Journal of Nuclear Medicine, published on December 14, 2017 as doi:10.2967/jnumed.117.203604

PSMA PET: Transformational Change in Prostate Cancer Management?

Hossein Jadvar[1], Leslie K. Ballas[2]

[1]Department of Radiology, and [2]Departemnt of Radiation Oncology, Keck School of Medicine, University of Southern California, Los Angeles, CA USA

Address for Correspondence:
Hossein Jadvar, MD, PhD, MPH, MBA
Division of Nuclear Medicine
Department of Radiology
Keck School of Medicine
University of Southern California
2250 Alcazar Street, CSC 102
Los Angeles, CA 90033 USA
Tel: 323-442-1107
Fax: 323-442-3253
Email: jadvar@med.usc.edu

In the world of business, the words "disruptive" or "transformative" are typically used to denote schemes that impact the commerce or market at a fundamental level. Medical imaging has also experienced such events after the discovery of x-rays by Wilhelm Conrad Roentgen in 1895. These events include, but are not limited to, development of computed tomography, use of radioactivity in imaging and treatment of disease, magnetic resonance imaging, and positron emission tomography. While the concept of theranostics started about 75 years ago with the use of radioiodine in thyroid disorders, it is now reemerging strongly in the context of precision medicine, most recently in the management of neuroendocrine tumors and prostate cancer.

Prostate specific membrane antigen (PSMA) is not an antigen (it is a transmembrane protein), not specific to the prostate gland (it is expressed in other normal tissues), and not specific to prostate cancer (it is expressed in many benign conditions and cancers other than prostate cancer). Nevertheless, PSMA is highly relevant in prostate cancer theranostics in view of its marked overexpression in prostate cancer (1, 2). Over the past several years, there have been major strides in the design, synthesis, and evaluation of small molecule radionuclides targeting PSMA for imaging and therapy (3). Most studies have employed ^{68}Ga-PSMA-11 and focused on the biochemical recurrence phase of the disease. However, growing literature is demonstrating additional diagnostic utility in the primary staging of intermediate-high risk disease and in the late metastatic phase of prostate cancer. In primary staging, PSMA PET/CT may localize lesions that are not evident on standard of care imaging and thus upstage the disease leading to major impact on

the initially planned curative intent management (4). Similar impact have been reported on the decision-making of radiation oncologists in the clinical settings of staging before definitive or post-prostatectomy salvage radiotherapy with negative or equivocal standard of care imaging (5-8). In biochemical recurrence phase of the disease, PSMA PET typically demonstrates higher lesion detection rate at lower serum prostate specific antigen (PSA) levels than other relevant PET radiotracers or standard of care imaging with major implications on subsequent therapy including salvage prostate bed radiotherapy, salvage lymphadenectomy, or oligometastasis-directed therapy. In castrate resistant metastatic prostate cancer, PSMA PET confirms target expression and hence suitability for PSMA radioligand therapy. Keeping pace with the rapid pace of developments in PSMA, growing literature is emerging on the nuts and bolts of clinical practice (e.g. procedure guidelines, safety profile, interpretation and reporting standards), which is remarkable given that PSMA is not approved and not readily available for use in the United States, although it is available in several centers around the world (9-14).

In the xxxxxx issue of the *Journal of Nuclear Medicine*, Calais and colleagues reported on a multicenter post-hoc retrospective analysis of an intention-to-treat (with salvage radiotherapy) cohort of 270 post-prostatectomy men with biochemical recurrence of prostate cancer with PSA<1 ng/mL who had undergone ^{68}Ga-PSMA-11 PET/CT a (15). The main goal of the study was to decipher the potential impact of ^{68}Ga-PSMA-11 PET/CT on salvage radiotherapy treatment fields. Salvage radiotherapy may potentially be curative or enhance progression-free probability in patients with biochemically recurrent disease after prostatectomy (16-18). Although the American Society for Therapeutic Radiology and Oncology-American Urological Association (ASTRO-AUA) recommend salvage radiotherapy to all men with biochemical recurrence without evident metastases, salvage radiotherapy is most effective at lower serum PSA levels (e.g. <1 ng/mL) (19, 20). Standard of care imaging (bone scintigraphy, contrast-enhanced CT of chest, abdomen, and pelvis, and in many cases multiparametric MRI of pelvis) are often negative or equivocal at very low PSA levels. However, a recent systematic review and metaanalysis (16 articles and 1309 patients) reported positive PSMA PET scans in 42%, 58%, 76%, and 95%, for PSA ranges of 0.-0.2, 0.2-1.0; 1-2; and >2 ng/mL, respectively (21). Despite the limitation with verification of PET findings, it appears that PSMA PET has a competitive advantage over other imaging modalities and PET radiotracers in this clinical setting. Calais et al found positive ^{68}Ga-PSMA-11 PET/CT in 49% of patients at a median serum PSA level of 0.48 ng/mL (range 0.03-1.0 ng/mL), which is in line with prior reports. The investigators also assessed whether the imaging information provided by PSMA PET might have major impact on radiation treatment planning. Major impact was defined as at least one PSMA-positive lesion that was not covered by consensus clinical tumor volume (CTV, that includes areas of gross tumor in anatomic prostate fossa, the seminal vesicles remnants and sites of possible occult tumor in presacral, common iliac, internal iliac, external iliac and obturator nodal basins). The most common locations for PSMA PET positive lesions outside of the consensus CTV were perirectal and distal external iliac lymph nodes. Salvage radiotherapy based on consensus CTV's would have not led to cure in 19%

