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Research Article

Diagnostic accuracy of F-18-Fluorocholine PET/CT and multiparametric MRI for prostate cancer

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ABSTRACT

Background: Positron emission tomography (PET) using different positron-emitting radiopharmaceuticals has emerged as a promising new metabolic diagnostic tool for the evaluation of a variety of malignant diseases. Thus, we investigated the diagnostic efficacy of F-18-Fluorocholine positron emission tomography/computed tomography (PET/CT) and multiparametric magnetic resonance imaging (mpMRI) for the detection and localization of tumors within the prostate with the correlating histopathology as the standard of reference.

Methods: Forty patients with histologically proven prostate cancer underwent both F-18-Fluorocholine PET/CT and mpMRI before robot-assisted laparoscopic radical prostatectomy (RARP). The maximum standard uptake values and the tumor-to-background ratio were measured on a sextant basis. In brief, the sextants were defined as right apex, right middle, right base, left apex, left middle, and left base. For each tumor region, the correlation of the tumor localization based on the sextant in both F-18-Fluorocholine PET/CT and mpMRI scans with the histopathological results was determined.

Results: The correlation between both imaging modalities and RARP pathology representing (1) all cancer and (2) clinically significant cancer defined as a ≥ International Society of Urological Pathology grade of 2 showed that the sensitivity and the area under the curve (AUC) were higher for mpMRI than for F-18-Fluorocholine PET/CT. In contrast, F-18-Fluorocholine PET/CT had relatively higher specificity than mpMRI. Importantly, we found a very high AUC value of over 0.8 in both imaging modalities.

Conclusion: mpMRI had results superior to F-18-Fluorocholine PET/CT in assessing intraprostatic tumor localization. However, F-18-Fluorocholine PET/CT showed superiority in terms of specificity. Thus, using both modalities in conjunction could provide better treatment planning.

1. Introduction

In late 2020, the United States Food and Drug Administration (FDA) approved Ga 68 prostate-specific membrane antigen (PSMA)-11 for the imaging of patients with PSMA-positive prostate cancer (PCa) in cases of suspected metastases or recurrence based on elevated serum prostate-specific antigen (PSA) levels.[1] In a recent meta-analysis, Perera et al[2] found that Ga 68 PSMA positron emission tomography (PET) improved the detection of metastases with biochemical recurrence (BCR), particularly at low pre-PET PSA levels of >0.2 ng/ml (33%) and 0.2–0.5 ng/ml (45%). In addition, high sensitivity (75%) and specificity (99%) were observed on a per-node analysis. A growing body of evidence has shown that PSMA-PET had high specificity in the detection of PCa lymph node metastases.[3,4] However, the detection performance for significant intraprostatic lesions has not yet been well elucidated.[5,6] Importantly, PSMA-PET is still not available in most countries except for the United States and Europe.[7]

Multiparametric magnetic resonance imaging (mpMRI) has been demonstrated to have good diagnostic accuracy in the screening for significant PCa.[8] The current status of mpMRI in the

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detection and management of PCa has emerged from two landmark studies, the PROMIS and PRECISION trials.[9,10] Despite its high negative predictive value (NPV), mpMRI is limited by its low positive predictive value (PPV) of 34–68%.[8,11] Low PPVs are usually derived from smaller tumor size, multifocality, and the presence of changes after biopsy, distorting the normal zonal anatomy.[12]

A multimodal imaging approach is currently implemented to highlight the advantages of each modality. For example, PET/MRI has improved the detection rate for PCa, which is commonly missed on mpMRI.[13] Hicks et al[14] reported that PSMA-PET/MRI had a higher sensitivity than mpMRI alone (74% vs. 50%, $P < 0.001$), whereas both were equally specific in a total of 32 patients with PCa who were scheduled for surgery.

In South Korea, PSMA-PET cannot yet be considered in clinical practice because regulatory approval for the use of PSMA is still pending. Instead, F-18-Fluorocholine PET/CT is currently performed by several institutions.[15] However, the role of Fluorocholine PET/CT is limited in the diagnosis and primary staging of PCa because of its relatively low sensitivity. Thus, the main use of Fluorocholine PET/CT remains in restaging in the setting of biochemical recurrence (BCR) or castration-resistant PCa (CRPC). Subsequently, studies on the detection performance for significant intraprostatic lesions are lacking.[16–18]

In the current study, we investigated the diagnostic efficacy of 18F-Fluorocholine PET/CT and mpMRI for the detection and localization of intraprostatic tumors, correlating the findings with those of histopathology as the standard of reference.

