The Prostate

WILEY

The Prostate

ORIGINAL ARTICLE OPEN ACCESS

Incidental Brain Metastases From Prostate Cancer Diagnosed With PSMA PET/CT and MRI: A Case Series and Literature Review

Mark Willy L. Mondia[1] | Prem P. Batchala[2] | Robert Dreicer[3] | Michael E. Devitt[3] | Matthew R. McCord[4] | Melike Mut[5] | Jason P. Sheehan[5] | David Schiff[1] | Camilo E. Fadul[1]

[1]Division of Neuro-Oncology, Department of Neurology, University of Virginia, Charlottesville, Virginia | [2]Division of Nuclear Medicine, Department of Radiology and Medical Imaging, University of Virginia, Charlottesville, Virginia | [3]Division of Hematology/Oncology, Departments of Medicine and Urology, University of Virginia, Charlottesville, Virginia | [4]Department of Pathology, University of Virginia, Charlottesville, Virginia | [5]Department of Neurosurgery, University of Virginia, Charlottesville, Virginia

Correspondence: Camilo E. Fadul (cef3w@uvahealth.org)

Received: 12 December 2024 | **Revised:** 21 February 2025 | **Accepted:** 4 March 2025

Funding: The authors received no specific funding for this work.

Keywords: brain metastasis | MRI | PET/CT | prostate cancer | PSMA

ABSTRACT

Background: Brain metastases (BMETS) from prostate cancer are rare. Hence, brain imaging in neurologically asymptomatic patients with advanced prostate cancer (aPC) is not routinely performed. Prostate-specific membrane antigen (PSMA) PET/CT uses a radiotracer that binds to prostate cancer epithelial cells and is FDA-approved for initial staging for high-risk prostate cancer, detecting prostate cancer recurrence, and determining eligibility for radionuclide therapy.

Methods: We report six patients with asymptomatic BMETS from aPC found on staging PSMA PET/CT or MRI. Along with cranial MRI, PSMA PET/CT may be useful for detecting asymptomatic intracranial metastasis in select patients with prostate cancer.

Results: Brain metastases were diagnosed in four patients by staging PSMA PET/CT scan—three after systemic disease progression and one during routine surveillance. In two other patients, BMETS were detected using MRI despite negative PSMA PET/CT for brain lesions. All were neurologically asymptomatic. Three patients had undetectable serum prostate-specific antigen (PSA) concentrations; one had neuroendocrine differentiation on histology.

Conclusion: In patients with poorly differentiated or neuroendocrine aPC, BMETS may occur without neurologic symptoms and stable PSA. PSMA PET/CT may complement brain MRI for identifying BMETS in these patients.

1 | Introduction

In the United States, prostate cancer is the most common non-cutaneous malignancy in males [1]. Distant metastasis is present in 4%–25% of prostate cancer patients [2], but intracranial metastases are rare (0.6%–2.9%) and involve the meninges (66%) more commonly than the parenchyma (33%) [3]. Advanced prostate cancer (aPC) with small cell and neuroendocrine-transformed types are more frequently associated with intraparenchymal brain metastases (BMETS) [4].

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein overexpressed in > 90% of prostate cancer. PSMA is an imaging biomarker for identifying locoregional and distant metastatic disease in patients with prostate cancer using small molecule PET radiopharmaceuticals [5]. FDA-approved PET

agents that bind to PSMA are Ga68 PSMA11, F18 Piflufolastat, and F18 Flotufolastat [6]. Unlike F18-FDG, PSMA PET/CT shows minimal background brain parenchymal uptake that improves lesion detection [7]. Additionally, PSMA serves as a therapeutic target. Recently, FDA-approved lutetium (Lu177) labeled PSMA-617 vipivotide tetraxetan (Lu177-PSMA), a peptide receptor radionuclide therapy (PRRT), has been shown to prolong progression-free and overall survival in metastatic castration-resistant prostate cancer disease (mCRPC) [8].

Advances in systemic therapeutic options, particularly the introduction of doublet androgen deprivation therapy (ADT), have shown improved survival for patients with metastatic prostate cancer [9]. However, the impact of more prolonged survival in the apparent increased incidence of BMETS has not been definitively established [10]. BMETS detection may have improved because of advanced imaging techniques [11–13], but intrinsic tumor characteristics may also predispose to organ-specific metastasis [14–17]. Early detection and treatment of BMETS may also be associated with improved survival outcomes [18–20]. We report a series of neurologically asymptomatic patients where BMETS from prostate cancer were identified by staging PSMA PET/CT and brain MRI.

2 | Case Series

Between January 2017 and June 2024, there were 18 patients diagnosed with brain metastasis from prostate cancer at the University of Virginia (UVA). Six patients were included in this series (Table 1). They were referred within 6 months (January 2024 to June 2024) for incidental brain lesions in the setting of progressive metastatic prostate cancer. Presenting symptoms for prostate cancer were variable. Case 2 experienced vague chronic abdominal pain and imaging showed enlarged prostate and lymph nodes and bone abnormalities. Case 6 presented with prolonged non-specific thigh pain. The rest had obstructive urinary symptoms with elevated prostate-specific antigen (PSA). Gleason scores ranged between 7 and 9 with a histopathologic diagnosis of high-grade adenocarcinoma (Figure 1). Cases 4 and 6 had repeat biopsies during progression. Systemic metastatic disease was present on initial diagnosis for Cases 2, 4, 5, and 6. Cases 1 and 3 presented with limited locoregional spread. Most were treated with upfront GnRH (gonadotropin-releasing hormone) analog as primary ADT, with docetaxel as intensification. Disease progression for mCRPC was treated either with an androgen-receptor pathway inhibitor, dendritic cell vaccine, PRRT with Lu177-PSMA, or salvage chemotherapy. These treatment modalities were utilized before the diagnosis of BMETS. For Cases 1 and 4 who received Lu177-PSMA before BMETS diagnosis, no brain lesions were identified on immediate post-therapy PSMA PET. None of the Lu177-PSMA-treatead patients developed any neurologic symptoms. Focal radiation therapy to the prostate, lymph nodes, and bone metastases was used for palliative purposes.

PSMA PET/CT was pursued as a staging modality for systemic recurrence after prior salvage therapies, except for Case 6 for which PSMA PET/CT was done as part of surveillance. At the time of presumed BMETS diagnosis, these patients presented with constitutional symptoms suspicious of clinical progression but without neurologic symptoms. Cases 2 (0.2 ng/mL), 4 (< 0.10 ng/mL), 5 (1.3 ng/mL), and 6 (2.8 ng/mL) had stable PSA before BMETS diagnosis. Cases 1 and 3 had PSA concentrations of 13.73 ng/mL and 6.35 ng/mL before BMETS diagnosis. Five patients had concurrent progressive disease based on systemic PSMA PET/CT during the time of BMETS diagnosis. Only one patient (Case 6) had good systemic disease control when intracranial spread was noted. They all had a good functional status as determined by Eastern Cooperative Oncology Group (ECOG) scores and all were in the Updated Recursive Partitioning Analysis (U-RPA) Class 2A [21]. Two patients had short intervals between initial diagnosis of prostate cancer and detection of BMETS (< 12 months in Cases 2 and 5), while the rest had prolonged intervals (36 to 288 months). Five cases had germline and somatic mutational analysis without evidence of actionable mutations [22].

