

What to Trust, PSA or [⁶⁸Ga]Ga-PSMA-11: Learn from Experience

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Abstract: Brain metastases from prostate cancer typically occur in the more advanced stages of the disease. Clinically, the early diagnosis of visceral disease is crucial, impacting on patient's management and prognosis. Although magnetic resonance imaging (MRI) is the modality of choice for the detection of brain metastases, it is not routinely performed in the surveillance of prostate cancer patients unless neurological manifestations appear. Prostate-specific membrane antigen (PSMA) is a glycoprotein, a membrane-bound metalloproteinase, overexpressed in more than 90% of prostate cancer cells. This molecular target is a suitable tissue biomarker for prostate cancer functional imaging. We present a case of a 73-year gentleman diagnosed with prostate adenocarcinoma and surgically treated (pT3bN1Mx, Gleason Score of 9) in February 2016. Subsequently, he underwent androgen deprivation therapy because of the occurrence of a bone metastasis. Between 2016 and January 2019 PSA levels were maintained under control. Starting from September 2019, it progressively raised up to 0.85 ng/mL with a doubling time of 3.3 months. Therefore, he performed a [⁶⁸Ga]Ga-PSMA-11 PET/CT which showed a focal radiopharmaceutical uptake in the right temporal lobe corresponding to the presence of a rounded cystic lesion on brain MRI. The subsequent excisional biopsy diagnosed a prostate adenocarcinoma metastasis. PSMA expression has been reported in brain parenchyma after ischemic strokes and in some brain tumors including gliomas, meningiomas, and neurofibromas. In our case, the lack of symptoms and the relatively low PSA level raised questions about the nature of the lesion, posing the differential diagnosis between brain metastases and primary brain tumor. Finally, our case shows the capability of [⁶⁸Ga]Ga-PSMA-11 PET/CT to detect metachronous distant brain metastases in a low biochemical recurrent asymptomatic prostate cancer patient, indicating that proper acquisition – from the vertex to thigh – should be always considered, regardless of the PSA level.

Keywords: [⁶⁸Ga]Ga-PSMA-11 PET/CT, biochemical recurrence, brain metastases, multimodal imaging, prostate cancer, PSA

Background

Prostate cancer (PCa) is prone to metastasize. Metastases to bones and lymph nodes have been long recognized as the most typical pattern of extra-prostatic tumor spread. Visceral metastases affect mainly patients with advanced castration resistance (CR) disease, typically involving lung, liver, and adrenals.^{1,2} Brain metastases are rare (<2%),³ and they are typically associated with extracranial metastases in the more advanced stages of the disease (generally when the life expectancy is less than one year).⁴ The most common neurological manifestations of brain metastases from prostate cancer are non-focal neurologic symptoms related to the intracranial

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hypertension.⁵ In some cases, patient do not complain any symptoms.⁶ Commonly brain metastases occur in the frontal lobes (86% of patients).^{5,7} Prostate-specific membrane antigen (PSMA) is a glycoprotein, a membrane-bound metallo-peptidase, that is overexpressed in over 90% of PCa cells. This molecular target is a suitable tissue biomarker for PCa functional imaging.⁸ PSMA expression levels progressively increase along with tumor grade and stage, as well as aneuploidy and biochemical recurrent disease. Higher levels of PSMA expression are associated with poorer outcomes and PSMA expression is upregulated when the castrate-resistant phenotype evolves.^{9,10} [⁶⁸Ga]Ga-PSMA-11 PET/CT provides the ability to identify and localize prostate cancer cells which overexpressed the target, impacting on patient management.¹¹

Case Presentation

Here, we present a case of a 73-year gentleman diagnosed with prostate adenocarcinoma in February 2016. Baseline serum prostate specific antigen level (PSA) was 9.6 ng/mL. He underwent a robot-assisted laparoscopic radical prostatectomy completed with a bilateral lymphadenectomy. After surgery PSA fall to 0.01 ng/mL. According to the AJCC 8th edition, the PCa was staged as IVA (T3bN1Mx) with a Gleason Score of 9 (4+5). He underwent a [^{99m}Tc]Tc-MDP bone scintigraphy which showed a bone metastasis in the sacrum. This finding led to upstage the disease from a stage IVA to a IVB (T3bN1M1b), and he started androgen deprivation therapy (ADT). Between 2016 and January 2019 PSA levels were maintained under control, resulting around 0.01 ng/mL. From September 2019, PSA progressively raised from 0.02 ng/mL up to 0.85 ng/mL in July 2020. The PSA doubling time was of 3.3 months (<https://www.mskcc.org>) (Figure 1). The patients were referred to our center to perform a [⁶⁸Ga]Ga-PSMA-11 PET/CT. Images – from vertex to mid-thigh – were acquired 60 minutes after the i. v. administration of 185 MBq of [⁶⁸Ga]Ga-PSMA-11, with a Discovery 710 PET/CT (GE Healthcare Milwaukee, Wisconsin, USA), according to the EANM guidelines.^{12,13} Visual and semiquantitative analysis was performed according to the EANM standardized reporting guidelines v1.0 for PSMA-PET.¹⁴ Images showed increased radiopharmaceutical uptake (score of 2/3) in the right temporal lobe (Figure 2), in a left common iliac lymph node, and in a right external iliac lymph node. The report concluded for miT0, miN1 and suspected – but not definite – CNS miM. At the time of PET/CT, the patient

