\( ^{11}\text{C-}\)choline PET/MRI for Characterization of Primary High-Risk Prostate Cancer: Correlations between Positron Emission Tomography Imaging Parameters and Clinical Features

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Abstract: Purpose: The aim of this study was to determine whether PET (positron emission tomography) imaging parameters from simultaneous \( ^{11}\text{C-}\)choline PET/MRI (magnetic resonance imaging) could be used to characterize primary prostate cancer. Methods: Forty-six patients with biopsy-proven high-risk prostate cancer (clinical T stage \( \geq cT2c \), a Gleason score \( \geq 8 \), or PSA (prostate-specific antigen) level \( > 20 \text{ ng/mL} \)) were prospectively enrolled. A SUV (standardized uptake value) histogram analysis including maximum SUV, mean SUV, MTV (metabolic tumor volume), and UVP (uptake volume product) was applied for the calculation of PET imaging parameters. Correlations between the PSA level and Gleason score were then evaluated. Results: Maximum SUV, mean SUV, MTV, UVP, and SUV variance were significantly correlated with PSA level, whereas SUV variance was the only parameter negatively correlated with the Gleason score. Multivariate logistic regression analysis demonstrated that MTV and PSA level at diagnosis were independent predictors of positive distant metastasis status. Conclusions: PET imaging parameters from simultaneous \( ^{11}\text{C-}\)choline PET/MRI were correlated with PSA level. However, \( ^{11}\text{C-}\)choline metabolic tumor heterogeneity was not associated with biospecimen-derived Gleason scores in prostate cancer. To apply PET texture quantification analysis to prostate cancer, a more specific PET radiotracer is required.

Key words: \( ^{11}\text{C-}\)choline PET/MRI, primary high-risk prostate cancer, staging.

1. Introduction

In Taiwan, the incidence of PCa (prostate cancer) has increased rapidly from 26.22 per 100,000 males in 2002 to 47.86 per 100,000 males in 2012. Notably, PCa has become the most increasingly diagnosed cancer and leading cause of cancer-related death among men [1]. Although prostate cancer is traditionally considered a relatively slow-growing tumor, it is potentially lethal in patients with a high Gleason score, advanced clinical stage, and elevated PSA.

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(prostate-specific antigen) levels. The conventional imaging modalities used to assess PCa include CT (computed tomography), MRI (magnetic resonance imaging), TRUS (transrectal ultrasound), and bone scintigraphy. However, simultaneous PET (positron emission tomography)/MRI in an integrated system is an advanced technology with great potential to enhance clinical practice by combining functional, molecular, and anatomic information [2, 3].

An IB (imaging biomarker) derived from medical images provides several advantages including ready availability, non-invasiveness, and the ability to perform serial patient monitoring. Different from biospecimen-based markers, the development of an IB requires technical, biological, and clinical validation, and an assessment of cost-effectiveness; moreover, it must cross translational gaps before it becomes a routinely used clinical tool according to a recent consensus [4]. Tissue organization biomarkers such as the ADC (apparent diffusion coefficient) from diffusion-weighted MRI and metabolic biomarkers such as the SUV (standardized uptake value) from PET were the most commonly used IBs in several neoplasm studies using a simultaneously integrated PET/MRI scan, including studies on gynecological neoplasms and lung cancer [5-8]. However, relevant data on PCa are still lacking. Although Kim et al. [9] showed that the MRI-assisted MTV (metabolic tumor volume) and UVP (uptake volume product) provided more accurate PCa characterization, the role of tumor metabolic heterogeneity is still unclear. Herein, we sought to identify clinically significant IBs in high-risk primary PCa by using integrated $^{11}$C-choline PET/MRI. PET imaging parameters were analyzed together to correlate them with clinical features.

2. Materials and Methods

2.1 Study Patients

This prospective observational study was approved by the hospital’s institutional review board (approval 102-3271A, ClinicalTrials.gov identifier: NCT02852122) and informed consent was obtained from all patients. Between January 2015 and December 2016, a total of 54 consecutive patients with a clinical indication for PCa staging were scheduled for an $^{11}$C-choline PET/MRI scan before treatment. The inclusion criteria were clinically suspicious and/or pathologically proven high-risk prostate cancer (clinical T stage $\geq cT2c$, a Gleason score $\geq 8$, or a PSA level $> 20$ ng/mL) according to the D’Amico Risk Classification [10].

