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Prostate-specific membrane antigen (PSMA) expression in primary and metastatic renal cell cancer (UroCCR-65 study)

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Abstract

Background Prostate-specific membrane antigen (PSMA) has been shown to be overexpressed in the neovasculature of renal cancers. However, studies investigating the pattern of PSMA expression in primary RCC and RCC metastases according to metastatic sites are rare. 44 frozen samples of RCC, 19 primaries (9 clear cell (cc) RCC, 7 papillary (pap) RCC, and 3 chromophobe (ch) RCC) and 25 (24 samples have ccRCC histology and one is unclassified) unpaired metastases (8 from adrenals, 8 from bones, 2 from lungs, 2 from liver and 5 others (1 lymph node, 1 pancreas, 1 brain, 1 gallbladder and 1 muscle)), were available from the UroCCR project (NCT03293563). PSMA expression was assessed by autoradiography using [^{177}Lu]Lu-PSMA-617 as binding agent and the specific binding (total binding—non-specific binding) was calculated and expressed as a percentage of total binding. A patient suffering from metastatic ccRCC was also administered [^{68}Ga]Ga-PSMA-11 to evaluate PSMA expression.

Results The mean specific binding was 28.9 ± 40.4% for primary renal cancer and 65.0 ± 38.9% for metastasis. Regarding histology, high PSMA expression was depicted in 33.3% of ccRCC, 33.3% of chRCC and 57.1% of papRCC. PSMA was more frequently expressed in primary samples of papRCC histology with renal capsule invasion ($p = 0.0286$). A higher PSMA-specific binding and a higher number of samples with high PSMA-expression were depicted in metastatic samples. Bone metastasis showed lower binding than other metastatic sites combined ($p = 0.0005$). The patient suffering from metastatic ccRCC showed high [^{68}Ga]Ga-PSMA-11 uptake on known distant metastases and additional site uncovered.

Conclusion PSMA showed high expression in metastases of ccRCC.

Clinical trial registration NCT, NCT03293563, prospectively registered September 20, 2017, http://www.clinicaltrials.gov.

Keywords Primary RCC, PSMA, Metastatic RCC, Clear cell RCC, Kidney cancer

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Introduction

Renal cancer accounts for about 2% of all neoplasms worldwide, and its incidence increases with age and has a higher incidence in men with a ratio of 2:1 [1]. Renal cell carcinoma (RCC) accounts for more than 90% of renal cancers. About 15% of patients have metastatic disease at initial diagnosis, and another 20% develop metastases during follow-up. RCC has several histological and molecular subtypes, including clear cell (cc) RCC, papillary (pap) RCC, and chromophobe (ch) RCC. Among them, ccRCC is the most common and the largest purveyor of cancer-related deaths [1].

Currently, the role of nuclear medicine imaging, with ^{18}F-fluorodeoxyglucose ([^{18}F]-FDG) positron-emission tomography/computed-tomography (PET/CT) or bone scintigraphy, is suboptimal and not well established, whether for evaluation of the primary tumor or metastatic disease. [^{18}F]-FDG is not well suited to image renal lesions, mainly due to its physiologic excretion and accumulation in the renal pelvis and bladder that potentially obscures [^{18}F]-FDG-avid kidney and bladder lesions. As for metastatic workup, the lytic nature of bone metastases from renal cell carcinoma makes it often challenging to be seen and diagnosed by a bone scan, which mostly depends on the osteoblastic activity.

Prostate-specific membrane antigen (PSMA), a type II transmembrane glycoprotein, has been shown to be overexpressed in the neo-vasculature of renal carcinoma with frequency varying with histologic sub-types [2]. However, studies investigating the pattern of PSMA expression in primary RCC as well as in RCC metastases are rare. Moreover, the PSMA expression across metastatic sites has not been well assessed. The objective of this work was therefore to study, using autoradiography, PSMA expression in a panel of samples of primary RCC and RCC metastases.

