The Role of Positron Emission Tomography With ^{68}Gallium (Ga)-Labeled Prostate-specific Membrane Antigen (PSMA) in the Management of Patients With Organ-confined and Locally Advanced Prostate Cancer Prior to Radical Treatment and After Radical Prostatectomy

Bhavan Prasad Rai, Richard Paul Baum, Amit Patel, Robert Hughes, Roberto Alonzi, Tim Lane, Jim Adshead, and Nikhil Vasdev

The role of positron emission tomography (PET) with ^{68}Gallium (Ga)-labeled prostate-specific membrane antigen (PSMA) imaging for prostate cancer is gaining prominence. Current imaging strategies, despite having progressed significantly, have limitations, in particular their ability to diagnose metastatic lymph node involvement. Preliminary results of PET with ^{68}Ga-labeled PSMA have shown encouraging results, particularly in the recurrent prostate cancer setting. Furthermore, the ability of PET with ^{68}Ga-labeled PSMA of playing a dual diagnostic and therapeutic setting (theranostics) is currently being investigated as well. PET with ^{68}Ga-labeled PSMA certainly has a role to play in bridging some of the voids in contemporary prostate cancer imaging tools. UROLOGY 95: 11–15, 2016. © 2016 Elsevier Inc.

Primary and recurrent prostate cancers have wide-ranging treatment options including deferred treatment, radical prostatectomy, radiotherapy, focal therapy, and androgen deprivation therapy. Appropriate advocacy of these treatment options hinges on accurate imaging. In the last decade, there has been significant progress in morphological and functional imaging modalities for prostate cancer diagnosis and staging. Despite the significant advances, the limitations of current available imaging modalities are undeniable, particularly in the detection of lymph node metastasis.

The role of transrectal ultrasound in prostate cancer diagnosis is primarily as a guide to systematic or targeted biopsies. Its sensitivity in identifying cancer focus within the prostate and differentiating between T2 and T3 disease is poor.[1] Multiparametric magnetic resonance imaging (MRI) boasts of high diagnostic accuracy in patients with larger volume and higher Gleason score. Its performance in low-volume disease and identifying extraprostatic extension of cancer is less impressive.[1] The ability of multiparametric MRI to identify clinically significant index lesions, which drive progression, is conflicting.[2] Recent advancement in targeted biopsies involving a combination of ultrasound scan and MRI images employing real-time and cognitive fusion strategies has improved the detection rates of clinically significant cancer. Despite this combination strategy, a significant minority of cancers[2] is missed. Bone scan is the main imaging modality for diagnosing bone metastasis in prostate cancer in contemporary practice. It however lacks specificity and positivity rate of less than 1% in low-risk prostate cancers.[1] The main failure of current imaging modalities is their inability to reliably diagnose lymph node metastasis in primary diagnosis or in recurrent prostate cancer. A meta-analysis of 24 studies reported the pooled sensitivity and specificity for computed tomography (CT) for lymph node diagnosis to be 42% and 82%, respectively.[3] For MRI, the review reported the pooled sensitivity and

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From the Hertfordshire and South Bedfordshire Urological Cancer Centre, Department of Urology, Lister Hospital, Stevenage, United Kingdom; the Department of Nuclear Medicine, Center for PET/CT, Zentralklinik Bad Berka, ENETS Center of Excellence, Bad Berka, Germany; the Department of Radiology, Lister Hospital, Stevenage, United Kingdom; and the Department of Oncology, Mount Vernon Cancer Centre, United Kingdom

Address correspondence to: Bhavan Prasad Rai, M.B.B.S, M.R.C.S. (Ed), M.Sc., F.R.C.S. (Urol), Hertfordshire and South Bedfordshire Urological Cancer Centre, Department of Urology, Lister Hospital, Stevenage, United Kingdom. E-mail: urobhavan@gmail.com

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specificity to be 39% and 82%, respectively.[3] Additionally, the ability of current imaging modalities to identify local recurrence, lymph node, bone and visceral metastasis in patients with biochemical relapse after initial curative treatment remains poor, in particular with low prostate-specific antigen (PSA) levels.

