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Platinum Priority – Case Series of the Month – Editor's Choice

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Radical Prostatectomy Without Prior Biopsy Following Multiparametric Magnetic Resonance Imaging and Prostate-specific Membrane Antigen Positron Emission Tomography

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Abstract

A biopsy-free diagnostic pathway in prostate cancer (PC) is limited by the diagnostic accuracy of multiparametric magnetic resonance imaging (mpMRI). The improved accuracy of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) raises the question whether this imaging modality can complement mpMRI to safely avoid biopsy prior to radical prostatectomy (RP). In this case series, we report the feasibility of primary RP without prior biopsy based on a high suspicion of significant PC in both mpMRI (Prostate Imaging Reporting and Data System [PI-RADS] score $\geq$4) and PSMA-PET (PET score $\geq$4 on a five-point Likert scale and maximum standardized uptake value $\geq$4.0) in 25 patients. All patients showed International Society of Urological Pathology (ISUP) grade $\geq$2 PC in postoperative histopathology. We report patient- and lesion-based comparisons with histopathology of the prostate specimen. Results of our case series may trigger the discussion about RP without prior biopsy as a possible option in well-selected patients. Our case series is limited by retrospective design and small sample size. We want to emphasize clearly that this practice should not be regarded as a standard procedure at the moment. Future studies with larger cohorts only inside a prospective, ethically approved study design are necessary to confirm these results.

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1. Case series

Most recently, the prospective PRIMARY trial (ANZCTRN12618001640291) showed that the combination of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) and multiparametric magnetic resonance imaging (mpMRI) was superior to mpMRI alone in diagnostic performance for detecting significant prostate cancer (sPC) [1]. Although the primary objective was to determine the proportion of men with positive mpMRI (Prostate Imaging Reporting and Data System [PI-RADS] score ≥3) but negative PSMA-PET, who can safely avoid biopsy due to PET-based exclusion of sPC, they also found that all men with an maximum standardized uptake value (SUVmax) of ≥12 in ^{68}Ga-PSMA11 PET had sPC on biopsy, independent of mpMRI results, and in case of a PI-RADS ≥4 lesion, an SUVmax of ≥9 had 100% specificity and positive predictive value (PPV) in sPC detection. The authors suggested that men with suspicious PSMA-PET and mpMRI findings could potentially avoid biopsy and undergo definitive treatment.

Supported by these recent findings, we present a retrospective case series of 25 consecutive prostate cancer (PC) patients who were treated with radical prostatectomy (RP) after molecular imaging-based diagnosis (mpMRI and PSMA-PET) without prior prostate biopsy between July 2015 and January 2021 (Fig. 1). The results of the current case series were not part of an initially planned study project. The first patient was operated in July 2015, and patients were retrospectively identified in January 2021. Initially, in all patients, the suspicion of PC was raised by their treating urologist (elevated prostate-specific antigen [PSA] and/or abnormal digital rectal examination [DRE]) in the outpatient sector. Subsequent mpMRI exhibited suspicious lesions (PI-RADS ≥4) in all patients. Diagnostic evaluation of all patients was complemented by PSMA-PET. Details of radiosynthesis and administration procedures have been described previously [2,3]. Results of the PSMA-PET were highly suspicious for PC (PET score of ≥4 on a five-point Likert scale). Both mpMRI and PSMA-PET were negative for distant metastases. After completion of both mpMRI and PSMA-PET, patients had been informed about their high risk of PC and counseled by their treating urologist in the outpatient sector. At referral to our clinic, all patients included in this case series expressed the explicit wish to avoid a biopsy and primarily undergo RP. In all cases, the surgeon himself discussed and explained in detail the usual diagnostic pathway including the necessity to perform a prostate biopsy for histopathologic PC confirmation and, in case of a subsequent PC diagnosis, all possible treatment types including active surveillance, RP, radiotherapy, and focal therapies. Especially, the risk of finding "no cancer" at the RP specimen was discussed and explained to the patient. Nonetheless, every patient wished explicitly an RP without prior biopsy despite the recommendation

