Assessment of Neuroendocrine Features Using 99mTc-Octreotide Scintigraphy in Patients with Metastatic Castration-Resistant Prostate Cancer: Does it Predict Response to 177Lu-PSMA Radioligand Therapy?

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Purpose: Neuroendocrine differentiation is a recognized phenotypic change in advanced prostate cancer. Neuroendocrine-like cells may lack androgen receptor or prostate-specific membrane antigen expression, potentially contributing to treatment resistance. This study evaluated octreotide scan positivity as a surrogate marker of neuroendocrine differentiation and its association with response to 177Lu-prostate-specific membrane antigen radioligand therapy in patients with metastatic castration-resistant prostate cancer.

Materials and Methods: Thirty-six patients with metastatic castration-resistant prostate cancer who were candidates for 177Lu-prostate-specific membrane antigen radioligand therapy were enrolled. Whole-body octreotide scintigraphy was performed after intravenous administration of 750 MBq of 99mTc-octreotide. Abnormal uptake was classified as mild, moderate, or severe relative to liver uptake. All patients subsequently received standard 177Lu-prostate-specific membrane antigen radioligand therapy and were followed for treatment response after at least two treatment cycles.

Results: Of the 36 enrolled patients, 8 who died within 2 months after the first treatment cycle were excluded from response assessment; therefore, 28 patients were included in the final response analysis. Among these 28 patients, 19 (67.9%) responded to treatment and 9 (32.1%) did not. Eight patients (28.6%) had negative octreotide scans, whereas 20 (71.4%) had positive scans, all showing mild uptake. Positive scans were observed in 13 of 19 responders (68.4%) and 7 of 9 non-responders (77.8%). No significant association was observed between octreotide scan positivity and treatment response ($P = 1.00$).

Conclusion: Octreotide scan positivity was relatively common in patients with metastatic castration-resistant prostate cancer but was not significantly associated with response to 177Lu-prostate-specific membrane antigen radioligand therapy. Larger studies are needed to confirm these findings.

Keywords: octreotide; prostate-specific membrane antigen; prostatic neoplasms; radioligand therapy; technetium Tc 99m

INTRODUCTION

Overall, prostate cancer (PC) is the second most common solid tumor and one of the leading causes of cancer-related death in men, with an estimated 375,000 deaths in 2020.[1,2] Castration-resistant prostate cancer (CRPC) is a severe form of the disease characterized by rising prostate-specific antigen (PSA) levels despite ongoing androgen deprivation therapy (ADT). Metastatic CRPC (mCRPC) is defined as disease progression despite castrate levels of testosterone and is associated with a 5-year survival rate of approximately 31%.[3]

Lutetium-177 prostate-specific membrane antigen (177Lu-PSMA) therapy is an approved treatment for patients with mCRPC and has shown promising outcomes, including prolonged survival, improved quality of life, and tumor regression.[4,5] However, treatment resistance and disease relapse still occur, and the underlying mechanisms remain incompletely understood. Tumor heterogeneity in mCRPC, including the coexistence of PSMA-positive and PSMA-negative clones, may contribute to variable therapeutic responses.[6]

Prostate epithelial cells consist of basal, luminal, and neuroendocrine (NE) subtypes, with NE cells being relatively rare. Neuroendocrine differentiation (NED) may occur during disease progression, particularly under therapeutic pressure. In advanced cases, treatment-emergent neuroendocrine prostate cancer (t-NEPC) may develop through histological transformation from adenocarcinoma into a poorly differentiated small-cell carcinoma phenotype. This process is associated with downregulation of androgen receptor signaling, PSA, and PSMA expression, leading to increased tumor aggressiveness and treatment resistance. However, NED exists on a biological spectrum and does not always correspond to full NEPC transformation.[7,8]

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Table 1. Baseline disease characteristics and prior treatment history

Baseline Patient Characteristics	Number (%)
Surgery	9 (32.14%)
Chemotherapy	23 (82.14%)
Radiotherapy	15 (53.57%)
Bone metastases	27 (96.42%)
Lymph node metastases	13 (46.42%)
Other metastases	3 (10.71%)

The diagnosis of NEPC relies on histopathological confirmation from tumor biopsy. Several biomarkers are used to assess neuroendocrine features, including chromogranin A (CgA), neuron-specific enolase (NSE), and synaptophysin. However, the accuracy of these markers may be influenced by factors such as biopsy site, tumor heterogeneity, and tumor burden.[9]

