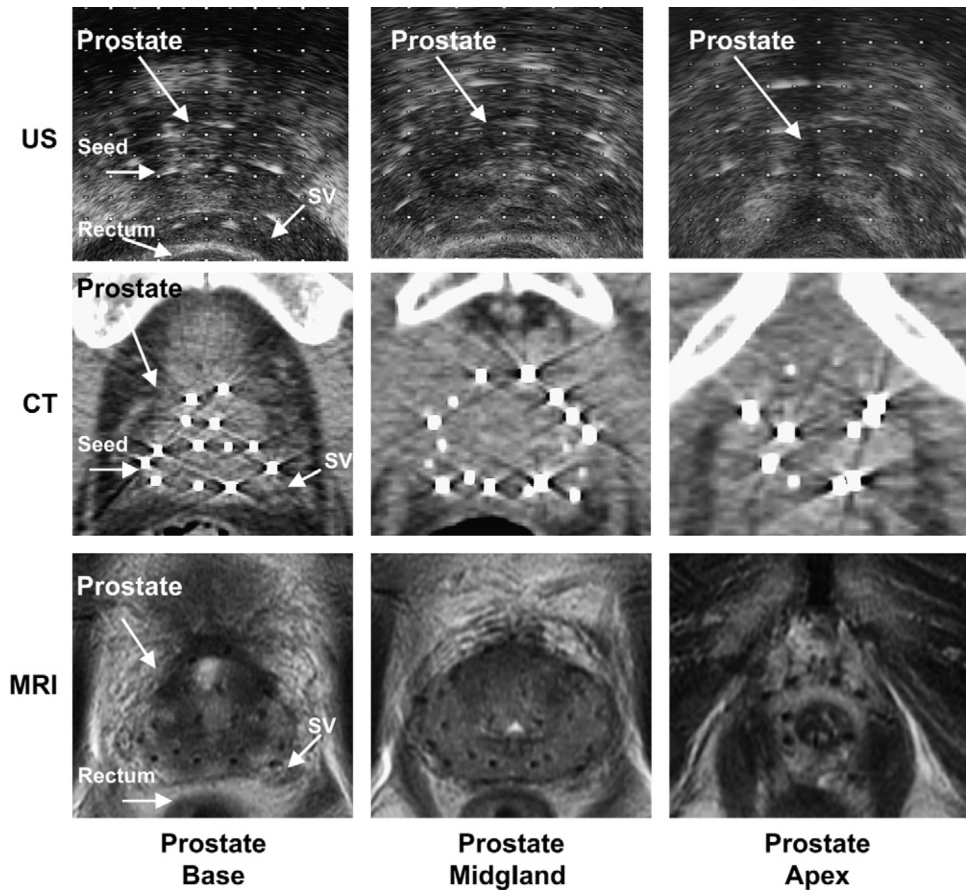

Fig. 1. Postimplant axial images of prostate obtained with ultrasonography (US), computed tomography (CT), and contrast-enhanced T1-weighted magnetic resonance imaging (MRI).

METHODS AND MATERIALS

Construction and development of novel contrast agent marker

To identify potential contrast agent markers, we investigated numerous agents—both commercially available and synthesized in our laboratories—with paramagnetic and superparamagnetic properties. The paramagnetic contrast agents included *Omniscan (Gadodiamide), L-PG-Bz-DPTA-Gd,* and *cobalt (II) chloride-glycine* compounds with different concentrations. The supraparamagnetic contrast agents included *Feridex IV*, *colloidal nanoparticle* solutions of Fe_3O_4, $CoFe_2O_4$, *Mn-Zn,* and *Ni-Zn*-ferrites. The MRI contrast agent based on the Co^{2+} ions was prepared by using anhydrous cobalt (II) chloride and glycine $[H_2N(CH_2)CO_2H]$ reactants. Reagents were purchased from Sigma Aldrich and used as received without further purification. The ratio among the reactants was set in the following stoichiometry: $(CoCl_2)_n(C_2H_5NO_2)_{1-n}$, where $n = 0.5–0.95$. The reactants were dissolved in deionized water and stirred at 60°C. Crystals of the synthesized compound were grown from the mixed aqueous solution of $CoCl_2$-glycine by slow water evaporation. The synthesis yielded crystals of compound ≤5 mm. Then, the crystals were dissolved in deionized water with amount of 0.3–10 wt.% and stirred at 60°C.

