MR detection of local prostate cancer recurrence after transrectal high-intensity focused US treatment: preliminary results

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Résumé
Détectio par IRM des récidives locales du cancer de prostate après traitement par ultrasons focalisés de haute intensité (HIFU) transrectaux : étude préliminaire.
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Objectif. Évaluer l’IRM T2 et dynamique dans la détection des récidives locales du cancer de prostate après traitement par ultrasons focalisés de haute intensité (HIFU) transrectaux.

Matériel et méthodes. Quinze patients traités par HIFU pour cancer de prostate et adressés pour récidive biologique ont été explorés par IRM. Des coupes T2 axiales, sagittales et coronales ont été suivies d’une acquisition dynamique (12 coupes axiales de 3 mm ; résolution temporelle : 15 secondes) après injection de gadolinium. Des biopsies transrectales ont ensuite été réalisées sous guidage écho-Doppler. Les résultats de l’IRM et des biopsies ont été comparés dans 10 secteurs prostatiques.

Résultats. Les biopsies ont montré une récidive tumorale chez 13/15 patients (23/108 secteurs). En T2, les prostates traitées présentaient un hyposignal focalisés de haute intensité (HIFU) transrectaux.

Conclusion. L’IRM, notamment dynamique, est une méthode prometteuse pour la détection et la localisation des récidives locales après traitement du cancer de prostate par HIFU transrectaux.

Mots-clés : Cancer de prostate. HIFU. IRM. IRM dynamique. Biopsie de prostate.

Abstract
Purpose. To assess T2W and dynamic contrast-enhanced (DCE) MR imaging in the detection of local tumor recurrence after transrectal high-intensity focused US (HIFU) treatment.

Materials and methods. Fifteen patients treated by HIFU for prostate cancer were referred for MR due to biological evidence of tumor recurrence. Axial, sagittal and coronal T2W images and DCE images (12 3-mm thick axial images, temporal resolution: 15 seconds) were obtained first. Transrectal biopsies were then obtained under US guidance. MR findings were compared to biopsy results for 10 prostate sectors.

Results. Biopsies demonstrated tumor recurrence in 13/15 patients (23/108 sectors). On T2W images, the treated prostate tissue was diffusely hypointense which interfered with interpretation. Three patients (5 sectors) had suspicious areas of T2W signal abnormality and 15 patients (29 sectors) had suspicious areas on DCE scans. An analysis per sector for T2W and DCE imaging showed sensitivity, specificity, positive predictive and negative predictive values respectively of 0.13, 0.98, 0.6 and 0.81 and 0.70, 0.85, 0.55 and 0.91. DCE MR was strongly predictive of positive biopsy results (Odds ratio: 12.8 (95% confidence interval: 4.4-37.3)) whereas T2W imaging was not (Odds ratio: 4.0 (95% confidence interval: 0.5-30)).

Conclusion. MR, especially DCE MR, is promising for the detection and localization of local prostate cancer recurrence after transrectal HIFU treatment.

Key words: Prostate cancer. HIFU. MR. Dynamic contrast-enhanced MR. Prostate biopsy.
Residual cancers detected on systematic biopsies or on biopsies obtained following a rise in PSA level can undergo repeat transrectal HIFU ablation (6, 9). As such, early detection of residual tumor is important. It is possible that random biopsies have a low sensitivity especially since the prostate becomes small, heterogeneous and difficult to interpret on US following HIFU (10).

The availability of Doppler US for guidance at the time of prostate biopsy has improved the biopsy process since it has a significant predictive value after HIFU ablation (11).

Unfortunately, Doppler US remains poorly sensitive (2/3 of viable tumor foci on biopsy are in non-hypervascular regions). In addition, it is not reliable in patients receiving neoadjuvant hormone-therapy (11). Indeed, hormonotherapy, even if discontinued at the time of HIFU ablation, may reduce vascularity in tumor foci (hence the ability for Doppler US to detect them) for months.

To our knowledge, the use of MR for the detection of residual or recurrent tumor following HIFU in patients with prostate carcinoma has not previously been evaluated. Yet, MR (especially dynamic gadolinium contrast material enhanced MR) is a sensitive imaging technique for detecting tumors in non-treated prostate (12-15) or for detecting recurrent tumor following HIFU (10).

The mean time interval between the last HIFU treatment and the MR was 22.5±16.5 months (range: 4-72 months). The mean PSA nadir after the last HIFU treatment was 2.4±2.8 ng/ml (range: 0.06-10.78). The level had then increased to a mean of 4.9±4.79 ng/ml (range: 1.26-22) prior to MR.

**MR protocol**

All examinations were performed on a 1.5T MR unit (Symphony, Siemens, Erlangen, Germany) with the help of a phased-array surface coil. A standard protocol was used for all patients.

