^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 PET/MRI in Staging of High-risk Prostate Cancer Patients: a Prospective Pilot Trial

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Abstract

Purpose: The aim of the present study is to investigate the synergic role of 68Ga-PSMA PET/MRI and 68Ga-DOTA-RM2 PET/MRI in PCa staging.

Methods: Fifteen patients with biopsy-proven PCa underwent both 68Ga-PSMA PET/MRI and 68Ga-DOTA-RM2 PET/MRI within one month. TNM classification based on image findings was performed and semi-quantitative PET and quantitative MRI parameters were collected for each scan. Finally, DICE score between regions of interest manually segmented on the primary tumor on 68Ga-PSMA PET, 68Ga-DOTA-RM2 PET and on T2 MRI was computed.

Results: All imaging modalities detected the primary PCa in 15 patients, with slight differences regarding the multifocality of intra-prostatic findings. Two patients presented seminal vesicles involvement on MRI, one of these was also detected by 68Ga-PSMA, with no uptake on 68Ga-DOTA-RM2 images. Regarding extra prostatic disease, 68Ga-PSMA PET, 68Ga-DOTA-RM2 PET and MRI resulted positive in 6, 2 and 4 patients at lymph-nodal level, respectively, and at bone level in 2, 0 and 1 patients, respectively, with 68Ga-PSMA PET detecting more lesions compared to 68Ga-DOTA-RM2 PET. The different findings detected by 68Ga-PSMA PET and 68Ga-DOTA-RM2 PET might reflect the complementary role of these radiotracers, as they detected different foci of intraprostatic disease, seminal vesicle invasion, lymph nodal and bone involvement.

Conclusion: These preliminary results suggest a synergic role of 68Ga-PSMA PET, 68Ga-DOTA-RM2 PET and mpMRI in PCa characterization during the staging phase.

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Introduction

Prostate cancer (PCa) is one of the worldwide leading causes of cancer-related death. Approximately 15% of men present with high-risk PCa, which is characterized by an increased risk of extracapsular extension, locally advanced disease, and/or bone metastases [1]. Hence, at diagnosis, a whole body staging for high-risk PCa patients is strongly recommended regardless of the surgical or radiation-based treatment decision [2].

The current staging of intermediate and high-risk PCa includes imaging of abdomen and pelvis performed by using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) and bone scan to evaluate potential sites of metastatic spread.

The current EAU-ESTRO-SIOG guidelines report that Positron Emission Tomography/CT (PET/CT) is a sensitive imaging modality that might be considered in men with high-risk disease undergoing initial staging. However, as no randomized-control trials demonstrating survival benefit are available yet, its role in guiding therapeutic decisions must be cautious [3].

Multi-parametric MRI (mpMRI) is a well-established imaging modality for PCa assessment and it is used to detect the primary tumor, guide biopsies and define the local extent of the disease; its usefulness for local staging has been largely reported, although local staging with MRI might be associated with limited sensitivity [4–6].

Molecular imaging with PET represents a valid imaging approach in PCa staging, with new PET tracers other than Choline having a relevant role in improving diagnoses, staging and follow-up of PCa [7–10].

In this regard, prostate-specific membrane antigen (PSMA), a transmembrane protein with a significantly increased expression in PCa cells, is an imaging probe that has been introduced in clinical practice, with recent data demonstrating good accuracy in PCa staging [11, 12].

Gastrin releasing peptide receptor (GRPR) is a G-protein coupled receptor overexpressed in different types of cancer including PCa [13, 14]. ⁶⁸Ga-DOTA-RM2 is a GRPR antagonist used as a PET imaging probe that has demonstrated promising, but still limited results in PCa imaging [15–17].

Hybrid PET/MRI allows for the simultaneous acquisition of metabolic, structural, and functional imaging information regarding PCa status in a whole-body single session examination, thus representing an innovative imaging approach capable to overcome the pitfalls of conventional imaging and, potentially, helping clinicians in the management of PCa. Only few and preliminary studies have compared ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2-PET radiotracers in PCa by using PET/CT or PET/MRI so far, with promising results in both patients presenting with biochemical recurrence and in those with newly diagnosed intermediate- or high-risk prostate cancer [15, 18, 19].

The aim of the present study is to report our experience on the synergic use of ^{68}Ga -PSMA PET/MRI and ^{68}Ga -RM2 PET/MRI in prostate cancer staging.

Materials And Methods

Patients

In this prospective pilot clinical study, 15 patients with biopsy proven PCa have been enrolled from 1 September 2020 to 31 March 2021 at IRCCS San Raffaele Scientific Institute.

Inclusion criteria were age greater than 18 years at the time of PET/MRI scan, biopsy proven high-risk PCa (defined as PSA > 20 ng/ml and/or clinical stage $\geq$ cT2c and/or biopsy ISUP grade $\geq$ 4, according to European Association of Urology guidelines [3]) in men referred to prostatectomy and pelvic lymphadenectomy. Exclusion criteria were inability to complete the required imaging examinations (i.e. severe claustrophobia), medical condition possibly interfering and significantly affecting study compliance, all contraindications to undergo MRI scan (i.e. metallic/conductive or electrically/magnetically active implants without MR-safe or MR-conditional labelling) and evidence of metastatic disease on conventional imaging contraindicating the surgical procedure.

All recruited patients underwent both ^{68}Ga -PSMA PET/MRI and ^{68}Ga -DOTA-RM2 PET/MRI in two different days (> 48 hours) and within one month one from the other, for staging purpose before radical prostatectomy.

This study was approved by the Institutional Ethics Committee of IRCCS San Raffaele Scientific Institute (EudraCT: 2018-001034-18) and all patients gave written informed consent to participate to the study.

