

Localization and restaging of carcinoma prostate by ⁶⁸Gallium prostate-specific membrane antigen positron emission tomography computed tomography in patients with biochemical recurrence

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ABSTRACT

Introduction: Radical prostatectomy (RP) and radical radiotherapy (RT) are well established primary curative options for localized prostate cancer. Despite technical improvements, prostate-specific antigen (PSA)-recurrence after RP and RT is a common clinical scenario. We aimed to assess the role of ⁶⁸Gallium (⁶⁸Ga) prostate-specific membrane antigen positron emission tomography computed tomography (PSMA PET/CT) in patients with biochemical recurrence of prostate cancer after RP or RT for the detection and localization recurrent and metastatic disease.

Materials and Methods: We ambispectively (70 retrospective and 100 prospective) analyzed the data of men with biochemical recurrence post-RP and post-RT who were evaluated by ⁶⁸Ga PSMA PET/CT at our institute. We aimed to assess the relationship between serum PSA levels and the probability of having a positive scan in patients with recurrent prostate cancer.


Results: The study included 170 men, all had adenocarcinoma of the prostate, 124/170 had previous RP and 46/170 had prior RT. The median serum PSA in the RP group was 1.8 ng/ml and 5.2 ng/ml in the RT group. In the post-RP cohort, the detection rate of ⁶⁸Ga PSMA PET/CT was 39.3% for PSA 0.2 to <0.5 ng/ml, 47.3% for PSA 0.5 to <1 ng/ml, 68.4% for PSA 1 to <2 ng/ml and 93.1% for PSA ≥2 ng/ml. In the post-RT group, the detection rate was 88.8% for PSA 2 to <4 ng/ml and 100% for PSA ≥4 ng/ml.

Conclusions: ⁶⁸Ga PSMA PET/CT provides a novel imaging modality for the detection of prostate cancer recurrence and metastases at low posttreatment PSA levels, which may help in directing appropriate salvage treatments.

INTRODUCTION

Prostate cancer is the most common solid cancer in men.^[1] Its incidence increases with age and thus is a major health concern for the aging population of the world.^[2] Following definitive treatment of prostate cancer by radical prostatectomy (RP) or radiotherapy, cancer recurrence is heralded by an increase in the serum prostate-specific antigen (PSA) levels which

is called the biochemical recurrence.^[3,4] Depending on the patient population studied, 15%–40% of the patients experience a rise in serum PSA levels.^[3-5] The European Association of Urology guidelines defines the biochemical recurrence after RP as an increase in the serum PSA value above 0.2 ng/ml and over a threshold of 2 ng/ml above the nadir value post radiation therapy.^[2,5]

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Determining whether the recurrence is local (within the prostate or at the urethral/bladder anastomosis), regional (pelvic) or distant (outside the pelvis) is critical when considering appropriate further treatment options.^[6]

The reported sensitivity of the currently available imaging methods such as the transrectal ultrasound, computed tomography (CT), and magnetic resonance imaging range between 25% and 54% for the detection of local recurrence and 30%–80% for the detection of lymph nodal metastasis.^[7–10] Although functional imaging with ¹⁸Fluorine-fluorodeoxyglucose or ¹¹Carbon-choline (¹¹C-choline) positron emission tomography (PET)/CT has better efficacy than the other imaging techniques, their sensitivity depends on the serum PSA levels and currently there are no reliable imaging methods to localize the disease in patients with biochemical recurrence.^[11–14]

Prostate-specific membrane antigen (PSMA) represents a cell surface target suitable for imaging as it is expressed by nearly all the prostate cancer cells with enhanced expression levels in the poorly differentiated, metastatic, and hormone-refractory carcinomas.^[15–17] PSMA is labeled with ⁶⁸Gallium (⁶⁸Ga), a generator produced positron emitting short lived radionuclide which makes them suitable for PET imaging. It can detect prostate cancer relapses and metastases with high diagnostic sensitivity.^[18–21] The present study aims to assess the role of ⁶⁸Ga PSMA PET CT in patients with biochemical recurrence after RP or radiotherapy, for the detection and localization of recurrent and metastatic disease and to identify the relationship between the detection rate of ⁶⁸Ga PSMA PET CT and post treatment serum PSA levels.

