ROBOTICS, LAPAROSCOPY & ENDOSURGERY

^{68}GA-PSMA LIGAND POSITRON EMISSION TOMOGRAPHY (PET) IN PROSTATE CANCER

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ABSTRACT

Prostate specific membrane antigene (PSMA) is a transmembrane protein with significantly elevated expression in prostate cancer cells compared to benign prostatic tissue. The detection of prostate cancer lesions by PET imaging using PSMA-ligands has gained high clinical impact during the last years and is increasingly used in clinical routine. In particular, ^{68}Ga-PSMA ligand PET/CT promises accurate staging of primary prostate cancer, re-staging after biochemical recurrence and the detection/ localization of malignant lesions in patients with suspicion of prostate cancer. First studies showed significantly higher detection rates for the localization of prostate foci and the detection of lymph node metastases compared to other modalities (including choline based PET/CT) in the primary setting. Similar encouraging results were obtained for patients with biochemical recurrence after radical prostatectomy. The advantage of ^{68}Ga-PSMA ligand PET is especially evident in patients with low PSA levels (PSA below 1ng/ml), where up to 72.7% of lesions may be detected using this new modality. One challenge however remains the identification of PSMA-negative prostate carcinoma, comprising around 8% of the examined patients.

Key Words: PSMA ligand PET, Prostate carcinoma, PET/CT, PET/MR

INTRODUCTION

Prostate cancer (PC) is the most common cancer and the second most common cause of cancer related deaths amongst men in the western world. Early detection of the disease and metastases is highly relevant in terms of prognosis and therapy management. Positron emission tomography/computed tomography (PET/CT) as a hybrid imaging technique combining functional and morphological information has been proven to exhibit highest diagnostic accuracy amongst all imaging modalities and is increasingly established as the primary staging tool in prostate cancer. Choline based (i.e. either 18F-Choline or 11C-Choline) PET/CT is widely used for this purpose, however there have been numerous studies reporting a low sensitivity and specificity especially in patients with low PSA levels (1,2). Therefore, the development of new radiotracers and the search for new targets was required. In this context, prostate specific membrane antigene (PSMA) targeted PET as a new imaging modality has been proven to be highly interesting and has already replaced choline based PET as the standard staging tool in some centers, including in our institution. PSMA is a type II transmembrane protein with significantly elevated expression in PC cells compared to benign prostatic tissue. The localization of the catalytic site of PSMA on the extracellular domain allows the development of small specific inhibitors that are internalized after ligand binding (3). Accordingly, different PSMA targeted PET probes are available up to now, however the ^{68}Ga labeled inhibitor PSMA-HBED-CC became one of the most successful regarding clinical application and is also used in our clinic (4). Increasing data on this

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tracer suggests a significantly higher diagnostic accuracy in the detection of primary prostate cancer, prostate cancer relapses and metastases compared to choline based PET. Accordingly, following indications for ^{68}Ga-PSMA-ligand PET/CT are being discussed: (I) Re-Staging after biochemical recurrence following radical prostatectomy, (II) primary staging of histologically verified prostate cancer and (III) elevated PSA levels with suspicion of prostate cancer but prior negative biopsy.

BIOCHEMICAL RECURRENCE

PSA relapse after radical prostatectomy is a common clinical scenario and PSA-levels >0.2ng/ml occur long before recurrent disease can be localized clinically or my conventional imaging (5). Moreover, it is essential to distinguish whether disease relapse is localized to the prostate bed or in in other sites in order to implement appropriate therapy. Extensive data is available for the use of choline based PET/CT in detecting recurrence, significantly enhancing detection rates compared to conventional imaging. However, one major limitation remains the low detection rate in patients with PSA levels below 1ng/ml. Moreover, high background signal and unspecific uptake in lymph nodes may hamper the diagnostic performance of this modality.

