DOI: *10.4081/aiua.2024.12358*

ORIGINAL PAPER

Negative biopsy histology in men with PI-RADS score 5: Is it useful PSMA PET/CT evaluation?

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Summary *Introduction: To evaluate the accuracy of PSMA PET/CT in men with mpMRI PI-RADS score 5 negative biopsy histology.*
Materials and methods: From January 2011 to January 2023, 180 men with PI-RADS score 5 underwent systematic plus mpMRI/TRUS biopsy; 25/180 (13.9%) patients had absence of cancer and six months from biopsy were submitted to: digital rectal examination, PSA and PSA density exams, mpMRI and 68GaPSMA PET/CT evaluation (standardized uptake value "SUVmax" was reported).
Results: In 24/25 (96%) patients PSA and PSA density significantly decreased, moreover, the PI-RADS score was downgraded resulting < 3; in addition, median SUVmax was 7.5. Only 1/25 (4%) man had an increased PSA value (from 10.5 to 31 ng/ml) with a confirmed PI-RADS score 5, SUVmax of 32 and repeated prostate biopsy demonstrating a Gleason score 9/ISUP Grade Group 5 PCa.
Conclusions: The strict follow up of men with PI-RADS score 5 and negative histology reduce the risk of missing csPCa especially if PSMA PET/CT evaluation is in agreement with downgrading of mpMRI (PI-RADS score < 3).

KEY WORDS: Prostate cancer; PSMA PET/CT; mpMRI; PI-RADS score 5.

Submitted 5 February 2024; Accepted 18 february 2024

INTRODUCTION

Multiparametric magnetic image resonance (mpMRI) is recommended in men with suspicion *prostate cancer* (PCa) (1), but, still today, systematic prostate biopsies should be always combined with mpMRI/TRUS fusion biopsy due to the false negative rate (2-4) of mpMRI (15-20% of the cases) (5). The aggressiveness of clinically significant (csPCa) is correlated with the mpMRI *Prostate Imaging Reporting and Data System* (PI-RADS) scores; the detection rate for csPCa of suspicious mpMRI lesions performing targeted biopsy ranges from 65.3 to 83.8% (6) and in the presence of a suspicious area with PI-RADS score 5 ranges from 59.2 to 86% of the cases (7, 8). Therefore, a negative biopsy in men with PI-RADS score 5 need a thorough clinical follow up to avoid missing csPCa diagnosis.
In our study, the follow up of men with negative biopsy histology of PI-RADS score 5 lesions has been reported including *prostate-specific membrane antigen* (PSMA) *positron-emission tomography* (PET/CT) evaluation.

MATERIALS AND METHODS

From January 2011 to January 2023, 2,405 men (median age: 64 years; range: 41-86 years) underwent extended (median 20 cores; range: 16-22) or saturation (SPBx: median 26 cores; range: 22-30) transperineal prostate biopsy for the suspicion of cancer (9-11). Informed consents were obtained from all participants included in the study following institutional ethical committee approval. Before biopsy the patients underwent pelvic mpMRI using a 1.5 and 3.0 Tesla scanner (ACHIEVA 3T; Philips Healthcare Best, the Netherlands) equipped with surface 16-channel phased-array coil; multi-planar turbo spin-echo T2-weighted, axial diffusion weighted imaging (high b-value - 2000 s/mm^2), and axial dynamic contrast enhanced MRI were performed for each patient (12). The systematic biopsy was performed transperineally and mpMRI lesions with PI-RADS score > 3 (1.380/2.405 equal to 57.4% of the cases) were submitted to targeted biopsy (TPBx: four cores performing a transperineal cognitive approach, anterior zone of the gland) or a fusion guided-biopsy (*Hitachi 70 Arietta ecograph, Chiba, Japan*) (13-15). All the patients were sedated and received a single intraoperative dose of antibiotic prophylaxis. The detection rate for csPCa has been evaluated (16); moreover, the Clavien-Dindo grading system for the classification of biopsy complications was used (17).
All the 180 men with PI-RADS score 5 had not dysuria, irritative urinary symptoms or stranguria. In 155/180 (86.1%) patients a stage T1c PCa was diagnosed, and 145/155 (93.5%) of them (Table 1) were classified as csPCa (International Society of Urologic Pathology "ISUP Grade Group "GG" > 2); in detail, 85/145 (58.6%), 30/145 (20.7%) and 30/145 (20.7%) csPCa were diagnosed in the peripheric, anterior or both zones of the prostate, respectively. The median total PSA was 8.9 ng/ml (range: 2.7-95 ng/ml); moreover, quantitative biopsy histology, PSA density (PSAD), PSA free/total are listed in Table 1. SPBx diagnosed 5/155 (3.2%) csPCa and 8/155 (5.2%) indolent PCa located outside the PI-RADS 5 lesions.
In the remaining 25/180 (13.9%) patients with absence of cancer: 1/25 (4%) had a specific granulomatous prostatitis (*Mycobacterium Tubercolosis*), 8/25 (32%) an aspecific granulomatous prostatitis, and 16/25 (64%) a normal parenchyma. None of the patients had significant complications (only Clavien-Dindo grade I) following prostate

