The Role of Tumor Oxygenation Tested by Magnetic Resonance Imaging (MRI) in Prostate Cancer Grading

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Background: Prostate cancer is a common malignant tumor in males. Prostate cancer grading is an important basis for evaluation of invasion. The purpose of this article was to use dynamic enhanced scan magnetic resonance imaging (MRI) to quantitatively investigate the relationship between tumor oxygenation value and prostate cancer pathological Gleason score.

Material/Methods: A total of 312 prostate cancer patients diagnosed by needle biopsy who received MRI dynamic enhanced scan were enrolled in this study. Multiparameter oxygen concentration image based on MRI was applied to test pO2 in tumors. Multiple spin resonance image relaxation time edit sequence and weak field diffusion model were used to estimate oxygen saturation level and pO2. hematoxylin and eosin staining and Gleason score were used to determine biological behavior and prognosis.

Results: According to the Gleason score system, there were 28 cases with a score of 10, 112 cases with a score of 9, 56 cases with a score of 8, and 116 cases with a score lower than 7. The enrolled patients were divided into groups: 116 cases into the middle-to-well differentiation group (Gleason score £7) and 196 cases into the poorly differentiation group (Gleason score at 8 to 10). Prostate cancer tumor oxygenation value was positively correlated with Gleason score (r=0.349, P<0.05) or PSA (r=0.432, P<0.05). Tumor oxygenation value in Gleason £7 group was obviously different from that in the group with Gleason score between 9 and 10 (P<0.05).

Conclusions: Tumor oxygenation value in prostate cancer was positively correlated with Gleason score. Tumor oxygenation value might be useful in clinics to evaluate prostate cancer grading and prognosis.

MeSH Keywords: Magnetic Resonance Imaging • Neoplasm Grading • Prostatic Neoplasms

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Prostate cancer is a common male reproductive system malignant tumor worldwide. As populations age and lifestyles change, prostate cancer morbidity and mortality has shown a rising trend that seriously threatens the health and well-being of many people [1,2]. Prostate cancer treatment often is administered according to the cancer degree and grading [3]. Gleason grading is currently the most widely used method. Many patients receive a clear pathological grading after application of Gleason score in evaluating prostate cancer. Gleason grading has become the standard of evaluating prostate cancer invasion [4,5]. Currently, ultrasound combined with prostate biopsy is not only used for diagnosis, but also for pathological grading. However, how best to combine ultrasound and Gleason grading together to evaluate prostate cancer diagnosis and prognosis is still unclear [6].

Dynamic enhanced scan magnetic resonance imaging (MRI) is widely used in clinics especially for tumor detection, location, and prognosis evaluation. Moreover, MRI can be used for tumor grading [7,8]. Previous studies have indicated that MRI can detect contrast agent distribution in different tissues and organs. It can distinguish malignant and benign tumors, and provide a new noninvasive method for tumor diagnosis [9,10]. Although contrast agent toxicity generally has a small incidence rate, it often causes a variety of clinical complications such as sepsis and infection [11]. Thus, research to find a better way without invasion and clinical complications is needed.

It is well known that the tumor microenvironment is a hypoxia environment, while the oxygen content in normal tissues and organs is relatively definite [12]. We aimed to explore how best to use MRI combined with tumor oxygenation for prostate cancer diagnosis and pathology grading.

This article applied MRI combined with tumor oxygenation to evaluate prostate cancer grading and prognosis. We performed prostate periphery dynamic MRI scans to quantitatively determine tumor oxygenation values and explore its correlation with Gleason score. This study will provide a basis for the relationship between noninvasively evaluation of the biological invasion of prostate cancer and pathological Gleason score for use in clinics. Inclusion criteria of this study were as follows [13,14]: 1) patients diagnosed by needle biopsy with complete pathology and related information. 2) Patients received MRI dynamic enhanced scan with complete information. 3) No patients received surgery, immune therapy, radiotherapy, or chemotherapy before needle biopsy and MRI scan. 4) The time interval between MRI scan and surgery or biopsy was less than 30 days. Exclusion criteria [13,14] included: 1) incomplete pathological information; 2) incomplete scanning information; 3) patients received surgery, immune therapy, radiotherapy, or chemotherapy before needle biopsy and MRI scan; and 4) the time interval between MRI scan and surgery or biopsy was longer than 30 days.

**MRI**

MRI scan was performed using a routine method [15,16]. Patients received fluid and laxative to keep intestinal tract clean. MRI scan was performed on GE 1.5T and 5.0T Signa Twin Speed scanner. Phased-array coil with 16 channels were applied. In order to reduce the influence of breathing, the scanning coil was fixed by binding. Specific scanning sequence was as follows: 1) local prostate gland axis (T1WI) scan parameter: layer thickness 6 mm, TR 460 ms, scanning twist angle 5°, TE 16 ms, interlamellar scanning spacing 0.6 mm, FOV 25×25 cm, NEX 2, matrix 125×256. 2) Coronary pressure fast spin resonance and local prostate gland axis scanning parameter: TR 3600 ms, scan echo chain length 20, scanning thickness 6 mm, TE 88 ms, interlamellar scanning spacing 0.6 mm, scanning view 36×36 cm, NEX 8, matrix 256×128. 3) Scanning parameters from the median sagittal echo or abdominal aortic bifurcation horizontal axis to the base of the prostate: FOV 30×48 cm, NEX 2, TR 480–560 ms, interlamellar scanning spacing 2–4 mm, TE 16 ms, scanning thickness 6–10 mm, matrix 128×256.

