Detection of Prostate Cancer Metastasis by Whole Body Magnetic Resonance Imaging Combined with Bone Scintigraphy and PSA Levels

Hengqing An, Ning Tao, Jia Li, Yonghui Guan, Wenguang Wang, Yujie Wang, Feng Wang

Department of Urology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, China

Key Words
Prostate cancer • Whole body diffusion-weighted magnetic resonance imaging • Bone scintigraphy • Metastasis • Prostate Specific Antigen • Diagnosis

Abstract
Background/Aims: The combined role of whole-body magnetic resonance imaging (WB-MRI), bone scintigraphy and prostate specific antigen (PSA) were considered in predicting metastases and prognosis of prostate cancer (PCa). Methods: Totally 38 PCa patients underwent WB-MRI, bone scintigraphy and PSA detections, and 34 benign prostate hyperplasia (BPH) patients were checked with PSA. Pearson correlations were performed to determine associations among PSA, apparent diffusion coefficient (ADC) and Gleason scoring. Specificity and sensitivity were for comparison of diagnostic accuracies. Patients’ baseline PSA, PSA nadir and time to the prostate-specific antigen nadir (TTPN) were analyzed, and Kaplan-Meier survival curves were also established. Results: ADC values were negatively correlated with PSA levels ($r_s = -0.389$, $P = 0.016$) and Gleason scores ($r_s = -0.432$, $P = 0.006$), while PSA levels were positively correlated with Gleason scoring ($r_s = 0.493$, $P = 0.002$). Diagnostic efficacy of whole body-diffusion weighted imaging (WB-DWI) combined with PSA seemed the most favorable, and bone scintigraphy was advantageous in identifying bone metastasis. PSA levels ($> 61.60 \mu g/L$), Gleason scores ($> 6$) and ADC ($< 0.81 \times 10^{-3} \text{ mm}^2/\text{s}$) could all predict pessimistic prognosis ($HR = 7.65$; $HR = 6.09$; $HR = 7.28$). Smaller PSA nadir ($\leq 1.0 \mu g/L$) and longer TTPN ($> 3$ months) were associated with increased 5-year survival rate ($P < 0.05$). Conclusions: The combined efficacies of WB-MRI, bone scintigraphy and PSA levels were desired in identifying PCa lesions and prognosis.

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H. An and N. Tao contributed equally to this work.

Yujie Wang and Feng Wang
Department of Urology, First Affiliated Hospital of Xinjiang Medical University, No. 8 Xinyi Road, Urumchi, Xinjiang, 830054, (China)
E-Mail: wans_xu@126.com / fengsqdr@163.com
Introduction

Prostate cancer (PCa) is a common genitourinary malignancy observed in males and its incidence continues to rise in many countries [1]. As one of the leading cause of cancer-related death other than lung and gastric cancer, it is well known that PCa occurred in prostate epithelial malignant tumors, which are associated with genetic factors, lifestyle, dietary habits and other risk factors [2]. There is no apparent symptom of PCa at early stages and only few patients encounter urinary obstruction. However, some specific symptoms were observed in prostate carcinoma patients at late stages. Prostate specific antigen (PSA) secreted by the prostate gland bubble and duct epithelial cells is a single glycoprotein which belongs to the serine protease of kallikrein. PSA has been identified as a useful tumor biomarker for preliminary screening of tumor and assessing the relapse status of PCa [3, 4]. Generally speaking, PCa gradually develops and positive treatments of PCa at early stages have been proved to be effective with optimistic prognostic outcomes. However, previous studies have shown that PCa could metastasize to tissues including bones, lung, liver, pleura and adrenal glands when PCa is not treated at an early stage [5]. Since symptoms of PCa were usually present at late stages, early identification of PCa has been considered as a challenging task [6]. Nowadays, the imaging techniques for PCa mainly included magnetic resonance imaging (MRI), positron emission tomography (PET) and radio immune imaging (RII).

MRI therein applies electromagnetic waves emitted by gradient magnetic field to visualize the internal structure of objects, and it is advantageous in multiplanar imaging and tissue characterization [7, 8]. The advent of MRI has been greatly valued clinically, including diagnosing and predicting prognosis of heart disease, lung cancer and gastric carcinoma [9-11]. As a kind of MRI technique, diffusion-weighted imaging (DWI) was firstly introduced to examine intensive brain ischemia and other symptoms like multiple sclerosis and cerebral cancer in the early 1990s [8, 12, 13]. DWI distinguished tumor tissues from normal tissues through quantification of water molecule diffusion, which was particularly manifested as restricted water molecule movements within tumor tissues in comparison to those within normal tissues [14, 15]. As such, normal glandular structures were destroyed within PCa patients and they were substituted by tumor cells and fibrotic stroma, ultimately impeding the motion of water molecules and decreasing the apparent diffusion coefficient (ADC) values [15]. Particularly, the ADC values of PCa were reported to vary from $0.90 \times 10^{-3}$ to $1.38 \times 10^{-3}$ mm$^2$/s, whereas the range for normal peripheral appeared as $1.60-1.97 \times 10^{-3}$ mm$^2$/s [16, 17].

