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ORIGINAL RESEARCH ARTICLE

Value of two-phase [^{68}Ga]Ga-PSMA PET/CT imaging in comparison with optimized delayed imaging in detecting locoregional prostatic metastases

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ABSTRACT

Introduction: [^{68}Ga]Ga-PSMA PET/CT has gained acceptance for localizing local and distant metastases; However, urinary activity remains a confounding factor in interpreting local metastases. The aim of this study was to evaluate the diagnostic value of two-phase protocol (i.e., early and regular imaging, TPP) in comparison with delayed optimized protocol (i.e., combined regular and delayed post hydration and diuresis images, DOP) to detect locoregional prostatic metastases.

Methods: Forty-one prostate cancer patients referred for staging (n = 12) or the evaluation of rise in PSA level in prostate cancer (n = 29) were prospectively assessed. In this study, each patient received an early 5-10 min image from pelvic region for two bed position, regular (RP) (60 min) and finally delayed static images. The scan findings were characterized as positive, negative or equivocal. The diagnostic significance of TPP was compared with DOP for prostatic, periprostatic, locoregional lymph nodes and pelvic bone involvement.

Results: The diagnostic agreement between DOP and TPP for prostate/prostate bed lesions was comparable with the agreement of DOP and RP (Kappa: 0.78, p value <0.001) vs. (Kappa: 0.8, p value <0.001). TPP in comparison with RP, had superior sensitivity for prostate/prostate bed lesions (95% vs. 80%). The sensitivity for lymph node metastases, extraprostatic extension and osteometastases was identical between the two protocols.

Conclusion: TPP has the potential to replace DOP for the evaluation of prostate/prostate bed lesions; however, there remains instances where delayed imaging is helpful in characterizing the anatomic abnormality especially in the lymph node region.

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INTRODUCTION

As a transmembrane glycoprotein, prostate specific membrane antigen (PSMA) provides an ideal molecular target for imaging in prostate cancer [1, 2]. [^{68}Ga]Ga-PSMA-11 PET/CT is acquiring more acceptance for prostate cancer imaging worldwide. The most important indication is the evaluation of biochemical recurrence [3, 4]; however, more indications have been introduced according to the recent report of "appropriate use criteria for PSMA PET/CT imaging" and the updates that have been made on this newer version [4, 5]. In these criteria, PSA rise after radiotherapy or radical prostatectomy as well as initial staging in high-risk patients and assessment of castration resistant prostate cancer (CRPC) patients with no evidence of metastasis on conventional imaging as well as patients candidate for [^{177}Lu]Lu-PSMA therapy were considered appropriate [4, 5]. Also, in this report several other indications have been included as "may be appropriate" for PSMA PET/CT imaging, including application of PSMA PET/CT in CRPC patients with rise in PSA level presenting with known metastasis based on conventional studies who are not considered for [^{177}Lu]Lu-PSMA therapy [5]. Standard imaging technique in these patients is performed by 60 min acquisition. However, the urinary activity remains a limiting factor in evaluation of locoregional metastases mainly because [^{68}Ga]Ga-PSMA-11 is excreted through the urine. Several attempts have been made to reduce urinary activity by different protocols including furosemide administration at different times post-injection and even at the same time as PSMA injection [6]. Recent European guidelines also considered oral hydration and furosemide injection for imaging with [^{68}Ga]Ga-PSMA-11 PET/CT imaging [7]. Furosemide administration is not always possible, as some patients have contraindications or have urinary symptoms. Other attempts have been made such as bladder catheterization and diluting urine with normal saline which is practically an invasive method, making the procedure unpleasant to the patient and increases the risk of radiation exposure to the staff [8].

