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ORIGINAL RESEARCH ARTICLE

Evaluation of [^{99m}Tc]Tc-HYNIC-PSMA-11 avidity in subtypes of renal cell carcinoma tumors

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ABSTRACT

Introduction: Renal cell carcinoma (RCC) is one of the most lethal urologic malignancies. The role of prostate-specific membrane antigen (PSMA) in prostate cancer is well known. PSMA has been shown in other tumors including renal cell carcinoma. [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT is known as a cost effective alternative to [^{68}Ga]Ga-PSMA in prostate cancer. We prospectively evaluated the bio-distribution and diagnostic role of 99mTc-HYNIC-PSMA SPECT/CT in patients with renal tumors before surgery; and also investigated whether the intensity of Tc-PSMA uptake will be different based on tumor histopathology.

Methods: 14 patients with primary renal tumors, clinically suspicious for RCC, underwent [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT before surgery. All SPECT/CT images were reviewed separately. For quantitative analysis, volume of interest (VOI) was drawn over the tumor as well as the liver and maximum and mean counts were determined.

Results: In visual analysis, all renal lesions showed decreased uptake compared to the adjacent parenchymal tissue and liver. Whole body [^{99m}Tc]Tc-HYNIC-PSMA-11 scan in all cases could detect the region of tumoral lesion and the size and limits of the tumor were compatible with CT findings and histopathologic results. The ratio of maximum count of the tumor to the mean count of the liver showed no statistically significant difference between different subtypes (P value =0.50); however, the mean value was higher in clear renal cell RCC compared to non-clear cell RCC type (1.40 vs 1.23).

Conclusion: In our study, the low and inconsistent uptake of [^{99m}Tc]Tc-HYNIC-PSMA-11 in primary tumor of RCC suggest that this radiopharmaceutical is not an ideal agent for imaging this patient population.

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INTRODUCTION

The incidental detection of localized renal masses has been increasing worldwide [1]. The majority of these masses are malignant lesions with significant variability in histopathology and aggressiveness [2]. Kidney cancer is the 14th and 9th most frequently diagnosed cancer in women and men respectively. Renal cell carcinoma (RCC) makes up more than 90 % of these cases [3]. RCC has still remained one of the most lethal urologic malignancies despite the recent improvement in cancer diagnosis and treatment [4].

RCC mostly present as a localized disease with a relatively good prognosis; however, 25 to 30 percent of the patients present with metastatic disease at initial diagnosis with a negative impact on prognosis with a 5-year survival of only 12% [3, 5, 6]. Frequent sites of metastases include lung (50-60 percent), bone (30 to 40 percent), liver (30 to 40 percent), and brain (5 percent) [5].

Histologically, RCC consists of a heterogeneous group of tumors originating from renal nephrons. Among these, clear cell RCC is the most frequent pathology (ccRCC, 65–70%), followed by papillary RCC (pRCC, 10–15%), and chromophobe RCC (chRCC 5%) [7, 8]. Although Renal mass biopsy has a definite role in the assessment of renal tumor histology, it is an invasive procedure and is not routinely used. Therefore, imaging modalities remain the mainstay of diagnostic evaluation [9, 10]. Computed tomography (CT) with intravenous contrast agent is still the standard imaging modality in diagnosis and staging of RCC; however, small metastatic foci remain difficult to be detected [3]. Detection of metastasis has a significant impact on disease management, especially in oligometastatic cases, which have a chance for definitive local therapy [11].

Despite a number of treatment options and available drugs such as novel immune checkpoint inhibitors, RCC remains mostly incurable [12].

The utility of metabolic imaging with 18FDG PET/CT is well established for several malignancies; however, 18FDG PET/CT in RCC is not shown to be promising therefore, not routinely recommended by the current guidelines [13, 14]. To overcome the limitations of available imaging tools, various molecular imaging agents have been explored for RCC [15, 16].

