Title

Imaging Prostate Cancer With Prostate-Specific Membrane Antigen PET/CT and PET/MRI: Current and Future Applications.

Journal

AJR. American journal of roentgenology, 211(2)

ISSN

0361-803X

Authors

Hope, Thomas A
Afshar-Oromieh, Ali
Eiber, Matthias
et al.

Publication Date

2018-08-01

DOI

10.2214/ajr.18.19957

Peer reviewed

HHS Public Access

Author manuscript

AJR Am J Roentgenol. Author manuscript; available in PMC 2020 February 05.

Published in final edited form as:

AJR Am J Roentgenol. 2018 August ; 211(2): 286–294. doi:10.2214/AJR.18.19957.

Imaging prostate cancer with PSMA PET/CT and PET/MRI: current and future applications

Thomas A. Hope, MD[1,2,3], **Ali Afshar-Oromieh, MD**[4,5], **Matthias Eiber, MD**[6], **Louise Emmett, MD**[7,8,9], **Wolfgang P. Fendler, MD**[10], **Courtney Lawhn-Heath, MD**[1], **Steven P. Rowe, MD PhD**[11]

[1]Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA [2]Department of Radiology, San Francisco VA Medical Center, San Francisco, CA [3]UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA [4]Department of Nuclear Medicine, Bern University Hospital, Bern, Switzerland [5]Department of Nuclear Medicine, Heidelberg University Hospital, Heidelberg, Germany [6]Department of Nuclear Medicine, Klinikum Rechts der Isar, Technical University of Munich, Germany [7]Department of Diagnostic Imaging, St. Vincent's Public Hospital, Sydney, Australia [8]The Garvan Institute of Medical Research/The Kinghorn Cancer Centre, Sydney, Australia [9]University of New South Wales (UNSW), Sydney, New South Wales, Australia [10]Klinik für Nuklearmedizin, Universitätsklinikum Essen, Germany [11]The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD

Abstract

PSMA PET is a highly promising modality for staging prostate cancer patients due to its higher detection rate compared to conventional imaging. Both PET/CT and PET/MRI offer benefits with PSMA radiotracers and PSMA PET leads to frequent changes in management. It is imperative we test subsequent treatment changes to show improved outcomes. Additionally, PSMA PET has potential applications including patient selection for PSMA based radioligand therapy and evaluation of treatment response.

Introduction

Prostate cancer (PC) is the most common malignancy in men and is the third most common cause of cancer related death in the United States (1). Staging in various clinical contexts of prostate cancer, such as in the preoperative setting and in biochemical recurrence, has been limited due to the low detection sensitivity of bone scans, MRI, and CT. Numerous radiotracers targeted to biological processes that are upregulated in prostate cancer have been evaluated over the years including ^{11}C-choline, ^{18}F-fluorocholine, ^{11}C-acetate, and ^{18}F-fluciclovine, but it was the development of small molecule radiotracers that target the prostate-specific membrane antigen (PSMA) that is leading to a change in practice of the

Corresponding Author: Thomas A. Hope, MD, 505 Parnassus Avenue – 0628, Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA 94143-0628, Phone: (415) 353-1905, thomas.hope@ucsf.edu.

management of patients with prostate cancer. Early studies demonstrated the superiority of PSMA-based PET over choline biochemical recurrence patients, particularly those with low PSAs (2,3), and since the publication of those studies, PSMA PET is quickly becoming a preferred imaging modality outside of the United States for staging prostate cancer.

PSMA radiotracers

The majority of PSMA targeted radiotracers utilize a highly negatively charged, urea-based backbone that binds to the PSMA active site; these compounds were initially developed as inhibitors intended for use in the brain (4–7). These small molecules have significant benefit over prior antibody approaches as they rapidly accumulate in PSMA expressing tissue and are cleared quickly from the blood pool. This family of compounds includes SPECT and PET agents such as ^{99m}Tc-MIP-1404, ^{18}F-DCFBC, ^{18}F-DCFPyL, ^{68}Ga-PSMA-11 (previously termed ^{68}Ga-PSMA HBED-CC) and ^{18}F-PSMA-1007 (8–12). Other classes of small molecules that have been developed to target PSMA include the phosphoramidate scaffolds that bind irreversibly to the enzyme (currently undergoing first in human studies (13) and the phosphonomethyl-based compounds for which the prototype first-in-human compound is BAY 1075553 (14). Overall, it is not clear if there is a clinically significant benefit between individual small molecule radiotracers, and in the context of this review they will be discussed as a class. The EANM/SNMMI guidelines on PSMA PET imaging, provide a thorough overview on how to perform 68Ga-PSMA-11 PET {Fendler:2017ip}.

Notes on interpretation

This manuscript will not provide an exhaustive review of guidelines for interpretation, as many other reports are available for review (15). One thing to note is that PSMA is in fact not specific to prostate cancer. There are a number of false positives that readers need to be aware of, including both malignant (renal cell carcinoma, thyroid cancer and hepatocellular carcinoma etc) and benign lesions (Paget’s disease, hemangiomas, fibrous dysplasia etc) (16,17). When interpretating images, clinical context, prior imaging studies and characteristics on conventional imaging need to be considered when characterizing PSMA avid lesions. In particular ureteral activity needs to be considered when evaluating pelvic uptake, as urine activity can be misinterpreted as nodal disease (Figure 3).

Reporting recommendations

Three reporting guidelines were proposed in the past year to guide interpretation of PSMA PET studies. The first of these reporting systems is unnamed and used a Delphi consensus process to develop a standardized interpretation method (18). This approach divides up the body into five regions (local site, local lymph nodes, skeletal, distant lymph nodes and other), which are then subdivided depending on the region. Regions of uptake on PSMA PET are then further characterized as anomalous or pathologic. This approach was intentionally developed to minimize inter-reader variability in interpretation of PSMA PET.

The second approach is the PSMA-RADS approach, which parallels a number of previously described organ-based reporting and data systems (19). Lesions are graded from PSMA-RADS-1 for benign uptake to PSMA-RADS-5 to represent lesions that are almost certainly

malignant, with follow-up recommendations for those lesions that are indeterminate. The PSMA-RADS system is most tailored to characterize individual extraprostatic lesions seen on PSMA PET and does not address primary disease within the gland.

The third is the PROMISE system, which approaches PSMA interpretation within the framework of a TNM-based reporting metric (20). Uptake is categorized based on avidity compared to the blood pool, liver, and parotid glands. Nodes are categorized by nodal regions and distant metastases are categorized by extrapelvic nodes (a), bones (b) and other sites (c). The PROMISE system is the most thoroughly detailed, and consequently the most complex, of the proposed standardization frameworks.

As we move forward, the approach or combination of approaches that will be adopted is not yet clear and will likely depend on the clinical role of the imaging study (selecting patients for radioligand therapy in castration resistant prostate cancer (CRPC) patients versus selecting patients for targeted external beam radiation therapy in castration sensitive patients). In settings where characterization of lesions is paramount, such as patients undergoing initial staging, the PSMA-RADS approach may be most useful, while in settings where more extensive disease is present or a detailed description of lesions is of benefit (such as in large clinical trials), it is likely that the PROMISE or Delphi consensus approaches may be most appropriate.

