

Retrospective analysis of risk factors for bone metastasis in newly diagnosed prostate cancer patients

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Abstract. – OBJECTIVE: The aim of the study was to analyze the clinical data of newly diagnosed prostate cancer (PCa) patients with bone metastasis and to explore the relevant risk factors.

PATIENTS AND METHODS: The clinical data of 251 patients with PCa, who were initially diagnosed in our hospital from February 2015 to October 2021, were retrospectively analyzed. According to the whole-body bone scan results, patients were divided into the bone metastasis group (n = 66) and the non-bone metastasis group (n = 185). The patient's age, total prostate-specific antigen (TPSA), free PSA (fPSA), prostate volume, alkaline phosphatase (ALP), Gleason score, erythrocyte sedimentation rate (ESR), and pelvic lymph node metastasis were collected. Univariate correlation and multivariate regression analyses, together with receiver operating characteristic curve, were used to analyze PCa bone metastasis-related factors.

RESULTS: The incidence of bone metastasis in newly diagnosed PCa was about 26.29% (66/251). Among them, the incidence of pelvic metastasis was the highest, at 78.78% (52/251), and multiple bone metastases were significantly higher than single bone metastasis (80.31% vs. 19.69%). Univariate correlation analysis indicated that age, Gleason score, ESR, TPSA, ALP, fPSA/PSA, capsular infiltration, and pelvic lymph node metastasis ($p < 0.05$) were highly correlated with PCa bone metastasis. Multivariate Logistic regression analysis showed that TPSA (95% CI: 0.977-1.284, $p = 0.007$), ALP (95% CI: 1.008-1.080, $p = 0.016$), Gleasons core (95% CI: 2.110-82.349, $p = 0.006$), ESR (95% CI: 1.062-1.104, $p = 0.003$), and pelvic lymph node metastasis (95% CI: 1.537-33.239, $p = 0.012$) were independent risk factors for bone metastasis of PCa. The cut-off values for TPSA, ALP, Gleason score, and ESR were 33.78 ng/ml, 73.65 U/L, 7.5, and 23.5 mm/h, respectively. Additionally, the respective sensitivities for TPSA, ALP, Gleason score, and ESR were 81.8%, 75.8%, 68.2% and 77.3%, and the respective specificities was 90.3%, 98.9%, 98.4%, and 74.6%.

CONCLUSIONS: TPSA, ALP, Gleason score, ESR and pelvic lymph node metastasis are independent risk factors for bone metastasis of PCa.

Key Words:

Prostate cancer, Prostate-specific antigen, Risk factors, Gleason score, Alkaline phosphatase.

Introduction

Prostate cancer (PCa), as the most common malignant tumor in men and the second leading cause of death in men with cancer, is most prone to bone metastasis¹. The rate of bone metastasis in metastatic PCa patients is as high as 90%²⁻⁴. Severe bone pain, pathological fractures, nerve compression, and other skeletal-related events (SREs) occur after PCa bone metastases, which seriously affect the patient's quality of life⁵⁻⁶. Studies have shown that the mortality rate of PCa patients with bone metastasis is significantly higher than that of those without, with greater harm caused by bone metastasis rather than PCa itself⁷. Therefore, early detection of bone metastasis has important clinical significance for treatment options and prognosis in PCa patients.

At present, the ^{99m}Tc-MDP bone scan is the most commonly used method for diagnosing bone metastasis of PCa, which can image the whole body at one time with high sensitivity^{7,8}. ^{99m}Tc MDP bone scan found bone metastasis 3-6 months earlier than X-ray, but its cost is high and has certain radiation hazards^{7,8}. Therefore, it is of great clinical value to explore the risk factors for bone metastasis of PCa, and to perform early warning and ^{99m}Tc MDP bone scan in high-risk groups for early prediction of bone metastasis. Previous literature^{2,9-12} reports that bone metastasis of PCa may be related to age, Gleason score,

total prostate-specific antigen (TPSA), alkaline phosphatase (ALP), and other factors, but the opinions of different studies are inconsistent. In this study, the clinical data of 251 patients with newly diagnosed PCa were analyzed by univariate and multivariate logistic regression to explore the characteristics and related risk factors of bone metastasis of PCa, so as to provide references for early detection of bone metastasis of PCa.