Numerous articles and guidelines in the literature have shown the role of prostate-specific membrane antigen (PSMA) in the management of prostate cancer. In recent years, there has been growing interest in describing the PSMA utilization in other cancers including RCC as the potential target [17].

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein type II that is highly expressed in prostate cancer cells [18].

Besides prostate cancer, PSMA has been shown to be expressed in the neovasculature of various solid malignant tumors including renal cell carcinoma, specifically the clear cell subtype (ccRCC) [3].

PSMA is also present physiologically in other normal tissues, such as liver, spleen, salivary glands, proximal renal tubules, brain, bladder, thyroid gland and intestine [19, 20].

There have been some small-scale studies evaluating the use of PSMA PET in metastatic RCC patients with promising results [3].

Recent studies in patients with prostate cancer demonstrated that, [^{99m}Tc]Tc-HYNIC-PSMA SPECT/CT is a cost-effective modality which could be an acceptable alternative to Ga-68 PSMA, even in patients with low PSA level showing no significant difference in M staging [21].

In this study, we prospectively evaluated the bio-distribution and diagnostic potential of SPECT/CT using [^{99m}Tc]Tc-HYNIC-PSMA-11 in patients with renal tumors before surgery; and whether the intensity of [^{99m}Tc]Tc-HYNIC-PSMA-11 uptake will be different based on tumor histopathology.

METHODS

Fourteen patients with primary renal tumors, clinically suspicious for RCC, underwent [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT before surgery in our nuclear medicine department. 11 were ultimately proven RCC based on tissue results and prospectively enrolled in this study.

All the patients were informed about the procedures and possible additional imaging procedure to complete the research project and an informed consent was obtained. This study was approved by ethics committee of Mashhad University of Medical Sciences (ethics code: IR.MUMS.MEDICAL.REC.1399.275).

The patients had previously undergone conventional imaging with ultrasonography and CT of the chest, abdomen, and pelvis and Primary diagnosis of RCC was made based on these conventional imaging. These patients were then undergone nephrectomy in a short time interval after the scan and histopathologic assessment was performed by a pathologist who recorded pathologic features. The patients' prior imaging data including ultrasonography and CT scan images were documented. All [^{99m}Tc]Tc-HYNIC-PSMA-11 whole body and SPECT/CT images were reviewed separately by two nuclear medicine specialists (Figures 1 and 2). For each [^{99m}Tc]Tc-

HYNIC-PSMA-11 SPECT/CT, the following features were recorded: physiologic foci of uptake, lesion location, lesion size, presence or absence of focal radiotracer uptake and visual and quantitative PSMA uptake in the tumoral lesion comparing with the mean uptake value of the liver uptake.

For quantitative analysis of imaging, on axial fusion images, volume of interest (VOI) was drawn on tumor lesion and maximum count was determined. Tumor regions adjacent to renal collecting system were excluded in order to avoid spillover of the urinary activity. Furthermore, low-density regions compatible with necrosis were excluded. Another similar volume of interest was drawn on the liver (segment V) and the liver mean count was recorded. The ratio of maximum count of lesion to the mean count of liver was calculated for each patient and this ratio was compared with the final histopathology report of each lesion.

[^{99m}Tc]Tc-HYNIC-PSMA-11 PET/CT protocol

Four hours after intravenous injection of 740 MBq of [^{99m}Tc]Tc-HYNIC-PSMA-11, whole body scan was done using a dual-head gamma camera (GE) equipped with low-energy and high-resolution parallel-hole collimator (12 cm/min bed speed, matrix size of 256×1024 and 140 keV energy window with 10% width). SPECT images (128×128 matrix using 64 projections in a non-circular orbit with 20 seconds per step) were also obtained and reconstructed by iterative method (OSEM, number of iterations 8 subsets 4). The CT part of the SPECT/CT was performed for anatomical correlation and attenuation correction (spatial resolution 3mm, 120 kV and 60-80 mAs).