^{68}Ga -PSMA PET/MRI acquisition protocol

^{68}Ga -PSMA-11 was synthesized by a fully automated synthesis module (Neptis Mo-saic-RS, ORA, Neuville, Belgium) connected to a $^{68}\text{Ge}/^{68}\text{Ga}$ generator (1.85 GBq Galli Ad, IRE ELiT, Fleurus, Belgium) and equipped with a disposable single-use cassette kit (ABX GmbH, Radeberg, Germany). A standardized labelling sequence with 15 μg (15 nmol) of unlabelled PSMA 11 (ABX GmbH) was used. The final product was sterilely filtered over 0.22 μm PVDF filters. For quality control, ^{68}Ga -PSMA 11 was analysed by radio analytic high-performance liquid chromatography on a modular system (Waters) equipped with a diode array detector and a radio detector using an RP-18 column (ACE 5 μm C18, 150 x 3 mm, Advanced Chromatography Technologies Ltd, Aberdeen, Scotland). A gradient elution over 13 minutes at a flow of 1.5 mL/min from 90%A to 30%A and again 90%A was employed, where Solvent A was Water + 0,1% TFA and Solvent B was CH₃CN + 0,1% TFA. Other quality controls performed before release included TLC on iTLC strips with MeOH/1M AcONH₄, pH measurement and radionuclidic purity. Residual HEPES determination, Ethanol quantification and Microbiological purity were assessed on decayed product. Uncorrected radiochemical yield was over 70% with a radiochemical purity > 91%.

Fasting condition was requested on the day of ^{68}Ga -PSMA PET/MRI scan. Images were acquired on a SiPM-based TOF-PET GE Signa PET/MR 3 Tesla system (GE Healthcare, Waukesha, WI, USA) from the skull base to mid-thigh. The ^{68}Ga -PSMA PET/MRI scan started approximately 60 minutes (mean $\pm$ SD, 59 $\pm$ 6 min) after injection of 122–255 MBq (mean $\pm$ SD, 184 $\pm$ 36 MBq) of ^{68}Ga -PSMA.

The ^{68}Ga -PSMA PET/MR examination protocol included a high statistic (HS) scan (20 minutes), covering a single bed position, that was simultaneously acquired to the following MR sequences:

- an axial T2 weighted sequence with large field of view (FOV): FSE, TR = 10235ms; TE = 99.7ms, FOV = 32x32cm²; voxel size = 0.9x0.9x5mm³;
- an axial T2 weighted sequence with small FOV: PROPELLER, TR = 9578ms, TE = 151ms, FOV = 18x18cm², voxel size = 0.6x0.6x3mm³,
- a coronal T2 weighted sequence with small FOV: PROPELLER, TR = 9578ms, TE = 151ms, FOV = 18x18cm², voxel size = 0.6x0.6x3mm³,
- a diffusion weighted imaging (DWI) sequence with small FOV: TR = 6643ms, TR = 79.5ms, FOV = 18x9cm², voxel size = 1.8x1.8x3mm³; b = 50, 800, 1400s/mm²
- T1-Lava Flex sequence of the whole pelvic region pre-contrast and post-contrast: TR = 5ms, TE = 1.7ms, FOV: 44x35.2cm, voxel size = 1.3x1.2x2mm³
- a high temporal resolution T1 perfusion sequence after IV injection of 0.1 mmol/kg bolus of gadobutrol (Gadovist, Bayer Schering Pharma, Germany) at a flow rate of 3.5 ml/s: DISCO, TR = 5.1ms, TE = 1.7ms, FOV = 29x29cm², Voxel size = 1.9x2.2x3mm³, 88 dynamics.

Following the single bed acquisition, a total-body (TB) PET scan (5–6 FOVs, 4min/FOV) was then simultaneously acquired to a MRI TB T1 Lava Flex sequence and a TB DWI with b = 50, b = 1000 sec/mm².

PET images were reconstructed using a Bayesian penalized likelihood reconstruction algorithm [20] with a reconstructed FOV of 60 cm and image matrix of 192x192. The algorithm includes a Point Spread Function and Time of Flight information.

Attenuation Correction (AC) of PET data was performed using MR AC technique based on the processing of the LAVA-Flex sequences acquired simultaneously with the PET data.

^{68}Ga -DOTA-RM2 PET/MRI acquisition protocol

^{68}Ga -DOTA-RM2 was synthesized by a kit-like procedure developed for the radio-labeling with GalliAd® generator (IRE Elite). Briefly, the eluate from the $^{68}\text{Ge}/^{68}\text{Ga}$ generator (1.85 GBq Galli Ad, IRE ELiT, Fleurus, Belgium) was added to a sterile vial containing 40 µg of DOTA-RM2 (Life Molecular Imaging, Fribourg, Germany) in format buffer and ascorbic acid. Reaction vial is placed in a pre-heated thermostat at 115°C for 10 minutes. Successively, vial is left to cool down for 10 minutes at room temperature. No purification step was needed. The solution is sterile filtered over sterile 0.22 µm PVDF membrane and dispensed as injectable solution. For quality control, ^{68}Ga -DOTA-RM2 was analysed by radio analytic high-performance liquid chromatography on a modular system (Waters) equipped with a diode array detector and a radio detector using an RP-18 column (ACE 5µm C18, 150 x 3 mm, Advanced Chromatography Technologies Ltd, Aberdeen, Scotland). A gradient elution over 16 minutes at a flow of 1.0 mL/min from 80%A to 20%A and again 80%A was employed, where Solvent A was Water + 0,1% TFA and Solvent B was CH₃CN + 0,1% TFA. Unbound gallium was quantified by iTLC strips with MeOH/1M AcONH₄ while ionic gallium with TLC strips with 0.1 M sodium citrate pH5. pH of the final solution was 3.2–3.8. Radionuclidic purity was assessed before release, microbiological purity was assessed on decayed product. Uncorrected radiochemical yield was over 60% with a radio-chemical purity > 91%. ^{68}Ga -DOTA-RM2

^{68}Ga -DOTA-RM2 PET/MRI scan was performed within one month (mean: 3 days, range: 2–16 days) from ^{68}Ga -PSMA PET/MRI. As for ^{68}Ga -PSMA PET/MRI, fasting condition was requested on the day of the examination and the same PET/MRI scanner was used.

Images were acquired from the base of the skull to mid-thigh and started approximatively 50 minutes (mean ± SD, 54 ± 10 min) after injection of 74–222 MBq (mean ± SD, 164 ± 41 MBq) of ^{68}Ga -DOTA-RM2.

