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Title: Correlation of ^{68}Ga-RM2 PET with Post-Surgery Histopathology Findings in Patients with Newly Diagnosed Intermediate- or High-Risk Prostate Cancer

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Abstract

Rationale: ^{68}Ga-RM2 targets gastrin-releasing peptide receptors (GRPR), which are overexpressed in prostate cancer (PC). Here, we compared pre-operative ^{68}Ga-RM2 PET to post-surgery histopathology in patients with newly diagnosed intermediate- or high-risk PC.

Methods: Forty-one men, 64.0±6.7-year-old, were prospectively enrolled. PET images were acquired 42 – 72 (median±SD 52.5±6.5) minutes after injection of 118.4 – 247.9 (median±SD 138.0±22.2)MBq of ^{68}Ga-RM2. PET findings were compared to pre-operative mpMRI (*n*=36) and ^{68}Ga-PSMA11 PET (*n*=17) and correlated to post-prostatectomy whole-mount histopathology (*n*=32) and time to biochemical recurrence. Nine participants decided to undergo radiation therapy after study enrollment.

Results: All participants had intermediate (n=17) or high-risk (n=24) PC and were scheduled for prostatectomy. Prostate specific antigen (PSA) was 8.8±77.4 (range 2.5 – 504) ng/mL, and 7.6±5.3 (range 2.5 – 28.0) ng/mL when excluding participants who ultimately underwent radiation treatment. Pre-operative ^{68}Ga-RM2 PET identified 70 intraprostatic foci of uptake in 40/41 patients. Post-prostatectomy histopathology was available in 32 patients in which ^{68}Ga-RM2 PET identified 50/54 intraprostatic lesions (detection rate = 93%). ^{68}Ga-RM2 uptake was recorded in 19 non-enlarged pelvic lymph nodes in 6 patients. Pathology confirmed lymph node metastases in 16 lesions, and follow-up imaging confirmed nodal metastases in 2 lesions. ^{68}Ga-PSMA11 and ^{68}Ga-RM2 PET identified 27 and 26 intraprostatic lesions, respectively, and 5 pelvic lymph nodes each in 17 patients. Concordance between ^{68}Ga-RM2 and ^{68}Ga-PSMA11 PET was found in 18 prostatic lesions in 11 patients, and 4 lymph nodes in 2 patients. Non-congruent findings were observed in 6 patients (intraprostatic lesions in 4 patients and nodal lesions in 2 patients). Both ^{68}Ga-RM2 and ^{68}Ga-PSMA11 had higher sensitivity and accuracy rates with 98%, 89%, and 95%, 89%, respectively, compared to mpMRI at 77% and 77%. Specificity was highest for mpMRI with 75% followed by ^{68}Ga-PSMA11 (67%), and ^{68}Ga-RM2 (65%).

Conclusion: ^{68}Ga-RM2 PET accurately detects intermediate- and high-risk primary PC with a detection rate of 93%. In addition, it showed significantly higher specificity and accuracy compared to mpMRI and similar performance to ^{68}Ga-PSMA11 PET. These findings need to be confirmed in larger studies to identify which patients will benefit from one or the other or both radiopharmaceuticals.

Key words: ^{68}Ga-RM2; ^{68}Ga-PSMA11; PET; Prostate Cancer; Histopathology

Introduction

Prostate cancer (PC) remains the most-common non-cutaneous cancer in American men and the second highest cause of cancer-related mortality (*1*). Cancer stage at diagnosis defines subsequent management. While low-risk PC (Gleason score 6, pre-treatment prostate specific antigen [PSA] <10 ng/mL, and clinical stage T1–T2a) may be managed with active surveillance, patients with higher grade, clinically significant cancers typically receive treatment. Imaging plays a crucial role in initial staging. Multiparametric magnetic resonance imaging (mpMRI) is widely used for initial evaluation. However, mpMRI may miss clinically significant PC in 5-8% (*2*) to 35% (*3*) of cases.

Molecular imaging with positron emission tomography and computed tomography (PET/CT) or PET/MRI is changing the landscape of PC staging with the development and regulatory approval of new radiopharmaceuticals. The most promising radiopharmaceuticals target prostate-specific membrane antigen (PSMA). PSMA is highly overexpressed in 90-95% of PC (*4-7*). However, it is not specific to PC (*8,9*) and false positive (FP) findings have been reported (*10-13*). Thus, there is a continued need for other imaging targets. ^{68}Ga-RM2 is a bombesin receptor antagonist that targets the gastrin-releasing peptide receptor (GRPR) with high affinity (*14*). GRPR is highly overexpressed in several cancers including breast (*15,16*), small cell lung cancer (*17*), gastrointestinal stromal and neuroendocrine tumors (*18,19*) and in PC (*20-24*), especially in earlier stages, making it an attractive target for initial staging (*20*).

In this study we compared pre-operative ^{68}Ga-RM2 PET and mpMRI to histopathology after radical prostatectomy (RP) in patients with newly diagnosed intermediate- or high-risk PC. In a subgroup of patients, comparison with ^{68}Ga-PSMA11 PET was also available.

Materials And Methods

Participants

Patients scheduled to undergo RP for newly diagnosed, non-treated, intermediate- or high-risk PC were prospectively enrolled in 2 clinical trials evaluating the performance of ^{68}Ga-RM2 (NCT03113617) and ^{68}Ga-PSMA11 (NCT02678351). This study was approved by the local institutional review board. Written informed consent was obtained from all participants. Pre-surgical clinical assessments included serum PSA, Gleason score, clinical stage, and risk assessment according to the D'Amico classification (*25*). Patients were followed-up to evaluate time to biochemical recurrence (BCR).

Scanning protocols

^{68}Ga-RM2 PET

Discovery 690 PET/CT (*n*=19), Discovery MI PET/CT (*n*=19) or SIGNA PET/MRI (*n*=3) scanners (GE Healthcare, Waukesha, WI, USA) were used. Details of PET/CT and PET/MRI acquisitions were previously described (*26,27*). The choice of PET/CT or PET/MRI was dictated by the funding available to support the clinical trials. Discovery MI PET/CT and SIGNA PET/MRI use the same SiPM-based detectors and we previously reported their clinical evaluation (*28,29*).

