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ABSTRACT

Objective: There is not a definitive consensus for the methods to verify the suspicious lesions in bone scintigraphy (BS) for bone metastases in patients with prostate cancer (PCa) diagnosis. In this study, we aimed to compare the accuracy rates of imaging modalities used for patients with suspected lesions in BS.

Design: Retrospective cross-sectional study

Setting: Tertiary university hospital

Subjects: One hundred and twenty-six PCa patients with bone metastases

Intervention: BS was applied to all patients for bone metastases screening. Patients underwent computerized tomography, X-ray, magnetic resonance imaging (MRI) and positron emission tomography for bone metastasis verification for suspicious lesions in BS.

Main outcome measures: Comparison of metastasis detection rates of the imaging modalities and the evaluation of sensitivity of BS according to the location and the number of lesions

Results: MRI provided the highest rate of metastasis confirmation (81.3%). We found that the rate of detection of metastases in thoracal vertebrae, pubic bones, femur, L3-5 vertebrae and multiply involved cases was statistically significant ($p < 0.05$). Metastasis verification rate in non-vertebral lesions was significantly higher than vertebral lesions (58.2% vs 25.9%, $p = 0.018$).

Conclusion: MRI is the most accurate method providing metastasis verification for suspect foci in BS. As the number of lesions increases and in the involvement of non-vertebral locations, the ability of BS to distinguish true metastases from false-positive metastases increases. Prospective, randomized trials are needed to routinely recommend MRI as a first-line procedure for the diagnosis of bone metastases.

KEY WORDS: bone metastases, diagnostic accuracy, magnetic resonance imaging, prostate cancer, scintigraphy

INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous cancer of men and is the second most common cause of cancer-related deaths. The majority of cases diagnosed with PCa are asymptomatic. In these cases, the diagnosis is based on abnormal prostate-specific antigen (PSA) and / or digital rectal examination (DRE) findings. After making a PCa diagnosis by ultrasound guided biopsy, the primary aim is to stage the disease correctly. PCa staging is performed according to the TNM staging system of the American Joint Cancer Committee (AJCC)[1]. Pre-treatment parameters are used in the clinical staging of prostate cancer in order to predict the prognosis, evaluate the extent of the disease and decide on appropriate treatment. These include serum PSA and its derivatives, DRE, biopsy-detected Gleason Score, positive core number, tumor length in the cores, and imaging findings[2]. In low-risk localized disease, imaging is not necessary for staging purposes[3]. According to the guidelines of the European Association of Urology (EAU), additional imaging should be utilized if it changes the treatment plan of the patient[3].

There is no consensus on the standard procedures for the detection of metastatic disease. For this reason, in a joint opinion study, taking into account the guidelines used, the Radiographic

Assessments for Detection of Advanced Recurrence (RADAR) group recommends bone scintigraphy (BS), abdomen, pelvis and thorax computerized tomography (CT) for initial evaluation. Additional recommended evaluation tools are direct X-ray imaging, magnetic resonance imaging (MRI) and NaF-Positron Emission Tomography (PET)[4]. Another imaging modality, prostate-specific membrane antigen (PSMA) PET / CT, using a radiotropic substance named Gallium 68 (68Ga) - PSMA 11 is very effective in diagnosing prostate cancer-related lymph nodes, soft tissue and bone metastatic disease. There is a great deal of evidence in the literature on the clinical success of PSMA PET / CT for staging and disease location in biochemical recurrence in high-risk prostate cancer[5]. BS is the most commonly used method to detect bone metastases due to PCa. BS using Tec99m is sensitive to osteogenic activity and it is possible to evaluate the whole body with this method. However, there are some limitations. BS shows the tumor's secondary effects on the bone rather than its own proliferation. Trauma and many other non-cancerous foci may cause false positive results[6]. It does not show microscopic involvement and its sensitivity and specificity are low for osteolytic lesions. Its diagnostic significance is affected by PSA level, clinical stage and the tumor's Gleason score.