Another potential approach for the detection of locoregional metastases is acquiring early dynamic images or static images within the first five minute of injection, before activity is seen in the bladder or while the bladder activity is minimal [9]. It has been suggested that the tumoral PSMA activity appears before the bladder activity. Current studies suggest that the advantage of this protocol is primarily beneficial in detecting more lesions; however, its impact in patient management is uncertain and it is not commonly practiced in many centers. Some newer imaging agents such as [^{18}F]F-PSMA-1007 , which have more biliary excretion, may alleviate the need for other approaches to reduce bladder activity or acquire early images [10]. It's worth noting that [^{18}F]F-PSMA-1007 is cyclotron produced, whereas [^{68}Ga]Ga-PSMA-11 is generator produced and is more accessible and cost effective [11], it would continue to be the primary PSMA radioligand utilized for prostate imaging at many centers. Therefore, there is still a need for reducing bladder activity and repeat imaging to better characterize locoregional metastases. This study evaluates the diagnostic value of two-phase protocol (early and regular images) in comparison with an optimized protocol including regular and delayed images based on the location of lesions such as those confined to prostate gland, periprostatic extension (mainly in seminal vesicles), locoregional lymph node involvement and pelvic bone metastasis.

METHODS

Patients and procedures

Forty-one patients referred for the evaluation with [^{68}Ga]Ga-PSMA-11 PET/CT were enrolled in this prospective study. The baseline characteristics of the studied patients are summarized in Table 1.

The patients underwent imaging according to the following protocol. [^{68}Ga]Ga-PSMA-11 (provided by Pars Isotope company, Tehran, Iran) as a ready-to-use vial was injected to patients according to their body weight with a dose of 1.8-2.2 MBq/kg. PET/CT imaging was performed by a Biograph True Point HD PET/CT scanner (Siemens medical solutions, Erlangen, Germany). For attenuation correction, low dose CT was acquired before each PET emission with the following parameters: 80 mAs, 120-130 keV, pitch of 1.3 and slice thickness of 5 mm. The early imaging was performed within five minutes of injection. Two-bed static image of the pelvic region (from a few centimeters below pelvic floor to a few centimeters above iliac bone) was acquired with the duration of 3 min/bed for PET emission. Subsequently, the standard imaging was obtained at 60-minute post injection. Image acquisition was performed

covering the vertex to mid-thigh region. During this imaging, PET emission data was acquired in the caudocranial position with an acquisition time of 4 min per bed position. In addition, delayed images using the same bed position as early imaging, however with duration of four minute per bed position were acquired after proper hydration and diuresis. Reconstruction was performed by ordered subset expectation maximization algorithm (OSEM) utilizing 2 iterations and 21 subsets. Siemens' Syngo software TrueD was employed to estimate the SUVmax for the primary lesion.

Table 1. Baseline characteristics of the studied patients

Indication of PET/CT		**Post-treatment evaluation of recurrence (n= 29)**		**Pretreatment Initial staging (n= 12)**	**Total (n=41)**
		Radical prostatectomy	Non-surgical treatment		
		22	7		
Age (years)	Mean ± SD	69.9 ± 9.2		67.4 ± 7.4	69.2 ± 8.7
Serum PSA level at the time of study (ng/mL)	Median (range) Mean ± SD	1.44 (0.16-47) 4.58 ± 9.6		27 (4-135) 44.5 ± 39.6	3 (0.16-135) 16.24 ± 28

Image analysis

Three different protocols for image interpretation were defined. The "Regular protocol" (RP) defined as standard one-hour whole body imaging without considering the results of either early or delayed images. The "two-phase protocol" (TPP) combines interpretation of early and standard images, while the "delayed optimized protocol" (DOP) uses both the standard and delayed images simultaneously for the final interpretation. The findings of each imaging protocol were evaluated separately by two board certified nuclear medicine physician while unaware of the result of the other protocol. Any structural abnormality showing PSMA avidity higher than surrounding background activity was considered abnormal in each imaging protocol. The lesions that could not be distinguished from urinary activity or any other physiological activity, were considered "equivocal". Quantitative analysis of the lesions was also performed by calculating the maximum standardized uptake value (SUVmax) for background tissue (gluteus muscle), blood pool (proximal femoral artery) and pathological lesions.

Statistical analysis

Baseline characteristics were analyzed descriptively. The number of positive, negative, and equivocal findings between two protocols were tabulated in cross-tables. For determination of specificity and sensitivity for the RP and TTP protocols, DOP was considered as reference protocol. We used Kappa coefficient to evaluate the agreement between two studied protocols (i.e. RP and TPP). For correlation of nonparametric data, Spearman's correlation was used. $P<0.05$ was considered as statistical significance.