^{68}Ga-PSMA11 PET

SIGNA PET/MRI scanner (GE Healthcare, Waukesha, WI, USA) was used. Details of PET/MR image acquisition were previously described (*27*).

^{68}Ga-RM2 and ^{68}Ga-PSMA11 were synthesized as previously reported (*30*).

mpMRI protocol

The protocol consisted of T2 weighted imaging (T2WI), diffusion weighted imaging, and dynamic contrast-enhanced imaging sequences using a 3T scanner (MR750, GE Healthcare, Waukesha, WI, USA). Details of mpMR image acquisition were previously described (*31*).

Histopathology

Hematoxylin-eosin–stained slides from whole-mount prostate specimens were analyzed according to standard of care. The slides were annotated by a genitourinary pathologist (CK) to outline areas of cancer across the entire gland.

Fusion of histology and PET/MRI

The RAPSODI registration framework was used to align corresponding pre-operative axial T2WI, whole-mount histopathology and ^{68}Ga-PSMA11 PET/MRI utilizing rigid, affine, and deformable transformations (*32*). This registration ensures a slice-to-slice alignment between histology – including ground-truth cancer labels – mpMRI, and PET/MRI. The methodology relies on precise prostate segmentations, automatically generated by a validated deep learning model, and its accuracy was evaluated using a Dice Similarity coefficient (*33*).

Image analysis

Two nuclear medicine physicians (HD, AI) reviewed and analyzed PET images independently and in a random, blinded fashion, however aware that participants were scheduled to undergo RP for known PC. Any focal uptake of ^{68}Ga-RM2 or ^{68}Ga-PSMA11 higher than the adjacent background and not associated with physiologic accumulation was deemed suspicious for PC (*34,35*). The number and location of each lesion and its maximum standardized uptake value (SUV_{max}) was recorded. A visual comparison was performed between annotated suspicious lesions on PET and ‘cancer’ annotated histology slides. A lesion was deemed true positive (TP) when annotations on PET and histopathology matched and considered true negative (TN) when uptake on PET was not above background and when there was no ‘cancer’ annotation on corresponding histopathology slide.

mpMRI were interpreted as standard of care using PI-RADS criteria version 2 (*36*). Lesions with PI-RADS score ≥3 were recorded. A PI-RADS score of 3 was considered equivocal, PI-RADS 4 likely, and 5 highly likely for PC.

Statistical analysis

A logistic regression model was used to determine the predictive value of pre-operative biopsy, mpMRI, ^{68}Ga-RM2, and ^{68}Ga-PSMA11 PET for final histopathology and risk prediction. Sensitivity, specificity, and accuracy were stratified to intermediate- and high-risk groups for ^{68}Ga-RM2 and ^{68}Ga-PSMA11. McNemar test determined difference between ^{68}Ga-RM2 and mpMRI for sensitivity, specificity, and accuracy. A Wilcoxon signed-rank test was performed to determine differences between SUV_{max}. Concordance correlation was used for ^{68}Ga-RM2 and ^{68}Ga-PSMA11 SUV_{max}. The degrees of correlation are: >0.99 almost perfect, 0.95 – 0.99 substantial, 0.90 – 0.95 moderate, and <90, poor agreement. Spearman correlation was used for evaluation of SUV_{max} and time to BCR. Statistical analyses were performed with Stata v16.1 (Stata CorpLLC College Station, TX, USA). Continuous data are presented as median±standard deviation (SD), minimum (min) – maximum (max) values. A *P*-value of <0.05 was considered significant except when Bonferroni correction was applied for concordance analyses (*P*-value <0.0025 significant), and risk prediction (*P*-value <0.017 significant).

Results

Forty-one men, 64.0±6.7 (range 50–78) year-old, scheduled to undergo RP for PC were prospectively enrolled. Seventeen (41.5%) participants had intermediate-risk and 24 (58.5%) had high-risk PC. PSA was 8.8±77.4 (range 2.5–504) ng/mL, and 7.6±5.3 (range 2.5–28.0) ng/mL when excluding participants who received radiation therapy (RT). PSA was undetectable 3 months after RP in all but 3 patients. In one patient, preoperative biopsy was not available and

PC was diagnosed by imaging and PSA. All participants (*n*=41) were imaged with ^{68}Ga-RM2 PET, 36/41 had additional mpMRI, and 17/41 ^{68}Ga-PSMA11 PET. Of these 41 patients, 32 underwent RP and 9 opted for RT after enrollment in the protocol and completion of the scan. Patient characteristics are shown in Table 1.

^{68}Ga-RM2 PET

^{68}Ga-RM2 PET identified 70 intraprostatic foci in 40/41 and focal uptake in 19 non-enlarged pelvic lymph nodes in 6/41 patients. One participant had a negative ^{68}Ga-RM2 PET scan.

In the 32 patients who underwent RP, ^{68}Ga-RM2 identified 54 intraprostatic foci, with 50/54 (92.6%) confirmed by histology (example showed in Figure 1). Four lesions in 4 patients were false negatives (FN). A total of 527 lymph nodes were removed of which 26/527 proved to be metastases in 8 participants. ^{68}Ga-RM2 PET identified 19 lymph nodes in 6 patients, of which 16 were verified by pathology. The 3 unverified positive lymph nodes were seen in the 3 patients whose PSA did not decrease after RP, suggesting TP for metastases. Two lesions were subsequently confirmed by standard of care ^{18}F-Fluciclovine PET after RP.

SUV_{max} of histologically verified intraprostatic lesions was statistically significantly higher than verified lymph node metastases (*P*=0.04) and benign prostatic uptake (*P*<0.001). ^{68}Ga-RM2 uptake in lymph node metastases was also significantly higher than benign nodes (*P*<0.001). SUV_{max} findings are summarized in Table 2.

mpMRI

mpMRI identified lesions in 36/41 participants: 43 PI-RADS ≥4 lesions (vs. 64 on corresponding ^{68}Ga-RM2) in 33, and 6 PI-RADS 3 lesions (vs. 5 on corresponding ^{68}Ga-RM2) in 3 patients. In the 30 participants who underwent RP, mpMRI detected 42 intraprostatic lesions with 38 confirmed by histopathology (vs. 50 seen and 48 verified lesions on corresponding ^{68}Ga-

RM2). One suspicious pelvic lymph node was seen and verified as PC metastasis on mpMRI (vs. 18 seen and 16 verified pelvic lymph nodes on corresponding ^{68}Ga-RM2 PET). Four lesions were FP on histopathology while 10 lesions were FN. Table 3 summarizes detection rates of the 3 modalities.

