PSMA- and GRPR-Targeted PET: Results from 50 Patients with Biochemically Recurrent Prostate Cancer

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Novel radiopharmaceuticals for PET are being evaluated for the diagnosis of biochemical recurrence (BCR) of prostate cancer (PC). We compared the gastrin-releasing peptide receptor–targeting ^{68}Ga-RM2 with the prostate-specific membrane antigen (PSMA)–targeting ^{68}Ga-PSMA11 and ^{18}F-DCFPyL. **Methods:** Fifty patients underwent both ^{68}Ga-RM2 PET/MRI and ^{68}Ga-PSMA11 (n = 23) or ^{18}F-DCFPyL (n = 27) PET/CT at an interval ranging from 1 to 60 d (mean ± SD, 15.8 ± 17.7 d). SUV_{max} was collected for all lesions. **Results:** ^{68}Ga-RM2 PET was positive in 35 and negative in 15 of the 50 patients. ^{68}Ga-PSMA11/^{18}F-DCFPyL PET was positive in 37 and negative in 13 of the 50 patients. Both scans detected 70 lesions in 32 patients. Forty-three lesions in 18 patients were identified on only 1 scan: ^{68}Ga-RM2 detected 7 more lesions in 4 patients, whereas ^{68}Ga-PSMA11/^{18}F-DCFPyL detected 36 more lesions in 13 patients. **Conclusion:** ^{68}Ga-RM2 remains a valuable radiopharmaceutical even when compared with the more widely used ^{68}Ga-PSMA11/^{18}F-DCFPyL in the evaluation of BCR of PC. Larger studies are needed to verify that identifying patients for whom these 2 classes of radiopharmaceuticals are complementary may ultimately allow for personalized medicine.

Key Words: ^{68}Ga-RM2; ^{68}Ga-PSMA11; ^{18}F-DCFPyL; PET; prostate cancer

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Prostate cancer (PC) is the most common noncutaneous cancer diagnosed in the United States, accounting for an estimated 191,930 new cases and 33,330 deaths (second only to lung cancer) in 2020 (*1*). Biochemical recurrence (BCR) within 10 y after primary treatment occurs in 20%–40% of cases after radical prostatectomy and 30%–50% of cases after radiation therapy (*2,3*). Despite a lack of consensus, the prostate-specific antigen (PSA) remains the biomarker of disease after primary treatment. BCR is characterized by heterogeneity; therefore, a single biologic target is unlikely to allow for complete understanding and accurate treatment.

Prostate-specific membrane antigen (PSMA) is currently the most evaluated PET molecular target for PC (*4*), showing better sensitivity and specificity than standard imaging for the detection of metastatic disease even at low PSA values (*5*). Commonly used radiopharmaceuticals targeting PSMA include ^{68}Ga-PSMA-HBED-CC (^{68}Ga-PSMA11) (*6*) and ^{18}F-DCFPyL (*7*). Another class of radiopharmaceuticals used for the assessment of PC patients is the gastrin-releasing peptide analogs. Among them, ^{68}Ga-BAY86-7548 (^{68}Ga-RM2) has been reported in clinical studies (*8,9*). Our group showed that the PC detection rate was higher for ^{68}Ga-RM2 PET than for MRI in a cohort of 32 patients (*9*).

Here, we compared ^{68}Ga-RM2 with ^{68}Ga-PSMA11 and ^{18}F-DCFPyL. In the age of personalized medicine and theranostics, it is important to identify which patients will benefit from one class of radiopharmaceutical or the other. To our knowledge, this cohort has not been previously reported.

MATERIALS AND METHODS

Patient Population

Participants with suspected BCR of PC after primary treatment were prospectively enrolled in 3 clinical trials evaluating the performance of ^{68}Ga-RM2 (NCT 02624518), ^{68}Ga-PSMA11 (NCT02673151), and ^{18}F-DCFPyL (NCT03501940). Twenty-three patients underwent both ^{68}Ga-RM2 PET/MRI and ^{68}Ga-PSMA11 PET/CT, whereas another 27 patients underwent both ^{68}Ga-RM2 PET/MRI and ^{18}F-DCFPyL PET/CT. BCR was diagnosed after prostatectomy with or without adjuvant radiotherapy at a PSA level of 0.2 ng/mL or greater, with a second confirmatory PSA level of at least 0.2 ng/mL (*10*). For patients after radiation therapy, BCR was diagnosed as a rise in PSA measurement of 2 ng/mL or more over the nadir (*11*). All participants gave written informed consent, and the protocols were approved by the local institutional review board. Data collected in these 3 trials were retrospectively analyzed for this comparison.