Clinical applications

Initial Staging

There are two main settings in which imaging is used at the time of diagnosis of prostate cancer. The first is in evaluation of the prostate gland itself, and this is currently the domain of multi-parametric MRI. Specific indications include determining whether or not a patient has clinically significant prostate cancer in patients on active surveillance and to improve the yield of transrectal ultrasound-guided biopsies for clinically significant disease in patients with prior negative biopsy or who have elevated serum prostate specific antigen (PSA) levels (21,22). To date, there is limited literature in regards to the role of PSMA PET in the active surveillance or secondary screening settings as previously reported studies have focused on patients with known prostate cancer who are being preoperatively staged prior to undergoing prostatectomy. Nonetheless, PSMA PET may be beneficial as it is not expressed in benign prostatic hypertrophy and it may have additive value for primary prostate cancer detection when combined with multi-parametric MRI (23).

The second clinical setting is the intermediate to high risk patients who are considering treatment with definitive therapy, either prostatectomy or radiation therapy. In these patients, the characterization of the primary tumor is no longer relevant, and the central issue is detecting nodal metastases prior to treatment, especially as prostatectomies are being performed in increasingly higher risk patients (24,25). The largest study to date in this population is a retrospective evaluation of 131 patients imaged with ^{68}Ga-PSMA-11 PET who subsequently underwent prostatectomy (26); in this population, PSMA PET detected 68% of regional nodal metastases with a specificity of 99.1% (Figure 1). Although not reported frequently in the literature, PSMA PET may be most helpful in detecting distant

metastases outside of the nodal field that may indicate that regional therapy would be futile (Figure 2).

Biochemical Recurrence

Up to 30% of patients treated with definitive therapy develop recurrence, and the ability of PSA to indicate the presence of early recurrence after definitive therapy and prior to the development of visualized local recurrence or metastatic disease creates a conundrum for clinicians (27). After prostatectomy, the American Urologic Association defines biochemical recurrence as two consecutive PSA levels greater than 0.2 ng/mL six to eight weeks after surgery (28). After radiation therapy, the ASTRO-Phoenix guidelines define recurrence as a rise in PSA of greater than 2.0 ng/mL over the post-treatment nadir (29). Many treatments, such as salvage radiation, assume that recurrence is local; otherwise, treating clinicians may administer systemic therapy as the site of recurrence is unknown. Detecting locally recurrent disease or establishing that a patient is oligometastatic is the most common indications for performing PSMA PET.

In change in management papers, a large portion of patients imaged are converted from systemic therapies or active surveillance to targeted treatments that include radiation therapy (30,31). The current issue with this approach is that there is no evidence that demonstrates that targeting PSMA avid lesions in patients with low PSA recurrence improves patient outcomes. Our initial assumptions on how to treat patients based on PSMA PET may be misguided. For example, it is often assumed that patients with BCR after prostatectomy who have negative PSMA PETs should not be treated. In one series of patients, 85% of patients treated with prostate bed radiation after a negative PSMA PET had a PSA drop, while 65% of patients who did not receive radiation had continued increases in their PSA (32). It is imperative that we design trials to evaluate our changes in management that result from PSMA PET imaging.

The majority of the literature in the use of PSMA PET in biochemical recurrence patients is with ^{68}Ga-PSMA-11, and the benefit in detection sensitivity is seen primarily in patients with low PSAs whom many believe may potentially be curable with external beam radiation therapy targeted to the prostate bed or stereotactic body radiation therapy to a limited number of sites of more distant disease. In these patients, the detection sensitivity of PSMA PET is dependent on the PSA at the time of imaging, with detection sensitivities (on the patient level) in the range of 50–60% when the PSA is as low as 0.2 to 0.5 ng/mL (33,34) (Figures 3 and 4).

PET/CT versus PET/MRI

The majority of the literature published using PSMA PET uses PET/CT, but there is a significant interest in understanding the role of PET/MRI for PSMA PET. PET/MRI has potential added value for characterizing primary tumors, as stand-alone multi-parametric MRI is the current conventional imaging modality for detecting clinical significant cancer in the prostate, particularly due to the strength of diffusion weighted imaging (Figure 1). PSMA appears to have a slight increase in detection sensitivity compared to multi-parametric MRI for primary disease, and it is possible that the combination has improved

sensitivities compared to either modality (23). All the literature to date in primary tumor characterization is in patients with intermediate to high risk disease, which is not the patient population where increased detection sensitivity is required. Therefore, further work in the active surveillance population is required.

Another added benefit of PET/MRI is the increased PET acquisition time that is possible due to the concurrent MRI sequences that are typically time limiting, which can result in increased rates of nodal detection (35), which is beneficial in both the initial staging setting as well as the biochemical recurrence setting. In particular dynamic contrast enhanced MRI is beneficial in detecting local recurrences (36), and the ability to combine multiparametric MRI with PSMA PET is likely helpful for detection of local recurrence (Figure 5).

The combined role of diffusion weighted imaging (DWI) and PSMA PET in the setting of PET/MRI has not yet been fully evaluated. Characterization of tumors using PSMA Pet is difficult to do, particularly in CRPC patients, as the relative uptake of PSMA is often effect more by the percentage of viable cells remaining rather than the receptor density on each cell. For example, determining whether or not a patient has a neuroendocrine variant or conventional prostate adenocarcinoma may become important in terms of therapeutic selection (13). One might hypothesize that PSMA uptake may be able to distinguish between the two cancer types, but this uptake will be strongly influenced by the percent of viable cells (15, 16). This is a setting where DWI can be used as a marker of cell density and therefore aid in tumor characterization (Figure 6).

Future applications

Patient Selection for Radioligand Therapy

Theranostics describes the use of the same compound for both therapy and imaging, and although recently popularized has been around since the use of iodine ablation treatments for thyroid cancer. The NETTER-1 trial and the recent approval of ^{177}Lu-DOTATATE for the treatment of somatostatin-receptor-expressing tumors has increased the excitement surrounding radioligand therapy (RLT), and particularly PSMA-targeted RLT in prostate cancer (37). After the publication of multiple retrospective studies out of Europe, the first prospective Phase II study evaluating ^{177}Lu-PSMA-617 out of Australia demonstrated a 50% drop in PSA in half of treated patients with progression free survival and overall survival of 6.3 and 12.7 months, respectively (38). The role of patient selection for PSMA RLT using PSMA PET will have to be understood, and the role of FDG PET in additional to PSMA PET for characterization of metastases will need to be evaluated. There are clear mismatches between PSMA and FDG PET which have important treatment implications for patients with CRPC (Figure 7) (38).

