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Imaging the Distribution of Gastrin Releasing Peptide Receptors in Cancer

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Noteworthy:

- GRPR, part of the bombesin (BBN) family, are overexpressed in many malignancies, including breast and prostate cancer, and therefore represent an attractive target for future development (pages 5-6)
- Peptides such as gastrin-releasing peptide receptors (GRPR)-targeting radiopharmaceuticals are small molecules with fast blood clearance and urinary excretion (page 5).
- Both diagnostic and therapeutic versions have been developed and are currently in clinical trials (pages 7-8)

No potential conflicts of interest relevant to this article exist.

ABSTRACT

Targeting tumor-expressed receptors using selective molecules for diagnostic, therapeutic or both diagnostic and therapeutic (theragnostic) purposes is a promising approach in oncological applications.

Such approaches have increased significantly over the past decade. Peptides such as gastrin-releasing peptide receptors (GRPR) targeting radiopharmaceuticals are small molecules with fast blood clearance and urinary excretion. They demonstrate good tissue diffusion, low immunogenicity, and highly selective binding to their target cell-surface receptors. They are also easily produced. GRPR, part of the bombesin (BBN) family, are overexpressed in many tumors, including breast and prostate cancer, and therefore represent an attractive target for future development.

INTRODUCTION

Cancer remains the number two cause of death in the U.S., second only to heart disease. It is estimated that approximately 606,880 Americans will die from cancer and 1,806, 590 new cancer cases will be diagnosed in the United States in 2020 (*1*). The receptor-mediated targeting of tumors is an area of investigation under constant development which attempts to identify a biomarker that is over-expressed on the surface of cancer cells and bind its ligand to carriers that allow tumor visualization and treatment. The success of this approach depends on the selectivity of the receptor for certain malignant cells, as well as on its binding specificity to the targeting ligand. Here, we will introduce the bombesin receptor family and focus on the gastrin-releasing peptide receptors (GRPR), which are overexpressed in various cancers (*2-8*). A special emphasis will be on prostate and breast cancers, where GPRP expression has been studied the most.

BOMBESIN

BBN is a 14 amino-acid peptide (Pyr-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly- His-Leu-Met-NH_2) purified for the first time in 1970 from the skin of two European frogs, *Bombina bombina* and *Bombina variegate (9,10).* BBN had a structural similarity to *ranatensin*, a peptide isolated only few months earlier from the skin of a different frog *(11).* In 1978, the mammalian counterpart to the amphibian BBN was isolated from porcine non-antral gastric tissue and called gastrin-releasing polypeptide (GRP) due to its main function, gastric acid stimulation due to the release of gastrin (*12*). Later on, Minamino *et al* identified the mammalian counterpart to the amphibian *ranatensin* in the porcine spinal cord, and they called it neuromedin-B (NMB) (*13*). These two mammalian BBN peptides are highly expressed in the human peripheral tissues and in the central nervous system (*14*). Three different receptors have been discovered for the mammalian BBN peptides: BB_1 (NMB-R), BB_2 (GRPR), and BB_3 (BRS-3) (*15-18*). These are seven-transmembrane-domain, G protein-coupled receptors. BRS-3 is an orphan receptor, which means that at present its natural ligand is unknown, but it has been included into the BBN receptor family because of its high homology to NMBR/GRPR (*19,20*).

Among them, the GRPR has been the most extensively studied.

GRP/GRPR NORMAL BIODISTRIBUTION AND PHYSIOLOGICAL FUNCTIONS

GRPR are highly concentrated in the pancreas and expressed at lower levels in the colon, breast, prostate and some regions of the central nervous system including hippocampus, hypothalamus, amygdala and pons (*21,22*). The first human atlas of the physiological uptake of a GRPR antagonist radiolabeled with Gallium-68 (^{68}Ga) has been recently published by our group: the highest uptake was seen in the pancreas, followed by clearance in the urinary system; mild to moderate uptake was seen in the gastrointestinal tract (*23*).

GRP binds with very high affinity to GRPR which mediates various physiological mechanism in the human body: it controls gastrointestinal motility/gastric emptying inducing smooth muscle contraction (*24*); it causes the release of endogenous gastrin by activating sensory neurons in the gastric mucosa (*25,26*); it regulates the release of pancreatic enzymes (*27*), it has a role in the immunological responses (*28,29*), and several brain functions like regulation of circadian rhythm (*30,31*), memory (*32*), stress, fear, and anxiety (*33-35*).

GRP/GRPR EXPRESSION IN VARIOUS CANCERS

GRP/GRPR expression and mechanisms of action have been widely studied both *in vitro* and *in vivo* for many different tumor types. Most of the studies have described GRPR acting as an autocrine growth factor receptor in tumor cells, increasing their ability to proliferate. Another hypothesis is that GRP/GRPR would act as a morphogen factor able to retain the tumor in a better-differentiated state. This has been evaluated in colon cancer *in vivo* xenograft studies where moderately differentiated tumors became better differentiated in mice expressing GRP/GRPR, while progressively degenerating into poor-differentiated tumors in GRP/GRPR negative mice (*36*).

