Hybrid PET/CT Molecular imaging in Carcinoma Prostate with $^{68}$ Ga labelled PSMA ligand - A large single centre experience

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Authors: P. Shriduth, A. Sasikumar, A. Joy; Trivandrum/IN
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Learning objectives

To evaluate the role of $^{68}$Ga labelled Prostate-Specific Membrane Antigen (PSMA) ligand hybrid PET/CT in Primary and Recurrent Carcinoma Prostate for lesion characterisation, lymph node involvement and skeletal and liver metastases in the following group of patients:

• Suspected Carcinoma Prostate with increase of tumor marker PSA.
• Initial staging in biopsy proven cases.
• Restaging after radiotherapy.
• Suspected recurrence of tumor or metastasis with rising serum PSA levels after radical prostatectomy or radiotherapy (Biochemical recurrence).
• RT planning.
• Thranostics using $^{177}$Lu PSMA endoradiotherapeutic treatment in patients with metastatic and castration resistant disease.
• Suspected prostate cancer despite negative biopsy, such as in the planning of a new, targeted biopsy.
Prostate Cancer (PCa) is the second most common cause of cancer and sixth leading cause of death among men worldwide. More than 1.1 million cases of PCa were recorded in 2012, accounting for around 8% of all new cancer and 15% in men\[^1\]. The worldwide PCa burden is expected to grow to 1.7 million new cases and 499,000 new deaths by 2030 \[^2\]. The incidence of PCa in India ranges from 3.38-5.39\%\[^3\].

Measurement of Prostate Specific Antigen in serum is a cornerstone in the screening and monitoring of PCa. Rising PSA levels are usually correlated with imaging, followed by biopsy for suspicious lesions. With regard to imaging, Transrectal ultrasound (TRUS) has a low diagnostic accuracy in the detection of local PCa and recurrence because of several limitations, which mainly include iso to hypoechoic lesions, post-treatment changes of the normal pelvic anatomy, and small volume recurrences. When TRUS enables the identification of suspected areas in the prostatic fossa, the use of TRUS-guidance for targeting the biopsy procedure increases the rate of positive sampling\[^4\]. However, a TRUS-guided negative biopsy is not adequate to rule out the presence of primary or local recurrence.

Multiparametric MRI (mpMRI) is an excellent imaging modality for anatomical information, especially because it provides good contrast between different soft tissues and currently considered as one of the most promising diagnostic modalities for evaluating PCa patients. In mpMRI, high resolution T2-weighted sequences are combined with functional techniques, including diffusion weighted imaging (DWI), dynamic contrast-enhanced (DCE) sequences, perfusion imaging, and spectroscopy. However, there are pitfalls that confound the interpretation of Multiparametric Prostate MRI which include, a) Normal anatomic structures that may be mistaken for tumor (Central zone, Thickening of surgical capsule, Periprostatic venous plexus, Neurovascular bundle), b) Noncancerous abnormalities that can mimic tumor (Postbiopsy hemorrhage, Stromal BPH nodule, Acute and chronic prostatitis and postinflammatory scars and atrophy, Granulomatous prostatitis), and c) Technical challenges related to diffusion-weighted imaging (Anatomic distortion of high-b-value diffusion-weighted images, Lack of suppression of benign prostate tissue on standard high-b-value diffusion-weighted images, Suboptimal windowing of the ADC map)\[^5\]. In addition, MRI often fails to differentiate benign from metastatic small lymph nodes. Knowledge on lymph node metastases is crucial for the prognosis and treatment of prostate cancer patients. The normal upper limit of the short-axis diameter of pelvic lymph nodes is 7-10 mm depending on the location. However, up to 80\% of metastatic lymph nodes in prostate cancer have a short axis diameter smaller than 7 mm \[^6,7\]. Therefore, it is not surprising that
a less sensitivity is reported for conventional computed tomography (CT) and magnetic resonance imaging (MRI), as they rely on the size criteria to differentiate between benign and malignant lymph nodes. Pelvic lymph node dissection is an invasive technique and underestimates the extent of lymph node metastases. Therefore, there is a need for more accurate non-invasive diagnostic techniques.