Krause et al. examined 63 patients with evidence of biochemical recurrence using ^{11}C- Choline PET/CT and found pathological uptake indicative for tumor tissue in 56% of the patients (6). Related to PSA level, detection rate was highest in patients with a PSA >3ng/ml (73%), however decreased continuously with lower PSA-levels. Patients with PSA <1ng/ml showed a relatively low detection rate of 36%. Another work by Castellucci et al. found positive findings in 28% of patients with mild biochemical recurrence (PSA below 1.5ng/ml) (7) in ^{11}C- Choline PET/CT.

The major contribution of ^{68}Ga-PSMA ligand PET/CT in this setting is to significantly enhance the detection of biochemical recurrence, which is in particular evident in patients with low PSA-levels (Figure 1). Moreover, tumor tissue seems to exhibit markedly superior contrast compared to choline based PET/CT with consequent superior confidence in the detection of tumor tissue (Figure 2). The diagnostic performance of both tracers has been directly compared by Afshar-Oromieh et al. in a cohort of 37 patients with a biochemical relapse of PC (8). In 86.5% of the patients at least one lesion characteristic for PC was detected in ^{68}Ga-PSMA ligand PET/CT, by contrast only 70.3% of the patients presented with pathological findings in ^{18}F-Choline PET/CT. ^{68}Ga-PSMA ligand PET/CT detected more lesions especially at lower PSA levels compared to choline. Results were confirmed by Morigi et al, who demonstrated a detection rate of 86% using ^{68}Ga-PSMA ligand PET/CT compared to 57% for ^{18}F-Choline PET/CT in patients with biochemical recurrence exhibiting a PSA between 0.5 – 2 ng/ml (9). The superiority of ^{68}Ga-PSMA ligand PET/CT was even more pronounced in patients with a PSA below 0.5ng/ml: Scan results were positive in 50% of the patients versus 12.5% for ^{18}F-choline PET/CT. Two recently published studies confirmed the superiority of ^{68}Ga-PSMA ligand PET/CT in a larger cohort comprising several hundred patients. Eiber et al evaluated 248 patients with biochemical recurrence after radical prostatectomy and found detection rates of 96.8%, 93%, 72.7% and 57.9% for