In the presence of suspicious lesions, confirmation with X-ray imaging, CT, MRI and PET / CT may be required. In the current literature, there is no definitive suggestion regarding which imaging method should be used in the first plan for these lesions. In the present study, we aimed to compare the accuracy rates of various imaging methods used for metastasis verification in patients with suspicious lesions after PCa diagnosis and to evaluate the clinicopathologic factors predicting metastasis in these patients. In addition, the sensitivity of BS according to location and number of the lesions was assessed.

SUBJECTS AND METHODS

Study population

In this study, data of 126 patients who were diagnosed with PCa by transrectal ultrasound-guided biopsy (TRUS-bx) between January 2010 and January 2017 and underwent BS for cancer staging were analyzed. Patient's age, PCa characteristics, location and number of lesions involved in BS, the imaging method used for the verification, and the metastasis status as a result of the verification were recorded from patient files and analyzed.

Imaging methods used in the diagnosis of bone metastases

Whole-body bone scintigraphy

A single-headed gamma camera with low-energy high-resolution parallel-hole collimator was used for imaging and the patients were injected intravenously with diphosphonate compounds (MDP or HMDP) labeled with Tc-99m at 15-30 mCi (according to patient's weight) for scintigraphic examination. After 2-3 hours from injection, whole body images were taken from all patients in anterior and posterior projections, and spot planar images were taken from suspicious areas if necessary. Foci of increased activity involvement (such as degenerative changes) were interpreted as suspected metastatic lesions.

X-ray imaging

A cassette or detector was selected at the point where it will not cut the targeted area. The tube-cassette distance was determined as 100 cm. The centralization was made to the center of the target and perpendicular to the film. The patient was instructed not to move after adjusting the patient position, and collimating in the required measurements. Radiographs were obtained with anteroposterior and lateral views with a high kilovoltage up to 120 kV. The X-ray graphy was performed with an average of 50 KV and 8 MaS.

Computerized tomography

A 64-slice scanner (Somatom Sensation 64; Siemens Healthcare) or a 16-slice scanner (Somatom Sensation 16; Siemens Helathcare) was used for CT. The iodinated contrast agent iomeprol was applied for better soft tissue resolution. Axial and coronal images were reconstructed in the bone windows with varying thicknesses from 1.25 mm to 5 mm.

Magnetic resonance imaging

A 1.5-T scanner (MAGNETOM Avanto; Siemens Healthcare) or a 3.0-T scanner (MAGNETOM Skyra; Siemens Healthcare) device was used for MRI images. Images were taken before and after administration of gadolinium contrast agent. Cortical bone invasion was suspected in the absence of a typical hypointense signal of the bone cortex in T1- and T2-weighted images. Bone marrow involvement was confirmed in the presence of a hypointense signal at T1, a hyperintense signal at T2, or contrast enhancement. In addition, bone invasion was considered when there was a diffusion restriction with a signal increase in the diffusion-weighted imaging and / or a decrease in the apparent diffusion of the coefficient value.

Positron Emission Tomography

Imaging was performed with a dual-modality two-detector row PET-CT scanner following injection of [18F] -fluoro-2-deoxy-D-glucose (FDG). The patients were recommended to have a 6-hour fasting before the procedure to provide blood glucose levels below 150 mg / dl. Intravenous buscopan was applied to prevent the first pass effect of FDG to smooth muscle. 20 mg furosemide was administered to increase renal excretion of the tracer and prevent accumulation in benign cells. One hour after the administration of FDG, a low-dose CT scan including neck, thorax, abdomen and pelvis was performed to optimize PET signaling. Then, an emission examination was performed using an integrated GSO crystal-based PET system with 3D row action maximum likelihood algorithm (RAMLA) reconstruction. Subsequently, diagnostic contrast-enhanced CT imaging was performed in the venous phase with administration of 120 ml of intravenous contrast agent. PET and CT images were then fused using a special software program. An average of 24 mSv ionization radiation dose was calculated for the entire examination.

Outcome assessment

The accuracy rates of the imaging modalities performed for the verification of the lesions involved in bone scintigraphy and the metastasis detection rates according to the location and number of the lesions were compared. The study was conducted in accordance with the Helsinki declaration, and the hospital's ethics committee for clinical trials approved the study (decision number: 17-3 / 1, date: 31.03.2017).