RESULTS

Baseline patient characteristics are represented in Table 1. The number of positive, negative and equivocal cases of prostate and extraprostatic extension lesions are demonstrated in Tables 2 and 3. The early scans were acquired with a median of 3 minutes (range, 1 to 7 minutes) after injection. Halo artifact (decreased activity in the surrounding bladder and kidney) which may potentially result-in false negative or equivocal results in pelvic region was seen in five patients on standard images while, no patient showed this artifact on early images.

Evaluation of prostate/prostate bed lesions

Using per patient analysis, the diagnostic agreement between DOP and TPP for prostate/prostate bed lesions (kappa: 0.78, $p < 0.001$) was comparable with the agreement of DOP and RP (kappa: 0.8, p value < 0.001). While the frequency of equivocal results by the three protocols was different (nine in RP, two in TPP and four in DOP, p= 0.013). In fact, the frequency of equivocal results by RP was significantly higher than that of the two other protocols (p= 0.020, p=0.025 for TPP and DOP respectively), while equivocal results was not different using TPP vs DOP (p= 0.08). In details, four cases (9.7%) were equivocal by RP while definitively positive using DOP. In contrast, one equivocal case (2.4%) on RP became negative on DOP whereas four cases were equivocal in both protocols.

Evaluation of locoregional lymph nodes

Detection of metastatic lymph nodes in different anatomic regions based on different imaging protocol in Table 4, Figure 1.

Table 2. Prostatic lesions based on PSA level in the three protocols

	TPP				RP				DOP			
	n	**Pos**	**Neg**	**Eq**	**n**	**Pos**	**Neg**	**Eq**	**n**	**Pos**	**Neg**	**Eq**
PSA<1	11	3	8	0	11	1	7	3	11	3	7	1
1≤PSA<2	5	1	4	0	5	1	3	1	5	1	4	0
2≤PSA< 10	13	7	4	2	13	5	4	4	13	7	4	2
PSA≥ 10	12	11	1	0	12	10	1	1	12	10	1	1
Total	41	22	17	2	41	17	15	9	41	21	16	4

TPP: Two-phase protocol (i.e., early and regular imaging)
RP: Regular protocol
DOP: Delayed optimized protocol (i.e., combined regular and delayed post hydration and diuresis images)
Pos: Positive
Neg: Negative
Eq: Equivocal

Table 3. Extraprostatic extension lesions based on PSA level in the three protocols

	TPP				RP				DOP			
	n	**Pos**	**Neg**	**Eq**	**n**	**Pos**	**Neg**	**Eq**	**n**	**Pos**	**Neg**	**Eq**
PSA<1	11	0	11	0	11	0	11	0	11	0	11	0
1≤PSA<2	5	0	4	1	5	0	4	1	5	1	4	0
2≤PSA< 10	13	2	10	1	13	2	10	1	13	3	10	0
PSA≥ 10	12	4	8	0	12	4	8	0	12	4	8	0
Total	41	6	33	2	41	6	33	2	41	8	33	0

TPP: Two-phase protocol (i.e., early and regular imaging)
RP: Regular protocol
DOP: Delayed optimized protocol (i.e., combined regular and delayed post hydration and diuresis images)
Pos: Positive
Neg: Negative
Eq: Equivocal

Table 4. Detection rate of metastatic lymph nodes in different anatomic regions based on different imaging protocols. (Total number of stations: 410)

Anatomical location of lymph node	**RP**	**TPP**	**DOP**
Right internal iliac	3	3	4
Left internal iliac	3	3	3
Right external iliac	3	3	3
Left external iliac	3	3	3
Right obturator	2	2	3
Left obturator	2	2	2
Right common iliac	3	3	4
Left common iliac	1	1	1
Right pararectal	0	0	0
Left pararectal	1	1	2
Total	21 (5.1%)*	21 (5.1%)*	25 (6.3%)*

*Percentages are calculated as the number of involved regions relative to the total number of lymph node stations
RP: Regular protocol
TPP: Two-phase protocol (i.e., early and regular imaging)
DOP: Delayed optimized protocol (i.e., combined regular and delayed post hydration and diuresis images)