Prostate-specific membrane antigen (PSMA), also known as Glutamate carboxypeptidase II (GCPII), or N-acetyl-L-aspartyl-L-glutamate peptidase I (NAALADase I), NAAG peptidase is a type II integral membrane glycoprotein expressed in many tissues, including the prostate, kidney, small intestine, and the central and peripheral nervous system. PSMA is strongly expressed in the human prostate, being a hundredfold greater than the expression in most other tissues. In cancer, it is upregulated in expression and has been called the second-most-upregulated gene in prostate cancer, with increase of 8- to 12-fold over the noncancerous prostate. Because of this high expression, it is being developed as a target for therapy and imaging. Recently, labelling procedures have been developed to label PSMA ligands with \(^{68}\text{Ga}\) which makes them suitable for PET / CT imaging.

The detection of prostate cancer lesions by PET imaging of the Prostate-Specific Membrane Antigen (PSMA) has gained highest clinical impact during the last years. Hybrid PET-CT Imaging with \(^{68}\text{Ga}\)-PSMA ligand can present lesions suspicious for prostate cancer with excellent contrast. \(^{68}\text{Ga}\)-PSMA PET/ CT proved to be clearly superior in detecting PCa at low PSA levels due to its high sensitivity and specificity, and presenting lymph node with high contrast when compared to \(^{18}\text{F}\) choline-based PET/ CT.
Findings and procedure details

Procedure details:

In our centre, radiolabelling of PSMA ligand with $^{68}$Ga is done using on-site commercially available $^{68}$Ge/$^{68}$Ga generator (itG) and synthesis module as per standard operating procedure supplied by the manufacturer and there is no need for a cost-intensive cyclotron. No fasting or special patient preparation is required prior to the study. Dose of 3-4mCi $^{68}$Ga PSMA is injected intravenously. The tracer is well tolerated. Whole body PET imaging and non contrast CT scan (Hybrid PET/CT) are done on 6 slice PET-CT machine one hour after injection.

With $^{68}$Ga PSMA having a short half life (68 minutes), excellent labelling chemistry, fast background clearance, early imaging is possible and high resolution PET images are produced.

Findings:

We prospectively analysed 150 males with a median age of 70 years (Range:37-90yrs) having a median PSA value of 11.6ng/ml (Range: 0.96 to 4156ng/ml) with a diagnosis or clinical suspicion of PCa done in our centre during June - December 2015. Patients were injected an average dose of 3.61mCi $^{68}$Ga PSMA (Range : 2.95-5.57 mCi). No adverse pharmacological reaction were noted after injection.

All images were interpretable, and lesions had excellent target to background ratio.

Image analysis:

Image analysis was performed using an appropriate workstation and software. Two certified consultants, a Nuclear medicine and a Radiologist, reported all PET/CT data sets respectively.

Normal physiological uptake is seen in salivary and lacrimal glands, liver, kidneys, spleen, bowel, and urinary bladder. Intense PSMA overexpression/avidity in the prostate gland
favours PCa. In our centre, all PSMA avid prostatic lesions were either biopsy proven malignancy and for those cases suspecting PCa, PSMA avid lesions were confirmed as PCa histologically. Intense avidity in lymph nodes, liver and skeleton suggest metastases.

Limitations:

PSMA has been suggested to be involved in tumor angiogenesis. Several studies suggested that PSMA expression is not restricted to prostate epithelial cells but can also be found in tumor-associated endothelial cells in many different solid malignancies\textsuperscript{[12-16]}. We had a patient (Fig.22), with rising PSA levels suspecting PCa, PET/CT showed normal prostate and PSMA overexpressing large liver lesion, which was histologically proven as HCC. However, due to selective overexpression of PSMA in 90-100\% of local PCa lesions, as well as in cancerous lymph nodes, and bone metastases\textsuperscript{[17-19]}, \textsuperscript{68}Ga PSMA is considered a reliable tissue marker for PCa and is an ideal target for therapeutic applications\textsuperscript{[20-24]}.

\textsuperscript{68}Ga PSMA PET/MRI in comparison to PSMA PET/CT has the advantages of different diagnostic sequences, higher contrast of lesions and higher soft tissue resolution, thus enabling a subjectively easier evaluation of the image\textsuperscript{[25]}. Infact, NCCT is not accurate at detecting insitu prostate cancer and can only be helpful prior to the onset of radiation therapy to identify bony landmarks for planning and to identify enlarged pelvic and retroperitoneal lymph nodes, hydronephrosis and osteoblastic metastases. Moreover, another advantage of \textsuperscript{68}Ga PSMA PET/MRI is that there is radiation related to CT. Eventhough, in our centre we follow a low-dose CT protocol, this can be avoided as with PET/MRI.

