

RESEARCH ARTICLE

Predictors of Positive Bone Metastasis in Newly Diagnosed Prostate Cancer Patients

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Abstract

Background: The prevalence of prostate cancer (PCa) has been increasing in recent years. Treatment strategies are largely based on the results of bone scan screening. Therefore, our aim was to investigate predictors of positive bone metastasis in newly diagnosed PCa patients. **Materials and Methods:** After extensive review, 336 consecutive patients newly diagnosed with PCa between April 2010 and November 2013 at our institution were enlisted in the study. Patients were divided into two groups according to bone scan results. Univariate analyses (Chi-square test for discrete variables and independent t-test for continuous variables) were applied to determine the potentially significant risk factors associated with distant bone metastasis. Binary logistic regression analyses were used to further investigate the influence of these factors on bone metastasis. **Results:** The patient mean age was 71.9 ± 8.6 years (range: 48 to 94 years). The mean prostate specific antigen (PSA) level and biopsy Gleason score were 260.2 ± 1107.8 ng/mL and 7.4 ± 1.5 , respectively. The body mass index (BMI) for the series was 24.5 ± 3.4 kg/m². Sixty-four patients (19.0%) had a positive bone scan result. Patients with positive bone scan results had a significantly lower BMI (23.3 ± 3.5 vs. 24.8 ± 3.3 ; $p=0.003$), a higher Gleason score (8.5 ± 1.1 vs. 7.1 ± 1.5 ; $p < 0.001$), and a higher PSA level (1071.3 ± 2337.1 vs. 69.4 ± 235.5 ; $p < 0.001$) than those without bone metastasis. Multivariate logistic regression analysis employing the above independent predictors demonstrated that a Gleason score of ≥ 7 , clinical stage $\geq T3$, BMI ≤ 22 kg/m², and an initial PSA level of ≥ 20 ng/mL were all independent predictors of bone metastasis. **Conclusions:** A bone scan might be necessary in newly diagnosed PCa patients with any of the following criteria: clinical stage T3 or higher, a Gleason score of 7 or higher, BMI equal to or less than 22, and a PSA level of 20 or higher.

Keywords: Prostate cancer - bone metastasis - prostate specific antigen - predictive actors

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Introduction

The prevalence of prostate cancer (PCa) has been increasing in recent years. There many risk factors been studied for Asian population (Bashir et al., 2014). Current screening tools for early detection are digital rectal examination (DRE) and measurement of prostate specific antigen (PSA) levels. If DRE and/or PSA test results show any abnormalities, a biopsy is then recommended.

Previous studies have reported that PCa-related mortality typically results from distant metastasis (Pound et al., 1999). Because the most frequent site of metastasis from PCa is bone (Logothetis., 2005) further treatment strategies are based on the results of bone scan screening. Whether bone scan screening should be performed routinely is still an issue of debate. The most recent summary of the European Association of

Urology (EAU) (Heidenreich et al., 2013) and American Urologic Association (AUA) (Greene., 2009) guidelines on PCa states that a bone scan may not be indicated in asymptomatic patients if the serum PSA level is less than 20 ng/mL. However, reports from Japan (Kosuda et al., 2002; Tanaka., 2011) showed that Asian PCa patients had lower PSA levels but a higher bone metastasis rate than those in Western countries.

Further investigation is needed to determine whether it is suitable to apply the current guidelines to Asian patients. Although PSA is a useful clinical marker for predicting disease progression, the relationship between PSA level and bone metastasis patterns have rarely been reported in Asia. We aimed here to delineate the bone metastasis patterns of PCa patients and to assess the impact of those patterns on patients' clinicopathological features and PSA levels.

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Materials and Methods

Patients

We extensively evaluated and enlisted 336 consecutive patients newly diagnosed with PCa at Kaohsiung Medical University Hospital between April 2010 and November 2013. Transrectal ultrasound-guided prostate biopsy was performed based on abnormal DRE or PSA test results. A routine bone scan was arranged in our conventional work-up for newly diagnosed PCa patients. Patients who tested positive for bone metastasis were divided into different groups according to seven different metastasis locations (spine, pelvis, scapula, limbs, skull, ribs, and sternum). We also compared the difference by dividing patients into different metastasis number.