2. Materials and methods

2.1. Ethics statement

The Institutional Review Board of Seoul National University Bundang Hospital approved this study (approval number: B-1903-531-001). The requirement for obtaining written informed consent from the patients was waived by the Institutional Review Board due to the retrospective nature of the study. Personal identifiers were completely deleted to ensure that the data were analyzed anonymously. Our study was conducted according to the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

2.2. Study cohort

Using a prospective case series design, we enrolled 40 consecutive patients with histologically proven PCa who underwent both F-18-Fluorocholine PET/CT and mpMRI before robot-assisted laparoscopic radical prostatectomy (RARP) performed by a single surgeon (S.K.H.) between May 2019 and Jan 2020.

2.3. mpMRI protocol and image interpretation

All mpMRIs were performed using a 3-Tesla system (Achieva Tx and Ingenia; Philips, the Netherlands) with a phased-array cardiac 6-channel coil without the endorectal coil. The mpMRI was comprised of axial T2-weighted imaging (T2WI), T1/T2-weighted registered imaging (T1/T2RI), and diffusion-weighted imaging (DWI) with the corresponding apparent diffusion coefficient (ADC) maps and dynamic contrast enhancement (DCE). The detailed protocols were described in our previous reports.[19] All images were reviewed by two high-volume radiologists (H.J.L. and S.I.H.) using a Picture Archiving and Communication Systems workstation (PACS, INFINITT Technology, Seoul, Korea). All lesions were graded on a level of suspicion ranging from 1 to 5 based on the ADC maps and T2WI using the Prostate Imaging Reporting and Data System version 2 (PI-RADSv2).[20]

2.4. PET/CT acquisition and image interpretation

F-18-Fluorocholine PET/CT images for staging were acquired within 30 days prior to surgical resection using a dedicated PET/CT scanner (Biograph mCT Flow, Siemens Healthineers, Malvern, PA, USA). The patients were injected with 3.7 MBq/Kg (range, 120–263 MBq) of F-18-Fluorocholine after at least 4 hours of fasting. CT images were first acquired from the cranial base to the upper thigh without contrast enhancement (Caredose 4D/CareKv 120, 3.0 mm slice thickness). PET imaging was performed 2 minutes after radiotracer injection. The PET images were sequentially acquired in a three-dimensional list mode (feet-first flow mode, 1.5 mm/sec). The acquired PET images were reconstructed on 128 x 128 matrices using an ordered subset expectation maximization algorithm (2 iterations and 21 subsets) and CT-based attenuation correction.

All PET/CT images were analyzed with dedicated software (MIM 6.5, MIM Software Inc., Cleveland, OH, USA). The PET, CT, and fused images were analyzed to determine the exact localization of the prostate cancers. The lesions were analyzed by one nuclear medicine physician (Y.S.) who had more than 15 years of experience and was blinded to the clinical data, pathological data, and mpMRI findings. The maximum standard uptake value (mSUV) and the tumor-to-background (T/B) ratio were measured in sextants, as previously reported.[21] In brief, the sextants were the right apex (Ra), right middle (Rm), right base (Rb), left apex (La), left middle (Lm), and left base (Lb). The base regions were defined as the upper third of the prostate to the bladder margin, the middle region as the central third region, and the apex as the inferior third region (Supplemental Figure 1).

2.5. Histopathological examination and correlation

Histological evaluations from RARP were reported according to the International Society of Urological Pathology (ISUP) protocol by a staff pathologist (G.C.) who had genitourinary expertise. He was blinded to both the mpMRI and PSMA-PET results. Each prostate was divided into the same six segments, as described above. The segments were reported to have no cancer, cancer, or clinically significant cancer ($\geq$ ISUP grade 2). All detected tumors were reported and recorded regardless of the tumor volume. For each tumor region, correlation with the histopathological results was defined for tumors localized to a sextant in both the F-18-Fluorocholine PET/CT and mpMRI results.