The ^{68}Ga -DOTA-RM2 PET/MR examination protocol included a HS scan (20 minutes), covering a single bed position, that was simultaneously acquired to the following MR sequences: an axial T2 weighted sequence with large FOV (32x32 cm²), an axial 3D T2 sequence with small FOV, a T1-Lava Flex sequence of the whole pelvic region. Following the single bed acquisition, a TB PET scan (5–6 FOVs, 4min/FOV) was then simultaneously acquired with a TB axial Lava Flex sequence and a TB sagittal STIR sequence on the spine. Reconstruction and attenuation correction of PET images were performed by using the same algorithms and parameters used for ^{68}Ga -PSMA PET images.

PET/MR image analysis

^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 image read-out has been performed on the Advantage Workstation (AW, General Electric Healthcare, Waukesha, WI, USA) on which PET, MRI and fused PET/MRI images could be visualized in axial, coronal and sagittal planes. HS PET acquisition bed on the pelvic region and TB PET examination of both ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 PET images were qualitatively interpreted by two experienced (more than 10 years of experience) Nuclear Medicine physicians, with knowledge of all the available patients' clinical and imaging information.

For the primary tumor assessment, HS and TB pelvic PET images were qualitatively evaluated for both ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2. The presence of ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 increased uptake was considered suspicious for malignancy with the anatomical site being defined on the basis of MRI anatomy, except for those areas of physiologically increased uptake [21, 22]. Regions of interest (ROIs) on the primary tumor, showing ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 uptake on HS PET images were semi-automatically defined on transaxial PET images. Furthermore, the following semi-quantitative parameters have been calculated for the primary tumor on HS PET images for both radiotracers: maximum standardized uptake value (SUVmax), mean SUV (SUVmean, using different thresholds, namely 40%, 50%, 60% of the maximum value - SUVmean40, SUVmean50, SUVmean60) and metabolic tumor volume (MTV) calculated at different thresholds (MTV40, MTV50, MTV60).

In addition, to determine the volume and the location of ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 PET primary tumor uptake, one experienced Nuclear Medicine physician manually segmented the primary tumor slice-by-slice using 3D Slicer software (revision 29402) [23] on both ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 PET images. Afterwards, all segmentations were co-registered and brought to a common reference volume (the one of the first PET study). To do that, the MRAC of the ^{68}Ga -DOTA-RM2 PET study was firstly co-registered to the one of the ^{68}Ga -PSMA PET, by means of 3D Slicer, and then the obtained transformations were applied to the ^{68}Ga -DOTA-RM2 PET images and the corresponding ROI segmentations.

After the evaluation of the primary prostatic tumor, the whole-body distribution pattern of both ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 were qualitatively assessed, and the presence of extra-prostatic ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 increased uptake was considered suspicious of malignancy, with the exception of areas of physiologically increased uptake. The number and the site of lymph nodal involvement were reported, as well as the presence of suspect distant metastases. The anatomical site was defined on the basis of MRI anatomy.

In case of suspect bone metastasis in PET images, the whole-body MRI sequences were screened to confirm the spreading of the disease.

MR images acquired during HS ^{68}Ga -PSMA PET were initially processed using AW software: small FOV DWI with b values of 50–800 were used to generate ADC maps. Volumetric ROIs of lesions visible to T2 and ADC images were created using 3D Slicer to obtain the following quantitative parameters: lesion volume, mean ADC (ADCmean) and minimum (ADCmin).

Qualitative and quantitative comparison of ^{68}Ga -PSMA, ^{68}Ga -DOTA-RM2 and MRI

A qualitative comparison between ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 intra-prostatic uptake and morphological findings detected on MR images was performed in order to describe the possible concordances and discrepancies between metabolic and morphologic imaging. Moreover, a qualitative comparison has been also performed in terms of number and sites of lymph nodal and distant metastases for all patients, considering all the three different imaging modalities.

Finally, DICE score between the ROIs manually segmented on the primary tumor on ⁶⁸Ga-PSMA PET and ⁶⁸Ga-DOTA-RM2 PET and on MRI was computed in order to evaluate the correspondence of the intra-prostatic findings referable to the site of primary tumor across modalities.

Correlations between PET semi-quantitative and MRI quantitative imaging parameters

To provide an improved characterization of the primary tumor, a correlation between multitracer PET and MRI parameters was performed. In particular, a Spearman correlation was calculated between the semi-quantitative PET parameters measured on HS ⁶⁸Ga-PSMA PET and HS ⁶⁸Ga-DOTA-RM2 PET images (SUVmax, SUVmean40, SUVmean50, SUVmean60, MTV40, MTV50, MTV60), the quantitative parameters measured on MRI (lesion volume, ADCmin, ADCmean) and clinical data (PSA, Gleason Score, ISUP score). A p value < 0.05 was considered statistically significant.

Results

Patients

Fifteen men (mean age: 68 years; range 52–80) with biopsy proven high-risk PCa have been enrolled so far in this prospective study. All patients had a Gleason score ≥ 7 on biopsy, with a mean PSA at time of diagnosis of 5.90 ng/mL (range: 3.03–11.13). Patients’ characteristics are reported in Table 1. All patients safely completed both ⁶⁸Ga-PSMA and ⁶⁸Ga-DOTA-RM2 PET/MRI scan with a good rate of compliance and no major discomfort.