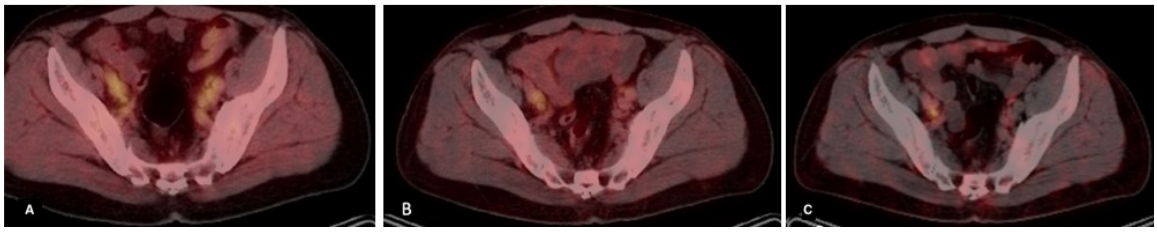

Figure 1. Early (A), standard (B) and delayed (C) images of a 63-year-old male with history of radical prostatectomy and PSA level of 18.30. A lymph node is seen in right external iliac region on delayed images (C) which is not clearly visualized in early (A) and standard (B) images

Evaluation of extraprostatic extension

For the evaluation of extraprostatic extension, the agreement between RP and TPP protocols was perfect; however, for two cases, equivocal findings were found for seminal vesicle invasion by both RP and TPP protocols. A sample of similar findings of TPP, RP and DOP are shown in Figure 2.

Comparison of diagnostic values of different protocols

The diagnostic value of TPP and RP in comparison with DOP are shown in Table 5. The diagnostic agreement of TPP vs. RP was 64% for prostate/prostate bed lesions. This value for lymph node involvement, extraprostatic extension and pelvic osteometastases was 100%. According to the Table 5, only the sensitivity of TPP method for the evaluation of prostate and prostate bed was higher than RP method (95% vs. 80%, p= 0.05) while the other parameters of diagnostic values are almost similar for the two protocols.

Quantitative analysis of the protocols

Concerning SUVmax and target-to-background SUVmax ratio of the lesions in the prostate and prostate bed, a significant rise in the tumor-to-background ratio was observed from early to late phase of imaging (Table 6). Finally, there was significant correlation between extent of involvement and PSA level for all three protocols, (RP: r= 0.75 p< 0.001, TPP: r= 0.71, p < 0.001, DOP: r= 0.69, P< 0.001) (Figures 3, 4 and 5).

DISCUSSION

Prostate cancer is the most common cancer in men. Decision making about treatment protocols and types of surgery is based on clinical and paraclinical presentations. PSMA is expressed in prostate cancer cells, it has physiologic uptake in lacrimal glands, liver, spleen, small intestine, and colon. The excretion is through kidney and bladder [12]. [^{68}Ga]Ga-PSMA-11 PET/CT has shown great value in detection of local and distant metastases in advanced stages of prostate cancer, such as cases with Gleason score> 7, PSA>20 or clinical stage beyond T2c/T3a [13, 14] and in patients with biochemical recurrence [4].