Materials and methods

Samples

Forty-four frozen samples of renal cancer, 19 primaries and 25 metastases (confirmed by histology), were available from the UroCCR project (NCT03293563). None of the patients received neoadjuvant treatment. Samples of primaries and metastases were unrelated and there was one metastatic sample per patient. Samples from patients with primary renal cancer accounted for nine patients having ccRCC, seven patients with (pap)RCC and three patients with (ch)RCC. Among the twenty-five samples from metastasectomy, 24 were from ccRCC and 1 from unclassified RCC. Metastasectomy sites were from: adrenal gland ($n=8$), bone ($n=8$), lung ($n=2$), liver ($n=2$), distant lymph node ($n=1$), pancreas ($n=1$), brain ($n=1$), gallbladder ($n=1$) and muscle ($n=1$).

Protocol of binding assay

The general principles were previously described in studies on prostate cancer [3, 4]. In brief, samples were cutted at 5 µm thickness and placed on slides. Slides were stored at -80 °C and placed at -20 °C three days prior to handling. On the day of the experiment, slides were pre-incubated in Tris-HCl buffer at pH 7.4 for 10 min at 37 °C. Then, a binding solution containing Tris-HCl buffer at pH 8.2, 1% of BSA (Sigma A2153), 40 µg/mL of bacitracin (Sigma®11,702), 10 nM of $MgCl_2$ (Sigma M8266) and 10 nM of [^{177}Lu]Lu-PSMA-617 either without (total binding) or with 10 µM PMPA as blocking agent (non-specific binding). In addition, slides with Hematoxylin-Eosin-Saffron (HES) staining were available to compare the tissue positioning with the registered signal.

Image analysis

The Beta Imager-2000 (tRACER, BiospaceLab, Paris, France) was used to register and quantify the signal (3.10^6 events were registered). Images from HES and autoradiography slides were merged and regions of interests (ROIs) were used to calculate the amount of specific binding. A first ROI was applied to estimate total binding, and a second ROI, corresponding to background noise, was placed around the tissue. The same ROIs were then transferred to the adjacent slice to determine non-specific binding. After subtracting background noise, specific binding (total binding—non-specific binding) was expressed as a percentage of total binding as follows:

$$\frac{Specific\ binding\ (\%)}{100} = \frac{(total\ binding - noise) - (nonspecific\ binding - noise)}{(total\ binding - noise)}$$

For association with clinical, biological and pathological parameters, data were dichotomized into two groups for each of the two categories of primaries and metastases samples: low PSMA expression group (0–10% specific binding) and high PSMA expression group (11–100% specific binding). The 10% cut-off to discriminate low from high PSMA expression was chosen as this value was reported to show significant higher SUVmax value on PSMA PET in prostate cancer [5] and is usually applied [4, 6]. No cross validation has been performed in the case of renal cancer.

Statistical analysis

Differences between categorized variables were assessed with the χ^2 test or Fischer exact test. Differences between the means were assessed using one-way, non-parametric ANOVA (Kruskal-Wallis test) and adjusted for multiple comparisons. All P values were two-sided, and a P value of less than 0.05 was considered statistically significant.

Statistical analysis was performed using the GraphPad software (v10.2.2).

Clinical case report

[^{68}Ga]Ga-PSMA-11 was applied to a patient suffering from metastatic ccRCC as part of the ongoing Phase I study PradR (NCT06059014) evaluating the efficacy of PSMA-targeted radionuclide therapy in this setting [7].

Results

Samples and demography

As previously stated, all samples from patients with primary renal cancer presented a dominant tumor type, with nine patients having ccRCC, seven patients (pap) RCC, and three patients (ch)RCC. According to WHO/ISUP grade, nine (47.4%) cases were grade II, six (31.6%) grade III and four (21.0%) grade IV. The mean tumor size was 6.6 ± 2.6 cm. The mean patient age (at diagnosis) was 59.2 ± 21.8 y. Eleven patients (58%) were male. Twenty-five samples from metastasectomy were analyzed including 24 ccRCC and 1 unclassified RCC (eosinophilic cell carcinoma (NOS) not otherwise specified). Metastasectomy sites were from: adrenal gland ($n = 8$), bone ($n = 8$), lung ($n = 2$), liver ($n = 2$), distant lymph node ($n = 1$), pancreas ($n = 1$), brain ($n = 1$), gallbladder ($n = 1$) and muscle ($n = 1$). Eighteen patients (72%) were male.

