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Comparison of ^{68}Ga-PSMA-617 PET/CT and ^{68}Ga-RM2 PET/CT in patients with localized prostate cancer candidate for radical prostatectomy: a prospective, single arm, single center, phase II study.

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ABSTRACT

Considering the wide range of therapeutic options for localized prostate cancer (active surveillance, radiation beam therapy, focal therapy, radical prostatectomy, etc), accurate assessment of the aggressiveness and localization of primary prostate cancer lesion are essential for treatment decision making. National Comprehensive Cancer Network guidelines recognize Prostate-Specific Membrane Antigen (PSMA) Positron Emission Tomography/Computed Tomography (PET/CT) for the initial staging of high risk primary prostate cancer. The Gastrin-Releasing Peptide Receptor (GRP-R) is a neuropeptide receptor over-expressed by low-risk prostate cancer cells. We aim to perform the first prospective head-to-head comparison of PSMA and GRP-R targeted imaging at the initial staging to understand how PSMA-PET and GRP-R-PET could be used or combined in clinical practice

Methods: This was a prospective, single-center, diagnostic cross-sectional imaging study using anonymized, masked and independent interpretations of PET/CT paired studies in 22 patients with ^{68}Ga-PSMA-617 (a radiolabelled PSMA-inhibitor) and ^{68}Ga-RM2 (a radiolabelled GRP-R-antagonist). We enrolled patients with newly diagnosed, biopsy-proven, prostate cancer. No patient had received neoadjuvant hormone therapy or chemotherapy. All patients underwent extended pelvic lymph node dissection. Histology served as reference.

Results: On a lesion-based analysis (including lesions <0.1cc), ^{68}Ga-PSMA-617 PET/CT detected 74.3% (26/35) of all tumor lesions and ^{68}Ga-RM2 PET/CT detected 78.1% (25/32; one patient could not be offered ^{68}Ga-RM2 PET/CT). Paired examinations showed positive uptake with the two tracers in 21/32 lesions (65.6%), negative uptake in 5/32 lesions (15.6%), and discordant uptake in 6/32 lesions (18.8%). Uptake of ^{68}Ga-PSMA-617 was higher in ISUP ≥ 4 vs ≥ 1 ($p < 0.0001$); and ISUP ≥ 4 vs 2 ($p = 0.002$). There were no significant differences in uptake between ISUP scores for ^{68}Ga-RM2. Median ^{68}Ga-RM2 SUVmax was significantly higher than median

^{68}Ga-PSMA-617 SUVmax in the ISUP 2 subgroup (p = 0.01). **Conclusion**: ^{68}Ga-PSMA-617 PET/CT is useful to depict higher, more clinically significant, ISUP score lesions and ^{68}Ga-RM2 PET/CT has higher detection rate for low-ISUP tumors. Combining PSMA-PET and GRP-R PET allows to better classify intraprostatic lesions.

INTRODUCTION

Prostate cancer (PCa) is the most common cancer in men and the third cause of cancer-related deaths (*1*). The range of therapeutic options for localized PCa varies from active surveillance or focal therapy to radiation beam therapy or radical prostatectomy depending on the local extension and risk classification of tumor progression. Therefore, the initial assessment of the aggressiveness of the primary tumor is of critical importance for treatment decision making. In combination with clinical examination, PSA level, and prostatic Magnetic Resonance Imaging (MRI), the risk classification of the primary tumor mainly depends on appropriate sampling by prostatic biopsies and on precise evaluation of the International Society of Urological Pathology (ISUP) score.

Prostate Specific Membrane Antigen (PSMA) is a type 2 glycoprotein expressed in secretory cells of prostatic epithelium. Several radiolabelled PSMA inhibitors have been developed (^{68}Ga-PSMA-11, ^{68}Ga-PSMA-617, ^{68}Ga-PSMAI&T or ^{18}F-PSMA1007 (*2*)). Uptake of radiolabelled PSMA inhibitors correlates well with ISUP Score and PSA level (*3*). Recently, National Comprehensive Cancer Network guidelines consider the use of PSMA PET/CT for the initial staging of high risk primary prostate cancer (*4*). However, the ability of PSMA PET/CT to also identify lower grade lesions is unclear.

The gastrin-releasing peptide receptor (GRP-R) is a G-protein coupled receptor of the bombesin receptor family (*5*) which can be targeted with radiolabelled antagonists such as ^{68}Ga-RM2 (6), ^{68}Ga-NeoBOMB1 (*7*) or ^{68}Ga-RM26 (*8*) for PET imaging. Contrarily to PSMA, GRP-R is over-expressed in low-risk prostate cancers (low Gleason score, low PSA value and low tumor size) (*9*–*11*). A study of the diagnostic performances of ^{68}Ga-RM2 PET/CT for the initial staging of prostate cancer on 41 patients reported a detection rate of 93%, a sensitivity of 98% and a specificity of 65% (6).

In a preclinical work, we have compared in vitro GRP-R and PSMA expression on primary PCa samples by means of ^{111}In-RM2 and ^{111}In-PSMA-617. Our results suggest that GRP-R and PSMA-based imaging may have a complimentary role to fully characterize PCa local extent and aggressiveness (GRP-R being a valuable target in low metastatic risk patients and PSMA a valuable target in higher risks patients (*12*)).

Additionally, a pilot clinical study using ^{68}Ga-PSMA-11 PET/CT and ^{68}Ga-RM2 PET/CT on eight patients, also suggest a complimentary role of these imaging modalities for the initial staging of PCa (*13*).