2.2 Sample Size Determination

The bone metastasis rate among high-risk PCa patients with PSA levels of 20–99.9 ng/mL was 21% (166/767) in a systematic review [11]. The estimated sample size would be 47 assuming that 20% more distant metastasis cases (i.e. achieving 41%) were identified by the PET/MRI scan using 90% power; the significance level of 0.05 was based on a one-sample proportion test. Moreover, according to a dropout rate of 10-13% and the achievement of clinical practice goals, it was determined that 54 subjects should be enrolled.

2.3 $^{11}$C-choline PET/MRI Protocol

After fasting for at least 6 h, subjects received a single intravenous bolus of 10-20 mCi (370-740 MBq) $^{11}$C-choline; the mean dose was 17.2 $\pm$ 3.2 mCi. Approximately 5 min after injecting $^{11}$C-choline and bladder evacuation, whole-body PET/MRI scanning was performed using an integrated PET/MRI system (Biograph mMR, Siemens Healthcare, Erlangen, Germany). PET scans were performed from the mid-thighs to the head in five bed positions (acquisition time, 3 min per position) with the patient in a supine arms-down position. Simultaneous MRI was performed with a transverse T2-weighted half-Fourier single-shot TSE (turbo spin-echo) sequence (1,000 ms repetition time [TR]/84 ms echo time [TE], 6 mm slice thickness, 320 $\times$ 256 matrix, 380 $\times$ 309 mm$^2$ field of view [FOV], 90° flip angle [FA], number of excitations...
[NEX] 1) and coronal T₁-weighted TSE sequence (500 ms TR/9.5 ms TE, 5 mm slice thickness, 1.5 mm intersection gap, 384 × 276 matrix, 450 × 310 mm² FOV, 140° FA, NEX 1) while acquiring PET data in each bed position.

Following the simultaneous whole-body PET/MRI acquisition, sagittal T₂-weighted TSE sequence (4,000 ms TR/91 ms TE, 4 mm slice thickness, 320 × 224 matrix, 200 × 200 mm² FOV, 150° FA, NEX 2), coronal T₂-weighted TSE sequence (4,000 ms TR/80 ms TE, 4 mm slice thickness, 0.4 mm intersection gap, 256 × 179 matrix, 180 × 177 mm² FOV, 150° FA, NEX 2), and transverse T₂-weighted TSE sequence (3,600 ms TR/80 ms TE, 4 mm slice thickness, 0.4 mm intersection gap, 256 × 179 matrix, 180 × 177 mm² FOV, 150° FA, NEX 2) acquisitions were performed in the pelvic region. The pelvic PET/MRI scan comprised a pelvic PET scan in one bed position with 15 min of emission time. The pulse sequence included axial diffusion-weighted echo-planar imaging under free breathing conditions (5,300 ms TR/61 ms TE, b values of 50 and 1,000 s/mm², 4 mm slice thickness, 130 × 130 matrix, 330 × 285 mm² FOV, NEX 2).

Attenuation correction of the PET data was performed using a four-tissue (air, lung, fat, and soft tissue) segmented attenuation map acquired with a two-point Dixon MRI sequence. Images were reconstructed using a high-definition PET (HD·PET) iterative algorithm (three iterations, 21 subsets) with a 5.4-mm post-reconstruction Gaussian filter and an image matrix of 344 × 344.

2.4 Definition of PCa Lesions and the Clinical TNM Classification

Lesions identified as having a low T₂-weighted MRI signal and restricted water diffusion were considered PCa lesions by our radiologist. Lesions with high metabolic activity on the pelvic PET scan were considered positive by our nuclear medicine physician; however, as ¹¹C-choline PET cannot accurately detect PCa [12], the positive lesion was considered a PCa lesion when there were corresponding MRI PCa features (Fig. 1). Because the majority of high-risk PCa patients will not undergo prostatectomy, the clinical TNM classification was assessed based on combined information from the imaging studies.