MATERIALS AND METHODS

Ambispective evaluation of 170 patients (70 retrospective and 100 prospective) with biochemical recurrence after treatment of prostate cancer was performed between May 2014 and January 2018. All these individuals underwent ⁶⁸Ga PSMA PET/CT scan based on the predefined inclusion criteria of serum PSA level >0.2 ng/ml and >2 ng/ml above the nadir, post RP and post radiotherapy, respectively. The patients who did not receive definitive treatment for carcinoma prostate and those, in whom the serum PSA level did not fall below 0.2 ng/ml after RP, were excluded from the study. Demographic data of each patient was recorded, including relevant clinical examination findings, histopathology, Gleason's score, serum PSA levels, and treatment history.

For the labeling of ⁶⁸Ga PSMA, ⁶⁸GaCl₃ in 0.6 M hydrochloric acid was obtained from ⁶⁸Ge/⁶⁸Ga generator (iThemba, South Africa). PSMA HBED-CC (40 µg in 0.4 ml) was added to GaCl₃ with 700 mg HEPES buffer (pH 5–6.5) in 0.5 ml distilled water. The mixture was allowed to react at 100°C for 20 min in water bath and then cooled to room temperature

for 30 min. After cooling, the solution was passed through C-18 purification cartridge to remove the unlabeled GaCl₃ and the radio labeled compound was eluted with 5 ml ethanol. All the patients were given intravenous injection of 132–222 MBq (4–6 mCi) of ⁶⁸Ga-PSMA and underwent PET/CT scanning from the vertex to the mid-thigh using a dedicated PET/CT scanner within 45 ± 15 min after injection. Between five and eight bed positions were used, with an acquisition time of 5 min for each position. PET images were reconstructed using the ordered set expectation maximization algorithm, CT attenuation correction, dead time correction, and decay correction. A delayed sequence of pelvis was acquired after furosemide injection. Images were interpreted at the advantage window workstation equipped with fusion software. All scans were evaluated independently and blindly by two experienced Nuclear Medicine physicians. PET images were scanned for areas of increased radiotracer uptake and any site of focal PSMA uptake higher than the background, at sites other than the physiological sites of PSMA uptake, were considered as a lesion. ⁶⁸Ga-PSMA uptake was expressed as the maximal standardized uptake value corrected for the administered dose and patient body weight.

Statistical analysis was performed with the Statistical Package for the Social Science System (SPSS) version 17.0 (Chicago: SPSS Inc.). Continuous variables were presented as mean ± standard deviation or median (interquartile range) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. Unpaired Student *t*-test was used to compare the mean values of different groups. Nominal categorical data between the groups were compared using the Chi-square test. For all the statistical tests, *P* < 0.05 was considered as statistically significant.

The study was approved by the ethics committee (EC/07/17/1203, Sir Ganga Ram Hospital, New Delhi), and an informed written consent was taken from all the patients. We confirm the availability of, and access to, all original data reported in this study.

RESULTS

The study included a total of 170 patients [Table 1] of adenocarcinoma prostate of which 124 had undergone prior RP with or without adjuvant radiotherapy or androgen deprivation therapy and 46 had received prior radiotherapy (either external beam radiation therapy [EBRT] or brachytherapy).

Post radical prostatectomy group

Out of the 124 patients who met the inclusion criteria, 62 patients did not receive any treatment after RP, 9 received adjuvant radiotherapy, 42 received hormonal therapy, and 11 had received both adjuvant radiotherapy and hormonal therapy. The mean time for serum PSA recurrence was

49.77 ± 44.44 months (range 2–184 months) and median serum PSA level was 1.8 ng/ml.

Eighty-seven of the 124 patients (70.1%) showed 1 or more areas of ⁶⁸Ga PSMA positivity, suggestive of recurrence [Figure 1 and Table 2]. The detection rates improved with the rising serum PSA levels (Chi-square statistic 32.074, *P* < 0.001). The mean serum PSA in patients with a positive scan was significantly higher than that in patients with a negative scan (*t*-statistic-2.452, *P* = 0.015).

Our data also reveal an improved rate of detection for patients with higher (postsurgery) Gleason’s score. The detection rate was 63.3% (38/60) for Gleason score ≤7 which increased to 76.5% (49/64) for Gleason score ≥8. This relationship between high Gleason score and detection rate was found to be statistically significant (Chi-square statistic 8.36, *P* value ~ 0.03).

Lymph nodal metastases was detected in 65.5% (57/87) of the patients and was found to be the most common site of metastases followed by the bone, local recurrence (prostatic bed region) and visceral metastases [Table 3]. The pelvic lymph nodal group was the most common site of metastases at all the serum PSA values [Table 4]. Visceral metastases were seen in 6 of the patients and were most commonly detected in the lungs.