Statistical analysis

Chi-square test was used to analyze the relationship of locations with metastasis status. Logistic regression analysis was performed according to the Forward Stepwise method. SPSS 23.0 package program was used for all statistical analyzes. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Bone metastasis due to prostate cancer was verified with other imaging modalities in 65 of 126 patients (51.5%) with suspicious involvement in BS. A total of 89 different locations were detected in the BS and the total number of lesions was 294. The number of positive lesions in the bone scintigraphy of patients ranged from 1 to 16 for a single patient and 38 patients had more than one involvement, and metastasis was confirmed in 89.5% of these patients. BS revealed 112 vertebral and 182 non-vertebral involvement and metastasis verification rate was 58.2% in non-vertebral locations, while it was 25.9% in vertebral locations ($p = 0.018$). The involved lesions in BS whose metastasis status was significant according to locations are given in Table 1. The specificity and sensitivitity of bone scintigraphy for metastasis diagnosis were 60.8% and 85.2% in patients with multiple lesion involvement, respectively ($p < 0.001$). MRI was the imaging modality that provided the highest metastatic confirmation rate for the lesions involved in scintigraphy (81.3%). The rates of metastasis detection according to different imaging protocols are given in Table 2.

All of the patients had adenocarcinoma histopathology. The most frequent Gleason score was 4 + 5 = 9/10 (38.1%) and the most commonly used verification method was CT (60.3%). BS provided 78.6% specificity and 90.8% sensitivity for the diagnosis of metastases in patients with more than one lesion involvement. In addition, its negative predictive value was 67.5% and positive predictive value was 49.2% ($p = 0.015$). In cases with more than 3, 5, and 9 lesion involvement in BS, the incidence of metastasis was found to be significantly higher than the cases with less lesion and as the number of positive lesions increased, the rate of metastasis increased (Table 3). Sensitivity and specificity of BS were 76.5% and 82.7% ($p = 0.036$) for vertebral involvement, and 92.4% and 78.6% for non-vertebral involvement, respectively ($p = 0.028$).

DISCUSSION

PCa causes systemic metastases most often in the bones, and early involvement of other sites is rare. Visceral metastases (lung, liver, etc.) arise in the late stages of the disease and bone metastases are present in 90% of patients who die from the disease[7]. When a diagnostic

examination of the bones is needed, the Technetium-99 radionuclide bone scanning continues to be the standard procedure[8,9]. Its high sensitivity, accessibility and cost-effectiveness are the key advantages[10]. The most important drawback of BS is its low specificity due to the non-tumor specificity of the radioactive adsorbent. However, bone scan is only indicated for symptomatic patients and asymptomatic men who are at high risk for occult metastases (prognostic groups IIB, III, or IV; serum PSA > 20 ng / ml or a T2 primary tumor with serum PSA >10 ng/ml or a Gleason 8 tumor or a T3 or T4 tumor)[11]. In our study, patients mostly had advanced stage tumors; 56.3% of them had a Gleason score of 8 and above tumor.

It is a very common scenario that bone metastases are suspected in the BS reports and recommended to be verified by other radiological methods. The fact that BS can give false positive results due to trauma and many other non-cancerous lesions reveals the necessity of verifying methods for metastasis diagnosis and direct X-ray imaging, CT, MRI and PET / CT are available options for this purpose. Although there are numerous studies evaluating all these modalities in the case of bone metastases in patients with PCa, their efficacy is still unclear and there is no consensus on their utilization. In this study, we aimed to determine the clinicopathologic factors predicting bone metastases in patients underwent BS after PCa diagnosis and compare the verification methods. To our knowledge, this is the first clinical trial evaluating the diagnostic accuracy of BS according to the locations and number of lesions involved in the skeletal system.

BS positivity rate is lower than 1% in low-risk patients. A large retrospective study conducted in United Kingdom showed that PSA level and Gleason score were the independent predictors of positive BS. The authors concluded that its negative predictive value was 100% when PSA <20 ng/ml and Gleason score <8[12]. The AUA and EAU guidelines also confirm these results. Another study showed that 25% of patients had bone metastases with PSA <20 ng/ml and Gleason score <7[13]. Similar to the results of these studies in our study, the sensitivity and specificity of BS for predicting metastases were increased in patients with PSA <20.7 ng/mL and Gleason score >8. Therefore, it is logical to perform an initial BS in patients with a palpable mass, Gleason score 7 and above and PSA >10 ng/mL[4]. BS should be performed in symptomatic patients regardless of PSA level, Gleason score and clinical stage[3].

