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ORIGINAL RESEARCH ARTICLE

Comparing the diagnostic efficacy of [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT scanning after 75 minutes and 4 hours of radiotracer injection in men with prostate cancer

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ABSTRACT

Introduction: Prostate-Specific Membrane Antigen (PSMA) is overexpressed in primary and metastatic prostate carcinoma (PCa) and could be targeted by a [^{99m}Tc]Tc-HYNIC-PSMA-11 scan for detection of metastases. Despite extensive studies, data on the most appropriate interval between radiopharmaceutical injection and image acquisition is scarce. We compared the metastasis detection rates of the [^{99m}Tc]Tc-HYNIC-PSMA-11 scan between 75-minute and 4-hour intervals of radiopharmaceutical injection.

Methods: From May 2021 to May 2022, we studied 30 consenting men with pathologically confirmed PCa who were referred to our department requesting a PSMA scan for primary staging, biochemical recurrence, pre-^{177}Lu-PSMA therapy, or surveillance. 75-minute and 4-hour [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT scan performed following injection of the radiopharmaceutical. The corresponding metastasis detection rates were evaluated in 75-minute and 4-hour intervals.

Results: The mean age of patients was 68.43±9.61 years, with a median PSA of 4.19 ng/ml and a median Gleason Score of 8. Nine cases had negative [^{99m}Tc]Tc-HYNIC-PSMA-11 scans, while 21 had positive scans (8 cases with bone, 2 with lung, 4 with lymph node, and 7 with multiple organ metastases). All metastases were detected in both checkpoints, except for one patient, where 75-minute images detected three pelvic metastatic lymph nodes, while four were seen in the 4-hour scan. This small missed right external iliac lymph node did not change the patient's management.

Conclusion: We found no significant difference in the detection rate of metastatic lesions in 75-minute and 4-hour time intervals. These findings could help to decrease waiting time and by more efficient scheduling improves patient's satisfaction at nuclear medicine departments.

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INTRODUCTION

Prostate cancer comprises 14.0% of new cancer cases in 2022 being 0.9% more than the previous year [1]. With 34,500 estimated deaths, it is considered the fifth cause of cancer death in 2022 [2]. While most (73%) of the PCa is confined to the gland, about 14% involve regional lymph nodes, 7% progress to the level of distant metastasis, and 6% remain unstaged [1]. The 5-year survival rate of localized and regional PCa is 100%, declining to 32.3% in the presence of distant metastasis [1].

The prostate-specific membrane antigen (PSMA) is a 3-domain membrane glycoprotein found in the primary and metastatic PCa and several other normal tissues, such as proximal convoluted tubules, seminiferous tubules, etc. [3, 4]. This receptor provides a molecular target for acquiring images and delivering highly specific therapies in PCa patients. Previous studies showed that the [^{99m}Tc]Tc-HYNIC-PSMA-11 scan represents less equivocal results in metastasis detection than the [^{99m}Tc]Tc-MDP scan [3, 5]. It has also been shown that in the setting of biochemical recurrence and high PSA levels, the [^{99m}Tc]Tc-HYNIC-PSMA-11 scan could provide similar results to the [^{68}Ga]Ga-PSMA PET/CT scan [6].

Despite such fame in metastasis detection of PCa, very few studies have addressed the optimal timing of image acquisition in SPECT scans of men with PCa. The present study evaluates the detection rate of metastatic lesions 75 minutes and 4 hours after a single injection of the [^{99m}Tc]Tc-HYNIC-PSMA-11 radiopharmaceutical in men with PCa.

METHODS

Patient population

This descriptive study was implemented from May 2021 to May 2022. We included 30 consenting men with pathologically confirmed PCa who were referred by a urologist or oncologist to our department requesting a [^{99m}Tc]Tc-HYNIC-PSMA-11 scan for primary staging, biochemical recurrence (PSA relapse) or pre-[^{177}Lu]Lu-PSMA radioligand therapy in metastatic castration-resistant PCa (mCRPC). [^{99m}Tc]Tc-HYNIC-PSMA-11 scans were performed 75 minutes and four hours following the injection of the radiopharmaceutical. The second scan was performed with no additional radiopharmaceutical injection. The Ethical Committee of Mashhad University of Medical Sciences approved the protocol of the present study.