Here, we present a prospective head-to-head comparison between ^{68}Ga-PSMA-617 PET/CT and ^{68}Ga-RM2 PET/CT for the initial assessment of localized primary PCa tumors. Our primary objective was to assess the uptakes intensity (SUVmax) with ^{68}Ga-PSMA-617 and ^{68}Ga-RM2 PET/CT at the level of prostatic lesions, and to compare SUVmax between ISUP score categories. Secondary objectives were to compare ^{68}Ga-PSMA-617 and ^{68}Ga-RM2 uptakes stratified by ISUP score, to compare SUVmax at two acquisition times (60 min and 120 min post-injection) and to evaluate the association between immunohistochemistry scores of the targets (PSMA and GRP-R) and ^{68}Ga-PSMA-617 and ^{68}Ga-RM2 uptakes.

MATERIAL AND METHODS

Study Design and Participants

This was a prospective, single-center, diagnostic cross-sectional imaging study using anonymized, masked and independent interpretations of paired ^{68}Ga-PSMA-617 PET/CT and ^{68}Ga-RM2 PET/CT (EudraCT 2017-000490-36, NCT03604757). ^{68}Ga-PSMA-617 PET/CT and ^{68}Ga-RM2 PET/CT were performed without specific order and any consideration on patients' characteristics and were performed before prostatectomy. We prospectively enrolled twenty-two

patients with newly diagnosed, biopsy-proven, prostate cancer. The French ethical committee n°2017/62 approved this study and all subjects signed a written informed consent.

Inclusion criteria were age greater than 18y, diagnosis of prostate cancer confirmed by biopsy and indication for prostatectomy. No patient had received neoadjuvant hormone therapy or chemotherapy. All patients underwent extended pelvic lymph node dissection.

Radiopharmaceuticals and PET/CT Protocol

^{68}Ga-PSMA-617 and ^{68}Ga-RM2 were produced according to our previous work with minor modifications (^{68}Ga was used as radionuclide and 10µg of PSMA-617 were used)*(12)*. The Discovery RX PET/CT (General Electric Medical System®) from University Hospital of Bordeaux was used for this study. Whole-body PET/CT images were acquired from vertex to mid thighs with 2.5min emission scans per bed position at 60 min and 120 min after intravenous administration of 2MBq/kg (min 80MBq, max 200MBq) of ^{68}Ga-PSMA-617 or ^{68}Ga-RM2. Images were reconstructed using an ordered-subset expectation maximization algorithm with 2 iterations and 21 subsets (matrix size 256x256, 47 slices corresponding to a 15.6cm transaxial field of view, voxel size of 2.376x2.376x3.27 mm^3). The CT acquisition was performed for attenuation correction, in helical mode, using 120kV, mAs modulation to optimally reduce the dose, a 512x512 matrix (voxel size of 0.9766x0.9766x2 mm^3).

PET/CT Image Analysis

PET/CT and mpMRI (when available) images were analysed using Pmod software (PMOD v3.5 Technologies LLC, Switzerland). A manual registration was performed between each modality, using a linear transformation, to aid visual analysis and accurate positioning of tumoral

lesion. Then, manual segmentation (MS) was performed by two experimented nuclear physicians blinded from histology, radiopharmaceuticals and patients' characteristics. Supra-vesical sections were removed because of physiological renal uptake for ^{68}Ga-PSMA-617 and physiological pancreatic uptake for ^{68}Ga-RM2. A consensus was found in case of discrepancies between the two interpretations. Uptake of ^{68}Ga-PSMA-617 and ^{68}Ga-RM2 were quantified according to maximum Standardized Uptake Value (SUVmax) and described for each lesion.

Histology

Prostatectomy samples were fixed and embedded in paraffin blocks. 5 µm-thick tissue slices were stained with Hematoxylin, eosin and saffron (HES) and an experimented pathologist manually surrounded tumoral lesions under microscopic examination and reported the ISUP score and size of each lesion. Lesions < 0.1cc were included in the analysis. Histological samples were then digitized using a slide scanner (NDP.scan, Hamamatsu®). Images obtained were arranged and reoriented to facilitate comparison between histology and PET imaging.

Immunohistochemistry

The immunohistochemical study was performed as previously described for GRP-R (*14*) and PSMA (*15*). Immunohistochemistry results was expressed as an immunoreactive score (IRS) that consider staining intensity and the percentage of stained tumor cells as previously described *(14)*. The final IRS score (product of staining intensity score and percentage of positive cells score) thus ranged from 0 to 12. No PSMA or GRPR expression referred to IRS 0-1, weak PSMA or GRP-R expression referred to IRS 2-3, moderate PSMA or GRP-R expression meant IRS 4-8, and strong PSMA or GRP-R expression meant IRS 9-12. IHC results were dichotomized into two groups: low

PSMA or GRP-R expression (absent/weak expression) and high PSMA or GRP-R expression (moderate/strong expression).

Cross-Sectional Analysis of the PET Signal and Histology

For each tumor lesion ^{68}Ga-PSMA-617 SUVmax and ^{68}Ga-RM2 SUVmax of the lesion were compared to histology (cancer or non-cancer area) allowing determination of concordance/discordance findings.

Cross-Sectional Analysis of the PET Signal and Immunohistochemistry Staining

For each tumor lesion, ^{68}Ga-PSMA-617 SUVmax and ^{68}Ga-RM2 SUVmax of the lesion were compared with the immunohistochemistry score of the whole tumor compartment.

Statistical Analysis

Sample size was fixed at 6 patients for each metastatic risk group defined at enrollment (before surgery): ISUP-1 and cT1-T2a and PSA < 10 ng/mL, Briganti < 5%; ISUP-2 or cT2b or PSA in 10-20 ng/mL; ISUP-3 or cT2b or PSA in 10-20 ng/mL; ISUP4-5 or cT2c or PSA > 20 ng/mL.