GPRP expression in prostate cancer is higher than in normal prostate tissue, but variable expression can be found in benign prostate hyperplasia (BPH) (*6,37,38*) and the degree to which this may confound image interpretation creating false positive findings is still under investigation. Several groups evaluated the correlation between GRPR expression and clinical features of prostate cancer such as Gleason score, stage of disease and PSA levels (*38-42*). The results are not definitive and prospective trials should be performed to evaluate the relationship between GRPR expression and stage of disease,

androgen naïve vs castration resistant patients, in order to better select cases in which the use of this molecular target is appropriate.

GRPR overexpression in breast cancer has been extensively demonstrated (*7,43-49*), particularly in estrogen receptor (ER) expressing tumors (*50-52*). A recent study analyzed and compared ^{68}Ga-RM2 (DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2) and ^{18}F-FDG specific binding in tumoral areas of 14 breast cancer samples using tissue micro imaging; IHC for ER, progesterone receptor (PR), Ki-67, HER2/neu and GRPR was also assessed in all specimens (*50*). The authors found a significantly higher specific binding of ^{68}Ga-RM2 in the ER+ and PR+ groups compared to the ER- and PR- tumors; ^{68}Ga-RM2 binding was higher in the low Ki-67 group, whereas no difference was associated with HER2/neu status. ^{18}F-FDG uptake was lower in ER+ vs ER- cancers, it looked similar in PR groups, higher in the high Ki-67 group and no differences were associated with HER2/neu status. ^{68}Ga-RM2 binding was significantly higher in tumors without ^{18}F-FDG uptake. These results suggest that ^{68}Ga-RM2 PET may be complementary to ^{18}F-FDG PET in ER+ tumors with low proliferation index.

Mattei et al analyzed 238 lung cancer specimens including both small/non-small cell lung cancer (SCLC and NSCLC) and correlated the IHC results with clinical stage, cell type, sex, and survival (*53*). GRPR expression was more abundant in advanced stage disease, and a significant correlation was found between higher clinical stage and strong intensity of GRPR expression. The overall GRPR expression between SCLC and NSCLC was similar, but the intensity of the expression was higher in NSCLC.

IHC study was performed by Carroll et al in 50 human colon cancer specimens (*54*). Both GRP and GRPR were highly expressed in the majority of cancers (62%), while no expression was detected in normal adjacent tissues. A very interesting finding was that the co-expression of the 2 proteins was seen always in well-differentiated tumors regions, while was never observed in poor-differentiated tumor areas, suggesting the strong relation between GRP/GRPR expression and tumor differentiation.

A large number of other tumors overexpress GRPR on their cell surface, including head/neck cancer, renal cancer, intestinal and bronchial carcinoids (*43,55*); however, aside from breast and prostate cancer, only few clinical studies are currently underway.

CLINICAL EVALUATION OF GRP/GRPR IN PROSTATE CANCER

Diagnostic studies

The use of GRP analogs in prostate cancer patients has increased recently. Various BBN analogs have been labeled with different radioisotopes (^{64}Cu, ^{18}F, ^{68}Ga). GRPR antagonists replaced agonists due to their more favorable pharmacokinetics; they block the receptor instead of activating it (as agonists do), resulting in no gastrointestinal side effects and increased binding (*56,57*).

Roivainen et al. reported the first-in-human study of ^{68}Ga-RM2 (*58*). Five healthy volunteers were included. The radiopharmaceutical was rapidly excreted via the urinary system and accumulated predominantly in the pancreas; acceptable radiation exposure (effective dose of 7.7 mSv for an injected dose of 150 MBq) was reported, with the urinary bladder wall and the pancreas being the organs with the highest absorbed doses (0.61 mSv/MBq and 0.51 mSv/MBq, respectively). Similar results were reported with two other radiopharmaceuticals: ^{68}Ga-RM26 (^{68}Ga-1,4,7-triazacyclononane-*N,N′,N″*-triaceticacid-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2), and ^{68}Ga-NODAGA-MJ9 (^{68}Ga-NODAGA-4-amino-1-carboxymethyl-piperidine-$_D$-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2) (*59,60*).

Kahkonen et al analyzed 11 patients with prostate cancer who underwent ^{68}Ga-RM2 PET/CT prior to surgery (*61*). Region-based PET accuracy across all patients was 83%, with a sensitivity and specificity of 89% and 81%, respectively. The authors reported significantly higher SUV_{max} in tumor foci compared to BPH and normal prostate tissue. Similar results were recently reported by Touijer et al (*41*). IHC was performed to look for both GRPR and prostate specific membrane antigen (PSMA) expression, since the latter is currently the target of the most used (but not yet FDA-approved in the United States) radiopharmaceuticals in the evaluation of PC. IHC showed no correlation between GRPR and PSMA expression, suggesting that they may provide complementary information. Fassbender et al analyzed 15 patients with biopsy proven prostate cancer and compared the PET scan performed prior to surgery with the histopathology results (*62*). Although 93% of the patients had at least one focus of pathological ^{68}Ga-RM2 uptake, the overall PET accuracy using the region-based visualization was rather low (63% across all patients). No significant correlations were found between region-based SUV_{max} and histopathology or between whole prostate SUV_{max} and post-operative T-category or ISUP score.

