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Prostate-Specific Membrane Antigen Radioligand Therapy in Patients with Aggressive-Variant Prostate Cancer

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Aggressive-variant prostate cancer (AVPC) is characterized by several high-risk features and is typically treated with chemotherapy. In this study, we evaluated the outcomes of patients with AVPC who received prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT). **Methods:** This retrospective study included patients with AVPC with metastatic castration-resistant prostate cancer who received PSMA RLT at 3 academic centers. Patients with AVPC were further stratified into 2 subcategories: AVPC-C (clinico-pathologic), referring to patients who met AVPC on the basis of clinical or pathologic features, and AVPC-MS (molecular signature), referring to patients who met AVPC criteria on the basis of genomic alterations. Prostate-specific antigen (PSA) response was calculated in the overall cohort, and PSA progression-free survival and overall survival (OS) were calculated in the paired cohort. In the segmentation cohort, SUV_{mean} and total tumor volume were quantified using MIM software. **Results:** In total, 82 patients were classified as having AVPC, of whom 47 (57%) had AVPC-C and 35 (43%) had AVPC-MS. In the overall cohort, the percentage of patients who had a reduction in PSA of at least 50% or more from baseline was similar between the AVPC and non-AVPC groups (62.1% vs. 60.7%, respectively). In the paired cohort, the median PSA progression-free survival in the AVPC group was 3.2 mo (95% CI, 2.5–5.7 mo), compared with 4.2 mo (95% CI, 3.5–5.1 mo) in the non-AVPC group ($P = 0.10$). The median OS was shorter in the AVPC group (11.8 mo; 95% CI, 9.7–14.9 mo) compared with the non-AVPC group (13.3 mo; 95% CI, 12.1–15.0 mo; $P = 0.04$). There was no difference in median OS between AVPC-MS and AVPC-C subgroups (11.9 mo vs. 10.9 mo, respectively; $P = 0.8$). In the segmentation cohort, there was a trend toward lower SUV_{mean} in patients with AVPC (5.9 vs. 6.6 in patients without AVPC, $P = 0.07$); however, there was no difference in median total tumor volume between the groups (253.4 mL vs. 298.6 mL, respectively; $P = 0.6$). **Conclusion:** Although patients with AVPC exhibited significantly worse OS after PSMA RLT, the percentage of patients treated with PSMA RLT who had a reduction in PSA of at least 50% or more from baseline was similar between the AVPC and non-AVPC groups. These findings

support the consideration of PSMA RLT as a treatment option in patients with AVPC who have adequate PSMA expression.

Key Words: aggressive-variant prostate cancer; AVPC; mCRPC; PSMA RLT; overall survival

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Prostate cancer is the second most common cause of cancer-related death in men in the United States (1). Metastatic castration-resistant prostate cancer, an advanced stage of the disease, is associated with a poor prognosis and limited treatment options (2). Aggressive-variant prostate cancer (AVPC) is a morphologically diverse prostate cancer characterized by high-risk clinical features and biologic behavior (including responsiveness to platinum-based chemotherapy) similar to small cell neuroendocrine prostate cancer. Patients with AVPC have a significantly shorter overall survival (OS) compared with those with non-AVPC (3). Biopsied lesions from these patients reveal a spectrum of histologic findings, ranging from poorly differentiated adenocarcinomas to pure small cell carcinomas with neuroendocrine differentiation (4,5).

AVPC has limited treatment options because of its aggressive behaviors and patterns of therapeutic resistance (5). However, some studies have shown that chemotherapy has efficacy in AVPC, although overall outcomes remain poor (6–8). These tumors are often less reliant on androgen receptor (AR) signaling and typically respond poorly to AR-targeted therapies (9,10).

Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) with ¹⁷⁷Lu has emerged as a promising treatment option for patients with metastatic castration-resistant prostate cancer whose disease has progressed after standard therapies. The VISION trial demonstrated that [¹⁷⁷Lu]Lu-PSMA-617 significantly prolonged OS and improved patients' quality of life (11). The PSMAfore trial evaluated [¹⁷⁷Lu]Lu-PSMA-617 in taxane-naïve patients and found that it significantly prolonged radiographic progression-free survival compared with switching to an alternative AR pathway inhibitor (12).

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The efficacy of PSMA RLT in patients with AVPC is not well understood. This study aimed to evaluate the therapeutic efficacy and clinical outcomes of [¹⁷⁷Lu]Lu-PSMA RLT in patients with versus those without AVPC.

