Value of magnetic resonance spectroscopy (MSR) and dynamic contrast-enhanced magnetic resonance (DCEMR) imaging for the characterization of high-grade prostatic intraepithelial neoplasia (HGPIN) foci

Alessandro Sciarra*, Valeria Panebianco, M.D., Stefano Salciccia, M.D., Alessandro Gentilucci, M.D., Andrea Alfarone, M.D., Luisa Dimare, M.D., Dino Lisi, M.D., Susanna Catturino, M.D., Giovanni Di Pierro, M.D., Magnus Von Heland, Mauro Ciccariello, M.D., Roberto Passariello, Vincenzo Gentile

Departments of Urology and Radiology, University Sapienza, Rome, Italy
Received 27 June 2009; received in revised form 20 July 2009; accepted 21 July 2009

Abstract

Background: Despite an increasing interest in high-grade prostatic intraepithelial neoplasia (HGPIN), the clinical suspicious aspect of this premalignant lesion remains poorly characterized. The aim of this study was to analyze the magnetic resonance spectroscopy (MSR) and dynamic contrast-enhanced magnetic resonance (DCEMR) imaging features of isolated HGPIN lesions.

Materials and methods: From January 2007 to January 2009, 330 cases were included in a protocol that involve the use of MSR and DCEMR for the diagnosis of prostate diseases. Of these, 27 patients with isolated (no associated prostate cancer diagnosis) HGPIN histologic diagnosis at the first prostate biopsy were included in the present study. All cases were previously submitted to MSR/DCEMR (1.5 T scanner) and, no later than 10 days to a random 12-core biopsy scheme. Biopsy targeting was done in zones corresponding to those analyzed with MSR and DCEMR.

Results: In the 27 patients, 30 HGPIN foci with a diameter of 6 mm or greater were analyzed and compared with 27 peripheral zone areas of normal prostate tissue. With MSR, HGPIN foci were characterized by a significantly higher (P < 0.05) absolute value of choline and choline/creatine/citrate ratio compared with normal tissue. With DCEMR, HGPIN foci were characterized by lower values of all dynamic parameters but differences did not reach statistical significance (P > 0.05).

Conclusions: In our experience, HGPIN lesions can be metabolically characterized by MSR through the absolute value of choline and the choline + creatine/citrate ratio. © 2009 Elsevier Inc. All rights reserved.

Keywords: Prostate neoplasm; High grade prostatic intraepithelial neoplasia; Magnetic resonance; Spectroscopy

1. Introduction

High-grade prostatic intraepithelial neoplasia (HGPIN) is now considered the most likely precursor lesion to adenocarcinoma of the prostate. The histologic diagnosis of an isolated HGPIN at prostate biopsy is clinically relevant and can condition the choice for the future follow-up of the patient. In fact, in a meta-analysis of 2,077 cases from 17 studies, the presence of HGPIN at prostate biopsy was associated with a 28% incidence of prostate cancer at follow-up biopsies. Moreover HGPIN lesion can also be associated with prostate cancer in the same patient. Qian et al. on 105 prostate cancer submitted to radical prostatectomy, reported HGPIN in 86% of the cases. Despite an increasing interest in HGPIN, the clinical suspicious aspect of this premalignant lesion remain poorly characterized. No specific markers have been found and PSA cannot significantly characterize patients with HGPIN compared with patients with benign prostatic lesions or prostate cancer. Moreover, HGPIN is currently unde-
tectable in transrectal ultrasonography (TRUS) of the prostate.

Recently, many studies [4–7] revealed the high diagnostic accuracy of combined proton 1H-magnetic resonance spectroscopy imaging (MSR) in the management of prostate cancer. The advantage of MSR is that the spectroscopic analysis provides metabolic informations regarding prostate tissue by displaying the relative concentration of chemical compounds within contiguous small volumes of interest (voxels). In the prostate, the substances analyzed by MSR are citrate, creatine, and choline. Citrate is produced by healthy prostatic epithelial cells and it decreases because of energetic metabolism in prostate cancer. Creatine is part of the phosphocreatine-creatine system of cellular energy storage but it does not change in prostate cancer. Choline is a cell membrane constituent whose concentration increases in cases of prostate cancer, as a result of high turnover [2,7–10]. Dynamic contrast-enhanced magnetic resonance (DCEMR) imaging consists in the acquisition of sequential images during the passage of a contrast agent within the prostatic tissue. The technique is based on the assessment of tissue neoangiogenesis, which is an integral feature of tumors [11,12]. In particular, MSR has been used not only in the definition of prostate tumor presence and localization but also in the characterization of tumor aggressiveness (Gleason score) [9,13]. To our knowledge, only one study [14] tried to characterize HGPIN foci at MSR in an initial experience on 11 cases. Considering that HGPIN is a premalignant lesion to prostate cancer, it is conceivable that HGPin might mimic cancer in MSR or DCEMR of the prostate. Therefore, the primary aim of this study was to characterize the MSR and DCEMR imaging features of isolated HGPIN lesions (not associated to prostate cancer).

