Clinical Utility of Gallium-68 PSMA PET/CT Scan for Prostate Cancer

Abstract

Background: Prostate cancer is biologically and clinically a heterogeneous disease that makes imaging evaluation challenging. One of the important challenges in this cancer is to detect recurrent disease. Biochemical response using Prostate Specific Antigen (PSA) and Imaging using several PET tracers have poor sensitivity and specificity. Therefore, we analyse the role of Ga68-PSMA (Prostate Specific Membrane Antigen) imaging in prostate cancer, which is a new PET tracer. **Methods:** In this study, we evaluated PET scans of 262 patients with diagnosis of prostate cancer. These patients were scanned using Ga68-PSMA for either staging or response evaluation. **Results:** 336 PSMA scans were performed. Ga68-PSMA scan resulted in the detection of extra-prostatic disease in 53.2% of cases when done at baseline before commencing any treatment. The sensitivity of Ga68-PSMA at baseline with histopathological diagnosis was 95% with 95% CI ranging from 86% to 98%. The positive predictive value was high at 98% with 95% CI ranging from 91% to 99%. In 26 (10%) patients who had surgical castration, Ga68-PSMA scan was able to detect disease progression / castration resistance in 100% of cases. The outcome of castration-resistant prostate cancer was compared with other cases where castration was not done. In those who did not undergo castration, there was a significantly better response by hormone therapy (p = 0.03) and radiotherapy (p = 0.01) on Ga68-PSMA. The sensitivity of Ga68-PSMA response with biochemical response was 66.7% with 95% CI ranging between 46 %- 82.7%. Ga68-PSMA response did not correlate with biochemical response. **Conclusion:** Ga68-PSMA has good sensitivity for diagnosis, staging, restaging, evaluation of therapy response and prognostication in prostate cancer.

Key words: *PET SCAN, Ga68-PSMA, diagnosis, molecular imaging, prostate cancer*

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Introduction

Diagnosis and treatment response in prostate cancer is a major challenge faced by oncologists and radiologists all over the world; as both PSA levels and imaging have had their limitations with respect to diagnosis, staging, and prognosis. Both conventional radiological imaging and PSA levels show high false positives during screening due to confounding effects of benign prostatic hyperplasia and prostatitis.[1] The advent of PET has seen the use of several radiotracers such has FDG PET, 11C-Acetate, F18-Choline, and C11-Choline for prostate cancer imaging. FDG-PET avidity in prostate cancer is minimal and variable and could be an incidental finding due to benign disease. There was no significant change between normal prostate, BPH and prostate cancer on SUV max values with 11C PET as well as early to late ratios indicating that 11C acetate is not a sensitive marker for detection of prostate cancer. This is because age causes physiological accumulation of 11C acetate and therefore careful interpretation of images is necessary.[2] Apart from this, 11C acetate uptake is also present in other tissues such as liver, cardiac, bladder etc. thereby being nonspecific for prostate cancer. The sensitivity and specificity of these imaging modalities are low with low PSA values.[3-8] PSA values show a lot of inter and intra-individual variations with time due to manipulations of the prostate and are less reliable as a standalone marker. The significance of PSA values has to be correlated with imaging modalities since lymph node and skeletal metastases can be present without any obvious increase in PSA values or PSA levels could increase after chemotherapy without any obvious underlying disease.[1,9,10] These problems have led to identification of more robust surface biomarkers in prostate cancer.

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One such molecule is Prostate specific membrane antigen (PSMA). Prostate-specific membrane antigen (PSMA) is a peptidase that is involved in the hydrolysis of *N*-acetyl-L-aspartyl-L-glutamate (NAAG) into the corresponding *N*-acetyl-L-aspartate (NAA) and L-glutamate.[11,12] Compared to healthy human prostate tissue or hyperplasia, in almost all Prostate Carcinoma (PCa) tumors, the expression of PSMA is 10-80 fold higher indicating that PSMA has an important role in carcinogenesis.[13] Further animal studies have also shown that PSMA is required for angiogenesis and is increased in neovasculature of other solid tumors as well.[14] Therefore, using PSMA tagged with appropriate radionuclide is a useful approach for diagnosis and prognosis of prostate cancer with PET.