did not experience any neurological symptoms. A brain MRI, requested to characterize the suspected lesion confirmed the presence of a right temporal rounded cystic lesion (42x33x31 mm) which appeared hypointense in T1 and hyperintense in T2, with an inferior and lateral solid part (20 mm of maximum diameter) (Figure 2C–F(i)).^{6,15,16} The patient underwent an excisional biopsy of the brain lesion which documented a prostate adenocarcinoma metastasis with high expression of PSA, PAP, ERG e pan-CK (Figure 2G–J).

After the excisional biopsy, PSA decreased to 0.05 ng/mL. Follow-up brain MRI excluded residual disease (Figure 2D(ii)–F(ii)). Accordingly, the patient was defined as oligometastatic and treated with external beam radiation therapy (EBRT) on pelvic nodal metastases.

Discussions

We report the case in which [⁶⁸Ga]Ga-PSMA-11 PET/CT identified a suspected brain lesion in an asymptomatic patient with biochemical recurrence from PCa and relative low PSA level (0.85 ng/mL). The lesion was confirmed to be a brain metastasis from prostate cancer. The [⁶⁸Ga]Ga-PSMA-11 PET/CT EANM Guidelines recommend to acquire images from the base of the skull to the mid-thigh, possibly extending the coverage to the skull and/or the entire lower extremity in presence of symptoms or disseminated disease.¹³ Our patient was completely asymptomatic, and the level of PSA did not support the hypothesis of a disseminated disease. However, if we did not include the skull in the field of view, the patient would be misdiagnosed and the diagnosis of brain metastases would be delayed until symptoms appear, possibly resulting in an unfavorable outcome. Indeed, although post-hoc studies of enzalutamide trials in the pre- and post-chemotherapy mCRPC setting demonstrate a certain degree of response, PCa patients with visceral metastases invariably have a worse prognosis than patients with bone-only metastases, and the unfavorable outcome related to visceral metastases is shown also in the oligometastatic subgroup.^{17–20} PSMA imaging is recommended – for its proved ability to positively influence the subsequent treatment strategy – by the European Association of Urology (EAU) guidelines on PCa for any case of biochemical recurrence after radical prostatectomy (PSA > 0.2mg/mL), as in the case of our patient. Indeed, in this clinical setting, PSMA-PET has proved to outperform other radio-tracers, such as choline or fluciclovine.^{21,22} However, despite the PSMA expression is predominant in PCa, it is

not specific and can be found in other benign conditions and malignant tissues, especially in tumor-associated endothelial cells in neovasculature.^{23,24} In particular, PSMA overexpression has been reported in brain parenchyma after ischemic strokes and in some brain tumors such as gliomas, meningiomas, paragangliomas and neurofibromas.^{25,26} As mentioned above, brain metastases from prostate cancer are rare, and typically occurred in the more advanced stages of the disease, in the context of a disseminated systemic symptomatic disease.^{3,4,27} Early diagnosis of visceral disease – and particularly brain parenchymal involvement – is crucial, possibly positively impacting on patient's management and prognosis.²⁸

MRI is the modality of choice for the detection of brain metastases. However, it is not routinely performed in the surveillance of PCa patients unless neurological manifestations appear.¹⁶ Intracranial metastases originating from prostate cancer may variably manifest, and can appear as hemorrhagic lesions (as in the case of metastases from melanoma, renal cell carcinoma, breast and thyroid cancer) or non-hemorrhagic lesions. On contrast-enhanced

MRI, intracranial metastases from prostate cancer appear as well-defined lesions, surrounded by edema with an enhancement pattern that varies from purely solid to ring-like and from mixed cystic to solid.⁶ In our patient, MRI showed a mixed cystic intracranial non-hemorrhagic lesion (Figure 2).