Unpublished data from our group indicates a high detection rate of newly diagnosed prostate cancer using ^{68}Ga-RM2 PET in 34 patients who underwent either surgery (*n*=27) or radiotherapy (*n*=7) after imaging. ^{68}Ga-RM2 PET/CT showed intraprostatic cancer lesions in 33 patients (one patient had a negative scan) and correlated with pathology in 27 patients who underwent prostatectomy. Increased uptake was identified in 4 pelvic lymph nodes, confirmed by pathology (n=3) or follow-up imaging (n=1). An example is showed in Figure 1.

^{68}Ga-RM2 was evaluated more extensively at biochemical recurrence of prostate cancer. Our group published preliminary results from 32 prostate cancer patients who underwent ^{68}Ga-RM2 PET/MRI at biochemical recurrence with negative conventional imaging (*63*). ^{68}Ga-RM2 PET and MRI identified recurrent disease in 23 and 11 of these patients, respectively. PET was positive for all the 11 patients with MRI pathological findings. Our unpublished data from 114 participants enrolled to date indicate the following trend of ^{68}Ga-RM2 PET positivity: 31.8% for PSA < 0.5 ng/dl (*n*=22), 60% for PSA 0.5 – 1.0 ng/dl (*n*=15), 64.7% for PSA 1.0 – 2.0 ng/dl (*n*=17), 81.8% for PSA 2.0 – 5.0 ng/dl (*n*=22) and 87.2% for PSA > 5.0 ng/dl (*n*=38) (*64*). An example is shown in Figure 2. Another study compared ^{68}Ga-RM2 with ^{18}F-fluoroethylcholine (^{18}F-ECH) PET/CT in patients with biochemically recurrent PC (*65*). The authors retrospectively analyzed 16 men with biochemical relapse and negative or inconclusive ^{18}F-ECH PET/CT. Overall, ^{68}Ga-RM2 PET/CT showed abnormal uptake in 10 of 16 patients (63%): for 2 patients with inconclusive results in ^{18}F-ECH PET/CT, ^{68}Ga-RM2 showed additional lymph nodes in the pelvis and multiple bone lesions. However, the median PSA at the time of ^{18}F-ECH PET/CT was lower than that at the time of ^{68}Ga-RM2 PET/CT (2.4 vs 5.5 ng/ml, respectively), so further investigation in larger prospective clinical trials is needed to confirm these data.

^{68}Ga was used to label other GRPR targeting peptides. The DOTA-conjugated GRPR antagonist SB3 (DOTA-paminomethylaniline-diglycolic acid-DPhe-Gln-Trp-Ala-ValGly-His-Leu-NHEt) was tested in 17 patients with breast and prostate cancer (*66*). All patients had disseminated disease, and many have had previous treatments, including hormonal therapies; a positive scan was registered in about 50% of cases. Data suggest that GRPR expression declines in advanced androgen-independent stages of prostate cancer, especially in osseous metastases (*6,38*). An optimized version, ^{68}Ga-NeoBOMB1, was developed by replacement of the C-terminal Leu^{13}-Met^{14}-NH_2 dipeptide of SB3 with Sta^{13}-Leu^{14}-NH_2 (*67*). At 30

minutes after injection, more than 90% of ^{67}Ga-NeoBOMB1 and 80% of ^{177}Lu-NeoBOMB1 were found still intact in peripheral mouse blood, a characteristic that was pointed out by the authors as it makes an argument for the use as theragnostic agents.

^{68}Ga-RM26 is another GRPR antagonist with high affinity to GRP (*59*). The first in human study included 28 patients with prostate cancer (17 newly diagnosed and 11 post-therapy). ^{68}Ga-RM26 PET/CT was positive in 15 out of 17 patients at initial diagnosis of PC (88.2%) and 11 out of 11 with biochemical recurrence. Twenty-two patients also underwent ^{68}Ga-BBN PET/CT, a GRPR agonist radiopharmaceutical. ^{68}Ga-RM26 detected more primary tumors, lymph nodes and bone metastases then ^{68}Ga-BBN, further confirming the improved performance of antagonists over agonists.