MATERIALS AND METHODS

Patient Population

In this retrospective study, we included 296 patients with metastatic castration-resistant prostate cancer who received PSMA RLT between May 2019 and May 2025 across 3 institutions: the University of California, San Francisco (54 AVPC and 173 non-AVPC patients), the Kantonsspital Baden (7 AVPC and 41 non-AVPC patients), and MD Anderson Cancer Center (21 AVPC patients). Patient selection for PSMA RLT across the institutions was based primarily on uptake on baseline PSMA PET scans and the use of prior therapies. The local institutional review boards approved the study. The requirement for informed consent was waived, or general consent for further use of clinical data was provided.

AVPC Classification

To categorize patients, a radiologist reviewed images to assess for visceral metastases, lytic bone metastases, bulky lymphadenopathy, or mass. Further aspects defining AVPC were collected from patient records: disease progression within 6 mo after the initiation of hormonal therapy; prostate-specific antigen (PSA), serum carcinoembryonic antigen, and lactate dehydrogenase levels; and pathology reports of tissue samples and genomic alterations in TP53, RB1, and PTEN. Patients were classified as having AVPC if they met at least one of the clinical or molecular criteria listed in Table 1 (8). Patients with AVPC were further stratified into 2 subcategories: AVPC-C (clinicopathologic), referring to patients who met AVPC on the basis of clinical or pathologic features, and AVPC-MS (molecular signature), referring to patients who met AVPC criteria on the basis of genomic alterations. If a patient met the criteria for both AVPC-MS and AVPC-C, they were categorized in the AVPC-C subgroup. All other patients were classified as non-AVPC.

Patient Treatment and Outcome Analysis

Patients were treated with [¹⁷⁷Lu]Lu-PSMA-617 for up to 6 cycles as part of the clinical standard of care. PSA response was determined by measuring the change in PSA from the date of the first treatment cycle to the lowest value (nadir). In accordance with Prostate Cancer Clinical Trials Working Group 3 criteria, PSA50 response was defined as a reduction in PSA of at least 50% or more from baseline, whereas progression was defined as an increase of more than 25% and greater than 2 ng/mL above the nadir (13). PSA progression-free survival (PSA-PFS) was defined as the interval from baseline PSA to the time of PSA increase. OS was calculated from the date of the first [¹⁷⁷Lu]Lu-PSMA RLT treatment to the date of death from any cause. Patients who were alive at the time of data cutoff were censored at the date of their last available follow-up.

For OS analysis, data were collected from 3 academic centers (overall cohort). However, 1 center was excluded from the paired analysis because of the absence of data from non-AVPC patients, limiting the paired comparison of AVPC and non-AVPC groups to the remaining 2 centers (paired cohort). Similarly, when comparing OS among AVPC-MS, AVPC-C, and non-AVPC subgroups, only patients from the 2 centers with both AVPC and non-AVPC patients were included. This patient inclusion strategy is summarized in Supplemental Figure 1 (available at <http://jnm.snmjournals.org>).

PSMA Segmentation Analysis

At 1 institution (segmentation cohort), all baseline PSMA PETs for both AVPC and non-AVPC patients were analyzed using MIM software version 7.3.5 (MIM Software Inc.). Semiautomated tumor segmentation was performed by applying the following thresholds: an SUV_{max} of 3 or greater for osseous and nodal lesions and an SUV of 1.5 or greater $\times$ the liver SUV_{mean} for visceral metastases. These thresholds were selected to delineate tumor regions with increased radiotracer uptake while minimizing the inclusion of background activity. Three parameters were calculated for each region: SUV_{max}, SUV_{mean}, and total tumor volume (defined as the summed volume of the segmented PSMA-avid lesions). A nuclear medicine physician assessed the presence of PSMA-negative disease on PSMA PET and

TABLE 1
AVPC Criteria Met by Study Patients (*n* = 82)

Criterion	Value
Exclusive visceral metastases	1 (1.2)
Predominantly lytic bone metastases	2 (2.4)
Low PSA and ≥ 20 bone metastases	
At time of initial presentation	0
At time of symptomatic mCRPC	2 (2.4)
Serum CEA or LDH $2 \times$ ULN at time of treatment	9 (10.9)
≤ 6 mo to mCRPC	12 (14.6)
Small cell or neuroendocrine carcinoma morphology	10 (12.1)
RECIST progression without evidence of PSA increase	4 (4.8)
Bulky lymphadenopathy* or mass [†] in prostate or pelvis	7 (8.5)
≥ 2 of the following genomic defects: TP53, RB1, PTEN	41 (50)

* ≥ 5 cm.