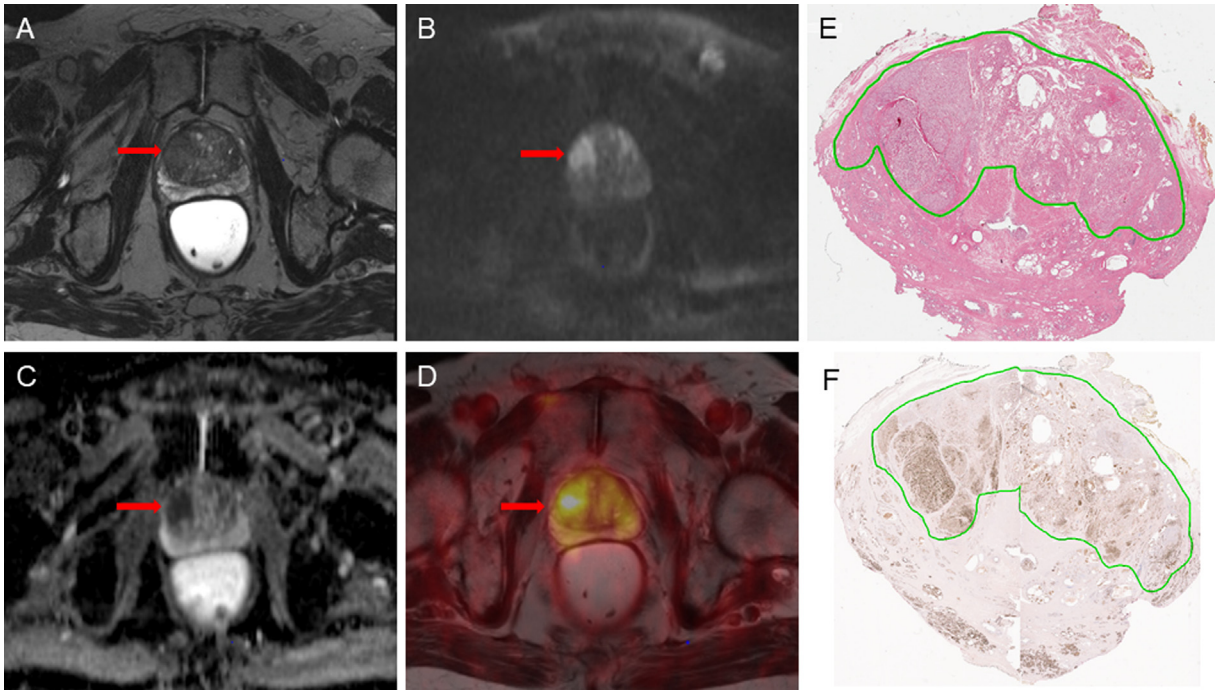

Fig. 1 – Example of a true-positive PSMA-PET/mpMRI lesion in a 79-yr-old patient (patient 10) presenting with a PSA level of 11.4 ng/ml and a normal DRE undergoing primary radical prostatectomy without prior biopsy. (A) T2-weighted MRI (red arrow) shows a noncircumscribed, homogeneous, moderate hypointense area with a maximum diameter of 23 mm in the right transition zone of the midprostate with corresponding diffusion restriction in both (B) high *b* values (red arrow) and (C) ADC map (red arrow) resulting in a PI-RADS 5 lesion. (D) Corresponding PSMA-PET shows a high focal PSMA ligand uptake (SUVmax of 8.0) in the right midprostate (red arrow) highly suspicious for prostate cancer, resulting in a PET score of 5. (E) Hematoxylin and eosin gross section histopathology as well as (F) PSMA immunohistochemistry showed a corresponding ISUP grade 2 tumor focus. ADC = apparent diffusion coefficient; DRE = digital rectal examination; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PET = positron emission tomography; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SUVmax = maximum standardized uptake value.

to perform a prior prostate biopsy according to current guidelines [4]. No patient who declined prior biopsy was excluded.