Image acquisition

After ten minutes of being at room temperature, 0.5 mL saline was added to the HYNIC-PSMA 11 kit (PARS-PSMA®-11, sterile and lyophilized powder, 25 micrograms). Following the addition of 1.0 mL of 40 mCi technetium pertechnetate from the ^{99}Mo/^{99m} Tc generator, the kit was placed in boiling water for ten minutes. Then we performed the quality control via the silica gel and two standardized solutions after the kit was allowed to cool at room temperature for 15 minutes.; if the assessed quality was satisfactory (over 95%), 20 mCi of the solution ([^{99m}Tc]Tc-HYNIC-PSMA-11) was intravenously injected.

Following 75 minutes as well as four hours post injection, we scanned participants with a low-energy high-resolution collimator and the photopeak of 140 keV (matrix size: 1024 x 256; Speed: 10 cm/min). Using the step and shot technique with a matrix size of 128 x 128, 120 SPECT images were taken at 360 degrees in 3 degrees intervals and 1 magnification. A low-dose CT scan of the SPECT field also was taken for attenuation correction and anatomical localization and matching. Following image acquisitions, we assessed the frequency of receptor-positive tumoral lesions for [^{99m}Tc]Tc-HYNIC-PSMA-11 in 75-minute and 4-hour images. The ratio of the highest lesion (if any) to liver uptake was evaluated in each body field (thorax, abdomen, pelvis) based on the type of metastasis (bone, lymph node, liver, lungs). These ratios were compared between the two consecutive scans.

Statistical analysis

We analyzed our data using SPSS software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test was applied to determine the normal distribution of continuous data. Parametric quantitative variables were described by mean±standard deviation (SD) and compared using paired t-test at 75-minute and 4-hour intervals of radiotracer Injection, while the non-parametric variables were reported using median (percentile 25-75) and compared by the Wilcoxon test. Frequency (percentage) was utilized to describe the qualitative variables and the Chi-Square or Fisher's exact test. The marginal homogeneity test was performed to compare the mentioned data. A p-value less than 0.5 is considered significant.

RESULTS

Thirty men with histologically verified PCa were referred to us for [^{99m}Tc]Tc-HYNIC-PSMA-11 scanning. As shown in Figure 1, the mean age of participants was 68.43±9.61 years (range: 46-90), and a median of 68.5 (63-74) (Figure 1a). The mean serum PSA of the patients was 23.14 ± 41.21 ng/ml (range: 0.4-165) with a median of 4.19 (1.1-22) (Figure 1b). The mean Gleason Score (GS) was 7.83 ± 1.20 (range: 5-10) and a median of 8 (7-9) (Figure 1c). The reason for referral was initial staging in 18 patients (60%), biochemical recurrence in 6 (20%), and pre-^{177}Lu-PSMA therapy in 6 (20%) patients. Only eight patients (66.26%) were previously treated with androgen deprivation. Ten patients (33.3%) had a Gleason score of < 8, and 20 (66.6%) patients had a Gleason score of ≥ 8. Of 30 patients, 21 (70%) had a positive scan for [^{99m}Tc]Tc-HINYC-PSMA-11 receptor-positive metastatic lesions, and nine cases (30%) had a negative scan in both 75-minute and 4 hours images. As shown in Table 1, only one patient showed a discrepancy in the number of detected lesions; of four metastatic pelvic lymph nodes in the 4-hour scan, only three lesions were detectable in the 75-minute scan, which did not change the management plan (Figure 2). Of 21 metastatic patients, 7 had widespread metastases, and 14 had single or multiple metastatic lesions. Positive and negative scans of participants were grouped and analyzed according to the history of hormonal therapy, GS, referral indication, and location of metastases, as shown in detail in Table 2. Only one case (without a history of ADT and with GS≥8 who was referred for initial staging) had three pelvic lymph nodes in the 75-minute scan out of four metastatic pelvic lymph nodes in the 4-hour scan (one small lymph node in the right external iliac missed in the planar and SPECT/CT images, which did not change the patient's management). There was no statistically significant difference in the diagnostic efficiency of metastatic lesions in the comparison of 75-minute and 4-hour images between the subgroups that had or did not have a history of hormone therapy, had a Gleason score< 8 or ≥ 8, or were referred with different indications.