^{68}Ga-PSMA11 and ^{68}Ga-RM2 PET

In 17 participants, ^{68}Ga-RM2 and ^{68}Ga-PSMA11 PET identified 27 and 26 intraprostatic lesions, respectively, and 5 positive pelvic lymph nodes each. Concordance was seen in 18 intraprostatic lesions (example showed in Figure 2) and 3 lymph nodes. Histopathology was available in 13 patients and confirmed 18/19 and 17/18 intraprostatic lesions, and 4/5 and 3/5 lymph node metastases for ^{68}Ga-RM2 and ^{68}Ga-PSMA11, respectively. On a per lesion analysis, ^{68}Ga-RM2 had 1 FP and 2 FN intraprostatic lesions, while ^{68}Ga-PSMA11 had 1 FP and 3 FN. Six patients had incongruent uptake (examples showed in Supplemental Figures 1 and 2): cancer was present in 5/6 lesions on ^{68}Ga-RM2 vs. 3/4 on ^{68}Ga-PSMA11.

^{68}Ga-PSMA11 SUV_{max} of verified PC was significantly higher than lymph node metastases (P=0.002). No statistically significant difference where noted when comparing SUV_{max} for ^{68}Ga-RM2 to ^{68}Ga-PSMA11 for intraprostatic cancers (P=0.43) or lymph node metastases (P=0.25). ^{68}Ga-RM2 and ^{68}Ga-PSMA11 were poorly correlated between the left and right prostate. Table 4 summarizes ^{68}Ga-RM2 and ^{68}Ga-PSMA11 findings.

Sensitivity, specificity, and accuracy

All 3 modalities, ^{68}Ga-RM2, ^{68}Ga-PSMA11 PET and mpMRI, were significant predictors for PC ($P \leq 0.0025$). For intraprostatic lesions, both ^{68}Ga-RM2 and ^{68}Ga-PSMA11 had higher sensitivity and accuracy rates than mpMRI while specificity was highest for mpMRI (Supplemental Table 1). For intraprostatic and lymph node lesions, specificity increased for both radiopharmaceuticals while sensitivity decreased for ^{68}Ga-PSMA11 (Supplemental Table 2).

Significantly higher sensitivity (P=0.01) and accuracy (P<0.01) were seen for ^{68}Ga-RM2 PET compared to mpMRI.

Sensitivity, specificity, and accuracy for ^{68}Ga-RM2 were slightly higher for high-risk than the intermediate-risk group. For ^{68}Ga-PSMA11, the opposite was found (Supplemental Table 3).

For the relationship and predictive value of PSA (grouped into <5, 5-10, 10.1-15 and ≥15 ng/mL), PI-RADS (3, ≥4), and SUV_{max} for histopathological outcome, the only significance found was a higher SUV_{max} of ^{68}Ga-RM2 in PSA ≥5 vs. PSA <5 (P<0.0025, Figure 3).

Follow-up

Six patients were lost in follow-up. Post-RP, patients (n=26) were followed for 28.6±11.7 (range 7.0–47.3) months. PSA remained undetectable in 15 patients, while 11 developed BCR 17.7±10.8 (range 2.8–32.0) months after RP. ^{68}Ga-RM2 SUV_{max} of intraprostatic lesions and time to BCR were negatively correlated (r=-0.34), meaning the lower the SUV_{max}, the longer the time to BCR. The correlation of PSA and time to BCR was also negatively correlated (r=-0.25), indicating the lower the PSA, the longer the time to BCR.

Discussion

In this study, we prospectively compared GRPR-targeting ^{68}Ga-RM2 PET with whole-mount histopathology after RP in patients with newly diagnosed PC. Sensitivity and accuracy were high for ^{68}Ga-RM2 at 98% and 89%, respectively, and were comparable to ^{68}Ga-PSMA11, and superior to mpMRI. However, specificity of 65% was lower than mpMRI. These results were comparable to previously reported sensitivity, specificity, and accuracy rates of 89%, 81% and 83% for prostate lesions, and sensitivity of 70% for lymph node metastases for ^{68}Ga-RM2 PET/CT in a smaller cohort of 14 men with primary PC and 3 with BCR (*37*).

^{68}Ga-RM2 and ^{68}Ga-PSMA11 both showed high detection rates for primary PC and lymph

node metastases but were poorly correlated to each other. A recently published study compared ^{68}Ga-RM2 and ^{68}Ga-PSMA11 PET/MRI in staging of 19 men with biopsy proven high-risk PC whereas histopathology was available in 12 patients. While the detection rate of 95% for the primary tumor is similar to our study, the positivity rates for lymph nodes were lower (37% for ^{68}Ga-PSMA11, 21% for ^{68}Ga-RM2). Apart from a negative ^{68}Ga-RM2 in 1 participant, concordant uptake was seen between ^{68}Ga-RM2 and ^{68}Ga-PSMA11 (*38*). The incongruent uptake pattern in our cohort might be due to our more heterogenous groups of intermediate- and high-risk PC. However, the difference in expression pattern of PSMA and GRPR is consistent with our previous findings in BCR PC (*30,39*) and is supported by immunohistochemistry showing that GRPR and PSMA expression are not correlated (*40*). Fassbender et al found in a voxel-based approach that ^{68}Ga-RM2 and ^{68}Ga-PSMA11 in 8 patients with primary PC showed similar averaged SUV_{mean} but, on a per patient basis, different intensity, revealing again a different expression pattern of GRPR and PSMA (*41*).

We found no correlation between ^{68}Ga-RM2 uptake and Gleason score or tumor volume, but a positive correlation between PSA and ^{68}Ga-RM2 SUV_{max}. SUV_{max} was also negatively correlated to time to BCR. This is supported by previous findings in patients with BCR PC showing a positive correlation between ^{68}Ga-RM2 positivity and PSA and PSA velocity and conversely, a negative correlation of SUV_{max} and PSA with time to BCR indicating the higher ^{68}Ga-RM2 SUV_{max} and PSA, the shorter the time to BCR (*27*). However, there is controversy (*24*) as to whether GRPR density is related to a better prognosis of PC (*20,21*) or found in high-risk tumors as our results indicate. Larger studies with longer follow-up are needed to understand these possible correlations.