Response Biomarker

Determining clinical and radiographic response in prostate cancer is difficult. First, bone lesions cannot be measured by RECIST and bone scans frequently have flare response or persistent uptake in the setting of responded lesions (39). Second, nodal lesions are often too small to measure using RECIST, and, given their small size, it can be difficult to determine

which nodes should be selected as true positives. Third, although PSA appears to be a perfect biomarker that is easily measured, its expression is regulated by the androgen receptor (AR) and so using PSA as a response biomarker while a patient is on AR targeted therapies is limited.

PSMA PET also can be influenced by AR activity (40), but could overcome the limitations of osseous and nodal disease characterization. It has yet to be evaluated and validated as a response biomarker in trials, but should be considered as a potential option moving forward. If PSMA PET becomes a standard imaging modality for staging patients with biochemical recurrence, it would be the preferred modality for a response marker instead of switching between radiotracers between treatments moving forward. In the setting of PSMA RLT, PSMA PET appears to function well as a response biomarker, although it is unclear what the added benefit over PSA is in terms of determining response as PSMA RLT is currently performed in the absence of AR targeted therapies that can decrease PSAs (Figure 8). We look forward to further research that demonstrates the role of PSMA PET as a potential response biomarker.

Path towards approval

In the United States there are two agents that are currently being studied in registration trials aimed at obtaining approval from the FDA: ^{18}F-DCFPyL and ^{68}Ga-PSMA-11. DCFPyL is being developed by a company and has the potential benefits that fluorinated compounds can be made in larger quantities and are more easily distributed as a result of a longer half-life (109 minutes compared to 68 minutes of ^{68}Ga). In order for PSMA PET to reach all centers in the United States, corporate distribution and insurance reimbursement is required. The path for ^{68}Ga-PSMA-11 currently depends on academic centers taking the agent to market, yet this agent has been studied in the literature more extensively due to its ease of synthesis and lack of patent protection. Although ^{68}Ga is currently dependent on generator availability with low elution quantities, the development of cyclotron produced gallium promises to change this equation and a gallium distribution network has recently been put into place for ^{68}Ga-DOTATATE for neuroendocrine tumors, which could theoretically be leveraged for ^{68}Ga-PSMA-11 (41).

Conclusion

PSMA PET is becoming a central tool in staging patients with prostate cancer. There are a large number of radiotracers that are currently being evaluated, some of which are on a path towards approval in the United States. Independent of which radiotracer becomes widely available, understanding how this new class of imaging agents should appropriately impact management decisions in patients with prostate cancer, particularly at time of initial staging and biochemical recurrence, will be critical. Additionally evaluating the use in new settings such as patient selection for radioligand therapy and as a marker of treatment response will become more important.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. American Cancer Society; 2017 1;67(1):7–30.
2. Morigi JJ, Stricker PD, van Leeuwen PJ, Tang R, Ho B, Nguyen Q, et al. Prospective Comparison of 18F-Fluoromethylcholine Versus 68Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. J Nucl Med. 2015 8;56(8):1185–90. [PubMed: 26112024]
3. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2014 1;41(1):11–20. [PubMed: 24072344]
4. Pomper MG, Musachio JL, Zhang J, Scheffel U, Zhou Y, Hilton J, et al. 11C-MCG: synthesis, uptake selectivity, and primate PET of a probe for glutamate carboxypeptidase II (NAALADase). Mol Imaging. 2002 4;1(2):96–101. [PubMed: 12920850]
5. Kozikowski AP, Nan F, Conti P, Zhang J, Ramadan E, Bzdega T, et al. Design of remarkably simple, yet potent urea-based inhibitors of glutamate carboxypeptidase II (NAALADase). J Med Chem. 2001 2 1;44(3):298–301. [PubMed: 11462970]
6. Banerjee SR, Foss CA, Castanares M, Mease RC, Byun Y, Fox JJ, et al. Synthesis and evaluation of technetium-99m- and rhenium-labeled inhibitors of the prostate-specific membrane antigen (PSMA). J Med Chem. 2008 8 14;51(15):4504–17. [PubMed: 18637669]
7. Kozikowski AP, Zhang J, Nan F, Petukhov PA, Grajkowska E, Wroblewski JT, et al. Synthesis of urea-based inhibitors as active site probes of glutamate carboxypeptidase II: efficacy as analgesic agents. J Med Chem. 2004 3 25;47(7):1729–38. [PubMed: 15027864]
8. Hillier SM, Maresca KP, Lu G, Merkin RD, Marquis JC, Zimmerman CN, et al. 99mTc-Labeled Small-Molecule Inhibitors of Prostate-Specific Membrane Antigen for Molecular Imaging of Prostate Cancer. J Nucl Med. 2013 6 3;54(8):1369–76. [PubMed: 23733925]
9. Cho SY, Gage KL, Mease RC, Senthamizhchelvan S, Holt DP, Jeffrey-Kwanisai A, et al. Biodistribution, tumor detection, and radiation dosimetry of 18F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. J Nucl Med. 2012 12;53(12):1883–91. [PubMed: 23203246]
10. Gorin MA, Rowe SP, Patel HD, Vidal I, Mana-Ay M, Javadi MS, et al. Prostate Specific Membrane Antigen Targeted (18)F-DCFPyL Positron Emission Tomography/Computerized Tomography for the Preoperative Staging of High Risk Prostate Cancer: Results of a Prospective, Phase II, Single Center Study. J Urol. 2017 7 20.
11. Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, et al. PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging. 2012 11 24;40(4):486–95. [PubMed: 23179945]
12. Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, Lehnert W, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging. Springer Berlin Heidelberg; 2017 4;44(4):678–88. [PubMed: 27889802]
13. Ganguly T, Dannoon S, Hopkins MR, Murphy S, Cahaya H, Blecha JE, et al. A high-affinity [(18)F]-labeled phosphoramidate peptidomimetic PSMA-targeted inhibitor for PET imaging of prostate cancer. Nucl Med Biol. 2015 10;42(10):780–7. [PubMed: 26169882]
14. Beheshti M, Kunit T, Haim S, Zakavi R, Schiller C, Stephens A, et al. BAY 1075553 PET-CT for Staging and Restaging Prostate Cancer Patients: Comparison with [18F] Fluorocholine PET-CT (Phase I Study). Mol Imaging Biol. 2015 6;17(3):424–33. [PubMed: 25315836]
15. Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-specific Membrane Antigen PET: Clinical Utility in Prostate Cancer, Normal Patterns, Pearls, and Pitfalls. Radiographics. 2018 1;38(1):200–17. [PubMed: 29320333]

16. Salas Fragomeni RA, Amir T, Sheikhbahaei S, Harvey SC, Javadi MS, Solnes L, et al. Imaging of Non-Prostate Cancers Using PSMA-Targeted Radiotracers: Rationale, Current State of the Field, and a Call to Arms. J Nucl Med. 2018 3 15.