Bone scintigraphy

Bone scintigraphy was performed after intravenous injection of 20 mCi (740 MBq) of technetium-99m methylene diphosphate. Whole body imaging was performed under a large field of view gamma camera (Siemens, E.cam, Erlangen, Germany) coupled with a high-resolution collimator. The scans were interpreted by two independent, experienced nuclear medicine physicians.

All data are expressed as mean \pm standard deviation. Dichotomous variables were evaluated using Chi-square analysis to define various patient groups according to variables that significantly correlated with positive bone metastasis findings. Risk factors for bone metastasis and mortality were determined using a univariate analysis. Only those variables that reached $p < 0.05$ were considered for the model. Once we identified these potential risk factors, a multivariate stepwise logistic regression analysis was performed to identify independent predictors. According to the bone metastasis risk stratification for

PCa patient previously reported by Briganti et al. (2010) patients with clinical stages T1-3 were classified into three groups. The low-risk scheme was defined by patients with either a) a Gleason score of ≤ 7 and clinical stage T1, or b) clinical stage T2-T3 with a PSA level of ≤ 10 ng/mL. Patients at intermediate risk were defined as those with a Gleason score of ≤ 7 , clinical stage T2-3, and a PSA level ≤ 10 ng/mL. Patients with a Gleason score of 8-10 were defined as high risk regardless of the PSA level and clinical stage. Our data was compared with Briganti et al.'s (Briganti et al., 2010) results. Statistical significance was set at $p < 0.05$. SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. This study was supervised by the Institutional Review Board of the Kaohsiung Medical University Hospital.

Results

The patients' mean age was 71.9 ± 8.6 years (range: 48 to 94 years). The mean PSA level and biopsy Gleason score were 260.2 ± 1107.8 ng/mL and 7.4 ± 1.5 , respectively. The body mass index (BMI) for the series was 24.5 ± 3.4 kg/m². Sixty-four patients (19.0%) had a positive bone scan result. Of this subset of patients, PSA levels were ≤ 10 ng/mL in 2 (3.1%) patients, 10.1-20 ng/mL in 4 (6.3%) patients, 20.1-100 ng/mL in 18 (28.1%) patients, and >100 ng/mL in 40 (62.5%) patients. The incidence of bone metastasis increased significantly and corresponded to an increase in initial PSA levels (Table 1).

Patients with positive bone scan results had a significantly lower BMI (23.3 ± 3.5 vs. 24.8 ± 3.3 ; $p = 0.003$), a higher Gleason score (8.5 ± 1.1 vs. 7.1 ± 1.5 ; $p < 0.001$), and a higher PSA level (1071.3 ± 2337.1 vs. 69.4 ± 235.5 ; $p < 0.001$) than those with negative bone scan results (Table 2). There were 13 (20.3%) patients with a single bone metastasis site, 7 (10.9%) with two

Table 1. Comparison of age, BMI, Gleason Score and PSA Values with Results of Skeletal Scintigraphy