Octreotide scanning, also known as somatostatin receptor scintigraphy, is used to evaluate somatostatin receptor expression in neuroendocrine tumors by targeting receptors expressed on the cell surface. Although it is commonly used in neuroendocrine tumor imaging, its role in detecting NED in PC remains limited and not fully established. Somatostatin receptor expression may reflect neuroendocrine features in a subset of tumors, but sensitivity and specificity in NEPC are variable.(10) Given the limited evidence in this area, this study aimed to investigate neuroendocrine features in patients with mCRPC using 99mTc-octreotide scanning and to assess whether octreotide scan findings are associated with response to 177Lu-PSMA radioligand therapy.

MATERIALS AND METHODS

Study Population

This prospective cohort study was conducted in patients with mCRPC referred to our department for 177Lu-PSMA therapy between 2020 and 2022. The study included patients with progressive mCRPC who had failed standard treatments, including ADT and chemotherapy, and who were considered eligible candidates for radioligand therapy (RLT) with 177Lu-PSMA. At baseline, demographic and clinical characteristics of all patients were recorded, including age, previous definitive treatments, serum PSA level, Gleason score, and laboratory parameters, including complete blood count (CBC), liver function tests (LFTs), and renal function tests (RFTs). Gleason scores were obtained from the histopathological findings of the initial prostate biopsy specimens. Patient eligibility was subsequently assessed according to the inclusion and exclusion criteria based on the European Association of Nuclear Medicine guideline.[11]

Inclusion Criteria

The inclusion criteria were as follows: diagnosis of mCRPC with documented disease progression despite standard therapy or documented ineligibility for such therapies; sufficient PSMA expression on 68Ga-PSMA positron emission tomography/computed tomography (PET/CT) or 99mTc-PSMA scan, with tumor uptake exceeding liver uptake and no dominant PSMA-negative lesions; adequate hematologic, renal, and hepatic function; Eastern Cooperative Oncology Group performance status of 0 to 2; and written informed consent.

Exclusion Criteria

The exclusion criteria were as follows: severe bone marrow suppression, renal impairment, or hepatic dysfunction precluding treatment; life expectancy less than 6 months; uncontrolled serious comorbidities or active infection; and incomplete clinical or follow-up data.

Procedures

Baseline Imaging and Neuroendocrine Assessment: Before initiation of 177Lu-PSMA therapy, all patients underwent a diagnostic 99mTc-octreotide scan to evaluate somatostatin receptor expression as a surrogate marker of NED. Imaging was performed 2 hours after intravenous injection of 750 MBq of 99mTc-octreotide using a Siemens dual-head gamma camera (Evo Voxel system). Whole-body anterior and posterior images were acquired at a scan speed of 10 cm/min with a matrix size of 256 × 1024. When indicated, single-photon emission computed tomography (SPECT) imaging was performed using a matrix size of 128 × 128, a zoom factor of 1.45, and 30 seconds per projection over 32 frames.

All lesions identified on other imaging modalities, including 99mTc-PSMA, 177Lu-PSMA post-therapy scans, and 99mTc-methylene diphosphonate bone scintigraphy, were reviewed and compared with 99mTc-octreotide imaging to identify concordant or discordant tracer uptake.

Image Interpretation: Abnormal 99mTc-octreotide uptake was recorded and classified semi-quantitatively based on intensity relative to liver uptake as follows: mild, uptake lower than liver; moderate, uptake equal to liver; and severe, uptake higher than liver.

Treatment Protocol: Patients received 177Lu-PSMA therapy at a dose of 6.5 to 7.4 GBq per cycle, administered every 8 weeks, according to national consensus guidelines for PSMA-based RLT.[11] Post-therapeutic scintigraphy was performed 24 to 48 hours after each treatment cycle, including planar whole-body anterior and posterior imaging, to assess radiotracer distribu-

Table 2. Comparison of baseline demographic, clinical, and laboratory characteristics between responders and non-responders