Post-radiotherapy group

Forty-six patients who met the predefined inclusion criteria were included in this study. Thirty-nine patients received additional hormonal therapy after radiotherapy. The mean time to serum PSA recurrence was 49.15 ± 24.32 months

Characteristics	RP	RT
Number of patients (n)	124	46
Age (years)		
Mean±SD	68.37±6.74	68.43±6.36
Range	47-83	51-81
Serum PSA (ng/ml)		
Median	1.8	5.2
Range	0.2-100	2.29-165.84
Gleason’s score		
0-6	10	9
7-8	92	32
9-10	22	5
Median	8	7.5
Range	6-9	6-9
Time to serum PSA recurrence (months)		
Mean±SD	49.77±44.44	49.15±24.32
Range	2-184	12-111

PSA=Prostate-specific antigen, SD=Standard deviation, RP=Radical prostatectomy, RT=Radical radiotherapy

Groups	PSA level (ng/ml)	Number of patients	PSMA positive	PSMA negative	Detection rate (%)
Post-RP	0.2<0.5	28	11	17	39.2
	0.5<1	19	9	10	47.3
	1<2	19	13	6	68.4
	≥2	58	54	4	93.1
	Total	124	87	37	70.1
Post-RT	2<4	18	16	2	88.8
	4<6	12	12	0	100
	≥6	16	16	0	100
	Total	46	44	2	95.6

PSMA=Prostate-specific membrane antigen, PSA=Prostate-specific antigen, RP=Radical prostatectomy, RT=Radical radiotherapy

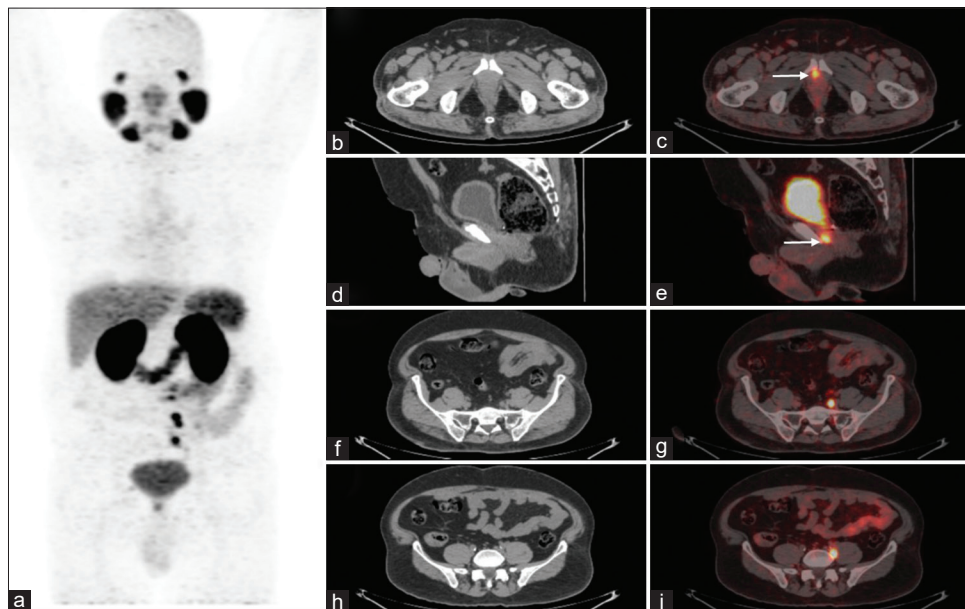


Figure 1: A 61-year-old male, known case of adenocarcinoma prostate (Gleason’s score 8), post radical prostatectomy with pelvic lymphadenectomy and raised serum prostate-specific antigen ~3.8 ng/ml. ⁶⁸Gallium-prostate-specific membrane antigen positron emission tomography computed tomography images show prostate-specific membrane antigen avid ill-defined lesion in the prostatic bed region (a-e) and prostate-specific membrane antigen avid abdomino-pelvic lymph nodes (a and f-i)

Table 3: Regions/combination of regions detected by ⁶⁸Ga prostate-specific membrane antigen positron emission tomography/computed tomography in the postradical prostatectomy and post-radiotherapy groups