In our case, the lack of symptoms and the relatively low PSA level (0.85 ng/mL at the time of PET/CT), raised questions about the nature of the lesion, posing the differential diagnosis between a brain metastases and a primary brain tumor. Indeed, literature shows that brain PCa metastases typically occur in patients suffering from advanced PCa with markedly elevated PSA values.^{6,29,30} In our patient multimodal [⁶⁸Ga]Ga-PSMA-11 PET/CT together with brain MRI findings were suggestive of brain metastases, anticipating any neurological symptoms eventually impacting on the natural history of the disease. The subsequent surgical treatment determined a biochemical drop in PSA level. Taking advantages of the experience gained in this case, we underline the importance of appropriate imaging acquisition protocols covering the whole-body

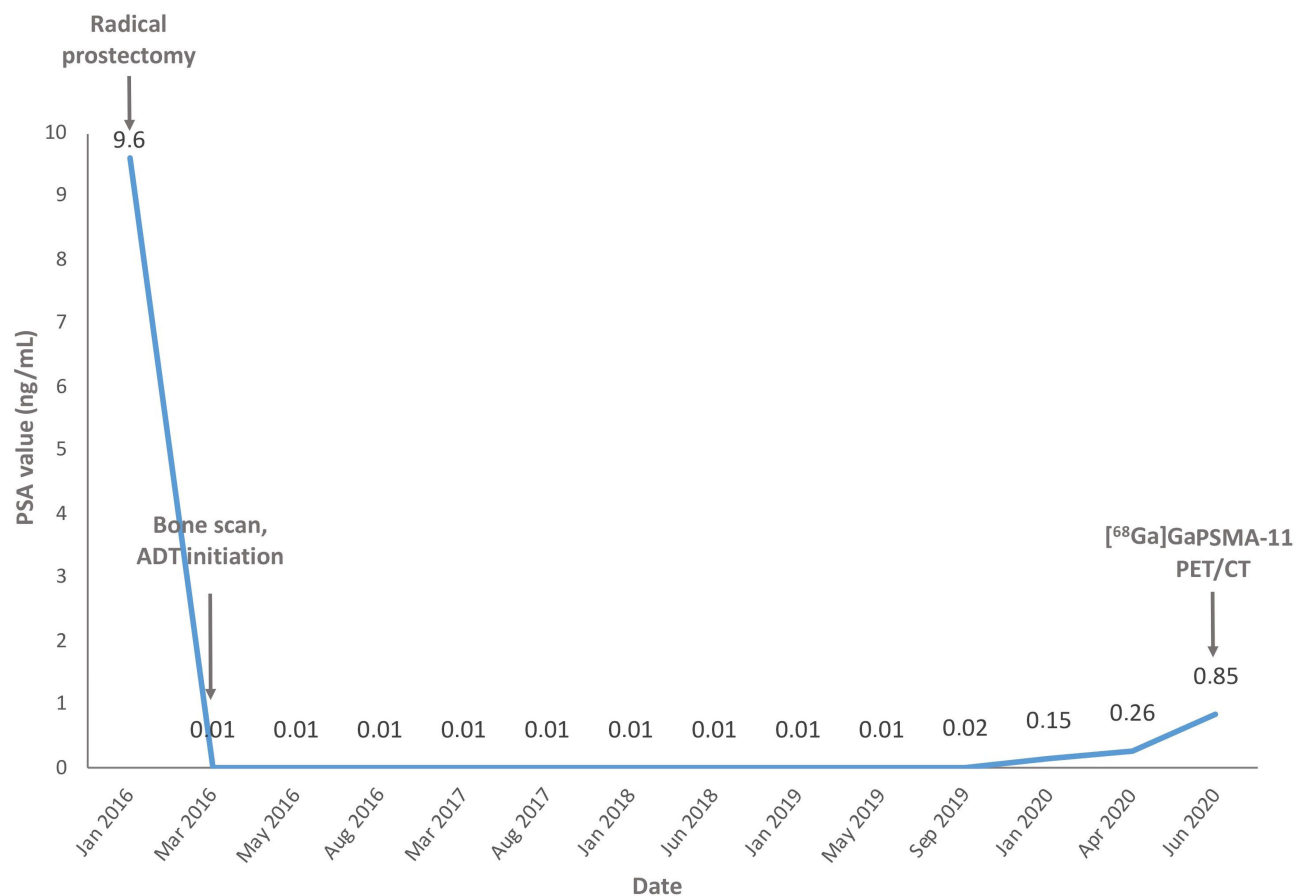


Figure 1 Timeline with main clinical events and patient's PSA variation from January 2016 to June 2020.