Variables[a]	Overall (N = 28)		Estimate Effect [95% CI]	*P* value
	Responders (N = 19)	Non-Responders (N = 9)		
Age, years mean ± SD	69.28 ± 8.08	68.95 ± 7.86	-1.05 [−8.54-6.44]	.754
Gleason score median (IQR)	8 (2)	8 (1)	1 [-1-0]	.075
Baseline PSA, ng/mL median (IQR)	47.15 (84.09)	40 (95.11)	-12 [−108.78-11.00]	.595
Baseline ALP, U/L median (IQR)	278.5 (386.0)	275 (250.5)	-269 [−2200-174]	.142
Baseline hemoglobin, g/dL mean ± SD	11.31 ± 2.20	11.36 ± 2.38	0.15 [−1.76-2.06]	.875
Baseline platelet count, $\times 10^3/\mu L$ mean ± SD	242.85 ± 87.55	257.3 ± 91.2	41.7 [−32.2-115.7]	.256

Abbreviations: PSA, prostate-specific antigen; ALP, alkaline phosphatase; IQR, interquartile range; SD, standard deviation.
[a]Continuous variables were compared using the independent-samples *t*-test or Mann–Whitney *U* test, as appropriate.

Table 3. Comparison of baseline octreotide scan findings between responders and non-responders

Octreotide Scan Finding	Result	Non-Responders (N = 9)	Responders (N = 19)	Total (N = 28)
Any uptake	Negative	2 (7.1%)	6 (21.4%)	8 (28.5%)
Any uptake	Positive	7 (25%)	13 (46.4%)	20 (71.4%)
Appendicular uptake	Negative	4 (14.3%)	10 (35.7%)	14 (50%)
Appendicular uptake	Positive	0 (0%)	5 (17.8%)	5 (17.8%)
Axial uptake	Negative	2 (7.1%)	11 (39.2%)	13 (46.4%)
Axial uptake	Positive	2 (7.1%)	4 (14.3%)	6 (21.4%)
Axial and appendicular uptake	Negative	2 (7.1%)	6 (21.4%)	8 (28.5%)
Axial and appendicular u ptake	Positive	5 (17.8%)	4 (14.3%)	9 (32.1%)

tion. Patients were followed every 8 weeks with clinical evaluation and laboratory tests, including CBC, LFTs, blood urea nitrogen, creatinine, and PSA. PSA levels were specifically assessed before each treatment cycle. Treatment Response Evaluation: Treatment response was evaluated after at least two cycles of 177Lu-PSMA therapy based on PSA kinetics. Patients were classified as responders if they demonstrated a decrease or stabilization in PSA levels, whereas non-responders were defined as those with a greater than 25% increase in PSA levels over two consecutive treatment cycles.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) after data entry and management in Microsoft Excel. Normality was assessed using the Shapiro–Wilk test and Q–Q plots. Normally distributed continuous variables were reported as mean ± SD and compared using the independent-samples *t*-test, with homogeneity of variance assessed using Levene's test. Non-normally distributed variables were reported as median (interquartile range [IQR]) and compared using the Mann–Whitney *U* test. Mean differences or Hodges–Lehmann estimates, as appropriate, were reported with 95% confidence intervals. Categorical variables were expressed as frequencies and percentages and compared using the chi-square or Fisher's exact test, as appropriate. A two-sided P value $< .05$ was considered statistically significant.

RESULTS

Thirty-six consecutive patients with mCRPC who met the criteria for 177Lu-PSMA radioligand therapy were included in the study. Eight patients who died within 2 months after the first treatment cycle were excluded from response assessment; therefore, the final analysis included 28 patients. The mean age of the patients was 69.28 ± 8.08 years. The demographic and clinical characteristics of the patients, including previous definitive treatments, are summarized in **Tables 1 and 2**.