Clinical parameters, including stage of disease, Gleason score, PSA nadir, PSA within 30 d of the scan, PSA velocity, and primary and subsequent treatments, were obtained from the electronic medical records.

Scanning Protocols

All ^{68}Ga-PSMA11 and ^{18}F-DCFPyL scans were acquired using a silicon photomultiplier–based PET/CT system (Discovery Molecular Insights; GE Healthcare). The scans were performed according to PSMA PET guidelines (*12*) and as previously described (*7*).

All ^{68}Ga-RM2 scans were acquired using a time-of-flight–enabled simultaneous PET/MRI scanner (Signa; GE Healthcare), as previously described (*9*).

The choice of PET/CT or PET/MRI was dictated by the funding available to support the clinical trials. The PET/CT and PET/MRI use the same silicon photomultiplier–based detectors, and we previously reported their clinical evaluation (*13,14*).

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Image Analysis

Two nuclear medicine physicians reviewed and analyzed all images using MIMvista, version 6.9.2 (MIM Software Inc.). One of these physicians subsequently recorded semiquantitative measurements (SUV_{max}). All areas of increased radiotracer uptake in sites not expected to show a physiologic accumulation were reported as abnormal. Increased uptake was defined as focal tracer uptake higher than the adjacent background level. ^{68}Ga-RM2 uptake was considered physiologic in the following tissues: gastrointestinal tract, liver, spleen, pancreas, kidneys, ureters, and bladder (*15*). This approach is similar to guidelines for standard image interpretation for ^{68}Ga-PSMA11 PET (*16*). The PET Edge tool (MIM Software Inc.) was used for evaluation of focal uptake outside the expected biodistribution. The diameters of anatomic structures corresponding to focal uptake were measured on T1-weighted MR images for ^{68}Ga-RM2 and on CT images for ^{68}Ga-PSMA11 and ^{18}F-DCFPyL.

Most patients with a positive scan (^{68}Ga-RM2 PET/MRI or ^{68}Ga-PSMA11/^{18}F-DCFPyL) started therapy after the examination; therefore, follow-up comparison with other imaging modalities was not possible. The findings were pathologically confirmed in 5 participants.

Statistical Analyses

Statistical analysis was performed with SPSS, version 26 (SPSS Inc.). Continuous data are presented as mean ± SD, range, and frequency (%). The Welch test was used to compare PSA and PSA velocity between positive and negative scans. The paired Wilcoxon signed-rank test was used to compare differences in lesion SUV_{max} between the radiopharmaceuticals. The Fisher exact test was used to correlate clinical parameters with positivity versus negativity of the 2 radiopharmaceuticals. A P value of less than 0.05 was considered significant.

RESULTS

Patients' Characteristics

Fifty patients, 52–81 y old (mean ± SD, 69.4 ± 7 y), underwent both ^{68}Ga-RM2 PET/MRI and either ^{68}Ga-PSMA11 PET/CT (n = 23) or ^{18}F-DCFPyL PET/CT (n = 27). Thirty-six of the 50 had radical prostatectomy as the primary treatment, and 14 had radiation therapy. Fifteen patients were treated with androgen deprivation therapy (ADT) before the scans, whereas 23 started ADT after the scans. The PSA level at the time of the scans ranged from 0.1 to 21.5 ng/mL (4.2 ± 5 ng/mL). Supplemental Tables 1 and 2 summarize clinical and imaging characteristics of this cohort of patients (supplemental materials are available at http://jnm.snmjournals.org).

The injected dose ranged from 111 to 155.4 MBq (114.3 ± 7.4 MBq) for ^{68}Ga-RM2, from 129.5 to 199.8 MBq (151.7 ± 14.8 MBq) for ^{68}Ga-PSMA11, and from 270.1 to 366.3 MBq (333 ± 25.9 MBq) for ^{18}F-DCFPyL.