Quantitative variables are described as mean (standard deviation), median (1st quartile-3rd quartile), minimum and maximum. Qualitative variables are described as frequency and percentage. Comparisons of SUVmax were performed at the patient level in normal tissues and at the lesion level in pathologic tissues. All comparisons of SUVmax (between ISUP scores, radiopharmaceuticals and acquisition time) used univariable mixed linear regression models including a random intercept to consider the intra-patient correlation (with a variance components structure). Model's hypotheses (normality and heteroscedasticity of residuals) were systematically

checked and led us to transform SUVmax values in pathologic tissues by the natural logarithm. Exponential of parameters estimated with these last models can be expressed as a multiplicative factor: < 1 means a lower value compared to the other group; > 1 means a higher value compared to the other group.

Comparisons of SUVmax in normal and pathologic tissues between 60 and 120 minutes were performed at first in order to select the adequate acquisition time for other analyses. Comparison of SUVmax between negative and positive immunochemistry scores used non-parametric Wilcoxon tests. For the two primary outcomes only, if global statistical test was significant at 2.5%, 2-by-2 comparisons tests between ISUP scores have to be interpreted using 0.4% (Bonferroni method). Statistical analyses used SAS® software (v9.4, SAS® Institute, Cary, NC, USA).

Role of the Funding Source

The University Hospital of Bordeaux funded and promoted this study. Life Molecular Imaging provided the RM2 precursor and the reference compound. Life Molecular Imaging had no role in the study design. The corresponding author had full access to all data and had final responsibility to submit for publication.

RESULTS

Radiopharmaceuticals, Patient and Lesion Characteristics'

Twenty-two men with newly diagnosed prostate cancer were enrolled in this study between April 25, 2018 and November 19, 2019. Demography and clinicopathological characteristics of the study population are presented in Table 1. The median time interval between the two PET/CT was 6 days (3-8). The median time interval between the last PET/CT imaging and surgery was 6 days

(1-15). Nine (41%) patients had ^{68}Ga-PSMA-617 PET/CT first, and 13 (59%) patients had ^{68}Ga-RM2 PET/CT first. One patient could not receive ^{68}Ga-RM2 PET/CT. The median injected activity was 167.2 MBq (118.7-210.2) for ^{68}Ga-PSMA-617 and 149.5 MBq (84.5-198.5) for ^{68}Ga-RM2. All images were acquired at 1h and 2h post-injection, except in one patient who received ^{68}Ga-RM2 imaging at 1h only

Thirty five lesions (including lesions < 0.1cc) were identified by histology on prostatectomy samples: nine ISUP-1 (25.7%), thirteen ISUP-2 (37.1%), three ISUP-3 (8.6%), three ISUP-4 (8.6%) and seven ISUP-5 (20.0%).

Dynamics of ^{68}Ga-PSMA-617 and ^{68}Ga-RM2 uptakes were then analyzed in normal and pathological prostatic tissues. In normal prostate, the median SUVmax with ^{68}Ga-RM2 was 3.20 (2.40-3.80) at 1h and 2.40 (1.85-3.85) at 2h for. ^{68}Ga-RM2 uptake was significantly lower at 2h (β = -0.59; CI_{95} [-0.95 - -0.24); p = 0.003). For ^{68}Ga-PSMA-617 in normal prostate, the median SUVmax was 2.55 (2.20-3.40) at 1h and 2.50 (2.00-3.10) at 2h with no differences between the two acquisition times (β = -0.10; CI_{95} [-0.31 - 0.10); p = 0.31).

In tumor areas, the median SUVmax with ^{68}Ga-RM2 was 5.20 (3.30-8.30) at 1h and 5.40 (3.75-7.90) at 2h (e^{β} = 0.99; CI_{95} [0.81 – 1.23); p = 0.96). For ^{68}Ga-PSMA-617 uptake in tumor lesions, the median SUVmax was 4.20 (3.00-6.10) at 1h and 4.10 (2.90-7.30 at 2h, with no significant differences between the two acquisition times (e^{β} = 1.00; CI_{95} [0.78 – 1.30); p = 0.98).

Therefore, given the lower uptake of ^{68}Ga-RM2 in normal prostate at 2h and equivalent uptake in tumor lesions at 1h and 2h, analysis was conducted using PET/CT data obtained 2h after injection. For ^{68}Ga-PSMA-617, as no differences were seen on uptake either in normal prostate or in tumor

area, the 1h uptake-time recommended by the joint EANM/SNMMI guidelines for ^{68}Ga-PSMA PET/CT was applied (*16*).

Lesion-based PET/CT Imaging

Of the 35 prostatic lesions evaluated with ^{68}Ga-PSMA-617 PET/CT, 26 (74.3%) were detected. Undetected lesions were ISUP score ≤ 2 (six ISUP 1 and three ISUP 2).

Of the 32 prostatic lesions evaluated with ^{68}Ga-RM2 PET/CT, 25 (78.1%) were detected by ^{68}Ga-RM2 PET/CT. Undetected lesions accounted for 4 ISUP1, two ISUP2 and one ISUP4 (Table 2).

Concordance and Discordance in PET/CT Imaging

Twenty-one (65.6%) of 32 histology proven lesions (whatever their volume) showed uptake of both ^{68}Ga-PSMA-617 and ^{68}Ga-RM2, 4 (12.5%) were seen only on ^{68}Ga-RM2, 2 (6.3%) were seen only on ^{68}Ga-PSMA-617 and 5 (15.6%) were negative on both ^{68}Ga-PSMA-617 and ^{68}Ga-RM2.

Association with Pathological Parameters

Regarding uptakes of the radiopharmaceuticals according to histology parameters, ^{68}Ga-PSMA-617 SUVmax values differed according to ISUP scores ($p = 0.003$), with higher SUVmax values with increasing ISUP scores (Tables 2 and 3). Especially, uptake of ^{68}Ga-PSMA-617 was higher in ISUP ≥ 4 vs 1 ($e^{\beta} = 2.41$; CI_{95} [1.65-3.50]; $p < 0.0001$); and ISUP ≥ 4 vs 2 ($e^{\beta} = 2.06$; CI_{95} [1.46-2.91]; $p = 0.002$).