BMETS were diagnosed for Cases 2 (Figure 2), 3, and 5 (Figure 3) through PSMA PET/CT. Brain MRI identified additional enhancing lesions without avid uptake in PSMA PET/CT for Cases 2 and 5. Initial PSMA PET/CT detected systemic progression without BMETS for Cases 1 and 4. PSMA PET/CT is theoretically unable to detect lesions less than 2 mm, which may explain the absence of avidity in PSMA PET/CT [23]. BMETS were diagnosed with screening cranial MRI after progressing on radionuclide therapy as a screening prerequisite for a clinical trial. The protocol varied—Cases 1, 3, and 5 only had a PET/CT scan starting from the skull base, while in Cases 2, 4, and 6 the imaging started from the vertex. Because the PSMA avid lesions in Cases 3 and 5 were located in the posterior and inferior intracranial areas, a PET/CT scan identified these lesions despite only starting from the base of the skull. The number of intraparenchymal brain metastases ranged from 1 to 15. Brain MRIs showed enhancing lesions with perilesional edema and no significant diffusion restriction or bleeding.

Five patients were treated with stereotactic radiosurgery (SRS) using Gamma-Knife Radiosurgery (GKRS) to target the individual lesions in the brain. The multicentricity, location, and relatively small size of the lesions with progressive extracranial disease precluded surgical excision to establish a histologic diagnosis for these patients [24, 25]. One patient (Case 6) had surgery (Figure 4) because the solitary lesion had a diameter of 4 cm, with significant edema, and was amenable to maximal safe resection with a low risk of causing neurological deficits [26]. Furthermore, MRI findings were atypical for BMETS including central necrosis with indistinct heterogenous borders that invaded the periventricular area, which is more commonly associated with diffuse infiltrative gliomas [27]. Two of the patients expired from non-neurologic complications of their cancer—both 4 months after diagnosis of BMETS, but more than 10 years from initial diagnosis of prostate cancer. The other four patients are alive and continue systemic medical treatment with surveillance central nervous system (CNS) imaging.

3 | Discussion

The identification of BMETS from prostate cancer may be increasing due to improved imaging [28, 29]. However, underreporting could remain an issue because current staging strategies do not routinely include CNS imaging without neurologic

TABLE 1 | Clinical, radiologic, and treatment details of patients included in the case series.

		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Pathology at diagnosis and molecular data	Histology	Poorly differentiated adenocarcinoma	Acinar adenocarcinoma	Poorly differentiated adenocarcinoma	Neuroendocrine differentiation	High-grade Adenocarcinoma	High-grade Adenocarcinoma
	Gleason Score	7 (3 + 4)	9 (4 + 5)	8 (4 + 4)	9 (4 + 5)	9 (5 + 4)	9 (5 + 4)
	Stage	T2aN0M0	T4N1M1b	T2bN0M0	T4N1M1b	T4N1M1b	T4N1M1c
	Genetic testing	Time of diagnosis *CTNNB1* T41A *CTNNB1* T41I	N/A	Time of diagnosis *TP53* D281E *AKT1* E17K *ATM*Y2954C *MET* A1354T *TP53* R175H	Time of progression PTEN loss CREBBP splice site TMPRSS2-ERG fusion	Time of diagnosis PTEN loss	Time of progression SFB31 TP53
Treatment before BMETS	Surgery	Radical prostatectomy and LN dissection	TURP	None	Radical prostatectomy and LN dissection	Transurethral resection median lobe of prostate	None
	First-line treatment	RT	ADT, docetaxel, RT	ADT, docetaxel, RT	ADT, docetaxel, enzalutamide	ADT, bicatulamide/ darolutamide, docetaxel, RT	ADT, bicatulamide, abiraterone, RT
	Salvage therapy for recurrence	RT, ADT, docetaxel, enzalutamide, Lutetium (Lu 177) vipivotide tetraxetan	ADT, enzalutamide	RT, docetaxel enzalutamide, dendritic cell vaccine (Sipuleucel)	Lutetium (Lu 177) vipivotide tetraxetan	RT, ADT, darolutamide, cabazitaxel	TURBT
Diagnosis of BMETS	Indication for CNS imaging	Screening for clinical trial	Radiologic progression	Radiologic progression	Screening for clinical trial	Radiologic progression	Surveillance
	Time lapsed (months)[a]	288	4	105	48	7	36
	Location and number of lesions	3: left putamen, left anterior parietal, left cerebellum	2: left parietal lobe, left centrum semiovale	1: left occipital	15 supra and infratentorial lesions	5 on MRI: bilateral cerebellum, left temporal, left parietal	1: left parietal
	PSMA PET/CT	N/A[b,c]	Top of the head to feet: left parietal lobe (SUV max 6.1)	Skull base to upper thighs: left occipital lobe (SUV max 2.2)	N/A[b,d]	Skull base to upper thighs: left tentorial leaflet (SUV max 5.4) and right cerebellum (SUV max 2.5)	Top of head to thighs: left frontoparietal mass (SUV max 7.8)
	PSA (ng/mL)	13.73	0.20	6.35	< 0.10	1.3	2.8

(Continues)

TABLE 1 | (Continued)

		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
	Active disease sites	LN, bone, liver, lungs, calvarium	LN, bone, liver, lungs, calvarium	LN, bone, lungs	LN, bladder, bone, lungs	Bone, calvarium, spleen	Bone, calvarium, LN, bladder, lungs
Post BMETS diagnosis	BMETS treatment	GKRS	GKRS	GKRS	GKRS	GKRS	Surgery + focal RT to cavity
	Systemic treatment	cabazitaxel, carboplatin	enzalutamide, leuprorelin	cabazitaxel, carboplatin	cabazitaxel, carboplatin	Lutetium (Lu 177) vipivotide tetraxetan	ADT, abiraterone, docetaxel
	Present status	Diseased	Clinically stable	Diseased	Clinically stable	Clinically stable	Clinically stable

Abbreviations: ADT, androgen deprivation therapy; BMETS, brain metastases; CNS, Central Nervous System; GKRS, gamma-knife radiosurgery; LN, lymph node; PSA, prostate-specific antigen; PSMA PET/CT, prostate-specific membrane antigen positron emission tomography/computed tomography; RT, radiotherapy; SUV max, maximum standardized uptake value; TURBT: Transurethral resection of bladder tumor; TURP: transurethral resection of the prostate.