17. Sheikhbahaei S, Afshar-Oromieh A, Eiber M, Solnes LB, Javadi MS, Ross AE, et al. Pearls and pitfalls in clinical interpretation of prostate-specific membrane antigen (PSMA)-targeted PET imaging. Eur J Nucl Med Mol Imaging. Springer Berlin Heidelberg; 2017 11;44(12):2117–36. [PubMed: 28765998]

18. Fanti S, Minozzi S, Morigi JJ, Giesel F, Ceci F, Uprimny C, et al. Development of standardized image interpretation for 68Ga-PSMA PET/CT to detect prostate cancer recurrent lesions. Eur J Nucl Med Mol Imaging. Springer Berlin Heidelberg; 2017 9;44(10):1622–35. [PubMed: 28536833]

19. Rowe SP, Pienta KJ, Pomper MG, Gorin MA. Proposal of a Structured Reporting System for Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging: PSMA-RADS Version 1.0. J Nucl Med. 2017 9 8.

20. Eiber M, Herrmann K, Calais J, Hadaschihk B, Giesel FL, Hartenbach M, et al. PROstate cancer Molecular Imaging Standardized Evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-ligand PET/CT. J Nucl Med. 2017 11 9.

21. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018 3 18;:NEJMoa1801993.

22. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017 2 25;389(10071):815–22. [PubMed: 28110982]

23. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, et al. Simultaneous68Ga-PSMA HBED-CC PET/MRI Improves the Localization of Primary Prostate Cancer. European Urology. 2016 11;70(5):829–36. [PubMed: 26795686]

24. Cooperberg MR, Carroll PR. Trends in Management for Patients With Localized Prostate Cancer, 1990–2013. JAMA. 2015 7 7;314(1):80–2. [PubMed: 26151271]

25. Bianco FJ, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function (“trifecta”). Urology. 2005 11;66(5 Suppl):83–94. [PubMed: 16194712]

26. Maurer T, Gschwend JE, Rauscher I, Souvatzoglou M, Haller B, Weirich G, et al. Diagnostic Efficacy of (68)Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. J Urol. 2016 5;195(5):1436–43. [PubMed: 26682756]

27. ROEHL KA, Han M, RAMOS CG, ANTENOR JAV, CATALONA WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol. 2004 9;172(3):910–4. [PubMed: 15310996]

28. Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D’Amico AV, Dmochowski RR, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol. 2007 2;177(2):540–5. [PubMed: 17222629]

29. Roach M, Hanks G, Thames H, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. 2006 pp. 965–74. [PubMed: 16798415]

30. Hope TA, Aggarwal R, Chee B, Tao D, Greene KL, Cooperberg MR, et al. Impact of68Ga-PSMA-11 PET on Management in Patients with Biochemically Recurrent Prostate Cancer. J Nucl Med. 2017 12;58(12):1956–61. [PubMed: 28522741]

31. Calais J, Fendler WP, Eiber M, Gartmann J, Chu F-I, Nickols NG, et al. Impact of68Ga-PSMA-11 PET/CT on the Management of Prostate Cancer Patients with Biochemical Recurrence. J Nucl Med. Society of Nuclear Medicine; 2018 3;59(3):434–41.

32. Emmett L, Van Leeuwen P, Nandurkar R, Scheltema MJ, Cusick T, Hruby G, et al. Treatment outcomes from 68GaPSMA PET CT informed salvage radiation treatment in men with rising PSA following radical prostatectomy: Prognostic value of a negative PSMA PET. J Nucl Med. Society of Nuclear Medicine; 2017 7 26;58(12):1972–6.
33. Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, et al. Evaluation of Hybrid ^{68}Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. J Nucl Med. 2015 5;56(5):668–74. [PubMed: 25791990]
34. Afshar-Oromieh A, Holland-Letz T, Giesel FL, Kratochwil C, Mier W, Haufe S, et al. Diagnostic performance of (68)Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur J Nucl Med Mol Imaging. 2017 8;44(8):1258–68. [PubMed: 28497198]
35. Lake ST, Greene KL, Westphalen AC, Behr SC, Zagoria R, Small EJ, et al. Optimal MRI sequences for (68)Ga-PSMA-11 PET/MRI in evaluation of biochemically recurrent prostate cancer. EJNMMI Res. 2017 9 19;7(1):77. [PubMed: 28929350]
36. Haider MA, Chung P, Sweet J, Toi A, Jhaveri K, Menard C, et al. Dynamic contrast-enhanced magnetic resonance imaging for localization of recurrent prostate cancer after external beam radiotherapy. Radiation Oncology Biology. 2008 2 1;70(2):425–30.
37. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017 1 12;376(2):125–35. [PubMed: 28076709]
38. Hofman MS, Sandhu S, Eu P, Price J, Akhurst T, Iravani A, et al. Lutetium-177 PSMA (LuPSMA) theranostics phase II trial: Efficacy, safety and QoL in patients with castrate-resistant prostate cancer treated with LuPSMA. Ann Oncol. 2017 9 18;28(suppl_5).
39. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008 pp. 1148–59. [PubMed: 18309951]
40. Hope TA, Truillet C, Ehman EC, Afshar-Oromieh A, Aggarwal R, Ryan CJ, et al. 68Ga-PSMA-11 PET Imaging of Response to Androgen Receptor Inhibition: First Human Experience. J Nucl Med. 2017 1;58(1):81–4. [PubMed: 27660139]
41. Pandey MK, Byrne JF, Jiang H, Packard AB, DeGrado TR. Cyclotron production of (68)Ga via the (68)Zn(p,n)(68)Ga reaction in aqueous solution. Am J Nucl Med Mol Imaging. 2014;4(4):303–10. [PubMed: 24982816]