MOLECULAR IMAGING AND NUCLEAR MEDICINE IN PROSTATE CANCER

Recent advancement in molecular imaging with positron emission tomography (PET) scans has added an extra dimension in imaging strategies for prostate cancer, with the potential to counter some of the current drawbacks in morphological and functional imaging. PET scans can be employed in isolation or be integrated with existing imaging modalities and consequently improve overall diagnostic accuracy.

Choline-based PET has shown encouraging results in restaging patients for bone and lymph node metastasis after biochemical relapse following initial radical treatment. A recent meta-analysis of 44 studies evaluated the diagnostic accuracy of choline-based PET scans.[4] In a primary staging cohort on a per-patient basis, Umbehr et al reported an overall sensitivity, specificity, diagnostic odds ratio, positive and negative likelihood of 84%, 79%, 20.4%, 4.02%, and 0.20%, respectively. On a per-lesion basis, they reported an overall sensitivity, specificity, diagnostic odds ratio, positive and negative likelihood of 66%, 92%, 22.7%, 8.29%, and 0.36%, respectively. In the restaging cohort, they reported, on a per-patient basis, an overall sensitivity, specificity, diagnostic odds ratio, positive and negative likelihood of 85%, 88%, 41.4%, 7.06%, and 0.17%, respectively. The review emphasizes the value of choline-based PET in prostate cancer imaging, particularly in the restaging groups. Fuccio et al reported that 15% of patients with biochemical relapse have bone metastasis on ^{11}C-choline PET undetected by bone scan.[5] They also reported the sensitivity PET/CT for lymph node metastasis on a patient analysis to be 60%, which is superior to reported sensitivity rates of MRI and CT.

Despite the advantages, choline-based PET scans are not without limitations. The detection rates of choline-based PET scans in patients with low PSA levels are poor. Giovacchini et al reported detection rates of a mere 19% in patients with PSA level of less than 1 ng/dL following radical prostatectomy.[6] This is particularly crucial as salvage radiotherapy is most effective in patients with a PSA of less than 1 ng/dL.[4] Additionally, Giovacchini et al's detection rates for residual local and lymph node disease after external beam radiotherapy are poor.[6] Furthermore, the detected rate of choline PET is poor in patients with a PSA doubling time >3 months and on androgen deprivation therapy, and can have false-positive results in inflammatory conditions and bowel activity.[7]

PET WITH ^{68}GALLIUM (GA)-LABELED PROSTATE-SPECIFIC MEMBRANE ANTIGEN

Prostate-specific membrane antigen (PSMA) is a type II membrane glycoprotein with an intracellular, transmembrane, and an extensive extracellular domain.[8-10] It has two unique enzymatic functions, cleaving terminal glutamate from the neuropeptide, N-acetyl-aspartyl-glutamate, and folate hydrolase activity, which cleaves the terminal glutamates from γ-linked polyglutamates.[9,10] PSMA is expressed on the cell surface and not released into the circulation and is internalized after target binding.[9,10] PSMA expression is increased in high-grade, androgen-independent, and metastatic prostate cancer. Furthermore, PSMA expression is minimal in benign prostatic hyperplasia.[8,9] Bostwick et al analyzed 184 radical prostatectomies specimen for PSMA expression with immunohistochemistry. PSMA expression was significantly lower in benign epithelium (69.5% of cells positive) when compared to adenocarcinoma (80.2% of cells positive).[11] They also reported increased PSMA expression with the grade of the disease. These properties make a very good target for nuclear imaging in prostate cancer.[11]

