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Diagnostic Value of PSMA PET Scan in Predicting Lymph Node Positivity in Patients with Prostate Cancer

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Abstract

Objective: Accurate staging of prostate cancer is of high importance for treatment decisions and patient management. Conventional imaging like MRI, CT are neither sensitive nor specific enough to reliably detect lymph node metastases preoperatively. At present, Pelvic Lymph Node Dissection (PLND) is considered the gold standard for evaluating the presence of nodal involvement and nodal staging. Recent data on the novel PSMA PET scan has shown promising results for the detection of LN metastases; but only few prospective studies are done. No Indian study has evaluated this.

The objective of the present prospective study was to assess the accuracy of 68Ga-PSMA PET scan for preoperative lymph node involvement in patients with prostate cancer, using postoperative histopathology as the 'gold standard'.

Methods: From January 2021 to June 2022, 50 patients of biopsy proven prostate cancer were prospectively enrolled as per eligibility criteria. Preoperatively 68Ga-PSMA PET scan was done in all the patients. Subsequently, they underwent Robotic Assisted Radical Prostatectomy (RARP) with Bilateral Pelvic Lymph Node Dissection (B/L PLND). The sensitivity, specificity, PPV and NPV of PSMA PET scan for lymph node involvement were evaluated using histopathology as reference.

Result: 12 patients (24%) had Lymph Node Metastasis (LNMs), in which PSMA PET scan detected lymph node involvement in 11 patients. Data analysis showed that PSMA PET scan had a sensitivity of 91.66%, specificity of 94.47%, PPV of 84.61% and NPV of 97.29% for the detection of LNMs.

Conclusion: PSMA PET scan has high sensitivity with high specificity for lymph node metastasis detection. PSMA PET scan has potential to replace currant imaging technique for lymph node staging in patients with prostate cancer planned for radical prostatectomy. In future, large multiple prospective studies may help to avoid PLND if PSMA PET scans is negative for LNMs preoperatively.

Keywords: 68GA-PSMA PET scan; Prostate cancer; Lymph node metastasis; Pelvic Lymph Node Dissection (PLND); Preoperatively

Abbreviations: 68Ga-PSMA: 68Gallium Prostate Specific Membrane Antigen; PET: Positron Emission Tomography; LN: Lymph Node; PCa: Prostate Cancer; RP: Radical Prostatectomy; ePLND: extended Pelvic Lymph Node Dissection; PPV: Positive Predictive Value; NPV: Negative Predictive Value; LNMs: Lymph Node Metastases; RARP: Robotic Assisted Radical Prostatectomy

Introduction

Prostate cancer is the most common malignancy in men aged 50 years and older and the second cause of cancer death among men [1]. Accurate staging of prostate cancer is of high importance for treatment decisions and patient management [2]. The selection of the type of therapy for prostate cancer is mainly influenced by the presence or absence of metastases. At present, there is no reliable imaging method for detecting lymph node metastases [3]. Conventional imaging techniques are inadequate for LN staging in prostate carcinoma. MRI, CT and fluorescence sentinel lymph node detection are neither sensitive nor specific enough to reliably detect lymph node metastases before radical prostatectomy [4,5]. Therefore, extended Pelvic Lymph Node Dissection (ePLND) remains the preferred technique for detection of nodal involvement and nodal staging. It is an invasive procedure and associated with complications such as lymphocele, deep venous thrombosis and longer hospital stay [6].

Recent data on the novel PET tracer agent Glu-NH-CO-NH-Lys-(Ahx)-(68Ga (HBED-CC)) (PSMA) has shown promising sensitivity (68%–85%) and specificity (82%–100%) for the detection of LN metastases [7–13]. This new PET tracer relies on the hyper expression of Prostate Specific Membrane Antigen (PSMA), a trans membrane folate hydrolase, on the surface of prostate cancer cells. This over expression has been observed in local, regional, metastatic lymph nodes and in soft tissue and bone [14].

Only few prospective studies and no Indian study have evaluated the accuracy of PSMA PET scan for nodal staging of primary Prostate cancer.

Therefore, we conducted this prospective study to assess the accuracy of 68Ga-PSMA PET scan for preoperative detection of lymph node metastasis in patients with prostate cancer, using postoperative histopathology as the 'gold standard.

Aims and objectives

To assess the diagnostic value of PSMA PET scan in predicting lymph node metastasis in patients with prostate cancer, using final histopathology from the PLND for comparison.

- To assess sensitivity and specificity of PSMA PET scan for lymph node metastasis in patients with prostate cancer.
- To assess positive and negative predictive value of PSMA PET scan for lymph node metastasis in patients with prostate cancer.

Material and Methods

From January 2021 to July 2022, 50 patients of biopsy proven prostate cancer were prospectively enrolled as per eligibility criteria.

Inclusion criteria

- Patient age between 45-80 years.
- Biopsy proven prostate cancer suitable for radical prostatectomy with PLND.
- Serum PSA level between 4 to 20 ng/ml.
- ECOG performance status of patient 0 or 1.
- Patients had received no previous therapy and had no previous other malignancy.

