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Research Article

Indication of Bone Scintigraphy in Asymptomatic Japanese Patients with Newly Diagnosed Prostate Cancer

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Abstract

Objective: Currently, international guidelines consider bone scintigraphy redundant in low-risk patients due to the very low risk of metastatic disease. The aim of this study was to retrospectively assess the correlation between the diagnosis and presence of bone metastasis on bone scintigraphy in Japanese patients newly diagnosed with PCa.

Methods: The study included 695 consecutive patients with newly diagnosed PCa between January 2004 and December 2013 at our institution. A total of 21 patients were excluded due to insufficient data. All patients were routinely staged using conventional total-body Tc-99m MDP or Tc-99m HMDP scintigraphy regardless of the baseline PCa characteristics. The rate of positive findings for bone metastases was evaluated according to age, the prostate-specific antigen level, biopsy Gleason score and clinical T stage, and univariate and multivariate logistic regression analyses were performed to identify predictors of positive bone metastasis.

Results: Among the 674 patients, 50 (7.4%) exhibited bone metastasis. According to the multivariate logistic regression analysis, statistically significant differences were found in a clinical tumor stage of ≥ cT2, PSA level of >10 ng/ml and biopsy Gleason score of ≥8 (P<0.001).The parameter with the highest odds ratio was a PSA level of >10 ng/mL (odds ratio: 34.300 [95% CI 7.211-614.471]).

The PSA levels and biopsy Gleason scores exhibited significant differences between the cT1c and ≥ cT2 groups (p <0.0001). All bone metastasis patients with clinical ≥T3 disease were identified based on a PSA level of >10 or biopsy Gleason score of ≥8.

Conclusions: Bone scintigraphy is not recommend in Japanese patients with newly diagnosed PCa, unless the following criteria are met: PSA > 10 ng/mL, biopsy Gleason score ≥ 8 or clinical stage ≥ T3. These criteria were observed in 41.4% of all cases. Additionally, it is possible to select patients based only on the PSA level or biopsy Gleason score.

Keywords: Prostate Cancer; Bone Scintigraphy; Bone Metastasis; Japanese; Prostate-Specific Antigen; Biopsy Gleason Score

Introduction

The incidence of prostate cancer (PCa) has recently increased in Japan, likely due to an increased rate of detection following the recent introduction of serum prostate-specific antigen (PSA) measurement and the aging of society. The medical insurance system in Japan differs greatly from that seen in other countries. Therefore, bone scintigraphy continues to be routinely applied to identify metastatic lesions in patients with newly diagnosed PCa in Japan. Currently, international guidelines consider bone scintigraphy redundant in

low-risk patients due to the very low risk of metastatic disease [1,2], although the definition of a low-risk patient differs slightly between guidelines. It is thus unclear whether established bone scanning guidelines, which are primarily based on data from Europe and the USA, are applicable to Japanese patients.

The aim of this study was to retrospectively determine the correlation of the diagnosis and the presence of bone metastasis on bone scintigraphy in newly diagnosed PCa patients in a Japanese population.

Materials and Methods

Patient Characteristics.

This study included 695 consecutive patients with PCa newly diagnosed between January 2004 and December 2013 at our institution. A total of 21 patients were excluded due to insufficient data. The characteristics of the patients are summarized in Table I. All patients were Japanese, with a median age of 71 years (range, 46-97 years) and a PSA level of 9.195 ng/ml (range, 1.077-7,354.517 ng/ml). The number of patients with clinical T1c and clinical ≥ T2 disease was 383 (56.8%) and 291 (43.2%), respectively. The number of patients with a biopsy Gleason score of ≤7 and ≥8 was 415 (61.6%) and 259 (38.4%), respectively. The clinical T stage was determined according to a digital rectal examination (DRE) based on the 2009 TNM classification [3]. Two pathologists evaluated the degree of malignancy of the biopsy specimens according to the 2005 International Society of Urological Pathology (ISUP) Consensus Conference on the Gleason grading system [4].