^{64}Cu and ^{18}F labeled GRPR antagonists were also evaluated in small cohorts of prostate cancer patients. ^{64}Cu-CB-TE2A-AR06 (^{64}Cu-4,11-bis(carboxymethyl)-1,4,8,11tetraazabicyclo (6.6.2) hexadecane)-PEG$_4$-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-LeuNH$_2$) was assessed in 4 patients with newly diagnosed prostate cancer (*68*); favorable tumor uptake and image contrast of the radiotracer were reported.as The longer half-life of ^{64}Cu will allow for dosimetry applications prior to therapy using a GRPR antagonist. ^{18}F-BAY 864367 (3-Cyano-4-^{18}F-fluorobenzoyl-Ala(SO$_3$H)-Ala(SO$_3$H)-Ava-Gln-Trp-Ala-Val-*N*MeGly-His-Sta-Leu-NH$_2$) was used in a first in human study evaluating 10 patients with primary prostate cancer (*n*=5) or recurrent disease (*n*=5) (*69*). ^{18}F-BAY 864367 PET/CT was compared to ^{18}F-Fluorocholine PET/CT and to histopathology when available. Among patients with primary prostate cancer ^{18}F-BAY 864367 PET/CT detected 3 out of 5 lesions; for the 2 negative scans, both ^{18}F-Fluorocholine PET/CT and histopathology confirmed the prostate lesions. Only 2 recurrent disease lesions were detected by ^{18}F-BAY 864367, while ^{18}F-Fluorocholine PET/CT identified suspicious lesions in all 5 patients.

Theragnostic studies

The first in human dosimetry study of a ^{177}Lu-labeled GRPR antagonist was published by Kurth et al. (*70*). Four patients with metastatic castration-resistant prostate cancer received a mean dose of 4.48 GBq of ^{177}Lu-RM2. The most intense physiological uptake was seen in the pancreas, as expected from diagnostic studies (mean absorbed dose of 4.5±1.6 Gy), but not as high as to prevent further administrations (*71*). For the bone marrow, the reported absorbed dose of ^{177}Lu-RM2 was low and similar to what was

previously described for PSMA ligand therapies (*72,73*), while for the kidneys the ^{177}Lu-RM2 mean absorbed dose was lower than for ^{177}Lu-PSMA-617 (*72*) and ^{177}Lu-DOTATATE (*74*). Bone metastases had the highest uptake, followed by lymph nodes and soft tissue lesions. This study confirmed a very high inter-patient variability in terms of tumor uptake, a characteristic already described (*62*) and which implies that different tumor biology affects GRPR expression. While these preliminary results are encouraging, further evaluations are needed.

Radiopharmaceuticals targeting GRPR are promising tracers for prostate cancer evaluation, showing high detection rate for local and loco-regional disease; they are accurate for the assessment of metastatic foci as well, whereas further evaluation is needed to understand the relation between GRPR expression and advanced hormonal resistant prostatic tumors. Compared to PSMA, whose high sensitivity and specificity in prostate cancer patients have been widely demonstrated (*75-83*), GRPR could play an important complementary role for PSMA negative cancer, and for tumors characterized by a heterogeneity of receptors expressed on their cell surface.

CLINICAL EVALUATION OF GRP/GRPR IN BREAST CANCER

Imaging studies

Although only a few pilot translational studies evaluating GRPR expression in breast cancer patients have been published so far, preliminary results seem to confirm what *in vitro* data already suggested: GRPR expression is strongly present in ER positive tumors; furthermore, when the primary tumor is GRPR positive, the lymph nodes metastases also show GRPR overexpression (*51,52,66*).

Stoykow et al evaluated the performance of ^{68}Ga-RM2 PET/CT in 15 patients with newly diagnosed breast cancer (*84*). Eighteen breast cancer lesions were known from core needle biopsy (3 patients had bilateral lesions). ^{68}Ga-RM2 PET/CT clearly detected 13 of these 18 lesions; the 5 PET false negative results were tumors with uptake level not distinguishable from normal breast tissue. However, in these cases, metastatic axillary lymph nodes were identified. All cancers seen on PET showed positivity for ER and PR expression; among the 5 cancers not detected by PET, only 1 was ER+, with an immunohistochemical ER expression of 30%. In the multivariate analysis, ER status was the primary predictor of ^{68}Ga-RM2 uptake.

Another group studied breast cancer patients using ^{68}Ga-RM26 PET/CT (*85*). ^{68}Ga-RM26 PET/CT detected 29 tumors out of 34 confirmed by histopathology. The 5 PET negative tumors had un uptake that was lower or equal to the normal breast tissue. PET positivity was correlated to ER status: 26 out of 28 ER+ primary cancers were also PET positive. Histopathology confirmed the presence of lymph nodes metastases in 18 patients; PET was positive in lymph nodes for 15 of them. ^{68}Ga-RM26 PET/CT missed metastases in 3 lymph nodes that were 1mm in size. The SUV_{max} was significantly higher in ER+ tumors compared to ER- tumors and positively correlated to the expression level of GRPR. Uptake level was associated with menstrual cycle in both normal breast tissue and cancer (SUV_{max} was significantly higher during the secretory phase compared to either the non-secretory phase or post-menopause phase); 4 out of 5 PET negative scans were performed in women during their secretory phase. Sensitivity, specificity and accuracy of ^{68}Ga-RM26 PET/CT increased either when ER negative tumors were not considered or when patients who underwent the scan during their secretory phase were removed from the analysis.