The aim of this case series is to report our experience using combined mpMRI and PSMA-PET as primary diagnostic tools to detect and subsequently treat sPC locally without additional biopsy. Results illustrate the need for a prospective evaluation within an ethically approved clinical trial, and have the aim to promote a debate on this approach and about our demands for biopsies in the future. Furthermore, we report patient- and lesion-based comparisons of mpMRI and PSMA-PET with gross-section histopathology. Details on surgery, imaging analysis, and histologic examination are presented in the Supplementary material.

A total of 25 patients were retrospectively identified and enrolled in this case series. Patient characteristics, imaging results, and oncologic outcomes are depicted in Table 1. The retrospective analysis was approved by our ethics committee. Of 25 patients, 14 had an initial suspicion of PC based on elevated levels of PSA and abnormal DRE, nine presented with an elevated PSA level, and two had only an abnormal DRE. The median PSA level at diagnosis was 7.3 ng/ml (interquartile range [IQR]: 3.9–13.0) and median age was 70.9 yr (IQR: 68.1–74.3). All patients had at least one suspicious lesion in mpMRI with a PI-RADS score of ≥4. PSMA-PET showed at least one highly suspicious lesion with a PET score of ≥4 with an SUVmax of ≥4.0 (median SUVmax 9.5 [IQR: 6.4–19.3]) in all patients. Both mpMRI and PSMA-PET concordantly suspected locally confined disease in 15 patients (60%), extracapsular extension (ECE) in six patients (24%), and seminal vesicle invasion in four patients (16%). One patient had a suspicion of lymph node invasion (cN1). Preoperative mpMRI and PSMA-PET showed no distant metastases.

Histopathologic evaluation of the RP specimens showed sPC, defined as International Society of Urological Pathology (ISUP) grade >1, in all patients. On a per-patient basis, sensitivity and PPV for both mpMRI and PSMA-PET in identifying sPC were 100% (25/25) and 100% (25/25), respectively. Eight out of 25 patients had ISUP grade 2, 15 patients had ISUP grade 3, and two patients had ISUP grade 5. Four patients had seminal vesicle invasion (pT3b), six patients had ECE (pT3a), and the remaining 15 patients had organ-confined disease (pT2). Lymph node invasion was found in four patients in the final pathology. PSMA-PET correctly identified one of these patients preoperatively. Both mpMRI and PSMA-PET correctly identified seminal vesicle invasion in all four (100%) patients (pT3b), ECE in four of the six (67%) patients (pT3a), and locally confined disease in 13 (52%) patients (pT2), while two (8.0%) patients suspicious for ECE in mpMRI and PSMA-PET showed locally confined disease and two (8.0%) patients suspicious for locally confined disease showed ECE on histopathology.

A lesion-based analysis showed that imaging (mpMRI and PSMA-PET) identified 52 lesions. Detailed information on localization and comparison between the imaging modalities and histopathology are depicted in Supplementary Table 1. Key results, that is, sensitivity and PPV of lesions found in mpMRI (PI-RADS ≥3) and PSMA-PET (PET score ≥3) to detect sPC foci, were high with values of 88% (95% confidence interval [CI] 78–98) and 90% (95% CI 81–99), respectively. When used in combination (PI-RADS ≥3/PET score ≥3; positive if either one of the imaging modalities is positive), sensitivity increased (98% [95% CI 93–100]) and PPV slightly decreased (87% [95% CI 77–97]; Supplementary Table 3). When using a more stringent definition of suspicious lesions (PI-RADS ≥4, PET score ≥4, as well as the combination PI-RADS ≥4/PET score ≥4), sensitivity and PPV decreased slightly (Supplementary Table 3). There were no suspicious lesions in both mpMRI and PSMA-PET (PI-RADS ≥3 and PET score ≥3) with negative histopathology (Supplementary Table 1). Further lesion-based analysis is presented in the Supplementary material.