Various strategies have been employed to target PSMA. Radiolabeled monoclonal antibodies such as J591 have been reported to accurately target bone and soft tissue metastasis from prostate cancer.[12] However, the widespread application of monoclonal antibodies in imaging is limited due to their long half-life and poor tumor penetration, in particular for bone metastasis.[8] In comparison, small-particle imaging agents, especially the ^{68}Ga labeled high-affinity urea-based inhibitors of PSMA, have nearly ideal pharmakokientics.[9,13] Banerjee et al first reported the application of ^{68}Ga PSMA for imaging in prostate cancer.[13] Preliminary studies with PET using ^{68}Ga-labeled PSMA have shown very promising results, with potential to bridge some of issues with choline-based PET scans. ^{68}Ga-PSMA-ligand PET imaging was reported to show a favorable lesion-to-background ratio compared with the presently used choline-based PET examinations.[14]

ROLE IN RECURRENT DISEASE AFTER RADICAL PROSTATECTOMY

Biochemical relapse following radical prostatectomy and radiotherapy occurs in 27%-53% of patients.[15] Over a quarter of patients with PSA recurrence will develop clinical recurrence in around 7-8 years.[15] The diagnostic yield of current mainstream imaging modalities for local recurrence, lymph node, and bone metastasis following radical prostatectomy is extremely poor. Bone scans diagnose less than 5% of bone metastasis in patients with PSAs less than 7 ng/mL.[15] CT scans have a sensitivity of 11%-14% in predicting lymph node and local recurrence in this cohort of patients.[15] The challenge clinician's face in this scenario is striking a balance between delaying metastatic disease and overtreatment. Furthermore, one of the major drivers

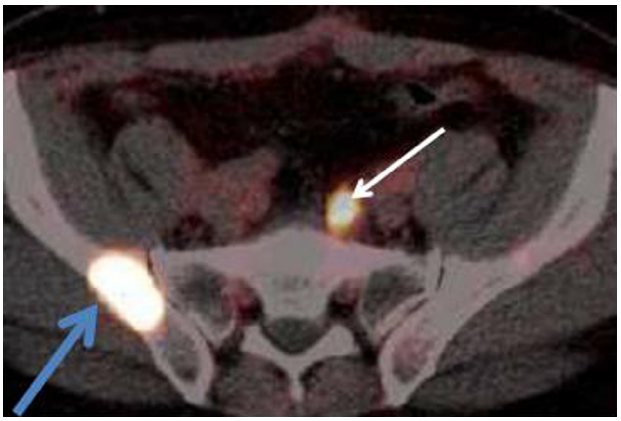

Figure 1. Status post radical prostatectomy (margin's positive, Gleason 9) and pelvic lymphadenectomy. PSA after 1 month = 0.37 ng/dL. ^{68}Ga PSMA PET/CT shows retroperitoneal and bone metastasis. CT, computed tomography; Ga, gallium; PET, positron emission tomography; PSMA, prostate-specific membrane antigen. (Color version available online.)

of interest in detecting very low-volume disease in the recurrent setting is now the feasibility of treating oligometastatic disease with technologies such as stereotactic radiotherapy and in doing so alter the natural history of the disease and potentially obtain a further clinical/biochemical remission.[16] ^{68}Ga-labeled PSMA ligand PET imaging has had its most promising outcomes in patients with recurrent prostate cancer and its ability to detect metastatic disease at low PSA levels (Fig. 1).