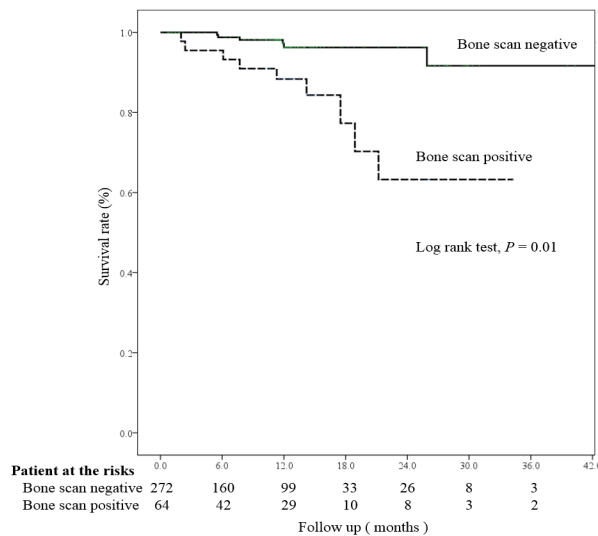
Variables	Total n=336	Bone scan positive for metastasis N=64	Bone scan negative for metastasis N=272	p-Value
Age (years)				
Mean \pm SD	71.9 ± 8.6	71.3 ± 9.7	72.1 ± 8.3	0.467
Median	72	72	72	
BMI				
Mean \pm SD	24.5 ± 3.4	23.3 ± 3.5	24.8 ± 3.3	0.003
Median	24.2	22.7	24.7	
Gleason score				
Mean \pm SD	7.4 ± 1.5	8.5 ± 1.1	7.1 ± 1.5	<0.001
Median	7	9	7	
PSA (ng/mL)				
Mean \pm SD	260.2 ± 1107.8	1071.3 ± 2337.1	69.4 ± 235.5	<0.001
Median	26.9	193.7	19.3	

Table 2. Univariate and Multivariate Analysis between Bone Scan Positive and Negative Groups

Univariate analysis	OR	95% CI	P value	Multivariate analysis	OR	95% CI	P value
Age ≥ 80	1.15	0.58-2.26	0.673	Age ≥ 80	1.06	0.42-1.28	0.894
Gleason score ≥ 7	6.93	2.68-17.9	<0.001	Gleason score ≥ 7	2.92	1.06-8.01	0.039
Clinical stage $\geq T3$	4.41	2.18-8.85	<0.001	Clinical stage $\geq T3$	2.26	1.05-4.79	0.033
BMI ≤ 22	2.93	1.56-5.52	0.001	BMI ≤ 22	1.51	1.16-3.38	0.025
PSA ≥ 20	9.8	4.06-23.81	<0.001	PSA ≥ 20	5.66	2.25-14.22	0.001

Table 3. Proportions of Bone Metastasis Compared to the Reports byof Briganti et al. and Tanaka et al.

	Total	Low risk		Intermediate risk		High risk	
		Patients(%)	Bone mets(%)	Patients(%)	Bone mets(%)	Patients(%)	Bone mets(%)
Briganti et al.	853	692(81.4)	3(0.4)	72(8.4)	6(8.3)	89(10.4)	15(16.9)
Tanaka et al.	837	506(60.5)	1(0.2)	171(20.4)	10(5.8)	160(19.1)	24(15.0)
Current report	328	62(18.9)	2(3.2)	125(38.1)	12(9.6)	141(43.0)	42(29.8)

**Figure 1. Kaplan-Meier curves for over-all survival in all prostate cancer patients according to bone metastasis status**

metastasis sites, 7 (10.9%) with three, 6 (9.4%) with four, 7 (10.9%) with five, 7 (10.9%) with six, and 17 (26.6%) with seven different metastasis sites, respectively. The PSA level is much higher in patients with more than 4 different metastasis sites (1719.8 ± 547.8 vs. 331.8 ± 150.4 ; $p=0.02$). The Gleason score also showed the similar results (8.8 ± 0.2 vs. 8.0 ± 0.3 ; $p=0.016$). The number of bone metastasis did not have correlation to the Age and BMI. The mean number of bone metastasis sites in our patients is four. There was no difference regarding overall survival between patients with bone metastases number. The number of patients with bone metastases to the following sites was as follows: 54 (84.4%) to the spine, 53 (82.8%) to the pelvis, 43 (67.2%) to the ribs, 31 (48.4%) to limbs or the scapula, 29 (45.3%) to the sternum, and 27 (42.2%) to the skull, respectively. There was also no difference in survival among the patients with respect to the location of metastasis (Table 3). Our univariate logistic regression analyses of each parameter to predict bone metastases demonstrated that a Gleason score of ≥ 7 , clinical stage $\geq T3$, BMI ≤ 22 kg/m², and an initial PSA level of ≥ 20 ng/mL were independent predictors of bone metastasis. Our multivariate logistic regression analysis employing the above independent predictors demonstrated that a Gleason score of ≥ 7 , clinical stage $\geq T3$, BMI ≤ 22 kg/m², and an initial PSA level of ≥ 20 ng/mL were independent predictors of bone metastasis (Table 4). According to the external validation criteria reported by Briganti et al. (2010), we excluded 8 patients with clinical stage T4 tumors. Among the 328 remaining patients, 62 patients were classified into the low-risk group, 125 into