Sites of metastases	Number of patients (%)	
	Post-RP	Post-RT
LR	14 (16.09)	6 (13.6)
LN metastases only	30 (34.44)	4 (9.09)
Bone metastases only	12 (13.79)	2 (4.5)
Visceral metastases only	2 (2.29)	0
LR + LN metastases	7 (8.04)	7 (15.9)
LR + bone metastases	2 (2.29)	7 (15.9)
LR + visceral metastases	0	1 (2.2)
LN + bone metastases	14 (16.09)	2 (4.5)
LN + visceral metastases	1 (1.14)	0
LR + LN + bone metastases	2 (2.29)	13 (29.5)
LN + bone + visceral metastases	3 (3.44)	1 (2.2)
LR + LN + bone + visceral metastases	0	1 (2.2)
Total	87	44

LR=Local recurrence, LN=Lymph node, RP=Radical prostatectomy, RT=Radical radiotherapy

Table 4: Positive lymph nodal/combination of lymph nodal groups detected by ⁶⁸Ga prostate-specific membrane antigen positron emission tomography/computed tomography in the postradical prostatectomy and postradiotherapy groups

Lymph nodal groups/combination of lymph nodal groups detected	Number of patients (%)	
	Post-RP	Post-RT
Pelvic LN only	45 (78.9)	14 (50)
Retroperitoneal (RP) LNs only	1 (1.7)	2 (7.1)
SPD LNs only	3 (5.2)	0
Pelvic + RP LN's	2 (3.5)	7 (25)
Pelvic + SPD LN's	1 (1.7)	2 (7.1)
RP + SPD LN's	0	0
Pelvic + RP + SPD LN's	5 (8.7)	3 (10.7)
Total	57	28

LN's=Lymph nodes, RP=Radical prostatectomy, SPD=Supra-diaphragmatic, RP=Radical prostatectomy, RT=Radical radiotherapy

(range 12–111 months) and the median serum PSA level was 5.2 ng/ml.

Forty-four of the 46 patients (95.6%) showed ⁶⁸Ga PSMA positivity, suggestive of recurrent disease [Figures 2, 3 and Table 2]. The probability of detecting recurrence post radiotherapy increased from 88.8% (16/18) for the patients with serum PSA between 2 to <4 ng/ml to 100% for patients with serum PSA ≥4 ng/ml. At serum PSA levels >2 ng/ml local recurrence was the most common site of PSMA avid recurrent disease followed by lymph node, bone and visceral metastases [Table 3]. Lymph nodal metastases were the second most common site of metastases and were present in 63.6% (28/44) patients with pelvic lymph nodes being the most common site [Table 4].

Improved recurrence detection rates were observed with increasing (Pre-radiotherapy) Gleason's score. The detection rate was 91.6% (22/24) for Gleason's score ≤7 and 100% (22/22) for Gleason's score ≥8; however, the results were not statistically significant.

Follow-up study

Follow-up studies [Figures 4 and 5] were available for 68 patients (54 post RP and 14 post radiotherapy). All these patients received hormonal treatment, 8 patients received additional chemotherapy and 8 patients had received radiotherapy for bone metastases. Following the treatment, one patient had complete response, 34 patients had partial response, 24 patients had stable disease, and 9 patients had progressive disease.

DISCUSSION

PSA relapse after RP and radiotherapy is a common clinical scenario. Biochemical recurrence is defined by the rise of serum PSA value above 0.2 ng/ml and 2 ng/ml more than nadir value after RP and radiotherapy, respectively, and occurs long before the recurrent disease can be localized clinically or by imaging. The goal in these patients is to distinguish prostatic bed recurrence from metastatic disease, as this affects further treatment. The localization of site of recurrence, in patients with biochemical recurrence, especially at low PSA values, is a major challenge for all the available imaging modalities.^[8,9,22]

In this study, we evaluated ⁶⁸Ga PSMA PET/CT for the localization and detection of recurrent disease in patients with biochemical recurrence. Our study cohort included 124 patients post RP and 46 patients post radiotherapy with biochemical recurrence. Overall, we observed a 70.1% detection rate in the post RP group. The detection rate improved with rising serum PSA levels with a highest detection rate of 93.1% which was achieved at serum PSA level more than 2 ng/ml. These findings are consistent with the meta-analysis performed by Perera *et al.*^[23] which showed a ⁶⁸Ga PSMA PET/CT positivity rate for serum PSA levels 0.2–0.99, 1.00–1.99, and >2.0 at 58%, 76%, and 95%, respectively. Another important finding of our study is the 42.5% detection rate at serum PSA values <1 ng/ml, which is higher as compared to that reported with choline based PET tracers which have a detection rate of 19% at PSA levels below 1 ng/ml.^[12,24,25] Comparative analysis of various studies reported in the literature with the present study is shown in Table 5.

