

Prostate Cancer with Bone Metastases: A Clinical Profile

Chun-Yin Huang, Horng-Chaung Hsu, Chao-Hsian Chang¹,

Kuo-Fung Tseng, Yi-Chin Fong

Department of Orthopaedics, ¹Department of Urology, China Medical

University Hospital, Taichung, Taiwan, R.O.C.

Purpose. Metastasis to bone commonly causes high morbidity and mortality rates in patients with advanced prostate cancer. Prostate-specific antigen (PSA) and bone scans are important modalities for evaluating and following the disease progression. We reviewed clinical symptoms, laboratory data, treatment and prognosis in order to analyze patients with bone-metastasized prostate cancer.

Methods. From January 1995 to December 2003, a total of 284 patients with prostate cancer were admitted to the China Medical University Hospital; of them, 97 patients were diagnosed as having bone metastases. The clinical files of the 97 patients with bone metastases were reviewed. The patients were categorized into two groups: group 1 comprised those in whom primary prostate cancer and bone metastases were identified simultaneously; group 2 was composed of those with bone metastases found after identification and treatment of prostate cancer.

Results. Bone metastasis was found in 34.2% (97/284 patients) of prostate cancer patients. Of the 97 patients with bone metastasis, the mean age was 71.5 years (range, 49 to 89 years) when prostate cancer was first diagnosed. Axial bones were more affected than appendicular bones. At the time bone metastasis was diagnosed, 69 patients (71.1%) had bone pain, 28 patients (28.8%) were asymptomatic and 6 patients in group 1 and 7 patients in group 2 had a serum PSA value less than 10 ng/mL. Four patients underwent surgical treatment for their pathological femoral fracture, resulting in good pain relief. The survival rate after bone metastasis had developed was not statistically significant between groups 1 and 2 ($p > 0.05$). Of the 3 factors being examined, the age at diagnosis of prostate cancer, the PSA value at first positive bone scan, and initial location and number of bone metastases did not statistically affect the survival rate in these two groups ($p > 0.05$).

Conclusions. A serum PSA level ≥ 10 ng/mL is an important marker in the metastatic work-up of prostate cancer; however bone metastases cannot be ruled out in patients with a serum PSA value of less than 10 ng/mL. There was no difference in the survival rate between untreated and treated prostate cancer patients with bone metastases. The age of the patient, the initial PSA value and the location of bone metastases did not appear to affect the outcome of the disease.

(Mid Taiwan J Med 2006;11:82-9)

Key words

bone metastases, prostate cancer, PSA

INTRODUCTION

Prostate cancer is a common malignant disease in males. Autopsies have revealed that

Received : 7 June 2005.

Revised : 6 September 2005.

Accepted : 29 March 2006.

Address reprint requests to : Yi-Chin Fong, Department of Orthopaedics, China Medical University Hospital, 2 Yuh-Der Road, Taichung 404, Taiwan, R.O.C.

80% of advanced prostate cancer is accompanied by the development of skeletal metastases [1,2]. Common complications caused by bone metastases included bone pain, pathological fracture and spinal cord compression [3]. Currently, treatment methods for patients with bone metastases are mostly palliative and include

Table 1. Location of lesions in 97 prostate cancer patients with bone metastases

Group/location	Spine	Pelvis	Rib	Femur	Scapula	Skull	Humerus	Clavicle	Tibia
Group 1 (n = 64)	52	48	44	31	21	14	15	10	1
Group 2 (n = 33)	29	23	22	7	5	7	2	3	0
Total	81	71	66	28	26	21	20	10	1

Group 1: Patients with primary prostate cancer and bone metastases identified simultaneously. Group 2: Patients with bone metastases identified after disease confirmation and initiation of treatment.

hormonal therapy, chemotherapy, pharmacological management, radiotherapy for pain and spinal cord compressions, surgical fixation for pathological fractures, and decompression for spinal cord, and the use of biphosphonates to inhibit osteoclast activity [4]. Prostate-specific antigen (PSA) is a very useful serum tumor marker in the follow-up of prostate cancer patients and a good predictor for the identification of metastases and the type of treatment. Tc-99m methylene diphosphonate (MDP) bone scan is the most widely used technique for detection and surveillance of metastatic spread to the skeleton [5-7].

Information about the clinical presentation and prognosis of prostate cancer patients with bone metastases in Taiwan is limited; therefore, we conducted a retrospective analysis of prostate cancer patients with bone metastases in our hospital to examine the clinical symptoms, PSA levels, locations of bone metastases, treatment modality of pathologic fracture and spinal cord compression, survival after bone metastasis, and their relationships in patients with prostate cancer.