First, axial, sagittal and coronal TSE T2W images [TR 6130 ms; TE 109 ms; 20 slices of 4 mm thick; 180x180 FOV; 256x192 matrix; 3 excitations; ETL of 21; 25% phase oversampling; acquisition time of 3 min 28 sec] were obtained. Then, an axial fat-suppressed FLASH (Fast Low Angle Shot) T1W sequence [TR 3.38 ms; TE 2.73 ms; flip angle 10°; 256x135 matrix; 240x204 matrix; 1 volume; 14 slices of 3 mm thick; 14% phase oversampling; 1 excitation; acquisition time of 15 sec] was obtained prior to contrast. The same sequence was then repeated 12 times after power-injected (Medrad, Warrendale, USA) bolus administration of 0.1 mmol/kg of gadoteric acid (Dotarem, Guerbert, Roissy, France) at 3 ml/sec followed by a 20 ml saline chase injected at a same rate. The first of the 12 acquisitions was manually started upon contrast arrival in the common femoral arteries. The entire examination lasted about 30 minutes.

**Materials and methods**

**Patient population**

Our patient population includes 14 patients aged between 55 and 80 years (mean: 69.8±6.2 years) referred between September 2005 and March 2007 for suspected biological recurrence of tumor following HIFU ablation for prostate carcinoma. All patients underwent MR prior to biopsy. One patient underwent two prostate biopsies at one year interval, with MR performed prior to each biopsy. As such, this patient was considered as two different patients for analytical purposes. Our database thus included correlation between MR and biopsy for 15 patients. All patients were treated with the Ablatherm unit (Edap, Vaulx-en-Velin, France), typically following TURP, using the routine technique [Poissonnier 2007] in one (n=10) or two (n=5) sessions.

The mean time interval between the last HIFU treatment and the MR was 22.5±16.5 months (range: 4-72 months). The mean PSA nadir after the last HIFU treatment was 2.4±2.8 ng/ml (range: 0.06-10.78). The level had then increased to a mean of 4.9±4.79 ng/ml (range: 1.26-22) prior to MR.

**Review of MR images**

The prostate was divided into 8 segments (right and left apex, middle portion, base and seminal vesicles).

Because no data is available describing the MR features of recurrent tumor following HIFU ablation, the diagnostic criteria for tumor recurrence were based on those used for tumor diagnosis in non-treated prostate (12) and diagnosis of recurrence following radiation therapy (16, 17).

It was expected that the post HIFU prostate would appear diffusely heterogeneous and/or hypo-intense on T2W images. This appearance was thus considered normal. On the other hand, all focal nodular lesions that appeared relatively more hypo-intense than the remainder of the gland were considered suspicious. Seminal vesicle involvement was suspected in the presence of wall thickening or hypo-intense endoluminal elements.

On dynamic MR, all nodular lesions showing early intense enhancement relative to the remainder of the gland were considered malignant. Seminal vesicle involvement was diagnosed in the presence of early wall enhancement or endoluminal enhancement.

**US-guided prostate biopsies**

Prostate biopsies were performed on average 7.4 days (range: 1-63 days) after MR. All biopsies were performed by four senior radiologists (respective experience: 2, 2, 5 and 15 years) using a Voluson 530D unit with endorectal probe S-ICS-9 (Kretz, AG, Zipf, Austria) at 7.5 MHz for B-mode imaging and 6.5 MHz for color Doppler imaging.

First, the prostate volume was calculated from sagittal and transverse images using the formula for ellipsoid volume (height x AP diameter x transverse diameter)/3x0.52. The biopsies were performed using an 18G automated biopsy-gun (Bard, Murray, Hill, NJ) following local peri-prostatic anesthesia.

In our institution, the post HIFU prostate biopsy protocol includes a single random biopsy sample per sextant, with additional directed biopsies if suspicious lesions are detected on color Doppler US (11). The MR images for our patients were available on PACS at the time of prostate biopsy to review areas of abnormality on T2W and/or dynamic contrast-material enhanced images.

When an abnormality was present in a given sextant, one or more biopsies were obtained in that sextant. A random biopsy was also obtained from each negative sextant on MR. To ensure a comprehensive evaluation, additional biopsies could also be obtained in regions showing abnormal Doppler signal and/or in the seminal vesi-
icles if they appeared abnormal on MR and/or US. In all cases, the procedure report clearly stated which biopsies were obtained in regions considered normal on MR and which were obtained in regions considered suspicious on MR. All biopsies were marked with China ink at the capsular surface and fixed in Bouin’s solution. The biopsy site was recorded, and the presence or absence of corresponding abnormality on MR was noted.

Histology
All specimens were processed according to the standard protocol in our institution. For each biopsy sample, the histology report described the presence or absence of cancer, and, when cancer was present, the length of involvement and Gleason score.