Statistical analysis

Descriptive statistics are reported as median. Values of lesion to liver counts were compared with pathological subtypes (clear cell and non-clear cell) by Mann-Whitney U test according to normality test. P value for differentiation was derived with 2-sided test and the statistical significance set at $P < 0.05$. Statistical analysis was performed with SPSS 23.0.

RESULTS

The characteristics of the 11 RCC patients are summarized in Table 1. The median age was 60 years (range 30 to 69) and 7 patients (63.6%) were men. The subtypes of 7 (63.6%) cases were clear cell, 2 (18.2%) were papillary, 1 (9.1%) was mixed clear cell/chromophobe and 1 (9.1%) was unclassified. Three patients with final diagnosis of pathologies rather than RCC (Wilms' tumor, malignant small, round cell tumor and fibrohyalinized un-determinate tumor) were excluded from further analysis. The WHO/ISUP grade distribution for the 11 RCC tumors was grade 1 in 1 patient (9.1%); grade 2 in 3 (27.3%); grade 3 in 5 (45.5%); and grade 4 in 2 patients (18.2%). One patient had lung metastasis diagnosed on prior CT scan, with a history of receiving chemotherapy one year previously. No abnormal PSMA uptake was observed in lung metastasis. Detailed histopathologic results are shown in Table 2.

Table 1. Descriptive features

Characteristics	
Age (years) (median (range))	60 (30-69)
Sex (n (%))	
Male	7 (63.6)
Female	4 (36.4)
Weight (Kg) (median (range))	70 (43-89)
Location (n (%))	
Right	6 (54.5)
Left	5 (45.5)
Prior chemotherapy (n (%))	1 (9.1)
Metastasis on CT scan (n (%))	1 (9.1)
Subtype (n (%))	
Clear cell	7 (63.6)
Papillary	2 (18.2)
Mixed clear cell/chromophobe	1 (9.1)
Unclassified	1 (9.1)

Table 2. Detailed histopathologic results after surgery

Histopathologic results	
Subtype (n (%))	
Clear cell	7 (63.6)
Papillary	2 (18.2)
Mixed clear cell/chromophobe	1 (9.1)
Unclassified	1 (9.1)
Tumor diameter (cm), median (range)	9.7 (2.2-15)
WHO/ISUP grade (n (%))	
1	1 (9.1)
2	3 (27.3)
3	5 (45.5)
4	2 (18.2)
T stage (n (%))	
T1	1 (9.1)
T2	6 (54.5)
T3	3 (27.3)
T4	1 (9.1)
N stage (n (%))	
N0	8 (72.7)
N1	1 (9.1)
Nx	2 (18.2)
Fecality (n (%))	
Uni-focal	10 (90.9)
Multi-focal	1 (9.1)
Lymphovascular invasion (n (%))	
Yes	6 (54.5)
No	4 (36.4)
Not evaluated	1 (9.1)
Tumor necrosis	
Yes	6 (54.5)
No	3 (27.3)
Not evaluated	2 (18.2)
Extra-renal tumoral foci (n (%))	
Yes	2 (18.2)
No	9 (81.8)

In visual analysis, all the renal lesions showed decreased uptake compared to the adjacent parenchymal tissue, liver, lacrimal and salivary glands (Figure 1). Whole body [^{99m}Tc]Tc-HYNIC-PSMA-11 scan in all cases was able to detect the region of tumoral lesion due to the obvious lower uptake than normal kidney parenchyma and the size and delineation of the tumor were compatible with CT findings and final histopathologic results. The ratio of maximum count of the tumor to the liver mean count showed no statistically significant difference between clear renal cell RCC and group of non-clear cell RCC (P value =0.50); however, the mean value of this ratio was higher in clear renal cell RCC compared to non-clear cell RCC (1.40 vs 1.23) (Table 3).