Our data shows a statistically significant higher detection rate in patients with a Gleason's score ≥8 versus ≤7, which could be potentially attributed to the fact that immunohistochemically, PSMA expression is usually higher in the lesions with a higher Gleason's score as compared to the lesions with a lower Gleason's score. Similar findings have been reported by Eiber *et al.*^[21] and Kabasakal *et al.*^[26]

⁶⁸Ga PSMA PET/CT scan has shown to improve the chances of detection of the site of recurrence, particularly at low serum PSA levels. In our study, we found that 39.2% (11/28) of the patients with serum PSA values between 0.2 to <0.5 ng/ml had metastatic disease, out of which,

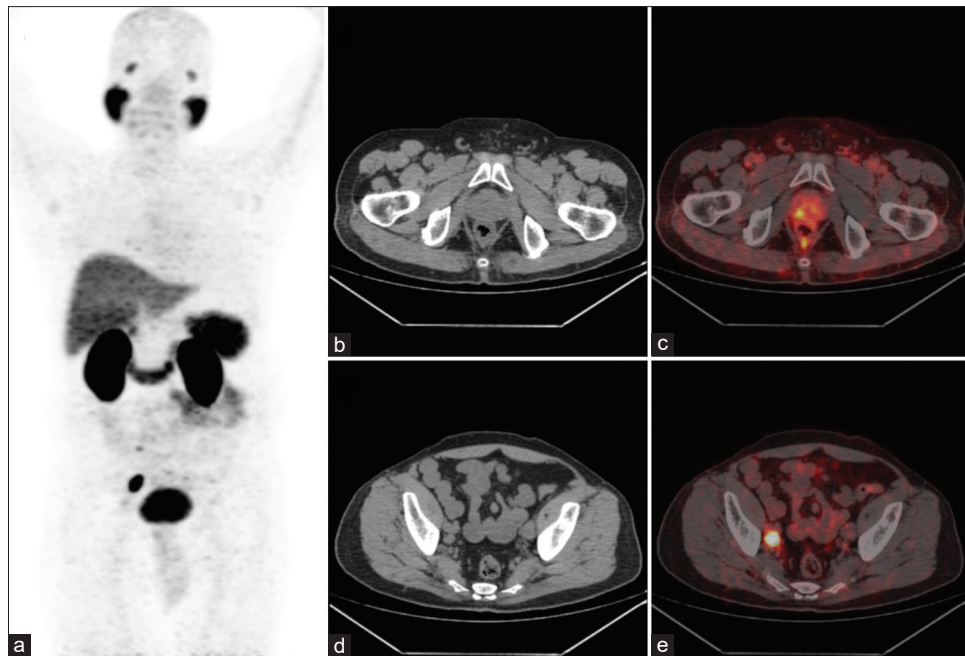


Figure 2: A 74-year-old male, known case of adenocarcinoma prostate (Gleason's score 6), post radiotherapy with rising serum prostate-specific antigen (9.5 ng/ml from 0.72 ng/ml). ⁶⁸Gallium-prostate-specific membrane antigen positron emission tomography computed tomography images, show prostate-specific membrane antigen avid ill-defined lesion in the prostate gland (b and c) and prostate-specific membrane antigen avid lymph nodes in the right iliac region (a, d and e)