Patients and Methods

Research Criteria

The clinical data of 251 patients with PCa, initially diagnosed in our hospital from February 2015 to October 2021, were retrospectively analyzed. Inclusion criteria were as follows: pathologically confirmed prostate adenocarcinoma following transrectal ultrasound-guided prostate biopsy or surgery; newly diagnosed cases; and no history of other tumors. The exclusion criteria were: non-prostate cancer patients; bone metastases caused by other malignant tumors; patients with severe infection and active liver disease; and incomplete medical records. This study was approved by the Ethics Committee of General Hospital of Northern Theater Command PLA and was carried out according to the Declaration of Helsinki. All research subjects signed the informed consent form.

Diagnostic Criteria for Bone Metastasis of PCa

Bone metastasis of PCa was diagnosed by ^{99m}Tc -MDP bone scanning. ^{99m}Tc -MDP whole-body bone scan, which is a sensitive and non-invasive method commonly used to screen for the bone metastasis of various malignant tumors. It has an important diagnostic value for bone metastasis of PCa^{13,14}. The bone scan pictures were jointly reviewed by two or more deputy chief physicians and judged according to the Soloway grading standard¹³⁻¹⁶. The Soloway grading standard was as follows: no bone metastasis (negative): grade 0; with bone metastasis (positive): grade I with 1 to 2 metastases, grade II with 3 to 5, and grade III with > 5 ¹³⁻¹⁶.

Clinical Data Collection

According to the whole-body bone scan results, patients were divided into the bone metastasis group ($n = 66$) and the non-bone metastasis group ($n = 185$). The age, TPSA, FPSA, prostate volume,

ALP, Gleason score, ESR, lymph node metastasis, and other indicators of the two groups were collected for statistical analysis. TPSA, FPSA, ALP, and ESR were measured using an early morning fasting vein. TPSA and FPSA were detected by a fully automatic time-resolved fluorescence immunoassay analyzer from Wallac Oy, Finland. The serum ALP value was detected by a 7170 automatic biochemical analyzer (Hitachi, Japan). The ESR was detected using an automatic erythrocyte sedimentation instrument Roller 20LC. A PHILIPS HD-11 GE-VOLUSON 730 EXPERT color Doppler ultrasound diagnostic instrument (Philips Healthcare, Inc., Amsterdam, The Netherlands) was also used to measure the anteroposterior, transverse, and cephalocaudal diameters of the prostate. The prostate volume was then determined according to the following formula: prostate volume = (anteroposterior diameter x transverse diameter x cephalocaudal diameter) $\times \pi/6$.

Statistical Analysis

Statistical analysis was performed using the SPSS 20.0 software (IBM Corp., Armonk, NY, USA). Normally distributed data are presented as mean \pm SD, and non-normally distributed data are presented as median. The t -test was used for the comparison of normally distributed data between groups, the Mann-Whitney U test for non-normally distributed data, and the χ^2 test for the rate test. Univariate and multivariate logistic regression analysis was used for correlation analysis of bone metastasis in PCa. The ROC curve was used to determine the best cut-off value of the analytical factors. $p < 0.05$ was considered statistically significant.

Results

General Features of PCa Bone Metastases

As shown in Figure 1A, a total of 251 PCa patients were included in this study, of which 66 (26.29%) had bone metastasis and 185 (73.71%) had non-bone metastasis. As shown in Figure 1B, the specific cases of bone metastasis are as follows: 52 pelvic metastasis (78.78%), 41 spinal metastasis (62.12%), 38 rib metastasis (57.57%), 23 extremity long bone metastasis (34.84%), 21 scapula metastasis (31.81%), 21 sternum metastasis (31.81%), 11 skull metastasis (16.67%) and 8 clavicle metastasis (12.12%). As shown in Figure 1C, only 13 cases (19.69%) of patients with bone

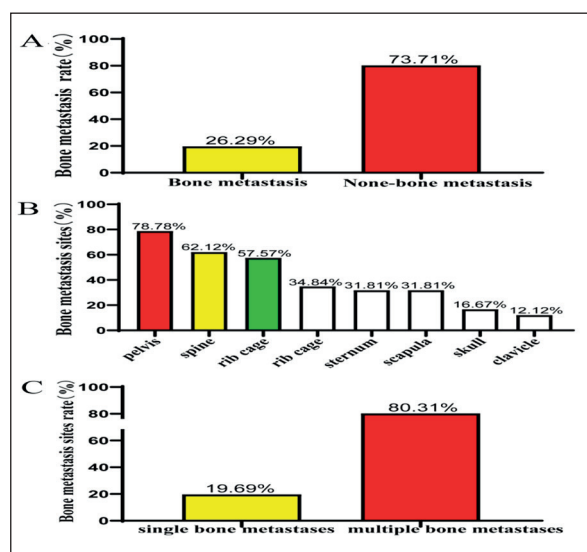


Figure 1. General features of PCa bone metastases. **A**, Rate of patients with PCa bone metastasis. **B**, Distribution of bone metastasis sites in PCa. **C**, The ratio of single and multiple bone metastases in PCa.