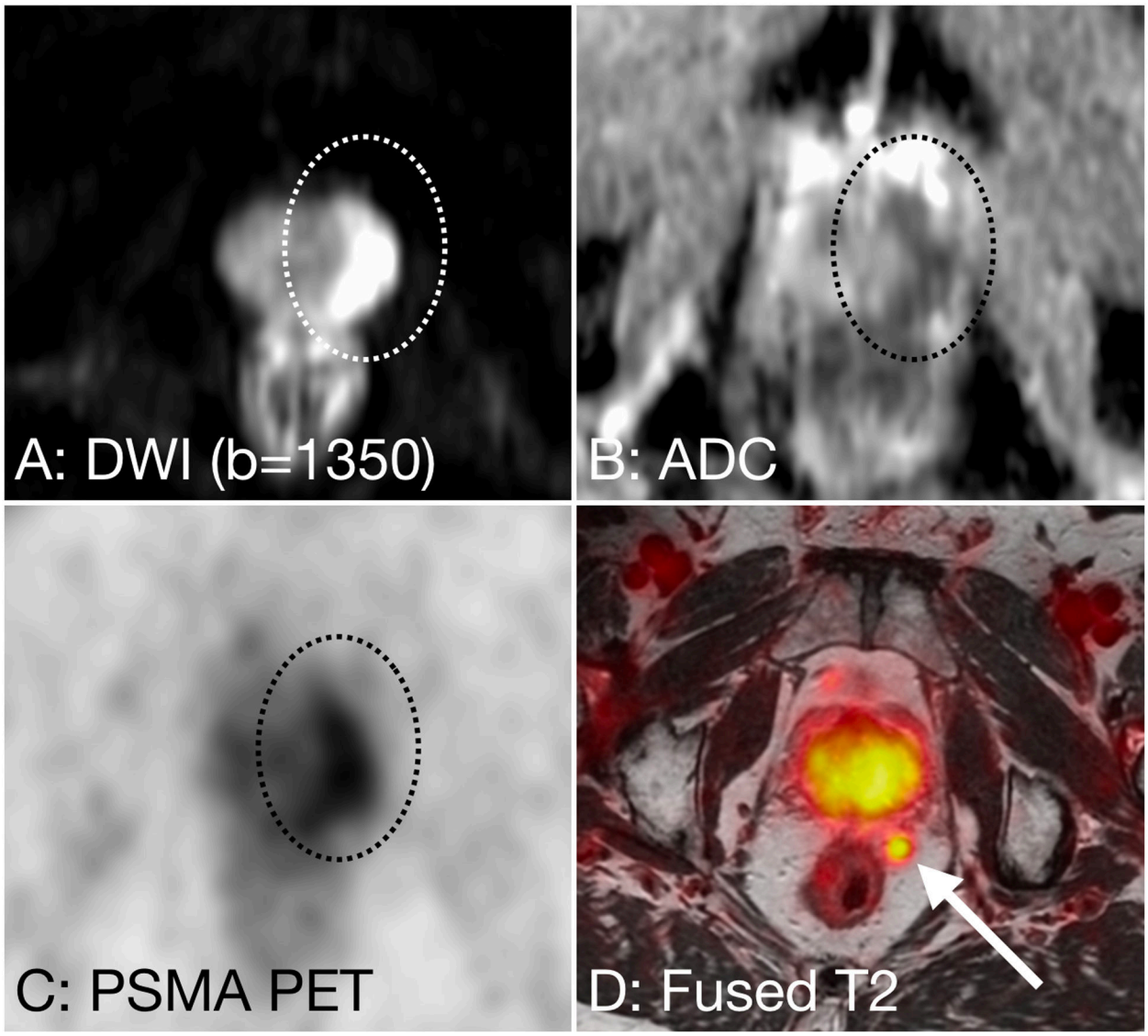

Figure 1:

Role of PSMA PET for initial staging. 56-year-old man with Gleason 4+4 on biopsy with 13/19 cores positive and a PSA of 5.0. ^{68}Ga-PSMA-11 PET demonstrates uptake in the prostate that correlates with a PI-RADS 5 lesion that demonstrates restricted diffusion (A-C, dotted circle) in addition to multiple PSMA positive pelvic nodal metastases (D, arrow).

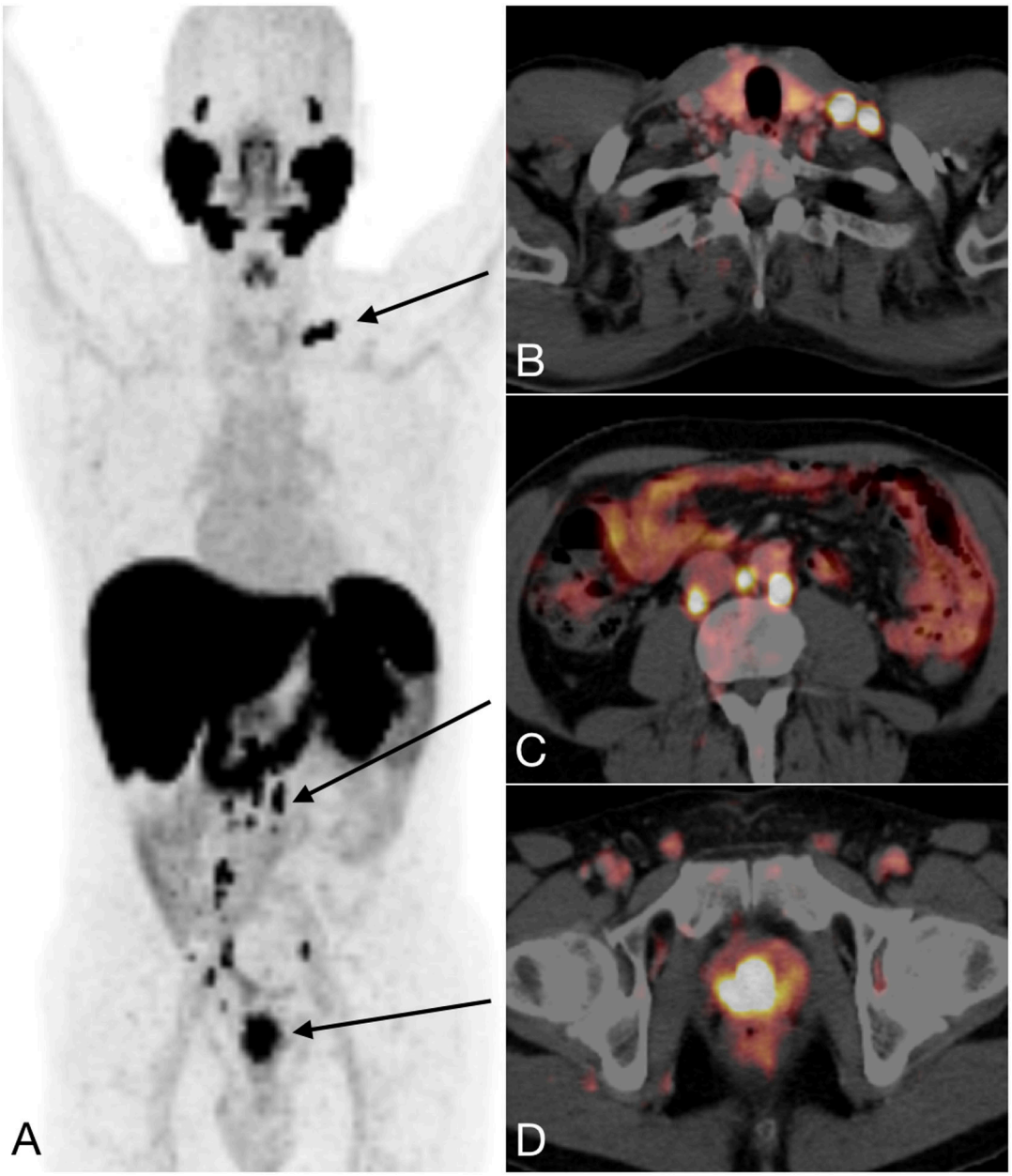

Figure 2:

Prostate cancer patient at initial diagnosis with a PSA of 77 and a Gleason score of 5+4. ^{18}F-PSMA-1007 PET (A, anterior whole body MIP) demonstrates focal uptake in the prostate consistent with the known tumor (D). Additionally, numerous pelvic and retroperitoneal nodal metastases (C) as well as left supraclavicular nodal metastases (B) are visualized.