The uptake time ranged from 39 to 100 min (52.7 ± 11 min) for ^{68}Ga-RM2 PET/MRI, from 45 to 107.9 min (66.3 ± 15 min) for ^{68}Ga-PSMA11 PET/CT, and from 60 to 120 min (81.2 ± 17 min) for ^{18}F-DCFPyL. The interval between the ^{68}Ga-RM2 and ^{68}Ga-PSMA11/^{18}F-DCFPyL scans ranged from 1 to 60 d (15.8 ± 17.7 d).

PSMA (^{68}Ga-PSMA11 and ^{18}F-DCFPyL) Versus ^{68}Ga-RM2 Findings

^{68}Ga-RM2 PET was positive in 35 (70%) and negative in 15 (30%) of the 50 patients. PSMA PET was positive in 37 (74%) and negative in 13 (26%) of the 50 patients. Both scans detected 70 lesions in 32 patients (42 in lymph nodes, 7 in the prostate bed, 6 in the seminal vesicles, 6 in the liver, and 9 in bone). The SUV_{max} for these 70 lesions ranged from 1.7 to 52.5 (8.1 ± 9.4) for ^{68}Ga-RM2 and from 1.6 to 79.3 (16.7 ± 17.4) for PSMA. The difference in SUV_{max} was statistically significant ($P < 0.001$).

PSA ranged from 0.3 to 21.5 ng/mL (4.4 ± 4.8 ng/mL) and from 0.1 to 19.2 ng/mL (3.6 ± 5.7 ng/mL) for ^{68}Ga-RM2–positive versus –negative scans, respectively, and the difference was not significant ($P = 0.775$). PSA ranged from 0.2 to 21.5 ng/mL (4.2 ± 4.7 ng/mL) and from 0.1 to 19.2 ng/mL (3.6 ± 6.1 ng/mL) for PSMA-positive versus -negative scans, respectively, and the difference was not significant ($P = 0.739$).

PSA velocity ranged from 0.1 to 42 ng/mL/y (5.7 ± 9.8 ng/mL/y) and from 0.1 to 21.3 ng/mL/y (3.5 ± 5.5 ng/mL/y) for ^{68}Ga-RM2–positive versus –negative scans, respectively, and the difference was not significant ($P = 0.320$). PSA velocity ranged from 0.1 to 42 ng/mL/y (5.6 ± 9.8 ng/mL/y) and from 0.1 to 12.2 ng/mL/y (2.9 ± 3.9 ng/mL/y) for PSMA-positive versus -negative scans, respectively, and the difference was not significant ($P = 0.174$).

The positivity rate for PSA ≤0.5, <0.5 to ≤1, <1 to ≤2, <2 to ≤5, and >5 ng/mL was 38% (n = 3/8), 90% (n = 9/11), 50% (n = 4/8), 89% (n = 8/9), and 79% (n = 11/14), respectively, for ^{68}Ga-RM2 and 22% (n = 2/9), 91% (n = 10/11), 75% (n = 6/8), 100% (n = 9/9), and 77% (n = 10/13), respectively, for PSMA.

^{68}Ga-RM2 detected 7 more lesions in 4 patients than did PSMA (3 lymph node lesions, 3 bone lesions, and 1 adrenal gland lesion). The average SUV_{max} of these lesions was 5.8, and 6 of the 7 had a diameter of less than 1 cm. The mean PSA in these patients was 5 ng/mL, and 3 of them had negative findings on the PSMA scan.

PSMA detected 36 more lesions in 13 patients than did ^{68}Ga-RM2 (27 lymph node lesions, 1 lung lesion, and 8 bone lesions). The average SUV_{max} of these lesions was 14.8, and 23 of the 36 measured less than 1 cm. The mean PSA value of these patients was 4.6 ng/mL, and 5 of them had negative findings on the ^{68}Ga-RM2 scan.