[a] Interval from prostate cancer diagnosis to development of brain metastases.

[b] Had prior PSMA PET/CT noting uptake in multiple bone metastasis, but none in the brain at that time, hence was started on Lutetium (Lu 177) vipivotide tetraxetan.

[c] PSMA PET/CT scanned from skull base to upper thigh.

[d] PSMA PET/CT scanned from vertex to upper thigh.

symptoms [30]. Conversely, despite an estimated post-mortem BMETS diagnosis frequency of 1%–6% from an autopsy series [31], it is unlikely that the presence of undiagnosed occult BMETS is an unidentified risk factor for mortality in aPC [5]. Although the median survival remains poor at 2.8–4.5 months [19], early detection of BMETS in neurologically asymptomatic high-risk prostate cancer patients may improve prognosis [32]. In this series, we report clinical characteristics and outcomes of six patients with asymptomatic intraparenchymal BMETS from prostate cancer diagnosed on staging studies.

PSMA PET/CT is considered appropriate for initial staging in patients with newly diagnosed unfavorable intermediate, high, or very-high-risk prostate cancer, for evaluating recurrence, and for assessing eligibility for PRRT [33, 34]. However, the role of PSMA PET/CT in diagnosing BMETS in patients with biochemical progression is uncertain. Previously reported cases of asymptomatic BMETS were diagnosed in the background of increasing PSA [35]. In addition to three case reports of BMETS diagnosed using PSMA PET/CT in neurologically asymptomatic patients who had increasing PSA [6, 35, 36], a retrospective study showed newly diagnosed BMETS on PSMA PET/CT, for workup for increasing PSA, in 5 of 2763 neurologically asymptomatic patients with prostate cancer [5]. Retrospective data have also suggested the possibility of using PSMA PET/CT scans for earlier detection of previously unknown BMETS without systemic disease progression [5, 37].

Unique to our series is that PSMA PET/CT or brain MRI were used to diagnose BMETS from prostate cancer with undetectable PSA in neurologically asymptomatic patients. Screening for BMETS in all patients with aPC would not be cost-efficient given its rarity. However, it may be reasonable to consider including brain imaging in cases of poorly differentiated (Cases 1 and 3) or neuroendocrine (Case 4) aPC during progression because these histologic subtypes seem to have a greater tendency to metastasize to the brain [38, 39]. A possible explanation for low PSA in progressive prostate cancer is the presence of visceral metastases with a high proportion of lytic bone disease (Case 2) [40] and histology of poorly differentiated or neuroendocrine differentiation (Cases 3, 4, and 5) [41]. Despite the non-elevated PSA concentration, disease progression, conceivably including to the brain, in the setting of aPC is still possible [42]; thus, the likelihood of the CNS lesions being non-metastatic, in our cases without pathologic confirmation, is low.

Concerning genetic alterations, two patients had mutations in TP53 (Cases 3 and 6) and one patient (Case 3) had an ATM mutation, genes that have been associated with prostate cancer brain metastasis (PCBM) [43, 44]. Moreover, PTEN loss was also present in two patients (Cases 4 and 5), as well as BRCA2, MSH2, and NF1 mutations in 3 patients in the UVA PCBM cohort. PTEN [45] and MSH2 [46] are common mutations in prostate cancer, while BRCA2 [43] may have some association with PCBM. In a small study of 7 patients with neuroendocrine pathology, they reported gene amplification of AURKA and MYCN in 40% of the patients [47]. None of the patients in our cohort had these mutations. From the above findings, neurologically asymptomatic patients with aPC and poorly differentiated histology with an upward PSA trend, neuroendocrine

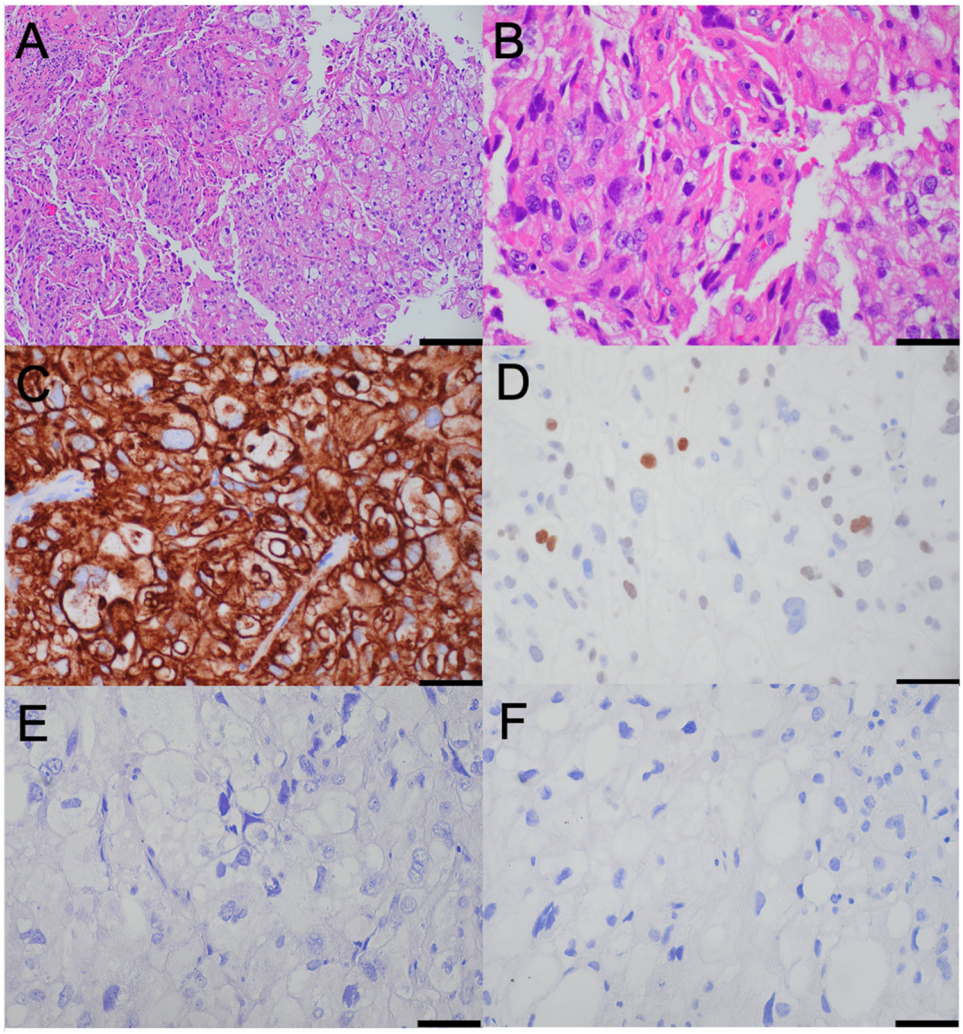

FIGURE 1 | Histopathologic findings for Case 6. Low power view (100× objective) of hematoxylin and eosin (H&E) stained section (A), illustrating compact, solid growth pattern. High power view (400×) of H&E section (B), illustrating pleomorphic epithelioid cells with vacuolated cytoplasm and prominent nucleoli. High power view (400×) of positive keratin cocktail stain (C). High powered view (400×) of positive staining for NKX3.1 (D) in a subset of tumor cell nuclei. No staining for synaptophysin (E) or chromogranin (F). Scale bar: 200 μM in (A), 50 μM in (B–F). [Color figure can be viewed at wileyonlinelibrary.com]