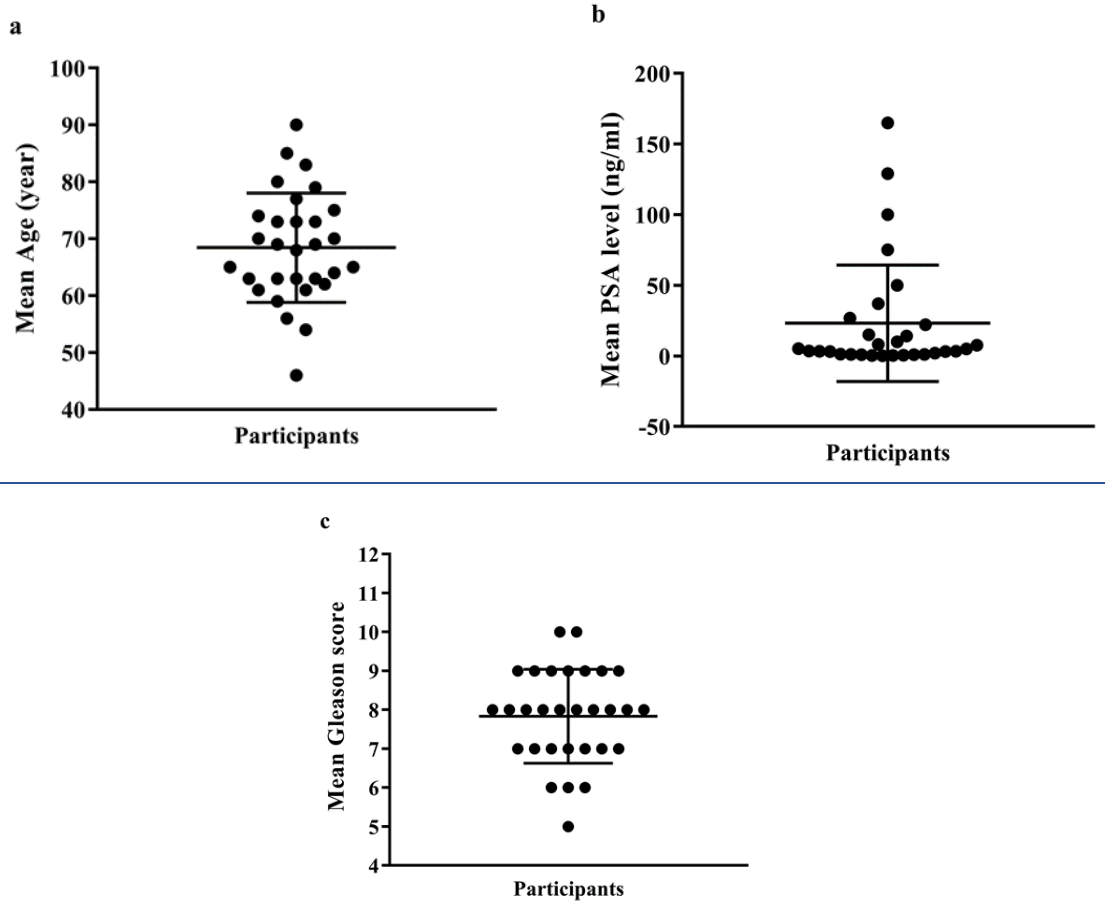

Fig 1. Scatter plots presenting the age (a), serum PSA (b), and Gleason Score (c) of participants

Table 1. Overall lesions detected in the 75-minute and 4-hour checkpoints

Scan Results		Number of cases	Overall lesions of 75-minute scan	Overall lesions of 4-hour scan	P value
Negative		9 (30.0)	0	0	>0.9
Positive	Single	5 (16.7)	5	5	
	Multiple	9 (30.0)	51	52	
	Widespread	7 (23.3)	100**	100**	