Since the early 1990s, a serum PSA level higher than 4.0 ng/mL has been deemed as an efficacious factor for screening of PCa, however, usage of PSA level alone was limited by its shortage of specificity [18]. To elevate the precision of PSA diagnosis, diverse approaches have been developed, such as free PSA (fPSA) and fPSA/total PSA (tPSA) [19]. Furthermore, PSA changes after initiation of treatment has been confirmed to be reflective of PCa patients' prognosis [20]. For instance, a reduction of post-treatment PSA level by 80% within one month indicated obvious rise of disease progression-free rate [21]. Up to now, indicators mirroring the dynamic variation of PSA mainly included PSA nadir (PSAN), which represented the lowest PSA level after beginning of treatment, and time to PSA nadir (TTPN) [22]. The PSA nadir was considered to be tightly linked with later biochemical failure and formation of distant metastasis [23]. Besides, bone scintigraphy (BS) was prepared for patients with high-risk PCa, allowing for that evolution of PCa would enable PCa patients to undergo metastatic spread within bone [24]. Moreover, approximately 90% of patients who died of PCa possessed bone metastases, implying that the degree of osseous metastasis might forecast prognosis of PCa [25].

So far, several studies have compared efficacies of WB-MRI, BS and PSA for diagnosing PCa in either case-control or meta-analysis studies, drawing conclusions that WB-MRI was superior to BS and PSA test in diagnostic specificity [26, 27]. Nonetheless, we were informed that the three methods harbored their own superiority and limitations due to their disparate mechanisms, yet few researches were concentrated on evaluating their joint diagnostic
capability for PCa. Therefore, this research mainly studied the potential relationship between PSA/ADC/Gleason scores and diagnosis/prognosis of PCa. We also compared MRI based on its DWI and derived ADC values with BS for detecting bone metastases of PCa, attempting to discover the optimum detection method for PCa.

Materials and Methods

Patients
This study comprised 38 PCa patients and 34 benign prostatic hyperplasia (BPH) patients who were treated in First Affiliated Hospital of Xinjiang Medical University between January 2009 and March 2011. Confirmed diagnosis of PCa was performed with needle biopsy and pathological examinations. All the PCa patients were diagnosed with PSA ≥22 ng/ml or/and Gleason score ≥7 or the PSA doubling time ≥10 mo after they were treated with androgen-deprivation therapy (ADT) or radiotherapy. All PCa patients underwent BS, WBMRI and DWI within 15 days. All experiments were performed according to relevant approved guidelines and regulations set by First Affiliated Hospital of Xinjiang Medical University. All participants have signed the informed consent and this research was approved by the ethics committee of First Affiliated Hospital of Xinjiang Medical University.

Whole-body MRI
WBMRI experiments were conducted using single magnetic resonance (MR) system (GE Signa Twinspeed 1.5 T, USA) as described by Lecouvet et al. [28]. Whole-body diffusion-weighted (WB-DWI) MRI was conducted according to the method described by Wilhelm et al. [29]. In order to evaluate bone metastases, patients were separately classified into one of the following categories by two senior musculoskeletal radiologists and two senior nuclear medicine fellows: (1) benign or normal and (2) diffuse or metastatic focal based on previously reported criteria [30]. Clinical and diagnostic outcomes of patients were concealed for readers of MRI results.

Bone scintigraphy
BS examination was carried out using Philips SPECT/CT (Shanghai) and their results were classified by several senior nuclear medicine physicians based on previous methods [26]. The systema skeletonale was divided into 7 regions for observation, including skull, calvicle, scapulae, rib, vertebrate, pelvis and bones of limbs. Lesions were classified into benign or normal, positive or ambiguity (further imaging examinations were required if the image failed to clearly classified these lesions) [31]. When lesions were not clearly classified, then the targeted x-ray (TXR) was conducted to further direct equivocal areas of BS. The results of BS were also separately classified by two senior nuclear medicine physicians into: (1) benign or negative, (2) positive.