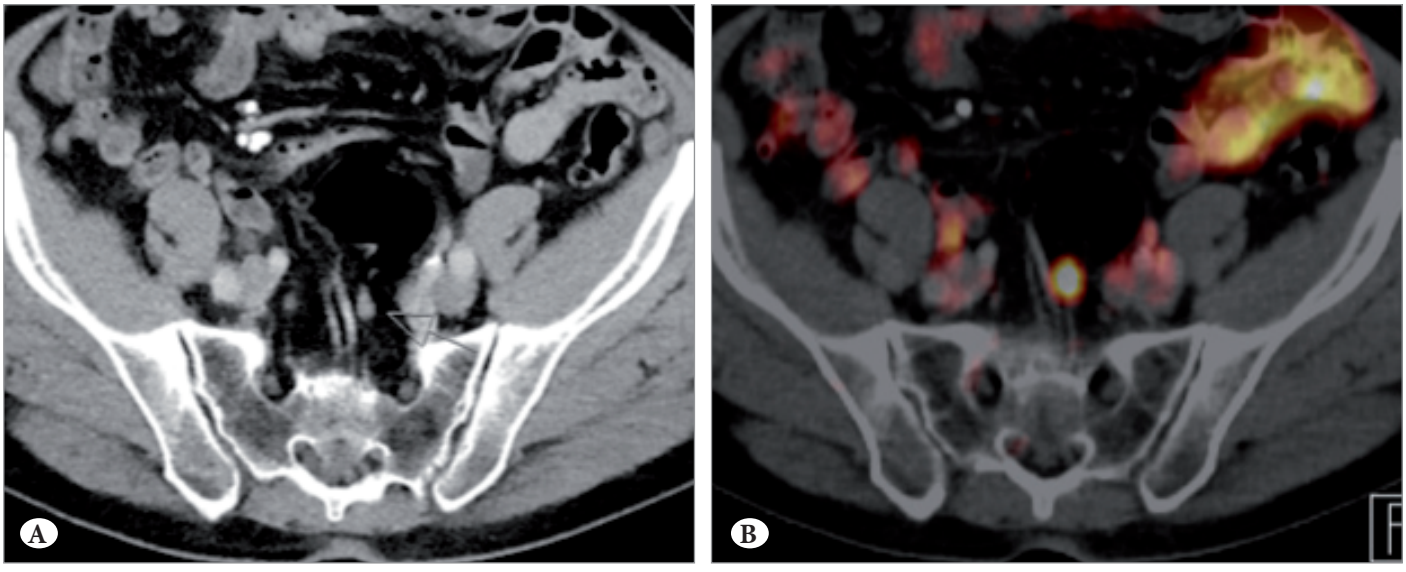

Figure 1: 81year old patient with with biochemical recurrence after radical prostatectomy. Contrast enhanced CT images **(A)** shows small lymph node in the pelvis, ^{68}Ga-PSMA ligand PET **(B, fusion images)** shows intensive PSMA expression of the lymph node. Consecutive surgery verified lymph node metastasis.