An example from our own experience with ^{68}Ga-RM2 PET/MRI in ER+ breast cancer is shown in Figure 3. Supplemental tables 1 and 2 summarize the clinical studies in prostate and breast cancer.

FUTURE DIRECTIONS

One area of development is to explore and understand the variability of GRPR expression in prostate cancer tumors, in order to select the optimal imaging and therapy strategy for each patient. For tumors expressing GRPR, the detection rates for both the primary lesions and metastases are high. The well-known concept of intra-tumor heterogeneity (i.e. types of receptors expressed, receptor expression level, grade of malignancy, resistance to therapy), led to the development of bivalent prostate cancer-targeting peptides, with the ability to target two receptors. In particular, heterodimers targeting both PSMA and GRPR have been evaluated (*86,87*). In addition, strategies to decrease the physiological uptake in the pancreas and to increase tumor uptake are evaluated by various groups.

Another avenue for future use of GRPR antagonists are novel indications, both in prostate cancer (biopsy guidance, evaluation or response to targeted local therapy) and in other cancers such as gastrointestinal and gynecological malignancies. Although PSMA imaging and therapy are gaining significant traction at various stages of prostate cancer, GRPR antagonists are likely to play a

complementary role. An example of ^{68}Ga-RM2 and ^{68}Ga-PSMA11 PET in the same patient showing 2 different primary prostate cancer lesions is shown in Figure 4.

Lastly, it seems clear that GRPR expression in breast cancer cells is highly correlated with ER+ tumors. This opens opportunities to expand the use of GRPR antagonists not only for diagnostic, but also for therapeutic purposes in this patient population.

CONCLUSIONS

Cancer imaging and therapy using peptide-based radiopharmaceuticals has ushered in a new era for nuclear medicine. Radiolabeled BBN analogs are promising theragnostic agents for GRPR expression tumors, where they are able to detect primary tumors and metastatic lesions with high sensitivity and specificity. Larger prospective clinical trials are needed to improve the understanding between the GRPR expression and biological behavior of different cancer cells, in order to better select patients who will benefit from their use.

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FIGURE LEGENDS:

Figure 1: 64-year-old man with newly diagnosed high-risk prostate cancer, PSA 6.42 ng/ml. Intense focal ^{68}Ga-RM2 uptake is seen in the prostate gland (arrows) on maximum intensity projection (MIP) (A), axial PET (B) and fused PET/CT (C), correlating with the location of cancer marked in black ink on post-prostatectomy histopathology slide (D).