Construction of titanium-acrylic and titanium-glass seed strands

Initially, the titanium and acrylic seeds were custom designed to have an outer and inner diameter of 3 mm and 1.5 mm and an outer length and inner hollow length of 4.5 mm and 3.5 mm, respectively. After injection of the cobalt-chloride complex contrast (C4) agent into the manufactured seeds, MRI was performed on the seeds and strand-like combinations. For the canine prostate experiments, standard nonradioactive titanium seeds were incorporated into a synthesized strand, with acrylic and glass tubes cut with an outer diameter of 0.8 mm and length of 5.5 mm, injected with the C4 agent (2 μL), and closed on the ends with two polymer taps.

Phantom and ex vivo prostate

All studies involving animals or animal tissues were performed under an Institutional Animal Care and Use Committee-approved protocol. For this experiment, after completion of another investigator's *in vivo* experiments, a canine prostate was excised at necropsy, placed in normal saline, and fixed in agarose gel (10% by weight, Type-A, Sigma-Aldrich, St. Louis, MO). The ECAMs were subsequently inserted into the prostate and imaged using MRI. Similarly, the ECAMs were inserted into an in-house–manufactured agarose phantom for direct visualization. The signal intensities of the agarose and prostatic tissue were similar on T1-weighted MRI, allowing substantial preliminary assessment of the relative contrast of the ECAMs without a tissue-based phantom.

1.5-T MRI T1-weighted sequences for contrast agent marker experiments

All studies were performed on a 1.5-T clinical MRI scanner (Excite HD, GE Healthcare Technologies, Waukesha, WI) equipped with a high-performance gradient hardware package (Cardiac

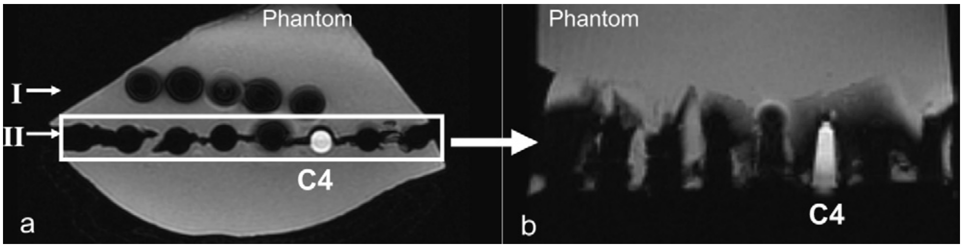

Fig. 2. Novel C4 agent with positive contrast in 1.5-T magnetic resonance imaging T1-weighted sequence. (a) Coronal and (b) sagittal images. I indicates manufactured titanium seeds with paramagnetic and supraparamagnetic contrast agents. ‘‘Blooming’’ susceptibility artifact of titanium seeds shown. II indicates various paramagnetic and supraparamagnetic contrast agents in plastic vials, with C4 agent showing positive magnetic resonance imaging contrast.

