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Predicting Bone Metastasis in Prostate Cancer Patients: Value of Prostate Specific Antigen

*Ling-Huei Wei[1], Jainn-Shiun Chiu[1], Shiou-Ying Chang[1], Yuh-Feng Wang[1,2]**

[1]*Department of Nuclear Medicine, Buddhist Dalin Tzu Chi General Hospital, Chiayi, Taiwan*
[2]*Department of Medicine, Tzu Chi University, Hualien, Taiwan*

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Abstract

Objective: Serum prostate specific antigen (PSA) concentration has been widely applied as a biomarker to diagnose and monitor prostate cancer. Technetium-99m methylene diphosphate (Tc-99m MDP) whole body bone scintigraphy is currently a well-accepted diagnostic procedure for bone metastasis in malignancy. The aim of this study was to establish a useful serum PSA cut-off value to predict the presence of bone metastasis in men with prostate cancer.

Material and Methods: Consecutive male patients diagnosed with prostate cancer were retrospectively analyzed. All of the subjects had received both Tc-99m MDP whole body bone scintigraphy and had their serum PSA concentration measured within 1 month. The proper cut-off value was established based on statistical analysis in order to predict the possibility of bone metastasis among prostate cancer patients.

Results: In total, 101 consecutive male patients (age, 71.92±0.76 years) with prostate cancer were enrolled, and 57 patients (56%) were confirmed by scintigraphic findings to have bone metastases. A serum PSA concentration of 13 ng/mL gave the best sensitivity (96.43%) and specificity (84.09%). The area under the receiver operating characteristics curve revealed excellent discriminatory power (0.93±0.02; $p=0.001$). The positive predictive value, negative predictive value and likelihood ratios for positive and negative test were 88.52%, 94.87%, 6.06 and 0.04, respectively. The resulting diagnostic accuracy and odds ratio were 73.87% and 142.76.

Conclusion: A cut-off value of 13 ng/mL appears to be an appropriate benchmark for stratifying metastatic bone disease in prostate cancer patients such that if a patient with newly diagnosed prostate cancer and without any skeletal symptoms has a serum PSA concentration of less than 13 ng/mL, we suggest that they would not need to undergo bone scintigraphy. (*Tzu Chi Med J* 2008;20(4):291–295)

*Corresponding author. Department of Nuclear Medicine, Buddhist Dalin Tzu Chi General Hospital, 2, Min-Sheng Road, Dalin, Chiayi, Taiwan.
E-mail address: nment@ms7.hinet.net

1. Introduction

Prostate cancer is one of the most commonly diagnosed malignancies in men. This leading cause of mortality has gradually increased throughout the world and results in more than 200,000 deaths annually [1]. In Taiwan, prostate cancer is the ninth leading cause of cancer-related death in male patients [2]. Although prostate cancer may be curable when it is identified at an early organ-confined stage, almost one fourth of patients present with advanced or metastatic disease at the time of diagnosis [3]. The most common site of metastatic spread in patients with prostate cancer is the skeleton, which accounts for up to 80% of all prostate cancer metastases [4]. Despite various therapeutic strategies, nearly half of patients with metastatic disease die within 30 months, and 85–100% of those who die from prostate cancer have skeletal metastasis [5].

When bone metastasis develops, the influence is not only on the prognosis of the disease but also on the quality of life. The clinical characteristics of skeletal metastasis in prostate cancer include bone pain, impaired mobility, pathologic fracture, and spinal cord or nerve root compression. To select an appropriate treatment, detection of osseous metastasis is essential in patients with prostate cancer for both disease staging and the creation of a subsequent follow-up plan. The current modality in clinical practice for assessing skeletal metastasis of prostate cancer is bone scintigraphy, which is a highly sensitive one-step procedure that uses whole body skeletal surveying. However, a serum tumor marker, prostate specific antigen (PSA), is widely used as an initial biomarker to screen, monitor, and predict disease severity among prostate cancer patients. In addition, a rising PSA level may occur several months before changes in bone scintigraphy can be seen. Herein, the intention of our study was to determine the appropriate PSA cut-off value for predicting skeletal metastasis in patients with prostate cancer.

2. Materials and methods

2.1. Patients

From June 2001 to November 2005, 101 consecutive patients with prostate cancer who underwent technetium-99m methylene diphosphate (Tc-99m MDP) whole body bone scintigraphy were retrospectively analyzed. The information was collected from the scintigraphic database at a regional teaching hospital. Patients who did not have a serum PSA concentration available within 1 month before or after the time of performing the Tc-99m MDP whole body bone scintigraphy were excluded from this study. Since this was a retrospective study, the treatment status and clinical stage at enrolment were not scrutinized. In addition, all patients did not necessarily have a pathological report available. Bony metastases were determined from the bone scan studies and no further correlation with histopathology or other imaging modalities were performed. To preserve patient confidentiality, direct patient identifiers were not collected.

