

Is it suitable to eliminate bone scan for prostate cancer patients with PSA \leq 20 ng/mL?

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Abstract

Purpose We evaluated the relationship between bone metastasis (BM) and clinical or pathological variables, including the serum prostate-specific antigen (PSA) concentration.

Methods This retrospective study included 579 consecutive patients with newly diagnosed prostate cancer (Pca) who underwent a bone scan study at our institution between 2002 and 2010. We used receiver operating characteristics curves to evaluate accuracy of bone metastasis between serum PSA 10 and 20 ng/mL.

Results A positive bone scan result was found in 83 men (14.3%) with PCa. However, 27 men (4.6%) with serum PSA between 10 and 20 ng/mL, 29/579 men (5.0%) with GS \leq 7, and 21/83 (25.3%) with serum PSA \leq 20 ng/mL and Gleason score (GS) \leq 7 had positive bone scans. In the logistic regression analyses, clinical T stage (odds ratio [OR] = 3.26; 95% CI, 2.29–4.33; P = 0.021), GS (OR = 3.41; 95% CI, 2.91–4.63; P = 0.019), and serum PSA (OR = 8.37; 95% CI, 3.91–19.21; P < 0.001) were predictive factors of detecting the BM. When the serum PSA concentration \leq 20 ng/mL and GS \leq 7, AUC value of bone scans for the detection of BM was 0.640 (P = 0.020; 95% CI, 0.563–0.717). With serum PSA at 10 ng/mL and GS \leq 7, the AUC values of bone scans were 0.828 (P < 0.001; 95% CI, 0.773–0.883).

Conclusions Bone scans might be necessary in men with serum PSA between 10 and 20 ng/mL. New guidelines for

eliminating bone scans in patients with newly diagnosed Pca are needed, especially in Asians.

Keywords Bone scan · Prostate cancer · Prostate · Bone metastasis · PSA

Introduction

Considering that the most frequent site of metastatic prostate carcinoma is bone [1], detection of bone metastasis is important when deciding the treatment strategy of prostate cancer. Bone scanning is the most sensitive modality for the detection of bone metastasis but it is also an expensive and time-consuming staging modality [2]. Therefore, it is important to seek a balance between cost and benefit. According to the American Urologic Association (AUA) and European Association of Urology (EAU) guidelines, scanning may not be necessary for those with serum prostate-specific antigen (PSA) \leq 20 ng/mL when they have Gleason score (GS) \leq 7 [3, 4]. These guidelines are reflected in the clinical guidelines for prostate cancer published by the Japanese Urological Association in 2006 [5].

However, it has not been sufficiently investigated whether this standard is suitable for Asians with relatively small prostates in size or lower serum PSA levels [6, 7]. In Japan, a multicenter retrospective study suggests the incidence of positive bone scanning in patients with low PSA levels is much higher than that in other studies conducted in North America and Europe [8]. According to mass population screening in Korea, the distribution of serum PSA values in Koreans was different from that obtained in Caucasians [9].

Therefore, we evaluated the relationship between bone metastasis and clinical or pathological variables, including

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the serum PSA concentration. With this evaluation, we tried to determine the clinical profiles of patients for whom bone scanning could be eliminated due to a low probability of bone metastasis.

Methods

This retrospective study included 579 consecutive patients who were newly diagnosed with adenocarcinoma of the prostate and underwent a bone scan study at our single tertiary referral institution between 2002 and July 2010. They all had transrectal ultrasound (TRUS) guided prostate biopsies, serum PSA levels, and bone scans within 3 months of one another. We excluded patients who had a history of 5-alpha-reductase inhibitors treatment for benign prostatic hyperplasia or that of other malignant diseases with possible development of BM. All prostate biopsies were performed using a standard 18-gauge biopsy gun, and the number of biopsy sites ranged from six to ten with additional targeted biopsies for any hypoechoic or suspicious lesion. For each needle biopsy, certain variables were assessed, including GS, the percentage of tumor as a function of all the biopsy tissues, the number of cancer-positive cores, and the total number of cores from all biopsy sites. The serum PSA level was determined by the Hybritech, Tosoh, or Abbot assay with the normal range set between 0 and 4.0 ng/mL.