MATERIALS AND METHODS

From January 1995 to December 2003, a total of 284 patients with prostate cancer were admitted to our institution; all of them underwent routine bone scans for evaluation of bone metastases. Bone metastases were diagnosed in 97 patients by Tc-99m bone scan; the clinical files of those patients were reviewed. The 97 patients were divided into two groups. Group 1 included those patients in whom primary prostate cancer and bone metastases had been diagnosed simultaneously. Group 2 comprised patients in whom bone metastases were identified after disease confirmation and initiation of treatment;

all had a negative bone scan at the time prostate cancer had been diagnosed. The follow-up period, age distribution, locations of metastases, clinical presentation, PSA levels, treatment and mortality rates were recorded for all patients in groups 1 and 2. The data obtained when the first positive bone scan was identified and recorded represented the time bone metastasis was diagnosed; the PSA level within one month before the positive bone scan was recorded; log-rank tests assessed the statistical differences between the two groups and the Kaplan-Meier method was used to draw the survival curve.

RESULTS

The incidence of bone metastasis in prostate cancer patients was 34.2% (97 of 284 patients). Of the 97 patients with bone metastasis, the mean age was 71.5 years (range, 49 to 89 years) when cancer was first diagnosed. All of the 97 patients showed adenocarcinoma formations. The sites of the bone metastases were as follows: spine (n = 81, 83.5%), pelvis (n = 71, 73.2%), rib (n = 66, 68.0%), femur (n = 38, 39.2%), scapula (n = 26, 26.8%), skull (n = 21, 21.6%), humerus (n = 20, 20.6%), clavicle (n = 13, 13.4%), and tibia (n = 1, 1%) (Table 1). Of the 97 patients, 69 patients (71%) had bone pain when the diagnosis of bone metastases was made and 28 (29%) were relatively asymptomatic.

Treatment and diagnostic modalities of primary prostate tumor in these metastatic patients included radical prostatectomy (n = 4, group 2) transurethral prostate resection (TURP) (n = 25, group 1; n = 26, group 2) and transrectal ultrasonographic biopsy (TRUS) (n = 39, group 1; n = 3, group 2). Eight patients with T-spine metastases developed quadriplegia and three of them underwent posterior decompression and

Table 2. PSA level at first positive bone scan in 97 patients with metastatic prostate cancer

Group/PSA(ng/mL)	< 10	10-50	50-100	100-500	> 500
Group 1 (n = 64)	6	13	9	22	14
Group 2 (n = 33)	7	9	4	9	4
Total	13	22	13	31	18

Group 1: Patients with primary prostate cancer and bone metastases identified simultaneously. Group 2: Patients with bone metastases identified after disease confirmation and initiation of treatment. PSA = prostate-specific antigen.

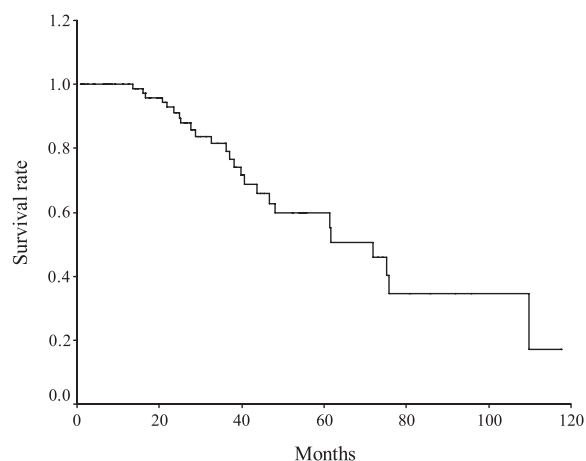


Fig. 1. Overall survival rate in 97 patients after diagnosis of prostate cancer (Kalpan-Meier method).

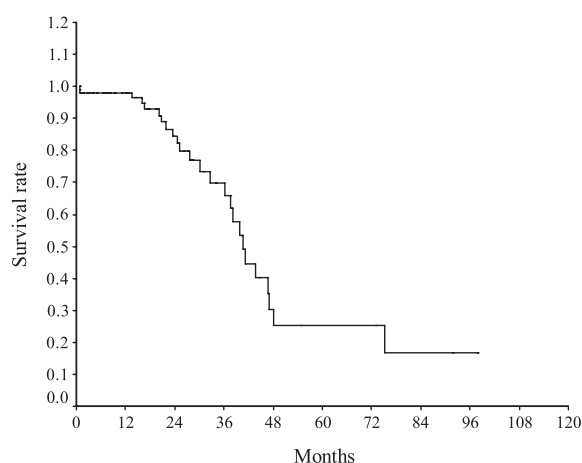


Fig. 2. Overall survival rate in 97 patients after development of bone metastases (Kalpan-Meier method).