Bone Scintigraphy and Additional Imaging

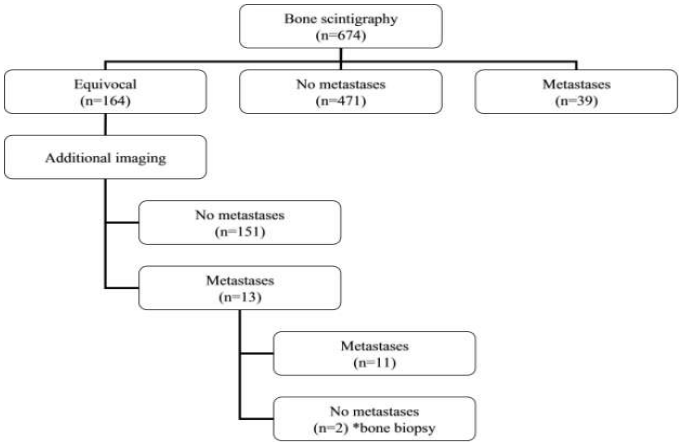
All patients were routinely staged using conventional total-body Tc-99m MDP or Tc-99m HMDP scintigraphy at our institution regardless of the PSA level, biopsy Gleason score, clinical T stage and/or symptoms. All bone scan studies were interpreted by qualified nuclear physicians. Patients diagnosed as equivocal additionally underwent computed tomography (CT), magnetic resonance imaging (MRI) and/or plain X-P to confirm the final diagnosis.

Statistical Analysis

Univariate and multivariate analyses were performed using a logistic regression analysis to identify predictors associated with bone metastasis. The variables were age and the PSA level, clinical T stage and biopsy Gleason score. The Mann–Whitney U test was used to determine differences between the negative DRE group and the positive DRE group according to the PSA level and biopsy Gleason score. The statistical analyses were performed using the JMP® Pro version 9.0.2 software program (SAS Institute, Inc., Cary, NC, USA). A P value of <0.05 was considered to indicate a statistically significant difference.

Results

1. Evaluation of bone scintigraphy in the prostate cancer patients (Figure 1)



On bone scintigraphy, 471patients (69.9%) were diagnosed as being negative for bone metastasis, 39 patients (5.8%) were diagnosed as being positive for bone metastasis and 164 patients(24.3%) were diagnosed as being equivocal for bone metastasis. Additional imaging tests were performed in cases involving a diagnosis of equivocal bone metastasis. Consequently, 151 patients were determined to be negative for bone metastasis and 13 were determined to be positive for bone metastasis. However, two patients were ultimately confirmed to be negative for bone metastasis histopathologically based on a bone biopsy, and 11 patients were ultimately confirmed to be positive for bone metastasis.

1. Clinicopathological characteristics according to the presence of bone metastasis (Table 1)

Characteristics	Total, no,(%) (n=674)	Patients without BM, no.(%) [n=624(92.6%)]	Patients with BM no.(%) [n=50(7.4%)]
Median age, years (range)	71(46-97)	71(47-97)	73(46-87)
Clinical stage, n(%)			
T1c	383 (56.8)	380 (60.9)	3 (6.0)
T2	229 (34.0)	217 (34.8)	12 (24.0)
T2ab	184 (27.3)	178 (28.5)	6 (12.0)
T2c	45 (6.7)	39 (6.3)	6 (12.0)
≥T3	62 (9.2)	27 (4.3)	35 (70.0)
Median PSA, ng/ml (range)	9.195(1.077-7354)	8.648(1.077-4377.300)	239.225(7.849-7354.517)
PSA, ng/ml, n(%)			
≤4	31 (4.6)	31 (5.0)	0
4<, ≤10	349 (51.8)	348 (55.8)	1 (2.0)
10<, ≤20	147 (21.8)	145 (23.2)	2 (4.0)
>20	147 (21.8)	100 (16.0)	47 (94.0)
Biopsy Gleason score, n(%)			
5-6	106 (15.8)	106 (17.0)	0
7	309 (45.8)	306 (49.0)	3 (6.0)
8-10	259 (38.4)	212 (34.0)	47 (94.0)
Biopsy cores, No.			
Median (range)	12(3-19)	12(3-19)	6(4-14)
Positive cores, No.			
Median (range)	3(1-12)	3(1-12)	6(1-12)
Positive cores, %			
Median (range)	25.0(5.9-100)	23.1(5.9-100)	83.8(12.5-100)