Resonance Module) and multichannel, fast-receiver hardware. The maximal achievable slew rate was 120 mT/m/s, maximal amplitude was 23 mT/m, and receiver bandwidth was ±500 kHz. For relaxation measurements, the samples were placed in a room-temperature water bath and imaged using a quadrature knee coil. T1-weighted measurements used an inversion recovery spin-echo technique (repetition time [TR]/excitation time [TE], 5,000 ms/10 ms; inversion time, 50–4,000 ms). The T2-weighted measurements used a spin echo sequence (TR, 5,000 ms; TE, 20–1,000 ms). T2*-weighted measurements used a multi-echo, fast, gradient echo acquisition (TR, 600 ms; TE, 2–57 ms, with an echo spacing of 3.3 ms). All imaging data were analyzed using in-house software written in MATLAB (MathWorks, Natick, MA). The MRI sequences used for the *ex vivo* experiments have previously been described (9) and used a high-resolution, three-dimensional, spoiled gradient recalled echo acquisition (TR/TE, 15.6 ms/2.5 ms; flip angle, 60°; voxel size, 0.4 × 0.4 × 0.8 mm, receiver bandwidth, 488.3 Hz/pixel). The large flip angle was used to accentuate the signal from the ECAMs (with lower T1-weighted relaxation times) against the background. The high bandwidth and short echo time were chosen to minimize susceptibility artifacts in the region of the titanium markers.

RESULTS

Of the various agents tested, the C4 agent with stoichiometry $(CoCl_2)_{0.8}(C_2H_5NO_2)_{0.2}$ demonstrated the highest signal on a conventional three-dimensional T1-weighted spoiled gradient recalled acquisition in phantom (Fig. 2). Acrylic and glass hollow seeds containing 0.5–5 μL of the $(CoCl_2)_{0.8}(C_2H_5NO_2)_{0.2}$ aqueous solution (0.3–10 wt.%) were well visualized in a phantom using 1.5-T MRI. Relaxivity measurements were obtained using the slope of the weighted least-squares regression of the relaxation rate versus concentration. Measurement of the spin-lattice relaxivity (r_1) at 1.5 T resulted in 0.093 ± 0.022 $mM^{-1}\ s^{-1}$ (Pearson’s $R^2 = 0.99$), and measurement of the spin-spin relaxivity (r_2) was 0.105 ± 0.01 $mM^{-1}\ s^{-1}$ (Pearson’s $R^2 = 0.99$). The ratio of the relaxivities were >1 ($r_2/r_1 = 1.21 \pm 0.29$), which is consistent with T1-weighted positive contrast agents.

C4 agent inside titanium and acrylic seeds

The C4 agent was able to generate increased signal on T1-weighted MRI using concentrations of 0.5–10% inside polymer seeds in phantom. The C4 agent could not be visualized inside the titanium seed. The C4 agent had positive T1-weighted contrast at lower concentrations in plastic seeds and was able to positively identify the location of the nonradioactive titanium seeds in phantom (Fig. 3).

Identification of titanium seeds in canine prostate

The various combinations of [acrylic/glass]-titanium-[acrylic/glass] and titanium-[acrylic/glass]-titanium rows of seeds were visualized in the canine prostate within an agarose phantom, and the calculations were verified the distance from the ECAM to the center of the titanium seeds (Fig. 4).

DISCUSSION

We have developed a novel ECAM with cobalt (II) chloride-glycine that might permit the positive identification of implanted radioactive seeds with high-signal intensity on MRI after placement of permanent prostate brachytherapy interstitial implants. The ECAM could not be adequately visualized inside a titanium seed but was adequately visualized inside acrylic or glass seeds, which could be used alone or

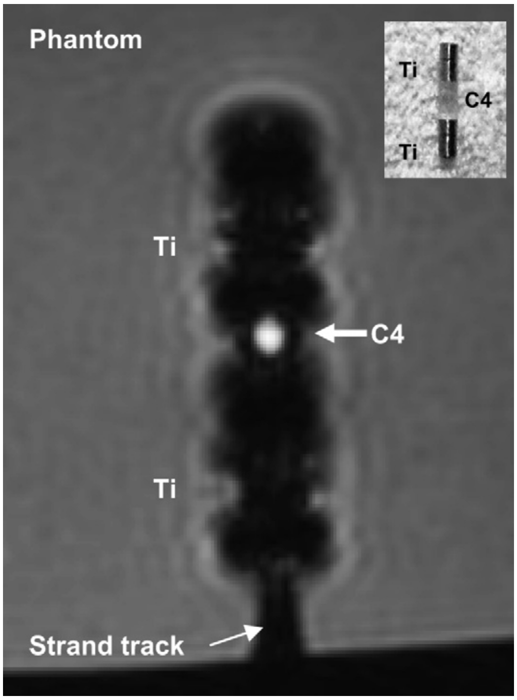

Fig. 3. Novel C4 agent permits positive identification of manufactured titanium seeds in phantom. Negative magnetic resonance imaging contrast of strand track in phantom shown.

