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Research paper

Risk factors for bone metastasis from renal cell cancer

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ABSTRACT

Objective: The prognosis for renal cell carcinoma (RCC) is related to a high rate of metastasis, including 30% of bone metastasis. In this study, we investigate the correlation between diverse clinical factors and bone metastases secondary from renal cell cancer (RCC), and to identify potential risk factors for bone metastasis in newly diagnosed patients and those who have already received treatment.

Methods: The clinical data of 372 patients with RCC were reviewed from January 2000 to August 2016. The correlations between age, gender, histopathologic types, alkaline phosphotase (ALP), CEA, AFP, CA-125, CA-153, CA-199, calcium, hemoglobin (HB) and bone metastases were analyzed. And the risk factors for bone metastases in RCC were identified by multivariate logistic regression analysis. The cutoff value, sensitivity and specificity of the independent correlation factors were calculated by receiver operating characteristic (ROC) curve.

Results: The bone is the second to the lung as a distant metastasis target site in patients with RCC. Thirty eight individuals were identified with bone metastases. Of these patients, significantly higher levels of ALP, calcium, HB were found than those without bone metastasis ($P < 0.05$, respectively). No significant differences were detected in CEA, AFP, CA-125, CA-153, CA-199, age, gender and histopathologic types between patients with and without bone metastases ($P > 0.05$, respectively). Multivariate logistic regression analysis indicated that ALP, calcium and HB were independent risk factors correlated with bone metastasis ($P < 0.05$, respectively). ROC curves demonstrated these factors had comparable accuracy at predicting bone metastasis (AUC were 0.749, 0.633 and 0.665, respectively). The cutoff values of ALP, calcium and HB were 105.5 U/L, 2.615 mmol/L and 111.5 g/L, respectively. The sensitivities of them were 57.9%, 36.8% and 71.1% for predicting bone metastasis, with specificities of 83.5%, 95.2% and 65.3%, respectively.

Conclusion: Based on our study, the concentrations of ALP, calcium and HB were potentially risk factors for bone metastasis in patients with RCC. For newly diagnosed patients, if the values of ALP > 105.5 U/L, calcium > 2.615 mmol/L and HB < 111.5 g/L were detected, intensive monitoring and bone scanning are warranted for them.

1. Introduction

Renal cell cancer (RCC) runs up to 3% of malignant tumors in human beings each year, and surgical resection of these tumors generally results in excellent long-term disease-free survival [1]. However, studies revealed that 20–50% of patients present with locally advanced and distant metastatic disease [2]. Moreover, patients with metastatic RCC (mRCC) of other organs represent an unfavorable subset of individuals. Especially the occurrence of the bone metastasis is widely accepted as a significant prognostic factor of life expectancy of patients [3].

Diagnosis of patients with bone metastasis currently primarily relies on plain X-ray, bone scanning, computed tomography (CT) and magnetic resonance imaging (MRI). The cost of these tests is expensive and early bone metastatic lesions may not be easily detected by imaging studies [4,5]. Given that, the early discovery of the occurrence of bone metastases will significantly influences the choice of RCC treatment. Identifying readily available and valuable risk factor is a meaningful clinical benefit for timely intervention to prevent and delay bone metastasis. Furthermore, these risk factors could help to avoid bone scanning and intensive monitoring for patients at a low risk of bone metastasis [5].

Many studies have attempted to identify risk factors of progression, prognosis and reaction to therapy in the patients with bone metastasis.

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Recently, several serum tumor markers, including alkaline phosphate (ALP) [6], calcium [7] and hemoglobin (HB) [8] have been extensively investigated and considered to be potentially predictive or prognostic factors for patients with bone metastases from cancer. However, risk factors for bone metastasis from RCC had been examined in a few studies and some results remained controversial. There are still no standard definition of risk factors and cut-off levels specifically [9]. The purpose of the current study was to investigate the correlation between clinical–pathological parameters, biomarkers, and bone metastases in RCC at the time of diagnosis, and to identified some independent risk factors for definition of patients with RCC at 'high risk' of bone metastases.

2. Materials and methods

2.1. Patient selection

This study was approved by the medical research ethics committee of the First Affiliated Hospital of Nanchang University.

A retrospective study was carried out and a series of consecutive patients with RCC between January 2000 and August 2016 were included in this study. All the patients were confirmed with primary RCC based on the histopathologic analysis of specimens obtained by needle biopsy or radical nephrectomy. And bone metastases were diagnosed by bone scanning and other organs metastases was diagnosed by plain X-ray, CT or MRI. Patients presenting with concomitant pathologies that could potentially affect the evaluation of the risk factors were excluded from this study, such as bone metabolic disorders, hyperparathyroidism, hepatic dysfunction and other malignant tumors.