Statistical analysis
Statistical analysis was performed by a professional statistician using the SPSS software (Chicago, USA). Results are presented as mean values ± standard deviation. Differences were considered statistically significant when the p value was <0.05.

For patients, true positive (TP), true negative (TN), false negative (FN) and false positive (FP) were defined as follows. Patients with at least one segment with positive biopsies and suspicious focus on MR (T2W and/or dynamic MR) in the same segment were defined as true positive, irrespective of biopsy results in other segment. True negative patients were defined as patients with no abnormality on MR and negative biopsies throughout the entire prostate. Patients with at least one positive biopsy and no abnormality in the corresponding segment on MR were defined as false negative. Patients with negative biopsies and at least one positive segment on MR were defined as false positive. Finally, patients with both FN and FP segment without TP segment were considered non-classifiable.

Results
US-guided prostate biopsies
The mean prostate volume was 10.1±7 cc (range: 2-28 cc). A total of 144 biopsies were performed from 108 prostate segments. Thirteen of 15 procedures showed residual cancer. Twenty-three of the 108 biopsied segments showed cancer (21.2%). The distribution of positive segments is summarized in table I. Gleason scores were 6, 7 and 8 in 8, 11 and 4 segments respectively. The mean length of cancer involvement was 4.6±5.1 mm (range: 0.3-20 mm).

MR findings
In all cases, the residual prostate gland was small, frequently with a large post-resection space and ill-defined margins. On T2W images, it was diffusely hypointense, sometimes heterogeneous, with loss of zonal anatomy, and overall difficult to assess. On the other hand, dynamic sequences were easier to interpret, with little enhancement of residual prostate tissue compared to local recurrent tumor (fig. 1 to 2).

Only 3 of 15 patients showed suspicious areas of signal abnormality on T2W images (5 sextants). On dynamic images, all patients showed signs of tumor recurrence, in a total of 29 segments. The distribution of positive findings on T2W and dynamic MR images is summarized in table II.

MR – histology correlation
Results for each patient are summarized in table III. Results for each segment are summarized in tables IV and V. Based on the analysis by segment, and considering biopsy as the gold standard, the sensitivity, specificity, positive predictive value and negative predictive value were 0.13, 0.98, 0.6 and 0.81 respectively for T2W MR and 0.70, 0.85, 0.55 and 0.91 respectively for dynamic MR. Results on dynamic MR were a significant predictor of biopsy results (Odds ratio: 12.8 [95% confidence interval (CI): 4.4–37.3]), while results on T2W MR were not (Odds ratio: 4 [95% CI: 0.5–30]).

Table I
Distribution of positive segments on biopsy.

<table>
<thead>
<tr>
<th>Segment</th>
<th>Number of positive segments on biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex</td>
<td>8</td>
</tr>
<tr>
<td>Middle portion</td>
<td>6</td>
</tr>
<tr>
<td>Base</td>
<td>6</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
</tr>
</tbody>
</table>

Table II
Distribution of positive segments on T2W and dynamic MR.

<table>
<thead>
<tr>
<th>Segment</th>
<th>Number of positive segments on T2W MR</th>
<th>Number of positive segments on dynamic MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Middle portion</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Base</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>29</td>
</tr>
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</table>

Table III
Correlation between MR and biopsy (analysis per patient).

<table>
<thead>
<tr>
<th>Segment</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>Non-classifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2W</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Dynamic MR</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

TP: true positive, TN: true negative, FP: false positive, FN: false negative.

Discussion
After HIFU ablation, the area of tissue destruction is completely devascularized and may easily be depicted on contrast enhanced Doppler US (18) or contrast enhanced (non-dynamic) T1W MR (19).

The zone of devascularization progressively regresses in a centripetal fashion over a 3-5 month period, as the area of HIFU induced coagulation necrosis is replaced by fibrous scar tissue (19). During the same period, the prostate undergoes significant atrophy, with the final volume
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Table IV
Correlation between T2W MR and biopsy (analysis per segment).

<table>
<thead>
<tr>
<th>Biopsy results</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2W results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Negative</td>
<td>20</td>
<td>83</td>
<td>105</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>85</td>
<td>108</td>
</tr>
</tbody>
</table>

Table V
Correlation between dynamic MR and biopsy (analysis per segment).

<table>
<thead>
<tr>
<th>Biopsy results</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic MR results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>16</td>
<td>13</td>
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</tr>
<tr>
<td>Negative</td>
<td>7</td>
<td>72</td>
<td>79</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>85</td>
<td>108</td>
</tr>
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frequently being less than 10 g. The prostate becomes heterogeneous and difficult to interpret on US (11). To our knowledge, the MR imaging features of the prostate over 6 months post HIFU ablation has not been described.