Among the 28 patients included in the response anal-

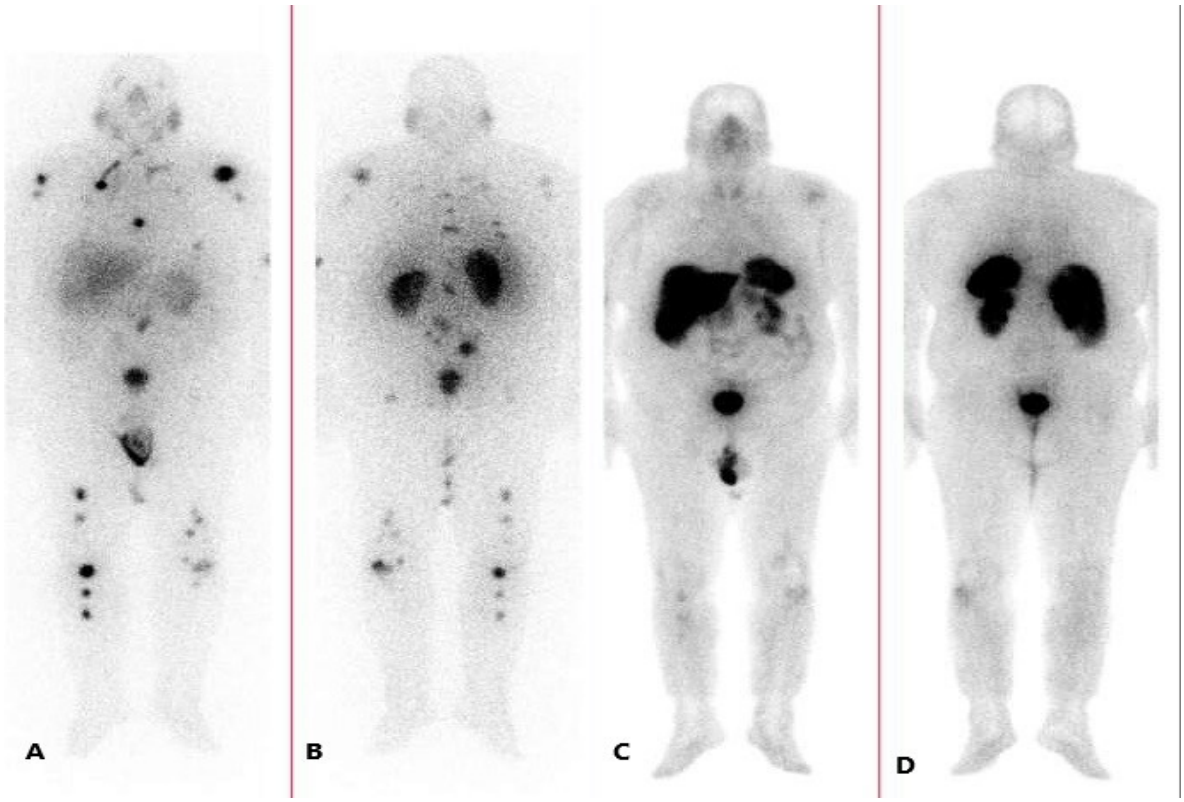

Figure 1. Whole-body post-therapy 177Lu-PSMA scan (**A:** anterior and **B:** posterior) shows multiple skeletal metastases. Whole-body 99mTc-octreotide scan (**C:** anterior and **D:** posterior) reveals minimal abnormal uptake around the knees and left shoulder, corresponding to the known metastatic lesions.