Prostate local dynamic enhanced MRI scanning process [17,18] was as follows: gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) as a contrast agent was injected to the patients through elbow vein at 0.1 mmol/L and the injection speed was 3.0–4.0 mL/sec. Another 20 mL normal saline was continued injected after contrast agent injection to flush the vein. A set of scans was performed for continuous 16 cycles as control before contrast agent injection. Dynamic enhanced MRI scan parameters were as follows: scanning layer thickness 3.8 mm, TE 2.0 ms, interlamellar scanning spacing 2.0 mm, FOV 40×48 cm, TR 5 ms, matrix 128×512. Each patient had 30 dynamic processes and 60 images in each dynamic scanning process.

**Prostate needle biopsy**

According to a routine method [19,20], prostate needle biopsy was performed under transrectal ultrasonography guidance. The prostate was routinely tested at first, based on size and the 8 zones method (8–16 needles). Doubtful procedures required...
another targeted puncture for 2–6 needles. The biopsy tissue was fixed in 10% formaldehyde solution and used for hematoxylin and eosin staining [21]. Gleason score was evaluated based on these results. Prostate cancer tissue structure grading was analyzed for 2 parts as 0–10.

**MRI scanning image analysis**

MRI scanning image was analyzed by tumor oxygenation computing system under MATLAB R2009a (Frontier Interdisciplinary Research Institute of Beijing University). DCE-MRI information and data were input to the system and tumor oxygenation value of target area was calculated [22]. Average tumor oxygenation value, ROI tumor oxygenation pseudo color map, gray-time curve, mean Kep value, and contrast vessel time-concentration curve of selected area were analyzed.

**Statistical analysis**

All data were analyzed on SPSS16.0 software. Numerical variables were presented as mean ± standard deviation. Gleason scores and tumor oxygenation value comparison were performed by one-way ANOVA. The correlation relationship between Gleason scores and tumor oxygenation value was analyzed by Spearman correlation analysis. P<0.05 was considered as statistical significance.

**Results**

**Needle biopsy pathological results**

A total of 312 cases of prostate cancer patients were enrolled in this study. As shown in Table 1, according to the Gleason score system, there were 28 cases with score 10, 112 cases with score 9, 56 cases with score 8, and 116 cases with a score lower than 7. The enrolled patients were divided into middle-to-well differentiation group (Gleason score ≤7) (n=116) and poorly differentiation group (Gleason score at 8–10) (n=196) (Table 2).

| Group | Middle to well differentiation group | Poorly differentiation group | Total |
|-------|-------------------------------------|-------------------------------|-------|
| Cases | 116                                 | 196                           | 318   |
| Percentage | 37.2%                                | 62.8%                         | 100%  |

**Table 1. Prostate cancer needle biopsy pathological score.**

**Table 2. Prostate cancer needle biopsy pathological grouping.**

MRI scanning case result

A 60-year-old male healthy volunteer underwent prostate MRI scan and showed high signal intensity in peripheral zone (PZ) in an axial T2 weighted image (prostate cross section) (Figure 1A). The signal strength in central gland (CG; dotted line) was lower than peripheral zone (PZ). Prostate capsule (arrow) was clearly found. Regarding Coronal T2W image through prostate (Figure 1B), PZ was surrounded by distal prostatic urethra and ejaculatory duct. Seminal vesicle was the tubular structure (SV) with high signal intensity and full of liquid.

In terms of patients with prostate cancer, T3 prostate cancer scanning was performed in peripheral zone. T2 weighted (Figure 2A) axial image and coronal plane (Figure 2B) image revealed low intensity tumor signal in left peripheral zone (arrow). Tumor nodule produced swell and irregular capsule, suggesting that patient in penetration period.
MRI scan tumor oxygenation value comparison between different Gleason score

Figure 3 shows MRI scans and tumor oxygenation value of the different Gleason score groups. Following the improvement of Gleason score, tumor oxygenation value presented an increasing trend. Tumor oxygenation value showed significant differences among groups (F=2.928, \(P<0.05\)) (Figure 3). Obvious characteristics were observed among different Gleason score groups: tumor oxygenation value in Gleason score ≤7 group was markedly different from that in Gleason score 9–10 group (\(P<0.05\)). However, no significant difference was observed among Gleason score ≤7, score 8, score 9, and score 10 (\(P>0.05\)).