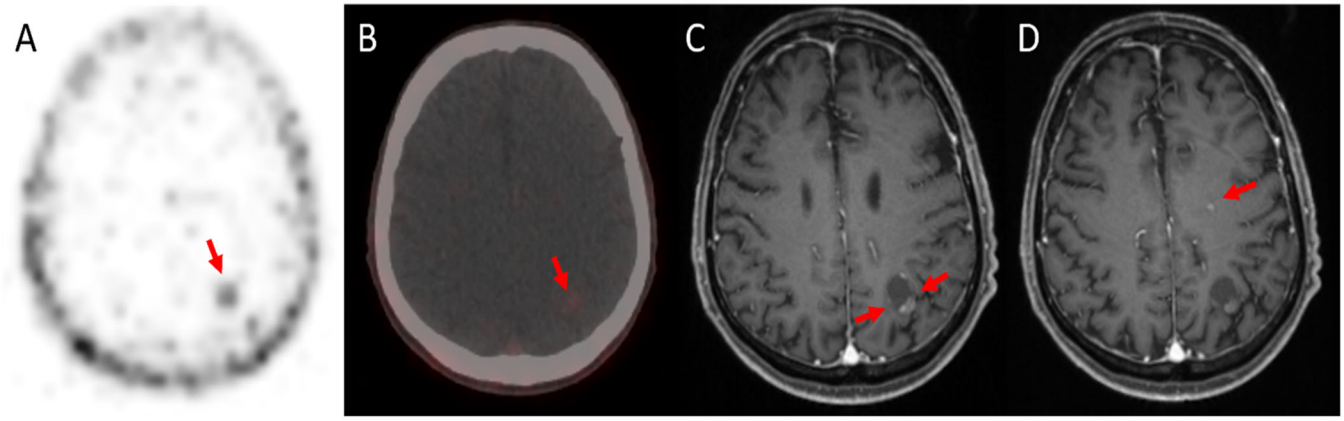

FIGURE 2 | Radiologic findings for Case 2. A 68-year-old man with metastatic prostate cancer. (A) Axial PSMA PET, and (B) Axial fused PET/CT revealed a 1.5 cm focus of mild uptake (SUV max 6.1) in the left parietal lobe (arrows). (C and D) Axial post-contrast T1WI from a follow-up MRI shows a heterogeneous enhancing lesion in the left parietal lobe (two arrows). An additional punctate enhancing lesion is seen in the left centrum semiovale (single arrow) without a corresponding radiotracer avid focus on the previous PSMA PET. This is likely due to background noise. However, this focus was identified in subsequent PSMA PET (not shown). [Color figure can be viewed at wileyonlinelibrary.com]

