PSMA-targeted Imaging: Beyond Prostate Cancer

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Introduction to PSMA

The prostate-specific membrane antigen (PSMA) is a type II membrane glycoprotein and glutamate carboxypeptidase that has recently been extensively studied for oncologic imaging and theranostic applications. Normal tissue distribution of PSMA includes prostatic epithelium, duodenal mucosa, proximal renal tubules, salivary glands, and brain. PSMA is particularly highly expressed in prostate cancer, and imaging of PSMA is finding application in such settings as pre-operative staging of high-risk prostate cancer and identifying sites of disease in biochemically recurrent prostate cancer.

The first PSMA-targeted imaging agent was In-111-capromab pendetide (ProstaScint®), for identification in metastases in men with biochemical recurrence. Disadvantages of ProstaScint® included slow target recognition and background clearance, leading to suboptimal sensitivity and specificity despite improvements in single-photon emission computed tomography/computed tomography (SPECT/CT) technology. To overcome such limitations a number of PSMA-targeted small-molecule agents have been developed, many of which are labeled with radionuclides—allowing for positron emission tomography (PET) with its attendant improved spatial resolution and intrinsically quantitative images. Currently the most promising of such agents include the Ga-68, and F-18-labeled ureas. Compared to Ga-68 and In-111-labeled agents, F-18-based PET agents offer advantages in availability, production, and, most importantly, image quality. For example, the radiotracer 2-(3-1-carboxy-5-[6-[F-18-fluoro-pyridine-3-carbonyl]-amino]-pentyl)-ureido)-pentanedioic acid, F-18-DCFPyL (Figure 1), has been shown to have very high uptake in sites of prostate cancer metastases and can provide high quality imaging of PSMA-expressing tumors (Figure 3). For a review of PSMA antigen and small-molecule based imaging of the prostate, please refer to the cited articles from Osborne et al. and Kiess Q et al.

Imaging cancers other than prostate with PSMA-targeted agents

PSMA is expressed in tumor neovasculature in the stroma of a wide range of malignancies, while lacking expression in normal vasculature. Interestingly, the tumor neovasculature of prostate cancer does not reliably express PSMA. Tumor neovasculature expressing PSMA includes that...
from breast cancer, renal cell carcinoma, glioblastoma multiforme and hepatocellular carcinoma, among others\(^1,15\).

**Renal Cell Carcinoma**

Renal cell carcinoma (RCC) has an incidence of approximately 60,000 cases per year in the United States, with the majority being clear cell RCCs (ccRCCs)\(^16\). Improved imaging would help identify sites of occult disease in both patients being preoperatively staged and those being surveilled for possible recurrent/metastatic disease. Given that a number of the agents used to treat metastatic ccRCC target the tumor neovascularature\(^17,18\), PSMA-based imaging agents may also have a role in predicting response to therapy. Among cancers other than prostate cancer, ccRCC has been most studied in patients with PSMA-targeted imaging agents. Under normal conditions PSMA is expressed in the proximal renal tubules, however, ccRCC tumor epithelium does not express PSMA\(^1\). Nevertheless, stromal tissue containing neovascularature within ccRCC has been found to express PSMA\(^1,19\) and has been shown to demonstrate significant radiotracer uptake\(^12,19–22\). The first reported example of PET imaging of ccRCC with a PSMA-targeted radiotracer was performed with a Ga-68-labeled small molecule and the authors found significantly higher uptake in sites of metastatic disease than was achievable with F-18-fluorodeoxyglucose (FDG) PET. Our group subsequently studied a small series of patients with metastatic ccRCC and found sites of presumed disease that were occult on contrast-enhanced CT and FDG PET, suggesting a role for PSMA PET in identifying small lesions\(^20\).

**Glioblastoma Multiforme**

Glioblastoma multiforme (GBM) has the highest number of cases of all malignant brain tumors with 12,120 cases predicted in 2016 and an average five-year survival rate of only 5.1%\(^10\). Recent advances have increased two-year survival from 8% to 37% by using a combination of chemotherapy and radiation. Chemo-radiation has indeed become the current standard of care for GBM. However, intensification of therapy has been accompanied by an increased recognition of transient or non-progressive increases in contrast enhancement, often with reversible neurological deterioration simulating disease progression. These findings are referred to as “pseudo-progression”\(^23\). Currently, no neuroradiological technique has been demonstrated to be sensitive and specific enough to differentiate reliably between pseudo-progression and early recurrence, although contrast-enhanced magnetic resonance imaging (MRI) is the current gold standard. The lack of a definitive, non-invasive method to diagnose recurrence results in increased dependence on brain biopsy, leading to increased morbidity, healthcare costs, and delayed treatment for patients with early progression.