In a recent retrospective series, Eiber et al reported the detection rates and factors influencing detection rates of hybrid ^{68}Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence following radical prostatectomy.[17] The hybrid ^{68}Ga-PSMA ligand PET/CT detection rates were 96.8%, 93.0%, 72.7%, and 57.9% for PSA levels of ≥2, 1 to <2, 0.5 to <1, and 0.2 to <0.5 ng/mL, respectively.[17] The detection rates improved, with PSA velocity reaching 100%, ≥5 ng/mL/year, and with higher Gleason scores (≤7 vs ≥8).[17] PSA doubling time and anti-androgen therapy did not appear to significantly influence detection rates.[17] The PSMA hybrid ^{68}Ga-PSMA ligand PET/CT performed better than CT scans. Fifty-eight percent of the patients had additional lesions detected by ^{68}Ga-PSMA ligand PET but missed by CT scans.[17] Afshar-Oromieh et al compared detection rates between ^{68}Ga-labeled PSMA ligand and ^{18}F-choline-based PET/CT in 37 patients who had biochemical recurrence after radical prostatectomy or radiotherapy.[18] ^{68}Ga-labeled PSMA ligand-based PET/CT had statistically significantly higher detection rates than ^{18}F-choline-based PET/CT.[18] Furthermore, ^{68}Ga-labeled PSMA ligand-based PET/CT detected all lesions picked up by ^{18}F-choline-based PET/CT.[18] Giesel et al compared the lymph node detection rates between ^{68}Ga-labeled PSMA ligand-based PET/CT imaging and 3D CT volumetric lymph node assessment in 21 patients with intermediate and high-risk prostate cancer who had biochemical recurrence after radical prostatectomy.[19] ^{68}Ga-PSMA PET/CT was more sensitive than volume-based CT evaluation of lymph node recurrence, with ^{68}Ga-PSMA PET/CT detecting nodal recurrence in two-thirds of patients who would have otherwise been missed by CT evaluation.[19]

ROLE OF LYMPH NODE STAGING PRIOR TO RADICAL PROSTATECTOMY

The accuracy of current imaging modalities for lymph node staging is poor. Therefore, clinicians are reliant on preoperative models using PSA levels, Gleason score, and T-stage to dictate lymphadenectomy protocols.[20] Clearly, lymphadenectomy adds a significant morbidity to the radical prostatectomy procedure and accurate staging can avoid this. The evidence favoring ^{68}Ga-PSMA ligand PET imaging for detection of lymph node metastasis in this cohort of patients is promising, although not as convincing as in the recurrent prostate cancer cohort.

Eiber et al prospectively evaluated ^{68}Ga-labeled PSMA ligand PET imaging for preoperative lymph node staging in 37 intermediate and high-risk patients undergoing radical prostatectomy and extended pelvic lymph node dissection.[21] In the PET positive cohort (33/37), on patient-based analysis, sensitivity and specificity were 75.0% and 96.0%, respectively (area under curve 0.848). On field-based analysis, the sensitivity and specificity were 64.7% and 98.2%, respectively (area under curve 0.813).[21] In the PET-negative patients (4/37), two had false-negative results.[21] In a recent retrospective series, Budäus et al reported less promising results with overall sensitivity, specificity, positive predictive value, and negative predictive value of ^{68}Ga-PSMA PET/CT for lymph node metastasis detection of 33.3%, 100%, 100%, and 69.2%, respectively.[22] This group hypothesized that in primary staging, a significant proportion of the PSMA ligand is taken up by the prostate as a result, limiting its availability in the lymph nodes.[22] Other suggestions for the less impressive outcomes were restricted perfusion in lymph node metastasis due to a critical size or vascularization threshold, variable expertise, and small sample size.[22]

THERANOSTICS

Theranostics is a concept wherein novel diagnostic tools have a therapeutic role as well. Newer ligands such as PSMA I&T can be labeled with ^{177}Lu. Preliminary reports have suggested that this combination has a dual diagnostic and therapeutic role in prostate cancer. ^{68}Ga and PSMA I&T has been reported to have favorable dosimetry and whole body distribution in patients with known prostate cancer[23] Weineisen et al reported the first "human proof of concept study" where they diagnosed and treated two patients with metastatic prostate cancer with ^{68}Ga- and ^{177}Lu-labeled PSMA I&T. These patients showed a positive molecular, biochemical (decrease in PSA) response, and a decrease in bone pain.[24] A larger series of 56

