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Feasibility of 3T Dynamic Contrast-Enhanced Magnetic Resonance-Guided Biopsy in Localizing Local Recurrence of Prostate Cancer After External Beam Radiation Therapy

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Objectives: The objective of this study was to assess the feasibility of the combination of magnetic resonance (MR)-guided biopsy (MRGB) and diagnostic 3T MR imaging in the localization of local recurrence of prostate cancer (PCa) after external beam radiation therapy (EBRT).

Materials and Methods: Twenty-four consecutive men with biochemical failure suspected of local recurrence after initial EBRT were enrolled prospectively in this study. All patients underwent a diagnostic 3T MR examination of the prostate. T2-weighted and dynamic contrast-enhanced MR images (DCE-MRI) were acquired. Two radiologists evaluated the MR images in consensus for tumor suspicious regions (TSRs) for local recurrence. Subsequently, these TSRs were biopsied under MR-guidance and histopathologically evaluated for the presence of recurrent PCa. Descriptive statistical analysis was applied.

Results: Tissue sampling was successful in all patients and all TSRs. The positive predictive value on a per patient basis was 75% (15/20) and on a per TSR basis 68% (26/38). The median number of biopsies taken per patient was 3, and the duration of an MRGB session was 31 minutes. No intervention-related complications occurred.

Conclusions: The combination of MRGB and diagnostic MR imaging of the prostate was a feasible technique to localize PCa recurrence after EBRT using a low number of cores in a clinically acceptable time.

Key Words: functional magnetic resonance imaging, prostate neoplasms, external beam radiation therapy, local recurrence, biopsy

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ORIGINAL ARTICLE

**TABLE 1.** Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Datum (Range)</th>
<th>No. Missing Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yr)</td>
<td>70 (60–83)</td>
<td>20</td>
</tr>
<tr>
<td>Preradiotherapy pathologic stage*</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>T1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>T2</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Median preradiotherapy Gleason score</td>
<td>7 (5–9)</td>
<td>2</td>
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<tr>
<td>Median preradiotherapy PSA (ng/mL)</td>
<td>15.6 (6.1–96.0)</td>
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</tr>
<tr>
<td>Median radiation therapy dose (Gy)</td>
<td>67.5 (66.0–78.0)</td>
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</tr>
<tr>
<td>No. patients who received hormonal therapy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Median PSA nadir (ng/mL)</td>
<td>0.26 (0.0–6.3)</td>
<td>2</td>
</tr>
<tr>
<td>Median PSA level (ng/mL) prior to MR imaging</td>
<td>4.4 (1.1–13.4)</td>
<td>2</td>
</tr>
<tr>
<td>Median time (yr) between radiation therapy completion and MR examination</td>
<td>4.4 (1.1–13.4)</td>
<td>2</td>
</tr>
<tr>
<td>Median time (wk) between MR examination and biopsy</td>
<td>4.1 (1.3–10.00)</td>
<td>2</td>
</tr>
</tbody>
</table>

*Data are numbers of men (n = 20) with the given cancer stages.

endorectal coil (ERC) (Medrad, Pittsburgh) and a pelvic phased-array coil. The ERC was inserted and filled with either a 40 mL perfluorocarbon or water preparation (FOMBLIN, Solvay-Solexis, Milan, Italy). Peristalsis was suppressed with an intravenous injection of 20 mg butylscopolamone bromide (BUSCOPAN, Boehringer-Ingelheim, Ingelheim, Germany), intramuscular injection of 20 mg butylscopolamone bromide and 1 mg of glucagon (GLUCAGON, Nordisk, Gentofte, Denmark).

The imaging protocol included the following sequences: T2-weighted turbo spin echo sequences were acquired (TR 4260 milliseconds/TE 99 milliseconds; flip angle, 120; 3 mm slice thickness; echo train length, 15; 180 × 90 mm field of view, and 448 × 448 matrix; voxel size, 0.2 × 0.4 × 3 mm) in axial, coronal, and sagittal planes. A 3-dimensional (3D) T1-weighted gradient echo sequence (TR 4.90 milliseconds/TE 2.45 milliseconds; flip angle, 10; 176 slices per 3D slab; 0.9 mm slice thickness; 288 × 288 field of view and 320 × 320 matrix; voxel size 0.9 mm × 0.9 mm × 0.9 mm) was used to assess lymph node and skeletal status. Finally, an axial 3D T1-weighted gradient echo sequence (TR 800 milliseconds/TE 1.47 milliseconds; flip angle, 14; 3 mm slice thickness; field of view 230 × 230 and 128 × 128 matrix; voxel size 1.8 mm × 1.8 mm × 3 mm) was used to obtain proton-density images, with the same positioning angle and center as the axial T2-weighted sequence (to allow calculation of the relative gadolinium chelate concentration curves), followed by 3D T1-weighted spoiled gradient-echo images (TR 38 milliseconds/TE 1.35 milliseconds; flip angle, 14; 10 transverse partitions on a 3D slab; 3 mm section thickness; 230 × 230 mm field of view; 128 × 128 matrix; voxel size 1.8 × 1.8 × 3 mm; GRAPPA parallel imaging factor 2; 2.5 s temporal resolution; and 2 minutes 30 seconds acquisition time) acquired during an intravenous bolus injection of a paramagnetic gadolinium chelate—0.1 mmol of gadopentetate dimeglumine (DOTAREM, Guerbet, Paris, France) per kilogram of body weight. This was administered with a power injector (Spectris; Medrad) at 2.5 mL/s and followed by a 20-mL saline flush.