The relationship between the number of lesions involved and the status of metastasis has been examined in the literature, but there is no study analyzing the success of imaging methods according to the location of the lesion. Gutzeit *et al* showed that the ability of whole body MRI to detect malign lesions in patients with more than 10 metastatic lesions was superior to that of BS, although the sensitivity of the two methods was similar in patients with less than 5 lesions[14]. In this study, we performed an analysis of the metastasis status at each locus involved in BS and found that the detection rate of metastases in patients with thoracic vertebrae, pubic bones, femur, L3-5 vertebrae, and multiple bone involvement was statistically significantly higher than other locations.

Verification with other imaging modalities may be required in the presence of suspected lesions in BS. It has been shown that PET / CT using NaF (18F sodium fluoride) or 18F coline has a higher sensitivity and specificity than the scintigraphy[4]. In a large meta-analysis, MRI and choline PET/CT have been found to be more accurate in detecting bone metastases in patients with prostate

cancer than SPECT and BS[15]. Whole body MRI has been shown to accurately demonstrate bone and lymph node metastases when using diffusion weighted imaging. Lecouvet *et al* have shown that diffusion-weighted whole-body MRI detects a higher rate of metastatic bone lesions than conventional BS[16]. In their studies involving 100 high-risk or relapsed patients, diffusion-weighted whole-body MRI was found to detect metastases with 99% sensitivity and 99% specificity[16]. In high-risk patients, whole body MRI (T2 weighted) and axial MRI have higher sensitivity and specificity than BS and targeted radiography. The accuracy of MRI in detecting bone metastases was found as good as 18F-NaF PET / CT[17]. MRI may be a better option because of its availability and low radiation dose. MRI can also provide useful information about soft tissues[18]. However, cost-effectiveness and availability are still significant disadvantages. Therefore, the first choice is still BS[3].

PSMA is a cell surface protein that is highly expressed in prostate cancer compared to other tissues. This protein provides a promising target for specific imaging and treatment depending on the transmembrane location after ligand binding[19]. 68Ga-PSMA PET/CT is highly sensitive for the imaging of lymph nodes and bone metastases in patients with PCa. Early reports have shown that this method provides better contrast enhancement in the lesions than Choline PET[20]. In a recent study including 140 PCa patients, it was shown that 68Ga-PSMA PET/CT demonstrated a higher rate of bone metastasis involvement than low-dose CT[21]. If supported by prospective studies, PSMA PET/CT has the potential to be a routine screening method for staging and treatment planning in PCa patients. A major disadvantage of this method is its high cost. This is an important factor limiting its routine utilization. For this reason, this assay seems to be an extreme way to be routinely used for screening purposes in PC a patients for the time being. We were not able to use this diagnostic test for screening in our patients because PSMA PET/CT was not covered by the Social Security Institution routine back-payment system and the need for some strict indications for the imaging in the period that we have planned our study. In our patients, the most commonly preferred radiologic verification method was CT which was used in 60.3% of the patients. However, MRI was the imaging method which detected metastases with the highest rate (81.3%). Our findings support the use of MRI as a first-line diagnostic tool for the detection of bone metastases in high-risk PCa patients. The strategy of single-step use of MRI in high-risk patients with PCa was previously described by Lecouvet *et al*[18]. However, the long application period of 40-50 minutes of this method prevents its widespread usage. With the development of the MRI equipment, it has been possible to perform the test under 30 minutes.

In our study, as the number of lesions involved in the BS increased, the rate of metastasis detection increased. The specificity of BS in detecting metastases in all locations was 82.8% and sensitivity was 90.8%. Early detection of bone metastases in the PCa is crucial for the selection of appropriate treatment, the detection of the tumor stage, the assessment of the prognosis of the patient, and the effectiveness of the treatment protocols[22-24]. In a patient with PCa, the extent of metastatic bone disease is an independent prognostic factor[25]. The false-negative bone scans that may occur in the BS may result due to the absence of reactive changes and the rapid growth of pure osteolytic metastases[26,27].