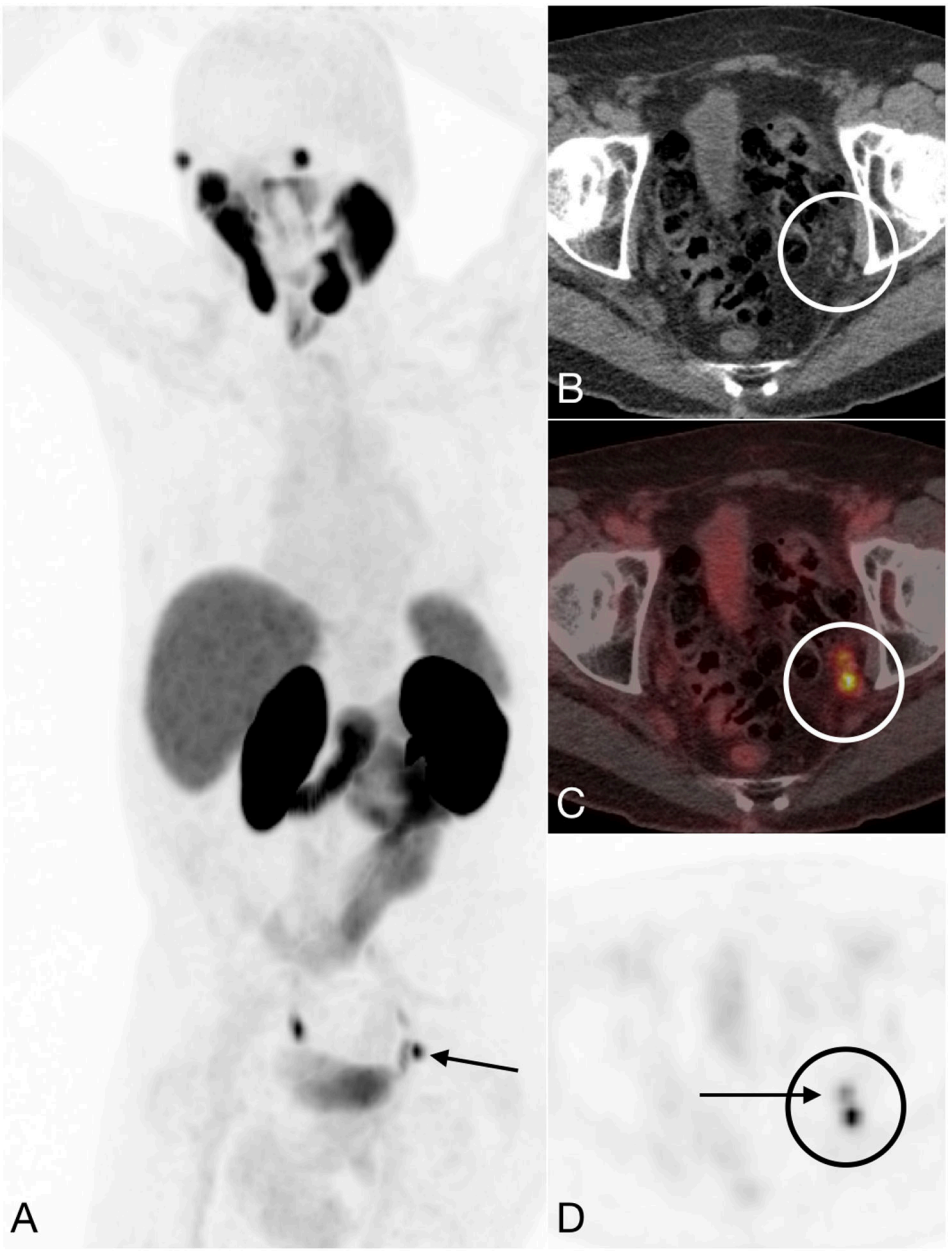

Figure 3:

80-year-old man with history of Gleason 3+4 prostate cancer status post external beam radiation therapy and brachytherapy 15 years prior to imaging with PSA nadir of 0.1 ng/mL and now with slowly rising PSA to 2.2 ng/dL. (A) Left anterior oblique whole body MIP image from ^{18}F-DCFPyL PET/CT study demonstrates intense focal radiotracer uptake posterior to the left ureter (D, black arrow). (B) Attenuation correction non-contrast axial CT, (C) axial PET/CT, and (D) axial PET images from the same study localize the abnormal uptake in the pelvis to a 0.3-cm left internal iliac lymph node (circle).