* Marginal Homogeneity test was used
** The number of lesions in widespread metastases is considered to be 100

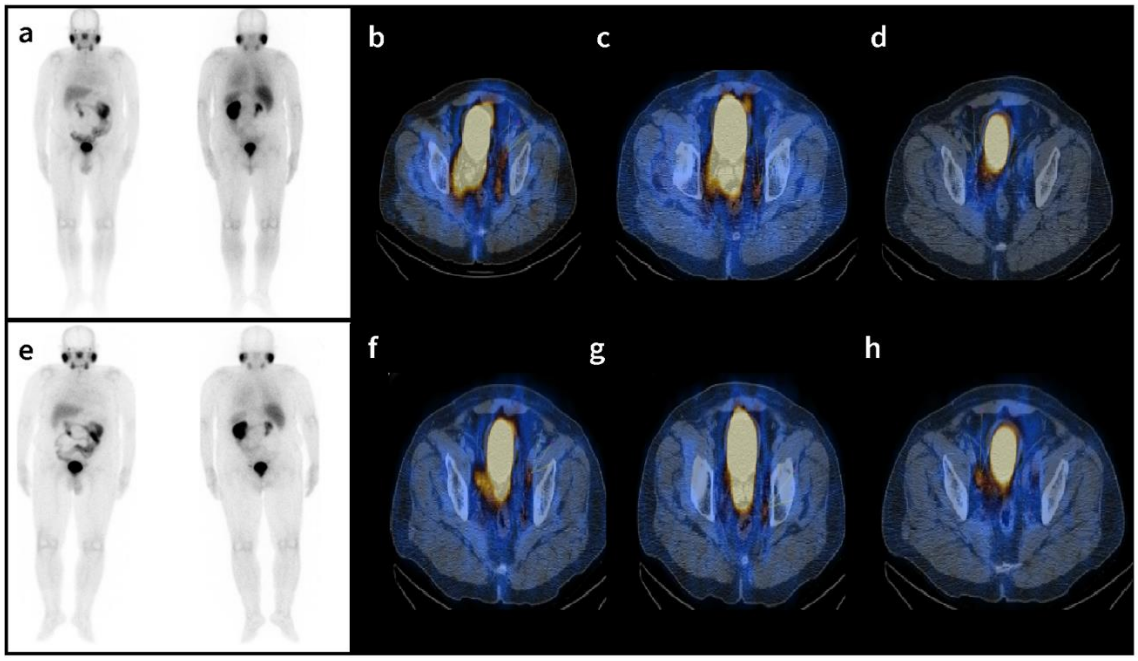

Fig 2. A case with mismatch lesions. (a-d) shows 75-minute scan; (b) Left external iliac lymph node, (c) Left internal iliac lymph node, (d) Right external iliac lymph node. (e-h) shows 4-hour scan of respective (a-d) images

Figure 3 shows images of two patients in two time points which were completely concordant.
In patients with positive scan results, we obtained the ratio of the highest lesions uptake to liver uptake for the detected lesions based on the type of metastasis (bone, lymph node, liver, lungs) and involved regions (thorax, abdomen, pelvis). The comparisons related to these ratios are shown in Table 3. For instance, the highest lesions uptake to liver uptake ratio of the detected skeletal lesions significantly differed between 75-minute and 4-hour scans in the thorax, abdomen, and pelvis (p = 0.026, 0.025, and 0.021, respectively). However, no significant difference was noticed in the visual diagnosis of these lesions. There was also no significant difference in the visual diagnosis of metastasis in the lymph node, liver, and pelvic regions.
Of 9 cases with negative scans, 6 were referred for staging; of whom, only one was high-risk (Gleason Score ≥8), and the others were low-risk patients. The rest of the cases with negative scans were referred for biochemical recurrence; all had Gleason Score ≥ 8, but one had serum PSA less than 1 ng/ml, and two men had PSA of 1-2 ng/ml.