Expression of PSMA has been demonstrated in the neovascularature of gliomas, with increased expression within neovascularature with concurrent increase in tumor grade\(^13,24\). Radiotracer uptake within GBM has been demonstrated\(^25\) such that molecular imaging is being investigated as a way to differentiate early recurrence from pseudo-progression. Another potential use of PSMA-targeted imaging in GBM would be in identifying tumor with mutated MGMT and IDH genes as their expression may affect NAAG levels and relate to glutamate carboxypeptidase activity\(^26\).

(Continued on page 3. See Prostate Cancer.)
A Better Way to Image Metastatic Prostate Cancer

Conventional imaging methods have limited sensitivity for detecting metastatic prostate cancer. With appropriate, timely treatment vital to survival and quality of life, better imaging has been an ongoing goal.

A recent study, reported in the January issue of *The Journal of Nuclear Medicine*, has now shown in a prospective, systematic manner that a PET/CT scan, using the radiotracer F-18-DCFBC to target prostate-specific membrane antigen (PSMA), is significantly more effective than other detection methods currently in use.

Prostate cancer is one of the most common forms of cancer in men. One in seven American men will have prostate cancer during his lifetime. The American Cancer Society estimates that there will be 180,890 new cases diagnosed in 2016. Approximately 2.8 million American men are living with the disease, and more than 26,000 deaths from it are predicted this year.

PSMA is expressed in the majority of prostate cancers, and high PSMA expression is associated with metastatic spread. In this study, the research team from Johns Hopkins Medical Institutions compared the results of PET/CT scans using F-18-DCFBC with conventional imaging modalities (expanded Tc-99m-methylene diphosphonate (MDP) bone scan and contrast-enhanced CT of the chest, abdomen, and pelvis).

In this study of lesion-by-lesion analysis of 17 patients, DCFBC PET was able to detect a larger number of lesions—592 positive versus 520 with the conventional methods. In lymph nodes, bone, and visceral tissue, DCFBC PET proved to have a much greater sensitivity for detecting prostate cancer lesions (0.92) compared with current methods (0.71).

Steve Y. Cho, MD, corresponding author for the study and now an associate professor of nuclear medicine at the University of Wisconsin School of Medicine and Public Health, said, “The results of this work, in combination with a number of other studies that have been published on PSMA PET, have highlighted the improved ability of PSMA-targeted PET imaging to detect metastatic prostate cancer. Improved detection of prostate cancer using F-18-DCFBC, as well as further advances in detection with newer and improved second generation F-18-DCFPyL and Ga-68-based low molecular weight PSMA PET radiotracers, will potentially allow for earlier detection and detection of more metastatic lesions.”

Looking ahead, Cho noted, “PSMA-based PET imaging is a striking example of molecular imaging’s ability to target and detect prostate tumor tissue, thereby markedly improving the imaging of a disease process.”

Authors of the article “Comparison of PSMA-based 18F-DCFBC PET/CT to Conventional Imaging Modalities for Detection of Hormone-Naïve and Castration-Resistant Metastatic Prostate Cancer” include Steven P. Rowe, Katarzyna J. Macura, Anthony Ciarallo, Esther Mena, Amanda Blackford, Rosa Nadal, Emmanuel S. Antonarakis, Mario Eisenberger, Michael Carducci, Ashley Ross, Daniel P. Holt, Robert F. Dannals, Ronnie C. Mease, Martin G. Pomper, and Steve Y. Cho, Johns Hopkins Medical Institutions, and Philip W. Kantoff, Dana Farber Cancer Institute, Harvard Medical School.

Colorectal Cancer

Colorectal cancer is the third leading cause of cancer-related deaths in the United States when men and women are considered separately, and the second leading cause when both sexes are combined27. Colorectal cancer is expected to cause 49,190 deaths during 2016. Stage IV colon cancers have a five-year survival rate of about 11%27. However, there may be multiple treatment options available for people with stage IV disease. For example, patients with colorectal cancer isolated to liver or lung may be eligible for surgical resection. In those cases, resection has led to cure and/or potentially better five-year survival rates over current chemotherapeutic regimens28–32. Accordingly, surgery is the treatment of choice for such individuals, but identification of appropriate candidates for surgery remains an important dilemma. The majority of colon cancers express PSMA1,12,14,15,33, and a recent case report confirmed uptake in a primary rectal cancer initially detected as an incidental finding in a patient being staged for prostate cancer with PSMA PET34. PSMA-targeted imaging may ultimately be shown to have advantages over FDG PET by demonstrating higher specificity as the latter also tends to identify postsurgical and other inflammatory changes. Furthermore,
PSMA-targeted small-molecule therapeutic agents may be useful in the setting of biochemical recurrence. For those reasons PSMA-targeted imaging of colorectal cancer is currently being investigated\(^3^4\).