There were no significant differences in uptake between ISUP scores for ^{68}Ga-RM2 ($p = 0.11$).

Median ^{68}Ga-RM2 SUVmax was significantly higher than median ^{68}Ga-PSMA-617 in the ISUP-2 subgroup (6.30 (5.30-7.50) vs 3.60 (3.40-4.50), p = 0.01). In other ISUP groups, no differences in uptakes were seen between ^{68}Ga-PSMA-617 and ^{68}Ga-RM2 (Tables 3 and Figures 1 and 2).

Immunochemistry was also conducted on samples from prostatectomy of patients included in this study. Sixteen samples were available for GRP-R staining and eighteen for PSMA staining (remaining samples were considered as non-contributive by the pathologist and were excluded from the analyses). GRP-R staining was considered positive (IRS ≥4) in 11 (68.8%) of 16 lesions. Median GRP-R IRS score was 4 (3-6). PSMA IRS was considered positive (IRS ≥4) in 15 (83.3%) of 18 lesions. Median PSMA IRS score was 11 (IQR (6-12). Median ^{68}Ga-RM2 SUVmax was 6.40 (3.70-7.50) in samples low for GRP-R vs 7.35 (5.30-9.00) for samples positive for GRP-R (p=0.50)(Figure 3 and Supplemental figure 1). Median ^{68}Ga-PSMA-617 SUVmax was 3.60 (3.00-5.30) for PSMA-low samples and 6.80 (4.50-8.50) for PSMA-positive samples (p=0.12)(Figure 3 and Supplemental figure 2).

DISCUSSION

Several radiopharmaceuticals have been developed to help staging of prostate cancer. ^{11}C-Acetate, marking lipid metabolism, cannot reliably distinguish benign prostatic hyperplasia from prostate tumors. Moreover, the radiolabeled amino-acid ^{18}F-FABC (^{18}F-Flucicovine) did not show good diagnostic performances for characterization of primary lesions (*17*). Finally, ^{11}C/^{18}F-Choline, also marking lipid metabolism, showed lower sensitivity than mpMRI for primary detection of prostate cancer (*18*). Thus, improvements in current molecular imaging of prostate cancer appear necessary for initial assessment of the aggressiveness of the primary tumor.

PSMA and GRP-R are differently overexpressed in prostate cancer, which raises hopes for precise molecular imaging of tumor lesions within the prostate gland. Few studies have prospectively investigated the role of these radiopharmaceuticals at initial staging, before surgery. In a prospective study enrolling 56 intermediate grade prostate cancer patients before prostatectomy, PSMA PET was found to be accurate in detecting intraprostatic lesion of ISUP ≥ 2. Contrarily, the detection rate of PSMA PET was low for ISUP1 lesions. Touijer et al., prospectively investigate ^{68}Ga-RM2 PET/CT in 16 patients before radical prostatectomy. The performances of ^{68}Ga-RM2 PET/CT imaging did not significantly differ compared to mpMRI in terms of sensitivity, specificity, and accuracy (*19*). Therefore, the objective of this work was to perform a head-to-head comparison of PSMA and GRP-R targeting, covering various metastatic risks, at the initial staging of prostate cancer using ^{68}Ga-PSMA-617 and ^{68}Ga-RM2 radiopharmaceuticals. Our aim was to better understand how PSMA-PET and GRP-R-PET could map progression risk and how they could be used or combined in clinical practice. Due to the exploratory nature of this study we were not aiming at assessing the diagnostic performances of the radiopharmaceuticals.

An interesting result of our work is the lower uptake of ^{68}Ga-RM2 in non-pathological prostate tissue at 2 hours post-injection despite equivalent results on tumoral lesions uptake at 1h and 2h. This result can be extracted from preclinical studies (*20*) but has never been translated into PET/CT studies. This observation suggests that results from previous studies using 1 hour post-injection time point for ^{68}Ga-RM2 PET/CT imaging are not at their best. Surprisingly, uptake of ^{68}Ga-PSMA-617 was similar between 1h and 2h which is contrasting with literature reporting increasing uptake between 1h and 3h but study population were different *(21)*.

On a lesion-based analysis and using histology as reference, pretty good primary lesion detection were depicted by ^{68}Ga-RM2 PET/CT compared to ^{68}Ga-PSMA-617 PET/CT. A previous study evaluating ^{68}Ga-RM2 PET/CT diagnostic potential for primary prostate cancer, found higher

sensitivity (0.98)(*6*). This difference can be explained by exclusion of all lesions ≤ 0.1cc. When removing these very small lesions in our study population, which are below the spatial resolution of PET scanners, ^{68}Ga-RM2 PET/CT detected 86% of lesions and ^{68}Ga-PSMA-617 PET/CT detected 83% of lesions. The high uptake of ^{68}Ga-PSMA-617 in tumor lesions of high ISUP score correlates with the known efficacy of PSMA imaging of intra-prostatic tumors in newly diagnosed high-risk prostate cancer patients (*3*). Additionally, ^{68}Ga-RM2 PET/CT outperformed ^{68}Ga-PSMA-617 PET/CT for the detection of ISUP-2 lesions (Figure 4).

Therefore, in order to better classify intraprostatic lesions, we propose that both PSMA PET and GRP-R PET should be performed as discordant uptake occurs in 6/32 (18.8%) of lesions. We suggest that PSMA PET should be performed first for staging high risk lesions. Next, addition of GRP-R PET would allow a more extensive characterization of lower risk prostate cancer lesions. Indeed, a low ^{68}Ga-PSMA-617 uptake, associated with a high ^{68}Ga-RM2 uptake would suggest a low grade prostatic tumoral lesion. This double-PET strategy could also be used for biopsy-guiding to decrease discordance rate of staging on biopsies and final staging on prostatectomy samples (*22*). Finally, the possibility of precision detection and characterization of intra-prostatic lesions opens new avenues for radiotherapy planning and/or focal treatments.