2.5 PET Imaging Parameter Analysis

The PMOD 3.3 software package (PMOD Technologies Ltd., Zurich, Switzerland) was used for tumor segmentation. A VOI (volume of interest) was manually drawn around the PCa lesion according to an SUV cutoff of 2.5 in accordance with previous studies [9, 13]. An SUV histogram analysis was applied for the calculation of PET imaging features. The maximum SUV, mean SUV, SUV variance, SUV entropy, MTV, and UVP were derived according to the following equations: SUV = (tissue radioactivity [Bq]/tissue weight [g])/(total radioactivity [Bq]/body weight [g]); SUV variance = Σ (Xi-μ)²/N, where Xi is the intensity of voxel i, μ denotes the mean tumor intensity, and N is the total number of voxels in the tumor. SUV entropy = -Σ Pi ln(Pi), where Pi indicates the probability of distinct resampled values (the intensity of the tumor was resampled to 64 different values). The UVP was the mean SUV multiplied by the MTV. The computations for imaging features were performed using the CGITA (Chang-Gung Image Texture Analysis) toolbox implemented using MATLAB 2012a (MathWorks, Inc., Natick, MA, USA) [14].

2.6 Statistical Analysis

Data are presented as the median (range) for continuous variables and as the count (%) for categorical variables. The Mann-Whitney U test and Fisher’s exact test were used to compare continuous and categorical variables, respectively. Bivariate analyses among PET parameters, PSA level, and Gleason score were based on Spearman’s rank correlation coefficient. A multivariate stepwise logistic analysis based on the forward method was used to identify independent predictors of metastasis status.
Fig. 1  The definition of a prostate cancer lesion. (A) T2-weighted MRI, (B) T1-weighted MRI, (C) 11C-choline PET, and (D) diffusion-weighted imaging (DWI) of a 64-year-old patient with a PSA level of 7.34 ng/mL, Gleason score of 4 + 4, and T2cN1M0 clinical stage are shown. The red arrow indicates the prostate cancer lesion with a low T2-weighted signal, increased 11C-choline uptake, and high DWI signal. The yellow arrow indicates the heterogeneous signal intensity of the central gland on T2-weighted MRI and also increased 11C-choline uptake; this was considered to be benign nodular hyperplasia rather than prostate cancer because of a lack of DWI signal. The blue arrow indicates a hemorrhage on T1-weighted MRI causing a low T2-weighted MRI signal but no increase in 11C-choline uptake.

All calculations were performed with IBM SPSS statistical software, version 20 (IBM, Armonk, NY, USA). Two-tailed p values < 0.05 were considered statistically significant.

3. Results

3.1 Patient Characteristics

A total of 46 patients were included in the final analysis because four patients dropped out from the study, one patient had ADT (androgen deprivation therapy) before the PET/MRI scan, one patient did not yield final pathology for adenocarcinoma, and two patients underwent a PET/CT scan instead of PET/MRI because of claustrophobia.

The baseline characteristics of the study participants are shown in Table 1. The median age was 70 years (range, 52-95 years), and the median PSA level was 35.7 ng/mL (range, 4.5-591.9 ng/mL). A total of 24 (52.2%) patients were considered to have distant metastasis; among them, 12 (26.1%) patients had distant lymph node metastasis, 19 (41.3%) patients had distant bone metastasis, and one (2.2%) patient had distant lung metastasis. The presence of at least two clinical risk features was highly associated with regional lymph node metastasis, distant lymph node metastasis, and distant bone metastasis (p values of 0.040, 0.047, and 0.040, respectively), whereas PSA level and a Gleason score greater than 8 alone were significantly correlated with regional or distant lymph node metastasis and distant bone metastasis.

3.2 Imaging Interpretation

The MRI and PET imaging was interpreted by one experienced radiologist and nuclear medicine physician (Li-Jen Wang and Tzu-Chen Yen, respectively;
Table 1  Baseline characteristics, clinical risk features, and metastasis status.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N = 46)</th>
<th>Regional lymph node metastasis</th>
<th>Distant lymph node metastasis</th>
<th>Distant bone metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (N = 27)</td>
<td>Yes (N = 19)</td>
<td>No (N = 34)</td>
<td>Yes (N = 12)</td>
</tr>
<tr>
<td>Age, y</td>
<td>70 (52-95)</td>
<td>72 (57-84)</td>
<td>68 (52-95)</td>
<td>0.461</td>
</tr>
<tr>
<td>PSA, ng/mL</td>
<td>35.7 (4.5-591.9)</td>
<td>30.1 (4.5-591.9)</td>
<td>50.4 (7.3-416.2)</td>
<td>0.361</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>3 (6.5)</td>
<td>3 (11.1)</td>
<td>0 (0)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>III</td>
<td>10 (21.7)</td>
<td>10 (37.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>33 (71.7)</td>
<td>14 (51.9)</td>
<td>19 (100.0)</td>
<td>0.513</td>
</tr>
<tr>
<td>PSA &gt; 20 ng/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12 (26.1)</td>
<td>6 (22.2)</td>
<td>6 (31.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34 (73.9)</td>
<td>21 (77.8)</td>
<td>13 (68.4)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td></td>
<td></td>
<td></td>
<td>0.387</td>
</tr>
<tr>
<td>Negative</td>
<td>5 (10.9)</td>
<td>4 (14.8)</td>
<td>1 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>41 (89.1)</td>
<td>23 (85.2)</td>
<td>18 (94.7)</td>
<td></td>
</tr>
<tr>
<td>GS ≥ 8</td>
<td></td>
<td></td>
<td></td>
<td>0.038*</td>
</tr>
<tr>
<td>No</td>
<td>21 (45.7)</td>
<td>16 (59.3)</td>
<td>5 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (54.3)</td>
<td>11 (40.7)</td>
<td>14 (73.7)</td>
<td></td>
</tr>
</tbody>
</table>