2.2. Bone scintigraphy

Tc-99m MDP is commercially available and was provided by Daiichi Radioisotope Labs, Ltd. (Tokyo, Japan). Following the *Procedure Guideline for Bone Scintigraphy* announced by the Society of Nuclear Medicine (version 3.0, approved June 20, 2003), a whole body bone scintigraphy scan (from the toes to top of the head) was performed using a whole-body moving camera technique (anterior and posterior) 3–4 hours after intravenous injection of 20–25 mCi of Tc-99m MDP. All images were acquired using a two-headed gamma camera scintillation system (DST-XL, General Electric Medical Systems, Buc, France) equipped with large field-of-view, low-energy, high-resolution collimators. The energy peak and window level were set at 140 keV ± 20%. The matrix size was 512 × 2048 pixels, and the scan speed was 16 cm/min. One independent nuclear medicine physician with more than 10 years of experience interpreted all scintigraphic images, the blind serum PSA levels and any available clinical findings. The final results were clarified as negative (Fig. 1) or positive (Fig. 2) for skeletal metastasis, according to the bone absorption of the radiopharmaceutical.

2.3. PSA immunoradiometric assay

The serum PSA concentrations of all patients were measured by radioimmunometric assay (Immunotech-PSA total IRMA kit; A Beckman Coulter Company, Fullerton, CA, USA). The principle of this assay is a "sandwich"-type assay. Serum or plasma samples are incubated in tubes coated with the first monoclonal antibody in the presence of the second monoclonal antibody, which is labeled with I-125. After incubation, the contents of the tubes are rinsed in order to remove unbound I-125 labeled antibody. The bound radioactivity was then measured in a gamma counter. The total PSA concentration in the sample is directly proportional to the radioactivity, and normal values were between 0 and 4 ng/mL. All examinations, namely the scintigraphic imaging and the radioimmunometric assays, were conducted in the same department.

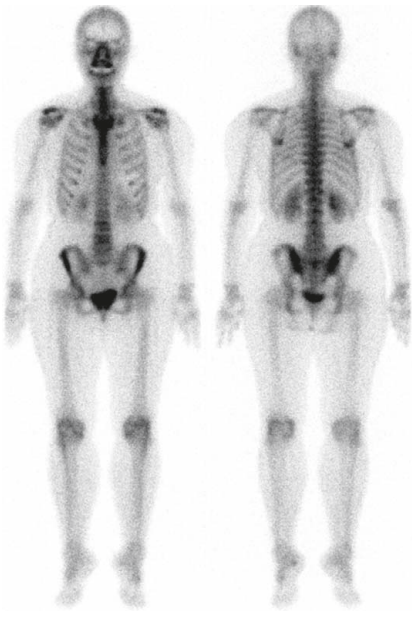

Fig. 1 — A patient with "normal" bone scintigraphy. No definite bony destruction events are present in this Tc-99m MDP whole body bone scintigraphy scan of a patient with prostate cancer.

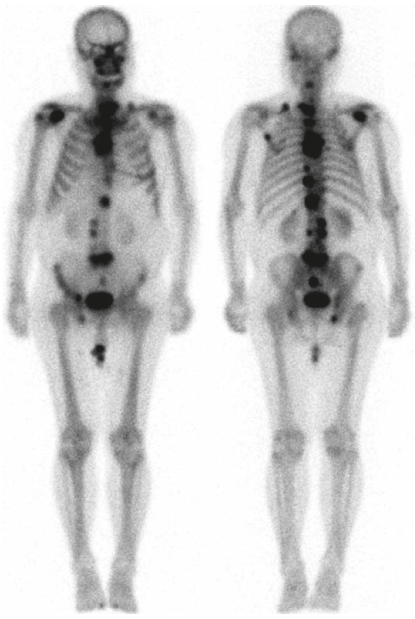

Fig. 2 — Multiple bony metastases are shown in this Tc-99m MDP whole body bone scintigraphy scan of a patient with prostate cancer.