metastasis had single bone metastasis, and the remaining 53 cases (80.31%) had multiple bone metastasis. The results suggest that prostate cancer is most prone to pelvic metastases, followed by spine and ribs, and bone metastasis are often multiple metastases.

Comparison of Clinical Data Between Bone Metastasis Group and Non-bone Metastasis Group

As shown in Table I, the results of univariate correlation analysis indicated no significant differences in prostate volume, diabetes, hyperten-

sion, and coronary heart disease between the two groups ($p < 0.05$). However, there were significant statistical differences between the two groups in age ($p < 0.001$), Gleason score ($p < 0.001$), ESR ($p < 0.001$), TPSA ($p < 0.001$), ALP ($p < 0.001$), fPSA/PSA ($p = 0.035$), capsular infiltration ($p < 0.001$) and pelvic lymph node metastasis ($p < 0.001$).

Logistic Regression Analysis of Bone Metastasis of PCa

As shown in Table II, multivariate logistic regression analysis found that TPSA (95%CI: 0.977-1.284, $p = 0.007$), ALP (95% CI:1.008-1.080, $p = 0.016$), Gleasonscore (95%CI: 2.110-82.349, $p = 0.006$), ESR (95%CI: 1.062~1.104, $p = 0.003$) and pelvic lymph node metastasis (95%CI: 1.537-33.239, $p = 0.012$) were independent risk factors for bone metastasis of newly diagnosed PCa.

ROC Curve, Cut-Off Value, Sensitivity and Specificity Analysis of TPSA, ALP, Gleason Score, ESR, and Pelvic Lymph Node Metastasis

As shown in Table III and Figure 2, when the cut-off value for TPSA was 33.78 ng/ml, the area under the curve of TPSA was 0.911, and the sensitivity and specificity were 81.8% and 90.3%, respectively. By contrast, when the cut-off value for ALP was 73.65 U/L, the area under the curve of ALP was 0.896, and the respective sensitivity and specificity values were 75.8% and 98.9%. When the cut-off value for Gleason score was 7.5, the three values were 0.881, 68.2% and 98.4%, respectively. Moreover, the area under the curve of ESR was 0.746, and the sensitivity and specificity

Table I. Clinical characteristics of PCa bone metastasis group and non-bone metastasis group.

Parameter	Bone metastasis (n = 66)	Non-bone metastasis (n = 185)	p-value
Age	75.45 ± 5.71	68.97 ± 7.41	< 0.001
TPSA	254.77 ± 525.63	18.84 ± 14.52	< 0.001
fPSA/PSA	0.13 ± 0.16	0.34 ± 0.81	0.035
ALP	156.45 ± 86.91	55.85 ± 12.64	< 0.001
Gleason score	8.02 ± 0.88	6.73 ± 0.48	< 0.001
ESR	32.40 ± 16.53	19.07 ± 12.71	< 0.001
Prostate volume	46.14 ± 24.68	51.88 ± 21.26	0.073
Capsular infiltration	41/66 (62.12%)	21/185 (11.35%)	< 0.001
Pelvic lymph node metastasis	38/66 (57.57%)	34/185 (18.38%)	< 0.001
Diabetes	15/66 (22.72%)	36/185 (19.46%)	0.571
Hypertension	24/66 (36.36%)	55/185 (29.73%)	0.391
Coronary heart disease	10/66 (15.15%)	30/185 (16.25%)	0.993

ESR: erythrocyte sedimentation rate; TPSA: total prostate specific antigen; fPSA/PSA: free prostate specific antigen/total prostate specific antigen; ALP: serum alkaline phosphatase.

Table II. Logistic regression analysis of bone metastasis of PCa.