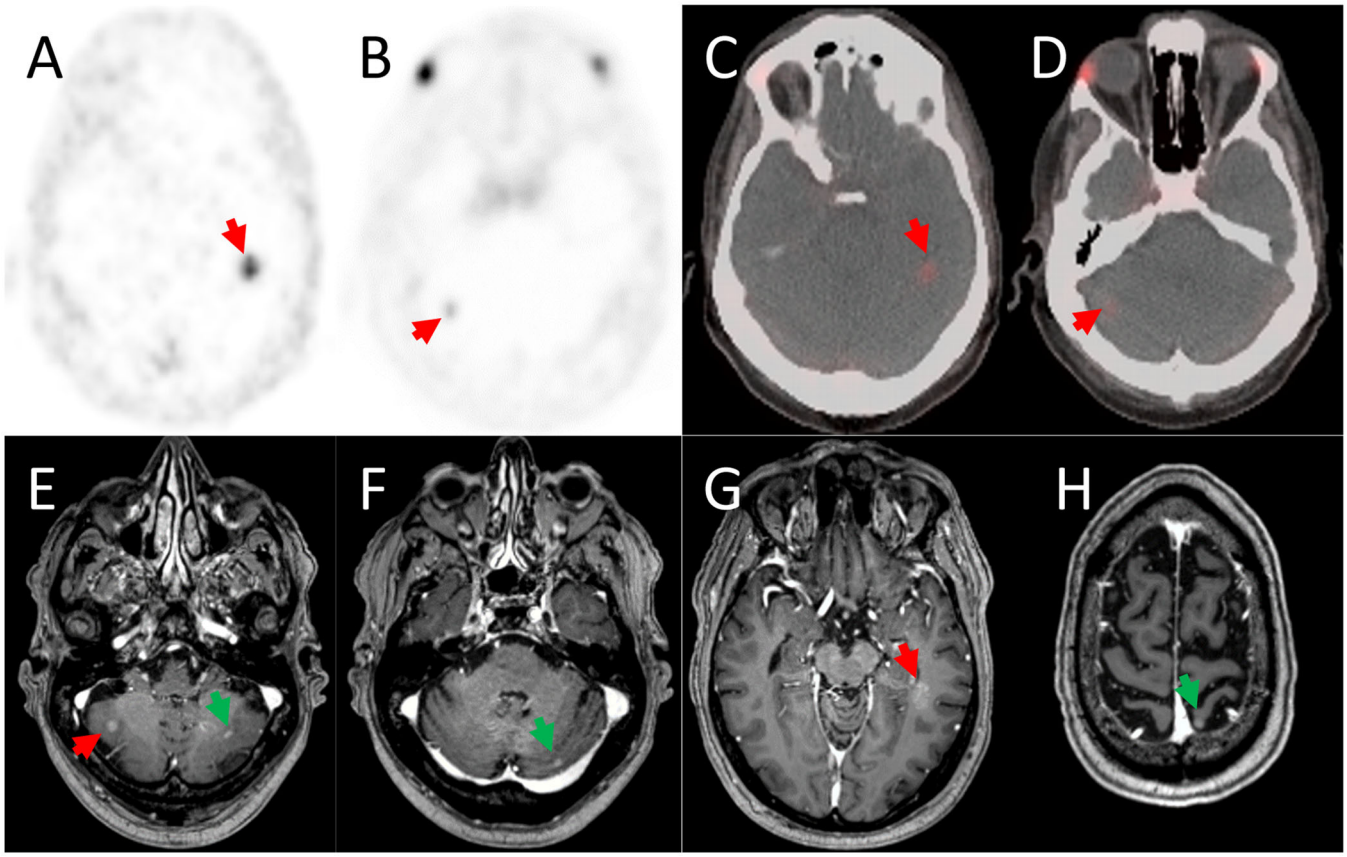

FIGURE 3 | Radiologic findings for Case 5. A 67-year-old man with castration-resistant metastatic prostatic carcinoma. (A and B) Axial PSMA PET, and (C and D) Corresponding axial fused PET/CT (coverage was from skull base to upper thighs) show radiotracer avid lesions (red arrows) in the left posterior temporal lobe (1 cm size, SUV max 5.4, intermediate PSMA expression) and right cerebellum (5 mm size, SUV max 2.5, low PSMA expression) consistent with prostate cancer metastasis. (E–H) Axial post-contrast T1WI done 2 weeks after the PSMA PET/CT shows corresponding enhancing lesions (red arrows). However, there are additional enhancing < 5 mm size metastatic lesions in the left cerebellum and left parietal parasagittal cortex. This discrepancy is likely due to the limited resolution of these small lesions on PSMA PET/CT and the lack of coverage of the left parietal lesion. [Color figure can be viewed at wileyonlinelibrary.com]

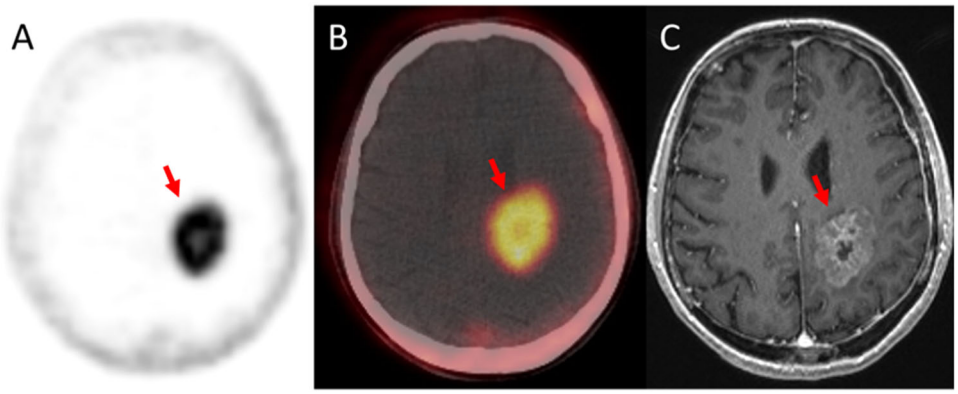

FIGURE 4 | Radiologic findings for Case 6. A 62-year-old man with metastatic prostatic carcinoma screened for brain metastasis as part of surveillance. (A and B) Axial PET, and fused PET/CT showing an incidental 4 cm left parietal lobe mass (arrows) with significant PSMA expression (SUV max 7.8). (C) Axial post-contrast T1WI showing a corresponding enhancing mass (arrow). [Color figure can be viewed at wileyonlinelibrary.com]

histology with stable PSA, or tumor-harboring mutations with increased risk for intracranial spread may benefit from BMETS screening.

Joint procedure guidelines from the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM) for PSMA PET/CT, recommend coverage from the vertex to mid-thigh [33]. Some of our cases were scanned from the skull base to the thighs, which may have affected BMETS detection. On the other hand, PSMA uptake may also be seen in highly vascular primary CNS tumors like GBM [48, 49]. For this reason, surgical resection for Case 6

was recommended to achieve tissue diagnosis and locoregional control. The sensitivity and specificity of PSMA PET/CT for BMETS diagnosis are unknown. In patients undergoing PSMA PET/CT, it could be reasonable to image from the vertex to mid-thigh to include the entire CNS. This may facilitate early detection and treatment of BMETS, potentially improving prognosis [11].

PSMA PET/CT outperforms MRI to identify disease activity in lymph nodes and bone, but the modalities are complementary when interpreted in conjunction [50]. We are unaware of reports comparing PSMA PET/CT versus MRI to diagnose PCBM. Although difficult to ascertain due to the time interval between the two imaging modalities, Cases 2 and 5 demonstrate the possibility of increasing the accuracy of detecting the number of BMETS by combining both PSMA PET/CT and MRI. Interestingly, despite including the whole brain for the PSMA PET/CT done for Case 2, the left centrum semiovale lesion was only detected via MRI. On the other hand, in Case 5, PSMA PET/CT was from the skull base and hence could not assess brain lesions seen on MRI.

In Cases 1 and 4, the BMETS were diagnosed using brain MRI during systemic disease progression despite being on Lu177-PSMA PRRT. Although selective intra-arterial administration had a 15-fold higher uptake of PSMA radioligand in brain tumors compared to the intravenous route, a false negative PSMA PET/CT of the brain is rare [51]. It is possible that BMETS developed simultaneously with systemic disease progression despite PRRT, especially in cases with high Gleason scores [52]. Additionally, PSMA avidity in the brain can decrease while on PRRT and serve as a surrogate to monitor treatment response [6]. Hence, cranial MRI in conjunction with PSMA PET/CT may be reasonable for the surveillance of progressive disease and monitoring of treatment response.

Thus, the treating oncologist may opt to include the brain in the scanned field once PSMA PET is being considered for systemic metastatic screening for aPC. Ideally, this would be regardless of the presence of neurologic symptoms. Since most PSMA PET protocols do not image the brain unless specified, the addition of imaging the cranial vault should theoretically be a minor issue of extending the scanning field. Imaging frequency will depend on clinical status and response to therapy, but may reasonably adapt standard surveillance imaging in metastatic disease, which is usually every 2 to 3 months. In cases where accessibility and cost may be issues, limiting CNS screening to those with poorly differentiated or neuroendocrine aPC may be reasonable. Pursuing additional brain MRI in cases of a negative PSMA PET may be reserved for clinical trials for now until more robust data can support the use of combined imaging.