The need now is to understand if and how these radiopharmaceuticals may provide complementary and useful information in patients with PC at various stages and risks. Given the high tumor heterogeneity in PC, and that neither ^{68}Ga-RM2 nor ^{68}Ga-PSMA11 are 100% sensitive

or specific and hence attributing to FP and FN lesions, a bispecific tracer that targets GRPR and PSMA simultaneously may present a promising imaging option (*42*).

Limitations of this study include the relatively small number of patients, especially of participants undergoing both ^{68}Ga-RM2 and ^{68}Ga-PSMA11 PET, and the different imaging modalities used, i.e., different PET/CT scanners and PET/MRI. In addition, not all participants had histopathology data since some elected to undergo RT. Correlating lymph node positivity to histopathology is a challenge as not all lymph nodes seen on PET were resected. PET data were analyzed by readers who were aware that participants were scheduled to undergo RP for known PC, while readers for mpMRI were unaware that participants were scheduled for RP as mpMRI was part of clinical care for PC diagnosis.

Conclusion

^{68}Ga-RM2 PET accurately detects intermediate- and high-risk primary PC with significantly higher specificity and accuracy compared to mpMRI and similar performance to ^{68}Ga-PSMA11 PET. The poor correlation between ^{68}Ga-RM2 and ^{68}Ga-PSMA11 underline the different expression patterns of GRPR and PSMA and the complex tumor biology of PC. Larger prospective studies are needed to identify which patients will benefit from one or the other or both radiopharmaceuticals.

Financial Disclosure

The study was partially supported by GE Healthcare.

Disclaimer

All authors declare that they have no conflict of interest.

Key Points

QUESTION: Is ^{68}Ga-RM2 PET a useful tool in initial staging of PC?

PERTINENT FINDINGS: 41 patients with newly diagnosed PC underwent ^{68}Ga-RM2 PET, a subgroup also had mpMRI (*n*=36) and ^{68}Ga-PSMA11 PET (*n*=17). ^{68}Ga-RM2 PET showed high sensitivity, accuracy, and detection rates of 98%, 89%, and 93%, respectively. Specificity at 65% was lower than mpMRI (75%). Poor correlation to ^{68}Ga-PSMA11 indicate the different expression patterns of GRPR and PSMA in PC.

IMPLICATIONS FOR PATIENT CARE: ^{68}Ga-RM2 PET accurately detected intermediate- and high-risk primary PC with significantly higher sensitivity and accuracy compared to mpMRI and similar performance to ^{68}Ga-PSMA11 PET. Larger prospective studies are needed to identify which patients will benefit from one or the other or both radiopharmaceuticals.

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Figures:

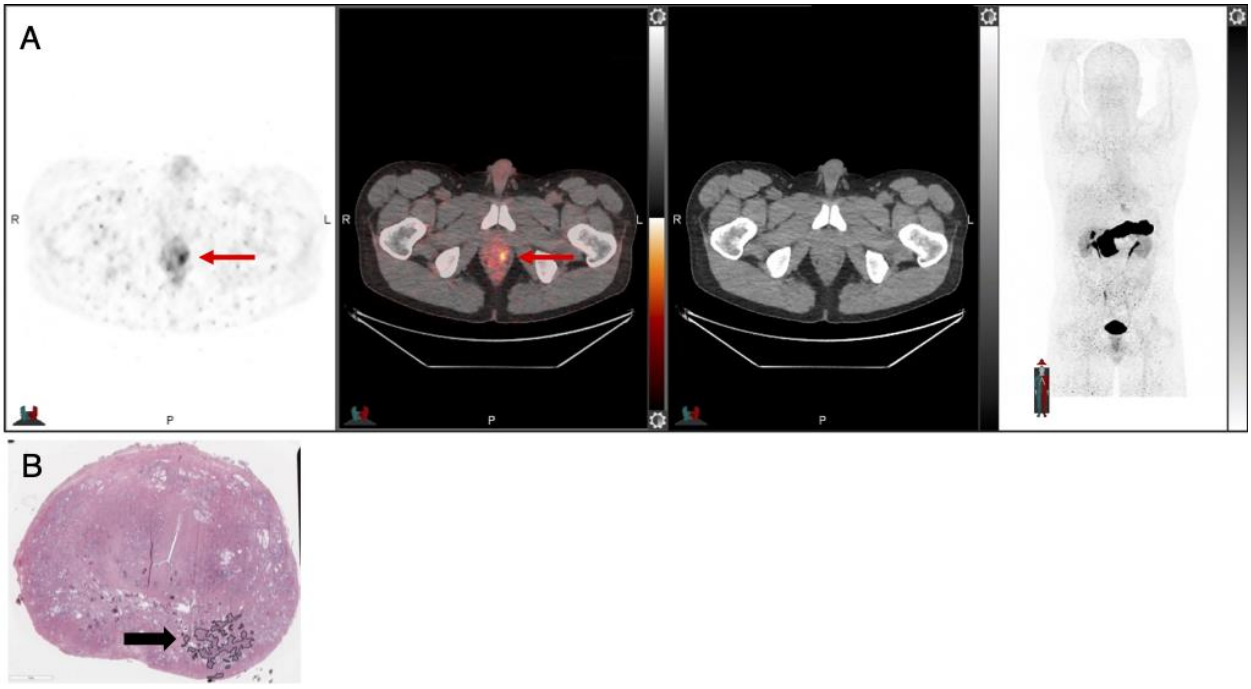


FIGURE 1: 50-year-old patient with intermediate-risk prostate cancer and PSA 5.27 ng/mL. ^{68}Ga-RM2 PET/CT (A, axial PET, fused PET/CT, CT, and maximum intensity projection [MIP] images, respectively) shows focal uptake in the left mid gland (red arrows) correlating to Gleason 4+3 prostate cancer (black arrow) on histology (B).

