Is ^{177}Lu-PSMA an effective treatment modality for mCRPC patients with bone and visceral metastasis?

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Abstract

Objective: We analyzed the clinical outcome of lutetium-177 prostate-specific membrane antigen (^{177}Lu-PSMA) in metastatic castration-resistant prostate cancer (mCRPC) patients with visceral metastasis. **Subjects and Methods:** Ten patients of mCRPC with visceral metastasis were enrolled for one cycle of ^{177}Lu-PSMA therapy. Number of efficacy and safety parameters, e.g., prostate-specific antigen (PSA), visual analog scale (VAS) and analgesic quantification scale (AQS), hemoglobin (Hb), total leukocytes counts (TLC), platelets, creatinine, & total bilirubin, were assessed and compared with Wilcoxon signed-rank test. The progression-free survival (PFS) curve was computed by the Kaplan-Meier method. The receiver operating characteristic curve (ROC) was also plotted for ^{177}Lu-PSMA dose. $P \leq 0.05$ was considered significant. **Results:** Liver (80%), lung (30%), adrenal (10%), and peritoneum (10%) were the sites of visceral metastasis in our study. On PSA response assessment, 10%, 60%, and 30% of the patients had partial response, stable disease, and progressive disease, respectively. Forty percent of the patients had improvement in the VAS, while 50% had improvement in the AQS score. Median PFS was 24 weeks in our study. A cut-off of 4.88GBq of ^{177}Lu-PSMA was the best-predicted progression with 66.67% sensitivity and 100% specificity on ROC analysis. Thirty percent of the patients showed grade 3 anemia. No other significant toxicity was seen. **Conclusion:** Lutetium-177-PSMA was a reasonable palliative treatment option with limited toxicity for these end-stage mCRPC patients with visceral metastasis with adequate PSA stabilization. A synergistic drug amalgamation may be an ideal way to boost the outcome in the future.

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Introduction

Prostate cancer is the most common cancer and the second most prevalent cause of cancer-related deaths among men in the United States [1]. Like rising trends in other parts of the world, in many metro cities in India, it has become the second most frequent cancer among men at an age-adjusted incidence rate of 10.9 per million person-years in Delhi [2]. An early-stage prostate cancer diagnosis is the key to long-term survival, while a late-stage disease indicates a poor outcome [3]. Visceral metastases generally follow in a later stage of the disease and suggest poor prognosis [4]. Common sites of visceral metastases in prostate cancer patients include lung (47.3%), liver (43.6%) and adrenal (9.1%) [5]. With multiple and effective treatment options, patients with prostate cancer live longer and therefore increased incidence of visceral metastasis in end-stage disease is becoming common. Lutetium-177 prostate-specific membrane antigen (^{177}Lu-PSMA) is a novel drug that has recently shown promising results in metastatic castration-resistant prostate cancer (mCRPC) patients across the world [6, 7]. In this retrospective analysis, we have evaluated the clinical outcome of mCRPC patients with visceral metastasis treated with one cycle of ^{177}Lu-PSMA. Among other research articles that study the therapeutic use of ^{177}Lu-PSMA, we highlighted its role in visceral metastasis mCRPC patients.

Subjects and Methods

Ten mCRPC patients with visceral metastasis were referred for ^{177}Lu-PSMA therapy on a compassionate basis following the consumption of all approved lines of treatment from September 2016 to 2019.All these patients did not undergo prostatectomy during their

treatment course. A positive gallium-68 prostate-specific membrane antigen (^{68}Ga-PSMA) positron emission tomography/computed tomography (PET/CT) was a pre-requisite before considering a patient eligible for ^{177}Lu-PSMA therapy. Further, a detailed blood workup was done to all the patients to ensure this therapy's suitability. A hemoglobin (Hb) ≥8g/dL, platelets >75,000 per mm^3, total leukocytes counts (TLC) >3000 per mm3, and creatinine ≤1.8mg/dL were the other criteria for inclusion. We excluded patients with different types of synchronous or metachronous cancers and patients with non-adenocarcinoma subtypes of prostate cancer. The hospital scientific and ethical committee approved this research study. All the patients signed a written informed consent before treatment.