Ten participants had both negative ^{68}Ga-RM2 scans and negative PSMA scans. Their PSA at the time of the scans ranged from 0.1 to 19.2 ng/mL (3.1 ± 6.1 ng/mL). This subgroup included 6 participants with a PSA of 0.5 ng/mL or less, 1 with 1.2 ng/mL, 1 with 1.4 ng/mL, 1 with 8.2 ng/mL, and 1 with 19.2 ng/mL.

We did not identify any significant correlation between radiologic findings (positive vs. negative ^{68}Ga-RM2 and PSMA scans) and clinical parameters such as Gleason score (≤3 + 4; ≤4 + 3), primary treatment (radical prostatectomy vs. radiation therapy), or ADT before imaging.

Figures 1 and 2 and Supplemental Figures 1 and 2 show pairs of ^{68}Ga-RM2 and ^{18}F-DCFPyL findings in different participants. We previously published images comparing ^{68}Ga-RM2 and ^{68}Ga-PSMA11 (*8*).

Lesion analysis for ^{68}Ga-RM2 versus PSMA is shown in Table 1.

DISCUSSION

Our study evaluated gastrin-releasing peptide receptor and PSMA PET radiopharmaceuticals in patients with BCR of PC. The ^{68}Ga-RM2 positivity rate was similar to our prior published reports (*8,9*). The overall semiquantitative analysis showed that SUV_{max} measurements were higher for PSMA radiopharmaceuticals than for ^{68}Ga-RM2, and the difference was statistically significant. However, there were differences between ^{68}Ga-PSMA11 and ^{18}F-DCFPyL measurements against ^{68}Ga-RM2, with higher and statistically significant values only for ^{18}F-DCFPyL. This finding may be due to differences between ^{68}Ga- and ^{18}F-labeled