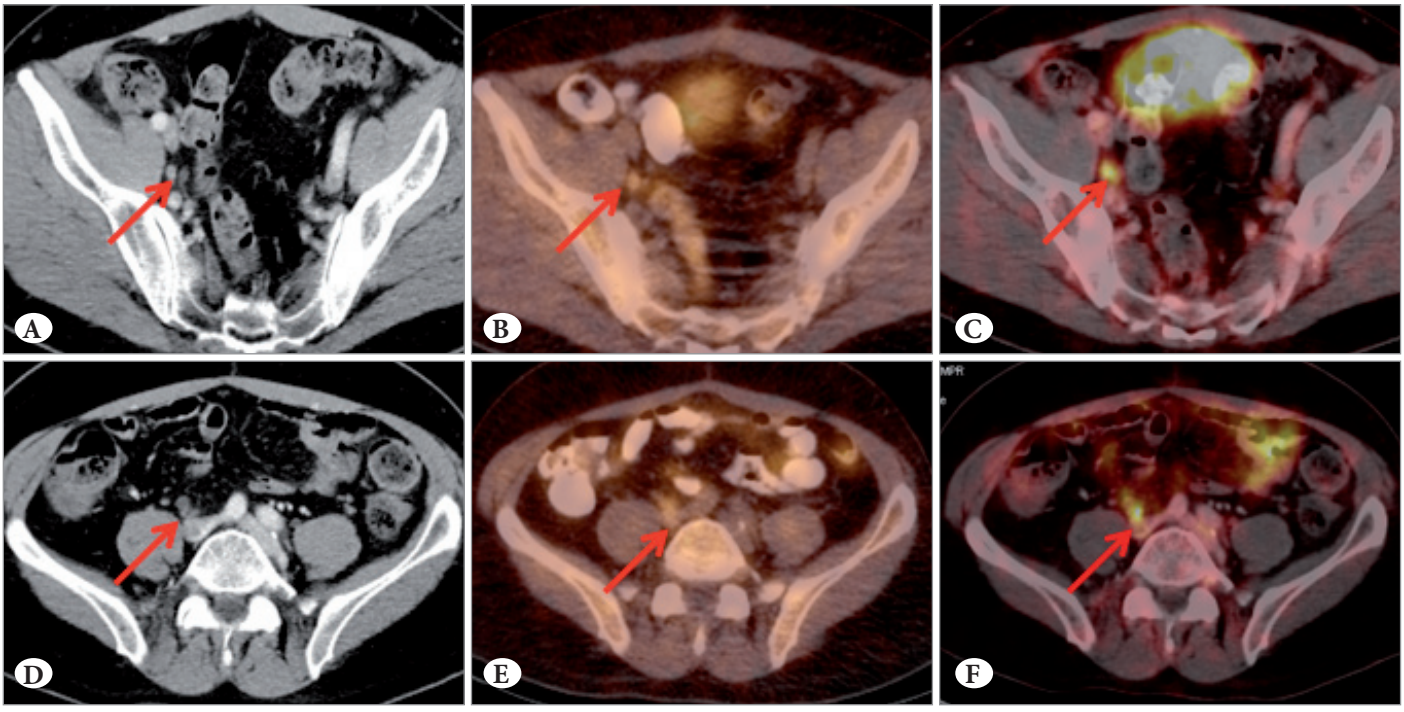

Figure 2: 66 year old patient after radical prostatectomy and antihormonal treatment with a PSA of 0.77ng/ml. Contrast enhanced CT **(A, D)** demonstrates two non enlarged lymph nodes in the pelvis. While 11C-Choline PET/CT (B,D, fusion images) shows only a faint positivity of both lymph nodes hampering diagnostic confidence, high PSMA expression in ^{68}Ga-PSMA ligand PET/CT is highly indicative for lymph node metastases **(C,F, fusion images).**

PSA levels of >=2, 1 to <2, 0.5 to <1, and 0.2 to 0.5ng/ml (5). Pathological findings included local recurrence, lymph node metastases, bone metastases and other localizations (e.g. lung, liver). Moreover, detection efficacy was rising in higher Gleason Scores (GS). Indeed, a positive correlation between higher GS and PSMA expression has been demonstrated in pre-clinical studies (10). Interestingly, data also showed a trend towards a higher detection rate in patients with antihormonal treatment, consistent with other reports stating a higher PSMA expression of PC tumor cells in the setting of antihormonal treatment (11).

Afshar-Oromieh et al. performed a retrospective analysis in 319 patients undergoing ^{68}Ga-PSMA ligand PET/CT for diagnosis of recurrent prostate cancer and observed in overall lower positive rates, probably due to a more heterogeneous study group including patients after radical prostatectomy and after primary radiation therapy (85.9%, 71.8%, 58.3%,50%, 47.1% for PSA-levels of 2.1-5, 1.1<2, 0.51<1, 0.21<0.5, <0.2ng/ml) (4).

PRIMARY PROSTATE CANCER

An early and correct diagnosis together with accurate staging is necessary for planning the most appropriate treatment strategy in primary PC. If PC has been histologically verified by biopsy, an accurate local and whole body staging for evaluation of local invasion and distant metastases is necessary. For local staging, MRI is routinely used in many centers, demonstrating good diagnostic performance. Hricak et al for example reported a sensitivity/ specificity of 80%/ 99% respectively for the detection of seminal vesicle invasion (12). However, the detection rate of lymph node metastases is in general low in conventional imaging modalities, since metastases are often localized in non enlarged lymph nodes, making the classical size measurements ineffective in this disease (13). This problem is especially evident in high risk patients, where the probability of lymph node metastases is increased. In this context, choline based PET/CT has been proposed for lymph node staging. However, although different studies reported high specificity rates reaching 96% in the detection of metastatic lymph nodes, sensitivity rates were significantly lower. A recent metaanalysis on initial lymph node staging in prostate cancer by Evangelista et al. revealed a pooled sensitivity of 49.2% and a pooled specificity of 95% (14).

According to first results, PSMA-ligand PET/CT seems to significantly enhance detection rate of lymph node metastases in the primary setting. Maurer et al. examined 130 patients with intermediate to high risk PC using the aforementioned modality and calculated sensitivity and specificity rates of 66% and 99% respectively on a patient-based analysis (15).