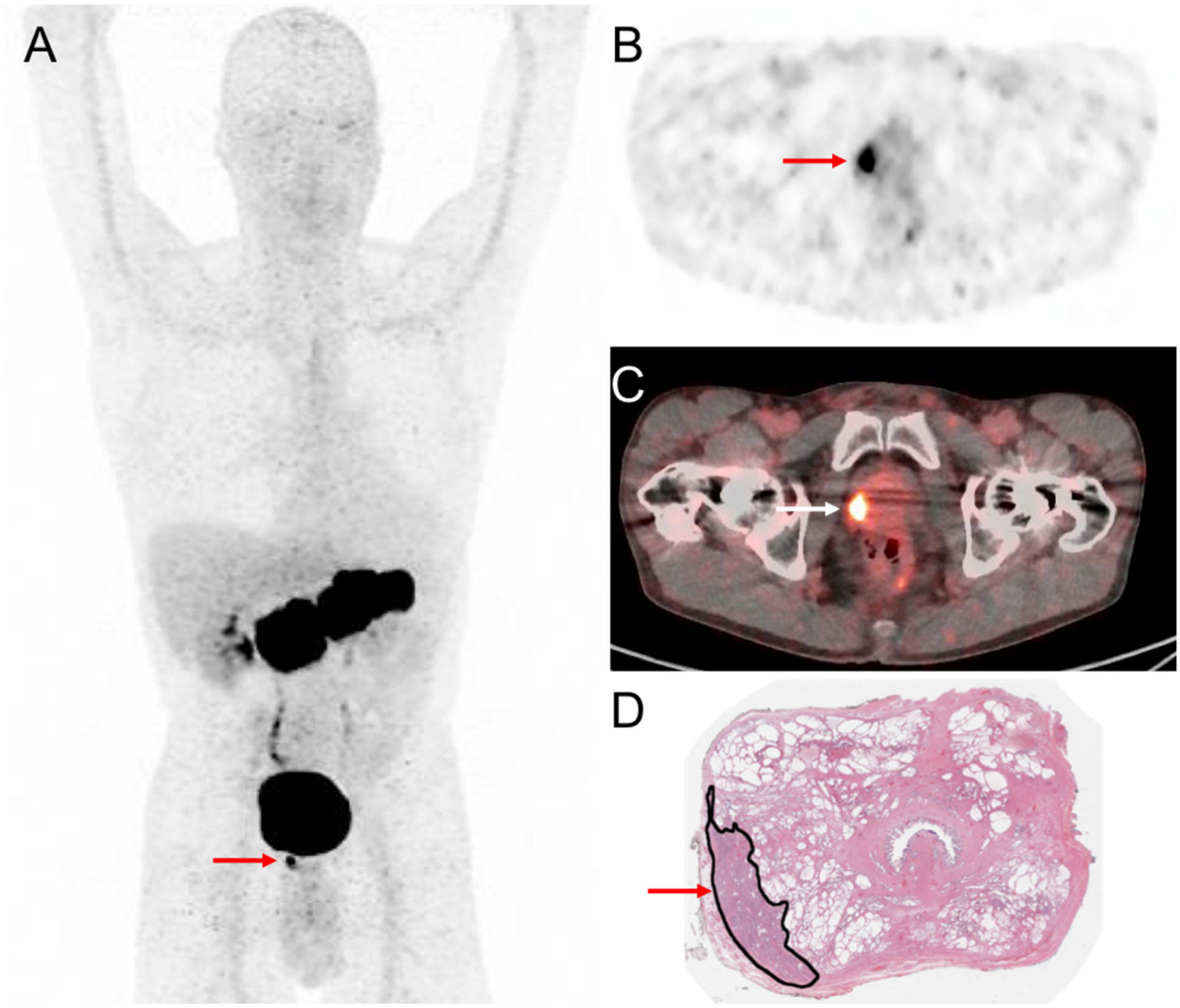

Figure 2: 72-year-old man with BCR prostate cancer, PSA 0.72 ng/ml. Intense ^{68}Ga-RM2 uptake is seen in the right prostate bed (arrows) on early MIP (A), axial PET (B) and fused PET/MRI (D). Corresponding axial T1-weighted MRI is also shown (C).

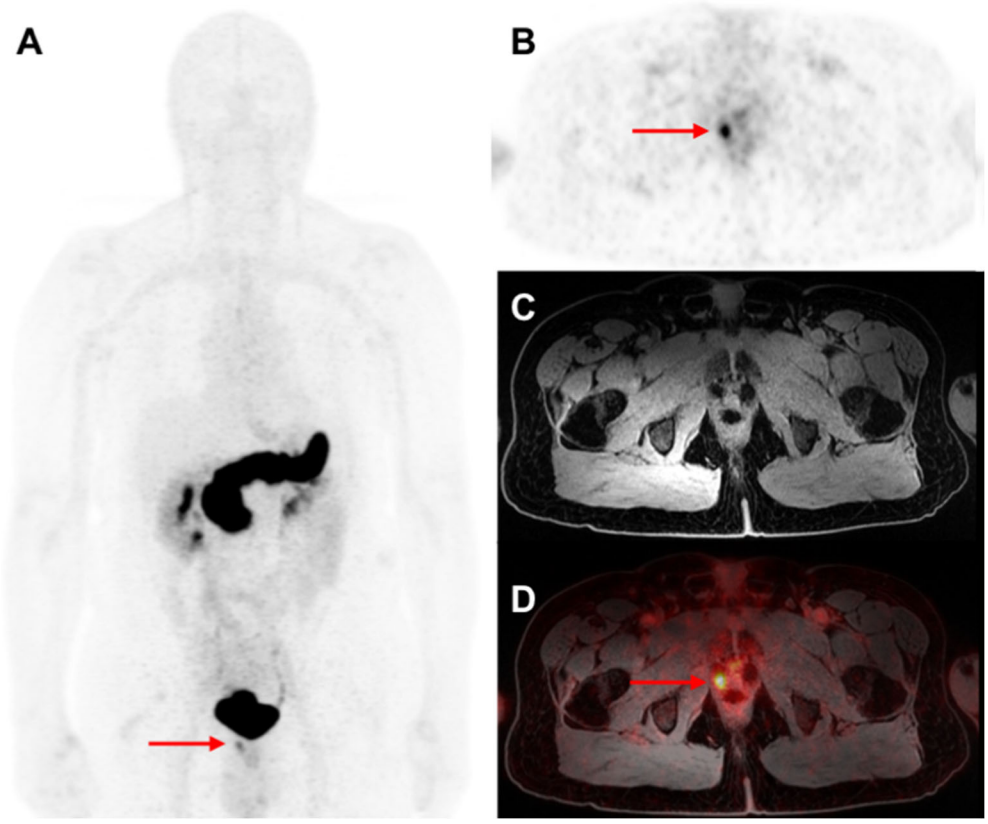

Figure 3: 36-year-old woman with newly diagnosed ER positive breast cancer. Intense ^{68}Ga-RM2 uptake is seen in the left breast (arrows) on MIP (A), axial T1-weighted MRI (B), axial PET (C) and fused PET/MRI (D).