the intermediate-risk group, and 141 patients into the high-risk group with a bone metastasis rate of 3.2%, 9.6%, and 29.8%, respectively (Table 5). Our results showed a significantly higher population of high-risk patients (43% vs. 10.4%; $p<0.001$) initially diagnosed with PCa compared to low- and intermediate risk patients. Our high-risk patients also had a higher bone metastasis rate (29.8% vs. 16.9%; $p=0.027$) than previous report (Briganti et al., 2010). The survival analysis showed a significant difference between patients with positive and negative bone scan results (Figure 1).

Discussion

Bone metastasis is one of strongest negative prognostic factors for PCa patients. Our positive bone metastasis rate was 19%, which is higher than that in the United States (12%) (Falchook et al., 2014) and lower than that in Japan (22.2%) (Kosuda et al., 2002). A recent paper (Falchook et al., 2014) showed that almost one-third of low-risk and almost one-half of intermediate-risk PCa patients underwent a staging bone scan. Only 62% of high-risk PCa patients were recommended for staging bone scan based on the National Comprehensive Cancer Network Guidelines. Aggressive surgical intervention may be arranged for the incurable circumstance. The prevalence of bone metastasis in low-risk, intermediate-risk, and high risk patients has reportedly ranged from 0.1-0.4%, 0.7-8.3%, and 12.2-16.9%, respectively (Tanaka., 2011; Briganti et al., 2010; Falchook et al., 2014). In comparison, our results showed a 3.2%, 9.6%, and 29.8% rate of positive bone metastasis in each group, respectively. A previous report (Kosuda et al., 2002) showed that Japanese PCa patients had a higher bone metastasis rate and lower PSA levels than those observed in Western countries. Our data support a higher prevalence of bone metastasis in low-risk patients. Another group reported (Cooperberg et al., 2007) that the proportion of low-risk patients was also dramatically increased in the PSA era; however, compared to our cohort, a relatively small population of low-risk patients was included in that study. Considering the high bone metastasis rate in our present study, the clinical benefit of the bone scan exam in low-risk patient merits further investigation.

Currently, the relationship between bone metastasis patterns and survival is not fully understood. Some reports (Singh et al., 2004; Soloway et al., 1988; Ost et al., 2014; Schweizer et al., 2013) have demonstrated that the number of PCa bone metastases is related to prognosis. The overall survival time from metastasis to death in the present study was not different from Singh's (2004) report. We also observed no difference in survival time. This may be

attributed to the same treatment strategy being used before and after metastasis (Singh et al., 2004). In our cohort, androgen deprivation therapy was the standard treatment. Other reports (Ost et al., 2014; Schweizer et al., 2013) showed that a lower number of metastases was related to improved survival time. Metastasis-directed therapy has been suggested (Ost et al., 2014) for oligometastasis patients. As for the bone metastasis location, the spine was reported as the most common site for metastasis (Harada et al., 1992). In our cohort, 84.4% of patients had metastasis to the spine. A previous report (Singh et al., 2004) revealed that the survival rate for patients with pelvic metastasis was worse than for those with vertebral metastasis. In contrast, Drzymalski et al. (2010) reported that patients with metastasis to the spine and a high PSA level had the worst prognosis. Our current data showed no significant difference in terms of survival time between patients with different metastasis locations. However, this might be because there were just four patients with only spine metastasis in our cohort.