Bone scintigrams were performed with technetium-99m HDP. The dose of Tc-99m HDP used was approximately 20 mCi (740 MBq), and scanning was performed by a single head—camera high-resolution collimator was used, and whole body anterior and posterior planner images, together with oblique and localized views for areas of interest, were reviewed. The bone scintigrams were reviewed by two experienced radiologists with knowledge of PSA, biopsy GS, and digital rectal examination findings. Patients with unclear bone scan findings underwent additional computed tomography and/or magnetic resonance imaging to confirm the bone scan findings. To evaluate accuracy of bone metastasis with serum PSA \leq 20 ng/mL or serum PSA \leq 10 ng/mL,

the receiver operating characteristics (ROC) curve analysis derived area under the curve (AUC) estimates determined the cutoff points of each predictor, and then their sensitivity, specificity, and positive predictive value (PPV) were analyzed. The SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for statistical analysis, and a probability (*P*) level of <0.05 was considered significant.

Results

Eighty-three patients (14.3%) had a positive bone scan. Median age of patients with and without bone metastasis was 74 and 68 years old, respectively ($P = 0.027$). The median PSA and biopsy GS were 49.6 ng/mL and 7.4, respectively, in patients with bone metastasis and 7.3 ng/mL and 6.4 in those without bone metastasis (Table 1).

Of 58 patients with bone pain, 49 (82.8%) had bone metastasis. Positive bone scans were obtained from 27 patients (4.5%) with a serum PSA between 10 and 20 ng/mL, one (0.2%) with serum PSA below 10 ng/mL, and 55 (9.5%) with serum PSA above 20 ng/mL. Of 29 patients with bone metastasis who had GS below 7, 1 (1.2%), 9 (10.8%), 19 (22.9%) patients were found in GS 5, 6, 7, respectively, (Fig 1). Of 83 patients with bone metastasis, 21 (25.3%) with a serum PSA \leq 20 ng/mL and GS \leq 7. In the logistic regression analyses, clinical T stage (odds ratio = 3.26; 95% CI, 2.29–4.33; $P = 0.021$), GS (OR = 3.41; 95% CI, 2.91–4.63; $P = 0.019$), and serum PSA (OR = 8.37; 95% CI, 3.91–19.21; $P < 0.001$) were the predictive factor detecting BM (data not shown).

With the serum PSA concentration \leq 20 ng/mL and GS \leq 7, the mean sensitivity was 74.7%, specificity 92.9% (Table 2), and the AUC value of bone scans for the detection of BM 0.640 ($P = 0.020$; 95% CI, 0.563–0.717) (Fig. 2). With the serum PSA at 10 ng/mL and GS \leq 7, the mean sensitivity was 98.4%, specificity 83.9%, and the AUC values of bone scans 0.828 ($P < 0.001$; 95% CI, 0.773–0.883) (Fig. 2).

Table 1 Patient characteristics and clinical stage at diagnosis

Clinical variables	Bone metastasis (+)	Bone metastasis (–)	<i>P</i> value
No. of patients	83	496	
Median age (years)	74 (53–89)	68 (46–87)	0.027
Median PSA (ng/mL)*	49.6 (7.9–1221.5)	7.3 (3.6–54.3)	<0.001
Biopsy Gleason score (mean)*	7.4 \pm 0.8	6.4 \pm 0.5	0.031
Clinical stage**			<0.001
T1–2	5 (6.0%)	393 (79.2%)	
T3	41 (49.4%)	84 (16.9%)	
T4	37 (44.6%)	19 (3.8%)	

