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EVIDENCE REVIEW

New frontiers in focal therapy for prostate cancer: Prostate-specific membrane antigen positron emission tomography/magnetic resonance imaging

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Abstract

Imaging has a central role in the context of focal therapy (FT) for prostate cancer (PCa). Prostate-specific membrane antigen (PSMA) positron emission tomography/magnetic resonance imaging (PET/MRI) is a novel imaging modality that combines the morpho-functional information of MRI with the molecular characterization of PET. Some papers reported the potential advantages of PSMA PET/MRI in different clinical scenarios. Limited evidence on PSMA PET/MRI is available in the setting of FT. PSMA PET/MRI can be an effective imaging modality for detecting primary PCa and seems to provide accurate local staging of primary PCa. PSMA PET/MRI also shows high performance for restaging and detecting tumor recurrence. The higher soft-tissue contrast and the reduction of ionizing radiation are the main advantages reported in the literature compared to PET/computed tomography. PSMA PET/MRI could represent a turning point in the management of patients with PCa in the context of FT. Further studies are needed to confirm its applications in this specific clinical

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setting.

Key Words: Prostate-specific membrane antigen; Positron emission tomography/magnetic resonance imaging; Prostate cancer; Focal therapy; High-intensity focused ultrasound; Cryotherapy

Core Tip: Prostate-specific membrane antigen positron emission tomography/magnetic resonance imaging can be an effective imaging modality for detecting primary and recurrent prostate cancer, besides it seems to provide accurate local staging and restaging. Multiparametric magnetic resonance imaging is considered the standard imaging modality in the context of focal therapy; however, the diagnostic performance of prostate-specific membrane antigen positron emission tomography/magnetic resonance imaging make it an excellent candidate as a technique of choice in this setting.

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INTRODUCTION

Prostate-specific membrane antigen (PSMA) is a membrane protein that is overexpressed in the vast majority of prostate cancer (PCa)[1]. PSMA can be used as a positron emission tomography (PET) target through specific ligands labeled with radioisotopes. PSMA PET/computed tomography (CT) is an established imaging technique for the evaluation of biochemical recurrence (BCR) of PCa[2] and showed possible applications also for tumor detection, staging, treatment planning, and assessment of response to therapy[3-6]. PSMA PET/magnetic resonance imaging (MRI) is a hybrid imaging technique that combines the morphological information of MRI with the molecular data of PET. MRI provides excellent anatomical characterization and soft tissue contrast, whereas PSMA PET offers a reliable molecular characterization of the tumor[7]. The first applications of PSMA PET/MRI in the PCa setting were described in 2013[8]; since that time, several papers reported the potential applications of this imaging modality in different clinical scenarios[9,10]. Multiparametric (mp) MRI is considered the standard imaging modality for tumor detection, local staging and follow-up in the focal therapy (FT) setting[11]; however, the demonstration of several intrinsic limitations of this technique highlighted the need to investigate alternative imaging modalities, including PSMA PET/CT and PSMA PET/MRI[12,13].

PRIMARY PROSTATE CANCER DETECTION AND STAGING WITH PROSTATE-SPECIFIC MEMBRANE ANTIGEN POSITRON EMISSION TOMOGRAPHY / MAGNETIC RESONANCE IMAGING

Eiber *et al*[14] found that patient-based sensitivity for the tumor detection of mpMRI, PSMA PET, and PSMA PET/MRI was 66%, 92%, and 98%, respectively. Patient-based sensitivity of PSMA PET and PSMA PET/MRI statistically significantly outperformed mpMRI (P = 0.001 and P < 0.001), while no significant difference was observed between PSMA PET imaging and PSMA PET/MRI (P = 0.250). With cut-off scores of 3 for mpMRI and 4 for PSMA PET and PSMA PET/MRI, lesion-based sensitivity and specificity of PSMA PET/MRI were 76% and 97% respectively, while mpMRI and PSMA PET showed less sensitivity (58% and 64%) and specificity (82% and 94%). A concordance subanalysis revealed that both mpMRI and PSMA PET were able to

