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Contribution of Lower Extremity ^{68}Ga PSMA PET/CT Imaging to Diagnosis and Treatment in Prostate Cancer

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Abstract

Objective: The aim of this study is to evaluate the effectiveness of routine additional acquisitions for lower extremity in the diagnosis and treatment of patients undergoing ^{68}Ga prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT).

Methods: The files of 59 prostate cancer patients who underwent additional acquisition of the lower extremities in addition to the vertex-upper thigh in ^{68}Ga PSMA PET/CT studies were included in the study. In our study, patients with both lower limb acquisition on clinical suspicion and with routine lower limb acquisition were included. Along with the difference in the effectiveness of the lower limb acquisition between these two arms, the efficacy and clinical utility of the additional acquisiton were evaluated in the entire sample.

Results: The rate of metastasis detected in the group with lower limb acquisiton with clinical suspicion (31.1%) is higher than in the other group (7.6%). However, metastases detected in both groups do not cause changes in the treatment.

Conclusion: Considering the loss of time caused by additional acquisitons in the clinic, the radiation dose exposure of the patient and the outcomes in this study, it may be possible to say that the lower extremity acquisitons are not effective.

Keywords: Prostate cancer, ^{68}Ga PSMA, PET/CT, molecular imaging

INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide. It is the most frequently diagnosed cancer among men in many countries such as America, Northern and Western European countries, Sub-Saharan African countries, and Australia, with easier diagnosis in the last few decades especially with the widespread use of prostate-specific antigen (PSA). In 2018, 1.3 million new prostate cancer cases were seen worldwide, whereas 359 thousand prostate cancer-related deaths were reported in the same period (1). In a study evaluating the American cancer statistics, approximately 20% of cancers in men in 2019 are stated to be prostate cancer and 10% of cancer-related deaths are related to prostate cancer (2). In the Turkey Cancer Statistics published in 2018, incidence of prostate cancer in men according to the 2015 data is reported as 33.1/100,000 (3).

Besides the histopathological features, the existence of distant metastases is an important factor in determining the prognosis in prostate cancer. Skeletal system is the most common site of hematogenous metastasis in prostate cancer. In an autopsy series in which 1,589 prostate cancer cadavers were examined, hematogenous bone metastases were detected in 90% of cadavers (4). According to a study conducted by Shou et al. (5) among 265,900 cases of prostate cancer, at least one bone metastasis was observed in 59.43% of patients. Therefore, it is extremely important to focus on bone metastases when investigating distant organ metastasis. Bone scintigraphy has been used for many years to evaluate bone metastases in prostate cancer because of this basic information. Prostate-specific membrane antigen (PSMA), first described in 1987 and later revealed to be a transmembrane glycoprotein, is an important diagnostic

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alternative as it is expressed in prostate cancer cells, as well as being expressed more extensively in prostate cancer cells (6). PSMA-based positron emission tomography/computed tomography (PET/CT) imaging is becoming more and more important in the clinic because it provides significant tumor/background area ratio in the primary lesion as well as distant metastases and lymph nodes. Current literature shows that ^{68}Ga-PSMA PET/CT is a highly effective imaging method to detect bone metastases especially in cases of biochemical recurrence (7,8). Lower extremities can also be considered among the major areas of metastasis in cases with diffuse skeletal metastasis. Its effect on the treatment decision is controversial; however, it is a routine approach to include the lower limb in PET/CT acquisition according to both legal regulations and established clinical practices in our country.

This study aimed to understand the contribution of the lower limbs in diagnosis acquisition and provide any advantage over its drawback in prolonging the whole process duration.

METHODS

Patients

In our study, data from a total of 59 prostate cancer cases (mean age: 69 years, age range: 41-81 years) and their images in the picture archiving and communication system were retrospectively evaluated. In addition to routine vertex-upper thighs, lower extremities were also included in the acquisition of patients who underwent ^{68}Ga-PSMA PET/CT at the University of Health Sciences Turkey, Okmeydani Training and Research Hospital Nuclear Medicine Unit between June 9, 2017-September 19, 2018. A total of 36 patients were evaluated for staging, 23 for restaging, and none for secondary malignancy. Patients enrolled in the study were also grouped according to the indication of the lower-extremity acquisition. In 13 out of 59 patients, lower limbs were involved in the acquisition routinely. Meanwhile, the lower limbs were involved in the acquisition in the remaining 46 patients, only if there is high risk of illness, if the patient described symptoms, or in cases without recent scintigraphic imaging.

All patients signed a written informed consent form for evaluation purposes and data publication. This study was approved by the Ethics Committee of University of Health Sciences Turkey, Okmeydani Training and Research Hospital (04/10/2018-996).