**MR Data Analysis**

The prostate images of all patients were read in consensus by 2 radiologists with respectively 2 and 5 years of experience in prostate MR imaging. Functional dynamic imaging parameters were estimated from a fitted general biexponential signal intensity model for each MR signal enhancement–time curve, as described previously. The pharmacokinetic parameters (Ktrans, Vep, Keq, and WashOut) were computed using the standard 2-compartment model, and the arterial input function was estimated using the reference tissue method and automated per-patient calibration. Finally, these parameters were projected as color overlay maps over the T2-weighted images. This patented procedure for calculating pharmacokinetic parameters is being used in multiple centers. For the first 2 patients, lesions were identified as suspicious purely whether a focally enhancing region with DCE-MRI was seen irrespective of the degree of enhancement. To determine whether regions enhancing in the prostate were representing tumor, we applied a lesion directed biopsy approach. To establish a “cut-off” in the color coding of the pharmacokinetic maps, we used the “normal” regions of these 2 patients as a cut-off for future color coding. Above this “normal” threshold, radiologists then defined suspicious regions as focally enhancing spots shown on the color maps. The criterion for TSRs on DCE-MRI in the peripheral zone, the central gland, and the seminal vesicles was a cutoff value of 3.5 (minute−1) for Ktrans and −0.225 (AU) for washout. The criterion for TSRs on T2-weighted MR images was a low signal-intensity region within the prostate.

Per patient, the T2-w images were evaluated for TSRs individually and in color overlay (DCE-MRI). To locate the TSRs, the prostate was divided into 22 different axial and sagittal segments, to make a 3D spatial position estimation of the identified TSRs which was used during the second MRGB-session. A similar translation technique was described before by Hambrock et al.

**MR-Guided Biopsy**

After the initial tumor localization MR examination (median time between biopsy and initial localization MRI was 4.1 weeks; range, 1.3–10.00), patients underwent an MRGB using an MR-compatible biopsy device (In vivo, Schwerin, Germany) at 3T. All patients received oral ciprofloxacin 500 mg (CIPROXIN, Bayer, Leverkusen, Germany) the evening before, in the morning of the biopsy, and 6 hours after biopsy.

Relocation of the TSRs (by using the 3D spatial position estimation) determined during the first MR imaging localization was done by obtaining T2-weighted anatomic images in the axial direction. Prostate biopsies were performed with the patient in prone position, and a needle guider inserted rectally, which was attached to the arm of the biopsy device. The needle guider was pointed toward the TSR before obtaining the biopsy specimen. All biopsies were supervised by one experienced radiologist (4 years of experience) with MRGB of the prostate.

**Histopathology**

Samples were subsequently processed by a routine fixation in 10% buffered formalin, embedded in paraffin, stained with hematoxylin-eosin, before being evaluated by an experienced genitourinary pathologist (18 years experience of PCa histopathology) for the presence of tumor. The biopsies were classified as negative if there was no evidence of carcinoma or residual indeterminate carcinoma with severe treatment effect, defined as isolated tumor cells or poorly formed glands with abundant clear or vacuolated cytoplasm. All positive biopsies were assigned a Gleason score.

**Statistical Analysis**

Descriptive statistical analysis was applied. The positive predictive value of TSRs seen on MR images was calculated. The patient characteristics (median and range) were calculated by using SPSS 16.0.
RESULTS

Three patients with contraindications to an ERC (e.g., anorectal surgery, inflammatory bowel disease) were scanned with a pelvic phased-array coil only.

