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ORIGINAL PAPER

^{68}Ga-PSMA PET/CT evaluation in men enrolled in prostate cancer Active Surveillance

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Summary ***Introduction: To evaluate the accuracy of 68Ga-prostate specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) in the diagnosis of clinically significant prostate cancer (csPCa: Grade Group ≥ 2) in men enrolled in Active Surveillance (AS) protocol.***

Materials and methods: From May 2013 to December 2021 200 men aged between 52 and 74 years (median age 63) with very low risk PCa were enrolled in an AS protocol study. During the follow up 48/200 (24%) men were upgraded and 10/200 (5%) decided to leave the AS protocol. After five years from confirmatory biopsy (range: 48-60 months) 40/142 (28.2%) consecutive patients were submitted to mpMRI and 68Ga-PSMA PET/CT imaging examinations before scheduled repeated biopsy. All the mpMRI (PI-RADS ≥ 3) and 68Ga-PET/TC standardized uptake value (SUVmax) ≥ 5 index lesions underwent targeted cores (mpMRI-TPBx and PSMA-TPBx) combined with transperineal saturation prostate biopsy (SPBx: median 20 cores).

Results: Multiparametric MRI and 68Ga-PSMA PET/CT showed 18/40 (45%) and 9/40 (22.5%) lesions suspicious for PCa. In 3/40 (7.5%) men a csPCa (GG2) was found; 68Ga-PSMA-TPBx vs. mpMRI-TPBx vs. SPBx diagnosed 2/3 (66.6%) vs. 2/3 (66.6%) vs. 3/3 (100%) csPCa, respectively. In detail, mpMRI and 68Ga-PSMA PET/TC demonstrated 16/40 (40%) vs. 7/40 (17.5%) false positive and 1 (33.3%) vs. 1 (33.3%) false negative results.

Conclusion: Although 68PSMA PET/CT did not improve the detection for csPCa of SPBx (1 false negative result equal to 33.3% of the cases), at the same time, would have spared 31/40 (77.5%) scheduled biopsies showing a better diagnostic accuracy in comparison with mpMRI (83.3% vs. 70.2%).

KEY WORDS: Prostate cancer; 68Ga-PSMA PET/CT; Active Surveillance; PCa.

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INTRODUCTION

Active surveillance (AS) has become an alternative to radical treatment of low/very low risk *prostate cancer* (PCa), reducing the risk of overtreatment and improving quality of life of the patients (1-3). However, the time of confirmatory biopsy has been established within one year from initial diagnosis (4) there are no data regarding the number of systematic needle cores and the best imaging procedure to use for omitting or postponing scheduled repeated biopsies; in this respect, *Multiparametric Magnetic Resonance Imaging* (mpMRI) is strongly recommended in AS follow up (4, 5).

Recently, *Prostate-specific membrane antigen* (PSMA) inhibitors conjugated with the radionuclides ^{68}Gallium (^{68}Ga) and ^{18}fluoride (^{18}F) have been well-explored and successfully translated for the clinical diagnosis of PCa (6, 7). Moreover, tumour uptake, which represents PSMA expression (*standardised uptake value "SUVmax*), resulted highly correlated with the Gleason score of the primary prostatic tumour (9). However, a limited number of studies have focused on the primary prostatic lesion (8, 9). ^{68}Ga-PSMA *positron emission tomography/computed tomography* (PET/CT) has shown to be sensitive for the detection of primary prostatic lesions and regional lymphadenopathy (10, 11). Recently, the use of ^{68}Ga-PSMA PET/CT combined with mpMRI has been suggested to improve the accuracy to identify men suitable for active surveillance (12).

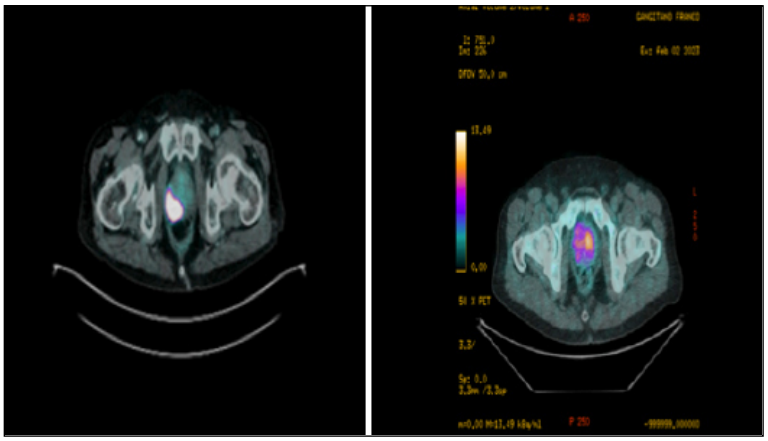
The aim of this study is to prospectively evaluate the diagnostic accuracy of ^{68}Ga-PSMA PET/CT in the diagnosis of csPCa (Grade Group ≥ 2) (13) in men enrolled in AS protocol.