Radio-labelling and therapy protocol of ^{177}Lu-PSMA

Peptide PSMA-617 and non-carrier added ^{177}Lu were purchased from ABX advanced biochemical compounds, GmbH, Germany, and ITG, Germany, respectively. Vendor-specific protocol was followed for the in-house synthesis of ^{177}Lu-PSMA by a well-experienced radio-chemist. Following quality check with thin layer chromatography, a fixed high dose of ^{177}Lu-PSMA was infused into the patient with 50mL normal saline (NS) drip over 15 minutes. One liter of NS @ 250mL per hour was used for patients hydration, which was started 30 minutes before the radiopharmaceutical drip.

Biochemical efficacy parameter

Prostate-specific antigen (PSA) is a recommended biomarker for prostate cancer, which helps diagnose and is used for response assessment and in follow-up [8]. Pre and 8-10 week post ^{177}Lu-PSMA therapy PSA was recorded. Depending on the PSA response, patients were categorized into the partial response (PR ≥50% decrease in PSA) or progressive disease (PD ≥25% increase in PSA and a minimum of 2ng/mL increase in absolute value as well) [9]. A change in between PR and PD was categorized as stable disease (SD).

Clinical efficacy parameters

The Eastern cooperative oncology group (ECOG) performance status (PS) of the patient was analyzed pre and 8-10 week post ^{177}Lu-PSMA therapy [10]. Pre and 8-10 week post ^{177}Lu-PSMA therapy, the intensity of pain was reported as per the visual analog scale (VAS) of 0-10 points [11]. An improvement of 2 points in pain score was noted as a response. Pre and 8-10 weeks post ^{177}Lu-PSMA treatment, the analgesic quantification scale (AQS) on a 0 to 6 scale was also recorded [7, 12]. An improvement of one point in AQS post ^{177}Lu-PSMA therapy was noted as a response.

Safety parameters

Pre and post ^{177}Lu-PSMA therapy Hb, TLC, platelet counts, creatinine, and total bilirubin, were recorded. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used for toxicity analysis [13].

Progression-free survival

Progression-free survival (PFS) was considered as the primary analysis point. The time from the start of ^{177}Lu-PSMA therapy until the progression of PSA or death of the patient due to any cause or therapy discontinuation due to severe treatment-related side effects was considered as PFS. In case of incomplete information due to loss to follow-up of the patient, the data was censored for PFS analysis.

Statistical analysis

Mean, median, and range were analyzed for quantitative data, whereas absolute frequencies and percentages were analyzed for categorical data. Wilcoxon signed-rank test was used to compare pre and post ^{177}Lu-PSMA therapy efficacy and safety parameters. Univariate PFS curve was computed by the Kaplan-Meier method and compared with the Log-Rank test. A receiver operating characteristic curve (ROC) was plotted to determine the cut-off value of ^{177}Lu-PSMA dose to predict PFS. Univariate analysis was performed to determine which pre-therapy parameter, e.g., age, Gleason score, ^{177}Lu-PSMA dose, ECOG PS, VAS, and AQS score, was a significant predictor of PFS. For the statistical analysis, MedCalc Statistical Software version 19.1.5 (MedCalc Software bv, Ostend, Belgium) was used. P≤0.05 was considered of statistical significance.