It should be noted that ^{68}Ga-PSMA-617 PET/CT was the only imaging modality that was able to detect the single metastatic lymph node confirmed by histology (ISUP-5) in our study. No significant uptake in this lymph node was seen on the ^{68}Ga-RM2 PET/CT nor on a previously ordered ^{18}F-Choline PET/CT (*23*). This result illustrates the higher sensitivity of PSMA PET for depicting metastatic disease in high risk or recurrent PCa (*24*).

Overall, the majority of intraprostatic lesions were detected by PSMA and/or GRP-R PET. It should be stressed, however, that there still are some lesions (5/32, 15.6%) unseen by both modalities.

Results from this molecular imaging PET study were consolidated by GRP-R- and PSMA-immunohistochemistry conducted on surgical samples. A meaningful higher tracer uptake was seen on IHC positive samples for PSMA but this was not confirmed statistically. Other IHC scores should also be considered *(11)*.

Limitation of our monocentric phase II study is obviously the limited number of patients enrolled in this institutional study. The small sample size may have led to underpowered results. Moreover, SUV of ^{68}Ga-PSMA-617 might not be directly transferable to ^{68}Ga-PSMA-11 used in the clinics. Finally, visual analysis between histology and PET imaging can be sub-optimal. Methods for accurate spatial registration of PET images and histopathology, using fiducial markers, have been developed (*25*) and deserve to be implemented.

CONCLUSION

This prospective head-to-head comparison showed remarkable potential of the combination of ^{68}Ga-RM2 PET/CT and ^{68}Ga-PSMA-617 PET/CT to evaluate different aspects of prostate cancer biology. ^{68}Ga-PSMA-617 PET/CT is useful to depict higher, more clinically significant, ISUP score lesions. In low ISUP scores ^{68}Ga-RM2 has higher detection rate than ^{68}Ga-PSMA-617 but had similar uptake than ^{68}Ga-PSMA-617 in higher ISUP scores. Importantly, almost 20% of lesions were seen only by GRP-R PET (~13%) or PSMA PET (~6%) revealing the complimentary role of these imaging procedures. Combining PSMA-PET and GRP-R PET allows to better classify intraprostatic lesions.

DISCLOSURE

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Molecular Imaging outside of the submitted work research support. No other potential conflicts of interest relevant to this article exist.

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KEY POINTS

Question: What is the role of targeting the Gastrin-Releasing Peptide Receptor (GRP-R) at the initial staging of localized prostate cancer in the context of Prostate Specific Membrane Antigen (PSMA) PET/CT?

Pertinent Findings: In a prospective, head-to head comparison of 22 paired PET/CT using ^{68}Ga-RM2 (a radiolabeled GRP-R antagonist) and ^{68}Ga-PSMA-617, median ^{68}Ga-RM2 SUVmax was significantly higher than median ^{68}Ga-PSMA-617 SUVmax in the ISUP2 subgroup. As expected ^{68}Ga-PSMA-617 PET/CT is useful for initial staging of high ISUP score tumors.

Implication for Patient Care: Combining PSMA-PET and GRP-R PET allows to better classify intraprostatic lesions.

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FIGURES

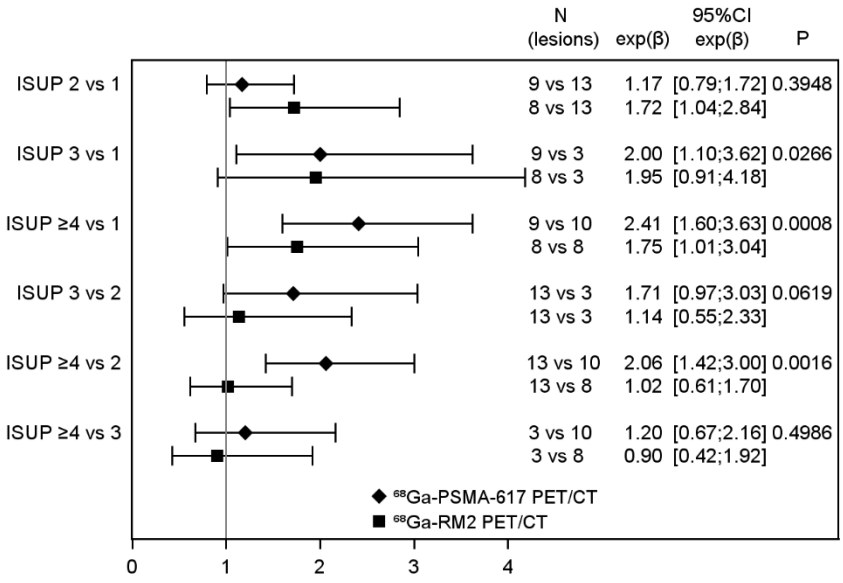


FIGURE 1. Comparison of ^{68}Ga-PSMA-617 and ^{68}Ga-RM2 uptakes to ISUP scores. Estimates > 1 (< 1) indicated higher (lower) SUV max in higher ISUP.