Prostate-specific membrane antigen (PSMA) is a cell surface protein expressed abundantly in PCa cells.[15] While Choline metabolism has not increased in a large number of cases, prostate-specific membrane antigen (PSMA) is over expressed in most PCa.[16] Secondly, the transmembrane location of PSMA with large extracellular domain allows for its internalization after ligand binding, providing an accurate target for prostate carcinoma specific imaging and therapy.[17,18] Recently, procedures have been developed to label PSMA ligands with Ga68, 99mTc, and 123/124/131-Iodine. Earlier observations with Glu-NH-CO-NH-Lys-(Ahx)-[68Ga (HBED-CC)] (Ga68-PSMA) suggests that this novel tracer can detect PCa relapses and metastases with high sensitivity.[16,19,20] A recent meta-analysis has shown that PSMA seems to have a greater likelihood of detecting extra-prostatic disease, along with lymph node and bone lesions compared to Choline or Acetate PET scans.[21] Though this meta-analysis addressed issues with Choline PET imaging, the number of studies with Ga68-PSMA was proportionately limited to arrive at findings that are more conclusive. Several other studies have shown a strong correlation between PSMA, stage of disease and Gleason's score.[22] Hormone refractory cancers also show high PSMA[23] and high PSMA is an independent marker of disease recurrence.[12,24]

In this retrospective observational study, we report our experience of prostate cancer imaging with Ga68-PSMA and other PET Tracers used in the period 2012-2014.

Materials and Methods

336 PSMA scans of Prostate Cancer patients with a median prostate-specific antigen (PSA) 25.5 ng/ml were retrospectively analyzed with Ga68-PSMA PET/CT in 262 subjects with prostate cancer. 128 patients had follow-up scans using Ga68-PSMA. Radiotracer uptake was semi-quantitatively analyzed by measuring the maximum standardized uptake values (SUVmax) of the scans acquired 1-hour after injection of Ga68-PSMA tracer (median 111 MBq, range 74-185 MBq).

Imaging protocol

Images were obtained with the Ga68-labelled HBED-PSMA that was synthesized as reported in an earlier study.[25] 68Ga3+ (half-life 68.3 min) was obtained from a Ge68/Ga68 radionuclide generator[26] and complexed with the HBED-PSMA conjugate as per published protocol.[16,25,27] The final product was dissolved in isotonic phosphate buffered saline (PBS) with subsequent sterile filtration for human use.

The Ga68-PSMA complex solution was administered to patients via an intravenous bolus injection (median 111 MBq, range 111–185MBq).

The whole body contrast diagnostic CT scan was acquired with 3.75mm slice thickness with reconstruction interval of 3.27mm and with standard reconstruction kernel, where the PETCT scan initiated 1-hour post-intravenous injection of Ga68-PSMA. Following CT acquisition, a whole body PET image was acquired with 192*192 Matrix. For each bed position, we used 2 min acquisition time with 15% overlap in 15.7cm axial field of view. The emission data was attenuation corrected along with scattering, random and decay correction. Reconstruction was conducted with an ordered subset expectation maximization algorithm incorporated with the time of flight technology and point spread function to maintain the uniform resolution across the field of view. The OSEM reconstruction was performed using two iterations/18 subsets and Gaussian-filtered to the spatial resolution of less than 3mm at FWHM. Attenuation correction was performed with contrast-enhanced CT data with automatic contrast correction algorithm. The PETand CT data was acquired with single contrast injection and single CT acquisition for both attenuation correction and co-registration in advanced Rad Rx PETCT protocol on Discovery PETCT 690 scanner. Due to high contrast and significantly higher accumulation of Ga68-PSMA in the malignant tissue, one hour delayed images do not affect the assessment of prostatic bed even though there is urinary bladder activity. Dual phase scan for the prostate bed is not necessary unlike F18/C11-Choline scans in our experience.