MATERIALS AND METHODS

From May 2013 to December 2021 200 men aged between 52 and 74 (median age 63) with very low risk PCa were enrolled in an AS protocol study. After institutional review board and ethical committee approval were granted, informed consents were obtained from all participants included in the study. Presence of the following criteria defined eligibility: life expectancy greater than 10 years, clinical stage T1c, PSA below 10 ng/ml, *PSA density* (PSA-D) < 0.20, ≤ 2 unilateral positive biopsy cores, Gleason score 6/*International Society of Urologic Pathology* (ISUP) *Grade Groups* (GG) 1, maximum core percentage of cancer (GPC) ≤ 50% (3). All the patients underwent confirmatory biopsy 6-12 months later the PCa diagnosis previous mpMRI evaluation. During the follow up 48/200 (24%) men were upgraded and 10/200 (5%) men autonomously decided to leave the AS protocol. After five

Figure 1.
^{68}Ga-prostate-specific membrane antigen (PSMA) PET/CT: presence of high vs. low suspicious area of clinically significant prostate cancer in the right (A) vs. left lobe (B) of prostate gland (axial valuation) with a standardized uptake value (SUVmax) equal to 88.8 vs. 6.5, respectively.

A. ***B.***



years from confirmatory biopsy (range: 48-60 months), also in the presence of stable clinical parameters, the last 40/142 (28.2%) consecutive patients were submitted to mpMRI and ^{68}Ga-PET/CT imaging examinations before scheduled repeated biopsy.

All mpMRI examinations were performed using a 1.5 or 3.0 Tesla scanner, equipped with surface 16 channels phased-array coil placed around the pelvic area with the patient in the supine position; multi-planar turbo spin-echo *T2-weighted* (T2W), axial *diffusion weighted imaging (DWI) and axial dynamic contrast enhanced (DCE)* were performed for each patient. The mpMRI lesions characterized by *Prostate Imaging Reporting and Data System* (PI-RADS) version 2 (4) scores ≥ 3 were considered suspicious for cancer; two radiologists blinded to pre-imaging clinical parameters evaluated the mpMRI data separately and independently; moreover, one urologist with more than 25 years of experience performed the biopsy procedure (4).

PET/CT imaging was performed using a CT-integrated PET scanner (*Biograph 6; Siemens, Knoxville, TN, USA*). ^{68}Ga-PSMA was prepared with a fully automated radiopharmaceutical synthesis device based on a modular concept (*Eckert & Ziegler Eurotope, Berlin, Germany*). ^{68}Ga-PSMA-11 was given to patients via an intravenous bolus (mean, 144 ± 12 MBq; range, 122-188 MBq), and the PET acquisition was started at a mean of 58 ± 12 min (range, 50-81 min) afterward. Scans were acquired in 3-dimensional mode with an acquisition time of 3 min per bed position. Emission data were corrected for randoms, dead time, scatter, and attenuation and were reconstructed iteratively using ordered-subsets expectation maximization (4 iterations, 8 subsets) followed by a postreconstruction smoothing gaussian filter (5 mm in full width at half maximum). For attenuation correction, a low dose unenhanced CT scan was performed from the skull base to the middle of the thigh. 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 by two experienced nuclear medicine specialists, who were blinded to the clinical data. The location of focal uptake on ^{68}Ga-PSMA PET/TC (Figure 1), three-dimensional size, and SUVmax values were reported on a per-lesion basis with a sextant scheme (apex, midgland, and base, each split into left and right) (4).

All the mpMRI (PI-RADS score ≥ 3) and ^{68}Ga-PET/TC index lesions (SUVmax ≥ 5) (14) underwent cognitive targeted cores (mpMRI-TPBx and PSMA-TPBx: four cores) combined with saturation prostate biopsy (SPBx: median 20 cores; range 18-22). The procedure was performed transperineally using a tru-cut 18 gauge needle (*Bard; Covington, GA, USA*) under sedation and antibiotic prophylaxis (15). The prostate targeted cores were done using an Hitachi 70 Arietta ecograph, Chiba, Japan) supplied by a bi-planar trans-rectal probe (16) performing a free-hand cognitive approach.

Results

The clinical parameters of the 40 men enrolled in Active Surveillance protocol are listed in Table 1.

Multiparametric MRI and ^{68}Ga-PSMA showed 18/40 (45%) and 9/40 (22.5%) lesions suspicious for PCa those were submitted to targeted cores combined with SPBx. In detail, mpMRI PI-RADS score resulted ≤ 2 *vs.* 3 *vs.* 4 in 22 (55%) *vs.* 15 (37.5%) *vs.* 3 (7.5%) men. The average intraprostatic SUVmax and tumor dimension was 4.6 g/mL (range: 3.2-19.8) and 7.0 mm (range 4-12 mm), respectively; only 9/40 (22.5%) men had a SUVmax ≥ 5 (range: 5.1-19.8), moreover, ^{68}Ga-PSMA PET/TC showed two suspicious areas in correspondence of iliac ala and spinal cord those resulted negative for metastases at targeted MRI for bone evaluation. In 3/40 (7.5%) men a csPCa (GG2) was found: both patients had a GPC equal to 20% with a number of positive cores equal to 3 and 4, respectively, moreover PSA density was 0.15, 0.16 and 0.18, respectively.