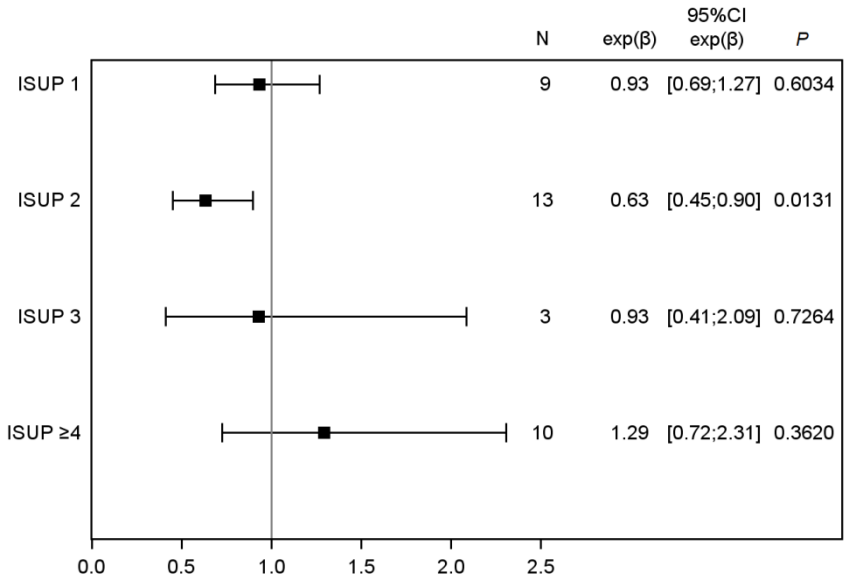


FIGURE 2. ^{68}Ga-PSMA-617 SUVmax compared to ^{68}Ga-RM2 SUVmax, according to ISUP groups. Estimates > 1 (< 1) indicated higher (lower) SUVmax with ^{68}Ga-PSMA-617. For the ISUP ≥4 group, when excluding the patient who only had ^{68}Ga-PSMA-617, values are 1.32 [0.72;2.44], P = 0.3459.

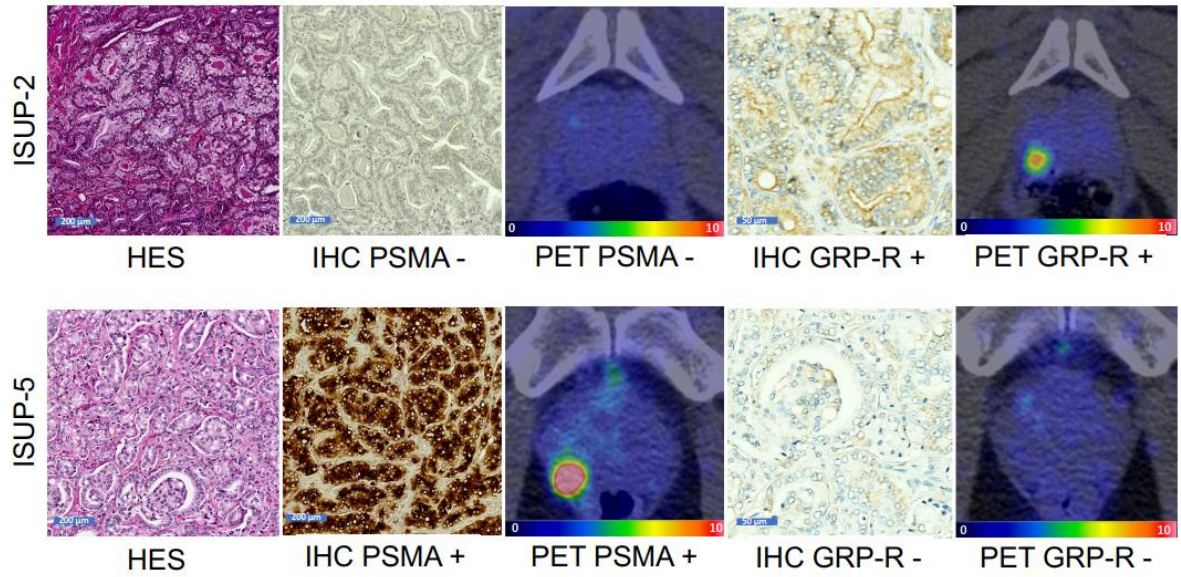


FIGURE 3. Representative GRP-R and PSMA immunohistochemistry with corresponding ^{68}Ga-RM2 and ^{68}Ga-PSMA-617 PET/CT images from two patients. HES staining of an ISUP-2 sample (5X magnification) with negative PSMA immunohistochemistry (5X magnification), negative ^{68}Ga-PSMA-617 PET/CT), positive GRP-R immunohistochemistry (20X magnification) and positive ^{68}Ga-RM2 PET/CT. HES staining of an ISUP-5 sample (5X magnification) with positive PSMA immunohistochemistry (5X magnification), positive ^{68}Ga-PSMA-617 PET/CT, negative GRP-R immunohistochemistry (20X magnification) and negative ^{68}Ga-RM2 PET/CT.