SUVmax

Lesions that were visually considered as suggestive of a primary tumor, relapses or metastases of prostate cancer were counted and analyzed with respect to their SUVmax. A cut-off value of SUVmax 4.0 over the prostate gland was considered as abnormal as per published literature.[16] Thus, SUVmax values of more than 4.0 and above over prostatic bed (primary or recurrence) were considered as suspicious of malignancy or recurrent tumor. Any abnormal Ga68-PSMA scan outside the prostate bed especially in lymph nodes and skeleton and in any visceral organs was considered as highly probable for metastatic disease. For calculation of the SUVmax, region of interest were highlighted with cursor selection around areas with focally

increased uptake in trans-axial slices and automatically adapted to a three-dimensional volume of interest at a 42% threshold segmentation method.

Results

A total of 336 [Table 1] Ga68-PSMAPET CT scans were done either to detect tumor lesions in de novo cases, confirm biochemical relapses, clarify suspicious findings with other imaging modalities and evaluate treatment response. The median age was 68.0 years (range 52-87) with a median Gleason score (GSC) of 7.0 (range 5-9) and a median prostate-specific antigen (PSA) level of 25.5 ng/ml.

In this retrospective observational study, 262 patients with a known diagnosis of carcinoma prostate or suspected recurrent prostate cancer were evaluated using Ga68-PSMAPET Imaging. The patients enrolled between years 2012-2014 were analyzed. The mean age of the study population was 67.6 ± 8.8 years. The clinical characteristics of the study population are elucidated in Table 1. There was a better resolution of prostatic bed disease with Ga68-PSMA scan despite urinary activity [Figure 1].

Table 1: Clinical characteristics of study population

Clinical Characteristics	N (%)
Mean age in years	67.6±8.8
Gleason score	
Low risk (<4 Score)	3 (1%)
Moderate risk (4-6 score)	62 (24.1%)
Intermediate risk (7-8)	125 (47.7%)
High risk (9-10)	70 (27.2%)
Disease extent	
Localized	164 (63.1%)
Loco regional	28 (10.7%)
Distant spread	68 (26.2)
New/Recurrent	
New	235 (90.4%)
Recurrent	25 (9.6%)

Urinary bladder activity does not affect the assessment of prostatic bed. Even though the urinary bladder is full with radioactivity, it is not difficult to assess the prostate malignancy in the prostate bed due to high contrast. It is difficult to assess prostate bed in F-Choline scans (see Figure1)
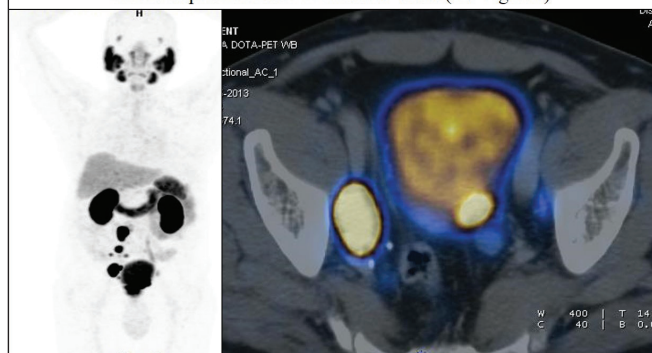
Figure 1: Activity in prostatic bed irrespective of activity in urinary bladder

Indication for scans

Most of the Ga68-PSMA scans (72%) were performed post treatment and 28% were performed during staging [Table 2].

In 80% of cases, Ga68-PSMA scan was done one time and in other 20%, it was done two or more times. Total number of scans done in 262 patients was 336 [Table 3].

Ga68-PSMA scan resulted in detection of extra prostatic disease in 53.2% when done at baseline before commencing any treatment. All of them had undergone non-PET conventional imaging with either ultrasound scan or pelvis, CT scan, MRI and other modalities. Ga68-PSMA scan picked up extra prostatic lesions that were not picked up by these scans resulting in upstaging of disease [Table 4].

Response following Treatment

In 72% of cases where Ga68-PSMA scan was performed following various cancer-directed treatments. Response was assessed using PERCIST criteria. Progressive disease was detected more following prostatectomy (48.9%), hormone therapy (47.7%) and post completion of all treatments (48%). Complete response was seen following stereotactic radio robotic surgery in 15 cases [Table 5]. Response evaluation after chemotherapy is illustrated in Figure 2.