The median SUVmax in PSMA-PET of all lesions identified in imaging was 6.4 (IQR: 4.5–10.2). SUVmax increased

Table 1 – Patient characteristics of the analyzed cohort (*n* = 25)

Age at surgery (yr), median (IQR)	70.9 (68.1–74.3)
Year of surgery, *n* (%)	
2015	1 (4.0)
2017	2 (8.0)
2018	10 (40)
2019	2 (8.0)
2020	9 (36)
2021	1 (4.0)
Preoperative characteristics	
PSA at diagnosis (ng/ml), median (IQR)	7.3 (3.9–13.0)
Suspect DRE, *n* (%)	16 (64)
Right lobe	8 (32)
Left lobe	6 (24)
Right and left lobes	2 (8.0)
Clinical tumor stage, *n* (%)	
cT1c	9 (36)
cT2	16 (64)
Extent of disease in imaging, *n* (%)	
Locally confined disease	15 (60)
Extracapsular extension	6 (24)
Seminal vesicle invasion	4 (16)
Lesions in mpMRI, PI-RADS v2, *n* (%)	
3	3 (7.5)
4	23 (58)
5	14 (35)
Lesions in PSMA-PET, *n* (%)	
3	2 (5.0)
4	10 (25)
5	28 (70)
Patient-based SUVmax, median (IQR)	9.5 (6.4–19.3)
SUVmax (all lesions), median (IQR)	6.4 (4.5–10.2)
Postoperative characteristics	
Pathological tumor stage, *n* (%)	
pT2a	1 (4.0)
pT2c	14 (56)
pT3a	6 (24)
pT3b	4 (16)
Pathological node stage, *n* (%)	
pN0	21 (84)
pN1	4 (16)
Pathological ISUP grade, *n* (%)	
2	8 (32)
3	15 (60)
4	0
5	2 (8.0)
Surgical margin, *n* (%)	
R0	20 (80)
R1	5 (20)

DRE = digital rectal examination; IQR = interquartile range; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SUVmax = maximum standardized uptake value.

with increasing ISUP grade of each lesion (Pearson's correlation coefficient $r = 0.82$; $p = 0.048$), that is, lesions containing no PC had a median SUVmax of 3.6 ($n = 9$, IQR: 0–10.2), ISUP grade 1 had a median SUVmax of 5.3 ($n = 2$), ISUP grade 2 had a median SUVmax of 8.0 ($n = 17$, IQR: 5.6–11.5), ISUP grade 3 had a median SUVmax of 6.2 ($n = 20$, IQR: 4.4–10.3), ISUP grade 4 had a median SUVmax of 17.4 ($n = 2$), and ISUP grade 5 had a median SUVmax of 44.6 ($n = 2$).

An additional segment-based analysis is presented in the Supplementary material.

2. Discussion

There is increasing interest in the use of novel imaging to detect sPC. Among imaging modalities, mpMRI has been demonstrated to have adequate diagnostic accuracy in the detection of sPC. However, besides from missing about 10% of significant cancers, it is limited by its low PPV of 34–68% [5]. To address this gap, molecular imaging approaches, such as the use of PSMA-PET, have been proposed. To date, PSMA-PET has been used mainly for staging high-risk PC after biopsy or for staging biochemical recurrence after local treatment [6,7].

To evaluate the accuracy of PSMA-PET in the localization of primary PC, Eiber et al [3] compared the diagnostic performance of ^{68}Ga-PSMA11 PET/magnetic resonance imaging (MRI) with that of mpMRI and PET alone, with histopathology of RP specimens as reference. Men with biopsy-proven PC were scheduled for simultaneous PSMA-PET/MRI, which improved diagnostic accuracy for PC (ie, sensitivity rates of mpMRI, PET imaging, and PSMA-PET were 66%, 92%, and 98%, respectively) and outperformed mpMRI (area under the curve [AUC]: 0.88 vs 0.73; $p < 0.001$) and PET imaging alone (AUC: 0.88 vs 0.83; $p = 0.002$) for localization of PC.

To date, the current diagnostic pathway recommends prostate biopsy in men suspected of having PC by elevated PSA and/or abnormal DRE. If an additional mpMRI examination reveals suspicious or equivocal lesions, a systematic + targeted biopsy is performed [3]. However, prostate biopsy is associated with potential morbidity, and many men therefore wish to avoid this invasive intervention. Recently, a large national population-based study from the UK found infectious complications such as sepsis (<1.5%), urinary retention (<2%), or hematuria requiring catheterization (<1%) to be associated with both transperineal and transrectal biopsy [7]. Whereas transperineal biopsy had a lower risk of readmission for sepsis (1.0% vs 1.4%), it had a higher risk of readmission for urinary retention than for transperineal biopsy (1.9% vs 1.0%) [8]. This raises the question whether there is the possibility in selected men to avoid unnecessary biopsies before local treatment with RP in cases of highly suspicious imaging results.