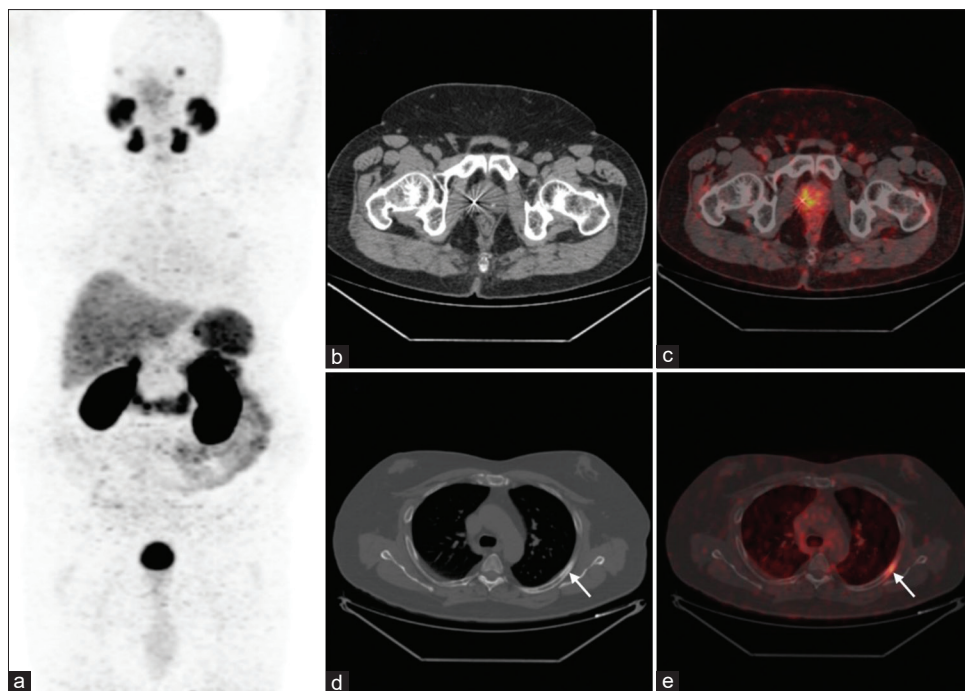


Figure 3: A 62-year-old male, known case of carcinoma prostate (Gleason's score 6), post radiotherapy with raised serum prostate-specific antigen ~2.78 ng/ml. ⁶⁸Gallium-prostate-specific membrane antigen positron emission tomography computed tomography revealed prostate-specific membrane antigen avid ill-defined lesion in the prostate gland (b and c) and prostate-specific membrane antigen avid sclerotic lesion in the left 5th rib (a, d and e)

in 36.3% the site of recurrence was bone and in 54.5% it was the lymph nodes [Table 3]. Differentiating between local and distant recurrence in patients with BCR and PSA levels <0.5ng/ml has particular clinical impact, as these patient are ideal candidates for salvage pelvic radiotherapy according to the European Urology Association Guidelines^[6]

which defines the PSA level of 0.5ng/ml as the upper limit for salvage radiotherapy. Hence, identifying the site of recurrence can change their clinical management. Also, we found that distant metastasis can be present at low PSA levels and salvage pelvic radiotherapy may not be an appropriate treatment option in these patients.

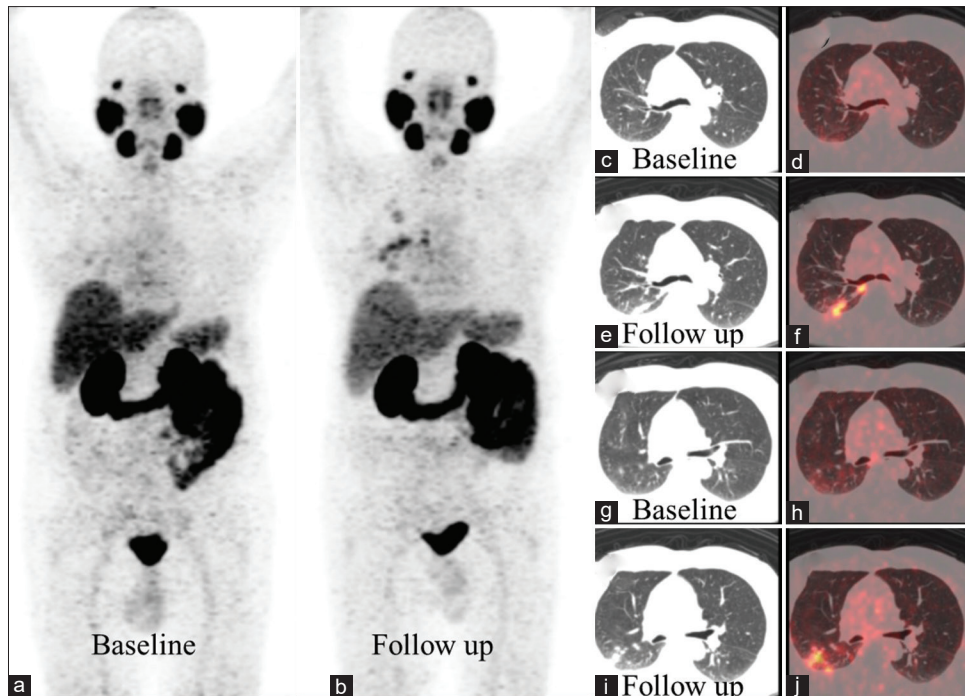


Figure 4: A 67-year-old male, known case of adenocarcinoma prostate (Gleason's score 6), post radical prostatectomy with raised serum prostate-specific antigen ~5.2 ng/ml, diagnosed with prostate-specific membrane antigen avid lung nodules in the initial baseline study, on hormonal treatment since 1 year, follow-up ⁶⁸Gallium-prostate-specific membrane antigen positron emission tomography computed tomography was done for rising serum prostate-specific antigen (13.2 ng/ml from 5.2 ng/ml). Comparative ⁶⁸Gallium-prostate-specific membrane antigen positron emission tomography computed tomography study, showed increase in size, number, and prostate-specific membrane antigen avidity in the right lung nodules in the follow-up study (b, e, f, i and j) on comparison with the baseline study (a, c, d, g and h)