**Breast Cancer**

The majority of both ductal and lobular breast carcinomas appear to express PSMA, making breast cancer an attractive target for future research in PSMA imaging\(^1^2,2^4,3^3\). A case report comparing PSMA PET to FDG PET found higher standardized uptake values (SUVs) and better tumor-to-background ratios with the PSMA-targeted agent\(^3^5\).

**Additional cancers**

To date, a number of other non-prostate cancers have been shown in case reports to have high radiotracer uptake on PSMA-targeted PET imaging. Those reports have primarily utilized Ga-68-labeled small molecular PET agents. Examples includes hepatocellular carcinoma\(^3^6\), differentiated thyroid cancer\(^3^7\), and non-small cell lung cancer\(^3^8\).

**Conclusions**

Taken together, the above mentioned anecdotal reports suggest that PSMA PET imaging may be a generalizable technique for managing patient with a variety of cancers, much as has been done with FDG PET. While potential false positive (thyroid adenoma\(^3^9\), retroperitoneal schwannoma\(^4^0\) and celiac ganglia\(^4^1\), Paget’s disease of bone\(^4^2,4^3\) and false negative (neuroendocrine dedifferentiated prostate cancer\(^4^4\)) findings have also begun to be reported, the overall high sensitivity and specificity of PSMA PET for tumor epithelium or neovascularity may convey advantages relative to FDG PET and other oncologic imaging agents. However, as enticing as it is to rely on the existing reports and small series, larger prospective imaging trials designed to address specific clinical questions in a variety of cancers in which PSMA is expressed—and has been shown to be detectable with existing small-molecule agents on PET—are needed.

**PET in the News**

PET/CT beats CT and bone scans for detecting metastatic prostate cancer: study
DotMed

PET/MRI Plus CT Helps Determine Colorectal Cancer Treatment
Diagnostic Imaging

Study Confirms PET-CT as Modern Standard for Staging Hodgkin Lymphoma
Cancer Therapy Advisor

Researchers at Sweden’s Uppsala University use PET/CT instead of biopsy to define appropriate breast cancer treatment
DotMed

PET/CT aids radiation treatment of patients with head and neck cancers
DrBicuspid

3D PET images show oxygen/CO2 transport in lungs
Aunt Minnie

Rubidium PET/CT reveals vascular problems in diabetes patients
Aunt Minnie Europe

PET-MRI combination may change management of high-risk cancer patients
News-Medical

PET/MRI shows value for cardiac sarcoidosis
Aunt Minnie
(President’s Report. Continued from page 1.)

Specific knowledge of normal biodistribution, variable appearances of pathology, and metabolic treatment response criteria for this arsenal of multiple tracers will be essential for accurate and clinically meaningful interpretation of PET/CT and PET/MR exams. Training in CT/MRI alone will not be sufficient for future PET readers; extensive training in molecular imaging, in additional to at least a basic/fundamental knowledge of clinical oncology (to understand how PET plays into the clinical management of patients with cancer), will be required as well.

This need for training in both cross-sectional imaging and molecular imaging has been recognized by residency programs nationwide, which are increasingly offering hybrid (NM/DR) pathways to train future nuclear medicine and molecular imaging experts. For current and future trainees, this represents an ideal way to accrue the skills and knowledge requisite for modern PET/CT and PET/MR interpretation.

For practicing nuclear medicine specialists, the PET Center of Excellence will be offering a wide range of opportunities for ongoing education/lifelong learning in key areas:

- Co-sponsored MRI case reviews and educational sessions related to PET/MR, as well as Ga-68 DOTA-(x) and other novel PET tracers (including prostate-specific agents), will be held at mid-winter and annual meetings.
- A Lifelong Learning and Self-Assessment Program (LLSAP) module on body MRI will be available through the SNMMI Education Center.
- A planned collaborative SNMMI/ISMRM PET/MR task-force, led by Thomas Hope, MD, will coordinate such activities as journal clubs and stand-alone workshops on PET/MR, and provide an online community for those involved in the clinical use of PET/MR.

Of course, nuclear medicine is not entirely about PET. Other aspects of our profession, including conventional gamma and SPECT/CT imaging, radionuclide therapy, and radiation safety, must remain key components of nuclear medicine training. But, as targeted PET tracers become increasingly available, there is no doubt that PET/CT and PET/MR imaging hold great promise and will likely be the cornerstone of molecular imaging for the foreseeable future. The PET Center of Excellence aims to support members by providing relevant educational material and opportunities to facilitate assimilation of these exciting technologies

(Prostate Cancer Continued from page 4.)

References


Figure 3. Renal cell carcinoma imaging using F-18-DCFPyL PET-CT scan. MIP of PSMA-targeted imaging demonstrating F-18-DCFPyL uptake by metastatic renal cell carcinoma (red arrows).