

PSMA PET: Transformational Change in Prostate Cancer Management?

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In the world of business, the words *disruptive* or *transformative* are typically used to denote schemes that affect commerce or the 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 CT, use of radioactivity in imaging and treatment of disease, MRI, and PET. Although the concept of theranostics started about 75 y ago with 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), is not specific to the prostate gland (it is expressed in other normal tissues), and is 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 used ⁶⁸Ga-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- to 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 a major impact on the initially planned curative-intent management (4). A similar impact has been reported on the decision making of radiation oncologists in the clinical setting of staging before definitive or postprostatectomy salvage radiotherapy with negative or equivocal results on standard-of-care imaging (5–8). In the biochemical recurrence phase of the disease, PSMA PET typically demonstrates higher lesion detection

rates 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 castration-resistant metastatic prostate cancer, PSMA PET confirms target expression and hence suitability for PSMA radioligand therapy. Keeping pace with the rapid developments in PSMA, growing literature is emerging on the nuts and bolts of clinical practice (e.g., procedure guidelines, safety profiles, and 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 this issue of *The Journal of Nuclear Medicine*, Calais et al. report 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 and a PSA level of less than 1 ng/mL who had undergone ⁶⁸Ga-PSMA-11 PET/CT (15). The main goal of the study was to decipher the potential impact of ⁶⁸Ga-PSMA-11 PET/CT on salvage radiotherapy treatment fields. Salvage radiotherapy may potentially be curative or enhance the probability of progression-free survival in patients with biochemically recurrent disease after prostatectomy (16–18). Although the American Society for Therapeutic Radiology and Oncology and the American Urological Association 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 the chest, abdomen, and pelvis; and in many cases multiparametric MRI of the pelvis) are often negative or equivocal at very low PSA levels. However, a recent systematic review and metaanalysis (16 articles and 1,309 patients) reported positive PSMA PET findings in 42%, 58%, 76%, and 95% of patients for PSA ranges of 0.0–0.2, 0.2–1.0, 1–2, and >2 ng/mL, respectively (21). Despite the limitation concerning 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 ⁶⁸Ga-PSMA-11 PET/CT results 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 a major impact on radiation treatment planning. A major impact was defined as at least one PSMA-positive lesion that was not covered by the consensus clinical tumor volume (which includes areas of gross tumor in the anatomic prostate fossa or seminal vesicle remnants and sites of possible occult tumor in the presacral,

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common iliac, internal iliac, external iliac, and obturator nodal basins). The most common locations for PSMA PET–positive lesions outside the consensus clinical tumor volume were the perirectal and distal external iliac lymph nodes. Salvage radiotherapy based on consensus clinical tumor volumes would not have led to cure in 19% of all patients and in 39% of PET-positive patients, because the clinical tumor volumes 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 not have been curative. The study had some limitations, including a relatively heterogeneous National Comprehensive Cancer Network risk cohort (60.5% high risk, 13.5% intermediate risk), use of androgen deprivation therapy within 6 mo before PET in 12.5% of patients (which could have increased PSMA expression), and a relatively wide range of serum PSA levels (0.03–1 ng/mL). Nevertheless, the data presented by Calais et al. support the notion of designing and executing prospective randomized clinical trials to determine 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. The potential contribution of PSMA PET to more accurate staging of patients at the time of initial diagnosis may also change the natural history of the disease and the incidence rate of biochemical recurrence. At this time, despite the “nonspecificity” of PSMA, all accumulating evidence is pointing toward a transformational change in prostate cancer management with PSMA PET in the coming years.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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