Median (range) for continuous variables; n (%) for categorical variables; PSA: prostate-specific antigen; GS: Gleason score; *p value < 0.05.
both with more than 20 years of experience). The mean longest dimension of the tumors measured on MRI was 3.62 ± 1.58 cm (range, 1.2-7.7 cm). Regarding the main tumor’s MRI characteristics, 42 (91.3%) involved both lobes, 41 (89.1%) had an extracapsular extension, 24 (52.2%) had neurovascular bundle invasion, 30 (65.2%) had seminal vesicle invasion, and 20 (43.5%) had side wall invasion or pelvic organ invasion. Four (8.7%), two (4.3%), and six (13%) patients had discordant regional lymph node, distant lymph node, and bone metastasis interpretation results; in detail, one, zero, and one patient, respectively, were interpreted as positive only on PET imaging compared with three, two, and five patients, respectively, who were positive only on MRI.

### 3.3 Correlations among PET Imaging Parameters, PSA Level, and the Gleason Score

Table 2 shows the correlations between IBs and clinical risk features. Maximum SUV, mean SUV, MTV, UVP, and SUV variance were significantly correlated with PSA level, whereas SUV variance was the only parameter negatively correlated with the Gleason score. The association between all PET parameters was statistically significant \(p < 0.05\), except for MTV and UVP with SUV entropy (Table 3).

### 3.4 Prediction of Distant Metastasis Status

A multivariate logistic regression analysis was performed to identify significant predictors of positive distant metastasis status using a stepwise procedure.

### Table 2 Correlation analysis of PET parameters (SUV statistics) according to PSA level and Gleason score.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All</th>
<th>PSA</th>
<th>Gleason score</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum SUV</td>
<td>6.4 (3.1-19.4)</td>
<td>0.45</td>
<td>0.003*</td>
<td>10.5 (6.3-16.9)</td>
<td>6.5 (4.3-19.4)</td>
<td>5.7 (3.1-13.3)</td>
</tr>
<tr>
<td></td>
<td>Mean SUV</td>
<td>3.7 (2.8-8)</td>
<td>0.40</td>
<td>0.008*</td>
<td>4.3 (3.6-8)</td>
<td>3.8 (3-6.7)</td>
<td>3.5 (2.8-5.7)</td>
</tr>
<tr>
<td></td>
<td>MTV</td>
<td>15.4 (0.8-156.7)</td>
<td>0.63</td>
<td>&lt; 0.001*</td>
<td>19.4 (3.5-107.2)</td>
<td>11.9 (2.2-61.4)</td>
<td>15.6 (0.8-156.7)</td>
</tr>
<tr>
<td></td>
<td>UVP</td>
<td>57.7 (2.3-860.3)</td>
<td>0.64</td>
<td>&lt; 0.001*</td>
<td>94.6 (13.7-860.3)</td>
<td>39.3 (7.1-392.4)</td>
<td>64.1 (2.3-721.2)</td>
</tr>
<tr>
<td></td>
<td>SUV variance</td>
<td>0.9 (0.1-3.3)</td>
<td>0.37</td>
<td>0.016*</td>
<td>1.7 (0.9-3.3)</td>
<td>0.9 (0.3-3.3)</td>
<td>0.7 (0.1-2.2)</td>
</tr>
<tr>
<td></td>
<td>SUV entropy</td>
<td>4.5 (4.4-7)</td>
<td>0.10</td>
<td>0.527</td>
<td>4.5 (4-4.7)</td>
<td>4.5 (4.2-4.7)</td>
<td>4.5 (4-4.7)</td>
</tr>
</tbody>
</table>

PSA: prostate-specific antigen; SUV: standardized uptake value; MTV: metabolic tumor product; UVP: uptake volume product; * p value < 0.05.