2. Materials and methods

2.1. Study design and population

A research protocol that involves the use of MR imaging with MSR and DCEMR for the diagnosis of prostate diseases was implemented at our center. The protocol has been approved by an internal protocol review board. The present article describes a prospective single center study of patients with isolated HGPIN histologic diagnosis at the first random TRUS-guided prostate biopsy. From January 2007 to January 2009, 330 cases were included in the protocol and submitted to MSR and DCEMR analysis. Of these, 27 patients [mean age 71.6 ± 5.5 years; mean PSA 8.0 ± 2.7 ng/ml; normal digital rectal examination (DRE)] with isolated HGPIN histologic diagnosis in the first TRUS-guided prostate biopsy were included in the present study. Exclusion criteria for the study were: previous hormonal, surgical or irradiation therapies for prostate diseases; cases in which a MR with a complete MSR and DCEMR study was not possible. Inclusion criteria for the study were: previous MSR/DCEMR imaging; isolated (not associated to prostate cancer) HGPIN histologic diagnosis at the first random TRUS-guided prostate biopsy. All prebiopsy MSR/DCEMR and all first random biopsies were homogeneously performed in our Radiologic and Urologic Centers by the same physicians (VP and MC respectively) as part of the patient’s urologic work-up. Twenty-seven eligible cases were included in the study. Informed consent was obtained from all cases, and the protocol was approved by the internal committee for clinical trials.

2.2. Prostate biopsy and histological review

No later than 10 days from MR imaging studies, all prostate biopsies were homogeneously performed in our Department of Urology by a single physician (MC) with long experience in this procedure. TRUS and biopsy were performed using an end-fire ultrasound transducer and biopsy gun with an 18 gauge needle. As is the common practice in our institution, a random, laterally directed 12-core (standard sextant scheme, plus laterally directed samples of the prostate apex, middle, and base) biopsy scheme was performed [15]. No sample in the transitional zone of the prostate was obtained. Biopsy targeting was done in zones corresponding to those analyzed with MSR and DCEMR, on the basis of the x and z-coordinates derived from T2-weighted MRI, as described elsewhere [16]. Each biopsy core was labeled, processed, and examined separately by two pathologists. All histologic assessments were performed blinded to MRI results. Presence, size, and location of inflammation, HGPIN, and prostate cancer for each biopsy sample were analyzed in all cases. HGPIN was identified by using widely accepted histomorphologic criteria for this entity, including the criterion of nuclear enlargement with atypia (including requirement of macronucleoli) with or without cellular stratification but with a lack of the infiltration growth characteristics of invasive carcinoma [17–19]. Each distinct focus of HGPIN consisted of a solid, confluent area of abnormality or an area of no more than 25% of interspersed benign peripheral zone glandular tissue. Areas of HGPIN that were separated by at least 1 mm of benign tissue without any intervening HGPIN were considered as separate lesions. The presence or absence of inflammation in prostate biopsy samples were also described. HGPIN foci that were surrounded by cancer or inflammation were excluded from the analysis, since the presence of encircling cancer or inflammation might confound the imaging feature analysis of HGPIN [14]. All 27 cases included in the study showed no histologic evidence of prostate cancer associated to HGPIN.