Table 1
Patients' characteristics

n.	Age	PSA level at diagnosis	GS on biopsy	ISUP grade on biopsy	Clinical T Stage
1	71	5.04	7 (4 + 3)	3	T2c
2	80	11.13	8 (3 + 5)	4	T1
3	74	4.73	9 (4 + 5)	5	T2a
4	71	5.80	7 (4 + 3)	3	T2c
5	69	3.03	9 (5 + 4)	5	T1
6	59	11.00	9 (4 + 5)	5	T3b
7	75	5.33	8 (4 + 4)	5	T2a
8	62	3.85	8 (4 + 4)	4	T1
9	74	6.37	9 (5 + 4)	5	T2a
10	53	3.13	9 (4 + 5)	5	T2b
11	69	5.31	9 (5 + 4)	5	T2c
12	74	5.03	8 (4 + 4)	4	T2a
13	64	4.40	8 (4 + 4)	4	T1
14	52	8.04	8 (4 + 4)	4	T2a
15	66	6.37	9 (4 + 5)	5	T2a
PSA: Prostate Specific Antigen; GS: Gleason Score; ISUP: International Society of Urological Pathology					

PET/MRI findings

An example of whole-body biodistribution of ^{68}Ga -PSMA PET and ^{68}Ga -DOTA-RM2 PET is reported in Fig. 1. Physiological high ^{68}Ga -PSMA uptake can be visualized in the salivary and lacrimal glands, liver, spleen, small intestine, kidneys, urinary bladder and ureters (Fig. 1A), while ^{68}Ga -DOTA-RM2 showed physiological high uptake in the pancreatic gland and urinary bladder. (Fig. 1B)

Both ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 PET detected intra-prostatic lesions in all patients. ^{68}Ga -PSMA PET images showed prostatic focal uptake in 9/15 patients, bifocal uptake in 3/15 patients and multifocal uptake in 3/15 patients. Additionally, 1/15 presented also seminal vesicles uptake. Pathological prostatic focal uptake of ^{68}Ga -DOTA-RM2 was seen in 12/15 patients, while multifocal prostatic uptake was reported in 3/15 patients. The specific sites of intra-prostatic ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 uptake are reported in Table 2.

Table 2
TNM findings of ⁶⁸Ga-PSMA and ⁶⁸Ga-RM PET/MRI

n.	⁶⁸ Ga-PSMA			⁶⁸ Ga-DOTA-RM2			MRI		
	T	N	M	T	N	M	T	N	M
1	Prostate (multifocal, bilateral)	Two left pre-sacral LNs, left Perivescical fat LN, left perirectal LN	Negative	Prostate (multifocal, bilateral)	Negative	Negative	Prostate (multifocal, bilateral)	External left iliac LN	Negative
2	Prostate (multifocal, bilateral)	Negative	Right iliac bone	Prostate (multifocal, bilateral)	Negative	Negative	Prostate (multifocal, bilateral)	Negative	Negative
3	Prostate (multifocal, bilateral), SVI	Left external iliac LN, bilateral perirectal LNs (three left, one right)	Negative	Prostate (multifocal, bilateral)	Three left perirectal LNs	Negative	Prostate (focal, bilateral), SVI, ECE	Internal left iliac LN, bilateral perirectal LNs	Negative
4	Prostate (bifocal, bilateral)	Negative	Negative	Prostate (focal, right)	Negative	Negative	Prostate (focal, right)	Negative	Negative
5	Prostate (focal, bilateral)	Left perivescical LNs, bilateral obturator LNs, left external iliac LN	Negative	Prostate (focal, bilateral)	Left external iliac LN, left obturator LN	Negative	Prostate (focal, bilateral), SVI, ECE	Pelvic LNs	Negative
6	Prostate (focal, left)	Left perirectal LN	Right ribs, left sacral ala	Prostate (focal, left)	Negative	Negative	Prostate (focal, left), ECE	Negative	Right ribs, left sacral ala
7	Prostate (focal, midline-right)	Bilateral external iliac LNs, right common iliac LN	Negative	Prostate (focal, midline-right)	Negative	Negative	Prostate (focal, midline)	Bilateral iliac LNs	Negative
8	Prostate (focal, right)	Negative	Negative	Prostate (focal, right)	Negative	Negative	Prostate (focal, right), ECE	Negative	Negative
9	Prostate (focal, left)	Negative	Negative	Prostate (focal, left)	Negative	Negative	Prostate (focal, left)	Negative	Negative
10	Prostate (focal, right)	Negative	Negative	Prostate (focal, right)	Negative	Negative	Prostate (focal, right), ECE	Negative	Negative
11	Prostate (bifocal, left)	Negative	Negative	Prostate (focal, left)	Negative	Negative	Prostate (focal, anterior), ECE	Negative	Negative
12	Prostate (focal, left)	Negative	Negative	Prostate (focal, left)	Negative	Negative	Prostate (focal, left), ECE	Negative	Negative

n.	⁶⁸ Ga-PSMA			⁶⁸ Ga-DOTA-RM2			MRI		
13	Prostate (bifocal, right)	Suspected left retropectoral LN and intercostal LN	Negative	Prostate (focal, right)	Negative	Negative	Prostate (focal, right)	Negative	negative
14	Prostate (focal, left)	Negative	Negative	Prostate (focal, left)	Negative	Negative	Prostate (focal, left), ECE	Negative	Negative
15	Prostate (focal, left)	Negative	Negative	Prostate (focal, left)	Negative	Negative	Prostate (focal, right)	Negative	Negative
LN: Lymph Node; ECE: extracapsular extension; SVI: Seminal Vesicles Invasion									

The analysis of semi-quantitative parameters of prostate uptake extracted from HS ⁶⁸Ga-PSMA images showed a mean SUVmax of 22.25 (range: 4.08–43.44), SUVmean40-50-60% of 13.64, 15.00 and 16.73, respectively (ranges: 3.02–25.92; 3.04–28.01; 3.18–30.76, respectively), MTV40-50-60% of 1.83, 1.33 and 0.89, respectively (ranges: 0.19–5.29; 0.14–3.83 and 0.08–2.85, respectively). All ⁶⁸Ga-PSMA PET-derived parameters, obtained from HS PET images simultaneously acquired with dedicated MRI acquisition on the pelvis, are reported in Table 3.