biopsy, requiring hospital admission. The men with granulomatous prostatitis underwent specific antibiotic therapy followed by laboratory showing negative culture of urine and semen; moreover, the urine and sperm search for Mycobacterium Tuberculosis test including the semen *polymerase chain reaction* (PCR) (TB-PCR) were negative. The clinical follow up of patients without proven diagnosis of PCa including PSMA PET/CT evaluation has been reported.

Results

All the 25 men with PI-RADS score 5 and negative histology six months from biopsy underwent: digital rectal examination (DRE), PSA, PSAD, mpMRI and PSMA PET/CT evaluation (Table 2). PET/CT imaging was performed using a CT-integrated PET scanner (Biograph 6; Siemens, Knoxville, TN, USA); 68Ga-PSMA-11 was given to patients via an intravenous bolus; images were processed to obtain PET, CT, and PET-CT fusion sections in the axial, coronal, and sagittal planes with a thickness of approximately 0.5 ~ cm. The location of focal uptake on 68Ga-PSMA PET/TC, three-dimensional size, and standardised uptake value (SUVmax) values were reported on a per-lesion basis with a sextant scheme (18, 19). Twenty-four (96%) patients did not underwent repeated prostate biopsy because PSA significantly decreased, moreover, the initial PI-RADS score 5 was significantly downgraded by a repeated mpMRI to PI-RADS score < 3 (Table 2); in addition, median SUVmax was 7.5 (range: 4-32). Only 1/25 (4%) man, who was submitted 3 years before to transurethral prostate resection for benign prostate enlargement, had an increased PSA value (from 10.5 to 31 ng/ml) with a confirmed PI-RADS score 5 and intraprostatic SUVmax of 32 and suspicious bone metastases; TPBx and systematic biopsy demonstrated the presence of a Gleason score 9/ISUP GG5 PCa (6/24 positive cores) located in the anterior zone of the prostate that extended outside the gland.

Table 1.
Clinical parameters in 155 men with prostate cancer and PI-RADS score 5 submitted to systematic plus fusion targeted biopsy (TPBx).

Quantitative biopsy histology	PI-RADS score 5
Number of patients (pts) initial biopsy repeat biopsy	155 pts 70/155 (45%) 85/155 (55%)
csPCa	145/180 (86.1%)
Median mpMRI index lesion diameter (range)	23 millimeter (16-31)
Detection of csPCa (ISUP GG > 2) Systematic prostate biopsy TPBx	145 pts 137 (94.5%) 138 (95.2%)
Median number of positive cores TPBx (range) Systematic biopsy (range)	13 3 (2-4) 10 (7-20)
Median GPC TPBx (range) Systematic biopsy (range)	75% 80% (60-100%) 75% (50-100%)
PSA density (range)	0.21 (0.16-0.26)
PSA free/total (range)	12% (7-32%)
Median prostate weight (grams)	50 (20-130 grams)

ISUP: International Society of Urologic Pathology Grade Groups; mpMRI: Multiparametric magnetic resonance image; GPC: Greatest percentage of cancer; PI-RADS: Prostate Imaging Reporting and Data System.

Table 2.
Clinical follow up (six months from prostate biopsy) in 25 men with initial PI-RADS score 5 and negative histology for prostate cancer.

Biopsy histology	Aspecific granulomatous prostatitis	*Specific granulomatous prostatitis	Normal parenchyma	csPCa ISUPGG5
Number of patients initial biopsy repeat biopsy	8 cases 6 (75%) 2 (25%)	1 case 1 (100%) -	15 cases 7 (46.6%) 8 (63.4%)	1 case 1 (100%)
Median PSA (range)	6.2 ng/ml (1.5-10.8)	3.2 ng/ml	4.7 ng/ml (3.1-12.7)	31 ng/ml
PSA density (range)	0.12 (0.10-0.18)	0.13	0.15 (0.12-0.16)	0.25
DRE	negative	negative	negative	negative
PI-RADS score < 2	4 (50%)	-	7 (46.5%)	-
PI-RADS score 3	4 (50%)	1	8 (63.4%)	-
PI-RADS score 4	-	-	-	-
PI-RADS score 5	-	-	-	1 (100%)
68GaPSMA PET/CT median SUVmax	7 (range: 4-10)	8 (range 5-11)	7 (4-11)	32