Results

Patients essential characteristics were tabulated (Table 1). The mean age was 67.1 years (median 69.5, range 45-77 years), and the Gleason score ranged 8 to 9 in our study group. The sites of visceral metastasis in our study group were liver (80%), lung (30%), adrenal (10%), and peritoneum (10%). Six patients had one site of visceral metastasis, while four patients had two sites of visceral metastases. All patients had bone metastases in our study. All patients had received docetaxel chemotherapy, while four patients had also received cabazitaxel chemotherapy before ^{177}Lu-PSMA. Six patients had received abiraterone, while two patients had also received enzalutamide as well. Lutetium-177-PSMA radioactivity dose was decided empirically. Dosimetry is the ideal way to plan an individual ^{177}Lu-PSMA dose. However, we designed a fixed amount of it in-between 3.7-7.4GBq based on the literature. The final dose varied due to logistics issues. The mean ^{177}Lu-PSMA radioactivity dose was 6.2GBq (median 7.1, range 3.7-7.7GBq) in our study group. Mean pre and post ^{177}Lu-PSMA therapy PSA were 145.4ng/mL (median 81.4, range 14.1-426.3ng/mL) and 150.4ng/mL (median 47.2, range 18.2-415ng/mL), respectively. One patient had PR; six patients had SD while three patients had PD on PSA response assessment following one cycle of ^{177}Lu-PSMA therapy. Overall, we found that seven (70%) patients had either stabilization or response in PSA following ^{177}Lu-PSMA therapy (Figure 1). Mean pre and post ^{177}Lu-PSMA therapy ECOG PS was 3.4 (median 3.5, range 2-4) and 3.2 (median 3.0, range 2-4), respectively. Two patients showed a one-point improvement in ECOG PS following therapy. Mean pre and post ^{177}Lu-PSMA therapy VAS scores were 5.6 (median 5.0, range 3-8) and 4.4 (median 5, range 1-6), respectively. Four patients (40%) showed 2 points improvement, while the two patient

(20%) showed a one-point improvement in VAS score following therapy. Mean pre and post ^{177}Lu-PSMA therapy AQS score was 3.6 (median 4.0, range 3-4) and 2.9 (median 3, range 1-4), respectively. One patient (10%) showed 2 points improvement, while the five patients (50%) showed a one-point improvement in AQS score following therapy. Wilcoxon signed-rank test showed significant statistical difference ($P \leq 0.05$) in VAS and AQS scores following post ^{177}Lu-PSMA therapy. Simultaneously, it was non-significant ($P \geq 0.05$) for the ECOG PS and PSA (Table 2).

In our study group, four patients were withdrew after the first follow-up following one cycle of ^{177}Lu-PSMA therapy despite stable PSA, not willing to take further treatment due to financial constrain. Hence, due to incomplete information, these patients were censored during PFS calculation. On Kaplan-Meier analysis, mean PFS was 21.2 weeks (95% confidence interval, CI: 12.1 to 30.3) and median PFS 24 weeks (95% CI: 8-36). On ROC analysis, a cut-off of 4.88 GBq of ^{177}Lu-PSMA dose was obtained to predict progression with 66.67% sensitivity and 100% specificity. The area under the curve (AUC) was 0.75 (95% CI: 0.39 to 0.96). Based on ROC analysis, patients were grouped in group 1 (^{177}Lu-PSMA dose ≤4.9GBq) and group 2 (177Lu-PSMA dose >4.9GBq). A significant difference (P=0.027, Hazard ratio: 0.18) was seen in PFS of groups 1 and 2 on the Log-rank test (Table 3). None of the pre-therapy parameters, e.g., age, Gleason score, ^{177}Lu-PSMA dose, ECOG PS, VAS, and AQS scores, was on Univariate analysis found to be a significant predictor of PFS (Table 4).