In our patients, the rate of detection of metastasis in non-vertebral locations in BS was higher than in vertebral locations (58.2% vs. 25.9%). In the literature, it has been suggested that MRI has low sensitivity for the metastases detection in small curved smooth bones such as ribs, which is a significant limitation, and the reason for this is the black appearance of the cortical bone in the T1 and T2 weighted sequences[28]. In some studies on MRI and bone SPECT, imaging protocols were limited to the entire axial skeleton and spine and skull, ribs, and extremities were overlooked. The reason for this is that in PCa, which predominantly metastasizes to the spine and pelvis, the possibility of metastasis at these sites without axial skeletal metastasis is insignificant[29,30].

The field of imaging for prostate cancer metastases has evolved dramatically in the last few years. Although the gold standard today for staging is either PSMA or sodium fluoride PET CT, these methods were not included because of the retrospective nature of the study. The cohort size is also relatively modest. These were the limitations of our study.

In the majority of men diagnosed with PCa, the primary location of metastases is the axial skeletal system and these lesions may lead to pain, weakness and functional impairment. In our study, we found that BS was more sensitive in non-vertebral locations than in vertebral locations, which is the most frequent metastasis site of PCa, and it is possible to say that BS is not very reliable in vertebral involvement according to this result.

CONCLUSION

MRI seems to be the most appropriate method for metastasis verification in suspected lesions deteceted in BS in high-risk patients with PCa. As the number of lesions and non-vertebral involvement increases, the power of BS distinguishing true metastases from false-positive metastases increases. BS may be insufficient for screening purposes in the axial skeletal system which is the most common metastasis site of PCa. Randomized, prospective clinical trials are required to routinely recommend MRI as a first-line imaging method for the diagnosis of bone metastases.

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Table 1: Lesions involved in bone scintigraphy with significant metastasis verification

Involved lesion	Lesion count	Metastasis status		P value	Sensitivity (%)	Specificity (%)
		Positive	Negative			
Thoracic vertebrae	5	-	5	0.019	0	46.3
Left pubis	4	4	-	0.049	100	50
Right pubis	4	4	-	0.049	100	50
Right femur	6	6	-	0.015	100	50.8
L3 vertebra	8	1	7	0.022	12.5	45.7
L4 vertebra	12	1	11	0.002	8.3	43.8
L5 vertebra	21	5	16	0.005	23.8	42.8
Multiple lesions	34	29	5	<0.001	85.3	60.9
Vertebral involvement	112	29 (25.9%)	84	0.036	76.5	82.7
Non-vertebral involvement	182	106 (58.2%)	75	0.028	92.4	78.6

Table 2: Imaging methods used for verification

Imaging method	Metastasis status		Total number
	Negative (%)	Positive (%)	
CT[1]	39 (51.3)	37 (48.7)	76
CT + X-ray graphy	2 (66.7)	1 (33.3)	3
X-ray graphy	12 (70.6)	5 (29.4)	17
MRI[2]	3 (18.8)	13 (81.3)	16
MRI+ CT	2 (40)	3 (60)	5
MRI+ X-ray graphy	1 (25)	3 (75)	4
PET-CT[3]	2 (50)	2 (50)	4
PET-CT+ MRI	0 (0)	1 (100)	1
Total	61 (48.4)	65 (51.6)	126

[1]Computerized Tomography; [2]Magnetic Resonance Imaging; [3]Positron Emission Tomography

Table 3: Metastasis status in imaging methods according to the number of lesions involved in bone scintigraphy

Number of positive lesions	Metastasis status		P value
	Negative	Positive	
≤ 3	42 (%71.2)	17 (%28.8)	< 0.001
≥ 4	19 (%28.4)	48 %71.6)	
≤ 5	50 (%65.8)	26 (%34.2)	< 0.001
≥ 6	11 (%22.0)	39 (%78.0)	
≤ 9	54 (%65.9)	28 (%34.1)	< 0.001
≥ 10	7 (%15.9)	37 (%84.1)	