Table 1 PSMA expression according to primary RCC tumors' characteristics

Characteristic	Category	n	PSMA expression		*P*-value
			Low (%)	High (%)	
Histology	ccRCC	9	66.7	33.3	0.825
	papRCC	7	42.9	57.1	
	chRCC	3	66.7	33.3	
Renal capsule invasion	Yes	12	50	50	**0.0436**
	No	7	100	0	
Perirenal fat invasion	Yes	6	33.3	66.7	
	No	13	69.2	30.8	
Micro vascular embolism	Yes	3	66.7	33.3	
	No	16	56.3	43.7	0.3189
Sarcomatoid component	Yes	3	33.3	66.7	> 0.9999
	No	16	62.5	37.5	0.5459
WHO/ISUP grade	II	9	66.7	33.3	0.4832
	III	6	66.7	33.3	
	IV	4	25	75	
pT	T_1	9	66.7	33.3	0.3543
	T_2	2	100	0	
	T_3	8	37.5	62.5	
Tumor size	< 7cm	11	63.6	36.4	> 0.9999
	≥ 7cm	8	50	50	

Parameters influencing PSMA expression in primary renal cancer

The mean specific binding among the 19 samples from primary renal cell carcinoma (RCC) was 28.9 ± 40.4%. Out of these samples, 11 exhibited low PSMA expression (≤ 10%), while 8 showed high expression. PSMA was found to be more frequently expressed (50%, 6/12) in samples with renal capsule invasion ($p = 0.0436$, see Table 1). Tumor size, histological subtype and WHO/ISUP grade were not significantly correlated with PSMA expression in this study (Table 1). Since PSMA expression has been previously found to be dependent on renal cancer histological subtypes, additional analysis, stratified by histology, was performed (Table 2).

PSMA expression in samples of renal cancer metastases according to metastatic site

The mean specific binding for the 25 metastasis samples was 65.0 ± 38.9%. Four samples had low (≤ 10%) expression, while 21 (84.0%) had high expression. A representative example of [^{177}Lu] Lu-PSMA-617 uptake into a metastasis sample from ccRCC is depicted in Fig. 1. Of note, 24 of the 25 metastatic samples had ccRCC histology; so PSMA expression in metastases from other subtypes could not be assessed. Table 3 showed the mean specific binding of [^{177}Lu]Lu-PSMA-617 stratified by metastatic sites from ccRCC.

When comparing PSMA expression in primary tumor and metastases, there were a higher mean specific binding in metastasis samples (65.0 ± 38.9% vs. 28.9 ± 40.4%) but also a higher percentage of high PSMA expressing metastatic samples (84.0 vs. 42.1%). This remains the case when restricting analysis to samples of ccRCC primary tumors and ccRCC metastases: 33.3% of primary ccRCC were PSMA positive vs. 83.3% for ccRCC metastatic samples. Similarly, the mean specific binding was higher in metastasis compared to primary ccRCC (66.4 ± 37.6% vs. 21.2 ± 38.8%).

Specific binding values were next stratified to metastasectomy sites to highlight potential differences.

Mean specific bindings were 82.52 ± 31.06% for metastasis from adrenals, 32.41 ± 36.69% for metastasis from bones, 85.93 ± 18.38% for liver metastasis, 68.80 ± 36.88% for metastasis from lungs and 92.77 ± 5.34% for other metastatic sites (Fig. 2; Table 3). Bone metastasis showed lower binding than other sites combined ($p = 0.0005$). PSMA-specific binding was significantly higher in metastasis from adrenals compared with bone metastasis (adjusted p-value = 0.043). There was also a trend for higher PSMA-specific binding in other metastatic sites compared with bone metastases (adjusted p-value = 0.0566).