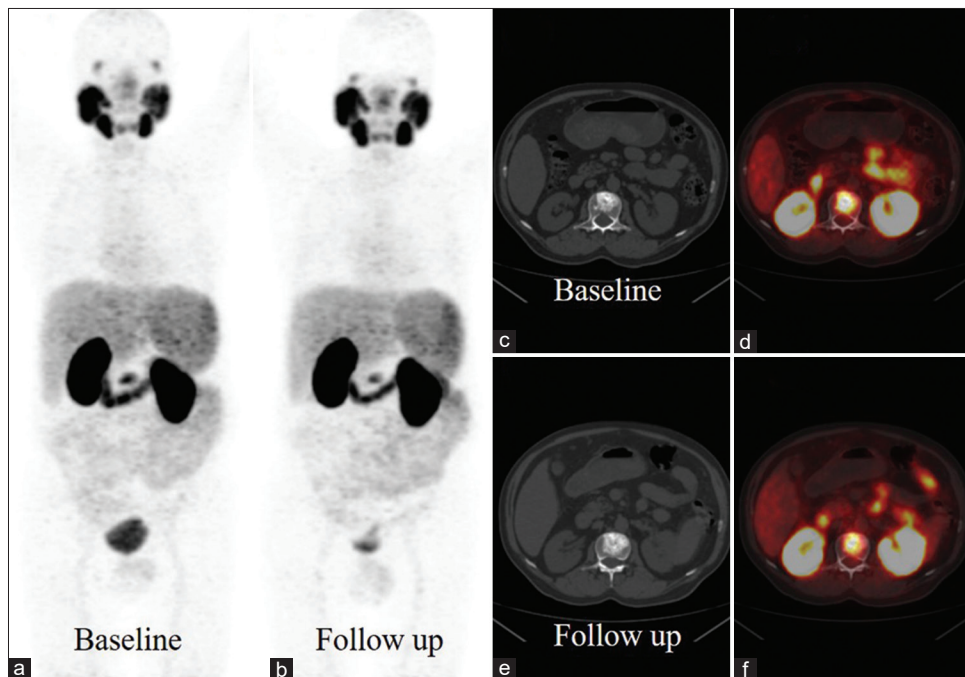


Figure 5: A 73-year-old male, known case of adenocarcinoma prostate (Gleason's score 7) status; post robotic radical prostatectomy with raised serum prostate-specific antigen 1.04 ng/ml. Diagnosed with bone metastasis to L2 vertebra in the initial baseline ⁶⁸Gallium-prostate-specific membrane antigen positron emission tomography computed tomography, post stereotactic radiotherapy to L2 vertebra and on hormonal treatment. Follow-up ⁶⁸Gallium-prostate-specific membrane antigen positron emission tomography computed tomography was done to assess the treatment response which showed increase in the extent of sclerosis with reduction in prostate-specific membrane antigen avidity of the lesion in the follow up ⁶⁸Gallium-prostate-specific membrane antigen positron emission tomography computed tomography (b, e and f) on comparison with the baseline (a, c and d)

In the post-RP group, lymph nodal metastases were the most common site of recurrence at all the serum PSA

levels, [Table 3] with pelvic lymph nodes [Table 4] being the most commonly involved (89.2%). These patients may

Table 5: Comparative analysis of various studies in the literature with the present study

References	PSA level (ng/ml)	n	Number of positive patients	Detection rate (%)
Kabasakal <i>et al.</i> ^[26]	0.2	13	4	31.0
	0.2-2.0	24	13	54.0
	2-5	16	14	88.0
Verburg <i>et al.</i> ^[32]	<1	27	12	44.0
	1-2	19	15	79.0
	≥2	109	97	89.0
Afshar-Oromieh <i>et al.</i> ^[20]	≤0.2	17	8	47.1
	0.21-1.0	34	19	55.8
	1.1-≤2.0	37	28	71.8
Eiber <i>et al.</i> ^[21]	>2	221	204	92.3
	0.2<0.5	19	11	57.9
	0.5<1	33	24	72.7
Meredith <i>et al.</i> ^[28]	1<2	72	67	93.0
	≥2	124	120	96.8
	0.2<0.5	79	21	26.6
Perera <i>et al.</i> ^[23]	0.5<1	45	24	53.3
	1<2	43	34	79.1
	≥2	134	128	95.5
Present study	<0.2	NA	NA	42.0
	0.2-0.99	NA	NA	58.0
	1.00-1.99	NA	NA	76.0
Present study	>2	NA	NA	95.0
	0.2<0.5	28	11	39.2
	0.5<1	19	9	47.3
	1<2	19	13	68.4
	≥2	104	98	94.2