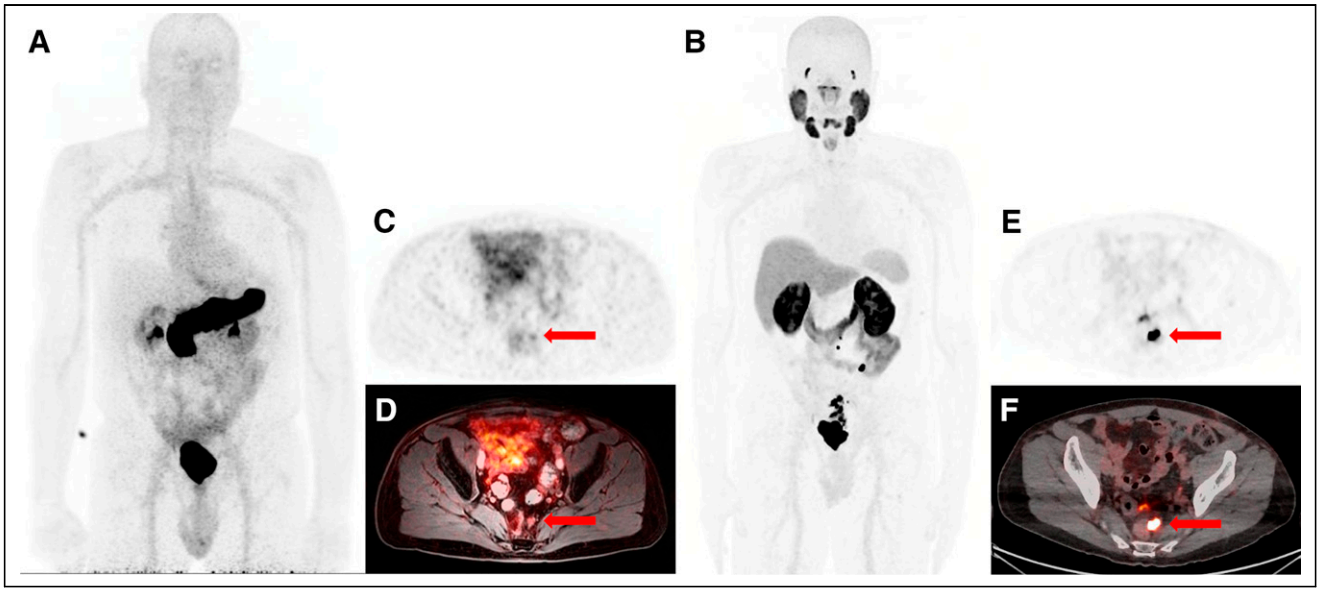

FIGURE 1. A 63-y-old man previously treated with radical prostatectomy, followed by salvage RT + ADT, presenting with BCR of PC (PSA, 0.4 ng/mL; PSA velocity, 1.6 ng/mL/y). Maximum-intensity-projection ^{68}Ga-RM2 (A) and ^{18}F-DCFPyL (B) PET images, axial ^{68}Ga-RM2 (C) and ^{18}F-DCFPyL (E) PET images, axial ^{68}Ga-RM2 PET/MR image (D), and axial ^{18}F-DCFPyL PET/CT image (F) are shown. Arrows mark left perirectal lymph nodes with significantly lower ^{68}Ga-RM2 uptake than ^{18}F-DCFPyL uptake.

radiopharmaceuticals. Prior work by Dietlein et al. showed that the same lesions have higher uptake measured on ^{18}F-DCFPyL than on ^{68}Ga-PSMA11 PET (*17*). PSA velocity for patients with positive versus negative scans was not statistically significant for either gastrin-releasing peptide receptor or PSMA PET in this cohort.

We previously reported the first comparison of ^{68}Ga-RM2 and ^{68}Ga-PSMA11 in a small pilot study (*8*). Here, we expanded with a new cohort of patients and 2 different PSMA-targeting radiopharmaceuticals. Hoberück et al. reported data from 16 patients with mostly advanced PC who underwent both and ^{68}Ga-RM2 PET/CT and either ^{68}Ga-PSMA11 PET/CT or ^{68}Ga-PSMA11 PET/MRI (*18*).