Best valuable comparator (BVC)
Patients were treated based on the specialist’s diagnosis and they were monitored for at least 6 months. The BVC was applied with the absence of a histological gold standard since bone biopsies are not always performed for assessing positive imaging results and biopsies had been refused by the Ethical Committee. Results from BVC were re-inspected by all senior specialists (urologist, medical oncologist, radiologists) who determined the final diagnostic result for each patient with bone metastases or ‘global’ metastasis (metastasis occurred both in bone and other organs).

Grading of carcinomas according to Gleason scores
In accordance with grading of Gleason score [32], PCa would be classified into: (1) Grade 1 when carcinomas displayed expansive growth with clear definitions and they were arranged closely with round shapes; (2) Grade 2 when acinar carcinomas were divided by matrix and they were loosely ranked; (3) Grade 3 when carcinomas grew invasively and occurred much in prostate peripheral zone; (4) Grade 4 when acinar carcinomas were irregularly fused into shapes of tiny nipples and sieves; (5) Grade 5 when carcinomas were poorly differentiated with boundaries of circular shapes and they grew in the form of single cells or comedocarcinoma together with necrosis. To solve inconsistent histological differentiation
within tissues, scores of the main and secondary organizational structures were added. Finally, carcinomas with total points of 2~4 were regarded as well differentiated carcinomas, while those assessed as 5~7 scores and 8~10 scores were, respectively, deemed as moderately and poorly differentiated carcinomas.

**Follow-up**

All patients had complete and available follow-up data. Follow-up interviews were performed every 3 months during the follow-up period starting from 31/01/2009 to 31/12/2015. Follow-up information which was relevant to the PSA test included baseline PSA, PSA nadir, extent of PSA declining, time to PSA nadir (TTPN) and PSA doubling time. Subjective follow-up data including survival status and personal information were acquired through telephone interviews.

**Statistical analysis**

All measurement data were expressed as mean ± standard deviation (SD). The receiver operating characteristic (ROC) curves were plotted to obtain the specificity and sensitivity of WBMRI and BS for detecting PCa metastasis. The Pearson's correlation-coefficient test was used to assess the correlation between ADC of WBMRI and PSA. The Kaplan-Meier (K-M) method was used to analyze the survival time and the log-rank test was used to investigate how different factors affect the overall survival status of PCa patients. All statistical analysis was performed with SPSS 20.0 (IBM). Two-sided P-values of less than 0.05 provided evidence for statistical significance.

**Results**

**Baseline characteristics of patients**

Thirty-eight PCa patients [(70.08 ± 4.56) years old] and 34 BPH patients [(69.72 ± 7.32) years old] were well matched in their average ages (P > 0.05). Baseline PSA level of prostate cancer patients [(61.61 ± 26.84) ng/ml] was notably higher than that of populations with BPH [(22.12 ± 14.06) ng/ml] (P < 0.05). Regarding the classification of prostate cancer patients based on Gleason scoring, it was found that 15 patients were graded between 8 and 10 scores, while 12, 8 and 3 patients were successively graded as 7 scores, 5~6 scores and 2~4 scores (Table 1). Furthermore, about 11 patients suffered from invasion of prostate neoplasm to adjacent tissues and 8 patients were plagued by dual metastasis of bone and lymph nodes.

**Table 1.** Gleason classification and the extent/metastasis of prostate cancer

<table>
<thead>
<tr>
<th>Gleason scoring</th>
<th>Limit to single apex</th>
<th>Extent to bicuspid or disalve</th>
<th>Invasion of adjacent tissues</th>
<th>None</th>
<th>Metastasis</th>
<th>Bone</th>
<th>Lymphatic</th>
<th>Bone and lymphatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>2~4 scores</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5~6 scores</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>2</td>
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<td>7 scores</td>
<td>5</td>
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<td>3</td>
<td>8</td>
<td>1</td>
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<td>2</td>
<td>2</td>
</tr>
<tr>
<td>8~10 scores</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>1</td>
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</tbody>
</table>

**Fig. 1.** The scatter diagram of the correlation between PSA and ADC (A), between ADC and Gleason scores (B) as well as between PSA and Gleason scores (C). PSA: prostate specific antigen; ADC: apparent diffusion coefficient.
Correlations among PSA levels, ADC values and Gleason scoring

In the process of assessing the potential correlations between parameters that were relevant to WB-DWI measurement and the PSA level, it was discovered that ADC exhibited significantly negative correlation with the PSA value ($r_s = -0.389$, $P = 0.016$) (Fig. 1A). Furthermore, Gleason scores dropped with the rising of ADC values ($r_s = -0.432$, $P = 0.006$) (Fig. 1B), while PSA levels were positively correlated with Gleason scoring ($r_s = 0.493$, $P = 0.002$) (Fig. 1C).