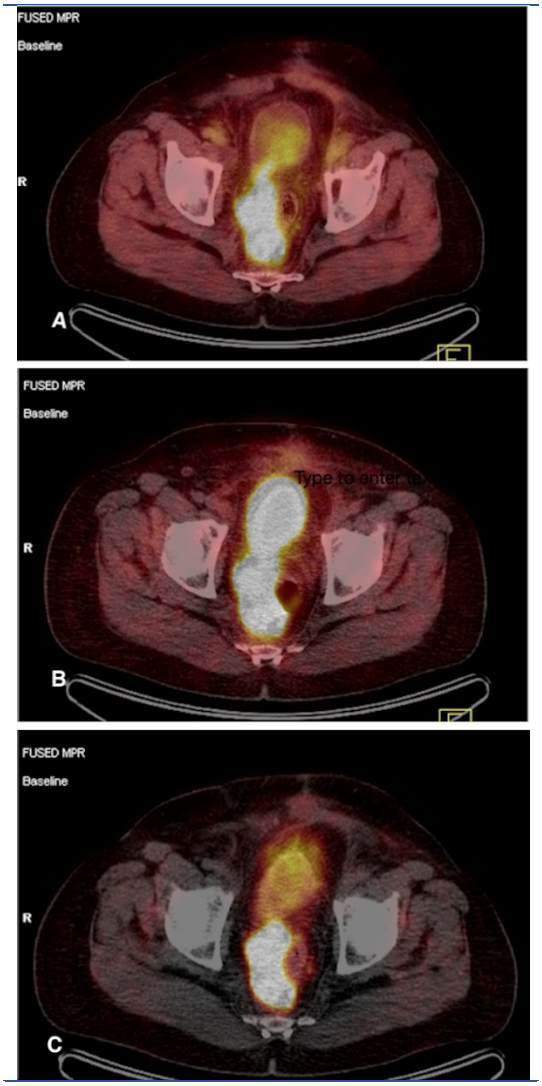

Figure 2. [^{68}Ga]Ga-PSMA PET/CT images in a 55-year-old male with previous history of prostatectomy and lymph node dissection, presented with rising PSA level to 47.9 ng/mL during follow-up, demonstrated a large lobulated [^{68}Ga]Ga-PSMA-avid tumoral mass in right pararectal and presacral regions, extending towards the right rectal wall and posterior wall of the urinary bladder on the right side, well-delineated on early (A), standard (B) and delayed (C) images

Table 5. The diagnostic value of TPP and RP in comparison with DOP

		TPP	RP	Kappa-value	p-value
Prostate/Prostate bed	Sensitivity	20/21 (95%)	17/21 (80%)	0.64	<0.001
	Specificity	15/16 (93.7%)	15/16 (93.7%)		
Extraprostatic extension/ SV bed involvement	Sensitivity	6/8 (75%)	6/8 (75%)	1	<0.001
	Specificity	33/33 (100%)	33/33 (100%)		
Lymph node involvement	Sensitivity	7/10 (70%)	7/10 (70%)	1	<0.001
	Specificity	31/31 (100%)	31/31 (100%)		
Bone metastasis	Sensitivity	6/6 (100%)	6/6 (100%)	1	<0.001
	Specificity	35/35 (100%)	35/35 (100%)		

SV: Seminal vesicle
TPP: Two-phase protocol (i.e., early and regular imaging)
RP: Regular protocol
DOP: Delayed optimized protocol (i.e., combined regular and delayed post hydration and diuresis images)

Table 6. Comparison of semi-quantitative data between three phases of imaging for prostate and prostate bed lesions

Semi-quantitative data	Imaging phase			
	Early	One-hour (Standard)	Delayed	p-value
SUVmax of target lesion	9.2±10.2	18.7±21.3	23.0±27.0	<0.001
SUVmax/blood pool ratio	4.5±5.0	14.0±17.0	19.0±24.8	<0.001
SUVmax/background ratio	11.1±13.6	28.4±35.4	36.6±47.4	<0.001