Table 3
High statistic ^{68}Ga -PSMA PET parameters.

n.	SUVmax	SUV mean40	SUV mean50	SUV mean60	MTV40 (cm ³)	MTV50 (cm ³)	MTV60 (cm ³)	Volume (cm ³)
1	16.71	9.08	10.36	13.67	1.74	0.84	0.16	4.83
2	37.04	23.12	25.31	28.96	0.19	0.14	0.08	3.95
3	20.19	14.55	14.86	16.04	1.95	1.85	1.38	31.16
4	4.08	3.02	3.04	3.18	3.39	3.34	2.85	1.61
5	43.44	25.92	28.01	30.76	0.95	0.71	0.43	6.49
6	35.32	21.87	24.21	25.93	5.29	3.83	2.77	10.19
7	12.97	7.22	8.04	8.92	1.57	1.03	0.57	4.91
8	21.78	13.39	14.65	17.00	1.06	0.79	0.43	2.69
9	29.47	17.58	20.14	22.82	1.33	0.84	0.52	3.82
10	19.38	11.35	13.03	14.17	1.85	1.11	0.76	5.58
11	16.23	9.82	10.62	11.97	2.36	1.76	1.00	3.62
12	40.08	24.40	27.53	29.80	0.59	0.41	0.30	2.60
13	21.26	14.13	14.83	16.22	0.41	0.35	0.24	1.33
14	8.64	5.10	5.77	6.32	2.33	1.49	0.98	1.19
15	7.18	4.03	4.57	5.11	2.47	1.47	0.81	1.98
Mean	22.25	13.64	15.00	16.73	1.83	1.33	0.89	5.73
Range	4.08–43.44	3.02–25.92	3.04–28.01	3.18–30.76	0.19–5.29	0.14–3.83	0.08–2.85	1.19–31.16
SUV: Standardized Uptake Value; MTV: Metabolic Tumour Volume; Volume: manually segmented volume on 3D Slicer								

Similarly, semi-quantitative parameters derived from HS ^{68}Ga -DOTA-RM2 PET images of prostate uptake showed a mean SUVmax of 15.93 (range: 4.22–30.93), SUVmean40-50-60% of 10.01, 11.16 and 11.99, respectively (ranges: 2.83–20.33; 2.98–22.62; 3.08–23.55, respectively), MTV40-50-60% of 3.03, 2.19 and 1.69, respectively (ranges: 0.60–7.09; 0.35–5.62 and 0.24–4.70, respectively). All ^{68}Ga -DOTA-RM2 PET-derived parameters, obtained from HS PET images simultaneously acquired with dedicated MRI acquisition on the pelvis, are reported in Table 4.

Table 4
High statistic ^{68}Ga -DOTA-RM2 PET parameters.

n.	SUVmax	SUV mean40	SUV mean50	SUV mean60	MTV40 (cm ³)	MTV50 (cm ³)	MTV60 (cm ³)	Volume (cm ³)
1	21.20	12.63	14.29	15.41	2.09	1.38	0.98	5.47
2	15.91	8.86	10.18	11.90	1.52	0.87	0.41	2.00
3	13.75	7.47	8.78	10.12	1.19	0.62	0.33	2.05
4	12.48	7.09	8.36	8.97	4.02	2.25	1.60	4.45
5	24.30	15.88	17.59	18.51	5.24	3.96	3.26	4.57
6	11.66	7.92	8.64	9.08	7.09	5.62	4.70	3.35
7	24.55	15.51	17.67	18.80	0.79	0.54	0.43	4.48
8	22.94	17.13	17.44	17.96	1.22	1.17	1.06	1.36
9	9.91	5.45	6.61	7.31	4.34	2.06	1.33	1.94
10	30.93	20.33	22.62	23.55	1.90	1.38	1.17	7.43
11	17.68	10.01	11.79	13.39	4.89	2.71	1.52	6.69
12	4.22	2.83	2.98	3.08	5.02	4.37	3.80	2.21
13	12.97	7.58	8.71	9.40	0.60	0.35	0.24	1.75
14	5.74	4.62	4.63	4.69	4.75	4.72	4.53	1.59
15	10.67	6.80	7.08	7.70	4.67	4.05	2.63	3.38
Mean	15.93	10.01	11.16	11.99	3.29	2.40	1.87	3.51
Range	4.22–30.93	2.83–20.33	2.98–22.62	3.08–23.55	0.60–7.09	0.35–5.62	0.24–4.70	1.36–7.43
SUV: Standardized Uptake Value; MTV: Metabolic Tumour Volume; Volume: Manually segmented volume on 3D Slicer								

TB ^{68}Ga -PSMA images revealed a suspicion for lymph nodal involvement in 6/15 patients, and for bone involvement in 2/15. In TB ^{68}Ga -DOTA-RM2 PET images a pathological focal uptake was detected at lymph nodal level in 2/15 patients and in 0/15 patients at bone level. The detailed description of sites of lymph nodal and bone ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 uptake are reported in Table 2.

MRI detected prostatic lesions in all patients (Table 2). MRI images showed prostatic focal disease in 13/15 patients and multifocal disease in 2/15 patients. 8/15 patients presented extracapsular extension (ECE) and 2/15 seminal vesicle invasion (SVI). 4/15 patients had pathologic pelvic lymph nodes and 1/5 had suspicious bone lesions.

Mean ADCmean value (over the patients) of the primary tumors was $0.84 \times 10^{-3} \text{ mm}^2/\text{s}$ (range: 0.65-1,1), while mean ADCmin value was 0.48 (range: 0.2–0.68) and mean lesion volume was 4.51 cm^3 (range: 0.49–30.66; Table 5).

Table 5
MRI quantitative parameters

n.	ADCmin ($10^{-3} \text{ mm}^2/\text{s}$)	ADCmean ($10^{-3} \text{ mm}^2/\text{s}$)	Volume (cm^3)
1	0.4	0.8	3.36
2	0.4	0.78	1.80
3	0.49	0.86	30.66
4	0.5	1.1	0.51
5	0.44	0.82	7.95
6	0.33	0.78	7.78
7	0.5	0.65	1.12
8	0.56	0.78	0.80
9	0.2	0.69	2.50
10	0.61	0.83	3.38
11	0.61	0.99	3.31
12	0.68	0.95	1.15
13	0.34	0.66	0.49
14	0.5	0.85	1.86
15	0.67	1	1.01
Mean	0.48	0.84	4.51
Range	0.2–0.68	0.65–1.1	0.49–30.66
ADC: Apparent Diffusion Coefficient; Volume: Manually segmented volume on 3D Slicer			

Comparisons between ^{68}Ga -PSMA PET, ^{68}Ga -DOTA-RM2 PET and MRI

Regarding intraprostatic disease, in 13/15 patients the site of the primary prostatic lesion was concordant among the three imaging modalities (patient n.10, see Fig. 2). In 1/15 one of the multifocal prostatic findings detected by MRI on the apex of the gland showed only ^{68}Ga -DOTA-RM2 increased uptake but not ^{68}Ga -PSMA uptake (patient n.2, see Fig. 3). In the other 1/15, (n.15, Table 2), both ^{68}Ga -PSMA PET and ^{68}Ga -DOTA-RM2 PET showed an increased focal uptake in the left side of the prostate, while MRI detected a lesion in the right peripheral zone of the prostate.