Table 2: Indication for scans

PSMA PET Scan	When performed		Total
	Post Treatment	Staging	N
	N	N	
PSMA PET	242	94	336

Table 3: Number of PSMA Scans

No of PSMA scans	No of cases	Total number
1	208	208
2	39	78
3	11	33
4	3	12
5	1	5
Total	262	336

Table 4: Upstaging with Ga68-PSMA PET scan at baseline

Upstaging at Baseline	Not upstaged N (%)	Upstaged N (%)
Baseline Ga68-PSMA PET (n=94)	44 (46.8)	50 (53.2)*
Lymph node metastases		38
Skeletal /Visceral Metastases		23
Both		12

*proven with biopsy in 10/10 cases in extra-prostatic sites

Sensitivity of Ga68-PSMA

The sensitivity of Ga68-PSMA at baseline with histopathological diagnosis was 95% with 95% CI ranging from 86% to 98%. The positive predictive value was high at 98% with 95% CI ranging from 91% to 99%. We were not able to determine specificity as most of these cases were malignant cases and non-malignant cases

in our data were negligible [Table 6]. PSMA scan was done prior to the prostate biopsy. Multi-core biopsy was done from the prostate gland after the PSMA scan. A proportional increased Ga68-PSMA accumulation in the prostate gland was observed with a higher tumor volume, high Gleason's score. However, this was not a significant correlation (r = 0.23). GA68-PSMA scan correlating with histopathological diagnosis is shown in Figure 3.

Ability of Ga68-PSMA Scan to predict Castration resistance

In 26 (10%) patients who had undergone orchidectomy, Ga68-PSMA scan was able to detect disease progression / castration resistance in 100%. The outcome of castration-resistant prostate cancer was compared with other cases where surgical castration was not done. There was a significant better radiological response following hormone therapy (p = 0.03) and following RT (p = 0.01) in those who did not undergo surgical castration [Table 7] in our study population. The response of castration-resistant tumors following antiandrogen therapy is illustrated in Figure 4 and Figure 5.

Correlation of Ga68-PSMAPET with Biochemical response

The best overall response with PSMA was assessed following treatment and patients categorized as responders on Ga68-PSMA Imaging. This was compared with the change in PSA levels. PSA levels ≤ 2.0 ng/dl was considered as the cutoff.[28] Those with PSA levels above this cut off were considered non-responders and those below were

Table 5: Frequency of type of response following cancer directed treatment using PSMA scans

Interval of PSMA PET Scan	Progressive disease N (%)	Stable disease N (%)	Partial response N (%)	Complete response N (%)
Post-surgery	24 (48.98)	14 (28.57)	11 (22.45)	0
Post-HT	21 (47.7)	12 (27.3)	6 (13.6)	5(11.4)
Post-RT	16 (37.2)	15 (34.8)	12 (27.9)	0.00
Post-CK	4 (16)	2 (8)	4 (16)	15 (60)
Post-CT			5 (83.3)	0
1 (16.7)				
0.00				
Post Overall treatment	36 (48)	8 (4.3)	17 (6.4)	14 (18.7)

Table 6: Sensitivity of PSMA scans with histopathological diagnosis of the primary prostate

Ga68-PSMA PET	Histopathology Diagnosis		Totals
	Non Malignant	Malignant	
Test Positive	1	71	72
Test Negative	0	4	4
Totals	1	75	76

Example of response evaluation for chemotherapy
(See Figure 2)

Before Chemotherapy SUVmax 35.6 (over Lumbar vertebra) PSA -237.6ng/ml	After 3 Cycles of Chemotherapy SUVmax 15.8 (over Lumbar vertebra) PSA- 173ng/ml