Preparation of ^{68}Ga-PSMA

A fully automated Scintomics Good Radiopharmaceutical Practice (GRP) synthesis module with Scintomics Control Center and GRP-Interface software was used for the radiolabeling of ^{68}Ga-DOTAGA-PSMA (named as ^{68}Ga-PSMA I&T). The ^{68}Ge/^{68}Ga generator was purchased from iThemba LABS, South Africa. DOTAGA-PSMA was purchased from Scintomics GRP, Germany via a local distributor. The synthesis of the ^{68}Ga peptides was performed using a cationic purification method with 20 µg of peptide used for the reaction. The labeling efficiency and radiochemical purity were determined using radio thin-layer chromatography and radio-high-performance liquid chromatography. The radiochemical purities of ^{68}Ga-labeled PSMA conjugates were ≥95%.

Imaging

Patients were imaged using an integrated PET/CT scanner that consisted of a full-ring HI-REZ LSO PET and a six-slice CT scanner (Siemens Biograph 6, Chicago, IL, USA). Each patient was injected with a standardized weight-based dose of 2 MBq/kg (range 70-180 MBq), and images were obtained in a dual-phase mode. At 60 min post-injection, a whole-body PET/CT scan was conducted with an emission time of 3 min per bed position. Before emission images, a low-dose CT was performed for attenuation correction and anatomic localization with the following parameters: 50 mA, 140 kV, and 5 mm section thickness. All patients were positioned feet first, supine on the scanning pallet with imaging from toe to vertex, and arms up.

Images Evaluation

Images were visually evaluated by two nuclear medicine physicians with at least 10 years of experience. Areas with markedly increased focal ^{68}Ga-PSMA uptake compared to background activity were evaluated in favor of metastasis when they were outside the prostate tissue and did not coincide with physiological involvement sites or known benign lesions that may have ^{68}Ga-PSMA uptake. Metastases observed in the skeletal system were classified into two groups as seen in routine acquisition area and additional acquisition area.

Statistical Analysis

When evaluating the findings obtained in the study, International Business Machines Corporation Statistical Package for the Social Science Statistics 25 (SPSS IBM, Turkey) program was used for statistical analysis. Descriptive methods (Frequency, Percentage, Average, Standard deviation) were used to evaluate the study data.

RESULTS

Lesions were detected in the lower extremities in 19 of 59 patients, wherein 3 had lesions in the vertex-upper thigh acquisition that could be detected because lesions were located in the femoral

head and/or proximal femur Figure 1. Therefore, involvement of the lower extremity to the acquisition did not provide any additional benefit in these 3 patients. In 1 of 16 patients whose lesions were detected by lower-extremity acquisition, intense patella involvement was observed in the form of "hot patella" without widespread metastasis in the body Figure 2. In this study, findings were considered suspicious since it was not confirmed histopathologically. Excluding the suspected positive case, 15 out of 58 patients (25.86%) provided additional information by involvement of the lower extremities in the acquisition. All of these 15 patients had extensive metastasis in the body. Because of that they didn't provided additional benefit from the involvement of the lower extremities in the acquisition Figure 3.

High-risk disease group includes 25 of 36 patients who underwent ^{68}Ga-PSMA PET/CT imaging for staging purposes. Lower-extremity metastases were detected in 8 of 24 patients (33%) when the suspicious case with patellar involvement was not included.

Lower limb metastasis was not detected in 11 patients in the low and medium risk group. In all patients who were evaluated for staging purposes, lower limb metastasis was detected in 17% thanks to additional acquisition.

When all restaging patients were considered, 7 of 23 patients had lower limb lesions detected with additional acquisition (30.4%), whereas 18 of these patients were metastatic and 8 of them had extensive bone metastasis. This group consisted of a group of patients who were expected to have a high rate of bone metastases in general Table 1.

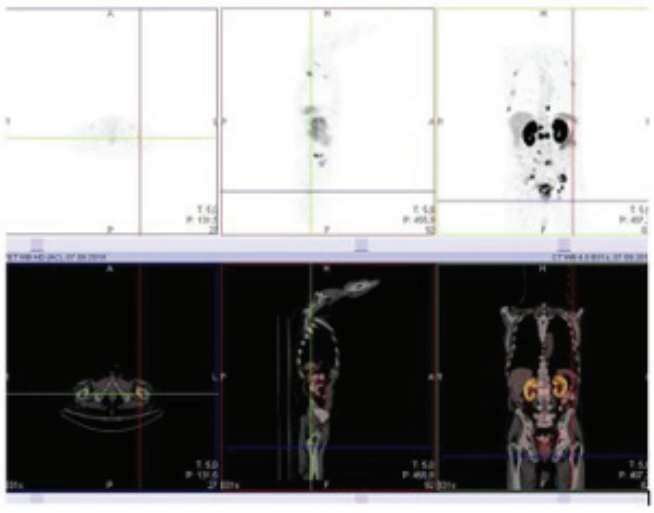

Figure 1. Axial, sagittal, and coronal PET and fusion images showing metastatic lesion located proximal to the upper femur and entering the routine area of acquisition
PET: Positron emission tomography

Figure 2. Maximum intensity projection image of ^{68}Ga-PSMA PET showing isolated patellar involvement not proven to be metastatic
PSMA: Prostate-specific membrane antigen, PET: Positron emission tomography

Results of patients who underwent lower-extremity acquisition with the suspicion of metastasis (group 1) and as part of routine acquisition (group 2) were shown in Table 2, excluding the case with suspicious metastasis. In the 1st group consisting of 46 cases, lower-extremity metastasis was detected in 14 patients (31.11%), whereas in the 2nd group consisting of 13 patients, only one case (7.69%) was detected with lower-extremity metastasis. No statistically significant difference was found between these two groups ($p>0.04$).