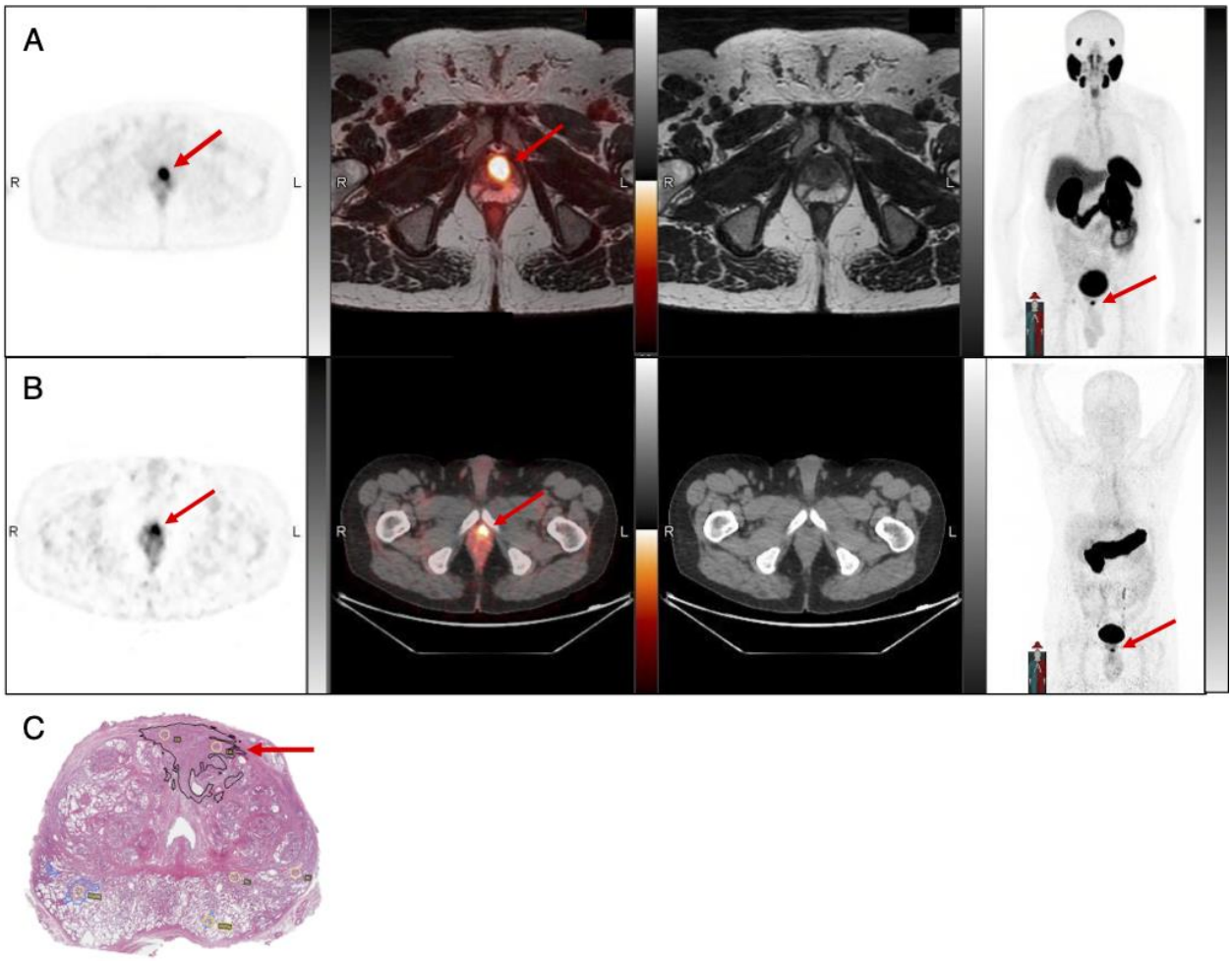


FIGURE 2: 65-year-old man, presenting with PSA 9.5 ng/mL and Gleason 3+4 lesion on pre-surgery biopsy. ^{68}Ga-PSMA11 PET/MRI (A) and ^{68}Ga-RM2 PET/CT (B) axial PET, fused PET/CT, CT, and MIP images, respectively, show concordant focal uptake in the left anterior apex of the prostate (arrows), correlating to Gleason 3+3 on histology (C, arrow).