Table 2. Scan findings based on the history of hormonal therapy, Gleason score, referral indication, and type of metastasis

Patients' Characteristics		Total Cases	Negative Scan	Positive Scan		P value
				Missed lesion between two checkpoints?		
				Yes	No	
Previous ADT	Positive	8 (26.7)	1 (3.3)	0 (0.0)	7 (23.3)	0.119
	Negative	22 (73.3)	8 (26.7)	1 (3.3)	13 (43.3)	
Gleason score	>8	10 (33.3)	5 (16.7)	0 (0.0)	5 (16.7)	0.052
	8≤	20 (66.7)	4 (13.3)	1 (3.3)	15 (50.0)	
Referral Indication	Primary Staging	18 (60.0)	6 (20.0)	1 (3.3)	11 (36.7)	0.176
	Biochemical Recurrence	6 (20.0)	3 (10.0)	0 (0.0)	3 (10.0)	

	Before 177Lu-PSMA therapy	6 (20.0)	0 (0.0)	0 (0.0)	6 (20.0)	
	Surveillance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Type of Metastasis	None	9 (30.0)	9 (30.0)	0 (0.0)	0 (0.0)	<0.001
	Bone	8 (26.7)	0 (0.0)	0 (0.0)	8 (26.7)	
	Lungs	2 (6.7)	0 (0.0)	0 (0.0)	2 (6.7)	
	Lymph node	4 (13.3)	0 (0.0)	1 (3.3)	3 (10.0)	
	Bone + Lymph node	5 (16.7)	0 (0.0)	0 (0.0)	5 (16.7)	
	Bone + liver	1 (3.3)	0 (0.0)	0 (0.0)	1 (3.3)	
	Liver + Bone + Lymph node	1 (3.3)	0 (0.0)	0 (0.0)	1 (3.3)	