2.3. MRI and MSR-DCEMR

All examinations were performed on a commercially available 1.5-T scanner (Magneton Avanto; Siemens Medical Solutions, Erlangen, Germany), equipped with a surface
phased-array and endorectal coil. The technique used for MR imaging, MSR, and DCEMR of the prostate has been previously described [4]. Morphologic imaging was performed acquiring axial and coronal planes. H-MSR data were acquired after a first review of morphologic images, and maximizing the coverage of the selected region of suspected prostate changes, while reducing the inclusion of surrounding structures (muscles, fat, rectal air, urine). The volume of interest (VOIs) were centered on each prostate gland hemi-portion (left and right), covering the entire gland, distinguishing the prostate in sextants. H-MSR was performed using a section-selected box, and a point-resolved spectroscopic sequence was obtained using a 3D chemical shift imaging (CSI) sequence with spectral/spatial pulses optimized for quantitative detection of choline and citrate. DCEMR images were acquired using 3D FLASH T1-weighted spoiled gradient-echo sequence, immediately following completion of an intravenous bolus injection of citrate. DCEMR images were acquired using 3D FLASH T1-weighted spoiled gradient-echo sequence, immediately following completion of an intravenous bolus injection of 10 ml of 1M Gadobutrol (Gadovist-Schering AG, Berlin, Germany).

2.4. MSR and DCEMR data analysis

MR images were analyzed in consensus by two radiologists with long experience in urogenital MRI (VP and RP) who were not informed of the histologic findings. As in previous studies [15,20], for comparison of MR with pathologic findings, and was also based on nominal MR spectroscopic imaging resolution. With respect to the latter, a HGPIN lesion would need, at a minimum, to be equivalent in volume to 1 MR spectroscopic voxel to be potentially detectable and to be characterizable at MR spectroscopic imaging. The MR spectroscopic voxel is cubical and has a resolution of 3 mm³. If the voxel were to be completely enclosed by a HGPIN focus, the axial diameter of the sphere would be at least 7 mm; the 6 mm size threshold for HGPIN foci account for the approximately 14% shrinkage of linear tissue that occurs during routine histopathologic fixation of prostate specimens [14,22]. For each HGPIN focus of 6 mm or greater in diameter, the reader noted the absolute value of Cho, Cit, Cr, the (Cho + Cr)/Cit ratio and also DCEMR parameters. For normal tissue (used as control), representative MR voxels were chosen to cover peripheral zone areas with an unequivocally benign appearance at histopathologic review.

Statistical data analysis was performed with the statistical software Med Calc Software Demo for Windows, version 9.3 (Mariakerke, Belgium). A P value of less than 0.05 was considered to indicate a significant difference. One way-analysis of variance (ANOVA) to test differences between means and a Student-Newman-Keuls (SNK) test for pairwise comparison were performed. MSR and DCEMR characteristics of HGPIN lesions were assessed by comparison with representative normal voxels from the same patient.

3. Results

Thirty HGPIN foci in 27 patients had a diameter of 6 mm or greater (mean diameter 12 mm, range 6–20 mm), with each patient having either 1 or 2 large HGPIN lesions. None of these cases showed a histologic diagnosis of prostate cancer in biopsy samples examined. None of these HGPIN lesions selected for the analysis showed adjacent inflammatory tissue or inadequate MSR or DCEMR coverage. For comparison, 27 peripheral zone areas with histologic diagnosis of normal prostate tissue were identified from the same patients.
3.1. MSR and DCEMR findings

In the 30 HGPIN foci analyzed with MSR and DCEMR, the median number of spectroscopic voxels examined per lesion was 2 (range 1–3). The corresponding median number for normal tissue voxels was 2 (range 1–6). A total of 30 HGPIN and 27 normal areas were included in the comparative analysis.

With MR imaging, HGPIN foci were not associated with any reduction in T2-weighted signal intensity. With MSR, metabolic findings from HGPIN foci showed some significant \( P < 0.05 \) differences from those in normal tissue (Table 1, Fig. 1). In particular, HGPIN foci were characterized by a significantly higher \( P < 0.05 \) mean ± SD absolute value of Cho (Table 1, Fig. 2). Also, ANOVA analysis and SNK test confirmed a constant and significant difference in Cho \( (P = 0.003; F\text{-ratio} = 2.354) \) and ratio \( (P = 0.001; F\text{-ratio} = 3.350) \) assessment between HGPIN and normal tissue. This result is consistent with independence of variables from a qualitative factor or statistical bias. With DCEMR, HGPIN foci showed OT, TTP, and \( P = \) mean ± SD values lower than that in normal tissue (Table 1 and Fig. 2) but differences did not reach statistical significance \( (P > 0.05) \).