Metastatic disease was evident on MR imaging in 4 of 24 patients. One patient had multiple low signal intensity areas in the left iliac and sacral bone and multiple enlarged lymph nodes (diameter greater than 10 mm) next to the right internal iliac artery. Two patients had multiple enlarged lymph nodes next to the right internal iliac artery. One patient had multiple areas with focal low signal intensities in the body of L4, the right acetabulum, and in the right anterior superior iliac spine. These patients received hormonal therapy and were excluded in the further analysis.

In the remaining 20 patients, a total of 38 TSRs were identified on combined T2-weighted and DCE-MRI and subsequently biopsied with MRGB. All TSRs that were identified on T2-weighted imaging were also identified on DCE-MRI. With DCE-MRI 8 TSRs, in 5 patients, were identified that were not identified on T2-weighted imaging. One patient had a hyperintense region compared with uninvolved prostate tissue as TSR on T2-weighted MR imaging and increased permeability on DCE-MRI (Fig. 1), which turned out to be recurrent PCa on histologic examination.

Median MRGB time was 31 minutes (range, 18–47) per patient and a median of 3 biopsy cores per patient (range, 2–5) was obtained. Median number of biopsies per TSR was 2 (range, 1–4). The MRGBs were tolerated well and no procedure-related complications occurred. Tissue sampling was successful in all patients and TSRs.

Histologically proven local recurrence was evident in 15 patients (Fig. 2). These patients were either treated with salvage cryosurgery (5 patients), salvage prostatectomy (1 patient), wait and see (1 patient), hormonal therapy (2 patients), were lost to follow-up (4 patients), or died (2 patients). Of the 38 different TSRs identified on MR imaging, 26 contained histologically proven recurrence (68%), 8 revealed radiotherapy induced atypia in preexisting glands (21%), 1 contained residual indeterminate PCa with severe radiation changes (3%), and the remaining 3 contained fibrosis (8%).

The PPV of MRGB for detecting local recurrence on per patient basis and per TSR basis was 75% (15/20) and 68% (26/38), respectively. There was no significant difference of the PPV when peripheral, central gland, and seminal vesicles were considered separate and also the use of a pelvic phased-array coil only had no influence on these results. Gleason score 10 was present in 2/26 (8%), Gleason score 9 in 8/26 (31%), Gleason score 8 in 3/26 (12%), Gleason score 7 in 9/26 (35%), and Gleason score 6 in 4/26 (15%) TSRs.

The site of recurrence within the prostate was present in the apical region in 6 of 26 TSRs, in the apex-mid in 5, in the mid in 9, in the midbase in 3, in the base in 1, and in the seminal vesicle in 2 TSRs. The local recurrence was identified in the peripheral zone in 19 of 26 (73%) TSRs and in the central gland in 7 of 26 (27%) TSRs.

Of the 5 patients, 3 with negative histology received hormonal therapy, 1 underwent salvage cryosurgery, and 1 underwent a follow-up MR examination. The patient with the follow-up MR had unchanged MR findings in combination with a declining PSA (PSA during the first MR examination was 6.4 ng/mL and during the follow-up MR imaging was 3.7 ng/mL).

DISCUSSION

Results of our study show that local recurrence after EBRT could be localized with the combination of MRGB and diagnostic MR imaging in a substantial proportion of patients (PPV of 68% and 75% on a per TSR and a per patient basis, respectively). With a median intervention time of 31 minutes, and no procedure-related complications, MRGB can be considered a feasible method in localizing local PCa recurrence following EBRT.

FIGURE 1. MR images obtained from a 70-year-old man with a TSR seen in the right ventral part in the midprostate, with a PSA of 0.4 ng/mL. The T2-weighted images showed a hyperintense TSR in the right ventral part in the midprostate (arrow) (A), also on DCE-MRI, there was a TSR (high $k_{trans}$ visible (arrow) (B). During a second session, an MRGB was performed, the needle guider was pointed toward the TSR in axial (TRUE-FISP image) (C) plane, and subsequently biopsied. Histopathology revealed a Gleason 9 prostate cancer recurrence.
MRGB was not able to assess the effect of false negatives, ie, areas of prostate cancer which did not enhance, because of the relative time-consuming character of this procedure. However, previous studies that have used 6 core TRUS-guided biopsy as the standard of reference in localizing radiation therapy recurrence, including from regions that did not enhance on DCE-MRI, have shown that the negative predictive value of this technique is between 78% and 95%.11,12 Undoubtedly, 6 core TRUS-guided biopsies have many limitations when used as the gold standard (eg, high false negatives and underestimating of true Gleason score), which probably means that these negative predictive values of the above mentioned studies are somewhat overrated. Correlating DCE-MRI with radical prostatectomy samples would be the best option and should be the next step in correlating recurrent disease seen on DCE-MRI. Nonetheless, when selecting patients with prostate cancer recurrence the mostly followed treatment strategy is still some form of whole-gland salvage therapy. Hence, false negatives are less of a problem. Merely detecting a recurrence, rather than mapping the recurrent tumor, will suffice for this particular group of patients. Thus, only biopsying TSRs seen on DCE-MRI should be considered as an advantage rather than a disadvantage of MRGB biopsies. MRGB is capable of detecting a recurrence with only 3 biopsies per patient omitting TRUS biopsy core schemes (with a PPV of 27%8) that use between 6 and 12 cores per patient. Consequently, it may lead to higher patient satisfaction.