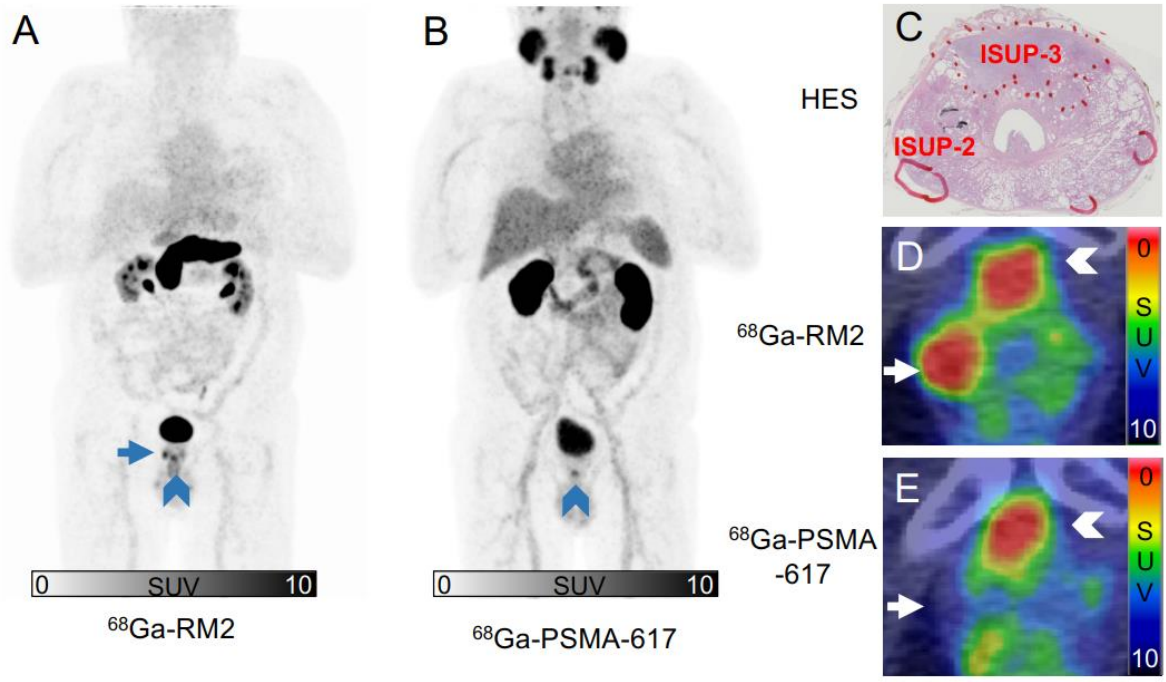


FIGURE 4. ***^{68}Ga-RM2 Maximum Intensity Projection (MIP) (A), ^{68}Ga-PSMA-617 MIP (B), HES staining of a histological slice from prostatectomy of patient-7 with manual demarcation of tumoral lesions (C), ^{68}Ga-RM2 transaxial PET/CT (D) and ^{68}Ga-PSMA-617 transaxial PET/CT (E). An anterior ISUP-3 lesion and a right basal ISUP-2 lesion were seen on histology with two small lesion < 0.1cc (C). ^{68}Ga-RM2 PET/CT and ^{68}Ga-PSMA-617 PET/CT showed similar uptake on the ISUP-3 lesion: SUVmax = 6.7 for ^{68}Ga-RM2 and 6.8 for ^{68}Ga-PSMA-617 (arrowhead). ^{68}Ga-RM2 was the only radiopharmaceutical able to well detect the ISUP-2 lesion (arrow): SUVmax = 7.3 for ^{68}Ga-RM2 and 3.4 for ^{68}Ga-PSMA-617.***

TABLES

Variable		Total (n=22)	
ISUP score		*At diagnosis*	*Histopathology*
	1 (Gleason 6)	5 (22.7%)	1 (4.5%)
	2 (Gleason 7(3+4))	6 (27.3%)	9 (40.9%)
	3 (Gleason 7(4+3))	4 (18.2%)	2 (9.1%)
	4 (Gleason 8)	2 (9.1%)	3 (13.6%)
	5 (Gleason > 8)	5 (22.7%)	7 (31.8%)
TNM stage	T2a	19 (86.4%)	0 (0.0%)
	T2c	3 (13.6%)	6 (27.3%)
	T3a	0 (0.0%)	11 (50.0%)
	T3b	0 (0.0%)	5 (22.7%)
	N_0	0 (0.0%)	20 (90.9%)
	N_1	0 (0.0%)	1 (4.5%)
	N_x	22 (100.0%)	1 (4.5%)
Age (y)			
	Mean (SD)	64.0 (5.9)	
	Median (Q1;Q3)	65 (59;68)	
	Min ; Max	52 ; 75	
PSA (ng/mL)			
	Mean (SD)	8.3 (4.0)	
	Median (Q1;Q3)	7 (6;9)	
	Min ; Max	3 ; 21	

TABLE 1. Patient characteristics'

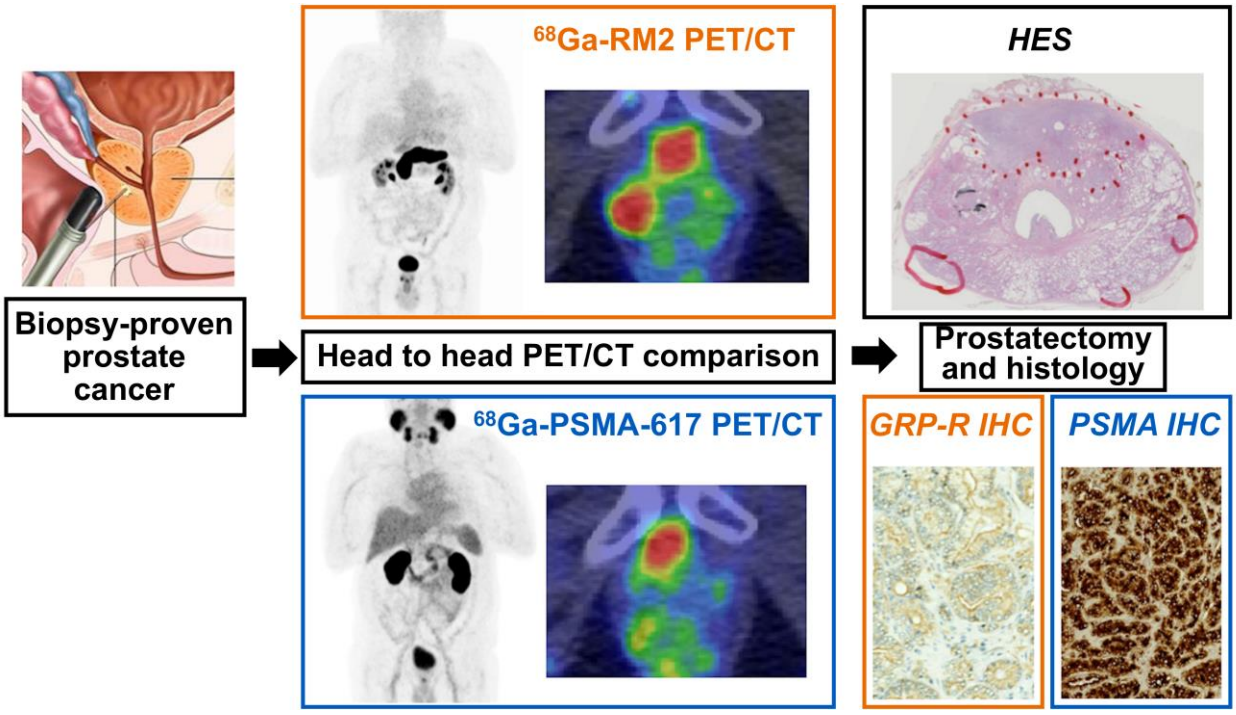
^{68}Ga-PSMA-617 PET/CT 60 min after intravenous administration						
Variable		**Total**	**ISUP-1**	**ISUP-2**	**ISUP-3**	**≥ ISUP-4**
Lesion on imaging	n	35	9	13	3	10
	No	9 (25.7%)	6 (66.7%)	3 (23.1%)		
	Yes	26 (74.3%)	3 (33.3%)	10 (76.9%)	3 (100%)	10 (100%)
^{68}Ga-RM2 PET/CT 120 min after intravenous administration						
Variable		**Total**	**ISUP-1**	**ISUP-2**	**ISUP-3**	**≥ ISUP-4**
Lesion on imaging	n (md*)	32 (3)	8 (1)	13	3	8 (2)
	No	7 (21.9%)	4 (50.0%)	2 (15.4%)		1 (12.5%)
	Yes	25 (78.1%)	4 (50.0%)	11 (84.6%)	3 (100%)	7 (87.5%)