Patients' pre and 8-10 weeks post ^{177}Lu-PSMA therapy, various safety parameters were tabulated (Table 5). Mean pre and post ^{177}Lu-PSMA therapy Hb were 10.7g/dL (median 10.5, range 9-13.4g/dL) and 10.1g/dL (median 9.7, range 7.4-13.1g/dL), respectively. Mean pre and post ^{177}Lu-PSMA therapy CTCAE grade for Hb were 1.3 (median 1.5, range 0-2g/dL) and 1.8 (median 2.0, range 0-3), respectively. Three patients (30%) showed grade-3 anemia post ^{177}Lu-PSMA therapy. However, all these three patients already had grade-2 anemia due to previous chemotherapies at baseline investigation. No patient with grade 0 or 1 anemia at baseline developed grade-3 anemia post ^{177}Lu-PSMA therapy. A maximum change in grade was one point following ^{177}Lu-PSMA therapy, which was seen in a total of five patients. Wilcoxon signed-rank test showed significant difference (P=0.02) in CTCAE grade of Hb following ^{177}Lu-PSMA therapy, while it was not significant for absolute Hb value (Table 6). Mean pre and post ^{177}Lu-PSMA therapy TLC were 7504 per mm^3 (median 7215, range 5120-11870 per mm^3) and 6926.3 per mm^3 (median 6950, range 4200-11200 per mm^3), respectively. All patients in our study had CTCAE grade 0 for TLC pre and post ^{177}Lu-PSMA therapy. No significant difference was seen in either CTCEA grade or absolute TLC following ^{177}Lu-PSMA therapy in our study. Mean pre and post ^{177}Lu-PSMA therapy platelet counts were 3.2lac/mm^3 (median 2.9, range 1.7-6.6lac/mm^3) and 2.4lac/mm^3 (median 2.1, range 1.5-4.2lac/mm^3), respectively. All patients in our study had CTCAE grade 0 for platelet counts pre and post ^{177}Lu-PSMA therapy. Wilcoxon signed-rank test showed a significant difference (P=0.01) in absolute platelet counts following ^{177}Lu-PSMA therapy, while it was not significant for CTCAE grade. Mean pre and post ^{177}Lu-PSMA therapy creatinine were 0.9mg/dL (median 1.0, range 0.5-1.8 mg/dL) and 0.9g/dL (median 0.9, range 0.6-1.9mg/dL), respectively. Mean pre and post ^{177}Lu-PSMA therapy CTCAE grade for creatinine were 0.1 (median 0, range 0-1g/dL) and 0.2 (median 0, range 0-2), respectively. No significant difference was seen in either CTCEA grade or absolute creatinine value following ^{177}Lu-PSMA therapy in our study. Mean pre and post ^{177}Lu-PSMA therapy total bilirubin were 0.8 mg/dL (median 0.8, range 0.6-1.1mg/dL)and 0.8g/dL (me-