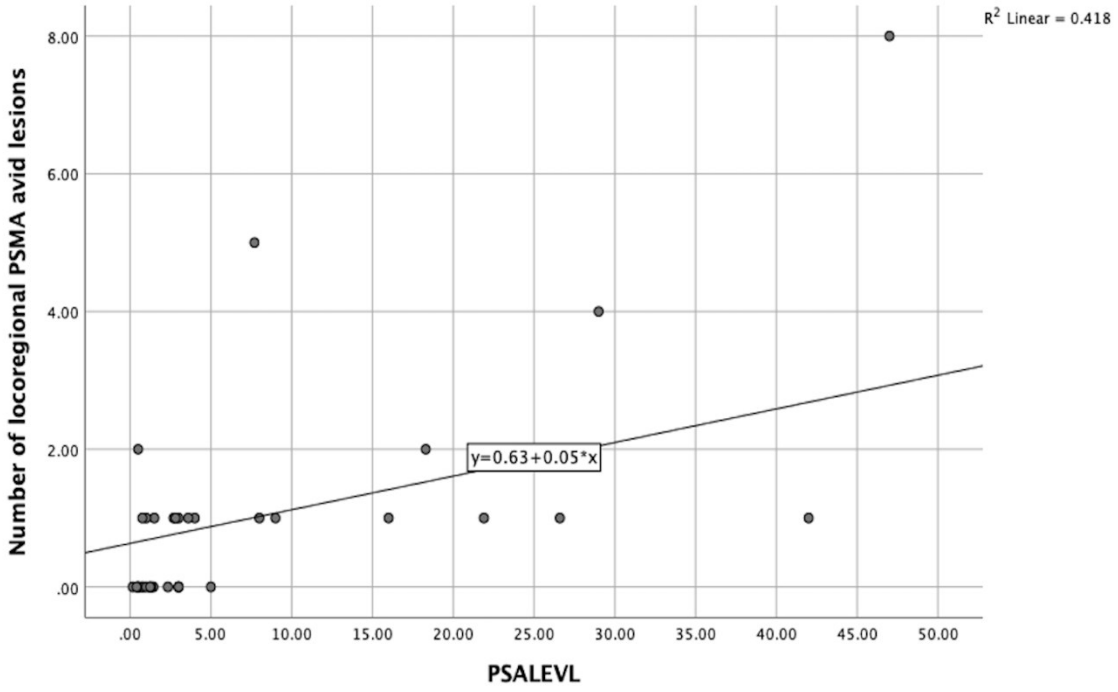

Figure 3. Correlation of PSA level and extent of locoregional involvement in two-phase protocol (i.e., early and regular imaging, TPP)

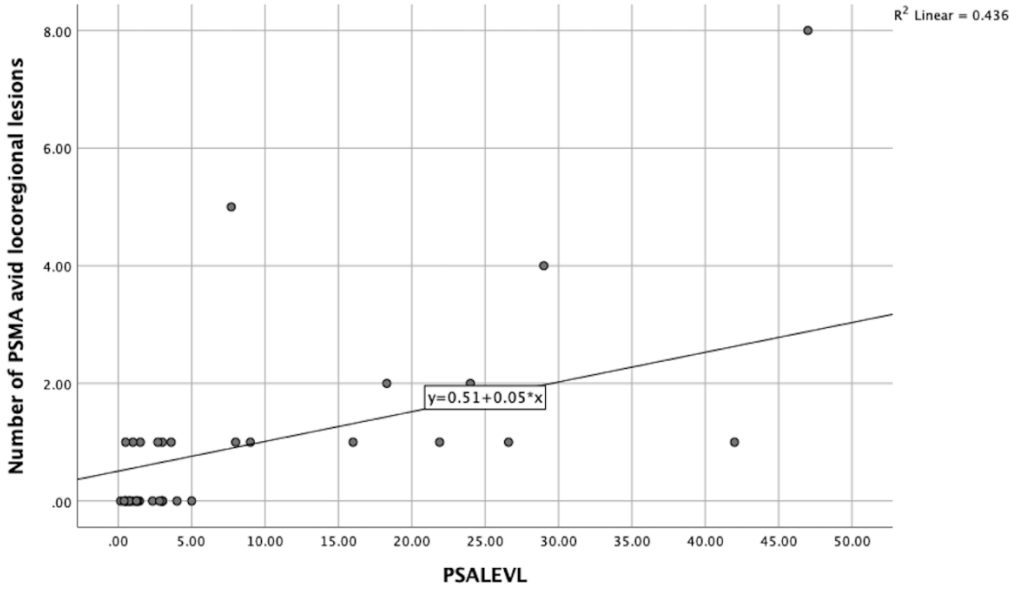

Figure 4. Correlation of PSA level and extent of locoregional involvement in regular protocol (RP)