2.6. Statistical analysis

Bivariate analysis was performed using a scatter plot and Pearson's correlation test to assess the correlation between (1) F-18-Fluorocholine PET/CT (mSUV and T/B ratio, respectively) and (2) mpMRI with the histopathological results. Logistic regression analysis, including receiver-operating characteristic curves and area under the curve (AUC) analysis, was also performed to explore the relationship between F-18-Fluorocholine PET/CT and mpMRI in detecting segments containing (1) all cancer and (2) clinically significant cancer ($\geq$ ISUP grade 2). In addition, sensitivity analysis was performed to evaluate the accuracy of each modality in predicting the histopathological results. Analyses were conducted using SAS (version 9.4; SAS Institute) and the statistical package for R, ver. 2.13.2 (R Foundation for Statistical Computing [http://www.r-project.org/]).

3. Results

3.1. Baseline characteristics

The patient characteristics are summarized in Table 1. In a total of 40 patients, the median (interquartile range [IQR]) age and PSA

Table 1
Baseline characteristics

Number of patients	N = 40
Median (IQR) age, years	67.0 (64.0–71.0)
Median (IQR) PSA value, ng/mL	8.75 (6.20–17.59)
Clinical stage, n (%)	
≤T2c	22 (55.0%)
≥T3a	18 (45.0%)
Radical prostatectomy pathology, ISUP grade, %	
1	0 (0%)
2	17 (42.5%)
≥3	23 (57.5%)

ISUP, international society of urological pathology (ISUP); PSA, prostate-specific antigen.

level were 67.0 (64.0–71.0) years and 8.75 (6.20–17.59) ng/mL, respectively. In total, 240 prostatic segments were analyzed from 40 patients, of which 64/240 (26.7%) had no cancer or ISUP grade 1 cancer, and the other 176/240 (73.3%) had ≥ ISUP grade 2 cancer, defined as clinically significant cancer. An example of a positive lesion on mpMRI and F-18-Fluorocholine PET/CT is shown in Fig. 1 with the associated whole-mount histopathology results.

Pearson's correlation and scatter plot analysis showed that both (1) F-18-Fluorocholine PET/CT (mSUV and T/B ratio, respectively) and (2) mpMRI were positively correlated with the pathologic Gleason score (GS, Fig. 2).

3.2. Diagnostic accuracy for the detection of all cancer

Table 2 and Fig. 3(A) summarize the diagnostic accuracy of diagnosing all cancer with the AUC, sensitivity, and specificity values. These showed that the sensitivity and AUC were higher for mpMRI than for F-18-Fluorocholine PET/CT. In contrast, F-18-Fluorocholine PET/CT had relatively higher specificity than mpMRI. The sensitivity and specificity of F-18-Fluorocholine PET/CT based on different quantitative mSUV cutoff values are shown in Table 2. An mSUV value of 2.385 resulted in 90.2% sensitivity and 51.5% specificity, and a value of 2.995 resulted in 80.4% sensitivity and 62.7% specificity.

Diagnostic accuracy for detecting clinically significant cancer (≥ ISUP grade 2).

Table 3 and Fig. 3(B) summarize the diagnostic accuracy for diagnosing clinically significant cancer (≥ ISUP grade 2). We also confirmed similar results for the detection of ≥ ISUP grade 2 cancer, as well as for all cancer. Notably, we found a very high AUC value of over 0.8 for both imaging modalities. An mSUV value of 2.47 resulted in 90.1% sensitivity and 54.8% specificity, and a value of 3.05 resulted in 80.2% sensitivity and 63.0% specificity.