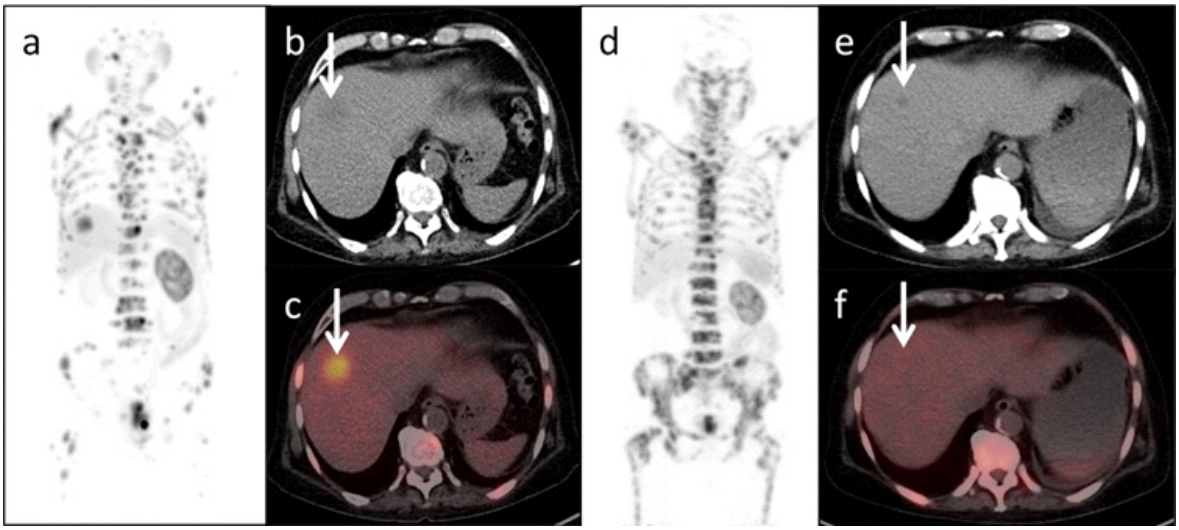

Figure 1. Gallium-68-PSMA PET/CT maximum intensity projection (images a and d), axial CT (image b and e), and axial fused PET/CT (image c and f) images. A 73 years old gentleman with metastatic adenocarcinoma prostate (Gleason 4+5) diagnosed eight years back. He was treated with bilateral orchidectomy, docetaxel, enzalutamide, and cabazitaxel at different time intervals. He presented with rising prostate-specific antigen (PSA) 297ng/mL, and ^{68}Ga-PSMA-11 PET/CT showed multiple highly PSMA avid bone lesions and a liver lesion (image a, b and c). He was treated with 7.5GBq of ^{177}Lu-PSMA. A follow-up PSA at eight weeks was 294.7ng/mL and the ^{68}Ga-PSMA PET/CT showed a response in liver lesion, while persistent extensive bone lesions (image d, e, and f).

Table 1. *Patients essential characteristics, ^{177}Lu-PSMA dose, various pre and 8-10 weeks post ^{177}Lu-PSMA clinical and biochemical efficacy parameters.*

SN	Age (Years)	Gleason score	Sites of visceral metastases	^{177}Lu-PSMA Dose (GBq)	ECOG PS score (0-5)		VAS score for pain (1-10)		AQS score (0-6)		PSA (ng/mL)		PFS (weeks)
					Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	70	9	Liver, adrenal	4.85	4	4	7	6	4	4	14.1	25.3	8*
2	69	9	Lung	4.88	3	3	5	6	4	4	277	400	8*
3	69	8	Liver	3.7	2	2	4	4	3	3	16.1	23.5	8*
4	70	8	Liver, Pleura	4.22	4	4	8	5	4	3	426.3	415	8*
5	77	9	Liver, Lung	7.7	4	4	8	6	4	3	206.2	214	8^
6	76	8	Liver	7.03	3	3	6	5	4	3	109.4	65.4	8^
7	45	9	Liver, Lung	7.33	4	4	5	3	3	2	31.9	28.9	8^
8	54	8	Peritoneum	7.18	4	3	5	5	4	3	22.6	19.4	8^
8	73	9	Liver	7.47	3	3	5	3	3	3	297	294.7	24*
10	68	8	Liver	7.62	3	2	3	1	3	1	53.4	18.2	36*

*^{177}Lu-PSMA: Lutetium-177 Prostate-specific membrane antigen, GBq: Gigabecquerel, ECOG PS: Eastern cooperative oncology group performance status, VAS: Visual analog scale, AQS: Analgesic quantification scale, PSA: Prostate-specific antigen, * Patients who developed PSA progression.^ Patients who lost following first follow-up*

Table 2. *Wilcoxon signed-rank test comparing pre and post ^{177}Lu-PSMA therapy various efficacy parameters.*

	Pre therapy	Post therapy	P-value
Parameters	**Mean±SD**	**Mean±SD**	
ECOG PS score (0-5)	3.4±0.7	3.2±0.79	0.157
VAS score for pain (0-10)	5.6±1.65	4.4±1.65	0.023
AQS score (0-6)	3.6±0.52	2.9±0.88	0.020
PSA (ng/mL)	145.4±147.04	150.44±165.18	0.799

Lutetium-177 Prostate-specific membrane antigen, ECOG PS: Eastern cooperative oncology group performance status, VAS: Visual analog scale, AQS: Analgesic quantification scale, PSA: Prostate-specific antigen, SD: Standard Deviation.