We described for the first time a possible biopsy-free diagnostic pathway for PC in selected men with a high suspicion of significant malignancy in both mpMRI and PSMA-PET. Patients suspected of having PC by elevated PSA and/or an abnormal DRE, and suspicious lesions in the mpMRI (PI-RADS $\geq$4) were scheduled for PSMA-PET. In case of a high suspicion of PC (PET score $\geq$4) and refusal of a biopsy by the patient, surgical treatment was offered after detailed discussion. However, if radiotherapy was the treatment option preferred by the patient, prostate biopsy should be performed, since the therapy regime (dose and additive androgen-deprivation therapy) has to be determined depending on tumor characteristics. Owing to the inability of current imaging techniques to confidently discriminate between patients eligible for active surveillance, focal therapies, or definitive treatment, this practice is limited to men who decline therapies other than prostate removal. This applies certainly not to the majority of PC patients.

We have to emphasize that this practice is not the current standard at our institution and only a tiny minority (1%) underwent RP without prior biopsy in the same time span. All patients presented at our department with the pre-existing and explicit wish to undergo RP without prior biopsy based on existing imaging results including PSMA-PET and mpMRI. Subsequently, these patients were counseled about the risk of a false-positive imaging result and the necessity to perform a prostate biopsy. Moreover, different treatment options in case of a PC diagnosis including active surveillance, radiotherapy, RP, and focal therapies were discussed extensively. Nonetheless, all the patients were well informed about the various risks and treatment options, and still elected to undergo RP without prior biopsy.

Certainly, there remains a risk of false-positive results leading to unnecessary surgery. Experienced nuclear medicine physicians and radiologists are essential to minimize this risk, and a prospectively validated SUVmax cutoff could help objectify the evaluation of lesions identified by PSMA-PET. The association of increasing SUVmax with higher ISUP grades described in our series is in line with the findings of a previous study [9]. Moreover, according to Scheltema et al [10], an SUVmax of 3.95 in ^{68}Ga-PSMA11 PET resulted in 94% sensitivity and 100% specificity in detecting sPC in a sample of 56 retrospectively assessed patients. The recently completed PRIMARY clinical trial aimed to provide prospective data on the diagnostic ability of PSMA-PET/computed tomography in addition to mpMRI in patients with a clinical suspicion of PC. Patients with an SUVmax of $\geq$12 in ^{68}Ga-PSMA11 PET had sPC on biopsy irrespective of mpMRI findings and 100% specificity of finding sPC if PI-RADS $\geq$4 and an SUVmax of $\geq$9 were found.

Results of the current retrospective case series were promising and showed that, in patients with a high suspicion of PC in mpMRI and PSMA-PET, avoidance of prostate biopsy prior to RP might represent a valid option in well-counseled, selected patients. Our findings were substantiated by the authors of the recently published PRIMARY trial suggesting "that men with intense uptake on PSMA and positive MRI could potentially avoid confirmatory biopsy and proceed directly to definitive therapy" [4]. Several benefits are arguable: no further complications after biopsies, reduced time from diagnosis to treatment, lower psychological burden, and anxiety in patients (ie, anxiety about biopsy-associated pain/complications and tumor seeding), and lower health economic costs (cost of additional PSMA-PET vs cost of unnecessary biopsies). However, this practice should not be regarded as a standard procedure

at the moment, and results illustrate the need for a prospective evaluation within an ethically approved clinical trial to confirm these results.

Conflicts of interest: Valentin H. Meissner and Matthias M. Heck certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript, are the following: Matthias Eiber reports previous consulting activities for Blue Earth Diagnostics, Progenics Pharmaceuticals, Keosys, Novartis, Telix Pharma, Amgen, and Point Biopharma, and a patent application for rhPSMA, outside of the submitted work. The remaining authors have nothing to disclose.

Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2021.11.019.

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