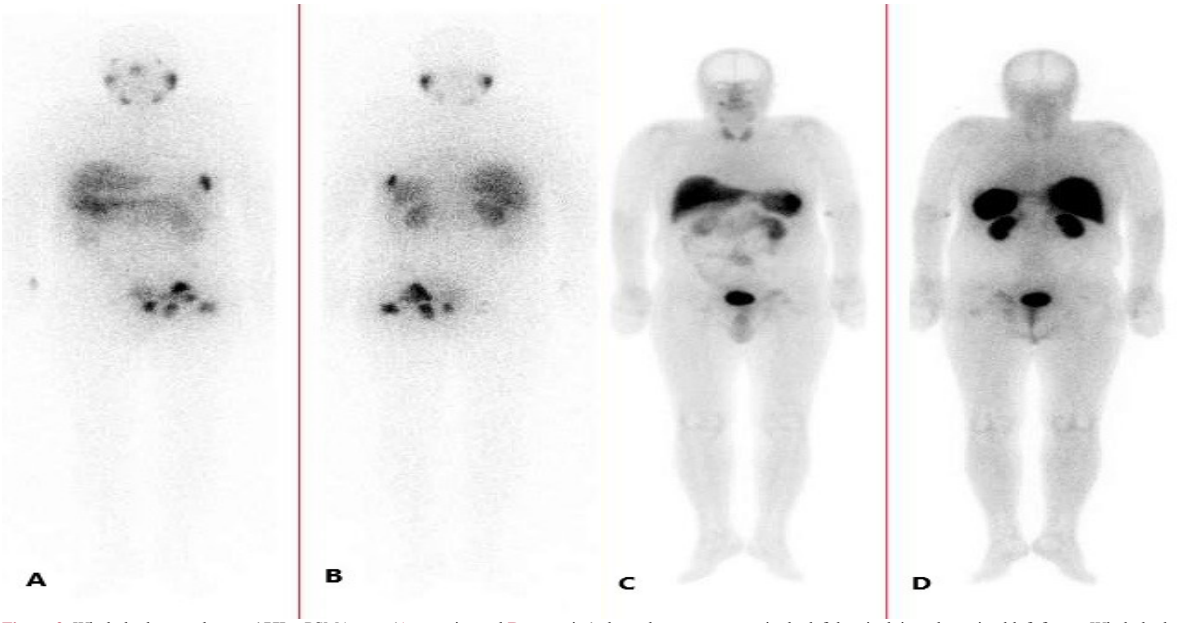

Figure 2. Whole-body post-therapy 177Lu-PSMA scan (**A:** anterior and **B:** posterior) shows bone metastases in the left hemipelvis and proximal left femur. Whole-body 99mTc-octreotide scan (**C:** anterior and **D:** posterior) reveals minimal abnormal uptake in the corresponding regions.

ysis, 20 (71.4%) had positive octreotide scans and 8 (28.6%) had negative scans. In all patients with positive octreotide scans, uptake was detected only in some skeletal metastases (**Figures1 and 2**). In patients with known metastatic lymph node or liver lesions, no octreotide uptake was observed in these lesions (**Figure 3**). All somatostatin receptor (SSTR)-positive skeletal lesions showed mild uptake, defined as less than liver uptake, and the number of SSTR-positive skeletal lesions was lower than the number of PSMA-positive lesions in all patients. Regarding the number of SSTR-positive lesions, 3 patients had 1 to 2 lesions, 7 had 3 to 5 lesions, and 10 had more than 5 skeletal metastatic lesions. Regarding lesion distribution, 6 patients (21.4%) had only axial lesions, 5 (17.8%) had only appendicular lesions, and 9 (32.1%) had both axial and appendicular lesions. The distribution of SSTR-positive lesions is summarized in **Table 3**.

Within 1 to 7 days after octreotide scintigraphy, 177Lu-PSMA radioligand therapy was initiated at a dose of 5.5 to 7.4 GBq, and patients received 2 to 7 treatment cycles at 8- to 12-week intervals. Based on