Table 2 PSMA expression according to primary RCC tumors' characteristics, stratified by histology

Characteristic	Category	*ccRCC*				*papRCC*				*chRCC*			
		PSMA expression				PSMA expression				PSMA expression			
		n	Low (%)	High (%)	*P*-value	n	Low (%)	High (%)	*P*-value	n	Low (%)	High (%)	*P*-value
Renal capsule invasion	Yes	6	50	50	0.4643	4	0	100	**0.0286**	2	50	50	> 0.9999
	No	3	100	0		3	100	0		1	100	0	
Perirenal fat invasion	Yes	2	50	50	> 0.9999	3	0	100	0.1429	1	100	0	> 0.9999
	No	7	71.4	28.6		4	75	25		2	50	50	
Micro vascular embolism	Yes	1	100	0	> 0.9999	2	50	50	> 0.9999	6	-	-	> 0.9999
	No	8	62.5	37.5		52	40	60		3	66.7	33.3	
Sarcomatoid component	Yes	1	100	0	> 0.9999	5	0	100	0.4286	-	-	-	> 0.9999
	No	8	62.5	37.5			60	40		3	66.7	33.3	
WHO/ISUP grade	II	4	75	25	> 0.9999	3	66.7	33.3	0.6571	2	50	50	> 0.9999
	III	3	66.7	33.3		2	50	50		1	100	0	
	IV	2	50	50		2	0	100		-	-	-	
pT	T_1	6	83.3	16.7	0.2262	2	50	50	> 0.9999	1	0	100	0.3333
	T_2	-	-	-		-	-	-		2	100	0	
	T_3	3	33.3	66.7		5	40	60		-	-	-	
Tumor size	< 7cm	6	83.3	16.7	0.2262	4	50	50	> 0.9999	1	0	100	0.3333
	≥ 7cm	3	33.3	66.7		3	33.3	66.7		2	100	0	

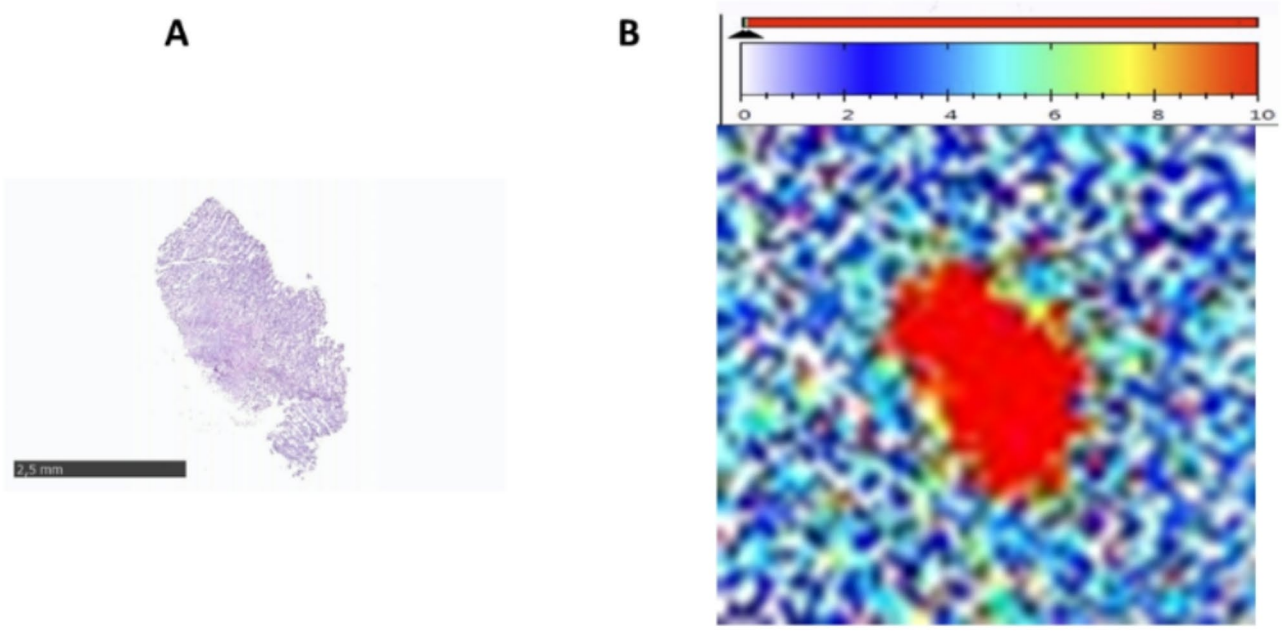

Fig. 1 (**A**) HES staining of an adrenal metastasis sample from ccRCC. (**B**) [^{177}Lu]Lu-PSMA-617 autoradiography to the same sample, showing high binding. The unit of the scale bar is cpm/mm^2