Parameter	β value	OR	95% CI	p-value
Age	0.113	1.120	0.977-1.284	0.104
TPSA	0.038	1.038	1.010-1.067	0.007*
fPSA/PSA	-1.921	0.146	0.003-6.367	0.318
ALP	0.043	1.043	1.008-1.080	0.016*
Gleason score	2.579	13.182	2.110-82.349	0.006*
ESR	0.060	1.062	1.062-1.104	0.003*
Pelvic lymph node metastasis	1.967	7.148	1.537-33.239	0.012*
Capsular infiltration	1.192	4.445	0.801-24.663	0.088

ESR: erythrocyte sedimentation rate; TPSA: total prostate specific antigen; fPSA/PSA: free prostate specific antigen/total prostate specific antigen; ALP: serum alkaline phosphatase.

were 77.3% and 74.6%, respectively, when the cut-off value for ESR was 23.5 mm/h. In the case of pelvic lymph node metastasis positive, the area under the curve for pelvic lymph node metastasis was 0.696, and the sensitivity and specificity were 77.3% and 74.6%, respectively.

Discussion

PCa is an osteophilic malignancy, and more than 70% of patients with advanced PCa develop bone metastasis, further leading to bone metabolism disorder, which can cause pathological fractures, spinal cord compression, hypercalcemia, and other SREs¹⁷. 41.9% of PCa patients with bone metastasis develop SREs within 2 years after the diagnosis of the metastasis^{18,19}. SREs not only impair the quality of life, but also increase the economic burden and mortality of patients^{18,19}. Therefore, it is imperative to assess the presence of bone metastasis in patients with early diagnosis of PCa, so as to take corresponding treatment measures to improve the overall survival rate and the occurrence of SREs in patients with PCa. There has been literature²⁰⁻²² reporting that the rate of metastasis from newly diagnosed PCa is as

high as 22%, of which the rate of bone metastasis is about 3-19%. In this study, we found that the incidence of bone metastasis in newly diagnosed PCa was 26.29% (66/251). In China, this result is significantly higher than that in Europe and in the United States, which may be due to the aging population and the laggard promotion of PSA screening in the country. In this study, we also found that the pelvis, spine, and ribs are the most prone to bone metastasis from PCa, which is mainly due to the existence of the Batson's venous plexus between the low lumbar vertebrae and the prostate tissue, through which tumor cells readily metastasize to bone^{23,24}.

Studies^{25,26} have shown that age is a risk factor for PCa morbidity and mortality. However, the relationship between age and bone metastasis of PCa is inconsistent in many studies. For example, Briganti et al²¹ suggested that age was not a risk factor for PCa bone metastasis, but, Merdan et al²⁷ reported the opposite. In this study, we found that older patients tend to suffer from bone metastasis as their age was significantly higher than those in the non-bone metastasis group, but multivariate logistic regression analysis found that age was not a risk factor for PCa bone metastasis. The reasons for the inconsistent results may be related to

Table III. ROC curve, cut-off value, sensitivity and specificity analyses of TPSA, ALP, Gleason score, ESR, and pelvic lymph node metastasis.

Parameter	Cut-off value	Specificity	Sensitivity	AUC	95% CI
TPSA	33.78	90.3%	81.8%	0.911	0.866~0.956
ALP	73.65	98.9%	75.8%	0.896	0.839~0.953
Gleason score	7.5	98.4%	68.2%	0.881	0.829~0.932
ESR	23.5	74.6%	77.3%	0.838	0.783~0.892
Pelvic lymph node metastasis	+	81.6%	57.57%	0.696	0.617~0.755

ESR: erythrocyte sedimentation rate; TPSA: total prostate specific antigen; ALP: serum alkaline phosphatase.

differences in sample size, and geographical and racial differences among studies. PSA in serum is one of the critical indicators for screening and diagnosing PCa. Studies have shown that when PSA > 100 ng/mL, the probability of bone metastasis of PCa is as high as 41.4% or even 79.9%, but when PSA < 20 ng/mL, the probability is lower^{12,28,29}. Previous literature reports^{21,27} suggest that PSA is an independent risk factor for PCa bone metastasis. In this study, we also found that the serum PSA level in the bone metastasis group was significantly higher than that in the non-metastasis group, and logistic regression analysis showed that PSA level was one of the risk factors for predicting bone metastasis from PCa. In addition, we found that the cut-off value of PSA was 33.78 ng/mL, meaning that, when PSA > 33.78 ng/mL, the probability of bone metastasis was higher, the sensitivity was 81.8%, and the specificity was 90.3%. Although this study found that PSA can be used to predict PCa bone metastases, caution should be taken in PCa patients with low PSA³⁰. Studies³⁰ have shown that some PCa patients with low PSA levels and high Gleason scores have bone metastases on bone scans. Because of the poor ability to express PSA in very poorly differentiated PCa tissues, bone metastases occurred despite low PSA levels³⁰.