### Table 3 Spearman’s bivariate correlation analysis of all PET parameters (SUV statistics).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Maximum SUV</th>
<th>Mean SUV</th>
<th>MTV</th>
<th>UVP</th>
<th>SUV variance</th>
<th>SUV entropy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spearman’s Correlation</td>
<td>Spearman’s Correlation</td>
<td>Spearman’s Correlation</td>
<td>Spearman’s Correlation</td>
<td>Spearman’s Correlation</td>
<td>Spearman’s Correlation</td>
</tr>
<tr>
<td>Maximum SUV</td>
<td>1</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SUV</td>
<td>0.91*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTV</td>
<td>0.62*</td>
<td>0.51</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UVP</td>
<td>0.73*</td>
<td>0.64</td>
<td>0.98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUV variance</td>
<td>0.97*</td>
<td>0.95</td>
<td>0.49</td>
<td>0.61</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SUV entropy</td>
<td>0.37*</td>
<td>0.62</td>
<td>0.13</td>
<td>0.24</td>
<td>0.48</td>
<td>1</td>
</tr>
</tbody>
</table>

SUV: standardized uptake value; MTV: metabolic tumor product; UVP: uptake volume product; * p value < 0.05.
Among all PET imaging parameters and clinical risk features, MTV was the only significant parameter predicting distant lymph node metastasis (odds ratio, 1.05; 95% confidence interval, 1.01-1.10; \( p = 0.016 \)), and PSA level was the only clinical feature related to distant bone metastasis (odds ratio, 1.01; 95% confidence interval, 1.00-1.02; \( p = 0.031 \)). The total Gleason score showed marginal significance for regional lymph node metastasis (odds ratio, 1.85; 95% confidence interval, 0.96-3.55; \( p = 0.065 \)).

### 4. Discussion

In our study cohort, clinical features including PSA level and the Gleason score were associated with lymph node metastasis and bone metastasis status. PET imaging parameters showed significant correlations with PSA level, and both MTV and PSA level were significant predictors of distant metastasis. However, the maximum SUV, mean SUV, MTV, and UVP did not show a correlation with the Gleason score, as previous studies indicated [9, 15]. Further, we included texture-based quantification in our study to determine whether tumor metabolic heterogeneity was correlated with the Gleason score.

Despite accumulating data using \(^{18}\text{F}\)-fluorodeoxyglucose (FDG)-PET for texture analysis, which textural parameters should be included in \(^{11}\text{C}\)-choline PET remains unclear. The reasons we chose SUV entropy as a representative parameter were as follows: (1) it is one of the robust texture features not affected by different segmentation, attenuation, or reconstruction methods [16-18]; and (2) unlike some texture indices that were highly correlated with MTV [19], SUV entropy did not have such a correlation and can capture different types of information (Table 3). However, we still could not determine an association between SUV entropy and the Gleason score.

Several promising radiotracers are currently used for PCa PET imaging; among them, tracers targeting choline and PSMA (prostate-specific membrane antigen) are now being clinically investigated. Increased cellular membrane synthesis is one basis for imaging PCa; choline enters the cell via the choline transporter and it is transformed to phosphatidylcholine by choline kinase, which are both upregulated in tumor cells and cause increased choline uptake [20]. However, it is still notable that several benign entities, especially benign prostate hyperplasia, will also have increased \(^{11}\text{C}\)-choline uptake [12]; this is the main reason a systematic review and meta-analysis recommended that it could only be meaningfully used for high-risk patients in a staging setting [21]. In our study cohort, SUV variance had a negative correlation with a higher Gleason score; to some degree, this reflects the fact that the SUV of high-grade PCa is less influenced by other benign entities.

To date, the U.S. FDA-approved indication for \(^{11}\text{C}\)-choline is for patients with suspected PCa recurrence rather than for initial staging. With MRI imaging, it is possible to differentiate the choline uptakes of cancerous lesions from those of other benign lesions (Fig. 1); this makes the use of \(^{11}\text{C}\)-choline more reasonable in a staging setting. In a prospective trial using fused PET/MRI, the diagnostic accuracy for PCa was significantly increased, especially for lesions greater than 5 mm in size and with higher Gleason scores [22]. In order to analyze the main tumor’s metabolic behavior using \(^{11}\text{C}\)-choline, PET/MRI rather than PET/CT is the modality of choice to avoid confounding interference.