BM, bone metastasis; PSA, prostate-specific antigen

The clinicopathological characteristics of the two groups according to the presence of bone metastasis are shown in Table 1. The groups with and without bone metastasis comprised 50 (7.4%) and 624 (92.6%) patients, respectively. In the group without bone metastasis, the median PSA level was 8.648 ng/ml, and 379 patients (60.7%) had a PSA level of ≤10, 380 patients (60.9%) had nonpalpable disease (cT1c) and 412 patients (66.0%) had a biopsy Gleason score of ≤7. In the group with bone metastasis, the median PSA level was 239.225 ng/ml, and 49 patients (98.0%) had a PSA level of >10, 47 patients (94.0%) had palpable disease (≥ cT2) and 47 patients (94.0%) had a biopsy Gleason score of ≥8.

2. Correlations between the characteristics and the presence of bone metastasis (Table 2)

Characteristics	Odds ratio	P-value	95% CI
Univariate analysis			
Age	0.973	0.145	0.937-1.001
cT1c vs. ≥cT2	24.399	<0.001	8.816-101.203
PSA ≤10 vs. >10	75.800	<0.001	16.448-1345.464
Biopsy Gleason score ≤7 vs. ≥8	30.447	<0.001	10.991-126.347
Multivariate analysis			
cT1c vs. ≥cT2	10.521	<0.001	3.621-44.748
PSA ≤10 vs. >10	34.300	<0.001	7.211-614.471
Biopsy Gleason score ≤7 vs. ≥8	14.592	<0.001	5.073-61.746

PSA, prostate-specific antigen

The correlations between the characteristics and the presence of bone metastasis are shown in Table 2. According to the univariate logistic regression analysis, the clinical tumor stage, PSA level and biopsy Gleason score were significant predictors. Meanwhile, statistically significant differences were found in the clinical tumor stage, PSA level and biopsy Gleason score in the multivariate analysis (P<0.001). The parameter with the highest odds ratio was a PSA level of >10 ng/mL (odds ratio: 34.300 [95% CI 7.211-614.471]).

3.PSA levels and biopsy Gleason scores according to the findings of the digital rectal examinations (Table 3)

Characteristics	Negative DRE (cT1c) (n=383)	Positive DRE (≥cT2a) (n=291)	P-value
PSA, n g /ml [n(%)]			
≤10	265(69.2%)	115(39.5%)	
<10	118(30.8%)	176(60.5%)	<0.0001
Median PSA, ng/ml (range)	7.861(1.170-378.130)	13.3(1.077-7354.517)	
Biopsy Gleason score, n(%)			
≤7	281(73.4%)	134(46.0%)	
≥8	102(26.6%)	157(54.0%)	<0.0001
Median GS (range)	7(5-10)	8(6-10)	

DRE, digital rectal examination; PSA, prostate-specific antigen; GS, Gleason score

The characteristics of the patients analyzed according to DRE are presented in Table 3. Among the negative DRE cases (cT1c), the number of patients with a PSA level of ≤10 and Gleason score of ≤7 was 265 (69.2%) and 281 (73.4%), respectively. Among the positive DRE cases (≥cT2), the number of patients with a PSA level of >10 and biopsy Gleason score of ≥8 was 176 (60.5%) and 157 (54.0%), respectively. The PSA values and biopsy Gleason scores displayed significant differences between the negative DRE and positive DRE groups (p <0.0001).