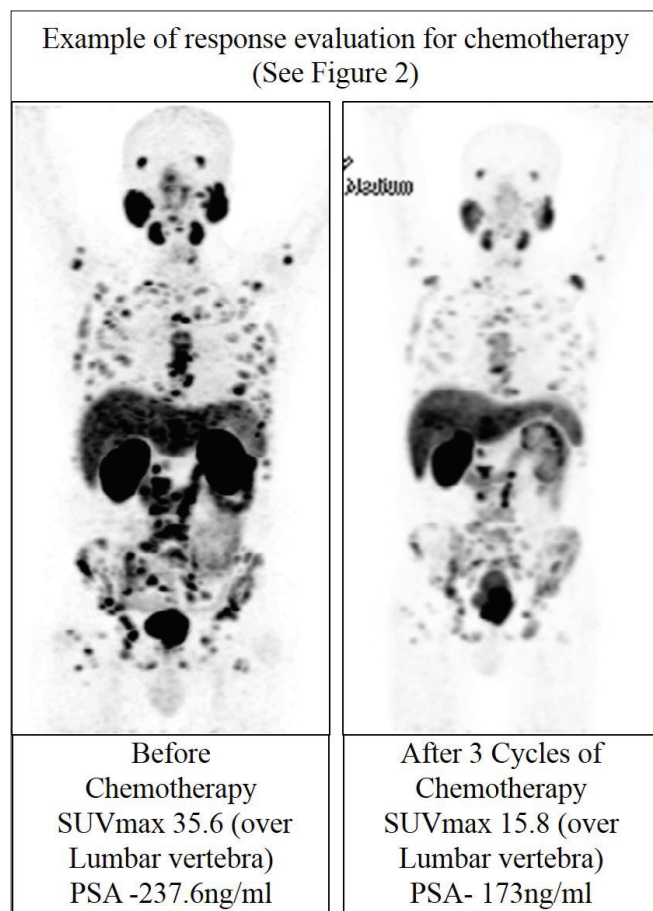**Figure 2: Partial response to chemotherapy is seen by way of demonstrating reduction in number as well as SUV of many PSMA avid metastases.**

Correlation of uptake pattern with histopathology report.

Higher PSMA accumulation in the cores from 1, 2, 3 region as mentioned in the diagram. (See Figure 3)
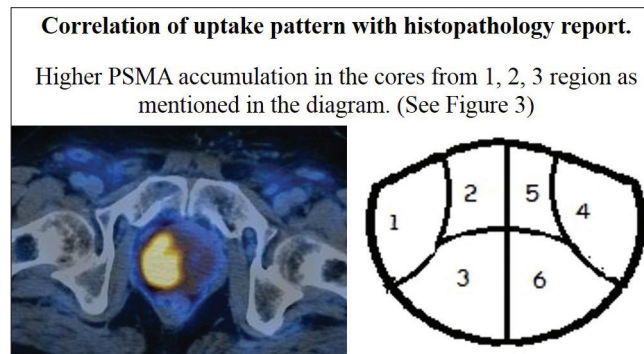

Figure 3: Cores from regions 1, 2 and 3 reported adenocarcinoma on histopathology.

Table 7: Comparison of response in Ga68-PSMA Scans following surgical castration vs. no castration in castration resistant prostate cancer

Treatment	Progressive disease N (%)	Stable Disease N (%)	Partial Response N (%)	Complete Response N (%)	Chi Square, p value
PSMA PET RESPONSE					
Post-Surgery					
Castration, No	19 (46.3)	11 (26.8)	11 (26.8)	0	2.77,
Castration, Yes	5 (62.5)	3 (37.5)	0	0	p=0.27
Post Hormone Therapy					
Castration, No	14 (37.8)	12 (32.4)	6 (16.2)	5 (13.5)	9.11,
Castration, Yes	7 (100)	0	0	0	p=0.03
Post Radiotherapy					
Castration, No	11 (31.4)	12 (34.3)	12 (34.3)	0	8.65,
Castration, Yes	7 (87.5)	1 (12.5)	0	0	p=0.01
Post SBRT					
Castration, No	3 (13)	2 (8.7)	3 (13)	15 (65.2)	4.62,
Castration, Yes	1 (50)	0	1 (50)	0	p=0.20
Post Chemotherapy					
Castration, No	230 (98.3)	4 (1.7)	0	0	3.75, p=
Castration, Yes	24 (92.3)	2 (7.7)	0	0	0.06
Post Overall Treatment					
Castration, No	29 (44.6)	7 (10.8)	15 (23.1)	14 (21.5)	3.35,
Castration, Yes	7 (70)	1 (10)	2 (20)	0	p=0.34

considered responders following cancer-directed treatment. There were fifty-one evaluable cases with pre and post-therapy values of both Ga68-PSMA scan and PSA values. There was no significant correlation between Ga68-PSMA response with biochemical response (Pearson's $\chi2$ = 1.53, p = 0.21). 37.9% of responders on Ga68-PSMA PET were non-responder's biochemically [Table 8]. Among them, in 18.6% disease persisted or progressed on follow-up Ga68-PSMA scans. Remaining was lost to follow-up.