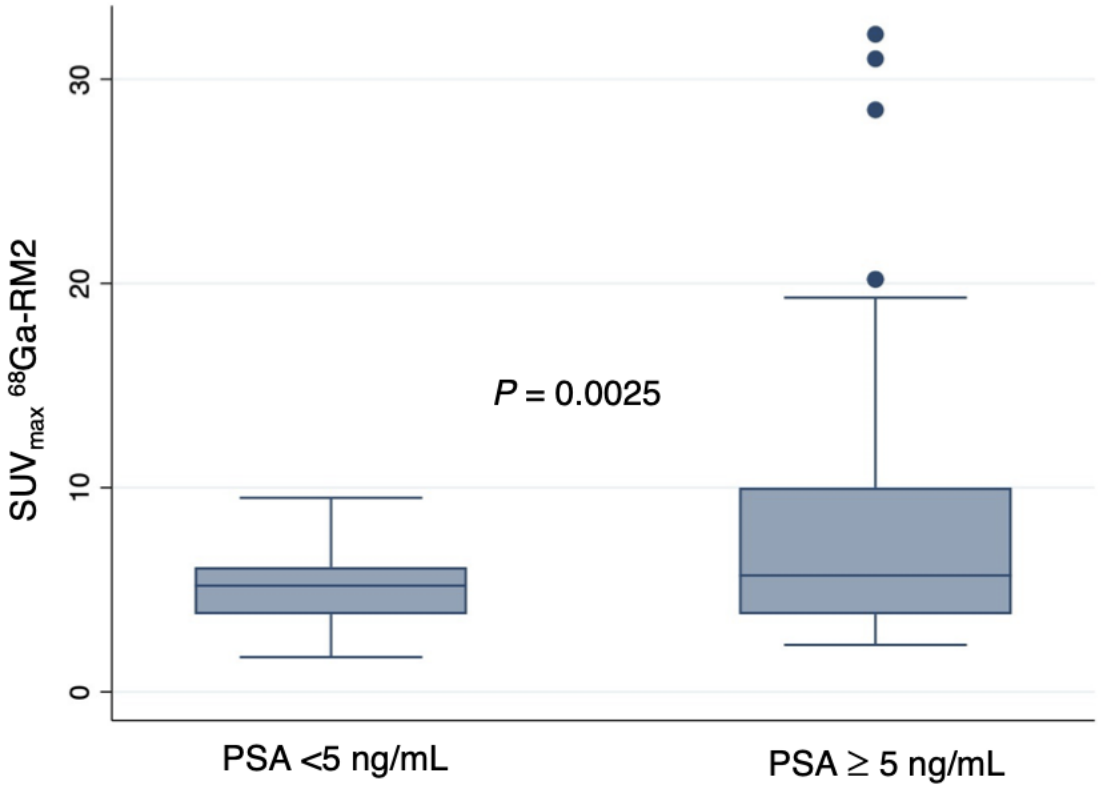


FIGURE 3: Boxplot of ^{68}Ga-RM2 SUV$_{max}$ stratified to PSA <5 ng/mL and ≥5 ng/mL. Patients with PSA ≥5 ng/mL had a statistically significantly higher SUV$_{max}$ (*P* = 0.0025).

Tables

TABLE 1: Patients' characteristics

N	41		
Age (years)	64 ± 6.7 (50 – 78)		
PSA (ng/ml)	8.8 ± 77.4 (2.5 – 504)		
PSA (excluding radiation therapy patients [ng/ml])	7.6 ± 5.3 (2.5 – 28.0)		
Risk *N* (%)	Intermediate: 17 (41.5%)	High: 24 (58.5%)	
Gleason score from pre-operative biopsy *N (%)**	Gleason score 7: 18 (45%)	Gleason score 8: 12 (30%)	Gleason score 9 10 (25%)
Clinical stage *N* (%)	cT1b: 2 (4.9%) cT1c: 18 (43.9%)	cT2a: 6 (14.6%) cT2b: 6 (14.6%) cT2c: 3 (7.3%)	cT3a: 6 (14.6%)
Pre-operative biopsy available (*N* patients)	40		
mpMRI (*N* patients)	36		
^{68}Ga-PSMA11 PET (*N* patients)	17		
Post-operative histopathology available (*N* patients)	32		

Numerical factors are expressed as median ± standard deviation (range).

*Gleason score of one patient was unavailable.

TABLE 2: SUV_{max} of ^{68}Ga-RM2 in verified intraprostatic lesions and lymph node metastases compared to benign prostate and lymph node uptake.

^{68}Ga-RM2	**SUV_{max}**	***P*-value**
SUV_{max} prostate cancer	6.1 ± 5.9 (2.3 – 32.2)	**0.04**
SUV_{max} lymph node metastases	4.7 ± 3.3 (1.9 – 12.2)	
SUV_{max} prostate cancer	6.1 ± 5.9 (2.3 – 32.2)	**<0.001**
SUV_{max} benign prostate	1.8 ± 0.5 (0.5 – 3.3)	
SUV_{max} lymph node metastases	4.7 ± 3.3 (1.9 – 12.2)	**<0.001**
SUV_{max} benign lymph nodes	0.5 ± 0.2 (0.1 – 0.9)	

Numerical factors are expressed as median ± standard deviation (range).

TABLE 3: Lesion detection rates with histopathological confirmation amongst modalities.

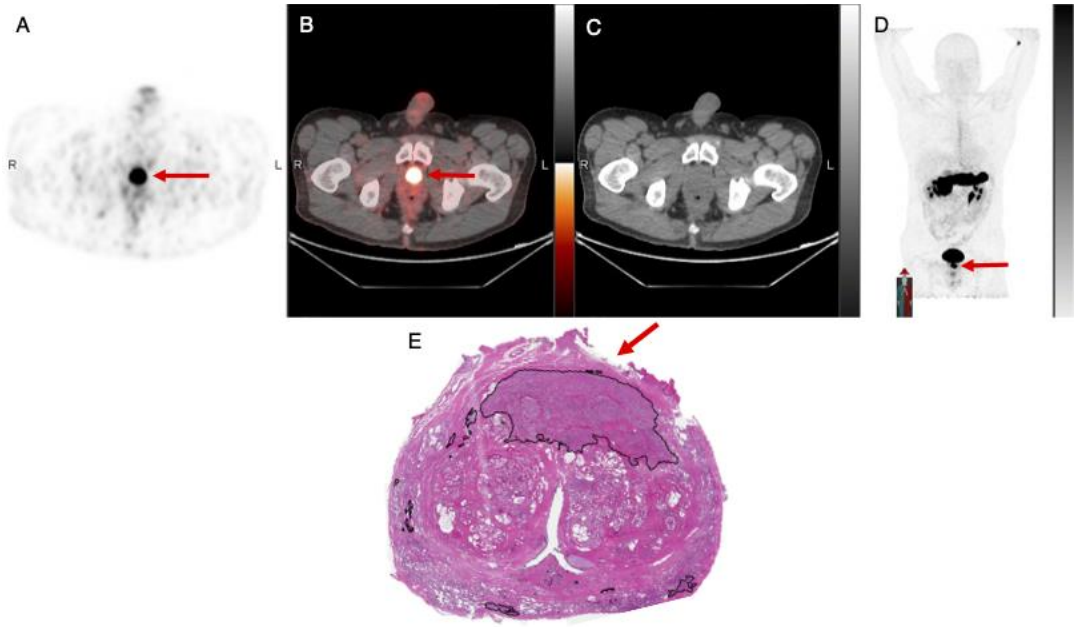
Pre-surgical						Post-surgical whole-mount pathology						
Modality	**Prostate lesions**	**Patient (*N*)**	**Lymph nodes**	**Patient (*N*)**	**Negative scan**	**Prostate lesions (%)**	**Lymph nodes (%)**	**FP (*N*) prostate**	**FN (*N*) prostate**	**FP (*N*) lymph nodes**	**FN (*N*) lymph nodes**	**Patient (*N*)**
^{68}Ga-RM2	70	40	19	6	1	50/54 (92.5%)	16/19 (88.9%)	4	4	2	1	32
^{68}Ga-PSMA11	26	17	5	4	0	17/18 (94.4%)	4/5 (80%)	1	2	1	1	13
mpMRI	49	36	1	1	2	38/42 (90.5%)	1/1 (100%)	4	10	-	-	30
- PIRADS 3	43	33	-	-	-							
- PIRADS ≥4	6	3	-	-	-							
Biopsy	151	40	-	-	0							
- Gleason score 6	34	16	-	-	0							
- Gleason score ≥7	116	40	-	-	0							

TABLE 4: Correlation of ^{68}Ga-RM2 and ^{68}Ga-PSMA11 PET in 17 patients and comparison to histopathological outcome in 13 patients.