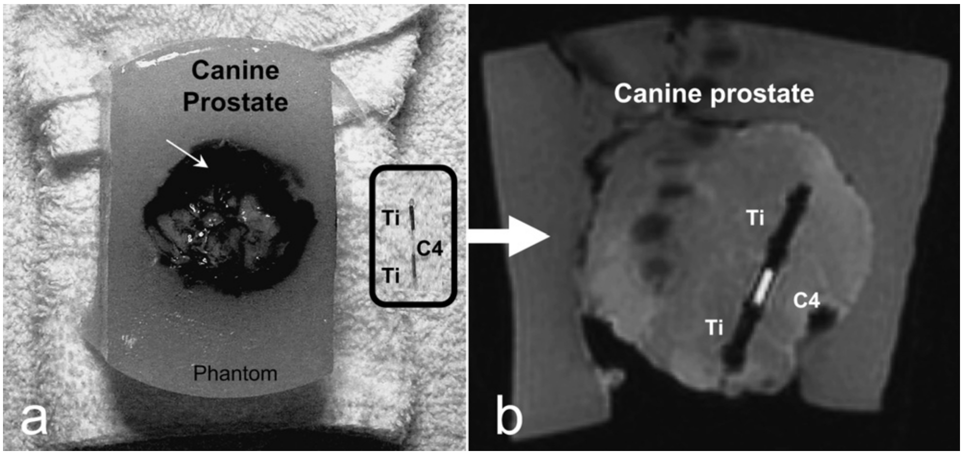

Fig. 4. Imaging of standard titanium seeds with embedded encapsulated contrast agent marker in canine prostate incorporated into phantom. (a) Canine prostate embedded in agarose gel phantom and strand of standard titanium seeds and encapsulated contrast agent marker with C4 agent between seeds. (b) Sagittal, 1.5T T1-weighted magnetic resonance image of canine prostate with strand of standard titanium seeds containing encapsulated contrast agent marker with C4 agent, permitting accurate identification of seeds.

incorporated into a strand with titanium seeds for brachytherapy.

The accurate identification of implanted radioactive seeds in the prostate using MRI would permit MRI-based dosimetry for prostate brachytherapy. MRI-based dosimetry can be performed at any center with access to an MRI scanner. It could become the new reference standard for implant quality evaluation because of the superiority of MRI compared with CT in imaging the prostate and surrounding critical organ structures. With an increasing number of clinicians performing monotherapy on intermediate-risk prostate cancer patients (10), MRI-based dosimetry could locate areas that require additional dose to optimize local control. MRI-based dosimetry, by permitting accurate evaluation of the dose to the base and apex of the prostate, penile bulb, rectum, bladder neck, and surrounding vasculature, might also help prevent the development of rectal fistulas, urethral strictures, and erectile dysfunction. CT-MRI fusion would no longer be required to evaluate implant quality, resulting in decreased cost to patients and healthcare systems. MRI-based dosimetry would minimize the interobserver variability common in CT-based dosimetry. Finally, MRI-based dosimetry would further standardize postimplant dosimetry and improve quality assurance in multi-institutional protocols.

CONCLUSION

We have developed a novel MRI ECAM that permits positive identification of the radioactive seeds used for prostate brachytherapy on MRI. Our novel ECAM might permit the standardization of prostate brachytherapy implants using MRI-based dosimetry and convert prostate brachytherapy from an art to a science, resulting in consistent high-quality treatment.

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