identify most tumors; however, each technique detected tumor-involved areas that were negative in the other modality, this contributed to the observed superiority of PSMA PET/MRI. No significant correlation was found between quantitative PET parameters and Gleason score (GS). Al-Bayati *et al*[15] found that lesion-based sensitivity for the tumor detection of mpMRI, PSMA PET, and PSMA PET/MRI was 59%, 81%, and 88%, respectively. PSMA PET and PSMA PET/MRI had a significantly higher sensitivity than mpMRI (P = 0.03 and P = 0.003), while they did not show a significant difference in between them (P = 0.5). The lesion-based specificity of mpMRI, PSMA PET, and PSMA PET/MRI was 66%, 100%, and 100%, respectively. PSMA PET and PSMA PET/MRI rated 4 and 6 Lesions as equivocal (5-point Likert scale 3), while mpMRI classified 15 Lesions as indeterminate (PI-RADS 3). In a considerable proportion of equivocal results with mpMRI, PSMA PET led to a correct shift towards higher malignancy suspicion. Hicks *et al*[16] showed the improved region-specific sensitivity for the tumor detection of PSMA PET/MRI compared to mpMRI. Besides, the authors found a significant correlation between tumor maximum standardized uptake value and GS. Park *et al*[17] concluded that PSMA PET/MRI offers incremental value over a dedicated mpMRI for preoperative PCa localization and staging. Sugawara *et al*[18] reported a higher accuracy for primary tumor diagnosis of PSMA PET/MRI compared to mpMRI, PSMA PET or clinical factors alone (*i.e.*, digital rectal examination and PSA), and the combination of PSMA PET/MRI with clinical profile improved the characterization of lesions; besides, the authors reported the significant association of maximum standardized uptake value with GS. Freitag *et al*[19] concluded that the lymph node (LN) and bone metastases were accurately and reliably depicted by PSMA PET/MRI with very low discordance compared to PSMA PET/CT. Both PET techniques were able to identify metastases in normal-sized LN (71.9%). Visibility of LN was significantly higher with MRI compared to CT using T1-w CE (P = 0.013), T2-w fat-saturated (P < 0.0001), and DWI (P < 0.0001) sequences. Two PSMA PET-positive bone metastases could not be confirmed morphologically using CT, but it was possible with MRI.

Maurer *et al*[20] found that PSMA PET/MRI and PSMA PET/CT for LN staging performed significantly superior to morphological imaging alone (CT or MRI) on a patient- (P = 0.002) and template-based analysis (P < 0.001). In contrast, no substantial difference between CT and MRI as morphological imaging components of PSMA PET was recorded. Thalgott *et al*[21] assessed the diagnostic potential of PSMA PET/MRI compared to preoperative staging nomograms and concluded that PSMA PET/MRI and clinical nomograms performed equally well to determine the clinical stage; besides, PSMA PET provided additional anatomical information useful for therapeutic planning. Grubmüller *et al*[22] reported the correct identification of PCa with PSMA PET/MRI in 122 patients (97.5%). The accuracy of T-and LN-staging in 80 patients was 82.5% (95% Confidence interval: 73%-90%) and 93% (95% Confidence interval: 84%-98%), respectively. Noteworthy, PSMA PET/MRI changed the therapeutic strategy in 28.7% of the patients. Muehlematter *et al*[23] compared the diagnostic accuracy of mpMRI and PSMA PET/MRI for the detection of extracapsular extension (ECE) and seminal vesicle infiltration. PSMA PET/MRI showed lower region-specific sensitivity for detection of ECE (90% *vs* 94%; P = 0.007) and seminal vesicle infiltration (94% *vs* 98%; P = 0.001), while patient-specific sensitivity for the detection of ECE was higher with PSMA PET/MRI (69% *vs* 46%; P = 0.04). No other significant differences were found. Ferraro *et al*[24] found that the patient-based sensitivity, specificity, PPV, and NPV for the LN metastases detection of PSMA PET/MRI were 58%, 98%, 88%, and 90%, respectively. The model combining PSA, Gleason score, and PSMA PET visual analysis of LN showed a tendency to improve patient selection for LN dissection over the currently used clinical nomograms. Kaufmann *et al*[25] investigated the accuracy for T-and LN-staging of PSMA PET/MRI, surprisingly reporting discordant results compared to the previous ones. The authors observed similar overall PCa detection between mpMRI and PET/MRI (both ^{11}C-choline and ^{68}Ga-PSMA). mpMRI was found to be more accurate than PET for T-staging. In particular, PET underestimated the local tumor extent and no additional value for PET concerning the primary tumor extend was found. mpMRI showed no inferiority compared to PET/MRI in N-staging, and the author reported the limitation of PET/MRI in detecting small LN metastases independent of the radiotracer used.