Exclusion criteria

- Patients with a positive bony metastasis in PSMA PET SCAN.
- Patients on any other therapy (e.g., hormonal therapy, radiotherapy, chemotherapy, etc.) at the time of initial OPD presentation.

Approval from ethical committee of ruby hall clinic, Poona medical research foundation with approval number RHC/BIOPMRFIEC/2020/316 on 12 August 2021. After clearance, male patients who fulfil the eligibility criteria were enrolled in this study only after patients consent.

Prostate cancer rarely causes symptoms at an early stage. Screening of suspected cases was done with Digital Rectal Examination (DRE) and serum PSA level. In digital rectal examination, size of prostate, consistency, surface, rectal mucosa assessment and tenderness were checked.

Trans abdominal ultrasound examination was done in order to assess the size of prostate gland, urinary bladder and post-void residual urine.

Trans rectal ultrasound guided biopsy was performed in all the patients included in the study. At least 12 prostate cores biopsy was taken under local/spinal anesthesia under adequate antibiotic cover. Addition targeted biopsy was taken if require from suspicious areas.

After diagnosis of prostate cancer, accurate staging was done to find out extent of the disease. PSMA PET SCAN was done in all the included patients to find out local extend of cancer, pelvic lymph node involvement, non-regional lymph node involvement, bony metastasis and distal metastasis.

Organ confined prostate cancer patients underwent Robotic Assisted Radical Prostatectomy (RARP) with Bilateral pelvic Lymph Node Dissection (B/L PLND). Specimen was sent for HPE.

Final histopathology report was assessed for tumor grade, presence of extra capsular extension, seminal vesicle invasion, and pelvic lymph node involvement. This report was compared with the PSMA PET SCAN report.

Results

In our study we analysed the data of 50 patients. Out of which 38 (76%) patients were found without lymph node involvement and 12 (24%) were with lymph node involvement based on the final histopathology report of Radical Prostatectomy (RP) with Pelvic Lymph Node Dissection (PLND) (Table 1).

Table 1: Comparing patient's basic characteristic between without lymph node involvement and with lymph node involvement groups.

S. no.	Variable	Statistics	Without lymph node involvement (n=38)	With lymph node involvement (n=12)	P-Value
1	Age (years)	Median	70	69	0.6696
2	Prostate size (cc)	Median	40	43	0.9584
3	PSA (ng/ml)	Median	10.2	15.365	0.0846
4	PSMA PET scan (SUVmax value)	Median	8.9	22.3	0.0151

Age, prostate size and PSA value had no statistically significant relationship with lymph nodes positivity. But PSMA PET scan SUVmax value had statically significant relationship with patients of prostate cancer with lymph node involvement (Table 2).

Table 2: Stage wise data analysis of patients.

S. no.	Variables		
1	Clinical stage	T1b	1 (2%)
		T2a	14 (28%)
		T2b	8 (16%)
		T3a	14 (28%)
		T3b	4 (8%)
		T3c	9 (18%)
2	Gleason score biopsy	3+3	14 (28%)
		3+4	11 (22%)
		4+3	17 (34%)
		3+5	1 (2%)
		4+4	3 (6%)
		4+5	2 (4%)
		5+5	2 (4%)
3	Pathological stage	pT2	20 (40%)
		pT3a	16 (32%)
		pT3b	14 (28%)
4	Histological grade	3+3	6 (12%)
		3+4	22 (44%)
		4+3	16 (32%)
		4+5	6 (12%)
5	Lymph node analysis	Number of patients with positive lymph node	12 (24%)
		Total number of lymph nodes examined	491
		Total number of positive lymph node	27
		No of lymph nodes removed per patient Mean Median	 9.82 9

All the patients with biopsy proven prostate cancer included in the study, and all patients had done PSMA PET scan pre operatively. All the patients had shown PSMA positive activity in scan for prostate cancer. Out of 50 patients, PSMA PET scan shown positive activity for lymph node metastasis in 13 patients, in which 11 patients had truly lymph node positivity in final histopathology report (Table 3).

Table 3: Sensitivity, specificity, PPV and NPV of PSMA PET scan in detection of LNMs.

	Sensitivity %	Specificity %	PPV %	NPV %
Lymph node analysis by PSMA PET scan	91.66	94.47	84.61	97.29

- Lymph node metastasis was truly diagnostic in 11 patients out of 12 by PSMA PET scan (True positive).
- In 2 patients, PSMA PET scan showed lymph node metastasis, but final HPE showed no LNMs (False positive).
- In 1 patient PSMA PET scan did not reveal lymph node metastasis, but final HPE was positive for LNMs (False negative).
- In 36 patients who had negative LNMs on HPE, PSMA PET scan also did not reveal lymph node metastasis (True negative).