ALP is a monolipid phosphohydrolase and a commonly used clinical marker of bone formation. ALP has a certain specificity for the diagnosis of PCa bone metastasis, but its sensitivity is low, and its level often increases significantly after extensive metastasis³¹. Basically consistent with literature reports, this study found that the serum ALP level in the bone metastasis group was significantly higher than that in the non-bone metastasis group, proving that ALP was an independent risk factor for PCa bone metastasis^{32,33}. In addition, the cut-off value of ALP was 73.65 U/L, meaning that, when ALP > 73.65 U/L, the probability of bone metastasis was higher, the sensitivity was 75.8%, and the specificity was 98.9%. However, since ALP has multiple isoenzymes and is affected by diseases of the skeletal system diseases and hepatobiliary system diseases, other lesions need to be excluded when diagnosing PCa metastasis^{32,33}. ESR is significantly elevated in malignant tumors, especially in highly malignant and rapidly growing tumors, and represents an independent risk factor for many tumors³⁴⁻³⁶. Previous studies^{35,36} have reported that, when ESR > 20 mm/h, it can be an independent risk factor for distinguishing invasive and non-invasive PCa, while high ESR is

an indicator of increased risk of PCa progression and death. In this study, we found that the level of ESR in the bone metastasis group was significantly higher than in the non-bone metastasis group, so ESR was an independent risk factor for PCa bone metastasis. When ESR > 23.5 mm/h, the probability of bone metastasis was higher, the sensitivity was 77.3%, and the specificity was 75.6%. However, since many factors can affect the elevated ESR level, when using ESR to predict bone metastasis of PCa, we recommend combining other indicators and excluding factors that interfere with the elevated ESR^{35,36}.

As the most commonly used method for grading PCa, the Gleason scoring system is an effective indicator for evaluating the degree of tumor malignancy^{37,38}. The European Association of Urology (EAU) guidelines point out that patients with PCa should be assessed for bone metastasis when PSA > 20 ng/ml or Gleason score > 7^{37,38}. American Society of Urology (AUA) guidelines indicate that patients with PCa are more likely to have bone metastasis when the Gleason score is higher than 8³⁸. In this study, we found that the Gleason score of the bone metastasis group was significantly higher than that of the non-bone metastasis group, and that was an independent risk factor for bone metastasis of PCa. At the same time, the cut-off value of Gleason score was 7.5, meaning that, when the Gleason score was greater than 7.5, the probability of bone metastasis was higher, the sensitivity was 68.2%, and the specificity was 98.4%. Studies^{39, 40} have shown that about 41% of newly diagnosed PCa patients developed lymph node metastasis, and some PCa can develop distant metastasis through lymph or blood when the primary tumor was less than 1 cm. Lymph node metastasis of PCa strongly indicates the presence of distal organ metastasis and poor prognosis^{41,42}. In this study, we found that pelvic lymph node metastasis was an independent risk factor for prostate cancer bone metastasis through multivariate regression analysis. Pelvic lymph node metastasis had a predictive value for the occurrence of PCa bone metastasis, with a sensitivity and specificity of 77.3% and 74.6%, respectively.

Conclusions

This study showed that TPSA, ALP, Gleason score, ESR, and pelvic lymph node metastasis were highly correlated with PCa bone metastasis

and were independent risk factors for PCa bone metastasis. For PCa patients with TPSA > 33.78 ng/mL, ALP > 73.65 U/L, ESR > 23.5 mm/h, and Gleason score > 7.5, whole-body bone imaging should be actively performed. For PCa found to have lymph node metastases, the risk of bone metastases should be highly guarded.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

Thanks to the General Hospital of Northern Theater Command PLA for research support.

Ethics Approval

Research was in accordance with Declaration of Helsinki. The study was approved by General Hospital of Northern Theater Command PLA Ethical Committee.

Informed Consent

Informed written consent has been obtained from each patient following explanation of any study-related procedures.

Authors' Contribution

CP, IG, CJ, WA, YJH and TRL conceived the study, designed the data collection tool and performed the study. Data were analyzed by CP, IG, CJ, WA, YJH and TRL. The manuscript was written by CP, IG, CJ, WA, YJH and TRL. The manuscript was reviewed and edited by all authors.

Funding

The study was supported by General Hospital of Northern Theater Command PLA.

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