4. Relationship between the PSA levels and biopsy Gleason scores in the patients with clinical ≥T3 disease (Table 4)

	Biopsy Gleason score≤7	Biopsy Gleason score≥8
	BM(+): n=2 BM(-): n=6	BM(+): n=33 BM(-): n=21
PSA≤10 BM(+): n=1 BM(-): n=3	BM(+): n=0 BM(-): n=1	BM(+): n=1 BM(-): n=21
PSA>10 BM(+): n=34 BM(-): n=24	BM(+): n=2 BM(-): n=5	BM(+): n=32 BM(-): n=19

PSA, prostate-specific antigen; BM(+), positive bone metastasis; BM(-), negative bone metastasis

The characteristics of the 62 patients with clinical ≥T3 disease assessed according to DRE are presented in Table 4. The number of patients with bone metastasis was 35 (56.5%); the number of patients with bone metastasis with a PSA level of ≤10 and >10 was one and 34, respectively, and the number of patients with bone metastasis with a biopsy Gleason score of ≤7 and ≥8 was two and 33, respectively. No patients with bone metastasis had both a PSA level of <10 and biopsy Gleason score of ≤7, while 32 patients had both a PSA level of >10 and biopsy Gleason score of ≥8. All bone metastasis patients with clinical ≥T3 disease were identified based on a PSA level of >10 or biopsy Gleason score of ≥8.

Discussion

Currently, international guidelines consider bone scintigraphy redundant in low-risk PCa patients due to the very low risk of metastatic disease, although the definition of a low-risk patient differs slightly between guidelines [1,2]. On the other hand, in the 2012 version of the clinical practice guidelines for prostate cancer in Japan [5], staging bone scans might be considered only for patients with a biopsy Gleason score >7 or a PSA level of >10 ng/ml and palpable disease (cT2/T3) prior to treatment, based on the data of non-Japanese patients reported by Briganti et al. [6]. In a recent prospective study of 635 consecutive patients, Zacho H.D found no

positive bone scans among 212 patients with a PSA level of < 10 ng/mL (independent of the clinical stage and Gleason score of the tumor) and 97 patients with a PSA level of < 20 ng/mL, stage < T3 and a Gleason score of < 8 [7]. However, some urologists have been experienced patients with bone metastasis on bone scintigraphy, even though the PSA level is less than 10 ng/ml, including us. Furthermore, several reports have demonstrated higher incidences of positive bone scans in subjects with a low PSA level on mass population screening in Asians, compared with Western data [8]. Therefore, we retrospectively examined Japanese patients with newly diagnosed PCa treated at our institution in order to determine whether bone scintigraphy can be spared to adapt to Japanese patients based on established bone scanning guidelines, such as those of the NCCN (National Comprehensive Cancer Network) and EAU (European Association of Urology) [1,2].

The results of the evaluation of bone scintigraphy are shown in Figure 1. Among the 674 patients with newly diagnosed PCa, the number of those with positive and equivocal bone metastasis on bone scintigraphy was 39 (5.8%) and 164 (24.3%), respectively. Additional imaging was performed in patients with equivocal bone scintigraphy findings, 13 of whom were diagnosed with positive bone metastasis. However, bone biopsies were carried out in two patients thought to be negative for bone metastasis based on their clinicopathological data, and the results confirmed the absence of bone metastasis histopathologically. Hence, a total of 50 patients(7.4%) were ultimately diagnosed with bone metastasis. The clinicopathological data for one patient included cT1c disease, a biopsy Gleason score of 6 and a PSA level of 5.918 ng/ml and the histopathological findings of the bone biopsy showed Paget's disease. The clinicopathological data for the other patient included cT2a disease, a biopsy Gleason score of 7 and a PSA level of 12.368 ng/ml, and the histopathological results of the bone biopsy showed no malignant tissue. In that case, a surgical castration was performed simultaneously with the bone biopsy. It was confirmed that the patient exhibited no changes on bone scintigraphy in the positive site at the two-year follow-up, although the PSA level had decreased continuously. The clinicopathological characteristics of the two groups according to the presence or absence of bone metastasis are shown in Table 1. In the group with bone metastasis, three patients (6.0%) also had nonpalpable disease (cT1c) and 35 patients (70.0%) had ≥ cT3 disease.