4. Discussion

Radiolabeled choline, either as C-11 choline or F-18-Fluorocholine has been extensively used in the last 20 years for PCa.[22] In the first decade of the 21st century, clinical studies on PCa patients using radiolabeled choline have been actively conducted. The most frequent studies were performed in patients with BCR occurring after radical prostatectomy or radiotherapy, and the other studies were performed in patients at the initial staging. The initial staging of PCa patients with choline PET/CT is primarily aimed at defining the presence of distant metastases, especially in lymph nodes (LNs).[23–26] Choline PET/CT has been highlighted as an advantageous imaging method to detect metabolically active LNs in sites other than the standard pelvic lymph node dissection area during RP (particularly in the sacral and common iliac lymph nodes) in terms of preoperative planning.[23,26]

In regard to intraprostatic tumor diagnosis or localization, Castellucci et al[27] reported that in the pathologic T (pT) stage, pT2 patients were compared to pT3 and pT4 patients without statistical significance. In contrast, the pN analysis (positive vs. negative) showed highly significant correlations with histopathological results as the standard of reference. The predictive role of the GS was also demonstrated in previous studies.[28,29] Cimitan et al[28] reported that a GS of ≥7 was predictive of a positive PET/CT compared to a reference category of <7 in a large sample of 1000 PCa patients.

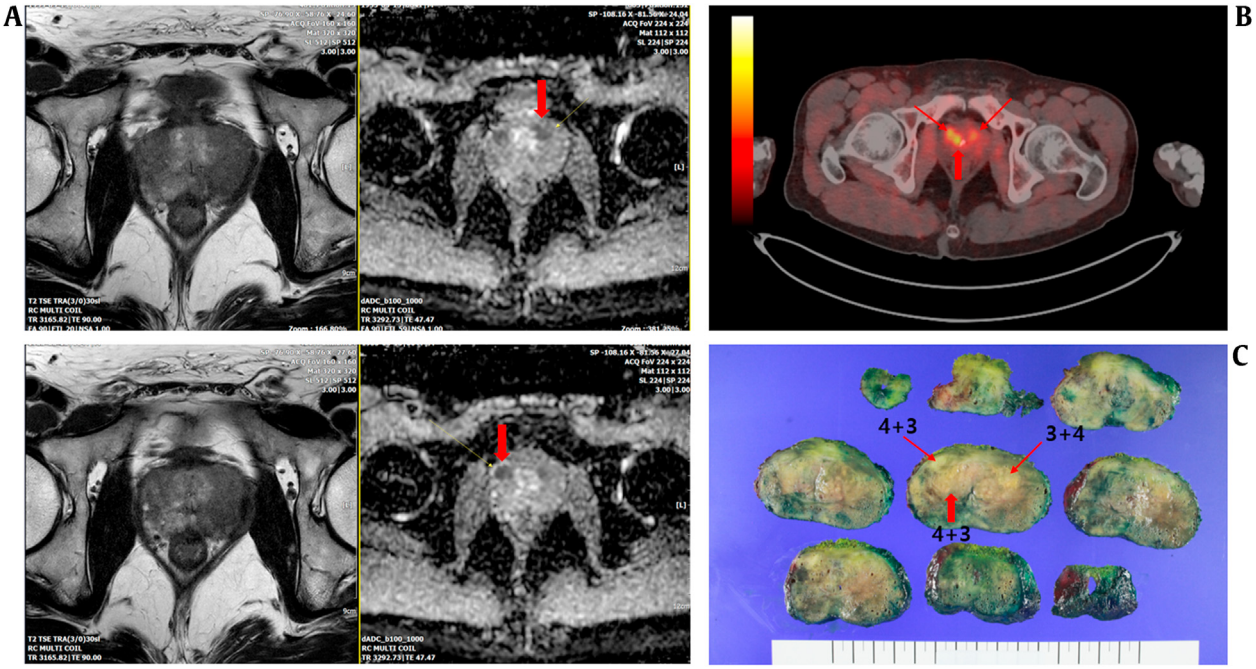

Fig. 1. Correlation of (A) multiparametric MRI and (B)18F-Fluorocholine positron emission tomography/computed tomography with (C) histopathological results on a sextant basis.