DISCUSSION

Not many studies in the literature are evaluating the clinical benefit of additional acquisition for the lower extremity; however, this issue is extremely important for the workflow of nuclear medicine clinics. Implementing acquisitions that have no clinical effect complicates the daily work plans of nuclear

Figure 3. Maximum intensity projection image of 68Ga-PSMA PET/CT showing diffuse metastatic involvement.
PSMA: Prostate-specific membrane antigen, PET: Positron emission tomography, CT: Computed tomography

medicine clinics in terms of planning the imaging studies and using time efficiently. In addition, taking additional acquisitions that will not affect the management of the patient, thus, exposing the patient to additional radiation caused by the PET/CT's tomography component is one of the issues that should be considered. Discussing the necessity of additional acquisition of the lower extremities is important since giving the lowest radiation dose to patients is our main approach in our daily practice depending on the as low as reasonably achievable (ALARA) principle (9).

In the current literature, several studies are reported on the necessity and effectiveness of adding the lower extremity to routine acquisition, especially in diseases with atypical metastatic patterns such as malignant melanoma and sarcoma (10-12); however, only few studies are reported about prostate cancer. Only 15 (25.4%) of 59 patients included in our study had metastases in the bones of lower extremity that were not detected by routine imaging. Many studies were reported in the literature evaluating the effectiveness of ^{68}Ga-PSMA PET/CT in detecting metastases of prostate cancer (13-15). Some of these studies have also included the metastases rates observed in the lower extremity (16); however, few articles are evaluating the contribution of detection of metastases in the lower extremities to its treatment. Simsek et al. (17) reported that lesions were detected in the lower extremity in 61 out of 701 cases (8.7%). Comparing these two studies is impossible, since the cases in our study were divided into two different groups according to clinical suspicion, not the presence of symptoms.

However, in both studies, it was observed that additional lower-extremity acquisition either with clinical suspicion or symptoms caused a detection of significantly higher rate of metastasis than others. In our study, metastases were detected in 31.1% of patients who underwent additional lower-extremity acquisition with clinical suspicion and 7.69% of patients who routinely underwent PET/CT examination with lower extremity involved.

Table 1. Detected lesions and their distribution

Groups	Existence of lesions in the lower extremity						Lesions detected only in additional images		
	Femoral head	Proximal femur	Distal extremity	Patella	No lesion	Total	Positive	Negative	Total
Group 1	**0**	**2**	**14**	**1**	**29**	**46**	**15**	**31**	**46**
Staging	0	1	7	1	21	30	8	22	30
Restaging	0	1	7	0	8	16	7	9	16
Group 2	**1**	**0**	**1**	**0**	**11**	**13**	**1**	**12**	**13**
Staging	0	0	1	0	5	6	1	5	6
Restaging	1	0	0	0	6	7	0	7	7

Table 2. Effects of additional acquisitions			
Group	Number of patients	Cases in which metastases were detected with extra images	
		Number	%
Group 1	45	14	31.1%
Group 2	13	1	7.69%
Total	58	15	25.86%

The common result of both studies is that metastases detected in the lower extremity did not cause any change in treatment. From this point of view, it can be beneficial to use less acquisition that does not contribute to patient management by considering the ALARA principle.

The retrospective structure of the study and the narrow sample size are the main drawbacks in our study. Narrow sample size also makes it difficult to evaluate statistical differences between groups. We believe that the proportional differences between the groups will be statistically significant in studies to be conducted in larger case groups. In addition, the treatment of patient groups included in the study with different treatment modalities, being at different stages of their treatment and not being homogenous in terms of treatment response make it difficult to make a comparison based on PSA for these patients. Therefore, a statistical evaluation on PSA values could not be performed in our study.

CONCLUSION

The addition of lower limbs to the routine acquisition areas, which did not cause any significant changes in the detection of distribution of metastases that eventually affect the treatment protocol of the patients, does not seem to be very suitable according to the data obtained in our study. However, in cases that are symptomatic and considered to be of clinical benefit, it may be wise to consider the additional lower extremities acquisition.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Turkey, Okmeydani Training and Research Hospital (04/10/2018-996).

Informed Consent: All patients signed a written informed consent form for evaluation purposes and data publication.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.Ö., T.Ö., O.G., S.S., Design: F.Ö., T.Ö., O.G., S.S., Data Collection or Processing: O.G., S.S., Analysis or Interpretation: O.G., S.S., Literature Search: O.G., S.S.K., S.S., F.Ö., T.Ö., Writing: O.G., S.S.K., S.S., F.Ö., T.Ö.

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