[†] ≥ 5 cm, Gleason score ≥ 8 .

mCRPC = metastatic castration-resistant prostate cancer; CEA = carcinoembryonic antigen; LDH = lactate dehydrogenase; ULN = upper limit of normal.

Data are expressed as number and percentage.

conventional imaging performed at disease progression. PSMA-negative disease was defined as lesions demonstrating radiotracer uptake equal to or lower than the background activity of the surrounding liver (11).

Statistical Analysis

Continuous variables were summarized as medians with interquartile ranges (IQRs) for nonnormally distributed data. Categorical variables were reported as frequencies and percentages. PSA-PFS and OS were analyzed using the Kaplan–Meier method, and differences between groups were assessed using the log-rank test. Median PSA-PFS and OS were estimated, along with their 95% CIs. A *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using R version 4.4.1 (R Project for Statistical Computing).

RESULTS

Patient Demographics

Of the 297 patients evaluated, 82 (27.6%) were classified as having AVPC, and the median follow-up time was 9 mo (IQR, 5–14 mo). Table 1 summarizes the number of patients meeting the

criteria for AVPC. Among these patients, 6 (7.3%) met the criteria for both AVPC-C and AVPC-MS criteria. Forty-seven patients (57.3%) were categorized in the AVPC-C subgroup, and the remaining 35 (42.7%) comprised the AVPC-MS subgroup. Patients had a median of 3 (IQR, 2–5) treatment cycles. Bone was the most common site of metastasis among AVPC patients, observed in 88.8% of cases. Further patient demographics and tumor characteristics are provided in Table 2. Of note, 5 (9.2%) of 52 AVPC patients progressed with PSMA-negative disease versus 10 (5.7%) of 173 non-AVPC patients (*P* = 0.3).

PSA Analysis

In the paired cohort, median baseline PSA levels were lower in AVPC patients (54.5 ng/mL; IQR, 7.4–187.2 ng/mL) compared with non-AVPC patients (119.2 ng/mL; IQR, 36.4–339.0 ng/mL); however, the difference was not statistically significant (*P* = 0.8). No significant difference was seen in the median PSA response between AVPC and non-AVPC patients (69.4% [IQR, 25.5%–87.7%] vs. 66.9% [IQR, 19.2%–92.1%], respectively; *P* = 0.8). There was also no significant difference in median PSA response between AVPC-C and AVPC-MS subtypes (73.8% [IQR, 33.2%–88.4%] vs. 52.7%

TABLE 2
Patient and Tumor Characteristics for Paired Cohort (*n* = 297)

Characteristic	AVPC	Non-AVPC
<i>n</i>	82	215
Age (y)	71.0 (66–78.5)	74.5 (67–78.7)
PSA (ng/mL)	54.5 (7.4–187.2)	119.2 (36.4–339.0)
Prior treatment*		
Radical prostatectomy	11 (20.3)	36 (20.8)
Radiation	29 (53.7)	103 (59.5)
ADT	75 (100)	173 (100)
ARPI	75 (100)	173 (100)
Chemotherapy	71 (94.6)	173 (100)
Site of disease on baseline PSMA PET*		
Prostatic fossa	14 (25.9)	54 (31.2)
Lymph node	38 (70.3)	107 (61.8)
Bone	48 (88.8)	166 (95.9)
Liver	14 (25.9)	26 (15.0)
Baseline PSMA PET segmentation*		
TTV	253.4 (80.8–1,215.7)	298.6 (68.4–772.8)
SUV _{mean}	5.9 (4.5–7.5)	6.6 (5.0–8.3)
SUV _{max}	26.1 (17.1–36.5)	33.2 (20.7–57.4)
No. cycles		
1	8 (9.7)	25 (11.6)
2	16 (19.5)	34 (15.8)
3	19 (23.1)	37 (17.2)
4	9 (10.9)	41 (19.0)
5	7 (8.5)	25 (11.6)
6	23 (28)	53 (24.6)

*Data not available for all patients (*n* = 227).

ADT = androgen-deprivation therapy; ARPI = androgen receptor pathway inhibitor; TTV = total tumor volume. Qualitative data are expressed as number and percentage; continuous data are expressed as median and IQR.

[IQR, 17.2%–87.3%], respectively; $P = 0.6$). Among those with AVPC, a reduction in PSA of at least 30% or more from baseline was seen in 68.9% of patients, while a reduction of at least 90% or more from baseline was observed in 20.2%. A PSA50 response was seen in 62.1% of patients with AVPC (Fig. 1).

The median PSA-PFS was shorter in the AVPC group than in the non-AVPC group (3.2 mo; 95% CI, 2.5–5.7 mo vs. 4.2 mo; 95% CI, 3.5–5.1 mo, respectively). However, this difference did not reach statistical significance (log-rank test, $P = 0.10$) (Fig. 2).