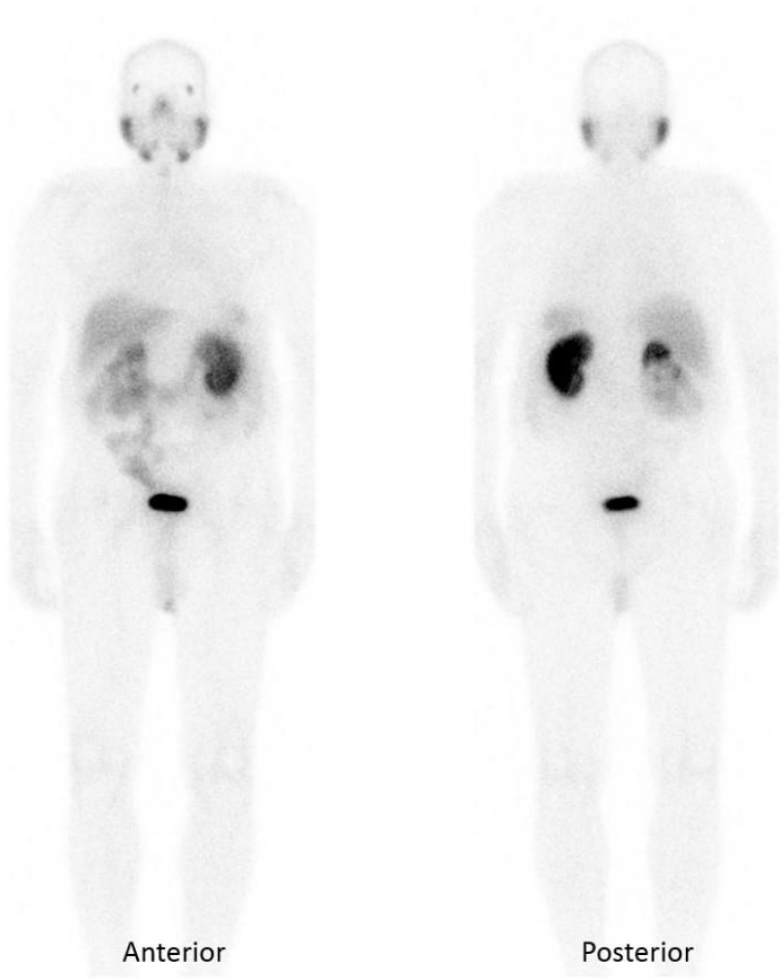

Figure 1. [^{99m}Tc]Tc-HYNIC-PSMA-11 whole body scan in a patient with renal cell carcinoma (papillary cell subtype) performed four hours after injection. A large zone of faint uptake in the inferior pole of the right kidney is consistent with the patient's malignant tumor

Table 3. Quantitative uptake calculated based on the drawn VOI on the tumor and liver

PSMA uptake (Clear cell RCC vs Non-clear cell RCC)		n	Min	Max	Mean	Standard Deviation
Lesion uptake (Max count)	CC	7	86	304	163.57	69.10
	Non-CC	4	158	270	196	50.79
Liver uptake (Mean count)	CC	7	63	170	120.71	42.5
	Non-CC	4	89	288	179.25	90.83
Lesion / liver uptake ratio	CC	7	0.88	2.10	1.40	0.43
	Non-CC	4	0.87	1.77	1.23	0.42

PSMA, Prostate Specific Membrane Antigen; RCC, Renal Cell Carcinoma; CC, Clear cell