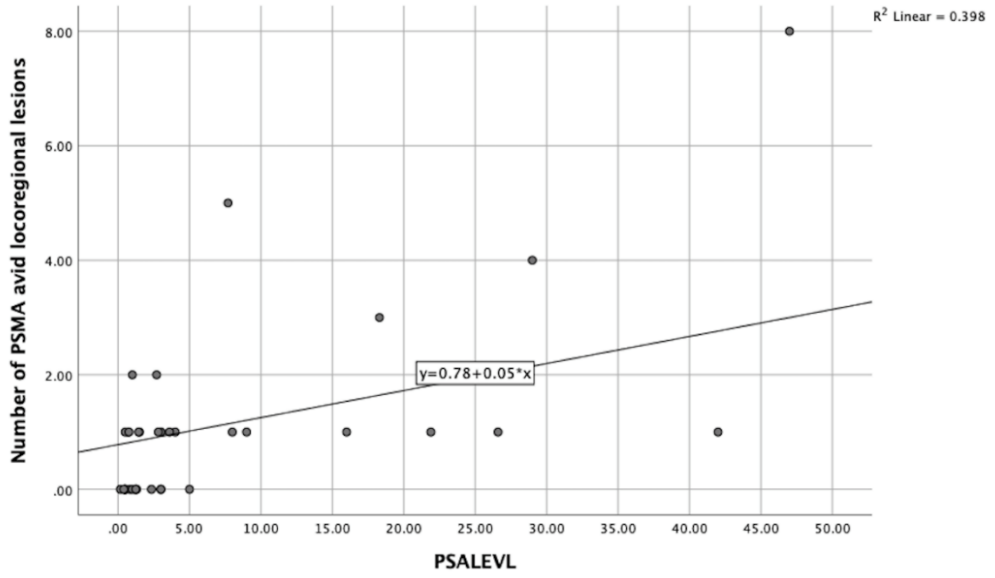

Figure 5. Correlation of PSA level and extent of locoregional involvement in delayed optimized protocol (i.e., combined regular and delayed post hydration and diuresis images, DOP)

Additionally , PSMA PET/CT is considered appropriate when the patient is being candidate for PSMA radioligand therapy [5]. The best criteria for patient selection is not well established; however, several criteria have been proposed, such as uptake greater than liver, SUV≥20 at one site , SUV≥ 10 at soft tissue site and no detectable FDG avid lesion [5].

Despite its good detection rate for distant metastases, it has limitation for revealing locoregional involvement due to intense urine activity and occasionally halo artifact. Utilization of intravenous furosemide and urinary catheterization cannot completely remove this problem and the urine activity can confound interpretation mainly at anastomosis site [6]. In the current study, we defined DOP as an achievable optimal protocol for the characterization of lesions near the urinary bladder. In this protocol, we acquired post-hydration images in addition to standard one-hour images and used both images for improvement of final interpretation as a reference method. Also, standard one-hour images were combined with early images and adjointly interpreted as TPP using the assumption

that lesions may be more conveniently discerned from urinary activity by this protocol, due to the fact that, these images are acquired before urine entry in the bladder (Figure 6). This assumption was confirmed by our study as TPP was shown to represent favorable diagnostic value in comparison with RP. In fact, higher sensitivity is acquired by this protocol in comparison with RP concerning the diagnosis of prostate/prostate bed lesions; however, we did not observe this superiority for lymph node and osteometastases. Similar to our observation, Uprimny et al. showed that in the early minutes of the study PSMA localizes in prostatic lesions significantly earlier than the urinary bladder [15]. Super early within 3 minute post-injection imaging has also proven to be valuable in detecting metastatic lesions [16]. When comparing lesion detectability, Kabasakal et al. found no difference in the number of lesions between early and RP imaging. In their study, both early and regular protocol detected 23 primary tumors, 19 lymph nodes and 14 bone metastases; however, the uptake was higher in the RP but the detectability of lesions around the bladder was considered significantly better on early images due to lower urinary activity [17]. Conversely, Barakat et al. detected 8/115 lesions only on early images (7 referred for restaging and 1 referred for staging) and one was revealed on RP only [18]. In this study, the benefit of early imaging has been described in patients referred for restaging rather than staging and mainly those with low PSA levels [18]; however, the latter conclusion may not be reliable due to limited number of detected lesions on early images.

Bayerschmidt et al. evaluated early imaging and optimized regular images but no delayed image was obtained after hydration [19]. In contrast with our result, they did not find additional value for early images and no statistically significance difference between positive, negative and equivocal cases for the early and optimized regular phase images. Furthermore, they did not show any additive diagnostic value using combined early and optimized regular images over the regular protocol. However, better results for prostate and prostate bed lesions have been obtained with delayed imaging especially following oral hydration and diuresis by other investigators [6, 20, 21].