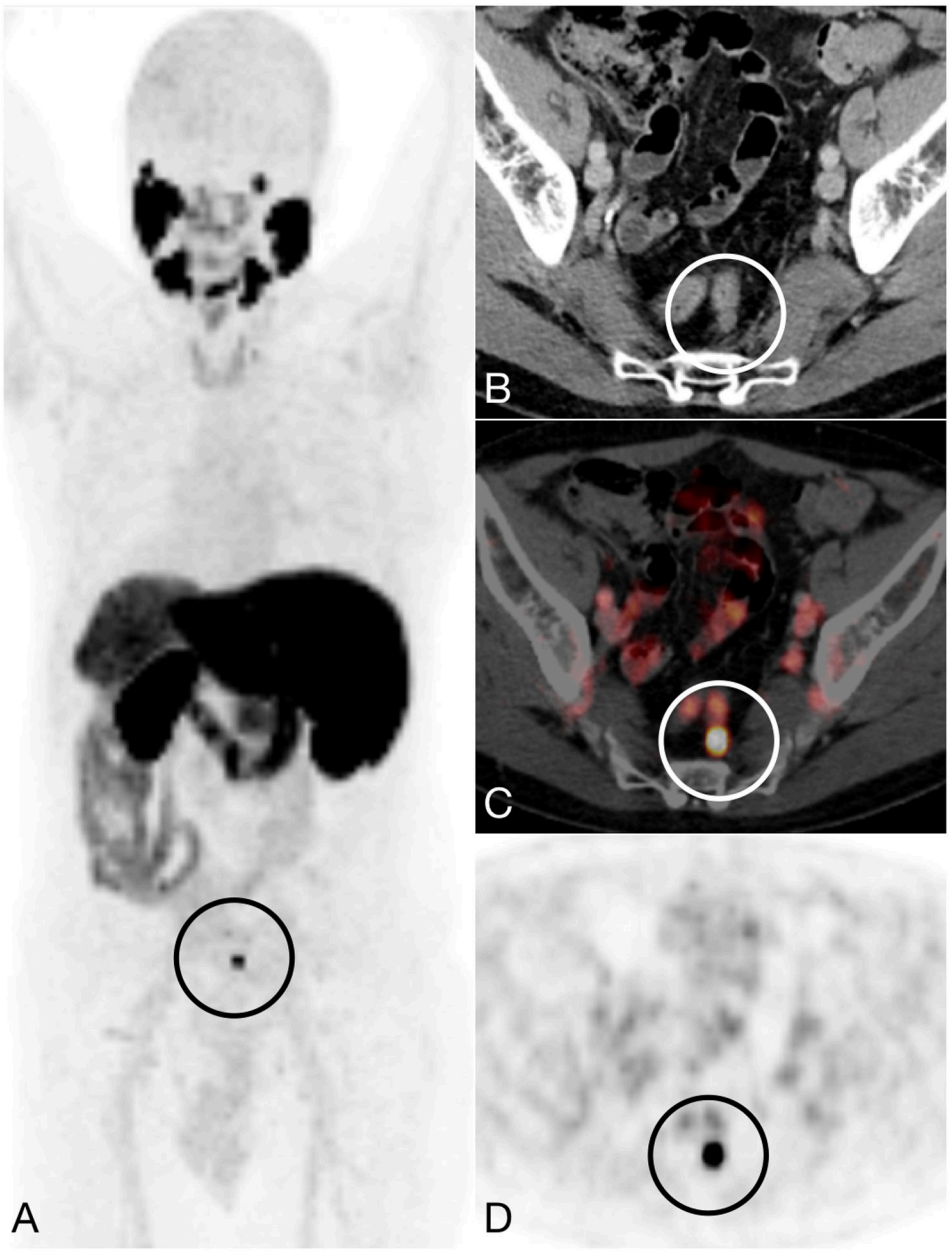

Figure 4:

Patient with biochemical recurrence after radical prostatectomy with a PSA of 0.36 at time of imaging. ^{18}F-PSMA-1007 PET/CT demonstrates a single presacral nodal metastases (A-D, circle) consistent with oligometastatic disease.

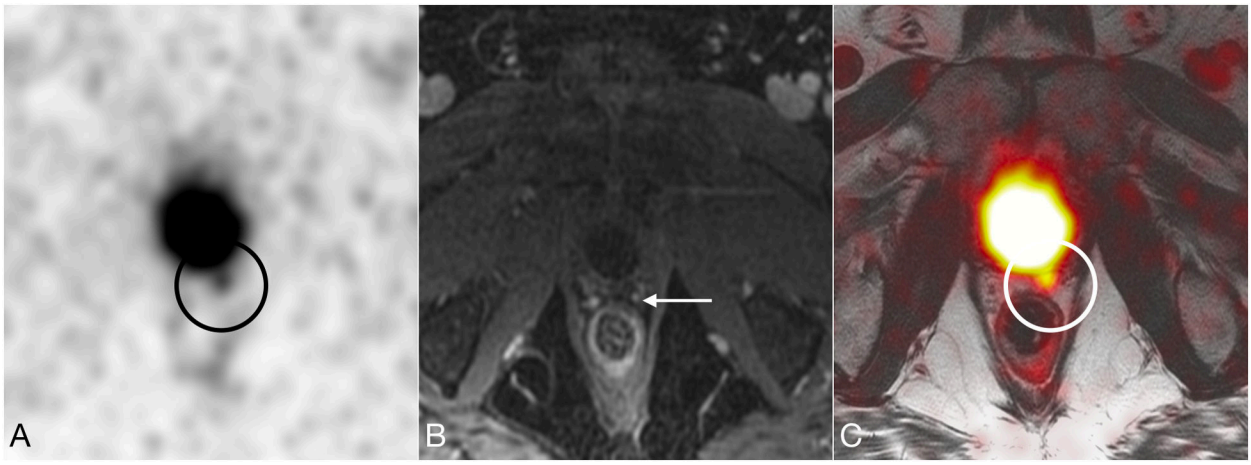

Figure 5:

Patient with biochemical recurrence after prostatectomy with a PSA of 0.29 five months after surgery. ^{68}Ga-PSMA-11 PET/MRI demonstrates focal uptake just posterior to the bladder (A and C, circle). No anatomic correlate is visualized on T2 weighted imaging, but dynamic contrast enhanced imaging demonstrates a 2 mm enhancing nodule that correlates with the PSMA uptake (B, arrow).

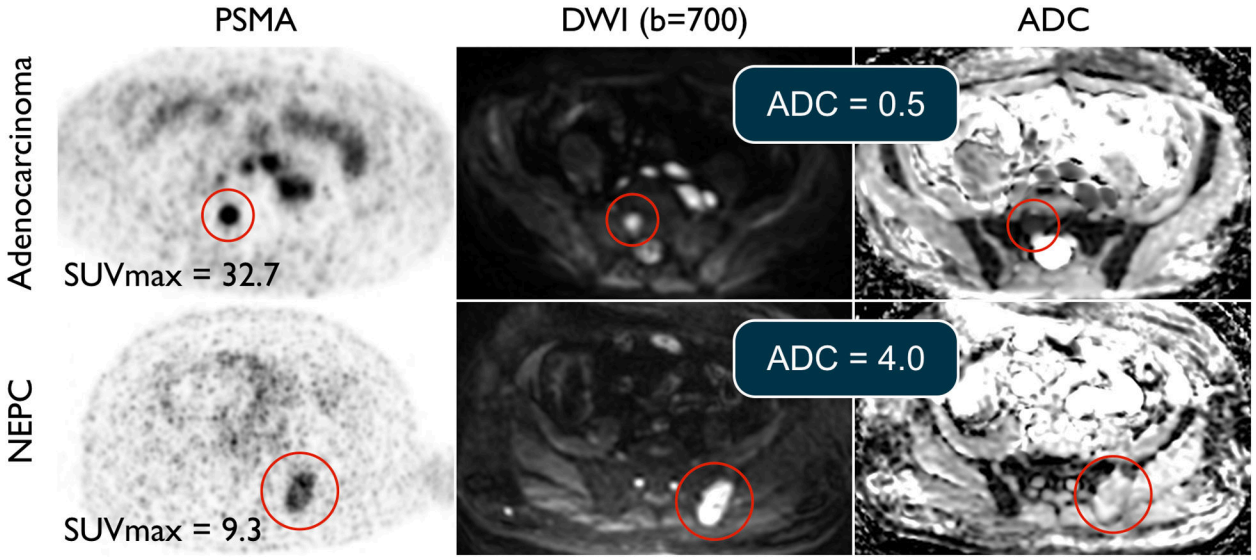

Figure 6:

Two patients with castrate resistant prostate cancer imaged with ^{68}Ga-PSMA-11 PET/MRI. The first patient (top row) has conventional adenocarcinoma which demonstrates high PSMA uptake, while the second patient (bottom row) has a neuroendocrine variant of prostate cancer (NEPC). The adenocarcinoma patient has much higher PSMA uptake, but the lesion is much more cellular (e.g. lower apparent diffusion coefficient or ADC) and therefore relative to cell density the uptake is not that much different than the NEPC patient. Moving forward diffusion weighted imaging (DWI) may help us interpret degrees of uptake seen on PSMA PET in CRPC patients.