* <0.05 by student's *t* test

** <0.05 by Pearson chi-square test

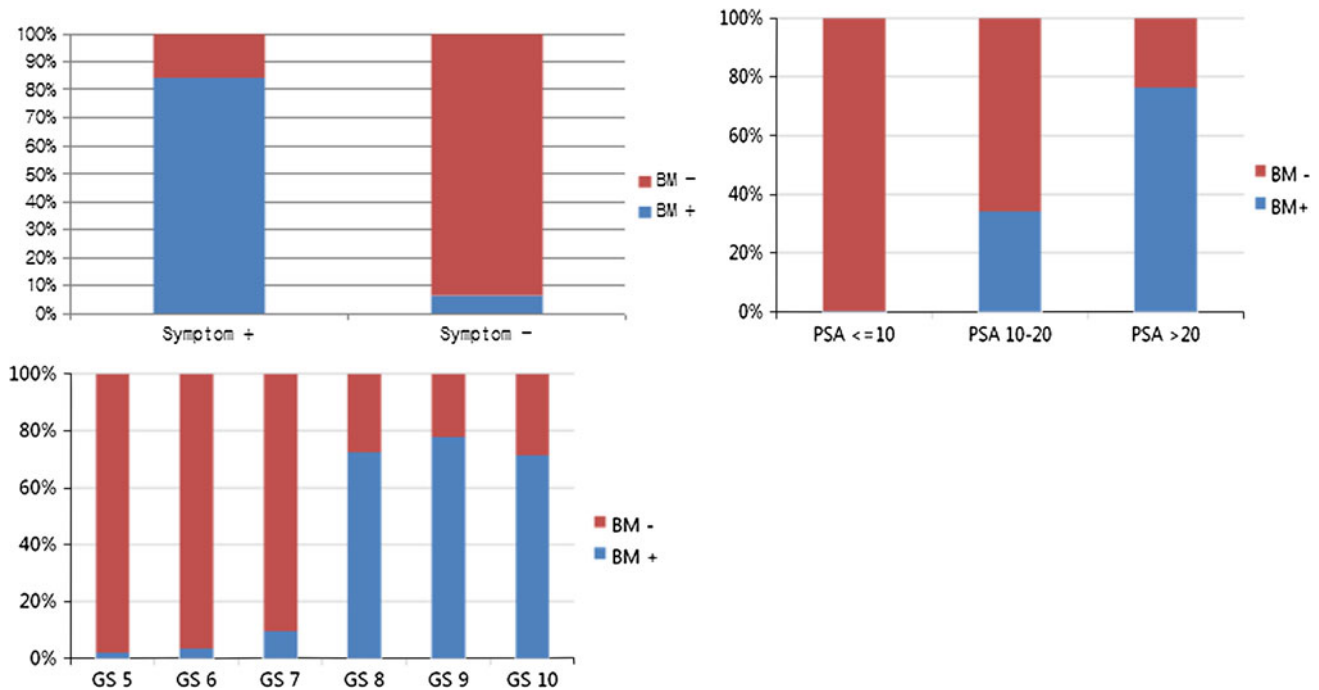


Fig. 1 Percentage of bone metastasis according to baseline symptom, PSA, and biopsy Gleason scores

Table 2 Comparison of diagnostic accuracy for assessment of bone metastasis according to PSA levels

	PSA \leq 20 and GS \leq 7	PSA \leq 10 and GS \leq 7
Sensitivity (%)	74.7	98.8
Specificity (%)	92.9	84.3
PPV (%)	63.9	51.3
NPV (%)	95.6	99.8

PSA prostate-specific antigen, GS Gleason scores, PPV positive predictive value, NPV negative predictive value

Discussion

We observed bone metastasis in 14.3% of newly diagnosed Pca, which is higher than that in the United States (8.9%) [10]. and lower than that in Japan (22.2%) [8]. Recently, the epidemiology of prostate cancer in the Asian population has changed, thanks to the increasing awareness of the disease entity, the advent of the PSA testing for screening, and the increase in life expectancy of the male population [11]. In South Korea, the incidence of prostate cancer is rapidly increasing, ranking fifth among the most common cancers in the male population in 2007 [12]. Therefore, our lower incidence of metastatic Pca compared to previous Asian studies [8, 13] might be due to the increasing awareness of PSA screening in Korea.