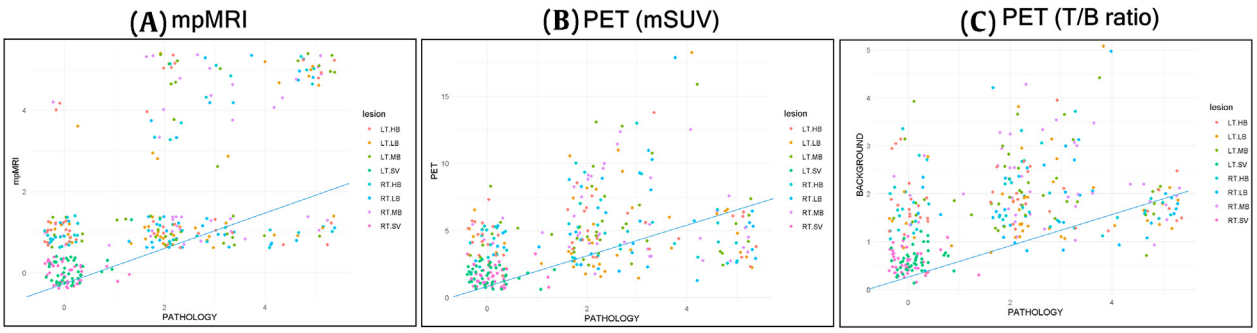

Fig. 2. Correlation analysis using a scatter plot, (A) multiparametric MRI, (B)18F-Fluorocholine positron emission tomography/computed tomography (mSUV), and (C) tumor-to-background ratio (T/B ratio).

Table 2
Correlation between mpMRI/choline PET and radical prostatectomy pathology (Cancer vs. no cancer)

	AUC (95% CI)	Cut-off (Sn> 0.9)	Sensitivity	Specificity	Cut-off (Sn>0.8)	Sensitivity	Specificity
mpMRI	0.8326 (0.7953–0.8699)	1	0.9690	0.5597	1	0.9690	0.5597
Choline PET	0.7945 (0.7461–0.8429)	2.385	0.9020	0.5149	2.995	0.8041	0.6268
T/B ratio[a)]	0.7867 (0.7334–0.8400)	1.085	0.9072	0.5746	1.315	0.8092	0.6417

AUC, area under the curve; mpMRI, multiparametric magnetic resonance imaging; PET, positron emission tomography, Sn, sensitivity.
[a)] Choline PET, tumor-to-background ratio.

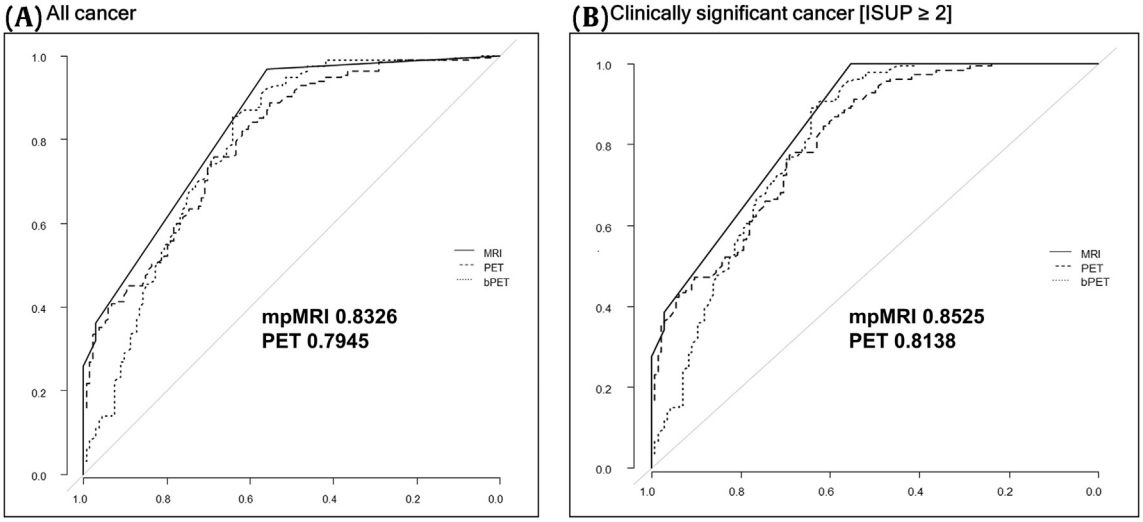

Fig. 3. Receiver-operating curve (ROC) for multiparametric MRI and 18F-Fluorocholine positron emission tomography/computed tomography for detecting (A) all cancer and (B) clinically significant cancer (ISUP ≥2).