Regarding the differences of intraprostatic findings among the imaging modalities, a prostatic uptake was detected on both ^{68}Ga -PSMA PET and ^{68}Ga -DOTA-RM2 PET images in 3 patients (n.1, n.2, n.3, Table 2), while MRI detected multiple lesions in 2/3 patients (n.1, n.2, Table 2).

In 3 patients ^{68}Ga -PSMA PET showed a bifocal prostatic uptake (n.4, n.11, n.13, Table 2), while a focal lesion was present on ^{68}Ga -DOTA-RM2 PET images. Similarly, MRI also detected a single lesion in these 3 patients.

In terms of local extension, SVI was detected by MRI in two patients (n.3, n.5, Table 2), by ^{68}Ga -PSMA in one patient (n.3, Table 2), while no uptake was present on ^{68}Ga -DOTA-RM2 images.

Moreover, MRI identified ECE in 8/15 patients, while both ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 PET are not suitable to identify ECE of PCa, because of the limited spatial resolution compared to MRI. The high rate of EPE detection at MRI was likely related to the

presence of high-risk prostate cancer in the present cohort.

In terms of lymph nodal involvement, ⁶⁸Ga-PSMA PET resulted positive at lymph nodal level in 6 patients (18 lesions), while ⁶⁸Ga-DOTA-RM2 in 2 patients (5 lesions) and MRI in 4 patients (7 lesions) (Fig. 4).

Regarding distant metastases, ⁶⁸Ga-PSMA showed increased pathological uptake at bone level in 2 patients (n.2, n.6, Table 2), with one of them (patient n. 6, Table 2) being positive also on MRI. ⁶⁸Ga-DOTA-RM2 did not detect any pathological uptake at bone level. (Fig. 5)

DICE score was computed to quantitatively assess the overlap between the volume of the primary intra-prostatic lesions manually segmented on ⁶⁸Ga-PSMA PET, ⁶⁸Ga-DOTA-RM2 PET and MR images at the individual level. On average, the DICE score between ⁶⁸Ga-PSMA and MRI = 0.60 (range: 0.00-0.79); between ⁶⁸Ga-PSMA and ⁶⁸Ga-DOTA-RM2 = 0.46 (range: 0.15–0.72); while the DICE score between ⁶⁸Ga-DOTA-RM2 and MRI = 0.42 (range: 0.07–0.72). DICE scores for each patient across the investigated modalities are reported in Table 6. (Fig. 6).

Table 6
DICE scores

n.	⁶⁸ Ga-PSMA vs MRI	⁶⁸ Ga-DOTA-RM2 vs MRI	⁶⁸ Ga-PSMA vs ⁶⁸ Ga-DOTA-RM2
1	0.7151	0.5189	0.6521
2	LNI	0.6052	LNI
3	0.7684	0.0859	0.1188
4	0.0000	0.0728	0.1524
5	0.7354	0.3723	0.4544
6	0.7907	0.5872	0.4856
7	0.3697	0.3529	0.5571
8	0.4178	0.4331	0.5981
9	0.7581	0.7220	0.6019
10	0.7057	0.5761	0.7174
11	0.7810	0.6259	0.6828
12	0.6056	0.4023	0.5357
13	0.5013	0.2749	0.3654
14	0.6162	0.2216	0.2918
15	LNI	LNI	0.2157
Mean	0.5973	0.4179	0.4592
SD	0.2276	0.2019	0.1992
LNI: Lesion not identified in a specific modality, DICE score could not be calculated.			

Correlations between PET semi-quantitative and MRI quantitative imaging parameters

None of the investigated semi-quantitative ⁶⁸Ga-PSMA PET parameters significantly correlated with its correspondent parameter on ⁶⁸Ga-DOTA-RM2 PET images, nor with MRI quantitative parameters (p value ≥ 0.05). Similarly, MRI quantitative parameters

did not correlate with ^{68}Ga -DOTA-RM2 PET semi-quantitative parameters.

^{68}Ga -DOTA-RM2 SUVmax, SUVmean50 and SUVmean60 correlated with PSA level at diagnosis (respectively, $\rho = -0.55$, -0.53 , -0.53 and p value = 0.04 , 0.04 , 0.04). ^{68}Ga -PSMA PET and MRI parameters did not correlate with any of the considered clinical data (p value ≥ 0.05).

Discussion

The present pilot study reports our preliminary experience on the use of ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 PET/MRI imaging in high-risk prostate cancer staging.

Few studies have investigated prostate cancer by using both ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 PET so far, both in the staging [15] and restaging setting of the disease [18, 19]

In our cohort of patients, differently to all the other published papers, all subjects have been studied by using a hybrid PET/MRI scanner both for ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 radiotracers [15, 18, 19].

In fact, among the few published studies that investigated the role of this peculiar multitracers approach in PCa, PET/MRI and PET/CT have been used alternatively for ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 PET scans [18, 19] or PET/CT have been adopted as the only hybrid imaging modality [15].