*DRE: Digital rectal examination; PI-RADS: Prostate Imaging Reporting and Data System; DRE: Digital rectal evaluation; *Mycobacterium Tubercolosis; GaPSMA PET/CT: Gallium prostate-specific membrane antigen positron-emission tomography; SUVmax: Standardized uptake value; ISUP GG: International Society of Urologic Pathology Grade Groups.*

Discussion

Multiparametric MRI has improved the cost-effectiveness of prostate biopsy by reducing the risk of overdiagnosis and number of unnecessary procedures (20, 21). Although mpMRI is strongly recommended in men candidate to prostate biopsy or enrolled in active surveillance protocols (2, 22, 23), extended or SPBx should be always combined with mpMRI/TRUS fusion biopsy because the false negative rate of mpMRI (24) and the variable accuracy of mpMRI/TRUS fusion biopsy platforms (25). The correlation of the PI-RADS score to the diagnosis of aggressiveness cancer has been well established; *Westphalen et al.* (7) and *Otti et al.* (8) showed in men with PI-RADS score 5 a detection rate for csPCa equal to 59.2 and 86%, respectively; we previously reported a detection rate of csPCa in the 86.7% of 105 men with PI-RADS score 5 who underwent repeated prostate biopsy (26). The systematic prostate biopsy detects only 3.4% of csPCa in case of negative MRI/TRUS targeted biopsy of PI-RAS score 5 lesions (27). Therefore, the presence of a negative histology of a PI-RADS score 5 lesion needs an accurate follow up to avoid the risk of missing a high grade csPCa; the use of PSA, PSAD, risk calculator, urinary genetic tests, and the repetition of mpMRI allow to reduce the risk of harboring a csPCa. In this respect, a second opinion regarding initial mpMRI (28) and histology evaluation (29) should be performed to decrease the risk of false negative results. Recently, PSMA-PET/CT has been proposed for the diagnosis of primary intraprostatic cancer (18, 19, 30, 31); the

presence of focal uptake on PSMA-PET/CT (SUVmax) and the maximal dimensions of PET-avid lesions have been correlated with the presence of csPCa (32). Although there is a range of proposed cut-offs to detect csPCa from SUVmax (33-35), the concordance between preoperative PSMA PET/TC evaluation and definitive prostate specimen ranges from 81.2 (36) to 96% (37).

Many anatomic feature, benign conditions and technical pitfalls could mimic prostate cancer on mpMRI (38,39); the analysis of mpMRI parameters (DWI signal intensity and ADC values) combined with noninvasive test could help to separate benign lesions from csPCa (40-42). *Gottlieb et al.* (43) reported that men with previous specific granulomatous prostatitits the presence of a PI-RADS score ≤ 3 may not required prostate biopsy; in our experience, 16 men with initial PI-RADS score 5 and negative histology demonstrated six months later a PI-RADS score < 3 with normal clinical parameters (PSA, DRE, PSAD) (26). Recently, *Wong et al.* (44) in 29 men with PIRADS score 4-5 and negative biopsy histology reported that a SUVmax > 20 was correlated with the presence of csPCa In our series, 25/180 (13.9%) patients with PI-RADS score 5 had negative biopsy histology; six months from prostate biopsy the reduction of PSA and PSAD in 24/25 (96%) patients combined with the downgrading of PI-RADS score from 5 to < 3 allowed to avoid a repeated prostate biopsy; at the same time, PSMA PET/CT evaluation showed SUVmax (median 7.5) values not suspicious for csPCa resulting in agreement with the mpMRI results. Only one man (4%) had an increased PSA value (31 ng/ml) with PI-RADS score 5, SUVmax of 32 and TPBx combined with systematic biopsy demonstrated the presence of a Gleason score 9/ISUP GG5 PCa.

In definitive, the strict clinical follow up of men with negative histology of PI-RADS score 5 lesions reduce the risk of missing csPCa especially if PSMA PET/CT evaluation is in agreement with downgrading of mpMRI (PI-RADS score < 3).

Regarding our results some considerations should be done. Firstly, the results were not evaluated on the entire prostate gland. Secondly, we do not know if the presence of a mpMRI PIRADS score 3 (13 cases) was predictive of csPCa because a new biopsy was not performed. Third, a greater number of patients should be evaluated. Finally, a longer follow up is needed.

Conclusions

A significant reduction of PSA and PSAD values combined with the downgrading of PI-RADS score to < 3 allow to avoid a repeated prostate biopsy in men with initial PI-RADS 5 and negative biopsy; 68GaPSMA PET/CT evaluation, in our series, was in agreement with mpMRI results.

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Conflict of interest: The authors declare no potential conflict of interest.