The small number of patients and the absence of histologic confirmation in most cases are the main limitations of this report. We recognize that this small case series provides limited data to formulate a compelling rationale for BMETS screening studies in aPC. Our findings lack statistical robustness for generalizability and are insufficient to provide evidence to support clinical guidelines. However, we want to call attention to the fact that patients in our series were diagnosed within 6 months mostly for screening after progressing on salvage therapy. Furthermore, since CNS imaging in neurologically asymptomatic prostate cancer patients may pose a unique constraint regarding cost-effectiveness, wherein universal clinical application may not be feasible. We also recognize the importance of tissue diagnosis in patients who are good surgical candidates before treating a potentially lethal disease. Moreover, non-prostatic tumors like gliomas, meningiomas, and other systemic cancers (e.g., lung and renal cell carcinoma) are possible false-positive avid lesions on PSMA PET/CT [53, 54]. Brain metastases from prostate cancer have also been misdiagnosed as abscesses, subdural hematomas, meningiomas, and schwannomas based on MRI [28, 55]. This highlights the importance of considering more common differential diagnoses before treating a PSMA PET avid brain lesion in the setting of aPC. Based on our best clinical judgment, considering the characteristics of CNS lesions in the setting of aPC, and the 2021 joint guidelines by the American Society of Clinical Oncology, Society of Neuro-Oncology, and American Society of Radiation Oncology [24], surgery was not indicated to confirm the pathologic diagnosis of brain metastases. However, we do recognize and still recommend the need for biopsy confirmation for surgically accessible lesions to account for false-positive PSMA PET avid lesions.

4 | Conclusion

Although data from large prospective randomized studies are lacking to make strong recommendations to include CNS imaging in the standard screening and surveillance, our study supports the need to improve the detection rate of BMETS in patients with high-risk prostate cancer. Our series may provide additional rationale for prospective trials investigating the sensitivity and specificity of PSMA PET/CT and MRI as a staging imaging modality in a BMETS high-risk subpopulation of aPC. PSMA PET/CT that images the whole brain may detect BMETS without neurologic symptoms and increasing PSA. Obtaining a cranial MRI In patients with positive PSMA uptake may identify additional occult CNS disease in the setting of oligometastatic prostate cancer. If combining both imaging modalities improves the BMETS detection rates, there is still a need to prove that early detection will improve the outcomes of patients with aPC.

Author Contributions

Mark Willy L. Mondia: conceptualization, data curation, writing – original draft, writing – review, and editing. **Prem P. Batchala:** data curation, radiographic data, writing review, and editing. **Robert Dreicer:** writing – review and editing. **Michael E. Devitt:** writing review and editing. **Matthew R. McCord:** data curation, pathology data, writing review, and editing. **Melike Mut:** writing – review and editing. **Jason P. Sheehan:** writing review and editing. **David Schiff:** writing – review and editing. **Camilo E. Fadul:** conceptualization, data curation, writing review, and editing. The first draft of the manuscript was written by Mark Willy Mondia, Michael E. Devitt and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We are indebted to Marc S. Ernstoff, MD for the critical review of this manuscript.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All datasets on which the conclusions of the paper are included in the manuscript or available upon request.

References

1. R. L. Siegel, K. D. Miller, N. S. Wagle, and A. Jemal, "Cancer Statistics, 2023," *CA: A Cancer Journal for Clinicians* 73, no. 1 (2023): 17–48, https://doi.org/10.3322/caac.21763.

2. G. Gandaglia, F. Abdollah, J. Schiffmann, et al., "Distribution of Metastatic Sites in Patients With Prostate Cancer: A Population-Based Analysis," *Prostate* 74, no. 2 (2014): 210–216, https://doi.org/10.1002/pros.22742.

3. M. A. Sutton, H. L. Watkins, L. K. Green, and D. Kadmon, "Intracranial Metastases as the First Manifestation of Prostate Cancer," *Urology* 48, no. 5 (1996): 789–793, https://doi.org/10.1016/S0090-4295(96)00238-5.

4. L. Bubendorf, A. Schöpfer, U. Wagner, et al., "Metastatic Patterns of Prostate Cancer: An Autopsy Study of 1,589 Patients," *Human Pathology* 31, no. 5 (2000): 578–583, https://doi.org/10.1053/hp.2000.6698.

5. L. A. McLaughlin, O. Yildirim, M. K. Rosenblum, et al., "Identification of Incidental Brain Tumors in Prostate Cancer Patients via PSMA PET/CT," *Journal of Neuro-Oncology* 163, no. 2 (2023): 455–462, https://doi.org/10.1007/s11060-023-04355-x.

6. A. Al-Zubaidi, S. Bezold, P. Bhargava, and J. Villanueva-Meyer, "Prostate Cancer Brain Metastases: Monitoring Response to Treatment With PSMA PET/CT," *Radiology Case Reports* 19, no. 6 (2024): 2367–2370, https://doi.org/10.1016/j.radcr.2024.02.110.

7. N. Galldiks, K.-J. Langen, N. L. Albert, et al., "PET Imaging in Patients With Brain Metastasis—Report of the RANO/PET Group," *Neuro-Oncology* 21, no. 5 (2019): 585–595, https://doi.org/10.1093/neuonc/noz003.

8. O. Sartor, J. de Bono, K. N. Chi, et al., "Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer," *New England Journal of Medicine* 385, no. 12 (2021): 1091–1103, https://doi.org/10.1056/NEJMoa2107322.

9. C. Corsini, H. Garmo, A. W. Orrason, R. Gedeborg, P. Stattin, and M. Westerberg, "Survival Trend in Individuals With De Novo Metastatic Prostate Cancer After the Introduction of Doublet Therapy," *JAMA Network Open* 6, no. 10 (2023): e2336604, https://doi.org/10.1001/jamanetworkopen.2023.36604.

10. R.-A. Rahnea-Nita, L.-F. Rebegea, A. Nechifor, et al., "The Complexity of Treatments and the Multidisciplinary Team—A Rare Case of Long-Term Progression—Free Survival in Prostate Cancer Until Development of Liver and Brain Metastases," *Journal of Clinical Medicine* 12, no. 17 (2023): 5579, https://doi.org/10.3390/jcm12175579.

11. K. Rajeswaran, K. Muzio, J. Briones, et al., "Prostate Cancer Brain Metastasis: Review of a Rare Complication With Limited Treatment Options and Poor Prognosis," *Journal of Clinical Medicine* 11, no. 14 (2022): 4165, https://doi.org/10.3390/jcm11144165.

12. C. Lin, S. Turner, H. Gurney, and A. Peduto, "Increased Detections of Leptomeningeal Presentations in Men With Hormone Refractory Prostate Cancer: An Effect of Improved Systemic Therapy?," *Journal of Medical Imaging and Radiation Oncology* 52, no. 4 (2008): 376–381, https://doi.org/10.1111/j.1440-1673.2008.01973.x.

13. A. W. Brenner and A. J. Patel, "Review of Current Principles of the Diagnosis and Management of Brain Metastases," *Frontiers in Oncology* 12 (2022), https://doi.org/10.3389/fonc.2022.857622.

14. A. Broderick, E. Pan, J. Li, et al., "Clinical Implications of Wnt Pathway Genetic Alterations in Men With Advanced Prostate Cancer," *Prostate Cancer and Prostatic Diseases* (2024), https://doi.org/10.1038/s41391-024-00869-1.