Table 3 Mean PSMA specific binding according to the site of metastasis from renal cancer *

	n	Mean PSMA specific binding (%)
Metastatic site		
-Adrenals	8	82.52 ± 31.06
-Bones	8	32.41 ± 36.69
-Liver	2	85.93 ± 18.38
-Lungs	2	68.80 ± 36.88
-Other	5	92.77 ± 5.34

* 24 of the 25 samples have ccRCC histology

Clinical case report

This patient was included in the phase I trial « PRaDR » evaluating the role of [^{177}Lu]Lu-PSMA-1 for metastatic clear cell renal cancer. [^{68}Ga]Ga-PSMA-11 PET was performed to evaluate PSMA expression in lymph nodes, pulmonary, adrenal, pancreatic and peritoneal lesions. A left femoral metastasis was diagnosed which was not known but could explain a grade 1 pain presented by the patient (Fig. 3).

Discussion

Molecular imaging can help assess biological characteristics in cancer patients. PSMA is known to be overexpressed in prostate cancer. Several studies have shown that other solid tumor types also express this protein, especially so in endothelial cells of the tumor-associated neovasculature [8–10]. In the largest retrospective cohort study conducted on 257 renal cell carcinomas (RCC) samples, a correlation between high PSMA expression and higher grade, more advanced tumors, as well as poorer overall survival rates was found [10].

Based on the increasing interest in PSMA-targeting for RCC, with its potential for imaging and targeted radionuclide therapy, we designed this preclinical study to report the level of PSMA expression in untreated RCC (primary and metastatic) using [^{177}Lu]Lu-PSMA-617 as binding agent. In primary tumors, high PSMA expression was found in ~40% of cases studied. PSMA was found to be more frequently expressed in samples with renal capsule invasion suggesting a potential role in the invasion process of renal cancer. By stratifying PSMA-expression to histology this finding is in fact found in papillaryRCC (Table-2). PapRCC were found to be rarely (30% or less) PSMA-positive but these studies were performed using immunohistochemistry methods [11], while quantitative autoradiography was used for our study. Further quantitative studies (autoradiography, PET, etc.) are needed to elucidate the impact of histology on PSMA expression in RCC. Other parameters studied showed no association with PSMA expression similarly to previous reports [2] but the number of samples per group is limited.

Evidence regarding the utility of PSMA PET imaging to image primary RCC are accumulating (sometimes with contrasting results) but its role has to be precisely defined in prospective large studies [12]. A literature review on the role of PSMA in ccRCC suggested that, based on currently available data, PSMA PET in localized RCC shows promise in predicting pT stage, ISUP grade, and adverse pathology. This may lead in changes treatment decision in ~40% of ccRCC [11].