Regarding the PSA levels, no patient had a level less than 4 ng/ml, the minimum value was 7.849 ng/ml and 47 (94.0%) patients had a level of > 20 ng/ml. With respect to the biopsy Gleason scores, only three patients (6.0%) had a score of ≤7, while 47 patients (94.0%) had a score of ≥8. Concerning factors related to bone metastasis, the minimum PSA value was 7.849 ng/ml, the minimum biopsy Gleason score was 7 and the lowest clinical T stage was cT1c. Based on these results, the use of criteria suggesting that bone scintigraphy can be spared according to a single factor may result in needless cases of bone scintigraphy. Therefore, the criteria indicating that bone scintigraphy can be spared should be considered based on multiple factors. Therefore, we further examined factors for bone metastasis of PCa.

Factors such as the number of biopsy cores, number of positive biopsy cores and rate of positive biopsy cores were excluded because we did not perform systemic prostate biopsies in the patients clearly diagnosed with prostate cancer according to the PSA level or DRE. Based on the univariate logistic regression analysis, the clinical T stage, PSA level and biopsy Gleason score were significant predictors ($p<0.001$). Meanwhile, statistically significant differences were found in the clinical T stage, PSA level and biopsy Gleason score in the multivariate analysis ($P<0.001$). The parameter with the highest odds ratio was a PSA level of >10 ng/mL (odds ratio: 34.300 [95% CI 7.211-614.471]). Based on these results, criteria stating that bone scintigraphy can be spared should be considered based on the following three factors: the clinical T stage, biopsy Gleason score and PSA level.

According to the EAU guidelines [1], most authors do not recommend systematic bone scans in asymptomatic patients unless the PSA level is > 10 ng/mL (9-14) or > 20 ng/mL (15,16), the Gleason score is ≥ 8 or the clinical stage is ≥ T3 [17]. Applying these criteria to the results of the present analysis, it would be possible to omit the use of bone scintigraphy in 279 patients(41.4%) selected based on a PSA level of > 10, with no cases of positive bone metastasis. Bone scintigraphy would also be omitted in 372 patients(55.2%) selected based on a PSA level of > 20 ng/ml, although this would include one bone metastasis patient. Furthermore, the NCCN guidelines recommend that bone scans are appropriate for symptomatic patients and/or those with a life expectancy greater than five years with any of the following characteristics: 1) T1 disease with a PSA level over 20 ng/ml or T2 disease with a PSA level over 10 ng/ml, 2) a Gleason score of 8 or higher; 3) T3 to T4 tumors or symptomatic disease [2]. Applying these criteria to the results of our analysis, bone scintigraphy could be omitted in 333 patients(49.4%), although bone metastasis would be observed in one patient. According to the 2012 version of the clinical practice guidelines for prostate cancer in Japan [5], staging bone scans may be considered only for patients with a biopsy Gleason score of >7 or PSA level of >10 ng/ml and palpable disease (cT2/T3) prior to treatment, based on the data for non-Japanese patients reported by Briganti et al. [6]. Applying these criteria to the results of the present study, bone scintigraphy would be omitted in 352 patients(52.2%), with bone metastasis