In the setting of PCa staging, Schollhammer and colleagues reported a clinical case of a patient undergoing PET/CT scans with ^{68}Ga -PSMA, ^{68}Ga -RM2 and ^{18}F -Choline, while Fassbender et al. used ^{68}Ga -PSMA PET/CT and ^{68}Ga -Ga-RM2 PET/MRI to study eight patients with primary diagnosis of PCa [15, 24]. The same heterogeneity in terms of type of scanners used for patients' scanning can be also observed in the few studies assessing the role ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 in patients with recurrent PCa. The first study performing a comparative evaluation between these two radiotracers in recurrent PCa is the one by Minamimoto et al. In this pioneering work, comparing the biodistribution of ^{68}Ga -PSMA-11 and ^{68}Ga -RM2 in a small cohort of patients with biochemically recurrent PCa, PET/CT was adopted for ^{68}Ga -PSMA studies while PET/MRI scanner was used for ^{68}Ga -DOTA-RM2 PET acquisitions [18].

Similarly, Baratto et al. recently published a study on the use of ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 in a cohort of patients with recurrent PCa, and compared the diagnostic performances of these two radiotracers. They showed that ^{68}Ga -PSMA11 and ^{18}F -DCFPyL might have a complementary role as they detect different sites of disease recurrence. Notably, the group used a PET/MR scanner only for ^{68}Ga -RM2 imaging and regarding PSMA PET/CT scans, ^{68}Ga -PSMA11 or ^{18}F -DCFPyL were alternatively used [19].

The use of a PET/MRI scanner in the staging phase of PCa allows to perform a diagnostic MRI on the pelvic region, thus obtaining all the necessary morphological and multiparametric information for an accurate identification and characterization of the primary tumor. Moreover, the possibility to simultaneously acquire a PET scan with two different radiotracers assessing different metabolic pathways provides additional information regarding primary tumor characteristics, together with a whole-body evaluation of the disease. Differently from other groups that investigated the dual tracer approach of ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 in PCa staging, or restaging, using a PET/CT scanner [15, 18, 19], one of the most relevant patients' advantage in the present study relies on the possibility to have received a diagnostic MRI simultaneously acquired to the PET image acquisition. In fact, MRI is expected to increase the diagnostic accuracy of PET imaging for local staging (ECE and SVI) [25], and the information derived from both modalities could be incorporated into clinical nomograms to significantly enhance the pre-operative staging accuracy [26, 27]. Moreover, MRI shows excellent diagnostic performance in the detection of bone metastases [28]. If used in combination with PET, MRI could provide complementary information on bone disease when PET findings are equivocal or when metastatic lesions do not show significant PSMA uptake. Finally, WB-MRI could be of added value in monitoring the response to loco-regional or systemic treatments [29, 30].

In our cohort of patients, the primary PCa was detected in all patients by all three imaging modalities, with slight differences regarding the multifocality of intra-prostatic findings. Even if the comparison with histological examination was not yet available for the patients included in the study, the different intra-prostatic findings detected by ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 might reflect the complementarity of these radiotracers; the same consideration might be applied to lymph nodal and bone localizations. These results enlightening a synergic role of ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 in prostate cancer are in line with previous published data [15, 18, 19].

For instance, Fassbender et al. in their cohort of 8 patients with primary PCa undergoing ^{68}Ga -PSMA PET/CT and ^{68}Ga -Ga-RM2 PET/MRI, concluded that the qualitative findings of PET scans could provide combined relevant information. In their study, both radiotracers partially showed the same tumor region and, in some cases, different tumor parts, thus providing a better PCa characterization and reflecting the heterogeneous and sometimes polyclonal behaviour that characterize PCa [15]. Similarly, the results reported by Baratto and colleagues, comparing RM2-PET and PSMA-PET in patients with biochemically recurrent PCa and by Iagaru and colleagues in patients with newly diagnosed intermediate- or high-risk prostate cancer suggested that the use of both ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 provided different and complementary information on PCa [19, 31].

To investigate the correspondence of the intra-prostatic findings referable to the site of primary tumor across modalities, DICE score between manually segmented primary intra-prostatic tumor volumes on ^{68}Ga -PSMA, ^{68}Ga -DOTA-RM2 PET and MR images were calculated. Volumes of the primary tumors, as defined in all the investigated imaging modalities largely overlap. The highest mean DICE score was the one between ^{68}Ga -PSMA PET and MRI. This may be partially explained by the fact that ^{68}Ga -DOTA-RM2 tumor volumes were generally smaller, and partially by the fact that ^{68}Ga -PSMA PET and MRI were simultaneously acquired, thus being intrinsically co-registered. Conversely, automatic co-registration tool on 3D Slicer, with manual adjustments when needed, was used to overlap ^{68}Ga -DOTA-RM2 PET images to ^{68}Ga -PSMA and MR diagnostic images. A residual component of noise might have hampered the computation of the DICE score, therefore resulting in minor overlap between ^{68}Ga -DOTA-RM2 PET and the other images.

Spearman correlations between multitracer PET and MRI parameters revealed no significant associations between parameters derived from different imaging modalities. This is in contrast with the strong association between ^{68}Ga -PSMA PET and ^{68}Ga -DOTA-RM2 PET SUVmax and SUVmean reported by Minamimoto et al. in 2016 [18]. However, that pioneering work relied on a very small sample ($n = 7$) of patients presenting with biochemical recurrence. Future studies with larger cohorts of patients are needed to unravel the possible association between semi-quantitative parameters derived from ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 PET. Furthermore, concerning the correlation between imaging parameters and clinical data, an inverse correlation was found between ^{68}Ga -DOTA-RM2 SUVmax, SUVmean40, SUVmean50 and PSA level at diagnosis. All the other tested correlations resulted non-significant and this is in line with what is reported by Fassbender et al. [15]. These results have to be interpreted with great caution and more evidence is needed before speculating on the clinical utility of these findings, since our sample was small and quantitative analyses might be susceptible to lack of statistical power. Future studies, with larger samples, will allow to unravel the possible association between semi-quantitative PET, quantitative MRI parameters and clinical data.

Some limitations should be pointed out regarding the present study. First of all, histopathological correlation with the post-surgical specimen was not performed because only a minority of patients have undergone radical prostatectomy so far. Therefore, being the present analysis a pilot study with only a preliminary evaluation of the PET/MRI data, we decided to only consider prostatic biopsies as standard of reference. This aspect, will be certainly improved as soon as all histological data will be available, with a detailed co-registration between imaging and histopathological data and subsequent data analysis.