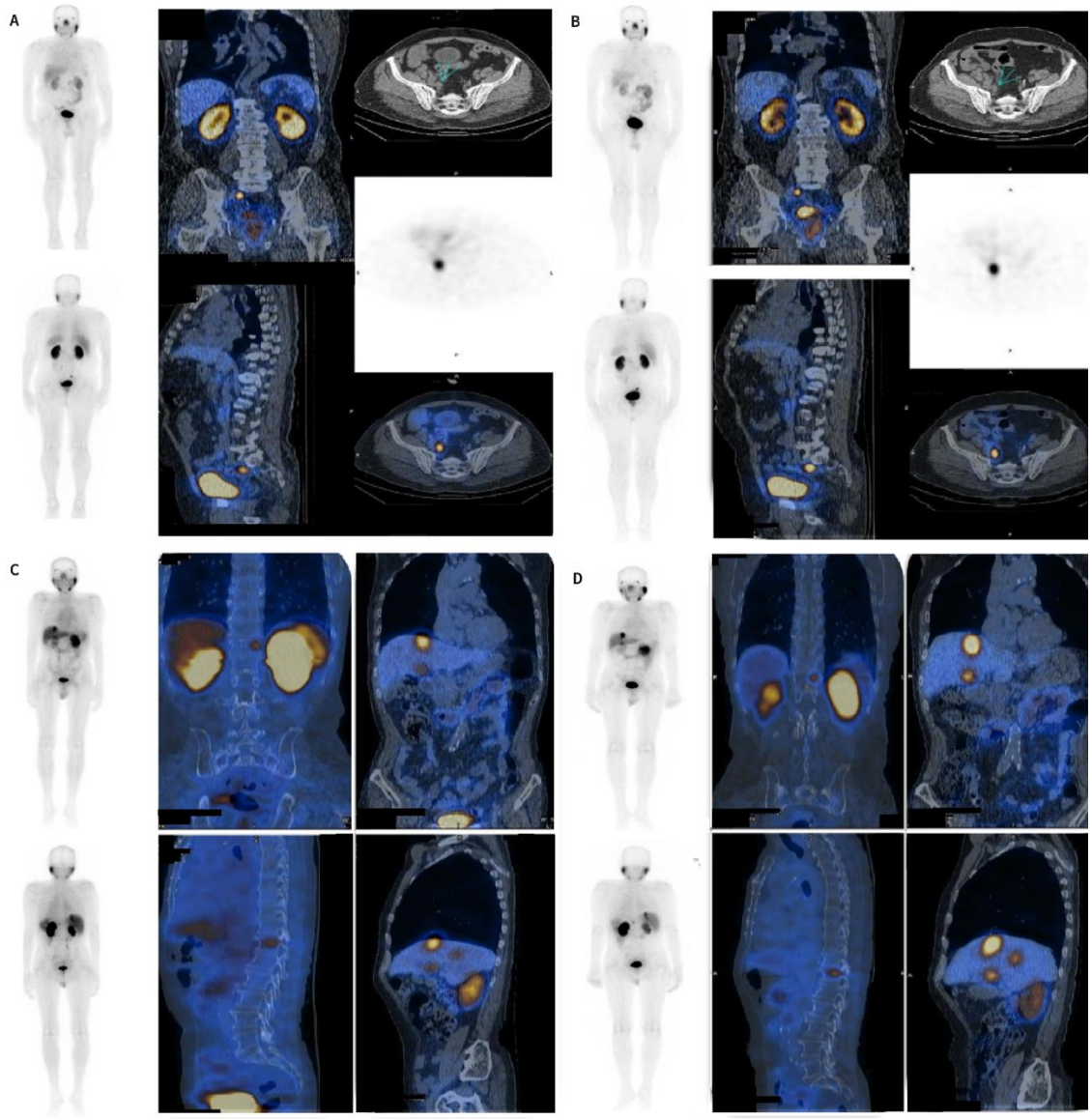

Fig 3. Two cases with matched lesions; (a) and (c) show 75 minutes scans of the first and second cases, respectively. (b) and (d) are corresponding 4 hour scans

Table 3. Comparison of the mean ratio of the maximum lesion to liver absorption in 75-minute and 4-hour checkpoints, based on the location of the metastasis

Lesion Location		Mean ratio of the maximum lesion to liver absorption in 75 minutes	Mean ratio of the maximum lesion to liver absorption in 4 hours	P value
Bone	Chest	0.57±1.08	0.85±1.56	0.026
	Abdomen	0.77±1.33	1.19±2.18	0.025
	Pelvis	0.80±1.36	1.24±2.32	0.021
Lymph node	Chest	0.35±1.04	0.44±1.28	0.048
	Abdomen	0.50±1.19	0.70±1.59	0.028
	Pelvis	0.63±1.23	1.02±2.25	0.017
Liver		0.14±0.55	0.21±0.88	0.180
Lungs		0.04±0.17	0.05±0.20	0.180

DISCUSSION

Image acquisition in the [^{99m}Tc]Tc-HYNIC-PSMA-11 scan is routinely performed three to four hours following radiopharmaceutical injection, considering the biological half-life of Tc-99m. We found no previously published study on the optimal time interval between injection and image acquisition. This study was designed to compare the diagnostic efficacy of a 75-minute post-injection versus a 4-hour post-injection of [^{99m}Tc]Tc-HYNIC-PSMA-11 scan in men with PCa. Of the overall 56 metastases in the 4-hour scan, 55 were seen in the 75-minute scan. The visual detection rate of skeletal, lymph node, hepatic, and pulmonary metastases did not differ significantly between 75-minute and 4-hour images (planar + SPECT/CT images).

Peng et al. presented a meeting report comparing the target to non-target ratios of skeletal, lymph node, liver, and kidney metastases at 0.5, 1, 2, and 3 hours after injection of [^{99m}Tc]Tc-HYNIC-PSMA-11 [7]. They observed that the liver uptake peaked in two hours, while skeletal, kidney, lymph node, and parotid metastases had the highest activity in the three-hour interval. Based on quantitative lesion uptake, they concluded that the 3-hour checkpoint had good quality and the highest uptake. In contrast to their study, we believe that routine interpretation of [^{99m}Tc]Tc-HYNIC-PSMA-11 scan for PCa metastasis assessment is rarely based on the quantitative criteria. Namely, the visual interpretation of this scan in detecting PCa metastases could result in similar clinical management with either a 75-minute or 4-hour interpretation without compromising metastasis detection rate significantly and independent of Gleason Score, history of hormonal therapy, referral indication, and lesion location. This is also true for liver metastases in the background of high physiologic liver uptake, which were visually detected at both time points equally.