Outcome Analysis

In the paired cohort, the median OS for AVPC patients was 11.8 mo (95% CI, 9.7–14.9 mo), compared with 13.3 mo (95% CI, 12.1–15.0 mo) for non-AVPC patients ($P = 0.04$) (Fig. 3). We investigated the role of genomic mutations by comparing OS between the AVPC-C and AVPC-MS subgroup, finding no significant difference in median OS for the AVPC-C and AVPC-MS subgroups (10.9 mo vs. 11.9 mo, respectively; $P = 0.8$) (Fig. 3). In the paired cohort, the median OS of patients with AVPC-MS and AVPC-C was shorter compared with that of non-AVPC patients; however, the differences were not statistically significant ($P = 0.15$ and $P = 0.10$, respectively) (Supplemental Fig. 2).

Segmentation Analysis

The segmentation cohort included 54 AVPC and 173 non-AVPC patients. PSMA PET quantification demonstrated a trend toward lower tumor burden and RLT uptake in AVPC patients, although these differences did not reach statistical significance. The median SUV_{mean} was 5.9 (IQR, 4.5–7.5) in AVPC patients and 6.6 (IQR, 5.0–8.3) in non-AVPC patients ($P = 0.07$). The median SUV_{max} was 26.1 (IQR, 17.1–36.5) in AVPC patients and 33.2 (IQR, 20.7–57.4) in non-AVPC patients ($P = 0.07$). The overall tumor volume between the 2 cohorts was similar, with a median total tumor volume of 253.4 mL (IQR, 80.8–1,215.7 mL) in AVPC patients and 298.6 mL (IQR, 68.4–772.8 mL) in non-AVPC patients ($P = 0.6$).

DISCUSSION

In this multicenter retrospective study evaluating the efficacy of [^{177}Lu]Lu-PSMA RLT in patients with AVPC, we demonstrated that, although AVPC patients had favorable PSA responses to PSMA RLT, they had a significantly shorter OS compared with non-AVPC patients who received PSMA RLT.

These findings are consistent with prior studies showing that AVPC patients have a poor prognosis and reduced OS (3,14). The rapid disease progression characteristic of AVPC limits the

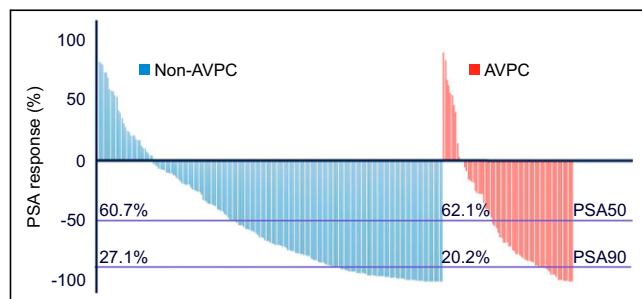


FIGURE 1. Waterfall plot of PSA response for AVPC and non-AVPC patients. PSA90 = PSA reduction of at least 90% or more from baseline.

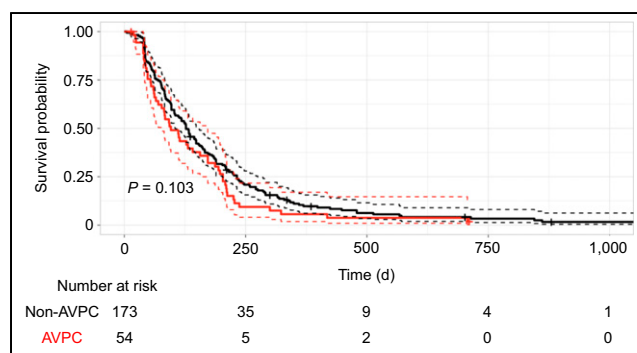


FIGURE 2. Kaplan-Meier curves for time to PSA progression in AVPC vs. non-AVPC patients. Median time to PSA progression was 96 d (95% CI, 77–172 d) for AVPC patients and 127 d (95% CI, 105–153 d) for non-AVPC patients.

durability of treatment responses and causes poor outcomes and shorter survival, even though PSMA RLT demonstrated efficacy as evidenced by PSA response. The median OS in AVPC patients in this study was 11.8 mo. A study evaluating salvage chemotherapy in AVPC patients reported a median OS of only 6 mo, despite clinical benefit from platinum-based regimens (6). In a prospective phase 2 study by Aparicio et al., platinum-based chemotherapy resulted in a median OS of 16 mo (8).