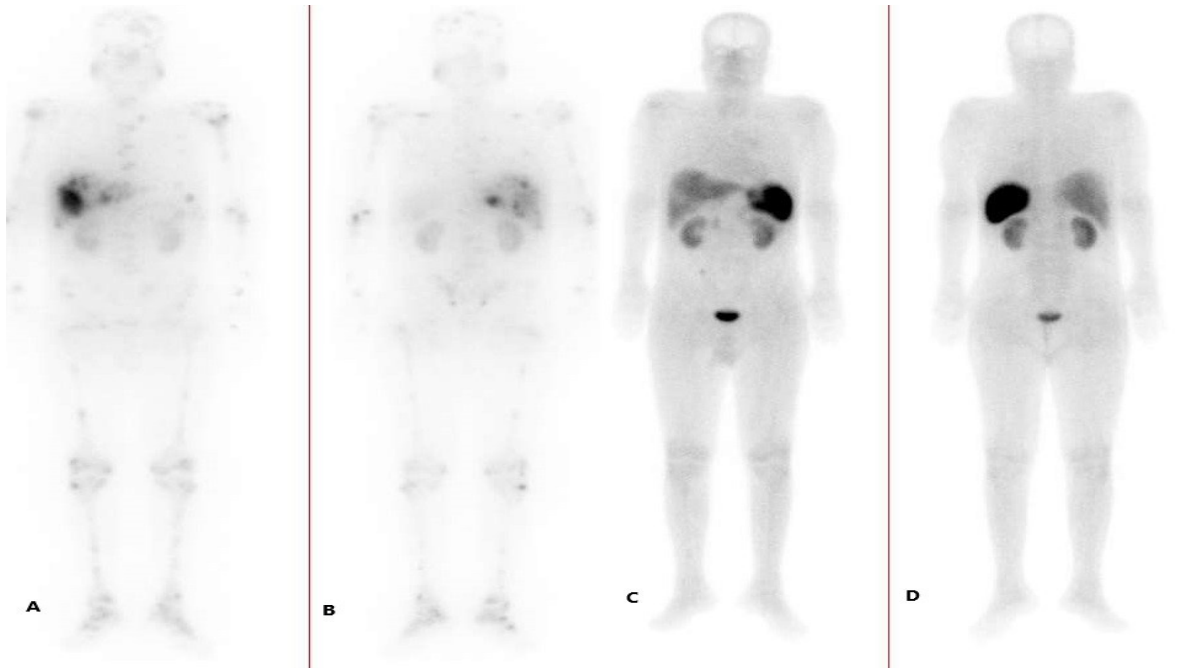

Figure 3. Whole-body post-therapy 177Lu-PSMA scan (**A:** anterior and **B:** posterior) shows widespread skeletal and multiple liver metastases. Whole-body 99mTc-octreotide scan (**C:** anterior and **D:** posterior) reveals minimal abnormal uptake around the knees and a large photopenic region in the liver corresponding to the known liver metastasis.

PSA kinetics after at least two treatment cycles, patients were categorized as responders (19 patients, 67.9%) or non-responders (9 patients, 32.1%). No statistically significant differences were observed between responders and non-responders in age, baseline PSA, hemoglobin, platelet count, alkaline phosphatase (ALP), or Gleason score. The corresponding effect estimates and 95% confidence intervals are presented in **Table 2**.

Octreotide scan positivity was observed in 13 responders (68.4%) and 7 non-responders (77.8%), with no significant association between octreotide scan positivity and treatment response ($P = 1.00$). Similarly, no significant association was observed between the presence of PSMA-avid bone or lymph node metastases and treatment response ($P = 1.00$ and P = .435, respectively). However, the presence of visceral metastases was significantly associated with non-response to treatment ($P = .026$).

DISCUSSION

Neuroendocrine differentiation is thought to emerge predominantly in advanced prostate cancer, particularly following prolonged ADT. Surcel et al.[12] and Hu et al.[13] reported that NED may contribute to resistance to androgen deprivation and other systemic therapies, potentially promoting disease progression and poor prognosis. The reported prevalence of NED varies considerably across studies, ranging from 10% to 100%, reflecting differences in diagnostic criteria, study populations, and detection methods.[14,15] Although histopathological examination identifies characteristic clusters of neuroendocrine cells in only approximately 5% to 10% of prostate cancers,[16] Derlin et al.[17] reported elevated serum levels of progastrin-releasing peptide, NSE, and CgA in 80%, 88%, and 74% of patients with mCRPC, respectively. Kessel et al.[18] demonstrated frequent expression of neuroendocrine-associated genes in circulating tumor cells from patients with mCRPC.

The biological mechanisms underlying NED and its potential impact on treatment response are complex. Prolonged androgen receptor (AR) pathway inhibition may promote phenotypic plasticity and transdifferentiation toward a neuroendocrine phenotype. Neuroendocrine-like cells may lose AR and PSMA expression and may exhibit altered expression of alternative molecular pathways, including SSTR. This phenotypic shift may result in heterogeneous tumor lesions with different molecular characteristics and variable PSMA and SSTR expression. Consequently, a single patient may harbor PSMA-avid adenocarcinoma lesions alongside lesions with neuroendocrine features, potentially contributing to heterogeneous treatment responses.[19]

Octreotide scintigraphy targets SSTR expression and is commonly used for the detection of neuroendocrine tumors.[10] Unlike biopsy, which is limited by tissue sampling error, the major advantage of octreotide scintigraphy is its ability to provide whole-body assessment. In the present study, 20 patients (71%) had positive octreotide scans. However, uptake was mild in all cases, and the number of octreotide-avid skeletal metastases was consistently lower than the number of PSMA-avid lesions. Furthermore, octreotide uptake was limited to a subset of bone metastases, whereas known metastatic lymph node and liver lesions did not demonstrate uptake. These findings suggest that neuroendocrine features, as indicated by octreotide uptake, may be relatively common in mCRPC but may be spatially heterogeneous and restricted to only a subset of metastatic lesions. Nevertheless, octreotide positivity should be considered a surrogate marker of neuroendocrine differentiation rather than definitive evidence of histologically confirmed NED.