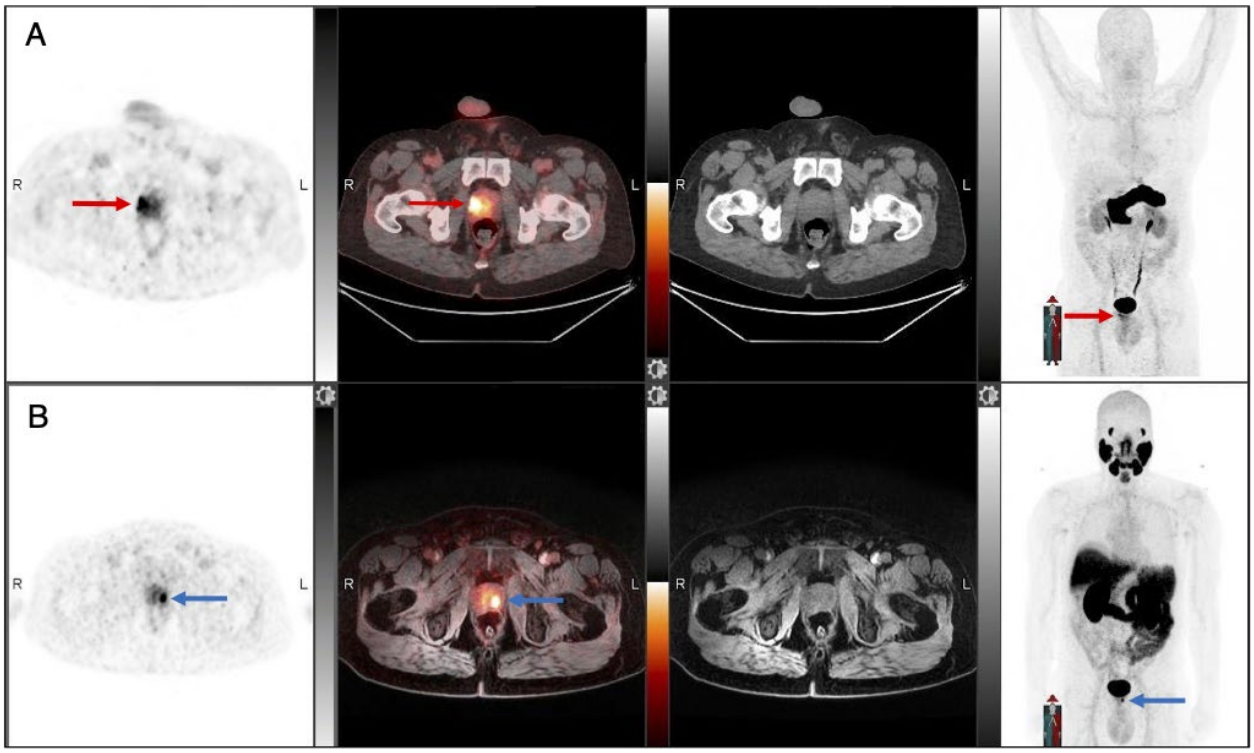
Modality	**^{68}Ga-RM2**		**^{68}Ga-PSMA11**	***N***
Injected activity (MBq)	140.6 ± 11.7 (125.1 – 162.8)		178.7 ± 31.7 (124.3 – 233.8)	17
Time to scan (min)	53.5 ± 7.4 (46 – 72)		48.0 ± 7.4 (40 – 75)	17
Time between ^{68}Ga-RM2 and ^{68}Ga-PSMA11 PET (days)	3.0 ± 5.6 (1 – 21)			17
PSA (ng/mL)	7.5±3.6 (2.5 – 14.7)			17
SUV_{max} prostate lesion (verified)	6.1 ± 4.6 (2.3 – 19.3)	*P*-value 0.43	7.7 ± 5.8 (3.6 –25.5)	13
SUV_{max} lymph node lesion (verified)	3.9 ± 3.4 (1.9 – 10.7)	*P*-value 0.25	4.3 ± 1.0 (2.3 – 5.1)	4
Post-surgical pathology	**^{68}Ga-RM2**		**^{68}Ga-PSMA11**	
***N*=13/17**	**Confirmed/total (%)**	**FP/FN**	**Confirmed/total (%)**	**FP/FN**
Prostate lesions	18/19 (94.7%)	1/2	17/18 (94.4%)	1/3
Lymph node lesions	4/5 (80%)	1/1	3/5 (60%)	2/2
Incongruent prostate lesions	5/6 (83%)	1/0	3/4 (75%)	1/0
Incongruent lymph node lesions	1/1 (100%)	0/2	0/1 (0%)	1/2
Concordance correlation	**Left prostate lesions**	**95% CI**	**Right prostate lesions**	**95% CI**
RM2 vs. PSMA11	0.77	0.56, 0.98	0.68	0.41, 0.95
Agreement	Poor			

Numerical factors are expressed as median ± standard deviation (range) and as mean (95% confidence interval).