15. A. S. Achrol, R. C. Rennert, C. Anders, et al., "Brain Metastases," *Nature Reviews Disease Primers* 5, no. 1 (2019): 5, https://doi.org/10.1038/s41572-018-0055-y.

16. L. Zhao, X. Ma, and J. Yu, "Exosomes and Organ-Specific Metastasis," *Molecular Therapy—Methods & Clinical Development* 22 (2021): 133–147, https://doi.org/10.1016/j.omtm.2021.05.016.

17. K. Hudson, M. W. Mondia, Y. Zhang, et al., "The Role of microRNAs in Brain Metastasis," *Journal of Neuro-Oncology* 166, no. 2 (2024): 231–241, https://doi.org/10.1007/s11060-023-04541-x.

18. Z. W. Myint and A. H. Qasrawi, "Prostate Adenocarcinoma With Brain Metastasis: A Surveillance, Epidemiology, and End Results Database Analysis 2010–2015," *Medical Science Monitor* 27 (2021), https://doi.org/10.12659/MSM.930064.

19. H. P. Bhambhvani, D. R. Greenberg, S. Srinivas, and M. Hayden Gephart, "Prostate Cancer Brain Metastases: A Single-Institution Experience," *World Neurosurgery* 138 (2020): e445–e449, https://doi.org/10.1016/j.wneu.2020.02.152.

20. F. Zhao, J. Wang, M. Chen, et al., "Sites of Synchronous Distant Metastases and Prognosis in Prostate Cancer Patients With Bone Metastases at Initial Diagnosis: A Population-Based Study of 16,643 Patients," *Clinical and Translational Medicine* 8, no. 1 (2019): 1–11, https://doi.org/10.1186/s40169-019-0247-4.

21. C. E. Fadul, G. Sarai, J. A. Bovi, et al., "Relevance of the Updated Recursive Partitioning Analysis (U-RPA) Classification in the Contemporary Care of Patients With Brain Metastases," *Cancers* 15, no. 12 (2023): 3255, https://doi.org/10.3390/cancers15123255.

22. M. Sekhoacha, K. Riet, P. Motloung, L. Gumenku, A. Adegoke, and S. Mashele, "Prostate Cancer Review: Genetics, Diagnosis, Treatment Options, and Alternative Approaches," *Molecules* 27, no. 17 (2022): 5730, https://doi.org/10.3390/molecules27175730.

23. F. L. Giesel, H. Fiedler, M. Stefanova, et al., ""PSMA PET/CT With Glu-urea-Lys-(Ahx)-[68Ga(HBED-CC)] Versus 3D CT Volumetric Lymph Node Assessment in Recurrent Prostate Cancer," *European Journal of Nuclear Medicine and Molecular Imaging* 42, no. 12 (2015): 1794–1800, https://doi.org/10.1007/s00259-015-3106-6.

24. M. A. Vogelbaum, P. D. Brown, H. Messersmith, et al., "Treatment for Brain Metastases: ASCO-SNO-ASTROce," *Journal of Clinical Oncology* 40, no. 5 (2022): 492–516, https://doi.org/10.1200/JCO.21.02314.

25. E. W. Sankey, V. Tsvankin, M. M. Grabowski, et al., "Operative and Peri-Operative Considerations in the Management of Brain Metastasis," *Cancer Medicine* 8, no. 16 (2019): 6809–6831, https://doi.org/10.1002/cam4.2577.

26. D. T. Krist, A. Naik, C. M. Thompson, et al., "Management of Brain Metastasis. Surgical Resection Versus Stereotactic Radiotherapy: A

Meta-Analysis," *Neuro-Oncology Advances* 4, no. 1 (2022), https://doi.org/10.1093/noajnl/vdac033.

27. W. B. Pope, "Brain Metastases: Neuroimaging," in *Handbook of Clinical Neurology* (2018), 89. –112, https://doi.org/10.1016/B978-0-12-811161-1.00007-4.

28. M. M. Al-Salihi, M. S. Al-Jebur, I. D. Lozada-Martinez, M. Rahman, and S. Rahman, "Brain Metastasis From Prostate Cancer: A Review of the Literature With an Illustrative Case," *International Journal of Surgery Open* 37 (2021): 100419, https://doi.org/10.1016/j.ijso.2021.100419.

29. O. Caffo, A. Veccia, G. Fellin, et al., "Frequency of Brain Metastases From Prostate Cancer: An 18-year Single-Institution Experience," *Journal of Neuro-Oncology* 111, no. 2 (2013): 163–167, https://doi.org/10.1007/s11060-012-0994-1.

30. R. S. Prabhu, B. E. Turner, A. L. Asher, et al., "A Multi-Institutional Analysis of Presentation and Outcomes for Leptomeningeal Disease Recurrence After Surgical Resection and Radiosurgery for Brain Metastases," *Neuro-Oncology* 21, no. 8 (2019): 1049–1059, https://doi.org/10.1093/neuonc/noz049.

31. I. W. Tremont-Lukats, G. Bobustuc, G. K. Lagos, K. Lolas, A. P. Kyritsis, and V. K. Puduvalli, "Brain Metastasis From Prostate Carcinoma," *Cancer* 98, no. 2 (2003): 363–368, https://doi.org/10.1002/cncr.11522.

32. S. Mirmoeeni, A. Azari Jafari, M. Shah, F. Salemi, S. Z. Hashemi, and A. Seifi, "The Clinical, Diagnostic, Therapeutic, and Prognostic Characteristics of Brain Metastases in Prostate Cancer: A Systematic Review," *Prostate Cancer* 2022 (2022): 1–18, https://doi.org/10.1155/2022/5324600.

33. W. P. Fendler, M. Eiber, M. Beheshti, et al., "PSMA PET/CT: Joint EANM Procedure Guideline/SNMMI Procedure Standard for Prostate Cancer Imaging 2.0," *European Journal of Nuclear Medicine and Molecular Imaging* 50, no. 5 (2023): 1466–1486, https://doi.org/10.1007/s00259-022-06089-w.

34. C. Kratochwil, W. P. Fendler, M. Eiber, et al., "Joint EANM/SNMMI Procedure Guideline for the Use of 177Lu-Labeled PSMA-Targeted Radioligand-Therapy (177Lu-PSMA-RLT)," *European Journal of Nuclear Medicine and Molecular Imaging* 50, no. 9 (2023): 2830–2845, https://doi.org/10.1007/s00259-023-06255-8.

35. C. Yin, B. Ho, L. Chan, and L. Emmett, "Asymptomatic Prostate Cancer Brain Metastases on 68Ga-PSMA PET/CT," *Clinical Nuclear Medicine* 44, no. 6 (2019): e382–e384, https://doi.org/10.1097/RLU.0000000000002548.