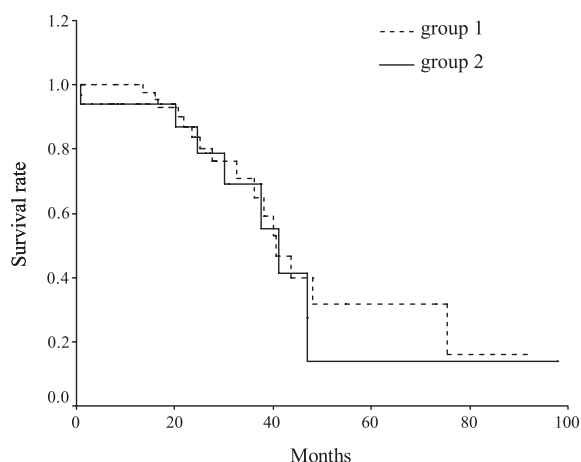


Fig. 3. Overall survival rate in group 1 (n = 64) and group 2 patients (n = 33) after development of bone metastases ($p = 0.487$).

fusion, but had limited neurologic recovery after operation. In these 97 patients, four patients had pathologic fractures of the proximal femur. Two of the four patients underwent hemiarthroplasty and the other two were treated by surgical fixation with implant and cement augmentation. All of

them had good pain relief after treatment of pathological femoral fractures.

Sixty-four patients were in group 1 and thirty-three were in group 2. In group 2, the average duration from confirmation of the disease to detection of bone metastases was 29.2 months (range: 2 to 83 mo). In group 1 (n = 64), 6 patients (9.37%) had a serum PSA value of less than 10 ng/mL, whereas in group 2 (n = 33), 7 patients (21.2%) had a serum PSA value of less than 10 ng/mL (Table 2). Bone scan was not regularly performed in group 2 patients during follow-up; however, it was arranged for 5 patients because they complained of bone pain and for 2 patients at their request.

The overall survival rate of these 97 patients after confirmation of prostate cancer was 81% after 3 years and 55% after 5 years (Fig. 1). When bone metastases were identified, the survival rate was 66% after 3 years and 25% after 5 years (Fig. 2). The survival rate after bone metastases was identified was not

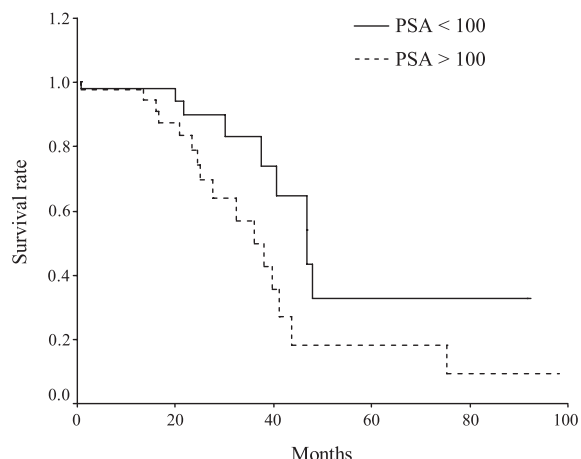


Fig. 4. Overall survival rates after development of bone metastases in patients with PSA > 100 ng/mL and PSA < 100 ng/mL at diagnosis of bone metastases ($p = 0.481$).

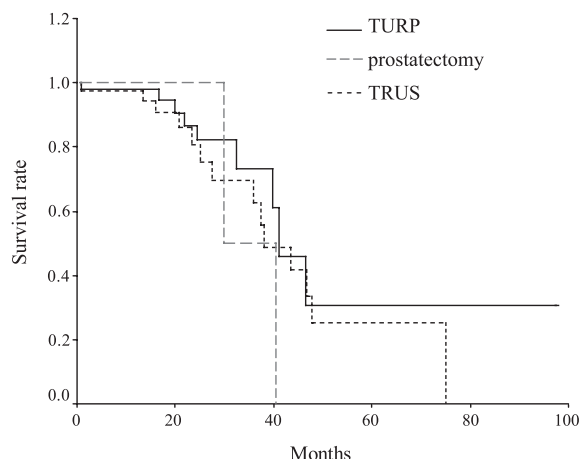


Fig. 5. Overall survival rates in patients treated by TURP ($n = 51$), TRUS ($n = 42$) and radical prostatectomy ($n = 4$) after development of bone metastases.