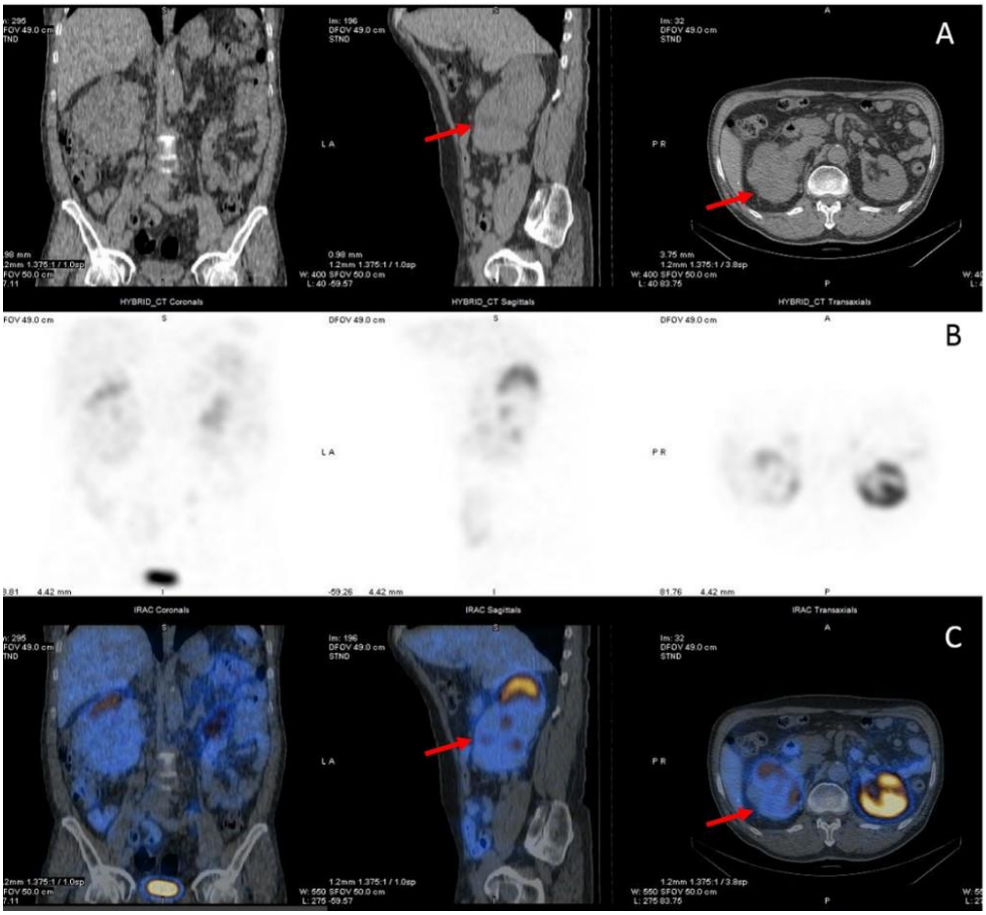

Figure 2. SPECT/CT images of [^{99m}Tc]Tc-HYNIC-PSMA-11 scan, confirmed the large tumoral mass in the inferior pole of the right kidney; which showed faint uptake on fused images compared to the adjacent parenchymal tissue

DISCUSSION

The value of PSMA-targeted imaging has been well established in the staging of primary, metastatic and biochemically recurrent prostate cancer [22-25]. There has been an increasing interest in the role of PSMA PET/CT imaging in other solid malignancies. Recently, it is suggested for ccRCC [26-28]. Immunohistochemical studies have revealed that PSMA expression is only seen in the endothelium of neovascular tissue in RCC tumors. Clear renal cell is the most common types of RCC (80–90 %), are highly vascularized and express PSMA in 82.5% of cases by IHC studies, whereas 71.4% of chromophobe RCC and only 13.6% of papillary RCC demonstrate PSMA on staining [20, 29].

In patients with RCC, PSMA PET/CT is reported to be able to change the management in 43.8% of patients in primary staging and 40.9% of patients in restaging process [17]. The promising results of [^{68}Ga]Ga-PSMA in RCC tumors are recently published [3, 9]. A recently published review article on the role of PSMA-ligands imaging in renal cell carcinoma has suggested that PSMA PET/CT could be a helpful imaging modality for diagnosis, staging, and therapy response evaluation in renal cell carcinoma, especially in clear cell RCC. This article concluded that more studies are still needed for this new imaging option [30]. On the other hand, [^{99m}Tc]Tc-PSMA SPECT/CT has shown to have comparable accuracy and detection rate with [^{68}Ga]Ga-PSMA PET/CT in prostate cancer evaluation [21].