Table 3
Correlation between mpMRI/choline PET and radical prostatectomy pathology (Clinically significant cancer [Gleason score ≥3 + 4] vs. others)

	AUC (95% CI)	Cut-off (Sn> 0.9)	Sensitivity	Specificity	Cut-off (Sn>0.8)	Sensitivity	Specificity
mpMRI	0.8525 (0.8195–0.8855)	1	1	0.5547	1	1	0.5547
Choline PET	0.8138 (0.7686–0.8591)	2.47	0.9010	0.5479	3.05	0.8021	0.6301
T/B ratio[a)]	0.8075 (0.7580–0.8570)	1.215	0.9065	0.6232	1.355	0.8076	0.6575

AUC, area under the curve; mpMRI, multiparametric magnetic resonance imaging; PET, positron emission tomography; Sn, sensitivity.
[a)] Choline PET, tumor-to-background ratio.

Koerber et al[29] found a mean PSMA mSUV of 1.88 ± 0.44 in normal prostate tissue compared to 10.77 ± 8.45 in PCa lesions (P < 0.001). They also reported that patients with higher PSA, higher GS, and higher d'Amico risk scores had statistically significant higher PSMA mSUVs on PET/CT (P < 0.001 each). In the current study, we also found a positive correlation between mSUV and pathologic GS (Fig. 2). This may suggest that not only PSMA-PET but F-18-Fluorocholine PET/CT can add a differentiating ability for high-grade intraprostatic tumors.

The accurate diagnosis of the presence or absence of PCa using a noninvasive technique instead of an invasive prostate biopsy is extremely essential. However, for this to be realized, accurate

imaging modalities exhibiting high sensitivity and specificity must take precedence. Even in the current mpMRI era, prostate biopsies are still needed due to the relatively low PPV of mpMRI.[9,10] In the current study, we found that F-18-Fluorocholine PET/CT had a relatively higher specificity than mpMRI (Tables 2 and 3) and a very high AUC value of over 0.8 in both imaging modalities. This may suggest a role for F-18-Fluorocholine PET/CT in either the initial diagnosis or subsequent surveillance for PCa. In addition, it may be used in patients who are candidates for focal therapy to detect or exclude the multifocality of clinically significant PCa.

The diagnostic accuracy of F-18-Fluorocholine PET/CT requires complementation with accurate PET scanning, the expertise of a nuclear medicine physician as a reader, and the development of an objective quantitative device that enables appropriate clinical judgment. In a previous study evaluating the ability of PSMA-PET to detect intraprostatic PCa, Matthijs et al[30] reported that a semi-quantitative mSUV value of 3.95 per hemigland on PSMA-PET had a sensitivity of 94% in detecting ISUP grade ≥2 PCa. In the current study, we found that a quantitative mSUV value of 2.47 had over 90% sensitivity, and a value of 3.05 had over 80% sensitivity in detecting ISUP grade ≥2 PCa (Table 3). Thus, these values could be objective quantitative measurement values. However, future large-scale studies are needed to verify the findings.

The present study had several limitations. First, we performed a (sextant) segment-based analysis, not a lesion-based. However, given the potential bias, the innate nature of multifocality in PCa should be regarded. Thus, we believe that this approach would be more useful in assessing the ability of mpMRI and F-18-Fluorocholine PET/CT to detect segments containing clinically significant PCa compared to the diagnostic accuracy of lesion-based analysis on face value. Second, even in a study of a large tertiary institution with a prospective database, the small number of patients was a crucial drawback. Subsequently, selection bias was introduced with all patients having biopsy-confirmed clinically significant PCa (ISUP grade ≥2, Table 1). In addition, only a small number of patients with positive LNs on imaging were obtained, so an additional analysis of LN metastasis could not be performed (Supplemental Figure 2). Therefore, further evaluation in a larger and prospective cohort would be helpful to validate these preliminary findings.

5. Conclusions

mpMRI had results superior to F-18-Fluorocholine PET/CT in assessing intraprostatic tumor localization. However, F-18-Fluorocholine PET/CT showed superiority in terms of specificity. Thus, both modalities in conjunction would be useful for better treatment planning.

Conflicts of interest

All authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2022.04.003.

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