RECURRENT PROSTATE CANCER DETECTION AND RESTAGING WITH PROSTATE-SPECIFIC MEMBRANE ANTIGEN POSITRON EMISSION TOMOGRAPHY / MAGNETIC RESONANCE IMAGING

Afshar-Oromieh *et al*[26] compared PSMA PET/CT and PSMA PET/MRI in BCR patients. The authors concluded that, outside the "halo artifacts" around the bladder and at the level of the kidneys, PSMA PET/MRI was more accurate and enabled a subjectively easier evaluation of the images than PSMA PET/CT, allowing to clarify unclear findings on PSMA PET/CT. Freitag *et al*[27] reported that 93 (78.2%) BCR patients had PSMA-positive lesions. Eighteen (15.1%) subjects had local recurrences in PET/MRI, while only 9 (7.6%) in PET/CT (P = 0.004). Bladder-to-local recurrence distance was identified as a statistically significant predictor of PSMA PET-positivity (P = 0.028), contrary to local recurrence size (P = 0.84). Hope *et al*[28] found that with PSMA PET/MRI and PSMA PET/CT the disease was detected in 103 (82%) BCR patients and major changes in the management was preferred in 67 (53.2%) cases; however, no sub-analysis was performed to compare the two PET techniques. Lütje *et al*[29] showed that in 14 (29.2%) patients neither PSMA PET/CT nor PSMA PET/MRI found lesions and 9 (19.7%) were excluded due to artifacts around the bladder. In the other 25 (52.1%) subjects, PSMA PET/MRI *vs* PSMA PET/CT identified 14 *vs* 9 recurrences in the prostate bed, 23 *vs* 20 PET-positive lymph nodes, and 4 *vs* 4 PSMA PET-positive bone lesions, respectively. The higher detection of tumor recurrences in the prostate bed of PSMA PET/MRI was attributed to the superior soft-tissue contrast of MRI component. Schiller *et al*[30] found that lesions suspicious for PCa were detected in 27/31 cases (87.1%) with PSMA PET/MRI or PSMA PET/CT compared to negative CT/MRI. Furthermore, 14 patients (45.2%) had a changed staging result with PSMA PET compared to CT/MRI. Grubmüller *et al*[31] showed that PSMA-positive lesions were found in 100 (85.5%) BCR patients with PET/CT or PET/MRI, reporting a detection rate of 65% for PSA levels of 0.2-0.5 ng/mL. PSMA PET detected lesions in 67 (57.3%) subjects who had no suspicious with MRI or CT and changed therapeutic management in 74.6% of them. The authors did not compare the performance of two PET modalities. Kranzbühler *et al*[32] reported positive PSMA PET/MRI in 44 (78.6%) BCR patients. Suspicious lesions were detected in 44.4%, 72.7%, 80%, 95.2% of subjects with PSA levels of < 0.2, 0.2-0.5, 0.5-2.0, > 2.0 ng/mL respectively. The detection rate of MRI was significantly lower than PSMA PET/MRI (24%), while the overall detection rate of PSMA PET was comparable with PSMA PET/MRI (76%). The high detection rate (54.5%) for recurrent PCa, even at low PSA levels (< 0.5 ng/mL), were confirmed in a subsequent study of the same group[33]. Burger *et al*[34] investigated PSMA PET/MRI's performance for the localization of disease recurrence in patients undergoing high-intensity focused ultrasound with proven significant PCa on transperineal template biopsy not detected with mpMRI. It is necessary to emphasize that this is the only paper available in literature analyzing PSMA PET/MRI in the specific context of FT. PSMA PET was positive in 6 (60%) patients. No false-positive lesions were reported. All negative subjects had GS 3 + 4 disease, while all lesions with GS 4 + 3 or higher were detected. The quadrant-based sensitivity, specificity, PPV, and NPV of PET were 55%, 100%, 100%, and 85%, respectively. Abufaraj *et al*[35] assess the accuracy of PSMA PET/CT or PSMA PET/MRI LN staging in patients with BCR after RP undergoing LN dissection. Patient-based sensitivity was 100%. At regional analysis, sensitivity of PET ranged from 72% to 100%, specificity from 96% to 100%, PPV from 95% to 100%, NPV from 93% to 100%, diagnostic accuracy from 95% to 98%. No differences in diagnostic performance were found between PSMA PET/CT and PSMA PET/MRI. The PPV in patients with a PSA level ≥ 1.4 ng/mL was almost always 100% in all regions and subregions except the presacral region (93%). Guberina *et al*[36] reported that tumor recurrence was localized in 62 (66.7%) BCR patients based on combined PSMA PET/CT and PSMA PET/MRI reading. The sensitivity of PSMA PET/MRI and PSMA PET/CT was 98.8 % and 93.2%, respectively. PSMA PET/MRI detected 148 out of 150 Lesions described in PSMA PET/CT (missing two LN lesions) and other 11 Lesions (5 LN lesions and 6 Local recurrences). A significant difference (P = 0.031) between PSMA PET/CT and PSMA PET/MRI for local recurrence diagnosis was found.