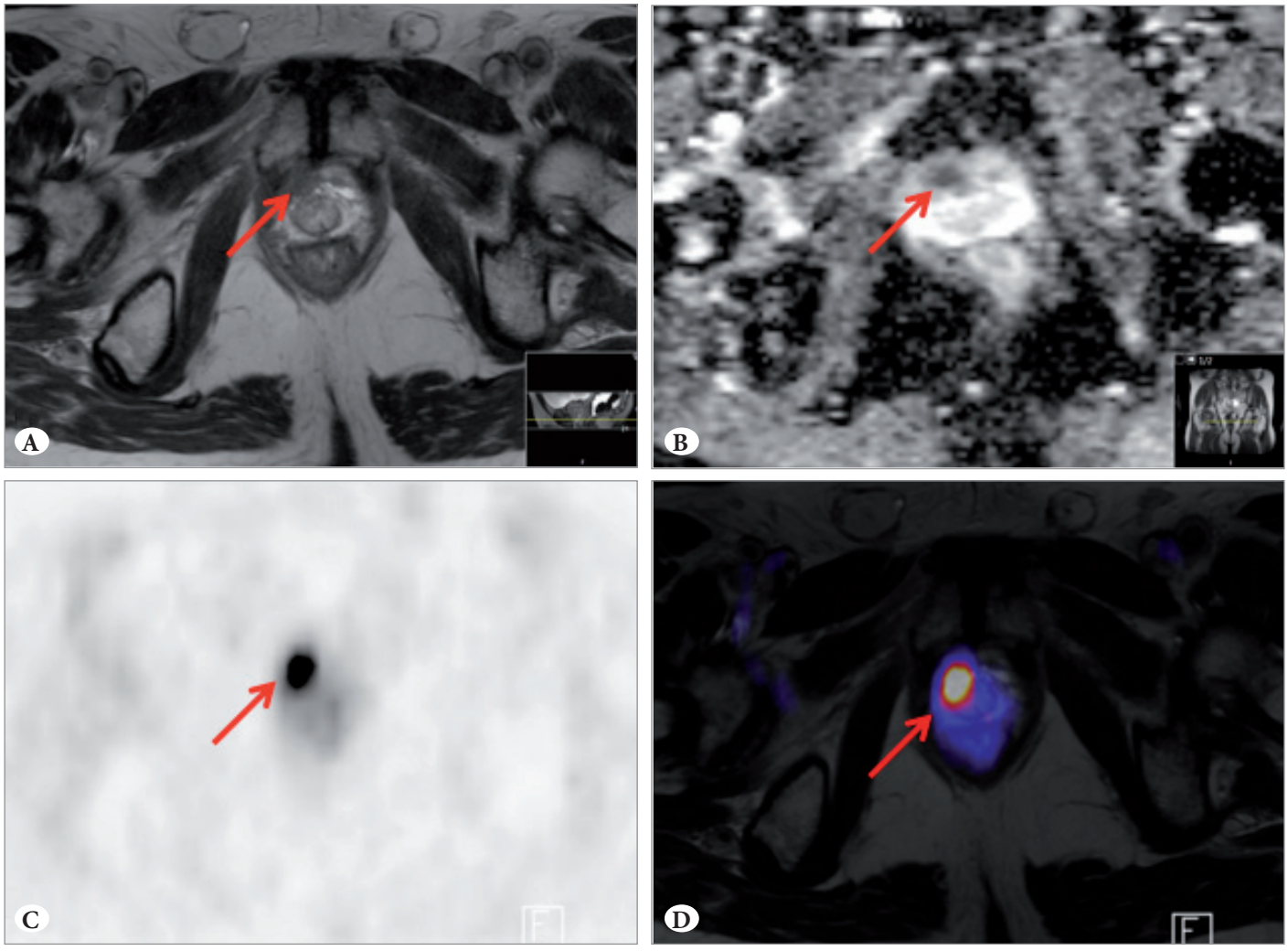

Figure 3: 68 year old patient with continuous PSA increase up to 10ng/ml. Performed transrectal biopsy was negative. After negative biopsy, patient underwent ^{68}Ga-PSMA ligand PET/MRI. MRI (T2w) shows suspicious hypointense lesion in the right apex of the prostate with diffusion restricted correlate in the diffusion weighted imaging (DWI). PET images demonstrate intensive PSMA expression of this lesion (C: PET; D: Fusion image). The images were used for guiding a re-biopsy. Histology confirmed invasive prostate cancer.