2.2. Data collection

Demographics and clinical characteristics of patients in this study included: patients' age at diagnosis of the primary tumor, gender, treatment for RCC, histopathologic types, metastases sites, laboratory findings at diagnosis of the primary tumor, such as ALP (140 U/L was considered to be the upper normal limit), calcium (2.6 mmol/L was considered to be the upper normal limit) and HB, common tumor markers (serum CEA, AFP, CA125, CA153 and CA199 values were determined in the same laboratory, the normal range was 0–6.5 ng/ml, 0–7 ng/ml, 0–35 U/ml, 0–25 U/ml, 0–27 U/ml, respectively). All the above factors were retrospectively collected and reviewed. The correlation between clinical parameters and bone metastases was analyzed, and the risk factors for bone metastases in RCC were identified.

2.3. Statistical analysis

Quantitative variables were reported as means ± standard deviation and compared with Independent sample t-test or Univariate analysis. Qualitative variables were expressed as numbers and percentages, and were assessed by the Chi-square test. The independent risk factors related to bone metastases were analyzed by Multivariate logistic regression analysis model. The sensitivity and specificity were calculated based upon optimal cut off scores. Accuracy was determined by the area under the curve (AUC), calculated from receiver operating characteristic (ROC) curves. Statistical significance was set as P value less than 0.05. All analysis was performed by IBM SPSS Version 22 (SPSS Inc. Chicago IL).

3. Results

3.1. Patient demographics

A total of 372 patients with RCC were included in this study. The patients' demographics were demonstrated in Table 1. The majority of the patients were man (233 cases, 62.6%) and most of the histopathologic types of them were clear cell carcinoma (280 cases, 75.3%). Of these patients, 111 patients with mRCC were identified. The distribution of metastatic organs was demonstrated in Table 1.

Table 1
Baseline characteristics of patients with RCC.

Patient characteristics	n (%)
Primary site	
Right	183(49.2)
Left	188(50.5)
Bilateral	1(0.3)
Age at diagnosis(years)	
Median	56
Range	3–86
Gender	
Man	233 (62.6)
Female	139 (37.4)
Histopathological type, n (%)	
Clear cell	280 (75.3)
Chromophobe	24 (6.4)
Papillary	24 (6.4)
Multilocular cystic	10 (2.7)
Other	11 (3)
Sarcomatoid	7 (1.9)
Undifferentiated	8 (2.2)
Granular cell	6 (1.6)
Radiological diagnosis	2 (0.5)
No. of patients with mRCC	111
Gender	
Man	76 (68.5)
Female	35 (31.5)
Site of metastases	
Lung	41 (36.9)
Bone	38 (34.2)
Lymph node	37 (33.3)
Liver	12 (10.8)
Brain	5 (4.5)
Adrenal	4 (3.6)
Other	26 (23.4)

Note: RCC, renal cell carcinoma; mRCC, metastases RCC.

3.2. The metastatic organs and sites of RCC in patients with different ages

The rate of old patients with mRCC was higher than that of young patients (58.6% vs 41.4%, young patients defined as individuals aged < 55 years [10]). For the metastatic organs second from RCC, young patients were easy to get bone and lymph node metastases. However, lung metastases were more common in old patients. The number of patients with single site metastases was larger than those patients with two or more metastatic sites (67 cases vs 44 cases). And the rate of patients with concomitant metastases decreased as age increasing (Table 2).

3.3. Distribution of bone metastases from RCC

The bone was second to the lung as a distant metastasis target site in patients with RCC. We detected 38 patients with bone metastases in this

Table 2
The metastatic organs and sites of RCC in patients with different ages.

	Overall	< 55 years	≥55 years	$\chi 2$	P-value
No. of mRCC patients	111	46(41.4)	65(58.6)	–	–
Lung	41(36.9)	15(32.6)	26(40)	0.632	0.427
Bone	38(34.2)	19(41.3)	19(29.23)	1.744	0.187
Lymph node	37(33.3)	21(45.7)	16(24.6)	5.364	0.021
No. of metastatic sites					
1	67(60.4)	17(36.9)	38(58.5)	3.936	0.047
≥2	44(39.6)	29(63.1)	27(41.5)		

Note: Patients, n (%) (N = 111).