Therefore, we aimed here to identify the bio-distribution and evaluate the uptake of PSMA RCC tumors by performing [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT scan. In this study, the bio-distribution and uptake intensity of [^{99m}Tc]Tc-HYNIC-PSMA-11 was evaluated in patients with a suspicious renal mass before their surgery; regardless of whether they have local or distant metastasis. The level of [^{99m}Tc]Tc-HYNIC-PSMA-11 uptake was documented and interpreted based on the histopathology reports after surgery. We observed inconsistent uptake of the [^{99m}Tc]Tc-HYNIC-PSMA-11 in 14 patients with primary renal tumor, of which 11 cases were proved to be RCC. No significant difference in visual or quantitative uptake was noticed among different histopathology types. However, the

ratio of maximum lesion count to liver mean count was higher in cc-RCC group; which is concordant with previous studies that suggest significantly more PSMA uptake in the subtype of cc-RCC. Probably, the small number of patients in the current study is the reason why we did not detect a significant difference.

There is conflicting data in literature regarding the expression of PSMA in primary tumour of RCC [31, 32] and the majority of studies state that the PSMA expression is seen only in tumor-neovasculature tissue [20, 33]. Raveenthiran et al. assessed PSMA PET/CT in 38 patients and the study showed 25% of cases with no PSMA uptake. The wide range of PSMA expression in renal cell carcinoma could be a confusing factor and one of the causes of a negative lesion on SPECT/CT [17].

Our results are concordant with the results of prior studies on PSMA PET/CT, which showed that no increased uptake is noted in the primary tumors, compared to the physiologically normal expressions in surrounding renal parenchyma [9, 17, 19, 34]. Although our data does not suggest utility of [^{99m}Tc]Tc-HYNIC-PSMA-11 imaging for primary renal tumors, the role of this scan in evaluating metastatic cases has still remained unknown. In this study, only one case with proven RCC had lung metastasis, which had already received chemotherapy and showed no uptake of [^{99m}Tc]Tc-HYNIC-PSMA-11 either in primary tumor or the metastases. The effects of chemotherapy in radiotracer uptake of the lung metastatic lesions needs to be taken into consideration.

The present study has some limitations. Most notably, small number of patients with some cases of non-RCC histopathologies, who were eventually excluded from study; thus limiting the accuracy of our observations. Additionally, only one patient with proven RCC pathology had metastasis; therefore, we were not able to reach to a reasonable conclusion concerning the uptake of [^{99m}Tc]Tc-HYNIC-PSMA-11 in RCC-related metastasis. Further studies with a larger sample size are necessary for clarification of this issue. In addition, the quantitative analysis used based on the SPECT/CT may not be as accurate as the verified values such as SUV in PET/CT acquisition. Additionally, due to high PSMA physiologic uptake by the kidneys, evaluation of renal tumoral lesions by this radiotracer remains challenging.

Although we couldn't definitively differentiate histopathologic subtypes of RCC based on [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT, all the lesion were delineated by this procedure, demonstrating relatively decreased tracer uptake in contrast to higher activity of the surrounding renal parenchymal tissue, all compatible with prior reports of diagnostic CT scan.

CONCLUSION

Although PSMA has been shown to have high staining in RCC tumors based on previous histopathologic studies; very low uptake of [^{99m}Tc]Tc-HYNIC-PSMA-11 in primary tumor of RCC was noted in our study. The current results with this limited number of patients does not support [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT as an appropriate imaging modality for RCC. We highly recommend to evaluate the utility of [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT for metastatic lesions in larger group of patients in the future.

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