detected in one patient. In this study, no cases of bone metastasis were observed among the patients for whom bone scintigraphy could be omitted based on the EAU guidelines (PSA>10, GS 8 or higher or T3 or higher). Therefore, these criteria may be said to be the most useful in terms of identifying bone metastasis patients. On the other hand, in accordance with the standards of other guidelines, there was only one bone metastasis patient in the patient group for whom bone scintigraphy could be omitted (the same patient). This clinical data for this patient included cT1c disease, a biopsy GS of 7 and a PSA level of 11.128 ng/ml. Bone scintigraphy in this patient showed accumulation in the sixth thoracic vertebra, and MRI also demonstrated bone metastasis based on diffuse signal abnormalities and progression to the spinal canal at the same site. Judging from the patient's clinical course, in which the progression to the spinal canal improved in association with a decreasing PSA value after surgical castration, the patient had bone metastasis on bone scintigraphy. Omitting such examinations has two points of view: the importance of not missing metastases and the high cost. Emphasizing the point that we are clinical urologists and it is not acceptable to miss bone metastases in prostate cancer patents, criteria stating that bone scintigraphy can be omitted unless the PSA level is > 10 ng/mL, the biopsy Gleason score is ≥ 8 or the clinical stage is ≥ T3 are reasonable and proper. There is an opinion that the detection of negative bone scintigraphy findings before treatment is also useful as a baseline assessment for comparing the findings observed at the time of recurrence. In addition, there is a report that omitting initial bone scintigraphy can be expected to increase the number of plain X-rays obtained during follow-up, thus increasing medical expenses [18]. Furthermore, the amount of relief provided by the negative bone scintigraphy findings cannot be overestimated for both the doctor and the patient. From this point of view, patients who can be omitted from undergoing bone scintigraphy should be selected according to the criteria of the EAU guidelines, which omit all bone metastasis patients. In this study, the clinical T stage was diagnosed using DRE only. The clinical T stage was diagnosed as more than cT2a based on findings of induration, irregularity and extension through the prostatic capsule on DRE. Moreover, the results of the multivariate analysis identified positive findings on DRE (≥ cT2a) to be a significant predictor of bone metastasis ($p<0.001$). However, prostate biopsies do not always detect PCa in lesions that were palpable on DRE. In addition, there is no clear description for the reclassification of the clinical T stage in the TNM classification, and no such reclassification is performed when prostate cancer is not detected at the same site [3]. Urologists frequently experience patients with a high PSA level who do not have any abnormal findings on DRE.

DRE is used to determine whether a lesion is palpable, the results of which are associated with the extent of local disease (clinical T stage). In addition, an abnormal DRE was recently reported to be associated with an increased risk of detecting high-grade (Gleason 8 to 10) PCa in a screened population [19]. However, due to its poor sensitivity and lack of reproducibility, DRE may both overestimate and underestimate the extent of disease [20-22]. Catalona et al. reported that when DRE and the PSA level are used in prostate cancer screening, the detection rate is higher with PSA than with DRE and highest with both tests together [23]. Because DRE and the PSA level do not always detect the same cancers (24), the tests are complementary and recommended in combination as a method for assessing prostate cancer risk. We also agree that the findings of DRE are very useful for the purpose of prostate cancer screening. However, it remains uncertain whether it necessary to use the clinical T stage on DRE for newly diagnosed PCa patients as a criterion for determining the indication for bone scintigraphy to detect bone metastasis.

Therefore, we examined the characteristics of the negative DRE group (cT1c) and the positive DRE group (≥ cT2a) according to the PSA level and biopsy Gleason score (Table 3). The differences in the PSA level and biopsy Gleason score between the negative DER group (cT1c) and the positive DRE group (≥ cT2a) were statistically significant ($p<0.001$). However, there is a high possibility of positive findings on DRE in patients with a high PSA level or biopsy Gleason score. Therefore, it is unnecessary to apply the clinical T stage determined on DRE, which has poor sensitivity and lacks reproducibility, as a definitive criterion. Based on the results of this study, the bone scanning indications in the EAU guidelines (PSA > 10 ng/mL, Gleason score ≥ 8 or clinical stage ≥ T3) are also appropriate for Japanese patients, although these indications also include the criterion of clinical stage ≥ T3. Therefore, only clinical stage ≥ T3 patients were additionally studied (Table 4). Among the 62 patients with clinical ≥T3, the number of subjects with bone metastasis was 35 (56.5%). No patients with bone metastasis had a PSA level of ≤10 and biopsy Gleason score of ≤7, and all bone metastasis patients with clinical ≥T3 were identified based on a PSA level of >10 or a biopsy Gleason score of ≥8. Based on these results, it is possible to omit the use of bone scintigraphy according to only two factors: the PSA level and biopsy Gleason score; the clinical T stage is not a necessary factor for these criteria.

Conclusion

Bone scintigraphy is not recommend in Japanese patients newly diagnosed with PCa, unless the PSA level is > 10 ng/mL, the biopsy Gleason score is ≥ 8 or the clinical stage is ≥ T3; these criteria accounted for 41.4% of all cases in the present study. Additionally, it is possible to

select patients based only on the PSA level or biopsy Gleason score.

Conflict of interest statement

None declared.

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