DISCUSSION

Prostate cancer is one of the most common cancers. Accurate staging of prostate cancer is of high importance for treatment decisions and patient management [15]. However, accurate staging and detection of lymph node metastasis is a difficult task with available conventional imaging modalities. An important characteristic of prostate cancer is the expression of PSMA, which makes the tumours ideal targets for functional imaging. Prostate Specific Membrane Antigen (PSMA) is a type II membrane glycoprotein that is highly expressed by all prostate cancers. The expression increases with tumor aggressiveness, metastatic disease and disease recurrence [16–18]. PSMA PET/CT imaging is currently the imaging technique of choice for patients with biochemically recurrent disease after initial curative local treatment (EAU guidelines) [19]. Its value for staging of primary PCa is less established. However, promising results are seen in few studies. We conducted prospective study of 50 patients of prostate cancer for accuracy of PSMA PET scan in detecting LNMs with using HPE of PLND for comparison (Table 4).

Several targeted radiotracers have been developed for PET imaging of prostate cancer.

Table 4: PET radiotracers used for prostate cancer imaging.

Name of agent	Mechanism of uptake	FDA approved?	Approved indication
$Na^{18}F$	Exchanges with hydroxyl groups on hydroxyapatite at areas of bone turnover	Yes	Imaging of bone to define areas of altered osteogenic activity
^{18}F-FDG	Glucose analogue that is taken up by glycolytically active cells	Yes	Assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer
^{11}C-choline	Choline analogue that is taken up by metabolically active cells undergoing phospholipid synthesis	Yes	Imaging of men with suspected prostate cancer recurrence and noninformative bone scintigraphy, CT, or MRI
^{18}F-FACBC	Amino acid analogue that is taken up by metabolically active cells undergoing protein synthesis	Yes	Imaging of men with suspected prostate cancer recurrence based on an elevated PSA level after prior treatment
^{68}Ga-PSMA-11	Small molecule inhibitor of PSMA	No	N/A
^{18}F-DCFPyL	Small molecule inhibitor of PSMA	No	N/A
^{68}Ga-RM2	Synthetic gastrin releasing peptide receptor antagonist	No	N/A

Lymph node metastases in patients with prostate cancer are characterized as an adverse prognostic factor and can be associated with systemic metastases. Extended pelvic lymph node dissection remains the gold standard procedure in the assessment of lymph node status in men undergoing RARP for PCa. It is well known that ePLND is primarily performed for staging purposes. Although the observation that a substantial proportion of men with pN1 disease will actually remain free of disease on follow-up, the majority of men undergoes ePLND with no benefit as no lymph node metastatic disease is present. Moreover, ePLND is associated with a risk of serious surgical complications, such as vascular and nerve injuries, and the formation of lymphoceles [20].

In our study, we find out that PSMA PET scan has high sensitivity (91.66%) and high specificity (94.47%) for detection of Lymph node metastasis. These results are similar as compared with previous study. PSMA PET scan has very high NPV (97.29%) for detection of LNMs (Table 5).

Table 5: Comparision of sensitivity, specificity, PPV, NPV of PSMA PET scan in detection of LNMs of our study with other studies.

Studies	Total no. of patients (n)	Sensitivity %	Specificity %	PPV %	NPV %
Our study	50	91.66	94.47	84.61	97.29
Pim J van Leeuwen, et al.	30	100	58	94	98
Gupta M, et al.	23	77.78	92.86	87.5	86.67
Jansen, et al.	117	41.2	94. 0	53.8	90.4
Dennie Meijer, et al.	434	37.9	94.1	64.3	84.4

In future, mpMRI PSMA PET fusion may be a better investigation for predicting lymph node positivity, as mpMRI prostate has better soft tissue differentiation than CT scan. Though, no prospective studies are done till date on this. Single investigation would give all the answers instead of doing mpMRI prostate and PSMA PET scan separately.

We recognise several limitations to the present study, including the single institution study design and small sample size. There is no randomisation and no cross over. This study did not assess the accuracy of PSMA PET scan for detecting distant metastases. Only patients undergoing RARP and ePLND were considered for analysis, which naturally excludes patients with distant metastases.

Conclusion

PSMA PET scan has high sensitivity with high specificity for lymph node metastasis detection. PSMA PET scan has potential to replace currant imaging technique for lymph node staging in patients with prostate cancer planned for radical prostatectomy. Since PSMA PET scan has high NPV for lymph node metastasis, Pelvic Lymph Node Detection (PLND) could be withheld in patient with negative lymph node metastasis in PSMA PET scan, in future.

Conflicting Interests

The Authors declare that there is no conflict of interest.

Informed Consent

Written informed consent was obtained from all subjects before the study.

Ethical Approval

Ethical approval for this study was obtained from Poona medical research foundation.

Contributorship

KSP and RC contributed to the conception and design of the study. KSP performed the literature searches and did the initial sorting of eligible papers. SS helped for data collection. KSP extracted data and drafted the manuscript. All authors critically revised the manuscript and approved the final version of the manuscript.

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