It is not surprising that the prostate should be difficult to interpret on T2W MR images. The prostate typically becomes diffusely T2W hypointense and/or heterogeneous with loss of normal zonal anatomy following external beam radiation therapy, brachytherapy or cryotherapy, resulting in reduced natural contrast between prostate tissue and recurrent tumor (16, 17, 20-23).

On the other hand, our results suggest that dynamic contrast material enhanced MR may be a useful technique to detect.

Fig. 1:
Images in a 76 year old patients with previous HIFU ablation 2 tears previously for Gleason 6 prostate carcinoma. The initial PSA was 8.3 ng/ml. The nadir level was 4.22 ng/ml. The PSA progressively increased to 6 ng/ml.

a. TSE T2W image (TR 6130 ms; TE 109 ms; slice thickness: 4 mm; FOV 180 mmx180 mm; matrix 256x192) showing a heterogeneous, diffusely hypointense prostate with loss of normal zonal anatomy. No definite area of suspicious abnormal signal is identified.

b. FLASH T1W images (TR 5.38 ms; TE 2.73 ms; flip angle10°; slice thickness 3 mm; FOV 240x204 mm; matrix 256x192; acquisition time 15 sec) with fat suppression, prior to (b) and following (c) gadoflumine injection. The enhanced dynamic image shows two suspicious foci with early intense enhancement: one in the left transitional zone anteriorly (c, arrow) and one in the middle portion of the right peripheral zone (c, arrowhead). Biopsies of the middle portion of the right peripheral zone showed residual carcinoma, 3 mm in size, with Gleason score of 6.
local recurrence of tumor. Seventy percent of positive segments on biopsy were positive on dynamic MR, compared to only 13% for T2W MR. This good sensitivity should improve the sensitivity from biopsies and allow earlier detection of recurrent disease.

However, it must be underscored that biopsies may not be the gold standard for detection of local recurrence. In the literature, the rate of positive findings on systematic biopsies after initial 10-12 negative biopsy samples ranges from 17-21% (24, 25), suggesting that a non-negligible number of recurrent cancers are missed on initial biopsies. It is thus possible that some negative segments on biopsy were in fact harboring recurrent tumor. Additional results from this pilot study should also be confirmed by larger studies.

First, we have used purely visual diagnostic criteria since they are easy to use, require no particular postprocessing, and were shown to be useful in the detection of cancer in non-treated prostates (12, 13) and recurrent cancer after radiation therapy (16). However, if temporal resolution is sufficient, pharmacokinetic parameters may be extracted from the dynamic dataset (14, 26). The value of dynamic parameters compared to simpler visual criteria and their ability to improve the PPV of dynamic MR have yet to be established.

Second, it is not certain that dynamic MR, irrespective of the diagnostic criteria used, will discriminate between recurrent tumor and residual adenomatous tissue. The enhancement pattern of cancer and adenomatous tissue is similar (27) and the ability of dynamic MR to detect foci of cancer in adenoma remains controversial (12, 28, 29). It is not possible to destroy tissues beyond the focal point of the transducer with HIFU. Therefore, an anterior band of residual adenomatous tissue is frequently observed after treatment (10). The ability of dynamic MR to detect foci of cancer in this anterior band of adenomatous tissue remains to be demonstrated.
Proton MR spectroscopy, able to detect recurrent tumor after cryotherapy (21), or contrast enhanced color Doppler US, with interesting preliminary results for prostate biopsy guidance (30), could be of value to detect recurrent tumors after HIFU ablation. To our knowledge, their role for this indication has not yet been assessed.

In this study, an endorectal coil was not used. Such a coil is expensive, increases patient discomfort, and may cause magnetic field inhomogeneity that may interfere with dynamic MR. Good results were recently published using only phased array coils (12, 13). However, given the significant degree of prostate atrophy after HIFU ablation, an endorectal coil providing superior SNR could improve the detection of recurrent tumor. In addition, the use of a 3T magnet could improve the spatial and temporal resolution of dynamic MR (31). Both of these points should be further assessed.

Finally, the use MR prior to prostate biopsy results in non-negligible added costs. Results from our pilot study do not provide an appreciation of the number of patients with recurrent disease on MR that would have been missed on standard random biopsies. Only a protocol with strict methodology with two US operators (one performing random biopsies, and one performing targeted biopsies of lesions seen on MR) could provide an answer to this question. Such a study is currently underway at our institution.

In conclusion, our preliminary results suggest that dynamic MR may reliably detect foci of recurrent prostate cancer following HIFU ablation. This could assist in achieving earlier diagnosis of recurrent disease and subsequent targeted repeat HIFU ablation. Additional evaluation with a larger patient population should be performed. Also, the cost-benefit ratio of dynamic MR to detect potential recurrent carcinoma in patients with biological evidence of tumor recurrence after HIFU ablation requires careful analysis.

Références

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