of all patients and 39% of PET-positive patients since the CTV's did not cover the PSMA-expressing lesions in the treatment field. However, it was unclear what might have been a balancing trade-off between extra coverage for delivery of therapy and potential for additional toxicity. Other interesting findings were detection of oligometastatic (≤5 metastatic sites) and polymetastatic disease in 9.5% and 6% of all patients, respectively. Metastasis-directed stereotactic body radiation therapy may have potentially been appropriate in patients with oligometastatic disease. On the other hand, in patients with polymetastatic disease, salvage radiotherapy would have not been curative. The study had some limitations including relatively heterogeneous NCCN risk cohort (60.5% high risk, 13.5% intermediate risk), prior use of androgen deprivation therapy within 6 month prior to PET in 12.5% of patients (which could have increased PSMA expression), and relatively wide range of serum PSA levels between 0.03 to 1 ng/mL. Nevertheless, the data presented by Calais et al supports the notion of designing and executing prospective randomized clinical trials in determining whether in patients with biochemical recurrence of prostate cancer at very low serum PSA levels, PSMA PET-based earlier detection and treatment of locally recurrent and oligometastatic disease with potential deferral of androgen deprivation therapy translates into improved patient outcome and quality of life. Potential contribution of PSMA PET to more accurate upfront staging of patients at the time of initial diagnosis may also change the natural history of disease and incidence rate of biochemical recurrence. At this time despite "nonspecificity" of PSMA, all accumulating evidence is pointing toward a transformational change in prostate cancer management with PSMA PET in the coming years.

References

1. Jadvar H. Radiotheranostics in prostate cancer: introduction and overview. J Nucl Med. 2016; 57(Suppl 3):1S-2S.
2. Ballas LK, de Castro Abreu AL, Quinn DI. What medical, urologic, and radiation oncologists want from molecular imaging of prostate cancer. J Nucl Med 2016; 57(Suppl 3):6S-12S.
3. Schwarzenboeck SM, Rauscher I, Bluemel C, et al. PSMA ligands for PET imaging of prostate cancer. J Nucl Med 2017; 58:1545-1552.
4. Demirkol MO, Acar O, Ucar B, et al. Prostate-specific membrane antigen based imaging in prostate cancer: impact on clinical decision making process. Prostate 2015; 75:748-757.
5. Shakespeare TP. Effect of prostate-specific membrane antigen positron emission tomography on the decision-making of radiation oncologists. Radiat Oncol 2015; 10:223.
6. van Leeuwen PJ, Stricker P, Hruby G, et al. 68Ga-PSMA has a high detection rate of prostate cancer recurrence outside the prostate fossa in patients being considered for salvage radiation treatment. BJU Int 2016; 117:732-739.
7. Bluemel C, Linke F, Herrmann K, et al. Impact of 68Ga-PSMA PET/CT on salvage radiotherapy planning in patients with prostate cancer and persisting PSA values or biochemical relapse after prostatectomy. EJNMMI Res 2016; 6:78.

8. Habl G, Sauter K, Schiller K, et al. 68Ga-PSMA PET/CT on salvage radiotherapy planning in patients with prostate cancer recurrences after surgery: individualized medicine or new standard in salvage treatment. Prostate 2017; 77:920-927.
9. Eiber M, Herrmann K, Calais J, et al. PROstate cancer Molecular Imaging Standardized Evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-ligand PET/CT. J Nucl Med 2017. [Epub ahead of print]
10. Rowe SP, Pienta KJ, Pomper MG, et al. Proposal of a Structured Reporting System for Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging: PSMA-RADS Version 1.0. J Nucl Med 2017. [Epub ahead of print]
11. Nielsen JB, Zacho HD, Haberkorn U, et al. A comprehensive safety evaluation of 68Ga-PSMA-11 PET/CT in prostate cancer. Clin Nucl Med 2017; 42:520-524.
12. Rauscher I, Mauer T, Fender WP, et al. 68Ga-PSMA ligand PET/CT in patients with prostate cancer: how we review and report. Cancer Imaging 2016; 16:14.
13. Sheikhbahaei S, Afshar-Oromieh A, Eiber M, et al. Pearls and pitfalls in clinical interpretation of prostate-specific membrane antigen (PSMA)-targeted PET imaging. Eur J Nucl Med Mol Imaging 2017; 44:2117–2136.
14. Fendler WP, Eiber M, Beheshti M, et al. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging 2017; 44:1014–1024.
15. Calais J, Czernin J, Cao M, et al. 68Ga-PSMA-11 PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA<1.0 ng/ml: impact on salvage radiotherapy planning. J Nucl Med 2017.
16. Zumsteg ZS, Daskivich TJ, Sandler HM. Salvage radiotherapy for biochemically recurrent prostate cancer after prostatectomy. J Clin Oncol 2016; 34:3829-3833.
17. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004; 291:1325-1332.
18. Goenka A, Magsanoc JM, Pei X, et al. Long term outcomes after high dose postprostatectomy salvage radiation treatment. Int J Radiat Oncol Biol Phys 2012; 84:112-118.
19. Valicenti RK, Thompson I Jr, Albertsen P, et al. Adjuvant and salvage radiation therapy after prostatectomy: American Society for Radiation Oncology/American Urological Association guidelines: Int J Radiat Oncol Biol Phys 2013; 86:822-828.
20. King CR. The timing of salvage radiotherapy after radical prostatectomy: a systematic review. Int J Radiat Oncol Biol Phys 2012; 84:104-111.