Ga68-PSMA correlation with Gleason's Score

Ga68-PSMA did not vary with varying grades of Gleason's Score. Positivity ranged from 97.1% to 100% across all risk grades on Gleason's Score [Table 9].

Data analysis: Data was analyzed using SPSS version 18 for windows and R software. Frequency distribution was determined for categorical variables. Chi square test for proportions was used to assess significance in response rates as per PERCIST criteria following cancer-directed treatment. Spearman's correlation was used to assess bivariate relationships between SUVmax, PSA levels and Gleason score.
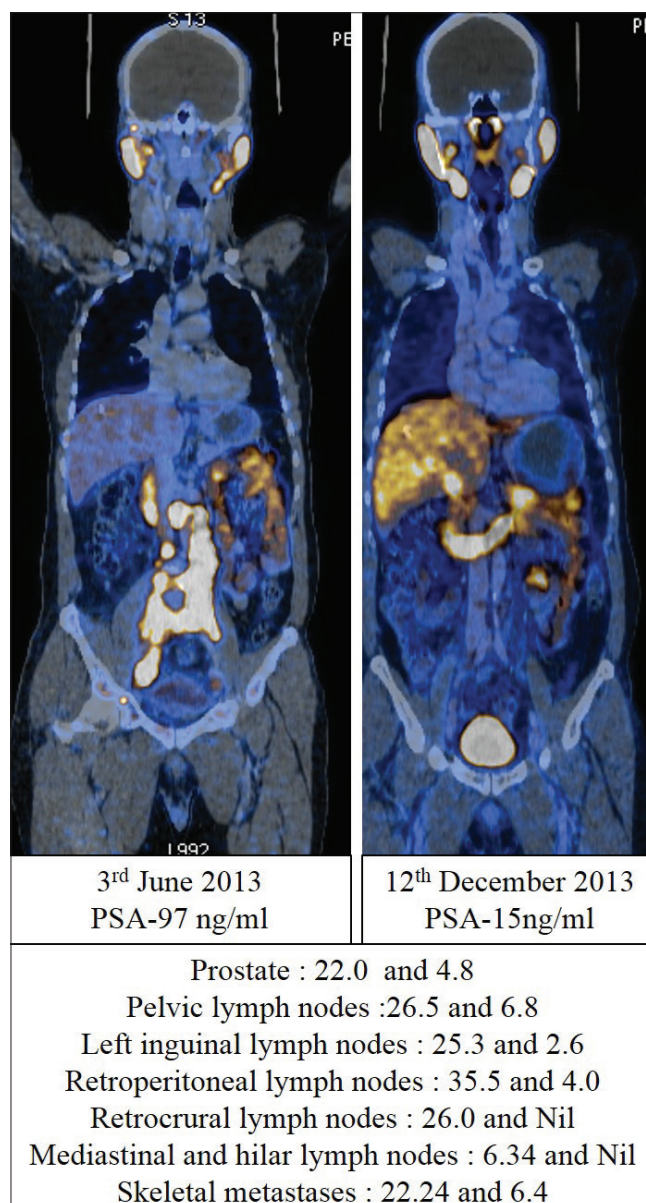

3rd June 2013 PSA-97 ng/ml	12th December 2013 PSA-15ng/ml

Prostate : 22.0 and 4.8
Pelvic lymph nodes :26.5 and 6.8
Left inguinal lymph nodes : 25.3 and 2.6
Retroperitoneal lymph nodes : 35.5 and 4.0
Retrocrural lymph nodes : 26.0 and Nil
Mediastinal and hilar lymph nodes : 6.34 and Nil
Skeletal metastases : 22.24 and 6.4

Figure 4: Response to antiandrogen therapy, SUV Max in following sites before and after therapy

Discussion

The overall results suggest clinical utility of Ga68-PSMA scan in prostate cancer. The Ga68-PSMA scan had high sensitivity with histopathological diagnosis. The scan was able to detect disease even with low PSA levels, and was helpful in early detection of castrate-resistant prostate cancer and prediction of response to cancer-directed treatments.