Currently, there is considerable heterogeneity in the criteria used to define AVPC. Interestingly, when AVPC patients were stratified into AVPC-C and AVPC-MS subgroups, no significant difference in OS was observed between groups. This finding

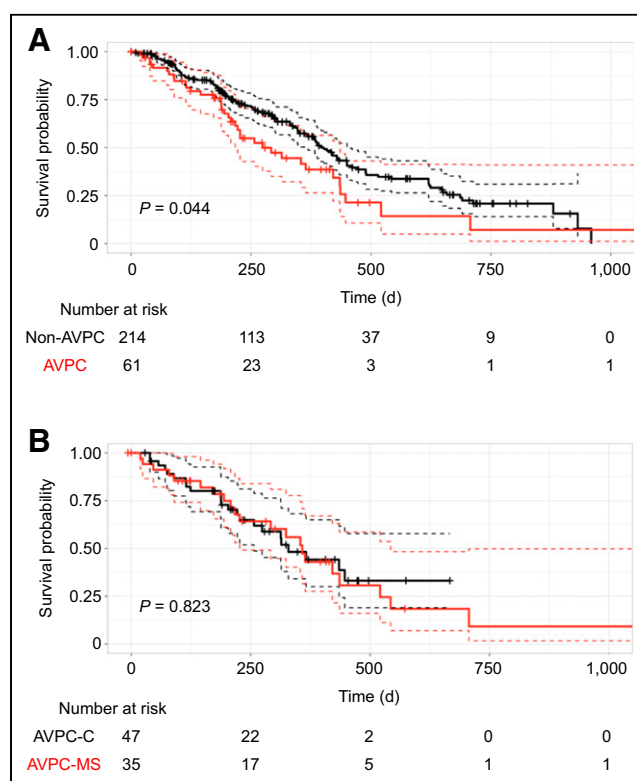


FIGURE 3. Kaplan-Meier survival curves for OS of AVPC patients vs. non-AVPC patients (A) and AVPC-MS vs AVPC-C subtypes (B). Median OS was 354 d for AVPC patients and 401 d for non-AVPC patients.

suggests that both clinical and molecular features correlate with the aggressive disease phenotype and similarly predict poor outcomes to PSMA RLT. The high percentage of patients in the AVPC-MS subgroup (50%) highlights the importance of molecular profiling for early identification of AVPC.

Neuroendocrine differentiation in some AVPC cases is associated with the loss of AR expression and resistance to AR-targeted therapies (3). PSMA expression may persist independently of AR signaling in a subset of these tumors. Recent evidence suggests that PSMA expression can be maintained in the absence of AR expression, potentially explaining the continued efficacy of PSMA RLT in AR-independent prostate cancer (15).

AVPC can be characterized by disproportionately low PSA levels, even in patients with extensive metastatic disease (16). Although biomarkers other than PSA have been suggested for disease monitoring in AVPC, such as carcinoembryonic antigen, neuroendocrine markers (e.g., chromogranin A, synaptophysin), and molecular imaging modalities (e.g., FDG PET, PSMA PET) (17), PSA response was similar in our cohort between AVPC and non-AVPC patients, suggesting that PSA response was adequate to evaluate the efficacy of PSMA RLT.

This study had several limitations. First, there was heterogeneity in the patient cohorts, including differences in prior treatments and follow-up intervals. In addition, data from non-AVPC patients were not available from 1 center, limiting comparative analyses across all 3 centers. A second important limitation is that we did not characterize patients who did not qualify for PSMA RLT because of low PSMA expression, which may occur at a higher rate in AVPC patients. Third, the timing of biopsies and depth of genomic alterations were not recorded across institutions, which hampered our ability to gain a deeper understanding of the nature of genomic defects on outcomes.

CONCLUSION

AVPC patients had favorable PSA responses to PSMA RLT but had a significantly shorter OS compared with non-AVPC patients treated with PSMA RLT. Nevertheless, the median OS of 11.8 mo for AVPC patients indicates that PSMA RLT is an effective therapeutic option in patients with AVPC who have adequate uptake on PSMA PET.

KEY POINTS

QUESTION: Does PSMA RLT provide clinical benefit in patients with AVPC?

PERTINENT FINDINGS: PSMA RLT achieved a PSA50 response rate in patients with AVPC, similar to that in non-AVPC patients, although OS was shorter in the AVPC group.

IMPLICATIONS FOR PATIENT CARE: PSMA RLT is an effective therapeutic option in patients with AVPC who have adequate uptake on PSMA PET despite a poorer overall prognosis.

DISCLOSURE

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