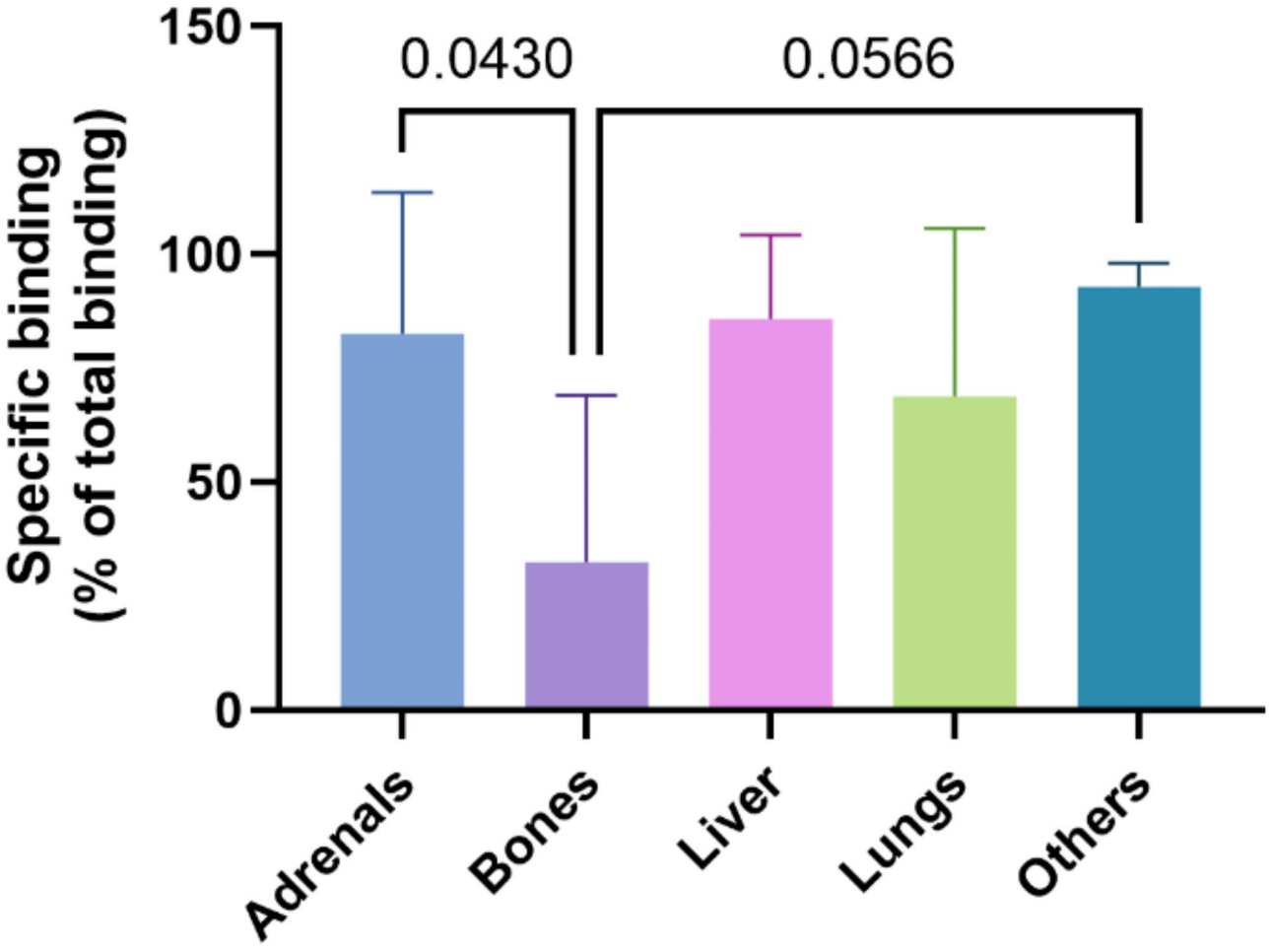

Fig. 2 PSMA expression according to metastatic sites

PSMA PET imaging may be useful to assess the treatment response to tyrosine kinase inhibitor and immune checkpoint inhibitors earlier than morphological changes in CT [13, 14]. One important point should be addressed for PSMA-based imaging of primary RCC. In this specific case, the choice of the PSMA-radiopharmaceutical seems crucial. Indeed, [^{68}Ga]Ga-PSMA-11, [^{18}F]-DCFPyL and [^{18}F]F-JK-PSMA-7 have a urinary excretion which is less pronounced in the case of [^{18}F]F-PSMA-1007 [15]. This might confers more advantageous diagnostic performances of [^{18}F]F-PSMA-1007 in imaging primary RCC compared to other PSMA-radiopharmaceuticals (although the higher rate of false positive uptake in bones might decrease the interpretability of skeletal events in the case of metastatic disease). Carbonic anhydrase IX (CAIX) is another cell surface target that is expressed in more than 95% of primary ccRCC and can be targeted using radiolabeled antibodies [16] and peptides [17]. Comparison with PSMA-imaging is clearly needed. Considering the successful results of [^{177}Lu]Lu-PSMA-617 and [^{225}Ac]Ac-PSMA-617 in metastatic castration-resistant prostate cancer patients [18, 19] similar achievements might be expected in metastatic RCC. Immunohistochemical studies showed higher PSMA expression in the neovasculature of metastases [10] which is confirmed by our results. Interestingly, in our study, 21 of 25 metastatic were PSMA-positive and among them 16 (76.2%) showed an intense signal (specific binding > 50%) needed for therapeutic applications. Thus 16/25 (62.5%) PSMA-positive metastatic samples showed high binding. In the literature, PSMA PET/CT was able to identify more metastatic lesions than CT [20] or than [^{18}F]-FDG PET/CT, with higher SUVmax values [21] resulting in a management change in about one-third of the patients [22]. Therefore, PSMA-based theranostics can be an option in metastatic ccRCC. However, the performance of PSMA PET/CT for metastatic patients has not been investigated according to the site of metastasis. Herein, we showed that bone mestastases express lower PSMA binding sites than other location investigated (adrenals, lungs and liver mainly). This is a valuable information as the dose delivered to bone metastasis by