Table 3. Statistical analysis of prognostic factors and survival rates in 97 patients (log-rank test)

	No. of patients	<i>P</i>
Age (yr)		
> 70	55	0.424
< 70	42	
Location of bone metastases		
Only axial bone	53	0.481
Axial and appendicular	44	
Number of bone metastases		
Single	13	0.548
Multiple	84	
PSA (ng/mL)		
> 100	44	0.481
< 100	53	
> 50	63	0.486
< 50	34	

PSA = prostate-specific antigen.

statistically significant between group 1 and group 2 ($p = 0.487$) (Fig. 3). Furthermore, there was no statistical difference between survival rates in patients older than or younger than 70 years or in patients with a PSA level greater than or less than 50 ng/mL or in patients with a PSA level greater than or less than 100 ng/mL at first positive bone scan or in the location of bone metastases in this study ($p > 0.05$) (Table 3, Fig. 4). Analysis of survival after bone metastases were diagnosed revealed no statistical differences between TURP, prostatectomy and TRUS for primary prostate cancer (Fig. 5).

DISCUSSION

Metastasis has a poor prognosis in all prostate cancer patients. A 5-year actual survival rate of 60% and a 10-year actual survival rate of 20.5% were reported in stage D prostate cancer patients [8]. Survival of this type of prostate cancer is dependent on the patients' response to local treatment for primary tumor and other palliative treatments for the metastatic lesions. Hormonal therapy (androgen deprivation therapy) is a common treatment for prostate cancer, but unresponsiveness to hormone therapy frequently results in poor prognosis in patients with bone metastases [9]. Some patients treated with hormonal therapy become resistant to their treatment over a few months or years and thus develop hormone refractory prostate cancer [9]. Other choices of treatment for prostate cancer are surgery, radiation and chemotherapy: the response to those treatments determines the prognosis. In the present study, although we did not analyze the relationship between treatment methods and survival rates, we found that if bone metastases occurred in patients with prostate cancer, age, PSA level and the surgical treatments for primary prostate cancer did not appear to affect the outcome. Furthermore, the survival rates of patients with primary metastatic prostate cancer and patients with bone metastasis identified after

disease confirmation and initiation of treatment did not differ.

Bone is the most common site for prostate cancer metastasis, followed by lung and liver. In an autopsy study of metastasized prostate cancer, cancer cell metastases to bone, lymph node, lung and liver were 81%, 82.5%, 46.7% and 30.7% [2]. Bubendorf et al [1] also reported that the bone, lung and liver were the most frequent sites of distal metastases. Hematogenous spread is thought to be the major pathway for bone metastasis. In our study of bone metastatic patients, 64 patients (65.9%) had bone metastases at the same time prostate cancer was diagnosed. Axial bones (spines, pelvis and ribs) were the most commonly affected in prostate cancer patients in our study. Patients with an isolated metastasis in the pelvis or dorsal vertebrae have been reported to have better prognosis than those in whom metastases were either diffuse or involved more distal sites such as the skull or the sternum [9]. The extent of bone metastasis was shown to predict survival rate in metastatic prostate cancer patients [10-12]. Recently, the percentage of the positive area on a bone scan was reported to be a novel parameter for predicting the prognosis of patients with advanced prostate cancer [13]. Although the location and number of lesions of bone metastases did not influence the outcome of our study, further investigation may be needed to analyze the relationship between extended bone metastasis in patients with advanced prostate cancer and their survival rate. The presence of bone metastases accurately reflected the prognosis for all patients, and early detection of metastatic bone disease is a critical component that affects the clinical decisions made for that patient.

Although bone scan is a common and highly sensitive method for detecting bone metastases and localizing lesions, it has a high false positive rate. Bone pain is common in patients with bone metastasis, possibly due to structural damage, periosteal irritation, and nerve entrapment; however, not all patients with prostate cancer in our study presented with bone

pain. This is consistent with the results of a similar study in which 22% of prostate cancer patients did not have bone pain when bone metastasis was detected [14], indicating that bone pain is not a reliable indicator of the presence or the location of metastatic bone disease.