SUMMARY OF EVIDENCE

PSMA PET/MRI may be an effective imaging modality to detect primary PCa,

showing a higher accuracy compared to mpMRI alone[14-16]. It provides accurate local staging of primary PCa; however, there are contradictory results in this setting when its reliability is compared to other imaging modalities[20,24,25]. PSMA PET/MRI also shows high performance for restaging and detecting tumor recurrence, but its superiority over PSMA PET/CT has not yet been clearly demonstrated[8,31,35] (Table 1). PSMA PET/MRI seems to favorably integrate the current clinical nomograms[21,24]. Artifacts can reduce the diagnostic performance of PSMA PET around the bladder and kidneys[26,27]. The reduction of ionizing radiation and the higher soft-tissue contrast and the main advantages reported in the literature compared to PSMA PET/CT, while the long duration, the high cost, the poor standardization of the technique, and the low availability are some relevant limitations[37,38].

CONCLUSION

The ideal imaging technique for prostate cancer patients in the focal therapy setting is not yet available but encouraging data regarding PSMA PET/MRI are emerging from the literature.

PSMA PET/MRI could represent a turning point in the management of patients with prostate cancer in the context of focal therapy; however, well-designed studies are needed to clarify the role of PSMA PET/MRI in this specific clinical setting.

Table 1 Diagnostic performance of imaging techniques in the focal therapy setting

	mpMRI	PSMA PET/CT	PSMA PET/MRI
Primary tumor detection	Intermediate	Intermediate/High	High
Loco-regional staging	Intermediate/High	Intermediate/High	Intermediate/High
Tumor recurrence detection	Intermediate	Intermediate/High	Intermediate/High

FT: Focal therapy; PSMA: Prostate-specific membrane antigen; PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; mp: Multiparametric.

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