As pelvic lymph node dissection is invasive, all nodal metastases could not be biopsied and proved histologically in our centre. However, a histopathologic confirmation in all patients is not feasible because practical and ethical issues, especially in the setting of recurrent PCa\textsuperscript{[26]}.

Although PSMA-negative PCa seems to be rare\textsuperscript{[27,28]}, we cannot totally exclude the possibility of false-negative PET/CT imaging in patients without pathological findings.
Fig. 3: Diagnosed PCa post RT for restaging, PET/CT depicting minimal normal diffuse uptake and calcifications seen with no focal PSMA overexpression in the gland to suggest residual tumor.

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**Fig. 4:** Same patient showing focal intense PSMA avidity in the right high frontoparietal bone representing metastasis.

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**Fig. 5:** Corresponding CT image of the above patient showing no definite calvarial lesion. Asymmetric slight sclerosis appreciated on right high frontoparietal bone.

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Fig. 6: Suspected PCa with rising PSA levels, PET/CT showing minimal diffuse normal glandular uptake and no PSMA overexpression to suggest tumor, so he was put on follow up.

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**Fig. 7:** Another suspecting PCa, PET/CT showing intense PSMA uptake involving the entire gland.

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**Fig. 8:** Above patient also shows a small left internal iliac lymph node with PSMA overexpression consistent with metastasis.

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Fig. 9: Corresponding NCCT image of the above patient showing small left internal iliac lymph node <10 mm in short axis dimension.

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**Fig. 10:** Diagnosed PCa with intense PSMA uptake in the gland and in the pelvic bone, latter suggesting metastases.

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Fig. 11: Above patient also has PSMA uptake in bilateral iliac lymph nodes and iliac bones consistent with metastases. Normal physiological bladder tracer accumulation is seen.(Image courtesy to our Technologist Jayakrishnan)

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**Fig. 12:** 75 yr old PCa patient, post RT restaging PET/CT showing no focal glandular PSMA avidity to suggest residual intraprostatic tumor.

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Fig. 13: Above patient shows a small preaortic lymph node showing intense PSMA uptake consistent with metastasis.

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Fig. 14: Corresponding NCCT image of the same patient showing small preaortic lymph node.

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**Fig. 15:** Same patient also had metastatic PSMA avid mediastinal lymphadenopathy.
**Fig. 1:** Generator and synthesis module in our centre with white Lead boxes containing radioactive (68)Ga-PSMA-HBED-CC(Image courtesy to our Radiopharmaceutical Chemist Raviteja Nanabala).

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Fig. 16: Focal PSMA uptake in vertebral body and left scapula in a patient with recurrence
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Fig. 17: Corresponding CT image of the above patient showing no visible focal bony lesions in spine or scapula

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Fig. 19: PET/CT of a patient with elevated PSA levels suspecting PCa. Focal large PSMA uptake seen in right lobe of liver, and no PSMA expressing lesions in prostate. Biopsy proved HCC.

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**Fig. 20:** NCCT of the same patient showing hypodense large right lobe liver lesion.

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Fig. 18: Whole body Maximum Intensity Projection image of another patient displaying focal uptake in right iliac station representing nodal metastasis.

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Conclusion

- Hybrid PSMA PET/CT imaging with $^{68}$Ga labelled PSMA ligand has a high detection rate in Primary and Recurrent Carcinoma Prostate.

- The most significant advantages of $^{68}$Ga-PSMA PET/CT are the increased detection of lesions even at low PSA levels, and excellent contrast in small lymph node metastases, primarily due to high radiotracer uptake.

- The superior contrast in $^{68}$Ga-PSMA PET/CT has also been demonstrated in most skeletal and liver metastases and local relapses and can also be directed for targeted TRUS guided biopsy, thus might be useful to reduce multiple investigations, and in aiding in decision making and impacting on patient management outcome.
Personal information

P. Shriduth is an MD Radiologist, and is now working as Consultant in DDNMRC KIMS Hospital, Trivandrum, Kerala, India.

Contact: dr.shriduth@gmail.com
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