n=Total number of patients, NA=Not available, PSA=Prostate-specific antigen

be amenable to salvage treatment with either lymph node dissection or targeted radiotherapy. Thus, early ⁶⁸Ga-PSMA PET/CT may be beneficial in identifying the patients who may benefit from salvage treatment.

Local recurrence (prostatic bed region) after RP was detected in about 28.73% (25/87) of the patients. This low rate of local recurrence can be attributed to complete surgical resection in most of the patients and also that many patients received adjuvant radiotherapy. Hence, most of the patients were expected to have site of recurrence outside the prostate bed.

Supra-diaphragmatic lymph nodes and visceral metastases were present in approximately 15.7% (9/57) and 6.9% (6/87) of the patients with serum PSA >1 ng/ml, respectively. The lungs were the most common site of visceral metastases and were involved in 5/6 patients. These uncommon sites can easily be detected with ⁶⁸Ga PSMA PET/CT owing to the high lesion to background ratio, better contrast, and whole-body imaging. Early detection of metastatic disease may also result in earlier referral for chemotherapy, which has recently been shown to improve survival in hormone naive metastatic prostate cancer.^[27]

We report an overall detection rate of 95.6% (44/46) in the post-radiotherapy group comprising of the patients who had been managed by EBRT or brachytherapy. Local recurrence (within the prostate gland) was identified in 79.5% (35/44) of the patients, followed by lymph node and bone metastases in 63.6% (28/44) and 59.09% (26/44),

respectively. Of the lymph nodal groups, pelvic lymph nodes were the most commonly involved (92.7%). We, in our study, have adhered to the definition of biochemical recurrence after post radiotherapy and thus included only those patient who had serum PSA >2 ng/ml above the nadir value, however, Meredith *et al.*^[28] showed that ⁶⁸Ga-PSMA PET CT can detect lesions in patients with serum PSA <2 ng/ml and suggested that if salvage treatment is being considered ⁶⁸Ga-PSMA PET CT should be performed before the serum PSA rises >2 ng/ml.

Compared to the reported detection rates between 34% and 88% for ¹¹C-choline, 43%–79% for ¹⁸F-choline, and 59%–80% for ¹¹C-acetate,^[29-31] ⁶⁸Ga-PSMA PET CT offers a substantially higher detection efficacy. As known from other PET tracers, the detection rate of ⁶⁸Ga-PSMA ligand PET CT also increases in proportion with the rising PSA values.^[4] We found an overall detection rate of 77.05% (131/170) and a detection rate of 97.02% (98/108) in patients with serum PSA ≥2 ng/ml.

Follow-up studies were performed for 68 patients (54 post RP and 14 post radiotherapy) to assess the treatment response. Persistence of similar findings, increase/decrease in the number, size and the PSMA avidity of the lesions following treatment indirectly validated the findings detected on the first ⁶⁸Ga PSMA PET/CT. In our study, 1 out of the 68 patients had complete response, 34 patients had partial response, 24 patients had stable disease, and remaining 9 patients had progressive disease following treatment.

One of the limitations of our study is its retrospective-prospective nature. Furthermore, the histopathological analysis of the lesions detected on ⁶⁸Ga-PSMA PET/CT was not performed, and could have resulted from false positive lesions. Although, the follow-up studies indirectly confirmed the findings of prior ⁶⁸Ga-PSMA PET/CT and reduced the false positive rates, they were available for only 68 patients. Another potential limitation is that the number of patients evaluated is quite small especially those with low PSA levels.

CONCLUSIONS

⁶⁸Ga-PSMA PET/CT imaging has a very high efficiency of >95% at serum PSA level ≥2 ng/ml for the detection of prostate cancer recurrence and metastasis. This modality currently surpasses all the other available imaging modalities for the restaging of prostate cancer. The findings of ⁶⁸Ga-PSMA PET/CT can affect treatment decisions; however, the overall impact of changing management decisions based on ⁶⁸Ga-PSMA PET/CT findings is still unknown and requires further research.

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