^{68}Ga-PSMA-TPBx *vs.* mpMRI-TPBx *vs.* SPBx diagnosed 2/3 (66.6%) *vs.* 2/3 (66.6%) *vs.* 3/3 (100%) csPCa, respectively. In detail, mpMRI and ^{68}Ga-PSMA PET/TC

Table 1.
Clinical parameters of 40 men enrolled in Active Surveillance protocol submitted to scheduled biopsy.

Clinical and biopsy findings	GG1 40 patients
Median PSA (range: 4.5-12.5 ng/ml)	4.8
Median PSA density (range: 0.10-0.20)	0.15
Median GPC (range: 10-50%)	40%
Median number of positive cores	2
Percentage of positive cores	98%
mpMRI	18
PI-RADS score ≥ 3	(45%)
^{68}Ga-PSMA PET/CT	9
suspicious for PCa	(22.5%)

GG: International Society of Urological Pathology Grade Group; mpMRI: multiparametric magnetic resonance imaging; PSA: prostate specific antigen; GPC: greatest percentage of cancer; PSMA: Prostate specific membrane antigen; PI-RADS: Prostate imaging reporting and data system; PET/TC: positron emission tomography/computed tomography.

demonstrated 16/40 (40%) *vs.* 7/40 (17.5%) false positive and 1 (33.3%) *vs.* 1 (33.3%) false negative results; in detail, one patient had PI-RADS score 2 and SUVmax of 6.8 and the second patient had PI-RADS score 3 and SUVmax equal to 4.5 g/mL. In addition, mpMRI and ^{68}Ga-PSMA PET/TC showed a diagnostic accuracy in the diagnosis of csPCa equal to 70.2 and 83.3%, respectively.

Discussion

The estimated risk-free treatment at 15 years in men enrolled in AS with GG1 PCa is equal to 58% (1). Although mpMRI is strongly recommended in the revaluation of men in AS (2, 5, 6), still today, scheduled systematic repeated prostate biopsies are recommended to reduce the false negative rate for csPCa of mpMRI equal to 15-20% of the cases (16); At the same time, the number of cores performed at initial and repeat evaluation is directly correlated with a lower risk of reclassification (6) during the follow up allowing to postpone scheduled repeated prostate biopsy in favour of clinical findings (i.e., PSA density, risk calculator) (17-19) and imaging revaluation (mpMRI) (5, 6).

In the last years, ^{68}Ga-PSMA-PET/CT has been suggested to improve the clinical staging of high-risk PCa and disease recurrence (20, 21); at the same PSMA PET/CT has been proposed for the diagnosis of primary intraprostatic cancer (22, 23). 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 (24, 25). There is a range of proposed cut-offs to detect csPCa from SUVmax 3.15 to up SUVmax 9.1 (26, 27); the concordance between preoperative PSMA PET/TC evaluation (SUVmax, dimension of the lesion) and definitive prostate specimen ranges from 81.2% (28) to 96% (29); moreover, PSMA PET/MRI seems reduce false positive rate of PET/CT (about 8% of cases) (30).

In our series, ^{68}Ga-PSMA-TPBx *vs.* mpMRI-TPBx *vs.* SPBx diagnosed 2/3 (66.6%) *vs.* 2/3 (66.6%) *vs.* 3/3 (100%) csPCa, respectively. In detail, mpMRI and ^{68}Ga-PSMA PET/TC demonstrated 16/40 (40%) *vs.* 7/40 (17.5%) false positive and 1 (33.3%) *vs.* 1 (33.3%) false negative results. In addition, mpMRI and ^{68}Ga-PSMA PET/TC showed a diagnostic accuracy in in the diagnosis of csPCa equal to 70.2 and 83.3%, respectively. In definitive, still today, diagnostic imaging should not replace scheduled prostate biopsy but is mandatory to detect targeted lesions suspicious for csPCa; in addion, several biochemical parameters, such as germline evaluation or PHI (prostate health index), could be helpful in decrease the ratio of scheduled biopsy.

Among our results some considerations should be made. First, the number of patients evaluated was low. Secondly, the results should be evaluated in the entire prostate specimen and not in biopsy histology; a more detailed histological evaluation of patients who underwent biopsy upstaging would be of interest, for example by adding supplementary staining for PSMA on the biopsy samples. Third, the low rate of reclassification (7.5% of the cases) could be explained because the patients previously underwent SPBx plus mpMRI evaluation before confirmatory biopsy. Four, ^{68}Ga-PSMA PET/TC evaluation could be proposed in men with negative mpMRI or in the presence of claustrophobia, severe obesity or cardiac pacemaker (13); moreover, a ^{68}Ga-PSMA PET/TC fusion platform would have increased the accuracy of targeted prostate biopsy.

In conclusion, although ^{68}PSMA PET/CT did not improve the detection for csPCa of SPBx (1 false negative result equal to 33.3% of the cases), at the same time, would have spared 31/40 (77.5%) scheduled biopsies showing a better diagnostic accuracy in comparison with mpMRI (70.2% *vs.* 83.3%).

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