36. M. I. Ross, N. Bird, I. A. Mendichovszky, and Y. L. Rimmer, "Neurologically Asymptomatic Cerebral Oligometastatic Prostate Carcinoma Metastasis Identified on [Ga]Ga-THP-PSMA PET/CT," *EJNMMI Research* 10, no. 1 (2020): 108, https://doi.org/10.1186/s13550-020-00696-0.

37. H. S. Nellaiappan, V. Rajaraman, D. Halanaik, and R. Ananthakrrishnan, "Incidental Detection of Asymptomatic Brain Metastases Due to Carcinoma Prostate in GA-68 PSMA HBED-CC Positron Emission Tomography-Computed Tomography: Reiterating Its Superiority in Assessing Disease Status," *Indian Journal of Nuclear Medicine* 37, no. 1 (2022): 99–100, https://doi.org/10.4103/ijnm.ijnm_100_21.

38. C. E. Erasmus, W. I. M. Verhagen, C. A. P. Wauters, and E. J. Lindert, "Brain Metastasis From Prostate Small Cell Carcinoma: Not to Be Neglected," *Canadian Journal of Neurological Sciences/Journal Canadien des Sciences Neurologiques* 29, no. 4 (2002): 375–377, https://doi.org/10.1017/S0317167100002250.

39. I. E. McCutcheon, D. Y. Eng, and C. J. Logothetis, "Brain Metastasis From Prostate Carcinoma," *Cancer* 86, no. 11 (1999): 2301–2311, https://doi.org/10.1002/(SICI)1097-0142(19991201)86:11<2301::AID-CNCR18>3.0.CO;2-D.

40. A. Sella, M. Konichezky, D. Flex, A. Sulkes, and J. Baniel, "Low PSA Metastatic Androgen-Independent Prostate Cancer," *European Urology* 38, no. 3 (2000): 250–254, https://doi.org/10.1159/000020289.

41. V. Conteduca, C. Oromendia, K. W. Eng, et al., "Clinical Features of Neuroendocrine Prostate Cancer," *European Journal of Cancer* 121 (2019): 7–18, https://doi.org/10.1016/j.ejca.2019.08.011.

42. D. K. Lee, J. H. Park, J. H. Kim, et al., "Progression of Prostate Cancer Despite an Extremely Low Serum Level of Prostate-Specific Antigen," *Korean Journal of Urology* 51, no. 5 (2010): 358, https://doi.org/10.4111/kju.2010.51.5.358.

43. A. Rodriguez-Calero, J. Gallon, D. Akhoundova, et al., "Alterations in Homologous Recombination Repair Genes in Prostate Cancer Brain Metastases," *Nature Communications* 13, no. 1 (2022): 2400, https://doi.org/10.1038/s41467-022-30003-5.

44. F. Khani, W. F. Hooper, X. Wang, et al., "Evolution of Structural Rearrangements in Prostate Cancer Intracranial Metastases," *npj Precision Oncology* 7, no. 1 (2023): 91, https://doi.org/10.1038/s41698-023-00435-3.

45. T. Jamaspishvili, D. M. Berman, A. E. Ross, et al., "Clinical Implications of PTEN Loss in Prostate Cancer," *Nature Reviews Urology* 15, no. 4 (2018): 222–234, https://doi.org/10.1038/nrurol.2018.9.

46. L. B. Guedes, E. S. Antonarakis, M. T. Schweizer, et al., "MSH2 Loss in Primary Prostate Cancer," *Clinical Cancer Research* 23, no. 22 (2017): 6863–6874, https://doi.org/10.1158/1078-0432.CCR-17-0955.

47. H. Beltran, D. S. Rickman, K. Park, et al., "Molecular Characterization of Neuroendocrine Prostate Cancer and Identification of New Drug Targets," *Cancer Discovery* 1, no. 6 (2011): 487–495, https://doi.org/10.1158/2159-8290.CD-11-0130.

48. A. Holzgreve, A. Biczok, V. C. Ruf, et al., "PSMA Expression in Glioblastoma as a Basis for Theranostic Approaches: A Retrospective, Correlational Panel Study Including Immunohistochemistry, Clinical Parameters and PET Imaging," *Frontiers in Oncology* 11, no. March (2021): 1–11, https://doi.org/10.3389/fonc.2021.646387.

49. S. A. M. van Lith, I. J. Pruis, N. Tolboom, et al., "PET Imaging and Protein Expression of Prostate-Specific Membrane Antigen in Glioblastoma: A Multicenter Inventory Study," *Journal of Nuclear Medicine* 64, no. 10 (2023): 1526–1531, https://doi.org/10.2967/jnumed.123.265738.

50. M. O. Awiwi, M. Gjoni, R. Vikram, et al., "MRI and PSMA PET/CT of Biochemical Recurrence of Prostate Cancer," *Radiographics* 43, no. 12 (2023): 5–10, https://doi.org/10.1148/rg.230112.

51. I. J. Pruis, P. J. van Doormaal, R. K. Balvers, et al., "Potential of PSMA-Targeting Radioligand Therapy for Malignant Primary and Secondary Brain Tumours Using Super-Selective Intra-Arterial Administration: A Single Centre, Open Label, Non-Randomised Prospective Imaging Study," *EBioMedicine* 102 (2024): 105068, https://doi.org/10.1016/j.ebiom.2024.105068.

52. R. Rathore, S. B. Rangrej, I. Kieme, et al., "Treatment of Advanced Metastatic Prostate Cancer Using Molecular-Targeted Therapy: Radioligand Lutetium-177 Prostate-Specific Membrane Antigen," *Cureus* 15, no. 4 (2023), https://doi.org/10.7759/cureus.37778.

53. P. Backhaus, B. Noto, N. Avramovic, et al., "Targeting PSMA by Radioligands in Non-Prostate Disease—Current Status and Future Perspectives," *European Journal of Nuclear Medicine and Molecular Imaging* 45, no. 5 (2018): 860–877, https://doi.org/10.1007/s00259-017-3922-y.

54. F. de Galiza Barbosa, M. A. Queiroz, R. F. Nunes, et al., "Nonprostatic Diseases on PSMA PET Imaging: A Spectrum of Benign and Malignant Findings," *Cancer Imaging* 20, no. 1 (2020): 23, https://doi.org/10.1186/s40644-020-00300-7.

55. Q.-F. Ma, C.-Y. Ou, Q.-H. Wang, and Y.-N. Wang, "Incidental Finding of Metastatic Prostatic Adenocarcinoma of Cerebellopontine Angle Presenting as Acoustic Neuroma: A Case Report and Review of Literature," *International Journal of Surgery Case Reports* 98, no. July (2022): 107493, https://doi.org/10.1016/j.ijscr.2022.107493.