PSA level is another important parameter in the evaluation and follow-up of patients with bone metastases. Kageyama concluded that bone scans may not be necessary in patients with serum PSA levels less than 10 ng/mL, except in those with poorly differentiated adenocarcinoma [15]. Wolff et al [16,17] also excluded bone metastases when serum PSA value is less than 10 ng/mL in newly diagnosed prostate cancer, but they questioned whether a staging radionuclide bone scan should be omitted in patients with serum PSA value less than 10 ng/mL. Although the incidence of bone metastases in patients with newly diagnosed, untreated prostate cancer with initial PSA level less than 10 ng/mL is low, metastatic bone disease should not be excluded [18]. In our study, bone metastasis was diagnosed in 6 patients (9.37%) in group 1 and 7 patients (21.2%) in group 2 with PSA values less than 10 ng/mL. We support that when the PSA value is less than 10 ng/mL, bone metastases cannot be excluded, even in patients without bone pain. When PSA levels increase or when clinical symptoms of suspected bone affection appear, such as bone pain, bone scan is recommended to evaluate the possibility of bone metastases.

Pathologic fractures are a relatively late complication of bone involvement and are rarely associated with metastatic prostate cancer [19]. Osteoblastic (80%) and the less common osteolytic (5%) or mixed osteoblastic-osteolytic (10% to 15%) change have been seen in patients suffering from bone metastases [10]. Most osteoblastic lesions and rare osteolytic lesions of bone metastases are the reason for the low incidence of pathologic fractures in prostate cancer patients. Severe pain, instability and neurologic compression of the spinal cord may lead to significant morbidity and mortality of patients with pathologic fracture. When

pathologic fracture occurs, surgical treatment with fracture stabilization can provide patients with better function and good pain control [20]. Although cancer-specific survival for patients after surgery for prostate carcinoma which has metastasized to the bone is still poor [21], surgical treatment is still advised in this condition for pain relief and improvement of life quality. An impending pathological fracture can be treated with surgery, radiotherapy, chemotherapy or hormonal manipulation. Spinal cord compression is not rare in patients with prostate cancer [22] and back pain with abnormality on plain spinal radiograph is a warning sign for the development of spinal cord compression. Further investigations, including bone scan and magnetic resonance imaging (MRI) can point to the possibility of spinal metastases and cord compression. If the spinal cord is compressed and neurologic deficits develop, combined treatment of laminectomy, stabilization and radiotherapy has been reported to be associated with improved neurologic function and longer survival [23].

Bone metastases in prostate cancer patients are mostly localized to axial bones. Bone metastases may occur in patients with prostate cancer and a PSA level less than 10 ng/mL. Age, PSA level, and location of bone metastases do not appear to affect the outcome or the survival rates of treated and untreated prostate cancer patients with bone metastases.

REFERENCES

1. Bubendorf L, Schopfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1589 patients. *Hum Pathol* 2000;31:578-83.
2. Harada M, Iida M, Yamaguchi M, et al. Analysis of bone metastasis of prostatic adenocarcinoma in 137 autopsy cases. *Adv Exp Med Biol* 1992;324:173-82.
3. Galasko CS. Skeletal metastases. *Clin Orthop Relat Res* 1986;210:18-30.
4. Papapoulos SE, Hamdy NA, van der Pluijm G. Bisphosphonates in the management of prostate carcinoma metastatic to the skeleton. [Review] *Cancer* 2000;88(12 Suppl):3047-53.
5. McGregor B, Tulloch AG, Quinlan MF, et al. The role of bone scanning in the assessment of prostatic carcinoma. *Br J Urol* 1978;50:178-81.
6. Pollen JJ. The role of radiography, computed tomography and bone scanning in prostatic cancer. [Review] *Prostate* 1980;1:251-8.
7. Pollen JJ. Bone scanning in prostatic cancer. *Urology* 1981;17(Suppl 3):31-2.
8. Yamamoto N, Shimabukuro T, Matsuyama H, et al. Clinical study of prostate cancer--statistical analysis in the last 10 years. *Hinyokika Kyo* 1991;37:705-10. (In Japanese; English abstract)
9. Rana A, Chisholm GD, Khan M, et al. Pattern of bone metastasis and their prognostic significance in patients with carcinoma of the prostate. *Br J Urol* 1993;72:933-6.
10. Pontes JE, Choe B, Rose N, et al. Reliability of bone marrow acid phosphatase as a parameter of metastatic prostatic cancer. *J Urol* 1979;122:178-9.
11. Knudson G, Grinis G, Lopez-Majano V, et al. Bone scan as a stratification variable in advanced prostate cancer. *Cancer* 1991;68:316-20.
12. Kubota Y, Numasawa K, Suzuki H, et al. Studies on prognosis of prostate cancer with bone metastasis by using pretreatment bone scintigraphy. *Hinyokika Kyo* 1989;35:1693-9. (In Japanese; English abstract)
13. Noguchi M, Kikuchi H, Ishibashi M, et al. Percentage of the positive area of bone metastasis is an independent predictor of disease death in advanced prostate cancer. [Review] *Br J Cancer* 2003;88:195-201.
14. Palmer E, Henrikson B, McKusick K, et al. Pain as an indicator of bone metastasis. *Acta Radiol* 1988;29:445-9.
15. Kageyama Y, Kihara K, Kamata S, et al. Relationship between pretreatment serum levels of prostate specific antigen and bone metastasis in prostate cancer. *Hinyokika Kyo* 1996;42:197-9. (In Japanese; English abstract)
16. Wolff JM, Bares R, Jung PK, et al. Prostate-specific antigen as a marker of bone metastasis in patients with prostate cancer. *Urol Int* 1996;56:169-73.
17. Wolff JM, Zimny M, Borchers H, et al. Is prostate-specific antigen a reliable marker of bone metastasis in patients with newly diagnosed cancer of the prostate? *Eur Urol* 1998;33:376-81.
18. Lin K, Szabo Z, Chin BB, et al. The value of baseline bone scan in patients with newly diagnosed prostate cancer. *Clin Nucl Med* 1999;24:579-82.
19. Higinbotham NL, Marcove RC. The management of pathological fractures. *J Trauma* 1965;5:792-8.