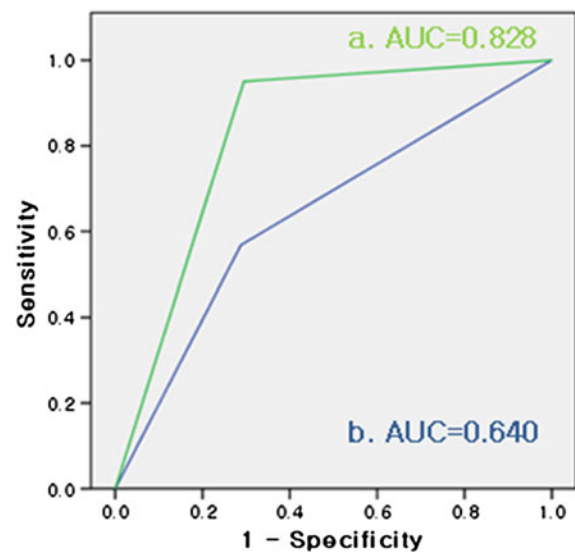


Fig. 2 Receiver operant characteristic curve for data obtained from patients with PSA \leq 20, Gleason score \leq 7 (a) and PSA \leq 10, Gleason score \leq 7 (b) with bone metastasis correlation

In our study, 83 men had a positive bone scan. Among them, 21 patients (25.3%) had serum PSA \leq 20 ng/mL and GS \leq 7 at the time of the diagnosis. The aim of bone scan is to detect occult locoregionally advanced or distant metastatic disease that would alter the primary treatment plan. Confining the bone scan analysis to less strict criteria would have increased the sensitivity but decreased positive predictive ability. However, what is important when determining

the overall bone scan stage is that the result should not impact our decision to recommend patients for prostatectomy. By applying the EAU or AUA guideline [3, 4], 3.6% (21/579) patients in our study would have not been detected with bone metastasis at proper time. Recently, Briganti et al. [14] suggested that staging bone scans might be considered only for patients with a biopsy GS > 7 or with PSA > 10 ng/mL and palpable disease (cT2/T3) prior to treatment (AUC range: 88.0%; $P < 0.002$). Similarly, AUC increased from 0.640 with PSA > 20 ng/mL to 0.828 with PSA > 10 ng/mL. These results suggest that skeletal screening may be required even for patients with a serum PSA level between 10 and 20 ng/mL.

In contrast to other studies conducted in Western countries, a multi-center retrospective study conducted in Japan revealed that bone metastasis was common in Japanese patients with newly diagnosed untreated prostate carcinoma with an overall positive rate of 22.2% on bone scans [8]. Moreover, Ito et al. [15] found 303 patients with CaP and 36 with bone metastasis among 9,671 patients. Among those with bone metastasis, 13 patients (36%) had PSA levels of 10 ng/mL or less. The incidence of positive bone scan in a patient group with low PSA levels is much higher than the other studies in the Western countries. In a Hong Kong study, Lai et al. [11] recommend omitting bone scan if serum PSA is 10 ng/mL or less. If imaging had been denied only to patients with a PSA level of 20 ng/mL or less, imaging sensitivity would have decreased to 94%.

Our data are inconsistent when applied to AUA or EAU guideline. Our results might be due to more aggressive and poorly differentiated PCa in Korean men, despite a low clinical stage or low serum PSA level [16]. In another report, twice as many Asian men had a GS of 8 or greater, the worst stage at presentation, and were, accordingly, classified as being at high risk, as compared with non-Asian men [17]. PSA expression is strongly influenced by androgens [18]. Thus, hypogonadal men with low testosterone levels may show low serum PSA levels because of decreased expression, and their serum PSA may not reflect the presence of prostate disease such as cancer [19]. Asian males tend to have lower total serum testosterone and hormone-binding levels, a reduction in 5- α -reductase levels, and lower testosterone production rates compared with white men [20]. A previous investigation involving a large number of healthy Japanese [6], Chinese [21], and Korean [9] men showed a lower median value of serum PSA for Asian men than that for Caucasians.

This study has several limitations. First, this is a retrospective study. Second, we could not confirm the histology of the bone metastasis detected by bone scans. Even though bone scintigraphy is accurate and highly sensitive, there might be a margin of error.

Conclusions

Based on our findings, bone scans might be necessary in men with a serum PSA between 10 and 20 ng/mL. Different guidelines for eliminating bone scans in patients with newly diagnosed prostate cancer are needed, especially in Asians.

Conflict of interest There is no conflict of interest.

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