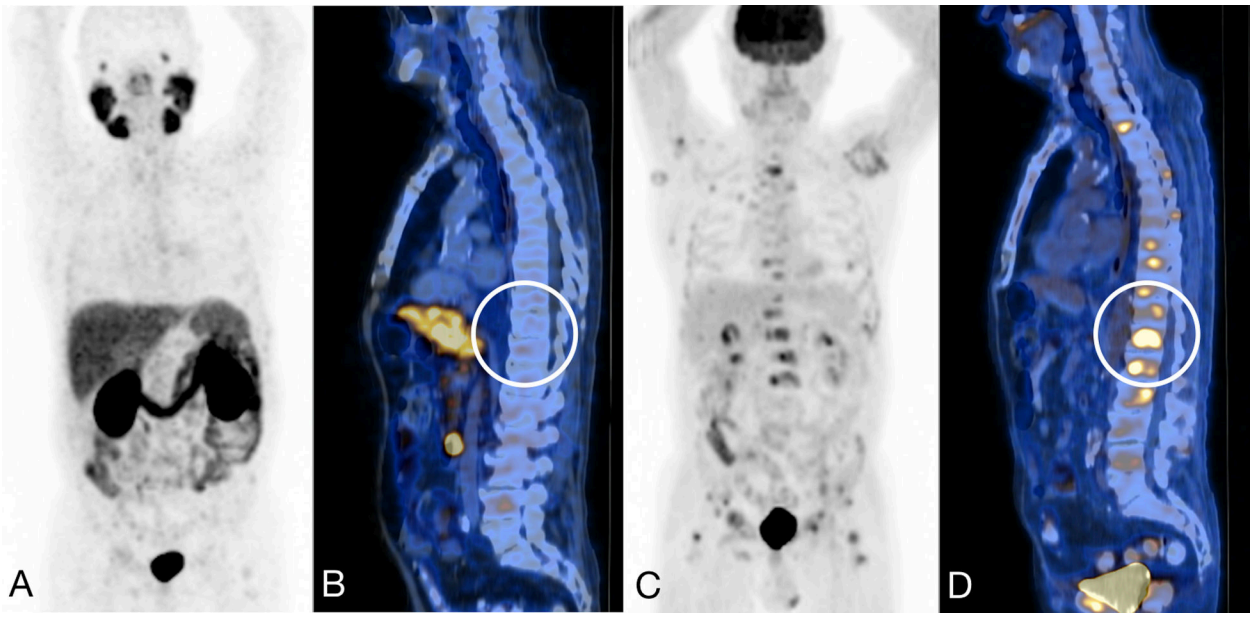

Figure 7:

Castrate resistant prostate cancer patient with a rising PSA after being treated with chemotherapy. ^{68}Ga-PSMA-11 PET (A and B) do not demonstrate any sites of PSMA avid disease. ^{18}F-FDG PET (C and D) demonstrates numerous sites of hypermetabolism consistent with a PSMA-FDG mismatch (B and D, circle). Therefore, this patient would not be a good candidate for PSMA radioligand therapy.

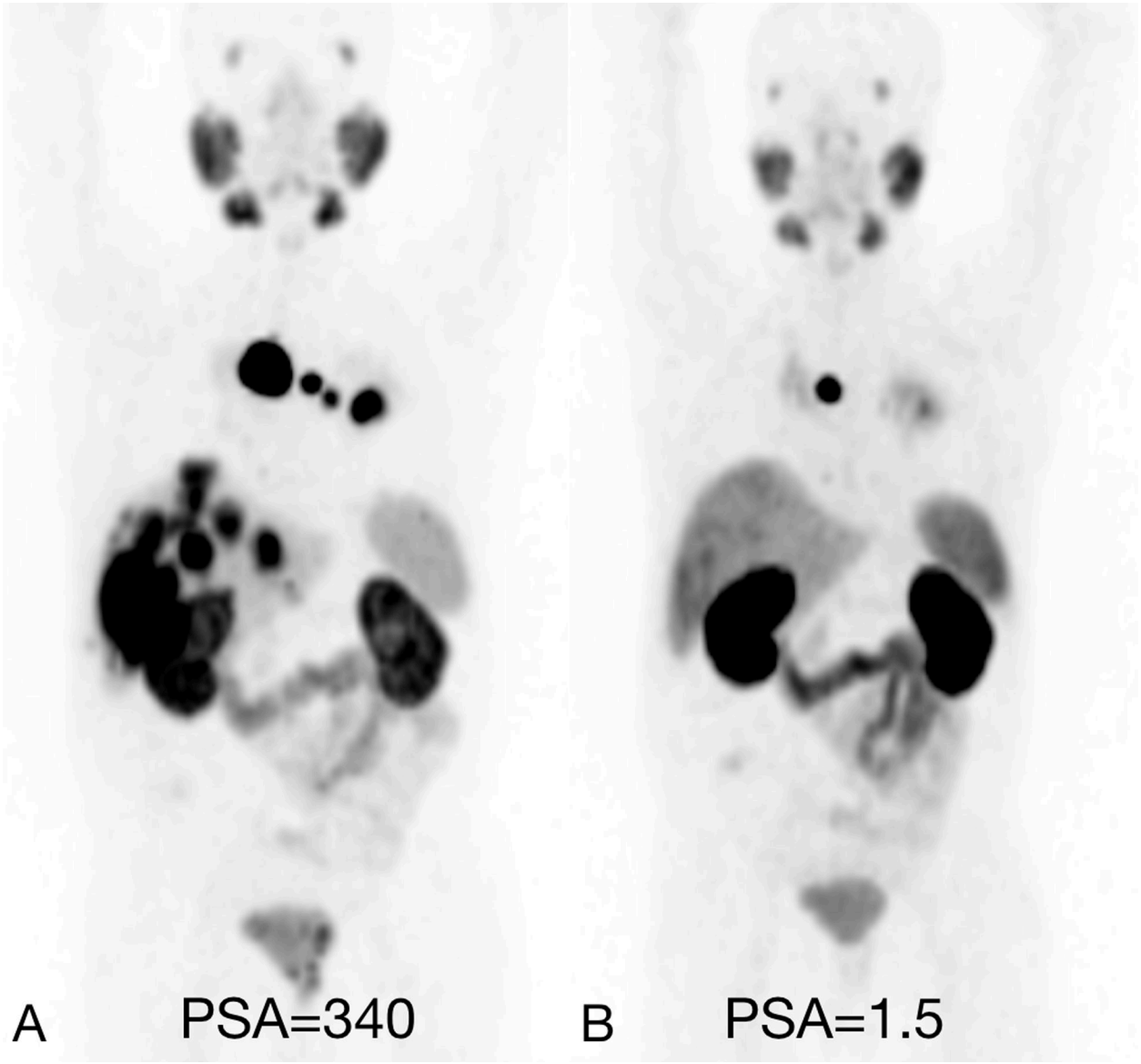

Figure 8:
72-year-old man imaged before and after four cycles of 177Lu-PSMA-617. Pretreatment 68Ga-PSMA-11 PET demonstrates hilar and hepatic metastases; at this time the PSA was 340 ng/mL. The patient subsequently underwent four cycles of therapy and the PSMA PET demonstrated marked improvement in the hepatic and hilar disease and the patient's PSA fell to 1.5 ng/mL.