*md = missing data. One lesion is missing for the patient who did not benefit from ^{68}Ga-RM2 PET/CT and the two other missing lesions correspond to the failure of the PET/CT device at 2h post-injection for another patient.

TABLE 2. ISUP-based stratification of lesions detected by ^{68}Ga-PSMA-617 PET/CT or ^{68}Ga-RM2 PET/CT.

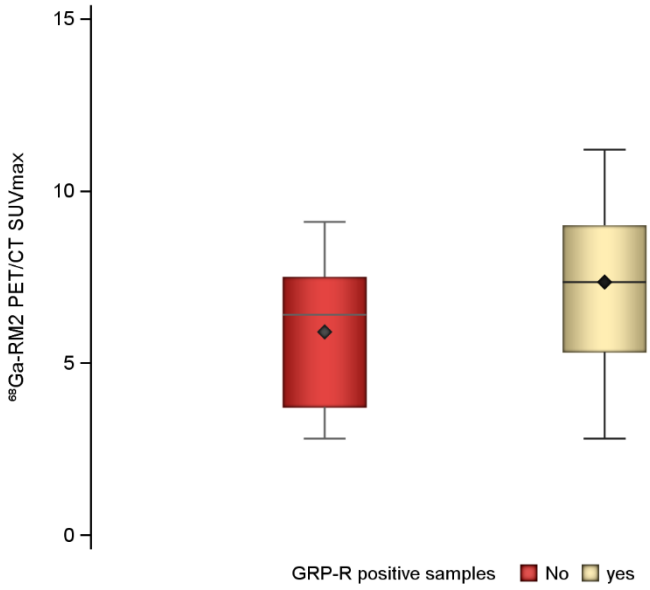
ISUP score	Median ^{68}Ga-RM2 SUVmax (Q1;Q3)	Median ^{68}Ga-PSMA-617 SUVmax (Q1;Q3)
1	3.45 (2.50;4.70)	3.00 (2.60;3.50)
2	6.30 (5.30;7.50)	3.60 (3.40;4.50)
3	8.30 (3.80;9.80)	6.80 (5.10;7.10)
≥ 4	7.35 (3.25;9.05)	7.45 (5.90;12.50)

TABLE 3. Comparison of ^{68}Ga-PSMA-617 and ^{68}Ga-RM2 uptakes to ISUP scores.

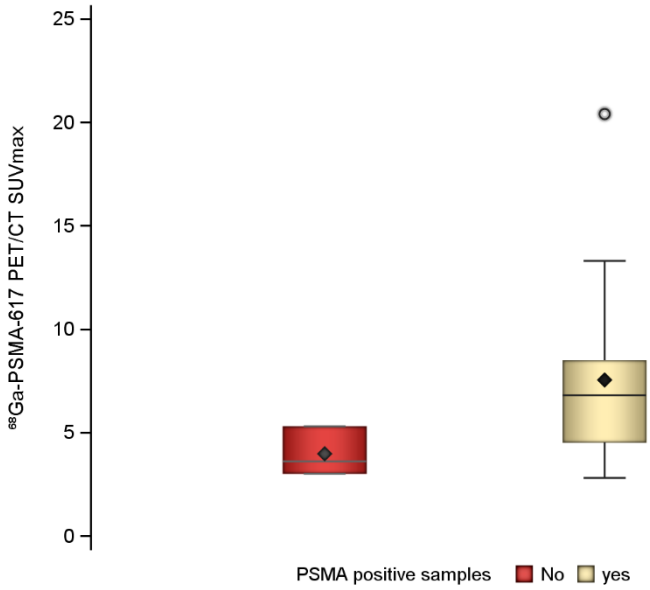


Graphical abstract

Supplemental figures



Supplemental figure 1. Association of GRP-R immunohistochemistry and ^{68}Ga-RM2 PET/CT SUVmax. Median ^{68}Ga-RM2 SUVmax was 6.40 in samples low for GRP-R vs 7.35 for samples positive for GRP-R (p=0.50).



Supplemental figure 2. Association of GRP-R immunohistochemistry and ^{68}Ga-PSMA-617 PET/CT SUVmax. Median ^{68}Ga-PSMA-617 SUVmax was 3.60 for PSMA-low samples and 6.80 for PSMA-positive samples (p=0.12).