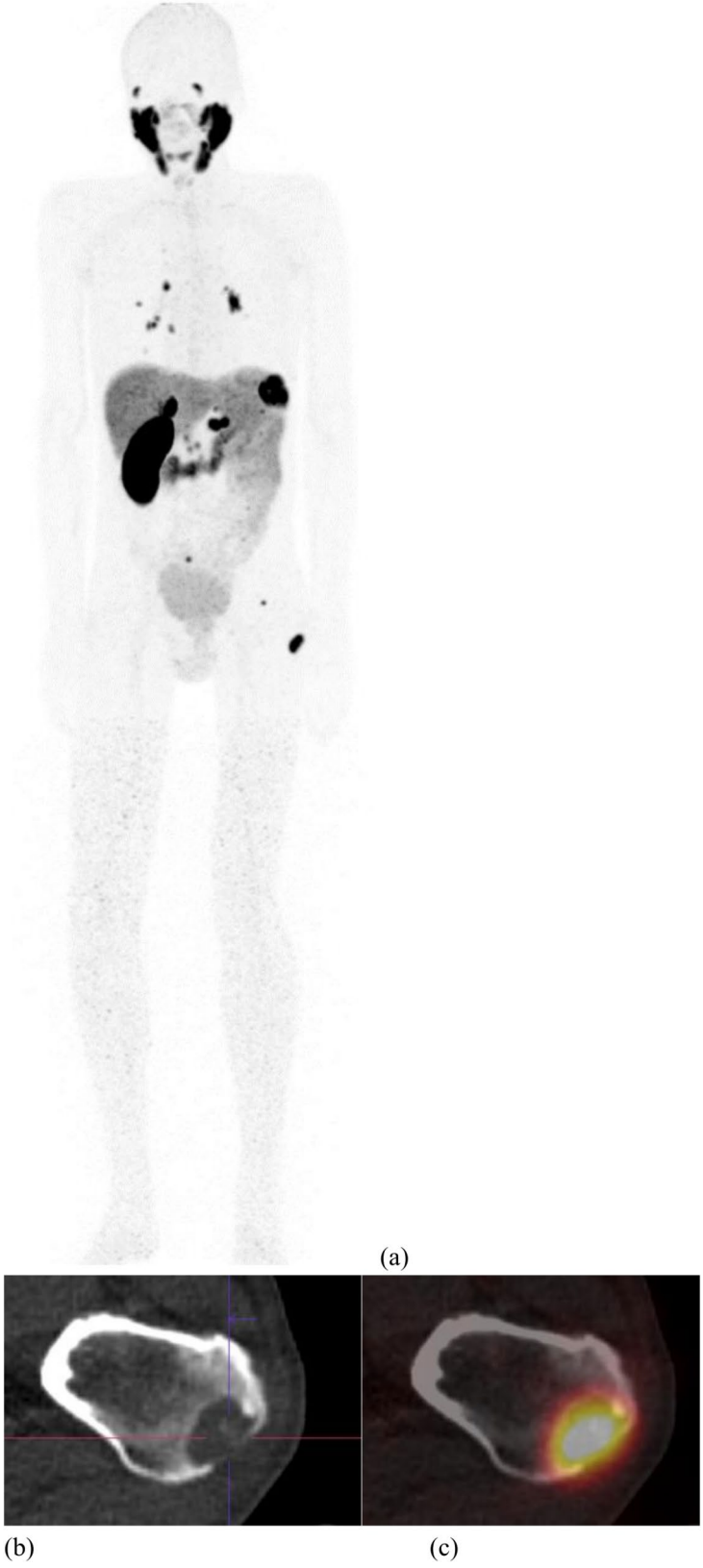

Fig. 3 (See legend on next page.)