Table 3. *Mean and median PFS of group 1 (^{177}Lu-PSMA dose ≤4.9GBq) and 2 (^{177}Lu-PSMA dose >4.9GBq).*

Group	Mean (weeks)	95% CI	Median (weeks)	95% CI
1	8.0	8.0 to 8.0	8.0	8.0 to 8.0
2	30.0	18.2 to 41.7	24.0	24.0 to 36.0
Overall	21.2	12.1 to 30.3	24.0	8.0 to 36.0

PFS: progression free survival, ^{177}Lu-PSMA: Lutetium-177 Prostate-specific membrane antigen, GBq: Gigabecquerel, CI: Confidence interval

Table 4. *Univariate analysis to find out which pre-therapy parameter was a significant predictor of PFS.*

Variables	P value	H.R	95% CI of H.R
Age	0.53	1.04	0.91 to 1.19
Gleason score	0.66	1.50	0.25 to 8.97
^{177}Lu-PSMA Dose	0.07	0.38	0.13 to 1.07
ECOG PS	0.65	0.73	0.17 to 2.93
VAS score	0.43	1.27	0.69 to 2.31
AQS score	0.55	2.00	0.20 to 19.22
PSA	0.37	1.00	0.99 to 1.00

PFS: Progression-free survival, ^{177}Lu-PSMA: Lutetium-177 Prostate-specific membrane antigen, ECOG PS: Eastern cooperative oncology group performance status, VAS: Visual analog scale, AQS: Analgesic quantification scale, PSA: Prostate-specific antigen, H.R: Hazard Ratio, CI: Confidence interval

Table 5. *Pre and 8-10 weeks post ^{177}Lu-PSMA therapy, various biochemical safety parameters.*

SN	Hemoglobulin (g/dl)				Total leukocytes counts (*10^3 per mm^3)				Platelets (lac/mm^3)				Creatinine (mg/dL)				Total bilirubin (mg/dL)			
	Pre	Grade^	Post	Grade^	Pre	Grade^	Post	Grade^	Pre	Grade^	Post	Grade^	Pre	Grade^	Post	Grade^	Pre	Grade^	Post	Grade^
1	9	2	7.4	3	6.31	0	4.2	0	2.3	0	2.1	0	0.7	0	0.8	0	0.7	0	0.7	0
2	11.4	1	12.3	1	11.87	0	11.2	0	2.6	0	2.6	0	0.7	0	0.7	0	0.6	0	0.7	0
3	9.9	2	9.8	2	7.7	0	7.5	0	1.7	0	1.8	0	1	0	1	0	0.8	0	0.8	0
4	9.7	2	7.5	3	8.7	0	8.6	0	6.6	0	2	0	0.5	0	0.6	0	0.7	0	0.6	0
5	11.5	1	9.6	2	7.53	0	6.4	0	2.2	0	1.5	0	1	0	1.2	0	0.9	0	0.8	0
6	9.2	2	7.6	3	5.12	0	4.3	0	3.6	0	3.5	0	1	0	1	0	1	0	0.9	0
7	13.1	0	12.8	1	5.42	0	5.01	0	3.6	0	2.5	0	1.1	0	1	0	0.8	0	0.8	0
8	11.2	1	11.3	1	5.71	0	4.8	0	2.5	0	1.9	0	1	0	0.9	0	0.9	0	0.8	0
9	9.4	2	9.6	2	6.90	0	8.55	0	3.3	0	2.1	0	1.8	1	1.9	2	0.8	0	0.9	0
10	13.4	0	13.1	0	9.78	0	8.69	0	4.5	0	4.2	0	0.6	0	0.6	0	1.1	0	1	0

^{177}Lu-PSMA: Lutetium-177 Prostate-specific membrane antigen, ^: as per Common terminology criteria for adverse events (CTCAE) version 4.03

