68Ga-Labeled PSMA Uptake in Nonprostatic Malignancies

Has the Time Come to Remove “PS” From PSMA?

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Abstract: PET/CT with 68Ga-labeled prostate-specific membrane antigen (PSMA) is increasingly recognized as the best imaging modality for disease staging and detection of recurrent prostate cancer. Despite its name, PSMA expression has been reported in a number of nonprostatic benign and malignant pathologies. Apparently, angioneogenesis is the mechanism attributed to increased 68Ga-PSMA uptake at these sites. Here we illustrate the utility of 68Ga-PSMA in 5 nonprostatic malignancies that could open up new possibilities for diagnostics and theranostic concepts with PSMA labeled radioligands in nonprostate tumor entities.

Key Words: 68Ga PSMA PET/CT, angioneogenesis, esophageal carcinoma, metastatic urinary bladder carcinoma, brain metastasis, gliomas, iodine-refractory thyroid cancer

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REFERENCES

A 78-year-old man, case of adenocarcinoma gastroesophageal junction, underwent $^{68}$Ga-labeled prostate-specific membrane antigen (PSMA)–PET/CT (maximum intensity projection [MIP], A) for elevated prostate-specific antigen levels (19.75 ng/mL), which revealed intense tracer uptake in the distal esophagus (B–D, arrows), gastroesophageal junction, and stomach (E–G, arrows). Focal PSMA uptake was also noted in the right lobe of the prostate (H–J, dotted arrows), which revealed adenocarcinoma on pathology. Prostate-specific membrane antigen uptake had been reported in multiple nonprostatic malignancies.\textsuperscript{1,2} Significant neovascularization is reported in gastric cancers, leading to increased PSMA expression.\textsuperscript{3} The significant angioneogenesis in gastric cancer can be potentially used for imaging with PSMA-PET/CT and PSMA-directed therapy in nonoperable cases.

FIGURE 2. A 70-year-old man, case of dual malignancy (carcinoma urinary bladder and prostate), underwent $^{18}$F-fluorodeoxyglucose (FDG)–PET/CT (MIP, A) for metastatic workup, which showed FDG-avid lesion in the left internal iliac region (B–C, arrow), pelvic, and retroperitoneal lymph nodes (D–G, dotted-arrow). To ascertain the nature, PSMA-PET/CT (MIP, H) was performed, which revealed PSMA avidity in the left iliac lesion (I–J, arrow), whereas no tracer uptake was observed in the rest (right internal iliac and paraaortic; K–N, dotted arrow) of the lymph nodes. Biopsy from the iliac lesion revealed metastatic carcinoma from urinary bladder. Prostate-specific membrane antigen avidity has been reported in adenocarcinoma of the urinary bladder.\textsuperscript{4} This case highlights the differential expression of PSMA on neovascularure of metastatic site but not on lymph nodes with absence of neovascularization.
FIGURE 3. A 37-year-old woman underwent $^{18}$F-FDG-PET/CT (MIP, A) for restaging of breast cancer, which revealed non-FDG avid lesion in the left cerebellum (C–D, arrow). To know the nature of the lesion, PSMA-PET/CT was performed, which showed tracer avid lesion in the left cerebellum (E–F, arrow), suggesting new metastatic site. Additionally, PSMA uptake was also noted in other known bone and lung metastases (G–J, dotted arrow). Prostate-specific membrane antigen expression has been reported in tumor-associated neovasculature including breast cancer. The present case highlights the better delineation of brain metastases with PSMA.

FIGURE 4. A 40-year-old woman, case of oligodendroglioma (postsurgery and radiotherapy) underwent $^{18}$F-FDG-PET/CT (A) for suspected recurrence, which revealed FDG avidity in the medial aspect of an ill-defined lesion with intermixed gliotic changes on CT images in the left parasagittal location (B–D, arrows). To characterize the lesion, PSMA-PET/CT (E) was done, revealing PSMA uptake in the lesion (F–H, arrows), and it was more accurately delineated than FDG. Stereotactic biopsy confirmed the diagnosis. Brain tumors are treatment resistant and major cause of cancer-related deaths. Prostate-specific membrane antigen expression had been reported in gliomas with increased expression in high-grade tumors attracting a potential PSMA-based therapy.
A 58-year-old man, case of radioactive-iodine refractory (RAIR) thyroid cancer with elevated thyroglobulin level (636 ng/mL), underwent PSMA-PET/CT (MIP, A) to explore the feasibility of $^{177}$Lu PSMA-directed therapy, which revealed tracer avid cervical lymph nodes (B–D, dotted arrow) and tracheoesophageal groove lesion (E–J, arrows). Prostate-specific membrane antigen in the thyroid gland is expressed by the endothelium of tumor-associated microvessels. High PSMA expression was observed in RAIR patients and was interrelated with tumor size and disease progression. Ability to recognize PSMA expression in RAIR thyroid cancer microvasculature might prove to be a promising target for PSMA-directed treatment in this subset of patients.