Sensitivity in this study is similar to that reported in earlier studies.[28,29] Specificity of Ga68-PSMA scans could not be ascertained due to the small number of benign and non-cancerous prostate lesions. Most of our scans were done on histopathologically proven prostate cancer and therefore
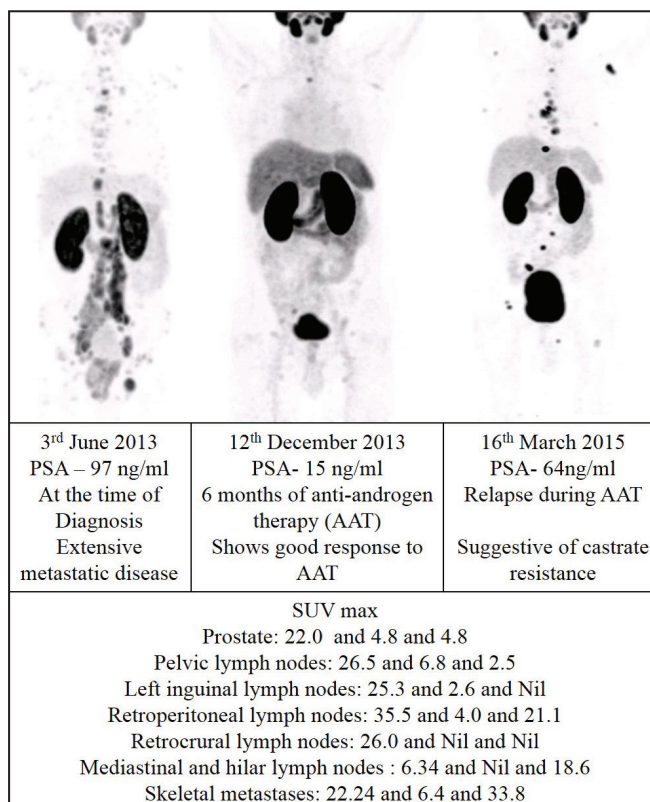
3rd June 2013	12th December 2013	16th March 2015
PSA – 97 ng/ml	PSA- 15 ng/ml	PSA- 64ng/ml
At the time of Diagnosis	6 months of anti-androgen therapy (AAT)	Relapse during AAT
Extensive metastatic disease	Shows good response to AAT	Suggestive of castrate resistance

SUV max
Prostate: 22.0 and 4.8 and 4.8
Pelvic lymph nodes: 26.5 and 6.8 and 2.5
Left inguinal lymph nodes: 25.3 and 2.6 and Nil
Retroperitoneal lymph nodes: 35.5 and 4.0 and 21.1
Retrocrural lymph nodes: 26.0 and Nil and Nil
Mediastinal and hilar lymph nodes : 6.34 and Nil and 18.6
Skeletal metastases: 22.24 and 6.4 and 33.8

Figure 5: Response with anti androgen therapy (AAT) and also prediction of castrate resistance using Ga 68 PSMA Scan

Table 8: Sensitivity of Ga68-PSMA with Biochemical response

Ga68-PSMA PET	PSA Biochemical response		Totals
	Non responders	Responders	
	N (%)	N (%)	
Responders	11 (37.9)	18 (62.1)	29
Non Responders	13(59.1)	9 (40.9)	22
Totals	24	27	51

Table 9: Positivity of Ga68-PSMA PET with Gleason score risks

Gleason's Score	PET PSMA	
	Negative, N (%)	Positive, N (%)
4-6 (Moderate Risk)	0	18 (100%)
7-8 (Intermediate Risk)	1 (2.9%)	33 (97.1%)
9-10 (High Risk)	0	22 (100%)

specificity could not be ascertained. The sensitivity for metastatic disease outside prostate was also high with small lesions being detected in skeleton and lymph nodes etc. even with low PSA levels. The detection rates were higher with higher PSA levels showing excellent contrast on Ga68-PSMA scan for local recurrence and metastatic disease.