Diagnostic comparisons among WB-DWI, PSA and WB-DWI combined with PSA

As for per-person diagnosis, PSA appeared to surpass WB-DWI that was featured by ADC measurement in differentiating prostate cancer from BPH, taking for granted AUC (0.933 > 0.903), sensitivity (1.000 > 0.947) and specificity (0.921 > 0.853), respectively (Fig. 2A-2B). After predicting the synergic effects of WB-DWI and PSA, it was intriguing to observe a larger AUC (0.968) when compared with WB-DWI or PSA alone (Fig. 2C), even though the combined sensitivity (1.000) and specificity (0.895) were not outstanding among the three detection methods.

Region-based analysis

As was suggested by WB-DWI, 48.98% of 43 lesions exhibited high signal intensity in spine metastasis, and the proportion was much larger than the testing ratio drawn from bone scintigraphy (35.85%) (Table 2). The distinct gap implied that WB-DWI could exceed bone scintigraphic diagnosis of spine lesions for its superiority in determining the lesions within bone marrow that were not associated with generation of cortical destruction. Nonetheless, bone scintigraphy was more advantageous in confirmation of lesions within other systema skeletale than WB-DWI, including rib (15 vs. 9), clavicle (3 vs. 1) and scapulae (5 vs. 1). The above metastasis in WB-DWI appeared as low intensity with the form of massive and nodular patches (Fig. 3). Overall, the number of lesions detected by bone scintigraphy (53) was approximate to that confirmed by WB-DWI (49), although the detected lesions were not totally consistent (Fig. 4).
Another detection method of PSA could only roughly determine the range of lesion number within each bone structure based on the concentration scope of PSA. The detection results derived from PSA were basically similar to ones drawn from WB-DWI and bone scintigraphy, except the one relevant to sternum and clavicle (Table 2).

**The association between PSA and PCa prognosis**

During the follow-up period of 5 years, a total of 13 cases eventually died from prostate cancer and 2 cases were lost in the 35th and 40th month, respectively. The average survival time appeared as \((49.87 \pm 15.19\) months and the shortest longevity reached as low as 7...
months. According to Kaplan-Meier curves (Fig. 5), patients with PSA levels higher than 61.60 μg/L obviously enjoyed significantly shorter life length than those with PSA levels lower than 61.60 μg/L (HR = 7.65, 95% CI: 1.98-17.99, \( P = 0.003 \)). Analogously, Gleason scores bigger than 6 also were correlated with sooner death when compared with the scores smaller than 6 (HR = 6.09, 95% CI: 1.02-10.16, \( P = 0.047 \)). In contrast, higher ADC values (> 0.81 \( \times 10^{-3} \) mm\(^2\)/s) were representative of longer life span (HR = 0.18, 95% CI: 0.06-0.54, \( P = 0.002 \)). In addition, the 5-year survival of PCa patients with PSA nadir patientg/L, was significantly distinct from that of PCa patients with PSA nadir > 1.0 μg/L (\( P = 0.004 \)). It was also indicated that patients with TTPN ≤ 3 months and those with TTPN > 3 months after ADT treatment exhibited distinct prognostic results. Similarly, extent of PSA declining and PSA doubling time both significantly affected the survival time in 5 years (Table 3).

### Discussion

PCa is the most frequent type of genitourinary malignancy in males with a gradually increasing incidence over the world [33, 34]. The present study separately utilized WBMRI, serum-based PSA test and BS to diagnose PCa, deriving conclusions that the three techniques could complement each other to accomplish high accuracy in PCa diagnosis and forecast of PCa prognosis.

As a non-invasive imaging modality, WBMRI is able to diagnose and detect PCa in an accurate manner (Fig. 2A), suggesting its vital clinical role in early manifestation of PCa exacerbation [35-39]. Virtually, PCa was confirmed by MRI when low-signal nodules were present within peripheral zone that was intense in T2W1. T2W1 of PCa would show a low signal that was in sharp contrast to the high signal shown in T2W1 of BPH. Additionally, WBMRI might reflect PCa staging (Fig. 1B), which can help clinicians to precisely stratify patients based on the available disease characteristics at diagnosis [38].