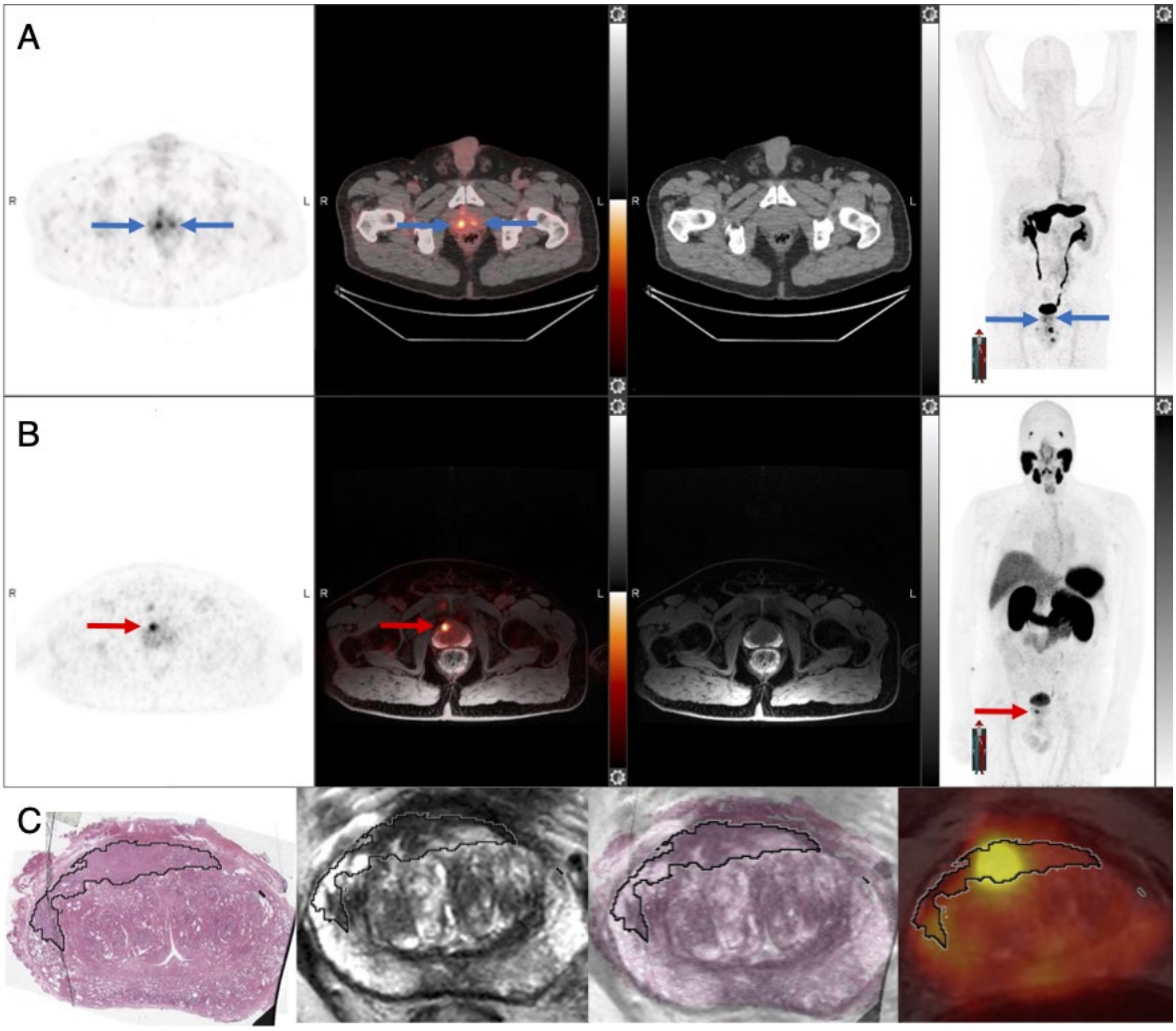
Graphical Abstract



Supplemental Materials



Supplemental Figure 1: 54-year-old patient with intermediate-risk prostate cancer and PSA 5.09 ng/mL. ^{68}Ga-RM2 PET/CT (A, axial PET, fused PET/CT, CT, and MIP) shows true positive focal uptake right mid-apex (red arrows) while ^{68}Ga-PSMA11 PET/MRI (B) is false negative, and shows false positive uptake mid-apex left of the prostate (blue arrows). Final histopathology demonstrated Gleason score 4+4 prostate adenocarcinoma right mid-apex.



Supplemental Figure 2 64-year-old patient with high-risk prostate cancer and PSA 8.8 ng/mL. ^{68}Ga-RM2 PET/CT (A, axial PET, fused PET/CT, CT, and MIP) shows focal uptake bilateral in the prostate (blue arrows) while ^{68}Ga-PSMA PET/MRI (B) demonstrates uptake right anterior (red arrows). Histology, overlaid with pre-operative axial T2WI and ^{68}Ga-PSMA11 fused PET/MRI (C) showed actual disease expansion crossing the midline to the left side (black outline) correlating to a Gleason score 3+4 prostate adenocarcinoma.

Supplemental Table 1: Sensitivity, specificity, and accuracy (95% confidence interval) of all modalities for prostate cancer localization.

Modality	Sensitivity	Specificity	Accuracy
^{68}Ga-RM2	97.9% (88.7, 99.9)	64.7% (38.3, 85.8)	89.1% (78.8, 95.5)
^{68}Ga-PSMA11	95.0% (75.1, 99.9)	66.7% (22.3, 95.7)	88.5% (69.8, 97.6)
mpMRI	77.3% (62.2, 88.5)	75.0% (47.6, 92.7)	76.7% (64.0, 86.6)

Supplemental Table 2: Sensitivity, specificity, and accuracy (95% confidence interval) of all modalities for prostate cancer and lymph node metastases localization.

Modality	Sensitivity	Specificity	Accuracy
^{68}Ga-RM2	87.1% (76.1, 94.3)	90.8% (81, 96.5)	89% (82.2, 93.8)
^{68}Ga-PSMA11	76.7% (57.7, 90.1)	95.5% (77.2, 99.9)	84.6% (71.9, 93.1)
mpMRI	57.6% (44.1, 70.4)	92.9% (82.7, 98.0)	74.8% (65.8, 82.4)

Supplemental Table 3: Sensitivity, specificity, and accuracy (95% confidence interval) for prostate cancer lesions of ^{68}Ga-RM2 and ^{68}Ga-PSMA11 PET, stratified to participants with intermediate- and high-risk PC.

^{68}Ga-RM2	**Sensitivity**	**Specificity**	**Accuracy**
Intermediate-risk	95.5% (77.2, 99.9)	62.5% (24.5, 91.5)	86.7% (69.3, 96.2)
High-risk	100.0% (86.3, 100.0)	66.7% (29.9, 92.5)	91.2% (76.3, 98.1)
^{68}Ga-PSMA11			
Intermediate-risk	100.0% (71.5, 100.0)	100.0% (29.2, 100.0)	100.0% (76.8, 100.0)
High-risk	88.9% (51.8, 99.7)	100.0% (29.2, 100.0)	91.7% (61.5, 99.8)