3.2. Comparison of 1H-MSR results between HGPIN cases and a series of prostate cancer cases

We had the opportunity to compare 1H-MSR results described in the present series of 27 HGPIN cases with those obtained in 27 cases with an histologic diagnosis of prostate cancer. These 27 cases with peripheral zone prostate cancer (no HGPIN associated) were obtained from the same entire population of 330 cases involved in our research protocol on the use of MSR for the diagnosis of prostate diseases (as under “Study design and population”). Methods used for MSR, prostate biopsy, and their assessment of spatial correspondence, are the same as reported for the HGPIN group. These 27 cases with prostate cancer have been distinguished in low grade (LGPC) (Gleason score ≤7 (3 + 4)) and high grade (HGPC) (Gleason score ≥7 (4 + 3)) prostate cancer on the basis of the histologic diagnosis. At MSR, the quantitative analysis of individual metabolites concentrations showed similar absolute choline values between HGPIN and LGPC \( (P = 0.1638) \) and significantly \( (P = 0.0462) \) lower choline in HGPIN compared with HGPC (Table 2). The Cho + Cr/Cit ratio in HGPIN was significantly \( (P < 0.001) \) lower than ratios in both LGPC and HGPC (Table 2).

4. Discussion

In HGPIN, different markers of proliferation are increased whereas those of secretory differentiation are downregulated [23]. On this basis, the metabolic evaluation performed by MSR with indicators of proliferation (choline) and more of differentiation and secretion (citrate) inside the prostate gland could represent a valid method for the clinical suspicions of HGPIN. To our knowledge, this is the first study in the literature in which a quantitative analysis of individual metabolites concentration with MSR and a DCEMR procedure have been specifically used to describe isolated (not associated to prostate cancer) HGPIN lesions. Similarly Hom et al. [14] described MSR features of HGPIN.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HGPIN</th>
<th>Normal</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline absolute value (ppm)</td>
<td>0.3970 ± 0.2988 (0.1680–0.6270)</td>
<td>0.0587 ± 0.0584 (0.0070–0.9090)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatine absolute value (ppm)</td>
<td>0.1280 ± 0.1874 (0.0158–0.2720)</td>
<td>0.1290 ± 0.1487 (0.0050–0.260)</td>
<td>0.9828</td>
</tr>
<tr>
<td>Citrate absolute value (ppm)</td>
<td>0.4480 ± 0.2125 (0.2840–0.6110)</td>
<td>0.7430 ± 0.7405 (0.0400–1.460)</td>
<td>0.090</td>
</tr>
<tr>
<td>Choline + creatine/citrate ratio</td>
<td>1.2140 ± 0.2208 (1.0450–1.3840)</td>
<td>0.5340 ± 0.5780 (0.0590–1.040)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OT (second)</td>
<td>33.3330 ± 9.3541 (26.1430–40.5240)</td>
<td>40.7250 ± 10.6740 (30.70–50.40)</td>
<td>0.092</td>
</tr>
<tr>
<td>TTP (second)</td>
<td>163.2220 ± 48.1243 (126.2310–200.2140)</td>
<td>217.5450 ± 48.0340 (175.560–257.660)</td>
<td>0.132</td>
</tr>
<tr>
<td>PE (signal intensity)</td>
<td>125.9560 ± 60.8425 (79.1880–172.7230)</td>
<td>165.0550 ± 97.490 (83.70–248.450)</td>
<td>0.465</td>
</tr>
</tbody>
</table>

Mean ± SD, (95% confidence interval). \( P \) value = HGPIN vs. Normal (F test).
but, differently from our study, in patients with a concomitant diagnosis of prostate cancer. Moreover, in the study of Hom et al. [14], no DCEMR evaluation was performed. HGPIN on biopsy was considered as a high risk of positive repeated biopsies and, for this reason, systematical re-biopsies were recommended 3 to 6 months after the first one [24]. Recently, contradictory data have been reported regarding the risk of associated cancer and necessity of early subsequent biopsies in case of HGPIN [24]. All our cases with isolated HGPIN resulted free from prostate cancer also at a second repeated prostate biopsy. The advantage of our analysis over that from Hom et al. [14] is that describing cases with only HGPIN and not prostate cancer, MSR and DCEMR results can be better related to the own HGPIN activity. Our analysis indicates that HGPIN (1) is not associated with any MR imaging abnormality or focal reduction in T2-weighted signal intensity (as also shown by Hom et al. [14]); (2) is metabolically different compared with normal tissue, showing significantly higher choline and choline + creatine/citrate ratio but no significant difference in creatine and citrate absolute values (MSR); (3) is not significantly characterized by rates of enhancement and therefore by rates of prostate vascularization and/or vessel permeability (DCEMR). The normal prostate tissue contains normal level of citrate and low choline levels. HGPIN lesions show an increase in choline levels (such as in prostate cancer), but they do not lose the ability to generate or concentrate citrate (such as often in prostate cancer). The elevated choline peak reflects an elevated cell proliferation rate in HGPIN. Hom et al. [14], in their study, did not report the absolute values for