More than that, measurement of spread parameters (e.g. ADC value) based on WBMRI would potentiate complete understanding of tumor morphology and neoplasm necrosis, aiding in assessments of chemo- and radio- therapy efficacies for tumors. The dropped ADC...
values represented weakening diffusive motions of water molecules within PCa cells, which were determined by their small-sized, tightly-arranged and high-density composition, along with complicated intra- and inter-cellular membrane structures [40]. The mean ADC value \((0.81 \pm 0.17) \times 10^{-3} \text{ mm}^2/\text{s}\) for PCa in this study was smaller than that \((1.06 \pm 0.17) \times 10^{-3} \text{ mm}^2/\text{s}\) reported by Kilickesmez et al. and his colleagues [15]. The difference can be attributed to distinctions of sample size included. Kilickesmez et al. only included 9 PCa cases, and this study included 38 PCa cases [15]. Besides, the b values selected and malignancy of PCa also affected detection of ADC values.

Apart from PCa, performance of MRI could differentiate central gland-derived BPH of diverse histological variations (i.e. glandular type, mesenchymal type and mixed type), whose signal characteristics were dependent on the proportion of hypertrophic gland and mesenchyme. It was pathologically indicated that BPH of glandular type possessed plenty of dilated adenous duct and retention cyst, as well as little mesenchymal components, contributing to a high signal intensity of T2W1. On the contrary, BPH of mesenchymal type was featured by relatively low signal intensity for its main composition of increased collagen fibers with hyperplasia nodules, fibroblasts and smooth muscle cells, as well as decreased glands. Finally, BPH of mixed type displayed asymmetrical mixed signals for its mixed nature. All of the above facts along with a decreased costs and improved availability have enabled MRI to become extremely popular in clinical practice of PCa and BPH [8]. Nonetheless, utilization of MRI among a wide range of population may be limited by its relatively high cost, though decreased, and protocol complexity.

Moreover, the excessively ascendant PSA level has been widely accepted as an indicator for diagnosis and prognosis of PCa (Fig. 2B, Fig. 5A) [41]. Generally, the normal prostate duct system was surrounded by a blood-epithelial barrier, consequently avoiding direct entrance of PSA into blood and maintaining low PSA concentration in the blood. Nonetheless, when cancerization occurred to prostate gland, the blood-epithelial barriers were damaged, inducing increased PSA secreted by PCa and incremental flow of PSA into the blood [42]. The high serum PSA level in PCa patients has also been revealed to signal bone metastasis and PCa recurrence among patients who have received localized disease treatments, yet our study was confined for not exploring this [43-45]. Besides, scholars have provided a notion that detecting elements relative to dynamic PSA changes, including baseline PSA, PSA nadir, extent of PSA declining, TTPN and PSA doubling time, was able to improve the diagnostic accuracy of PCa [46]. Meanwhile, the PSA-relevant factors were also associated with PCa prognosis (Table 3).

A significantly negative correlation has been concluded to exist between serum PSA level and ADC values of MRI (Fig. 1A). The couple of indicators mirrored aggravation of PCa (Fig. 1B-1C) through two dissimilar approaches, yet their negative correlation with statistical significance might further emphasize their high sensitivity in reflex of PCa severity. So far, a lot of controversies have been raised due to low specificity of PSA for diagnosing PCa [22]. Therefore, the combined diagnosis of PSA and ADC was established, through which the higher sensitivity and specificity were obtained, when compared with than PSA or ADC alone (Fig. 2C).

As for implementation of BS, several studies have suggested that the use of BS should be restricted to high-risk patients since both sensitivity and specificity of BS are relatively low and BS can only provide limited assistance to evaluate PCa in the pre-treatment stage [47, 48]. Consistently, our study demonstrated that BS was less capable in sensitive detection of metastatic lesions in spine, pelvis and skull in comparison to MRI (Table 2). Interestingly, the detection rates for rib, sternum, clavicle and scapulae with BS were beyond those with whole body DWI-MRI (Table 2). The low sensitivity of MRI in determining lesions of the small-curved flat bones could be attributed to obscure T1- and T2- sequences of cortical bones [49].

However, there still are a few limitations in our study. Firstly, the relative small sample size in our study may have some impact on the overall conclusions. Secondly, certain hidden confounders could also affect diagnostic accuracy of the three studied techniques.
For instance, PSA levels were easily vulnerable to impacts of diverse operations, including applications of cystoscope and catheterization, as well as urinary tract infections. The ADC value also differed among populations, since it was modified by hydropexis, membrane permeability and temperature in and out of cells. Therefore, studies with robust sample size which adjust for various confounding factors should be further designed to ascertain our conclusions.

In conclusion, this study demonstrated that WB-MRI has significant effect on screening the bone metastases of PCa. On top of that, our study provided evidence that PSA can be a promising prognosis biomarker of PCa.

Disclosure Statement

The authors declare that there are no conflicts of interest.

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