Ga68-PSMA scans showed lesions in tumors with low Gleason score and low PSA levels also. Our results correlating PSA levels with PSMA scan findings show high false negative rates of 40% with the biochemical response that could be attributed to the low sensitivity of PSA levels (i.e. PSA failure indicating recurrence unless proven otherwise). A PSA cut-off of 4.0 ng/ml was found to have a sensitivity of 67%-80%, which implies that 20-30% of cancers are missed when only the PSA level is obtained.[30] Therefore, recent NCCN recommendations have reduced PSA cut off to 2.5 ng/ml to improve sensitivity.[31] Another reason could be that the intra-individual variability of PSA levels is high around 20% over the time accounting for a high false negative rate. A recent meta-analysis has revealed that PSA levels show many false positives and should not be relied upon as a single marker for detection or response in prostate cancer. A biopsy or follow-up imaging will show the true validity of Ga68-PSMA scans.[21] This is the reason why in our data we could not arrive at a meaningful correlation of Ga68-PSMA scan with biochemical response.

Hence, we postulate that Ga68-PSMA scan should be used for evaluation of local recurrence, any distant metastases, and response to cancer-directed therapy in prostate cancer along with PSA values.PSA values ranged from 0.005 to 854ng/ml. In one case with low PSA values of 0.005, the patient had pelvic lymph nodes and skeletal metastases.

Androgen deprivation therapy is known to reduce metabolism in prostate cancer thereby may interfere with the uptake of PET tracers (F18/C11-Choline and FDG) immediately in the aftermath of such therapy. This suggests that FDG and F18/C11-Choline are less reliable to evaluate the effects of androgen deprivation therapy.[32-35] Ga68-PSMA uptake is independent of metabolism and androgen deprivation as it directly acts on androgen receptors on the surface making it a reliable diagnostic marker.[36] Unlike PSA levels that are less reliable for prognosis of prostate cancer due to its high false negativity, Ga68-PSMA scans have demonstrated lesions in cases where PSA was low. Ga68-PSMA did not show any variability with changes in Gleason's score between moderate to high risk. Unlike F18-Choline, C11-Choline and FACBC, which need cyclotron, it is easier to synthesize Ga68- PSMA using generator system. Ga68- PSMA tracer is also stable.

Limitations

There were several limitations in our study because this was a retrospective study. First, the specificity of Ga68-PSMA scan for malignant disease was not established, as we did not have non-malignant cases such as benign prostatic hyperplasia or prostatitis for analysis. Secondly, a biopsy was not done in many cases where the metastatic disease was established on Ga68-PSMA scan (Biopsy was done in (n = 10, 20%) of the cases with extra prostatic disease at baseline and all of these ten (100%) cases turned out to be positive for malignancy). Third, PSA values

were based on tests done in various other laboratories with heterogeneity in their cut off values and procedures making them less reliable. Nevertheless, Ga68-PSMA demonstrated clinical utility in staging, and response evaluation in prostate cancer.

Directions for future

Sensitivity and specificity of imaging modalities are very important in detecting recurrence in prostate cancer. Future studies should validate the sensitivity and specificity of Ga68-PSMA imaging in both prostatic and extra prostatic disease and validate them with biopsy where possible.

Compliance with Ethical Standards

- Disclosure of potential conflicts of interest- None

- Funding: None (Investigator Initiated academic study)

- Conflict of Interest: The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

Statement of human rights

Ethical approval: "All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. "The study was approved by HCG ethics committee study with Reg no. ECR/386/INST/KA/2013 vide approval letter dated 20/03/2014. "This is a retrospective study and hence formal written consent is not required. However, all the subjects gave the mandatory informed consent to undergo the procedure as per the hospital records"

Statement on the welfare of animals

"This article does not contain any studies with animals performed by any of the authors." C. Informed consent Informed consent: An informed consent was obtained from all individual participants included in the study for undergoing this procedure.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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