A second scenario inlcudes patients with suspicion of prostate cancer due to progressive/elevated PSA-levels, however transrectal biopsies failed to verify the primary lesion. In this case the primary aim of the imaging modality should be the detection and correct localization of prostate cancer in order to guide a re-biopsy. MR imaging may be used for lesion detection, exhibiting a good diagnostic performance in this setting. The troublemakers however include small lesions and lesions within a benign prostate hyperplasia with corresponding inhomogeneous parenchyma, hampering diagnosis.

Also, the use of choline based PET/CT failed to significantly contribute to better detection rates. Farsad et al for example evaluated 36 patients with biopsy proven prostate cancer and calculated a sensitivity of 66% for the correct localization of the primary tumor (16). Scher et al conducted a study on 58 patients with suspicion of prostate cancer and found a sensitivity/specificity of 86 and 62% respectively (17). Besides the limited diagnostic accuracy, the differentiation between benign prostatic hyperplasia, prostatitis or high grade intraepithelial neoplasia was not always possible in primary staging of prostate cancer using choline based PET/CT. Moreover, other studies showed a significant association between the detection rate and the size as well as configuration of the primary lesion (18,19). The detection of small and partly "rind-like" carcinomas was often not possible.

^{68}Ga-PSMA ligand PET may be a highly interesting modality in guiding prostate biopsies. Although larger prospective studies are not available yet, first results are promising (Figure 3). Maurer

et al. for example examined 130 patients with primary prostate cancer using ^{68}Ga-PSMA ligand PET/CT and found moderate to high uptake indicative for the primary focus in 92% (15). His results are concordant with our clinical experience on this tracer. Interestingly, around 8% of the primary prostate cancer showed no or only faint tracer uptake. The detection of this subgroup of PSMA negative lesions remains a challenge.

Recently hybrid PET/MR imaging became available, combining functional MR-imaging, high tissue contrast and molecular information. This new imaging modality has the potential to further increase detection rate with special regard to the aforementioned PSMA-PET negative tumors. In particular, the advantage of the MR component is the ability of multiparametric MR-imaging (mpMR) including diffusion weighted imaging, spectroscopy and perfusion sequences (Figure 3). First results in this setting are promising: Rowe at el for example examined 13 patients using local MRI and PSMA ligand PET and demonstrated highest sensitivity of 92% for MR imaging, while specificity was highest for PSMA ligand PET (96%). Consequently, their combination resulted in an excellent diagnostic performance (20). Potential use of ^{68}Ga-PSMA PET/MR employs image-fusion targeted biopsy in patients with prior negative biopsy but persistently elevated PSA-values.

Further advantages of ^{68}Ga PSMA ligand PET/MR are evident, when lesions are localized adjacent to the bladder. Since the bladder shows high signal due to physiological excretion of the tracer, ^{68}Ga PSMA ligand PET imaging can be hampered due to spill-over artefacts. Once again, multiparametric imaging offers the possibility to detect the tumor in other sequences. Certainly, more studies are necessary in the future to further delineate the diagnostic performance of PSMA ligand PET/CT and PET/MRI.

TAKE HOME MESSAGE

^{68}Ga-PSMA ligand PET/CT demonstrates higher diagnostic performance in staging of primary prostate cancer and re-staging after biochemical recurrence (in particular in patients with low PSA levels) compared to other imaging modalities including choline based PET/CT. Recently hybrid ^{68}Ga-PSMA ligand PET/MR became available, combining functional imaging with high tissue contrast. This new imaging modality has the potential to further increase detection rate especially by combing molecular information from PET with functional information from mpMR and might have a potential role for biopsy targeting.

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