Table 6. *Wilcoxon signed-rank test comparing pre and post ^{177}Lu-PSMA therapy various safety parameters.*

Parameters	Pre therapy	Post therapy	P-value
	Mean±S.D	Mean±S.D	
Hemoglobulin (Hb) g/dL	10.78±1.59	10.1±2.2	0.083
CTCAE Grade Hb	1.3±0.82	1.8±1.03	0.025
Total leukocytes counts (TLC) per mm^3	7504.5±2127.69	6926.3±2356.72	0.059
CTCAE Grade TLC	0±0	0±0	0.823
Platelets lac/mm^3	3.29±1.43	2.42±0.83	0.013
CTCAE Grade Platelets	0±0	0±0	0.986
Creatinine mg/dL	0.94±0.37	0.97±0.38	0.317
CTCAE Grade Creatinine	0.1±0.32	0.2±0.63	0.317
Bilirubin mg/dL	0.83±0.15	0.8±0.12	0.257
CTCAE Grade Bilirubin	0±0	0±0	0.978

^{177}Lu-PSMA: Lutetium-177 Prostate-specific membrane antigen, CTCAE: Common terminology criteria for adverse events, version 4.03, S.D: Standard deviation

dian 0.8, range 0.6-1.0mg/dL), respectively. All patients in our study had CTCAE grade 0 for total bilirubin pre and post ^{177}Lu-PSMA therapy. No significant difference was seen in either CTCEA grade or absolute total bilirubin value following ^{177}Lu-PSMA therapy in our study.

Discussion

In general, the appearance of visceral metastasis signifies a terminal stage of disease in a cancer patient. Most of the patients with visceral metastasis present with high volume disease, have symptoms, and receive multiple systemic treatments. Researchers in this field have noted that this subgroup's patients have not been well studied in the literature [14, 15]. Visceral metastasis has distinct cellular and systemic factors and tumor microenvironment profile, making it different from commonly found bone metastasis in prostate cancer [16-18]. Therefore, patients with visceral metastasis have a poorer outcome than patients with bone-only metastasis [19, 20]. Most of the clinical outcome data in this subgroup has been generated by post hoc analysis of some significant phase III randomized control trials (RCT). A decade later, post hoc analysis of the TAX327 trial, it was reported that patients with liver metastases have the shortest median overall survival (OS) [21]. In a subgroup analysis of AFFIRM trial patients data base, it was reported that enzalutamide was effective in mCRPC patients with liver or lung metastases compared to placebo [22]. In a population-level study using the Surveillance, Epidemiology, and End Results (SEER)-medicare database, it was concluded that patients with visceral plus bone metastases have the worst prognosis, followed by patients with visceral only, bone only, and lymph nodes only metastases [23]. In a meta-analysis of nine phase III RCT with 8820 mCRPC patients treated with docetaxel chemotherapy, the best OS was seen in patients with lymph node only metastases while the worst outcome was observed in patients with liver metastases [24].

Analysis of treatment outcome with any novel drug is of utmost importance in this subgroup of mCRPC patients before its approval for clinical use. In recent times, PSMA based radioligand therapy opened up a new personalized medicine area for mCRPC patients [25]. The PSMA expression level is the key to success for this therapy, which has to be assessed by the ^{68}Ga-PSMA PET/CT scan before initial treatment. This novel mechanism makes this therapy unique. Many single institutional studies have highlighted the role of ^{177}Lu-PSMA in the last five years [26-28]. Most of these studies have similar limitations of small sample size, retrospective nature, heterogeneity in disease distribution, ^{177}Lu-PSMA dose, and limited follow-up data. The first retrospective, multicentre German study (n-145), reported a 40% PSA response following one cycle and 45% PSA response following all cycles of ^{177}Lu-PSMA [29]. In their patient group, 20% of the patients had liver, 14% lung, and 2% other visceral metastasis sites. Patients with visceral metastasis were asso-