2.4. Statistical analysis

Statistical analyses were performed using MedCalc version 9.2 (MedCalc, Mariakerke, Belgium) for Windows, and expressed as mean±standard error. In order to inspect the suitability of the various possible PSA cut-off points for predicting skeletal metastasis in patients with prostate cancer, receiver operating characteristic (ROC) curve, sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio for a positive (LRP) test and likelihood ratio for a negative test (LRN) [6], Cohen's kappa [7], and diagnostic odds ratio (DOR) [8] were used. The area under the ROC curve (AUC) with best sensitivity and specificity simultaneously were used as measurements to determine the diagnostic efficacy [9,10]. An AUC of 1.0 infers perfect discrimination, whereas an AUC between 1.0 and 0.8 is classified as "excellent" discrimination, between 0.8 and 0.7 is "acceptable", and ≤0.5 is equivalent to a random model [11]. Cohen's kappa was utilized to compare the proportion of correct test-based classifications with the proportion of correct classifications expected with a random assignation of diagnoses [12]. Cohen's Kappa values indicate whether the agreement between measurements was poor (<0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), or very good (0.81–1.00) [13]. The DOR of the cut-off point is calculated as the LRP/LRN ratio with higher values signifying better discriminatory power; specifically, this does not depend on the prevalence of the target disease [8]. The cut-off point of the serum PSA concentration for predicting skeletal metastasis in prostate cancer patients was judged to be optimal if it resulted in a high diagnostic accuracy, a high Cohen's kappa and a high DOR.

3. Results

A total of 101 men with prostate cancer were enrolled in this study. Their mean age was 71.92±0.76 years (range, 51–88 years), and mean serum PSA concentration was 124.94±18.90 ng/mL (range, 0.10–838.00 ng/mL). Of these, 57 patients (56.43%) were identified as having bone metastasis based on scintigraphic diagnosis. The statistical results for sensitivity, specificity, PPV, NPV, diagnostic accuracy, LRP, LRN, Cohen's kappa, and DOR of the various different PSA cut-off values are shown in Table 1. Serum PSA concentrations between 15 ng/mL and 20 ng/mL gave the same statistical results as 15 ng/mL and so are not shown. The ROC analysis for predicting skeletal metastasis in prostate cancer resulted in an AUC of 0.93±0.02, indicating that this gave good diagnostic efficiency and represented a statistically significant discriminatory power ($p<0.001$), as shown in Fig. 3.

The PSA cut-off points of 13 ng/mL and 14 ng/mL gave good results and would be adequate for predicting

Table 1 — Sensitivity, specificity, positive predictive rate (PPR), negative predictive rate (NPR), diagnostic accuracy (DA), likelihood ratio positive (LRP) and negative (LRN), Cohen's Kappa (K), and diagnostic odds ratio (DOR) for various cut-off values of serum prostate specific antigen concentration

Cut-off value (ng/mL)	Sensitivity (%)	Specificity (%)	PPR (%)	NPR (%)	DA (%)	LRP	LRN	K	DOR
1.0	100.00	31.82	65.52	100.00	30.69	1.47	0.00	0.345	–
2.0	98.24	38.64	67.47	94.44	35.14	1.60	0.05	0.395	35.15
3.0	98.24	38.64	67.47	94.44	35.14	1.60	0.05	0.395	35.15
4.0	98.24	43.18	69.14	95.00	38.74	1.73	0.04	0.442	42.42
5.0	98.24	47.73	70.89	95.45	42.34	1.88	0.04	0.488	50.97
6.0	98.24	47.73	70.89	95.45	42.34	1.88	0.04	0.488	50.97
7.0	98.24	54.55	73.68	96.00	47.75	2.16	0.03	0.555	66.99
8.0	98.24	54.55	73.68	96.00	47.75	2.16	0.03	0.555	66.99
9.0	98.24	61.36	76.71	96.43	53.15	2.54	0.03	0.622	88.64
10.0	98.51	61.36	76.71	96.43	53.15	2.54	0.03	0.622	88.64
11.0	96.49	65.91	78.57	93.55	58.56	2.83	0.05	0.646	53.15
12.0	96.49	77.27	84.62	94.44	67.57	4.25	0.05	0.753	93.45
13.0*	96.43	84.09	88.52	94.87	73.87	6.06	0.04	0.817	142.76
14.0	94.74	86.36	90.00	92.68	76.58	6.95	0.06	0.817	114.04
15.0†	92.98	86.36	89.83	90.48	78.38	6.82	0.08	0.798	83.86
20.0†	92.98	86.36	89.83	90.48	78.37	6.89	0.08	0.798	83.86

*The best cut-off value for serum PSA concentration when predicting the presence of bone metastasis in prostate cancer patients; †the results of statistical analyses were the same for cut-off values of 15 ng/mL and 20 ng/mL.