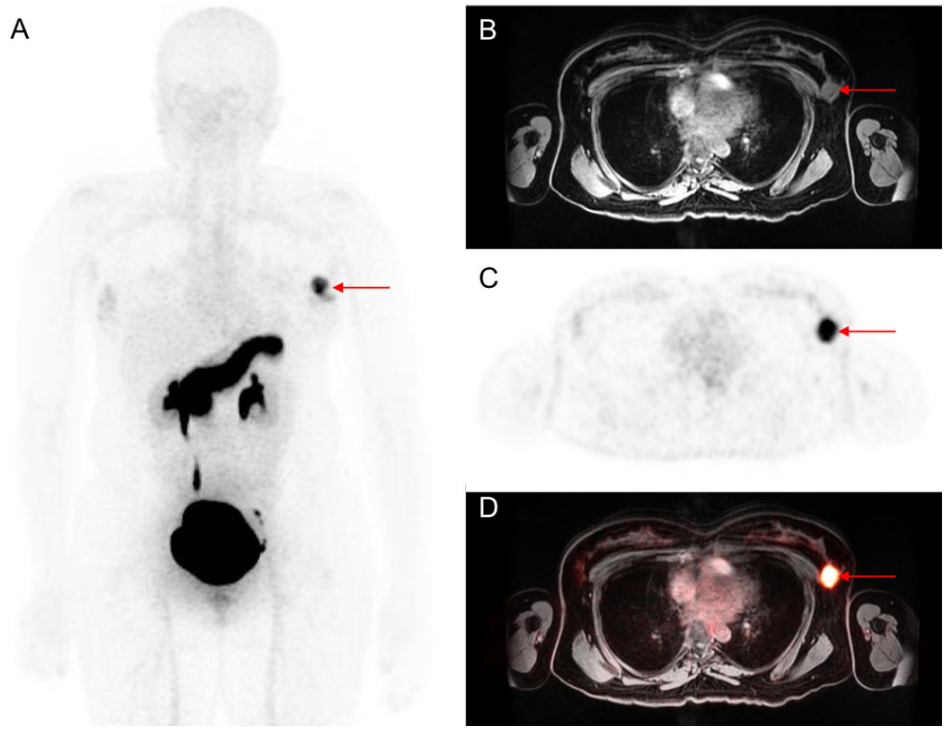

Figure 4: 54-year-old man with newly diagnosed intermediate-risk prostate cancer, PSA 5.09 ng/ml. Focal ^{68}Ga-RM2 uptake is seen in the right prostate gland (arrow) on axial fused PET/CT and PET (top row), while focal ^{68}Ga-PSMA11 uptake is seen in the left prostate gland (arrow) on axial fused PET/MRI and PET (bottom row). Both were prostate cancer on post-prostatectomy histopathology.