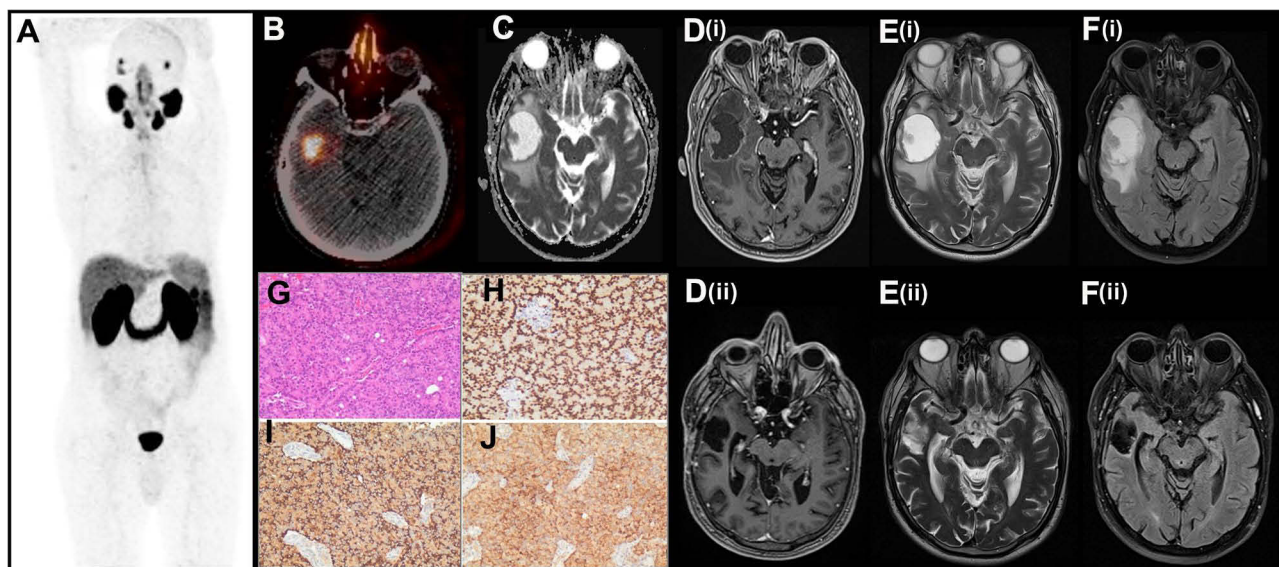


Figure 2 [^{68}Ga]Ga-PSMA-11 PET/CT and MRI findings in the patients showing heterogeneous mass in the right temporal region with central cystic components and peripheral solid components surrounded by peri-lesional edema finally diagnosed as intracranial metastasis due to prostate cancer. (A) [^{68}Ga]Ga-PSMA-11 PET/CT MIP image from vertex to upper thigh; (B) trans-axial PET/CT superimposed image showing increased radiopharmaceutical uptake at the right temporal lobe, further confirmed by MRI study; (C) trans-axial ADC map; (D(i), D(ii)) trans-axial contrast-enhanced T1-weighted images; (E(i), E(ii)) trans-axial T2-weighted images; (F(i), F(ii)) trans-axial FLAIR images; (G–J) At histopathological level, the tumor cells presented with rounded nuclei with small nucleoli, forming acinar structures (G), and expressed ERG (nuclear staining) (H), PAP (I) e PSA (J).

(from the top of the head to the thigh), and highlight the noteworthiness to evaluate brain parenchyma even in the low PSA cases avoiding misregistration due to movements artifacts. Such lesson on [^{68}Ga]Ga-PSMA-11 along with the proper education on its strengths and pitfalls is timely and necessary, given the promise for successfully treated mCRPC patients with radioligand therapy.³¹ Effective treatment options for PCa patients suffering from visceral metastases, are among the new therapeutic challenges in PCa for both survival length and quality of life.

Conclusion

Our case shows the capability of [^{68}Ga]Ga-PSMA-11 PET/CT to detect metachronous distant brain metastases in low biochemical recurrent asymptomatic PCa patient. Acquisition from the vertex to thigh, to include the evaluation to the whole brain parenchyma in the field of view, should be considered regardless of the PSA level.

Institutional Approval

The patient was studied within a clinical trial (EudraCT number: 2018-004458-14) approved by AIFA and the Comitato Etico Regione Toscana Area Vasta Nord Ovest. In addition, the patient provided a specific written informed consent for the utilization of both case details and imaging data here presented within this specific

publication; however, no further specific institutional board approved was requested.

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