A more specific radiotracer that can reflect tumor aggressiveness that is not affected by other benign etiologies is warranted. A PSMA-targeting agent may be a better surrogate; not only is it specific for PCa, but its expression is also increased in advanced-stage and castration-resistant PCa [23]. From previous data, there was also no evidence that it was affected by ADT as \(^{11}\text{C}\)-choline was (Fig. 2) [24].

Integrated PET/MRI is considered a modality with great potential to influence the diagnosis and management of PCa. Notably, the current results suggest that the performance of PET/MRI is at least
**Fig. 2** Effect of androgen deprivation therapy on $^{11}$C-choline uptake. (A) T$_2$-weighted MRI, (B) T$_1$-weighted MRI, (C) $^{11}$C-choline PET, and (D) an apparent diffusion coefficient (ADC) map of a 60-year-old patient with a PSA level of 1.36 ng/mL, Gleason score of 4 + 4, and T4N0M0 clinical stage are shown. The patient underwent androgen deprivation therapy before the $^{11}$C-choline PET/MRI scan, resulting in no $^{11}$C-choline uptake in the prostate cancer lesion with a corresponding low T$_2$-weighted signal and low ADC value.

equivalent to that of PET/CT [25]. PET/MRI was most likely to improve T-staging, but improvements in the detection of nodal disease or bone involvement appear uncertain [3]. Our study showed that four (8.7%), two (4.3%), and six (13%) patients had discordant regional lymph node, distant lymph node, and distant bone metastasis interpretation results, respectively. Detection of lymph node metastases by conventional MRI has limited accuracy as this method relies on morphological criteria such as shape and size. Although DWI (diffusion-weighted imaging) and PET imaging can provide additional functional/metabolic information, pelvic lymph node dissection is still the only reliable staging method [26]. Regarding bone metastasis, although PET/MRI is technically and clinically robust for the evaluation of bone lesions [27], special attenuation correction based on MRI sequences results in a 15-20% quantitative underestimation of SUVs in bone [28], and lower radiolabeled choline uptake in some osteoblastic lesions may cause some false-negative PET imaging results [29]. Among the six patients with discrepancies in their bone metastasis imaging results, five patients were considered MRI-positive only and one patient was considered PET-positive only. Certainly, PET/MRI represents a combination of two advanced imaging modalities and has the potential to improve diagnostic accuracy, although its role in replacing pathological staging remains ambiguous.

Tumor heterogeneity measured on $^{18}$F-FDG-PET is considered a potentially superior IB over conventional SUV indices and may provide additional prognostic information [30]. Specific $^{18}$F-FDG uptake imaging features were linked to gene expression and the radio-genomic profile was highly associated with survival [31]. Regardless of the accumulating data
showing that intratumor heterogeneity on \(^{18}\)F-FDG-PET scans was predictive of treatment outcomes in different solid malignancies [32], the question as to whether \(^{11}\)C-choline PET scans will have the same impact remains unanswered. Our data indicate that conventional SUV indices such as maximum SUV and MTV can be considered robust IBs for further clinical application in view of their significant correlations with PSA level, but it is inappropriate to apply an \(^{11}\)C-choline PET heterogeneity quantification analysis because it did not have any correlation with clinical features.

Our prospective study needs to be interpreted within the context of some limitations. Firstly, most high-risk PCa patients did not undergo prostatectomy, and the number of patients with a surgical specimen was small. Although Gleason scores from TRUS biopsies are acceptably accurate in predicting the malignancy of prostatectomy specimens, discrepancies may be found in 25-30% of cases [33]. Secondly, the roles of MRI tissue organization biomarkers such as the ADC were not investigated. Thirdly, because of the short follow-up duration, the prognostic significance of the IBs under scrutiny remains unknown.

5. Conclusions

\(^{11}\)C-choline PET imaging parameters—including maximum SUV, mean SUV, MTV, UVP, and SUV variance—were significantly correlated with PSA level. Among these metabolic biomarkers, MTV should be a routinely used clinical tool as an independent predictor of positive distant metastasis status, similar to the PSA level. Metabolic tumor heterogeneity cannot predict a biospecimen-derived Gleason score in PCa. The application of PET texture quantification analysis to PCa requires the development of more specific PET radiotracers.

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