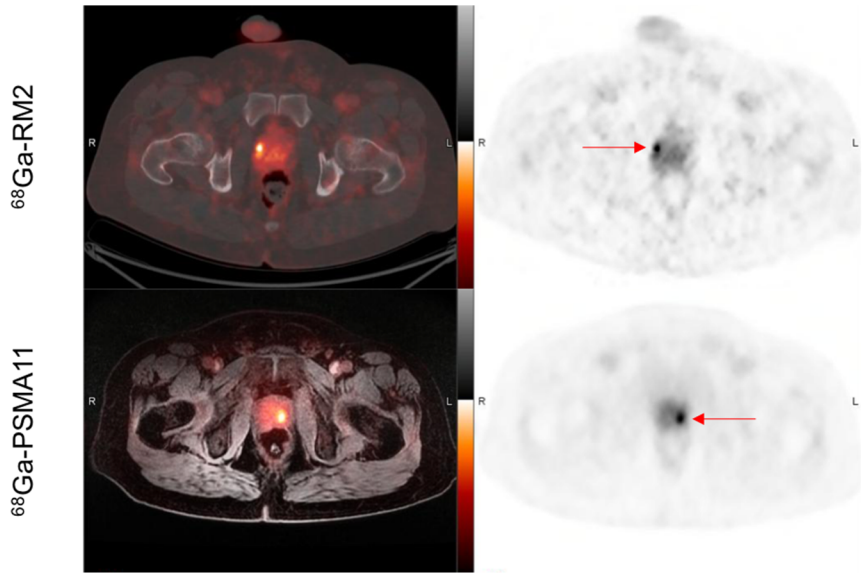

Table 1: Clinical studies of GRP/GRPR PET in prostate cancer

Authors	Year	Radiotracer	Hybrid Imaging Modality	Study Aims	Participants Evaluated	Results	Reference
Roivanen et al	2013	^{68}Ga-RM2	PET/CT	To evaluate the biodistribution and dosimetry of ^{68}Ga-RM2	5 healthy volunteers	^{68}Ga-RM2 was safe; Pancreas and Urinary System the most exposed organs	(*58*)
Zhang et al	2018	^{68}Ga-RM26	PET/CT	To evaluate biodistribution and dosimetry of ^{68}Ga-RM26; To assess ^{68}Ga-RM26 diagnostic value; To compare ^{68}Ga-RM26 with ^{68}Ga-BBN and with ^{99m}Tc-MDP	5 Healthy Volunteers and 28 PC patients (17 new diagnosis, 11 BCR)	^{68}Ga-RM26 was safe; Pancreas and Urinary System the most exposed organs; High detection rate in both groups; Better performance than ^{68}Ga-BBN; Detection of more bone lesions than MDP	(*59*)
Gnesin et al	2018	^{68}Ga-NODAGA-MJ9	PET/CT	To evaluate biodistribution and dosimetry of ^{68}Ga-NODAGA-MJ9;	5 PC patients with BCR	^{68}Ga- NODAGA-MJ9 was safe; Pancreas and Urinary System the most exposed organs	(*60*)
Kahkonen et al	2013	^{68}Ga-RM2	PET/CT	To evaluate the accuracy of ^{68}Ga-RM2 in detecting primary PC.	11 patients with primary PC	Accuracy:83% Sensitivity:89% Specifity:81%	(*61*)
Touijer et al	2019	^{68}Ga-RM2	PET/CT; mpMRI	To evaluate the detection rate of ^{68}Ga-RM2 in primary PC compared to mpMRI.	16 patients with primary PC	Accuracy of PET:78.8% Accuracy of mpMRI:76.6% Accuracy of PET/MRI:83.9% IHC: no correlation between GRPR and PSMA expression	(*41*)
Fassbender et al	2019	^{68}Ga-RM2	PET/CT	To evaluate accuracy of ^{68}Ga-RM2 in detecting primary PC	15 patients with primary PC	Overall accuracy: 63% High intra-individual accuracy variability	(*62*)
Minamimoto et al	2018	^{68}Ga-RM2	PET/MRI	To evaluate the detection rate of ^{68}Ga-RM2 in patients with	32 patients with BCR of PC	PET positive in 23 patients MRI positive in 11 patients	(*63*)

				BCR PC and to compare PET/CT with MRI			
Wieser et al	2017	^{68}Ga-RM2	PET/CT	To compare ^{68}Ga-RM2 and ^{18}F-ECH in BCR PC	16 patients with BCR of PC	^{68}Ga-RM2 detected more lesions than ^{18}F-ECH	(*65*)
Maina et al	2016	^{68}Ga-SB3	PET/CT	To evaluate ^{68}Ga SB3 accuracy in advanced PC and breast cancer	17 patients with advanced breast and PC	Detection rate for metastatic lesions higher than 50%	(*66*)
Nock et al	2017	^{68}Ga-NeoBOMB1	PET/CT	To evaluate biodistribution and dosimetry of ^{68}Ga NeoBOMB1; To assess ^{68}Ga NeoBOMB1 diagnostic value	4 patients with primary PC	^{68}Ga-NeoBOMB1 was safe; Pancreas and Urinary System the most exposed organs; High detection rate of primary tumor and metastatic foci	(*67*)
Wieser et al	2014	^{64}Cu-CB-TE2A-AR06	PET/CT	To evaluate biodistribution and dosimetry of ^{64}Cu-CB-TE2A-AR06; To assess ^{64}Cu-CB-TE2A-AR06 diagnostic value	4 patients with primary PC	^{64}Cu-CB-TE2A-AR06 was safe; Pancreas and Urinary System the most exposed organs ^{64}Cu-CB-TE2A-AR06 showed favorable tumor uptake and image contrast	(*68*)
Sah et al	2015	^{18}F-BAY 864367	PET/CT	To evaluate biodistribution and dosimetry of ^{18}F-BAY 864367; To assess ^{18}F-BAY 864367 diagnostic value	10 patients with primary or recurrent PC	^{68}Ga-NeoBOMB1 was safe; Pancreas and Urinary System the most exposed organs; High detection rate in early stage of PC	(*69*)
Kurth et al	2019	^{177}Lu-RM2	Scintigraphy; SPECT/CT	To evaluate safety and dosimetry of ^{177}Lu-RM2 for therapy of metastatic PC	4 patients with metastatic CR PC	Therapy was safe; dosimetry was favorable; Bone metastases were the ones which got the highest activity	(*70*)

PC: prostate cancer; mpMRI: multi parametric MRI; BCR: biochemical recurrence; IHC: immunohistochemistry.

Table 2: Clinical studies of GRP/GRPR PET in breast cancer

Authors	Year	Radiotracer	Hybrid Imaging Modality	Study Aims	Participants Evaluated	Results	Reference
Stoykow et al	2016	^{68}Ga-RM2	PET/CT	To evaluate the detection rate of ^{68}Ga-RM2 in primary breast cancer	15 patients with breast cancer	^{68}Ga-RM2 detected 13 out of 18 primary tumors; ER was the primary predictor of ^{68}Ga-RM2 uptake	(*84*)
Zang et al	2018	^{68}Ga-RM26	PET/CT	To evaluate the detection rate of ^{68}Ga-RM26 in primary breast cancer	35 women with suspicion of breast cancer	^{68}Ga-RM26 detected 29 out of 34 primary lesions; PET was positive in 26 out of 28 ER positive tumors. High accuracy for lymph nodes detection. Correlation between menstrual cycle and GRPR expression	(*85*)

PC: prostate cancer; mpMRI: multi parametric MRI; BCR: biochemical recurrence; IHC: immunohistochemistry.