Wen and colleagues conducted a similar study on the [^{68}Ga]Ga-PSMA PET/CT scan. Dynamic scans on 11 cases showed that the combination of early dynamic [^{68}Ga]Ga-PSMA PET/CT imaging (from 75-360 seconds) and conventional static 1-hour scan could decrease urinary bladder tracer interference and improve the detection of low PSMA-uptaking lesions. They concluded that the mean standard uptake value (SUV) of the metastatic lesions was similar at 35-59 minutes and 1-hour scans, and this imaging modality could also be implemented 35-59 minutes after injection. [8]. Our study was conducted on [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT images, which is an alternative to the [^{68}Ga]Ga-PSMA scan, which is not widely available, especially in developing countries, due to technologically more advanced scanners and higher costs.

In a study comparing the detection ability of biopsy-proven lymph node metastases by early (1-4 hours) and delayed (15-20 hours) [^{99m}Tc]Tc-PSMA-I&S SPECT/CT in early biochemically - recurrent PCa, Berliner and colleagues found that the rate of lesion identification was significantly higher in the late imaging group compared to the early imaging group, both on a patient basis (positivity rate: 79% in late group versus 27% in the early imaging group) and based on individual lesions (positivity rate: 60% versus 21% for late and early, respectively). These findings remained consistent with size stratification [9].

Werner et al. showed that despite the inferiority of the [^{99m}Tc]Tc-PSMA scan compared to PET imaging in men with biochemical recurrence PSA < 4 ng/ml, biochemical recurrence cases with higher PSA, the [^{99m}Tc]Tc-PSMA scan provides a high detection rate and could be used in primary staging and restaging of recurrent PCa [6]. Thus, although this scan is inferior to PET imaging, it could be considered in the specific patient population in resource-limited countries with limited PET availability. Albalooshi and colleagues conducted a similar study and showed that although [^{68}Ga]Ga-PSMA PET/CT

detected a significantly higher number of lesions than [^{99m}Tc]Tc-PSMA SPECT/CT, the M staging with these two modalities yielded similar results in PCa cases with PSA > 2.1 ng/ml [10]. Fallahi et al. compared metastasis detection rates of [^{99m}Tc]Tc-PSMA SPECT/CT and [^{68}Ga]Ga-PSMA PET/CT [11]. The PET detection rate was significantly higher than SPECT, and both showed similar detection rates after excluding prostate bed/gland lesions. They concluded that the [^{99m}Tc]Tc-PSMA SPECT scan could be an appropriate alternative to PET imaging in high-risk PCa cases, except when the prostate bed evaluation is intended.

Nine cases had negative scans in our study, and four had GS≥8 (high risk). This might be secondary to the lower sensitivity of [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT scan at low levels of PSA. It should be noted that the scan was negative at both checkpoints; thus, the 75-minute scan might be equally reliable compared to the 4-hour in men with high-risk PCa.

To the best of our knowledge, this study is unique in addressing the optimal time interval from injection to image acquisition of [^{99m}Tc]Tc-HYNIC-PSMA-11 SPECT/CT scan. Its results are valuable in saving patients' time, decreasing crowdies, providing efficient scheduling, and improving patient satisfaction in nuclear medicine departments. However, this study was limited by not having access to software for calculating standard uptake values in SPECT/CT images. Although our sample size is not small for this kind of study, it could consider a limitation in terms of application of the findings, and a larger sample size could get more robust results. We suggest future studies with dynamic imaging and time activity curve generation for more reliable results.

CONCLUSION

We found no significant difference in the detection rate of metastatic lesions in 75-minute and 4-hour intervals. Despite the fact that physiologic hepatic uptake declines with time, two patients with hepatic lesions had visually distinct metastasis in both intervals, and the quantitative uptake was not significantly different. According to These findings less waiting time, more efficient scheduling would be possible resulting more patient's satisfaction at the nuclear medicine departments.

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