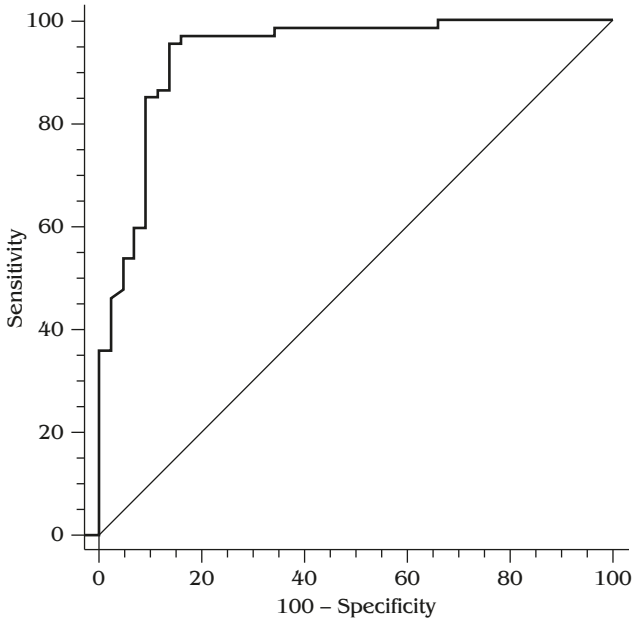

Fig. 3 — The receiver operating characteristic curve for predicting bone metastasis in prostate cancer patients.

prostate cancer with an incremental screening value. However, a serum PSA cut-off point of 13 ng/mL resulted in a higher DOR (142.76), sensitivity (96.43%), and NPR (94.87%). These were all higher than with a cut-off value of 14 ng/mL, but 13 ng/mL gave similar specificity (84.09%), PPR (88.52%), diagnostic accuracy (73.87%), LRP (6.06), LRN (0.04), and Cohen's kappa (0.817) as 14 ng/mL.

4. Discussion

Prostate cancer has become one of the most commonly diagnosed cancers in men and is a leading cause of death among men throughout the world. An improvement in the clinical outcome of this disease would be accomplished if malignancy can be detected at an early organ-confined stage. Therefore, the establishment of a useful serum PSA level to predict the presence of bone metastasis in men with prostate cancer is a major concern.

Bone scintigraphy is a highly sensitive one-step procedure for whole body skeletal survey; it has been the gold standard for detecting skeletal metastasis of underlying malignancy in cancers such as prostate cancer. However, despite its high sensitivity, it is too expensive to be applied as a routine screening procedure for bone metastasis. Measurement of serum tumor markers is another means of determining malignancy, and this approach is more cost-effective and more likely to achieve compliance in patients undergoing short- and/or long-term follow-up. It has become the most common test for detecting early prostate cancer and is widely used to monitor disease progression. An advancing clinical stage of prostate cancer, as well as the pathologic stage and tumor volume all result in a progressive increase in PSA level.

Rising PSA level will precede a patient's worsening symptoms and can provide information several months before other diagnostic procedures in patients with prostate cancer metastasis. It is useful as evidence in developing countries where patients cannot afford bone scintigraphy. A diagnostic cut-off value has

been established here based on several statistical analyses, and the best predictive value for prostate cancer patients with possible bone metastasis was found in this study to be 13 ng/mL. Our study result agrees quite well with that of Ishizuka et al [14], who suggested that bone scanning may not be necessary when the PSA level is less than 15 ng/mL. However, Chybowski et al [15] and Oesterling et al [16] both concluded that if a patient with newly diagnosed prostate cancer without skeletal symptoms has a serum PSA level of 10 ng/mL or less, then a staging bone scan is not necessary because such a PSA level is a strong negative predictor. Recently, some clinicians have discouraged the routine use of bone scan provided that the Gleason score is less than 7 (G1 or G2 tumors), except in patients with bone symptoms or a preoperative PSA level of 20 ng/mL or greater [15–17]. Due to the various different cut-off values that have been adopted, Rhoden et al [18] evaluated serum PSA cut-off values of 10 and 20 ng/mL for the prediction of bone metastasis in prostate cancer patients. According to their results, a serum PSA concentration over 20 ng/mL is a more accurate threshold than 10 ng/mL.

In our study, we did not only compare the cut-off points of 10 and 20 ng/mL, but also used a ROC curve and several indicators to establish an appropriate cut-off value for skeletal metastasis in patients with prostate cancer. However, there are some restrictions in this study. First, the number of enrolled patients was limited. More study patients should be enrolled in order to effectively lessen or avoid study bias. Second, bone scan images were interpreted by a single well-trained nuclear medicine physician and the personal subjective point of view of this person in terms of image interpretation needs to be considered. Third, the serum PSA concentration and bone scintigraphy were not acquired on the same day, which is an imperfection that is inherent in a retrospective analysis of this type. Another limitation of our study is that patients were not assigned to specific groups, such as newly diagnosed, pathological histology status, Gleason score, digital rectal examination finding, etc. In a future prospective study, the blood specimen should be taken on the same day as the bone scan is performed. In addition, the study should be designed prospectively with a larger total sample of patients randomly selected from different hospitals to minimize inter-institutional variation, and finally, there should be full classification of the patients' status.

In conclusion, our results showed that scintigraphic bone scanning is not essential in patients with newly diagnosed prostate cancer when their serum PSA level is less than 13 ng/mL, unless they have a history of bony involvement or the clinical examination is suggestive of such.

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