![Fig. 2. Comparison of metabolic signals at MSR* and dynamic signals at DCEMR† from a voxel representative of normal prostate tissue, HGPIN, LGPC, and HGPC. (Color version of figure is available online.)](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HGPIN</th>
<th>LGPC</th>
<th>HGPC</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline absolute value (ppm)</td>
<td>0.3970 ± 0.2988 (0.1680–0.6270)</td>
<td>0.2910 ± 0.2506 (0.1080–0.6890)</td>
<td>0.7240 ± 0.8549 (0.3380–1.7860)</td>
<td>0.1638*</td>
</tr>
<tr>
<td>Creatine absolute value (ppm)</td>
<td>0.1280 ± 0.1874 (0.0158–0.2720)</td>
<td>0.0855 ± 0.0642 (0.0167–0.1880)</td>
<td>0.3890 ± 0.5223 (0.260–1.0370)</td>
<td>0.0462†</td>
</tr>
<tr>
<td>Citrate absolute value (ppm)</td>
<td>0.4480 ± 0.2125 (0.2840–0.6110)</td>
<td>0.1860 ± 0.2607 (0.2290–0.6010)</td>
<td>0.4440 ± 0.3978 (0.0500–0.9380)</td>
<td>0.2701*</td>
</tr>
<tr>
<td>Choline + Creatine/Citrate ratio</td>
<td>1.2140 ± 0.2208 (1.0450–1.3840)</td>
<td>2.8130 ± 1.8350 (0.107–5.732)</td>
<td>2.4560 ± 1.9751 (0.0035–4.9080)</td>
<td>0.0002*</td>
</tr>
</tbody>
</table>

Mean ± SD (95% confidence interval).

$P$ value: * HGPIN vs. LGPC; † HGPIN vs. HGPC (F test).
each single metabolite at MSR. The choline + creatine/citrate ratio reported by Hom et al. [14] in their HGPIN lesion was intermediate between normal tissue and cancer. In our experience, considering the entire population of 330 cases involved in a research protocol on the use of MSR and DCEMR for the diagnosis of prostate diseases in our center, choline concentrations in HGPIN were similar to those described in low grade [Gleason score ≤7 (3 + 4)] prostate cancer and lower than those reported in high grade [Gleason score ≥7 (4 + 3)] prostate cancer. Also in our experience, choline + creatine/citrate ratios in HGPIN were intermediate between those in normal tissue and those in prostate cancer. Some authors [25] suggested that in prostate cancer, choline levels should be correlated with tumor aggressiveness and showed a correlation between Gleason score and ratio values. In our experience, the similar high choline absolute value in HGPIN and LGPC foci may reflect a similar elevated cell proliferation rate or membrane turnover in these two lesions. Methods used in our study are comparable to those used in previous experiences [14]. At MSR spectra were interpreted and scored based on prior research and on the current understanding of prostate metabolism [12–16]. For example, the corresponding median of spectroscopic voxels analyzed were similar to that used by Hom et al. [14] in their work. Our study has limitations. Although the method used is the standard of reference for radiologic tumor detection [14], it could be difficult to correlate the location of histopathologic and MR imaging findings with confidence. However, our results demonstrate significant differences between normal tissue and HGPIN in MSR patterns, which suggest that we did correctly localize distinct lesions. While Hom et al. [14] analyzed only HGPIN lesions of 6 mm or greater in diameter, we focused on the lesions most likely to have good correspondence between imaging and pathologic findings. The final number of HGPIN foci examined was limited (n = 30), but the highest in the literature. However, these cases were obtained from a larger initial population (330 cases) representative of patients involved in MR imaging protocols for prostate diseases, MR images were analyzed by two expert radiologists, and the assessment of the spatial correspondence between MSR/DCEMR findings and the pathologic evaluation was performed by a third radiologist who was not a reader of MR images.

5. Conclusion

In our experience, HGPIN lesions can be metabolically characterized by MSR, in particular showing choline and ratio values significantly different from those obtained in normal peripheral prostate tissue. In the future, investigations should also examine whether other metabolites can better characterize different metabolic signals in HGPIN, normal tissue, and cancer.

References