### Accuracy of MRI tumor oxygenation value on diagnosing prostate cancer

As shown in Table 3, the accuracy of MRI tumor oxygenation value on diagnosing prostate cancer were listed as follows: the accuracy rate of MRI tumor oxygenation value at ≤7, 8, 9, and 10 were 91/116 (78.5%), 47/56 (83.9%), 98/112 (87.5%), and 22/28 (78.6%), respectively with a mean accuracy of 82.3%. Table 4 showed the specific value of MRI tumor oxygenation. The data suggested that MRI tumor oxygenation value may be a potential index for prostate cancer.

### Correlation analysis of MRI dynamic enhanced scanning prostate cancer tumor oxygenation value with Gleason score or PSA

Correlation analysis showed a significant correlation of MRI dynamic enhanced scanning prostate cancer tumor oxygenation value with Gleason score or PSA.

**Table 3.** Accuracy of MRI tumor oxygenation value on diagnosing prostate cancer.

| Gleason score | MR tumor oxygenation (cases) | Total | Accuracy (%) |
|--------------|-------------------------------|-------|--------------|
| ≤7           | 91/116                        | 116   | 78.5%        |
| 8            | 47/56                         | 56    | 83.9%        |
| 9            | 98/112                        | 112   | 87.5%        |
| 10           | 22/28                         | 28    | 78.6%        |

**Table 4.** MRI tumor oxygenation value.

| Gleason score | MR tumor oxygenation value |
|--------------|-----------------------------|
| ≤7           | 1.02±0.16×10^{-4} mm²       |
| 8            | 0.86±0.05×10^{-4} mm²       |
| 9            | 0.63±0.17×10^{-4} mm²       |
| 10           | 0.43±0.04×10^{-4} mm²       |

**Table 5.** Correlation analysis of MRI dynamic enhanced scanning prostate cancer tumor oxygenation value and Gleason score.

| Detection method | Gleason score | Accuracy (%) |
|------------------|---------------|--------------|
| MRI tumor oxygenation | 258/312       | 82.7         |
| \(X^2\)          | 9.73          | 18.88        |
| \(P\)            | 0.043         | 0.017        |
value with Gleason score ($r=0.342$, $P<0.05$) (Table 5, Figure 4). In addition, we also found a correlation of tumor oxygenation value with PSA value ($r=0.432$, $P<0.05$).

**Discussion**

Prostate cancer is a seriously threat to men’s health and life. Gleason grading has become the standard of evaluating prostate cancer invasion. However, this method requires a biopsy procedure that is tedious and painful [23]. Although MRI is widely used in prostate cancer detection, location, and prognosis evaluation, contrast agents often cause a variety of clinical complications such as sepsis and infection [24]. Thus, there is an urgent need to find a more effective method with fewer side effects for prostate cancer diagnosis and grading.

In this study, we aimed to adopt MRI for prostate cancer diagnosis and grading from tumor oxygenation perspective according to the tumor microenvironment which is a hypoxia environment [25]. This study successfully established multiparameter oxygen concentration images based on MRI and tumor oxygenation. It was found that prostate cancer area tumor oxygenation value was positively correlated with Gleason score, indicating that tumor oxygenation value might be useful in the evaluation of prostate cancer grading and disease prognosis in clinics. However, due to the limited number patients enrolled in our study, a large cohort clinical study is required to confirm the value of tumor oxygenation in assessing the grade and prognosis of prostate cancer.

Previous studies have shown that MRI can quantitatively measure ADC values [26]. Furthermore, research found that ADC value was negatively correlated with the Gleason grade ($r=-0.39$ for peripheral zone cancer) [27]. Higher ADC values were also found to be associated with lower Gleason grades in the peripheral zone prostate cancers. Both ADC values and tumor volumes were found to significantly predict tumor aggressiveness, specifically in the peripheral zone (area under the curve, 0.78) [27]. indicating ADC values might help to predict prostate cancer, especially for tumors in the peripheral zone, which is consistent with the finding from our present study. The difference, however, is that one is a positive correlation, while the other is a negative correlation. Some studies have shown that the Cho+Cr/Cit ratio in prostate cancer tissue detected by MRI was positively correlated with Gleason score [28,29]. This indicates that following Gleason score elevation, Cho peak enlarged, while Cit peak decreased in prostate cancer area, which further supported our conclusions.

Our study had 3 limitations: 1) the limited sample size, thus a large size trial is needed in the future for validation. 2) We did not analyze Gleason subscore effect, as tumor oxygenation value in patients with Gleason score $<7$ was small and cannot be detected by MRI. 3) Our method and system were still immature, the feasibility and the accuracy of MRI tumor oxygenation value remains to be further researched.

**Conclusions**

In conclusion, we found that tumor oxygenation value in prostate cancer patients was positively correlated with Gleason score. Tumor oxygenation value might be useful in clinics to evaluate prostate cancer grading and prognosis.

**Conflict of interest**

None.

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