In order to quantify and interpret the bone scan results, the bone scan index (BSI) was developed as a quantitative tool (Imbriaco et al., 1998) BSI has been strongly associated with overall survival in previous studies (Imbriaco et al., 1998; Sabbatini et al., 1999; Dennis et al., 2012). Current efforts have been focused on developing techniques to express BSI not as a fraction of skeletal mass but as a percentage of active marrow to generate more evidence for further clinical applications (Sabbatini et al., 1999).

In our series, 64 patients had a positive bone scan. Among them, 2 (3.1%) patients had a serum PSA level of ≤ 20 ng/mL and a Gleason score of ≤ 7 at the time of diagnosis. According to the current guidelines by EAU or AUA (Heidenreich et al., 2013; Greene et al., 2009), a bone scan may not be necessary for patients with a PSA level of ≤ 20 ng/mL and a Gleason score of ≤ 7 , and bone metastasis in two (0.6%) patients in our cohort would have gone undetected. By applying the external validation developed by Briganti et al. (2010), all of our patients would have been included for a bone scan at the time of diagnosis. Although the incidence of bone metastasis with a PSA level of ≤ 20 ng/mL and a Gleason score of ≤ 7 is very low, we think performing the bone scan examination had greater clinical benefits to the patients.

A previous report (Lee et al., 2000) showed that the Gleason score, PSA level, and clinical stage were independent predictors for positive bone metastasis in 631 consecutive patients. Tanaka et al. (2011) found that the Gleason score and PSA level were strongly predictive of bone metastasis whereas clinical stage was not. Our results showed that clinical stage, the Gleason score, BMI, and PSA level were all independent predictors for bone metastasis. There were 184 (55%) patients with clinical stage T3 or higher. The higher incidence of late-stage PCa compared to that found in other recent (Tanaka et al., 2011; Lee et al., 2000) reports may be explained by more aggressive and poorly differentiated tumors in our cohort. As previous studies have shown, PSA expression strongly correlates to the testosterone level (Young et al., 1991; Morgentaler et al., 1996). Compared to Caucasians,

Asian men show a lower level of serum PSA (Oesterling et al., 1995; He et al., 2004) and lower baseline testosterone levels, raising the question of whether current guidelines for PSA testing is sufficient for detecting prostate diseases such as PCa in this population.

A recent meta-analysis (Hu et al., 2014) demonstrated that not only were overweight men underdiagnosed with PCa but that this population presented with more aggressive tumors (high-grade PCa; defined as a Gleason score of ≥ 7 at diagnosis). No statistical correlation between BMI and PCa was observed by their results. In our cohort 143 (42.5%) patients were classified as overweight (BMI > 25 kg/m²) and 213 (63.4%) patients had high-grade tumors. The difference in the proportion of overweight PCa patients with high-grade versus low or intermediate grade tumors (46.5% vs. 35.8%; $p=0.056$) was marginal. A previous study (Isom-Batz et al., 2005) showed that obese patients had lower total levels of testicular testosterone than patients who were not obese. The interaction between testosterone and PCa corresponds to an unfavorable pathological outcome (Isom-Batz et al., 2005). Furthermore, the tumor microenvironment of obese patients has been shown to promote carcinogenesis and block apoptosis (Nandeeshia et al., 2009) As for PCa patients with bone metastasis, we observed that these patients had a lower BMI compared to those without bone metastasis. Bone metastasis is often associated with a vulnerable state of anorexia, weight loss, and accelerated malnutrition. This cachexia often happens even if the progression is limited to a single site in PCa patients (Nakashima et al., 1998). Our results might be explained by the more aggressive and poorly differentiated prostate tumors observed in our cohort.

There are two notable limitations to be acknowledged. First, this is a retrospective analysis in a single-center series. Second, the positive results detected by bone scan cannot be confirmed by histological examination because of the high rate of false negative results. Therefore, further prospective multicenter studies are needed to identify whether the aforementioned confounding variables may have had an impact on outcomes.

Based on our results, a bone scan might be necessary in newly diagnosed PCa patients with any of the following criteria: clinical stage T3 or higher, a Gleason score of 7 or higher, BMI equal to or less than 22 kg/m², and a PSA level of 20 ng/mL or higher.

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