The main advantage of TRUS-guided biopsy over 3T DCE-MRGB is that the expertise and the technique itself are more generally available in routine clinical practice. Probably, performing MR-TRUS fusion for targeted biopsies by combining the high spatial resolution of MR imaging with the wide-spread availability of TRUS is the most optimal strategy as evidenced by promising results in 2 different studies.23,24 However, MRGB has the advantage of being directed toward TSRs using the same imaging modality used for localization. This way spatial misregistration between MR imaging and the biopsy core can be reduced to a minimum, which probably makes it a more precise method. Unfortunately, randomized controlled trials comparing MRGB, TRUS-guided biopsy, and MR-TRUS fusion are not available yet.

Future studies should focus on inclusion of a larger number of patients and to improve the reproducibility of quantitative pharmacokinetic parameters25 as well as to limit the subjectiveness of reader evaluation an automated per-patient arterial input function estimation, which was shown in a recent publication to be superior to fixed input models26 is more preferred.

The widely known and accepted criterion for prostate cancer on T2-weighted MR imaging, a region of low signal intensity, was used by us for localizing recurrence of PCa. It is interesting to note that we had a specific case with a hyperintense region compared with surrounding prostate tissue as a TSR, which was confirmed on histologic evaluation as PCa recurrence. This indicates that after EBRT a recurrence can also have a hyperintense character compared with surrounding prostate tissue on T2-weighted MR imaging. Furthermore, future studies may include other functional MR imaging techniques such as diffusion-weighted imaging26 and MR spectroscopy in guiding MRGB after EBRT. This may lead to a higher detection rate with a minimum number of biopsy cores.

Limitations of our study are related to the relatively small number of patients included and the incomplete data concerning patient characteristics, which was due to patient referral from outside our university hospital. In our study, we did not have any patient with a negative DCE-MRI on local prostate level. In other words, each patient we imaged had at least one TSR in the prostate detected with DCE-MRI. This can be interpreted as a selection bias. However, this is not surprising because of the inclusion criteria being 3 consecutive rises of PSA after reaching PSA nadir. Only 3 patients were examined without the use of an ERC. Because of the small number of this group, no further conclusions can be drawn from this result. Because our current study is prospective and no other studies exist on defining true pharmacokinetic cut-off values for the irradiated prostate we had to base our cut-off values on the first 2 patients we imaged and biopsied. Defining a cut-off for tumor is impossible with only 2 patients. These 2 were only used

**FIGURE 2.** MR images obtained from a 68-year-old man with a TSR seen in the right peripheral zone at the apex-mid, with a PSA of 2.1 ng/mL. The T2-weighted images showed a diffuse low signal intensity of the entire prostate and no TSR was detectable (A); however, on DCE-MRI, there was a TSR (high $K^{trans}$) visible (arrow) (B). During a second session, an MRGB was performed, by pointing the needle guider toward the TSR in axial (TRUE-FISP image) (C), plane and subsequently biopsied. Histopathology revealed a Gleason 7 prostate cancer recurrence.
to define a cut-off for “normal.” Above this “normal” threshold, radiologists then defined suspicious regions as focally enhancing spots shown on the color maps. To define true pharmacokinetic cut-off values for tumor versus benign enhancing spots versus normal in the irradiated prostate is subjective of a future publication and can only be determined retrospectively on a larger group of patients.

Salvage therapies can offer a possibility of cure in selected patients. This underlines the importance to select the patients who would benefit from it carefully. Unfortunately, the conventional methods for diagnostic workup of PCa recurrence (eg, DRE, PSA, TRUS, bone scan) all have their limitations. Therefore, there is a need for more accurate and versatile diagnostic tools like MR imaging, which has the advantage that both local and distant prostate disease can be evaluated at the same time. Moreover, the addition of other functional MR imaging techniques such as DWI can even possibly play a role in the assessment of tumor aggressiveness.

In conclusion, the combination of MRGB and diagnostic MR imaging of the prostate was a feasible technique to localize PCa recurrence after EBRT using a low number of cores in a clinically acceptable time.

REFERENCES