Some studies have shown an inverse correlation between PSMA expression or PSMA avidity and NE biomarkers.[18,19] However, limited data are available regarding the clinical efficacy of 177Lu-PSMA radioligand therapy in patients with NED. Derlin et al.[17] reported in a study of 50 men with mCRPC and abnormal NE biomarker profiles that NE biomarker levels did not reliably predict treatment failure or early disease progression. Similarly, Kessel et al.[18] found that common NED markers such as SYP and ENO_2, as well as FOXA1 expression, were associated with overall survival but did not correlate significantly with response to PSMA treatment or progression-free survival. In a case report, Assadi et al.[20] described a patient with mCRPC who developed neuroendocrine differentiation after 177Lu-PSMA therapy, suggesting that the emergence of neuroendocrine features may contribute to disease progression and influence subsequent treatment strategies. Webb et al.[21] and Priftakis et al.[22] reported that the emergence of neuroendocrine features in metastatic lesions may be associated with recurrence and reduced therapeutic effectiveness, despite an initial response to androgen-directed therapy or 177Lu-PSMA treatment. In our study, no significant association was observed between octreotide scan positivity and response to 177Lu-PSMA treatment. Among patients with positive octreotide scans, 13 of 20 (65%) responded to treatment. This finding may be explained by the heterogeneous distribution of neuroendocrine features within metastatic disease. Although some lesions may exhibit NE characteristics and potentially reduced PSMA expression, other lesions may retain sufficient PSMA expression to demonstrate substantial uptake of 177Lu-PSMA and respond to treatment. Therefore, the overall treatment response, particularly when assessed using PSA kinetics, may reflect the combined response of multiple tumor subclones with different phenotypes. In contrast to studies relying primarily on circulating biomarkers or molecular analysis, our study used whole-body 99mTc-octreotide scintigraphy to evaluate SSTR-positive lesions as a surrogate marker of neuroendocrine differentiation, allowing assessment of the spatial distribution of potentially neuroendocrine lesions. Our findings suggest that the presence of neuroendocrine features detected by octreotide scintigraphy alone may not be sufficient to predict response to PSMA-targeted radioligand therapy.

Regarding prognostic factors, several clinical and laboratory characteristics, including performance status, hemoglobin level, ALP, PSA, lactate dehydrogenase, and tumor burden, have been associated with treatment outcomes in patients with mCRPC undergoing 177Lu-PSMA radioligand therapy.[23-25] In the present study, baseline ALP levels were lower in responders than in non-responders; however, this difference was not statistically significant. Although elevated baseline ALP has been reported as a predictor of unfavorable outcomes in previous studies, we did not observe a significant association, possibly because of the limited sample size and the relatively small number of non-responders. Heck

et al.[24] reported that visceral metastases and elevated lactate dehydrogenase levels are associated with poorer outcomes after 177Lu-PSMA therapy, whereas Fendler et al.[25] found that patients with visceral metastases tend to have unfavorable outcomes. Consistent with these observations, our study demonstrated a significant association between the presence of visceral metastases and non-response to treatment. In contrast, other baseline clinical characteristics, including platelet count, age, and Gleason score, were not significantly associated with treatment response in our cohort. The lack of significant associations for these parameters may be related to the limited sample size and the relatively small number of non-responders.

Limitations

An important limitation of this study is that neuroendocrine differentiation was not confirmed histopathologically. Instead, 99mTc-octreotide scintigraphy was used as a surrogate marker of neuroendocrine features based on somatostatin receptor expression. Therefore, octreotide-positive findings should not be considered equivalent to histologically confirmed neuroendocrine differentiation. Further studies incorporating histopathological and molecular confirmation are warranted. Because of the COVID-19 pandemic during the study period, the number of patients referred for 177Lu-PSMA therapy was limited, and treatment was temporarily interrupted for some patients. Furthermore, because accurate information regarding the causes of death was unavailable for patients who died after treatment, we were unable to reliably assess overall survival, despite this being one of the study objectives. Finally, the relatively small sample size limited the statistical power of the study and precluded multivariable analyses to adjust for potential confounding factors. Therefore, the findings should be interpreted with caution, and larger prospective studies are needed to validate our results.

CONCLUSIONS

Neuroendocrine features, as indicated by positive 99mTc-octreotide scintigraphy, were relatively common in patients with mCRPC but were not significantly associated with response to 177Lu-PSMA radioligand therapy. The response to 177Lu-PSMA therapy may also be influenced by heterogeneous PSMA expression and other clinical factors. These findings suggest that the presence of neuroendocrine features alone should not preclude the use of 177Lu-PSMA therapy. Further prospective studies with larger sample sizes and longer follow-up are warranted to confirm these findings.

SUMMARY

Octreotide scan positivity was common in mCRPC but did not predict response to 177Lu-PSMA therapy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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