20. Colyer RA. Surgical stabilization of pathological neoplastic fractures. [Review] *Curr Probl Cancer* 1986;10:117-68.
21. Cheville JC, Tindall D, Boelter C, et al. Metastatic prostate carcinoma to bone: clinical and pathologic features associated with cancer-specific survival. *Cancer* 2002;95:1028-36.
22. Rosenthal MA, Rosen D, Raghavan D, et al. Spinal cord compression in prostate cancer. A 10-year experience. *Br J Urol* 1992;69:530-3.
23. Tazi H, Manunta A, Rodriguez A, et al. Spinal cord compression in metastatic prostate cancer. *Eur Urol* 2003;44:527-32.

前列腺癌合併骨轉移：臨床表現

黃俊寅 許弘昌 張兆祥¹ 曾國峰 馮逸卿

中國醫藥大學附設醫院 骨科部 泌尿部¹

目的 骨轉移常發生在前列腺癌病人，引起併發症及死亡。攝護腺特異性抗(PSA)及骨骼掃描是評估及追蹤骨轉移的重要方法。我們回溯性分析前列腺癌合併骨轉移病人，包括臨床症狀、檢查數據、治療、預後及其相關性。

方法 從1995年1月至2003年12月間，有284位前列腺癌病人在中國醫藥大學附設醫院住院治療。有97位病人被診斷骨轉移，臨床病例詳細查閱及紀錄。另外，我們將病人分成兩組：第一組病人是在診斷前列腺癌同時發現骨轉移；第二組病人是骨轉移發生在治療中的前列腺癌。

結果 前列腺癌的骨轉移病人佔34.2% (97/284)。在97位骨轉移病人中，診斷前列腺癌時平均年齡71.5歲。轉移中軸骨多於四肢骨，69位(71.1%)病人在診斷骨轉移時有骨骼疼痛，而28位(28.8%)病人沒有。第一組中有6個病人，而在第二組有7個病人診斷骨轉移時的PSA < 10 ng/mL。四個病人因股骨病理性骨折接受手術，皆得到很好的疼痛解除。骨轉移後的生存率在第一、二組間並沒有統計學上的差別($p > 0.05$)。前列腺癌診斷時的年紀、骨轉移時的PSA值、最初的骨骼轉移位置及數量並沒有影響生存率($p > 0.05$)。

結論 PSA值是前列腺癌病人重要的轉移與追蹤指標，當病人的PSA < 10 ng/mL時，骨骼轉移仍無法排除。發生骨轉移後，生存率在未治療及治療過的前列腺癌是沒有差別的，病人的年紀，PSA值及骨轉移位置亦不影響結果。(中台灣醫誌 2006;11:82-9)

關鍵詞

骨轉移，前列腺癌，攝護腺特異性抗原

聯絡作者：馮逸卿

地址：404台中市北區育德路2號

中國醫藥大學附設醫院 骨科部

收文日期：2005年6月7日

修改日期：2005年9月6日

接受日期：2006年3月29日