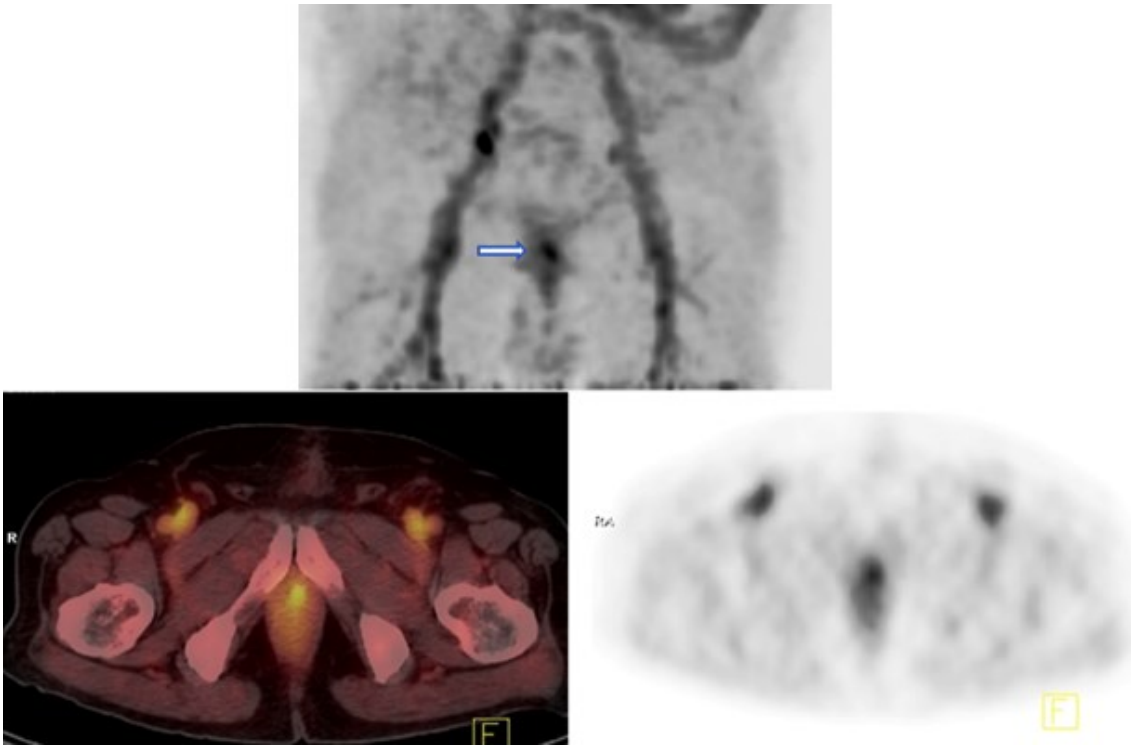

Figure 6. 70-year-old male post-prostatectomy with PSA level of 0.5. [^{68}Ga]Ga-PSMA-11 avid lesion in the bed of resected prostate gland in early image is highly suspicious for residual tumoral disease

Some studies indicated that delayed [^{68}Ga]Ga-PSMA-11 PET/CT detect more lesions with higher activity compared with regular images [20, 21]. These delayed images have also shown to reduce equivocal findings either in prostate bed or other locoregional sites [22]. For this reason, DOP was considered as reference method in our study. It should be noted that in our study, the number of equivocal cases for prostate/prostate bed lesions were reduced in DOP as compared with RP and a higher number of regional lymph nodes were localized on DOP. However, this protocol, despite good detection rate, is not favorable in high throughput centers. In addition, even with hydration or forced diuresis significant residual activity may be seen in urinary bladder of some cases [6, 12, 23]. Moreover, not all patients show compliance with ideal oral hydration and over diuresis setting. Thus, early imaging seems to be a valid option to offset this problem. It is noteworthy to mention that in the current study only one patient (2.4%) showed PSMA avidity in prostate/prostate bed lesion, which was better, discerned on DOP as compared with TPP.

Limitations

The limitation of the study is the lack of histopathological confirmation of the lesions located by [^{68}Ga]Ga-PSMA-11 PET/CT scan. This is because most patients were followed by hormone therapy or radiotherapy, and tissue sampling of the PSMA avid lesion was not achievable. Other shortcoming is the limited number of patients, which is acceptable considering the number of cases included in other similar studies.

CONCLUSION

TPP is superior to RP and has good agreement with DOP for prostate/prostate bed lesions while no advantage was demonstrated for the detection of locoregional lymph node metastases or extraprostatic extension by this protocol. Thus, the TPP may be an optimal protocol to replace RP and DOP for local evaluation of the primary tumor; however, since there are still some instances where DOP is more helpful to clarify local lymph node metastases, therefore, it may be resendable to optimize each protocol depending on the individual patient.

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