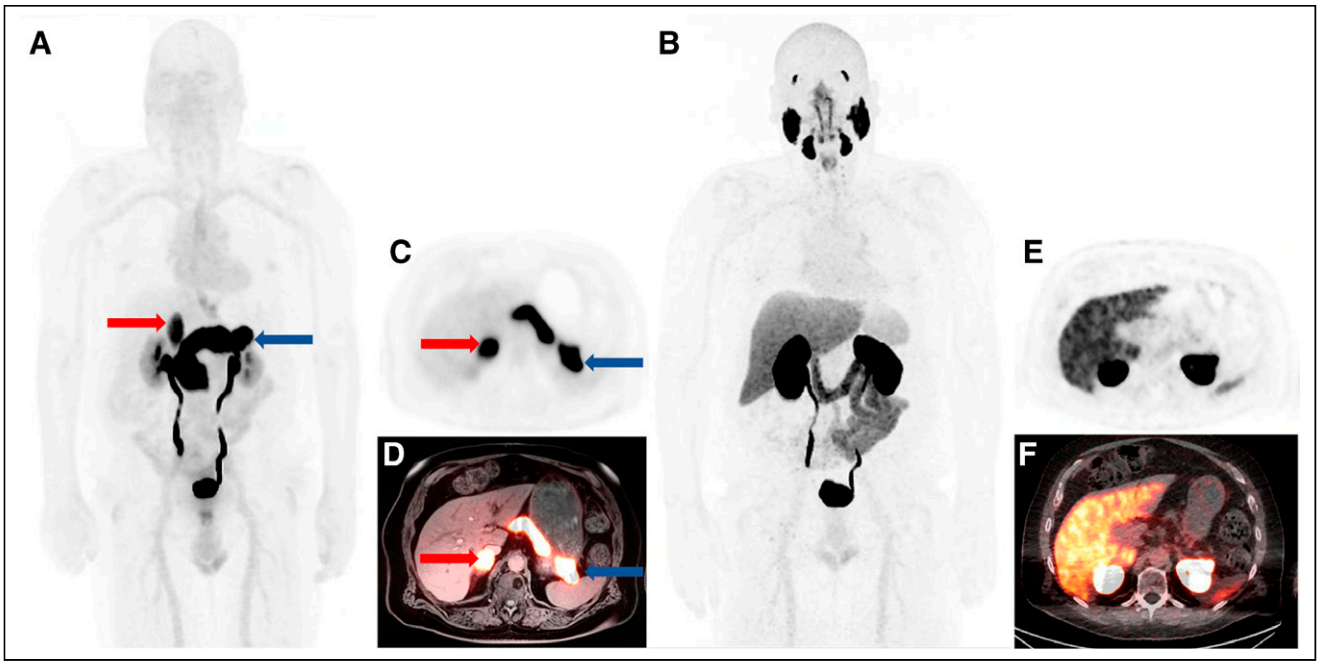

FIGURE 2. A 66-y-old man previously treated with RT + ADT, presenting with BCR of PC (PSA, 11.6 ng/mL; PSA velocity, 12.2 ng/mL/y). Maximum-intensity-projection ^{68}Ga-RM2 (A) and ^{18}F-DCFPyL (B) PET images, axial ^{68}Ga-RM2 (C) and ^{18}F-DCFPyL (E) PET images, axial ^{68}Ga-RM2 PET/MR image (D), and axial ^{18}F-DCFPyL PET/CT image (F) are shown. Red arrows mark right adrenal lesion clearly seen on ^{68}Ga-RM2 but not prospectively identified on ^{18}F-DCFPyL, given similar uptake in adrenal gland and liver parenchyma. Blue arrows mark physiologic ^{68}Ga-RM2 uptake in pancreas.

TABLE 1
Analysis of Lesions from ^{68}Ga-RM2 vs. ^{68}Ga-PSMA11/^{18}F-DCFPyL

	Local recurrence		Lymph node metastases		Bone metastases	
Agent	*n*	Average SUV_{max}	*n*	Average SUV_{max}	*n*	Average SUV_{max}
^{68}Ga-RM2	13	13.3	45*	7.9	12*	6.1
PSMA	13	11.6	69†	17.7	17†	14.3

*3 lymph nodes were not detected by ^{68}Ga-PSMA11; 3 bone lesions were not detected by ^{8}F-DCFPyL.
†27 lymph nodes were not detected by ^{68}Ga-RM2; 8 bone lesions were not detected by ^{68}Ga-RM2.
PSMA also identified 1 lung nodule. ^{68}Ga-RM2 also identified 1 adrenal gland metastasis. Both PSMA and ^{68}Ga-RM2 also identified 6 hepatic lesions.

^{68}Ga-RM2 PET/CT showed 2 osseous lesions not seen by ^{68}Ga-PSMA11, whereas the latter showed avid uptake in several locations not visible with ^{68}Ga-RM2. To our knowledge, no previous studies compared ^{18}F-DCFPyL and ^{68}Ga-RM2.

PSMA ligands have a high positivity rate even at low PSA values (*5*). One study showed 50% positivity when PSA was less than 0.5 ng/mL in a cohort of 319 participants (*19*). In our cohort, the positivity rate was similar for PSMA and ^{68}Ga-RM2 (2/9 and 3/8, respectively) at a PSA level of less than 0.5 ng/mL. Larger studies are needed to confirm these preliminary observations.

Gastrin-releasing peptide receptor is not highly expressed in advanced states of androgen-independent PC, especially in osseous metastases (*20*). Here, ^{68}Ga-RM2 identified 3 bone lesions in 1 patient that were not conspicuous on PSMA. This patient was previously treated with radical prostatectomy and ADT, subsequently becoming androgen-independent. On the other hand, ^{68}Ga-RM2 PET did not identify 8 osseous lesions seen by PSMA in other patients. These findings require further evaluation.

Some of the patients in this cohort received ADT before the scans, and this may have influenced the uptake of the 2 radiopharmaceuticals. PSMA uptake is regulated by androgen hormones, and ADT may considerably increase PSMA-ligand uptake (*21–23*). A single study suggested that ADT induces gastrin-releasing peptide activity, activation of nuclear factor κ-light-chain enhancer of activated B cells, and increased levels of androgen receptor splice variant 7 expression, resulting in progression to CRPC (*24*).