ciated with a lower PSA response rate (odds ratio 3.73). Heck et al. (2019) presented a retrospective single institutional study of 100 mCRPC patients treated with a median of two cycles of ^{177}Lu-PSMA imaging & therapy (^{177}Lu-PSMA-I&T) on a compassionate protocol [30]. In their study group, 35% of patients had visceral metastasis (18% liver, 11% lung, and 8% adrenal). Overall, partial PSA response was seen in 38% of the patients with median PFS 4.1 months. On subgroup analysis, the presence of visceral metastases was associated with the worst outcome, as only 26% of their patients with visceral metastases (n-35) showed PSA partial response. Results were even not very high in our experience, as only 10% of the patients had PSA partial response with a mean PFS of 21.2 weeks (5.3 months).

Kessel et al. (2019) reported a retrospective analysis of 109 mCRPC patients treated with a median of three cycles of ^{177}Lu-PSMA [31]. Overall, the PSA partial response was 25%, while the median OS was 9.9 months. In their study group, 44% of the patients had visceral metastases, which was associated with a significant decrease in OS (7.1 vs. 13.1 months). Liver metastases had the highest impact on OS (5.6 vs. 13.2 months), while the lung metastases had no significant effect. On multivariate analysis, the presence of visceral metastasis was the only significant factor as well. As we have reported earlier, 80% of our patients had liver metastases, which may be the reason for the poor outcome in our study. In our clinical experience of treating mCRPC with ^{177}Lu-PSMA, we found that patients with non-visceral metastases (n-15) had a better mean PFS of 24.2 weeks (6 months). However, it was not significantly high (P=0.411). A case report has recently described a complete regression of lung metastases in mCRPC patients treated with one cycle of ^{177}Lu-PSMA therapy [32]. This favorable outcome gives a strong desire to plan a prospective trial to assess the clinical value of ^{177}Lu-PSMA in mCRPC patients with visceral metastasis.

Thirty percent of our patients had grade 3 anemia. However, all these patients already had a compromised bone marrow. Therefore, an adequate bone marrow reserve is vital to avoid acute toxicity. We also noticed a significant change in the absolute number of platelet counts though CTCAE grade was stable. Long-term data on the safety and efficacy of ^{177}Lu-PSMA in mCRPC patients has been recently published [33, 34]. Twenty percent of their patients had visceral metastasis, while the remaining 80% of the patients had non-visceral metastases (76% bone and 4% non-regional lymph nodes only). Median PFS and OS were 6.9 months and 13.3 months, respectively. Grade 3 anemia was seen in 10% of the patients, while grade 3-4 thrombocytopenia was also reported in 10% of the patients. A low overall ECOG PS and compromised bone marrow reserve at baseline were likely attributed to higher grade 3 anemia in our study group.

Our study had a few limitations as well. Small sample size and retrospective analysis were the primary ones. Lutetium-177-PSMA therapy is considered to be the end resort for mCRPC patients. Hence, most of these patients already had a high volume of disease, toxicities due to previous therapies and financial constraints by this time. Affordability was also a factor for the small number of patients enrolled for this treatment. Due to 40% non-compliance during follow-up, we have described the results of one cycle of ^{177}Lu-PSMA therapy to avoid heterogeneity in data. Survival data was not available in our study group and that lowered the power of our analysis. Future studies analyzing survival outcome in mCRPC patients with visceral metastases treated with multiple cycles of ^{177}Lu-PSMA are wanted. It will also become imperative to assess efficacy in the setting of oligo verse multiple visceral metastases. The non availability of long term toxicity profile was another drawback of our study.

In conclusion, ^{177}Lu-PSMA was a reasonable palliative treatment option with limited toxicity for these end-stage mCRPC patients with visceral metastases with adequate PSA stabilization. A synergistic drug amalgamation may be an ideal way to boost the outcome in the future [35-37].

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