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Fig. 3 Patient was imaged with [^{68}Ga]Ga-PSMA-11 PET before therapy with [^{177}Lu]Lu-PSMA-1 within the frame of the «PRaDR» trial. The patient was known to have distant metastases at multiple sites, including right adrenal gland, head of the pancreas, lung, hilar lymph nodes, as well as peritoneal lesions, the largest being localized in the left hypochondrium. All these lesions presented with an intense PSMA expression as shown on the Maximum Intensity Projection (MIP) of the [^{68}Ga]Ga-PSMA PET acquisition (103 MBq of [^{68}Ga]Ga-PSMA-11; 1.3 min/bed acquisition on the Philips VEREOS) (**a**). An intense focal uptake, corresponding to an osteolytic bone lesion of the left femur on the CT component of the PET/CT (**b**) and the PET/CT fused image (**c**), was additionally uncovered

^{177}Lu-radiolabeled PSMA inhibitors or antibodies might not be high enough to achieve efficacy. Patients with metastatic ccRCC often harbor bony metastases, therefore our data are important to guide PSMA-theranostics in this setting. Indeed, this finding needs to be confirmed in vivo. Considering the high PSMA expression in ccRCC metastasis, [^{68}Ga]Ga-PSMA-11 was applied to a patient presenting with metastatic ccRCC. All known metastases were successfully identified and imaged and [^{68}Ga]Ga-PSMA-11 uncovered bone metastasis involving the left femur. This case is part of the ongoing Phase I study PRADr evaluating the role of [^{177}Lu]Lu-PSMA-1 for metastatic clear cell renal cancer. However, for therapeutic perspectives, it should be considered that the expression of PSMA differs significantly between prostate cancer and RCC, PSMA being expressed in prostatic tumor cells but in neovessels of RCC. As a consequence, two recent preliminary reports has shown a rapid clearance of [^{177}Lu]Lu-PSMA I&T from tumor lesion in a patient suffering from metastatic ccRCC [23, 24]. How this would affect the therapeutic efficacy of [^{177}Lu]Lu-PSMA-1 in metastatic ccRCC will be addressed in the PRADr study. This might be considered as a warning when PSMA expression in neo-vessels is intended to be used for targeted radionuclide therapy as it also the case in other solid tumors [25].

Several limitations of our study need to be pointed out. First, the number of samples remains relatively low. Second, as highlighted above, the autoradiography technique does not fully reflect the in vivo behavior of the radiopharmaceutical which is partly driven by the location of the target. Moreover, the range of the β-electron from ^{177}Lu (mean ~ 0.67 mm in water) degrades the spatial resolution on autoradiography, and it was not possible to discriminate the different cell populations expressing the PSMA in our small-size samples. The recent development of tritiated isotopologues of Lu-PSMA-617 [26] should allow both quantification and location of the target. However, these compounds are only academics and not widely available. Immunohistochemistry methods can also be used due to their excellent spatial resolution but are only semi-relative methods and need extensive validation [27].

Conclusion

PSMA showed a higher level of expression in metastatic samples from ccRCC compared with primary samples and could serve as an imaging/therapy target.

Acknowledgements

Not applicable.

Author contributions

SB performed autoradiography and analyzed the data. DK and ALG enrolled the patient for PSMA PET/CT imaging and analyzed the image. JCB, MGG and GM enrolled patient in the UroCCR database. MY did the histology analysis of the samples. EH revised the manuscript. CM supervised the study and revised the manuscript.

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Data availability

The datasets generated during and/or analyzed during the current study are covered by the data protection regulation and cannot be distributed.

Declarations

Ethics approval and consent to participate

The UroCCR project (NCT03293563), which is IRB-approved and has the CNIL authorization number DR-2013-206. The UroCCR database received approval from Comité de Protection des Personnes Sud-Ouest et Outre-mer III (DC 2012/108) and favorable opinion of the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS).

Consent for publication

Written informed consent was obtained for publication.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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