Recently, interest in metastasis-directed therapies in patients with minimal metastatic tumor burden (oligometastatic disease) has increased (*25*); in these patients, for whom the exact number and localization of the lesions is of great importance, having access to different classes of radiopharmaceuticals may be useful. Whether the PSA rise reflects a locoregional recurrence or distant metastatic disease still remains an important question in BCR of PC, because treatment planning would change accordingly from a potentially curative local therapy to watchful waiting or palliative systemic treatment. In this setting and considering how heterogeneous PC is, identifying patients for whom different classes of radiopharmaceuticals are complementary may ultimately allow for personalized medicine. The use of combination therapies with nonoverlapping toxicities may allow delivery of greater doses to lesions, as well as possibly less adverse events.

Our study had limitations, including the relatively small number of patients analyzed (albeit the largest dataset of gastrin-releasing peptide receptor vs. PSMA PET imaging results at BCR of PC) and the different methods used for scanning patients, dictated by available research funding. However, both PET/CT and PET/MRI used the same silicon photomultiplier–based detectors, which provide similar performance in both modalities. Magnetic resonance–based attenuation correction is not ideal for the skeleton; it is known that improperly accounting for bone may lead to underestimation of PET signal in tissues near bone (*26*), and this factor may have impacted the results of ^{68}Ga-RM2. Lastly, pathologic confirmation of the identified lesions was limited to a small number of participants (10%) because of a bias from the referring physicians who accepted putative sites of disease on imaging after initial biopsies had returned no false-positive ^{68}Ga-RM2 findings; in addition, PSMA findings are now widely accepted by treating physicians.

To determine whether there is a correlation between clinical features and gastrin-releasing peptide receptor versus PSMA-positive or -negative lesions, we ran the Fisher exact test but did not observe any significant associations. The cause may be the small cohort of patients enrolled. Furthermore, 20% of our participants had negative PSMA and ^{68}Ga-RM2 findings, including at a PSA level of more than 5 ng/mL. These issues underline the complexity of the PC biology and should be evaluated in larger prospective studies.

CONCLUSION

^{68}Ga-RM2 remains a valuable radiopharmaceutical even when compared with the more widely used ^{18}F-DCFPyL/^{68}Ga-PSMA11 in the evaluation of BCR of PC. Larger studies are needed to verify that identifying patients for whom these 2 classes of radiopharmaceuticals are complementary may ultimately allow for personalized medicine.

DISCLOSURE

The Clinicaltrials.gov identifiers for this work are NCT 02624518 (^{68}Ga-RM2), NCT02673151 (^{68}Ga-PSMA11), and NCT03501940 (^{18}F-DCFPyL). NCT 02624518 (^{68}Ga-RM2) was supported by Department of Defense Impact Award (W81XWH-16-1-0604). NCT02673151 (^{68}Ga-PSMA11) was partially supported by institutional support from GE Healthcare and by Department of Radiology discretionary funds. NCT03501940 (18F-DCFPyL) was partially supported by Department of Radiology discretionary funds. Life MI provided the RM2 precursor. Progenics Pharmaceuticals provided ^{18}F-DCFPyL as part of a

research access program. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is there a benefit to using gastrin-releasing peptide receptor PET in addition to PSMA PET in patients with BCR of PC?

PERTINENT FINDINGS: Of the 50 patients, ^{68}Ga-RM2 PET was positive in 35 (70%) and negative in 15 (30%), whereas PSMA PET was positive in 37 (74%) and negative in 13 (26%). Both scans detected 70 lesions in 32 patients (42 in lymph nodes, 7 in the prostate bed, 6 in the seminal vesicles, 6 in the liver, and 9 in bone). Forty-three lesions in 18 patients were shown by only 1 class of radiopharmaceutical: ^{68}Ga-RM2 detected 7 more lesions in 4 patients, whereas PSMA detected 36 more lesions in 14 patients (9 lesions were identified by ^{68}Ga-PSMA11 and 27 by ^{18}F-DCFPyL).

IMPLICATIONS FOR PATIENT CARE: ^{68}Ga-RM2 remains a valuable radiopharmaceutical even when compared with the more widely used ^{68}Ga-PSMA11/^{18}F-DCFPyL in the evaluation of BCR of PC. Larger studies are needed to verify that identifying patients for whom these 2 classes of radiopharmaceuticals are complementary may ultimately allow for personalized medicine.

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