Another limitation of this study is the low number of patient population. However, besides the fact that the few papers already published on PCa staging and using both ^{68}Ga -PSMA and ^{68}Ga -RM2 PET radiotracers included a number of patients even lower than the one presented in the present paper [15], we consider that these preliminary data are interesting to underlie the potential complementary and synergic role of the two different PET radiotracers together with mpMRI.

To conclude, based on the results of the present study, a potential complementary role of ^{68}Ga -PSMA and ^{68}Ga -DOTA-RM2 in PCa staging can be enlightened, in view of the different findings detected by the two imaging modalities in some of the patients

included in our cohort. In fact, the possibility to identify different sites of disease by using a multitracer approach, certainly improves the disease characterization and therefore it may ultimately have impact on patients' management and follow-up. Moreover, a synergic role of the three imaging modalities, namely ^{68}Ga -PSMA PET, ^{68}Ga -DOTA-RM2 PET and mpMRI for primary PCa characterization has been clearly showed. These findings should be validated on larger cohorts of patients to definitively assess the utility of hybrid ^{68}Ga -PSMA PET/MRI and ^{68}Ga -DOTA-RM2 PET/MRI in the clinical management of PCa.

Declarations

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Ethical approval and consent to participate

This study was approved by the Institutional Ethics Committee of IRCCS San Raffaele Scientific Institute (EudraCT: 2018-001034-18) and all patients gave written informed consent to participate to the study.

Consent for publication

NA

Competing interests

All the Authors have no conflicts of interest to disclose related to the present paper.

Availability of data and material

Available from the corresponding author on reasonable request.

Code availability

All code needed to replicate our analyses is available upon request from the corresponding author

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Figures

Figure 1

Physiological biodistribution of ^{68}Ga -PSMA (A) and ^{68}Ga -DOTA-RM2 (B) in patient n.3

Figure 2

A 53 years-old patient with biopsy proven PCa (pt n.10), Gleason score 9 (5+4) with a PSA level at diagnosis of 3.13 ng/mL. Concordant 68Ga-PSMA PET/MRI (top panel; A: transaxial 68Ga-PSMA PET; B: 68Ga-PSMA PET/MRI; C: Axial T2-weighted sequence; D: Axial T2-weighted small FOV; E: DWI (b=1400)) and 68Ga-DOTA-RM2 PET/MRI (bottom panel; F: transaxial 68Ga-DOTA-RM2 PET; G: 68Ga-DOTA-RM2 PET/MRI; H: axial T2-weighted sequence)

Figure 3

A 80 years-old patient with biopsy proven PCa (patient n.2), Gleason score 8 (3+5) with a PSA level at diagnosis of 11.13 ng/mL. Discordant 68Ga-PSMA PET/MRI (top panel; A: transaxial 68Ga-PSMA PET; B: 68Ga-PSMA PET/MRI; C: axial T2-weighted sequence; D: axial T2-weighted small FOV; E: DWI (b=1400)) and 68Ga-DOTA-RM2 PET/MRI (bottom panel; F: transaxial 68Ga-DOTA-RM2 PET; G: 68Ga-DOTA-RM2 PET/MRI; H: axial T2-weighted sequence)

Figure 4

A 75 years-old patient with biopsy proven PCa (patient n.3), Gleason score 9 (4+5) with a PSA level at diagnosis of 4.73 ng/mL. 68Ga-PSMA and 68Ga-DOTA-RM2 PET/MRI were discordant in detecting lymphnodal metastases. 68Ga-PSMA PET/MRI (top panel; A: transaxial 68Ga-PSMA PET; B: 68Ga-PSMA PET/MRI; C: post-contrast Water Lava-Flex sequence) showed bilateral pararectal and left external iliac lymphnodal uptake; 68Ga-DOTA-RM2 PET/MRI (bottom panel; D: transaxial 68Ga-DOTA-RM2 PET; E: 68Ga-DOTA-RM2 PET/MRI; F: Water-Lava Flex sequence) showed left pararectal and left external iliac lymphnodal uptake. White arrow indicates the lymph node clearly detected by both tracers; red arrows lymph nodes detected by 68Ga-PSMA PET/MRI only

Figure 5

A 59 years-old patient with biopsy proven PCa (patient n.6), Gleason score 9 (4+5) with a PSA level at diagnosis of 11.0 ng/mL. 68Ga-PSMA PET/MRI (top panel; A: 68Ga-PSMA PET/MRI; B: axial T2-weighted sequence of the pelvis; C: axial DWI (b=1000) displayed with inverted greyscale map) showed increased uptake in correspondence of the left sacral ala, where MRI detected a bone metastasis; 68Ga-DOTA-RM2 PET/MRI (bottom panel; D: 68Ga-DOTA-RM2 PET/MRI; E: axial T2-weighted sequence of the pelvis) did not show any 68Ga-DOTA-RM2 in correspondence of the bone metastases. Red arrows indicates bone metastases.

Figure 6

Images representing concordant (A) and discordant (B) contouring on DICE analysis. A: A 74 years-old patient with biopsy proven PCa (pt n.9), Gleason score 9 (5+4) with a PSA level at diagnosis of 6.37 ng/mL presenting a prostatic lesion located in the left lobe of the gland. The image shows a concordant identification of the lesion on 68Ga-PSMA PET images (blue), 68Ga-DOTA-RM2 PET images (yellow) and MRI (red). DICE SCORE: 68Ga-PSMA vs 68Ga-DOTA-RM2= 0.6019, 68Ga-PSMA vs MRI= 0.7581. 68Ga-DOTA-RM2 vs MRI= 0.7220. B: A 52 years-old patient with biopsy proven PCa (pt n.14), Gleason score 8 (4+4) with a PSA level at diagnosis of 8.04 ng/mL presenting a focal left prostatic. DICE SCORE: 68Ga-PSMA vs 68Ga-DOTA-RM2= 0.2918, 68Ga-PSMA vs MRI= 0.6162. 68Ga-DOTA-RM2 vs MRI= 0.2216