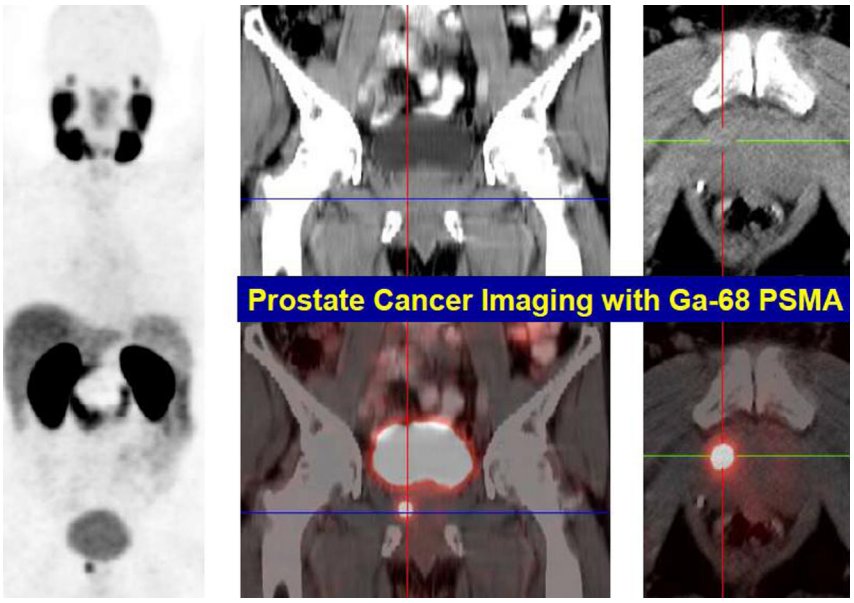

Figure 2. PSA = 8 ng/mL; initial transrectal ultrasound-guided prostate biopsy = negative. ^{68}Ga PSMA PET/CT shows tumor in the right prostate lobe. Repeat targeted prostate biopsy = Gleason 4 + 5 = 9. CT, computed tomography; Ga, gallium; PET, positron emission tomography; PSMA, prostate-specific membrane antigen. (Color version available online.)

patients with metastatic castration-resistant prostate cancer, treated by ^{177}Lu-PSMA radioligand therapy, was recently published by Baum et al with very encouraging results: the median progression-free survival was 13.7 months, and the median overall survival was not reached at follow-up of 28 months in these end-stage, heavily pretreated patients.[25]

OTHER POTENTIAL ROLES

The impact of ^{68}Ga-PSMA ligand PET imaging in primary local staging is less clear. It does, however, have the potential to address some of the current inadequacies in prostate cancer imaging. In contemporary practice, patients with suspicion of prostate cancer undergo diagnostic evaluation with direct transrectal ultrasound-guided prostate biopsies or cognitive and noncognitive fusion biopsies with primary reliance on multiparametric MRI prostate cancer staging. The ability of MRI to diagnose small-volume prostate cancer focus (<0.2 mm) and low-grade disease (Gleason 3 + 3) is limited. In this setting, additional molecular information provided by ^{68}Ga-PSMA ligand PET/MRI, in conjunction with high-resolution anatomical images and functional information from multiparametric MRIs, can further refine the targeting of suspicious regions[26] within the prostate (Fig. 2). Furthermore, the information gained by integration of MRI and ^{68}Ga-PSMA ligand PET could be very useful in focal therapy. However, prospective larger studies are required to confirm this hypothesis. MRI is a poor predictor of extraprostatic extension of prostate cancer. This is another area where ^{68}Ga-PSMA ligand PET could add valuable information. Finally, MRI and CT scans have a number of contraindications where perhaps ^{68}Ga-PSMA ligand PET can be employed as an alternative.

CONCLUSION

The advent of ^{68}Ga-PSMA ligand PET as a novel diagnostic tool in the imaging of prostate cancer is encouraging and exciting. Its role in detecting local and metastatic disease in recurrent prostate cancer at low PSA levels holds significant promise for the future. Its role in primary staging, although less convincing, is promising. Clearly, the technology requires further refinement before it can have widespread acceptance. Although further confirmatory data are required, ^{68}Ga-PSMA ligand PET can be cautiously introduced and relied upon in select group of patients.

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