The risk factors for bone metastases in patients with colorectal cancer

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Abstract
This retrospective analysis aims to evaluate the potential risk factors for bone metastases (BM) in patients who were diagnosed with colorectal cancer (CRC).

A total of 2790 patients diagnosed with CRC between January 2006 and December 2016 were collected in this study. All patients were divided into 2 groups, BM and no BM. The associations between biomarkers (including age, gender, histopathological types, alkaline phosphatase (ALP), carcinoembryonic antigen (CEA), cancer antigen 125, and so on), and BM in patients with CRC were analyzed. All the analyses were conducted by SPSS software (version 22.0, SPSS, Chicago, IL).

Of all patients, 74 (2.7%) were identified with BM. The level of serum ALP, CEA, and cancer antigen 125 in patients with BM were obviously higher than those without BM (P < .001, P = .005, and P < .001). And the cut-off values of ALP, CEA, and cancer antigen 125 were 85.5 U/L, 6.9 mmol/L, and 16.8 mmol/L, respectively.

ALP, CEA, and cancer antigen 125 were identified as the independent risk factors for BM in patients with CRC.

Abbreviations: ALP = alkaline phosphatase, AUC = area under the curve, BM = bone metastases, CA199 = cancer antigen 125 (CA125) and cancer antigen 199, CEA = carcinoembryonic antigen, CRC = colorectal cancer, ROC = receiver operating characteristic.

Keywords: bone metastases (BM), colorectal cancer (CRC), risk factors

1. Introduction
Colorectal cancer (CRC) is a commonly malignant tumors and is the main cause of cancer-related death in patients,[1–3] with approximately 1.2 million new cases occurred each year.[4] So far, surgery remained the most important option for treating CRC, but 30% of patients still developed metastases.[5] It was well known that liver and lung were the most common sites of distant metastases in CRC. But bone is also one of the commonly distant metastasis locations.[6–8] Although the median survival of patients with CRC was significantly improved, the risk of bone metastases (BM) was also increased. In addition, patients with BM will suffer a series of complications and skeletal-related event (SRE) due to bone destruction such as pain, pathological fractures, spinal cord compression, and hypercalcemia,[5,6,9,10] which would decrease the quality of patients’ life.[8,9] Although imaging study is still the primary method for diagnosing BM, it could not provide enough information for early diagnosis.[11] Thus, it is necessary to find a way to detect BM in patients with CRC for early diagnosing and treatment. The purpose of this study was to investigate the association between clinical parameters and BM, and to identify the risk factors for early detecting BM from CRC.

2. Materials and methods

2.1. Patient selection

This study was approved by the ethics committee of the First Affiliated Hospital of Nanchang University. A retrospective study was conducted and patients newly diagnosed with CRC between January 2006 and December 2016 were included in this study. All these diagnoses were confirmed by histopathological examination. And the diagnosing of patients with BM mainly relied on imaging studies, including computed tomography (CT) scan, magnetic resonance imaging (MRI), and bone scan. Patients who suffered from primary tumor other than CRC at the same time were excluded from this study.

2.2. Date collection

In this retrospective study, the demographic characteristics of patients with CRC were collected, such as the age, gender, histopathological types, the location of the original tumor (colon and rectal), serum level of calcium, hemoglobin, alkaline phosphatase (ALP), carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), and cancer antigen 199 (CA199) at the time of primary diagnosis. The associations between biomarkers and BM in patients with CRC were analyzed.
2.3. Statistical analysis

All the analyses were conducted by SPSS software (version 22.0, SPSS, Chicago, IL). The continuous variables in this study were expressed as mean ± standard deviation. Patients with CRC were divided into 2 groups: bone metastasis (BM) and none bone metastasis (NBM). And Chi-square test, Fisher exact test and Student t test were used to determine the differences between the 2 groups. Then, the independent risk factors for bone metastasis in patients with CRC were identified by binary logistic regression analysis. In additions, receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was calculated, which was used to assess the accuracy of predicting the risk factors for BM. A value of P less than .05 was defined as statistically significant.

3. Results

3.1. Patient demographics

In this study, a total of 2790 patients diagnosed with CRC were included in it. Of these patients, 1635 (59.3%) were male and 1135 (40.7%) were female, with an average age of 58 years (ranged from 15 to 95 years). Table 1 demonstrates the demographic characteristics of patients with CRC. Among these patients, rectal cancer accounted for 52.33%, colon cancer account for 47.63%, and only 0.01% of them identified with both rectal and colon cancer. The main histopathological type of these patients was adenocarcinoma (86.49%). Other histopathological types included mucinous adenocarcinoma (8.35%), signet ring cell carcinoma (0.75%), neuroendocrine cancer (0.25%), and so on.

3.2. Distribution of bone metastases in patients with CRC

The distribution of BM in CRC patients is described in Table 2. Seventy-four patients were identified with BM, and 43 (58.11%) were male and 31 (41.89%) were female. Of these patients, the most common histopathological type was adenocarcinoma, which accounted for 87.84%. For the site of bone metastasis, the most common one was the spine (62.16%), followed by pelvis (55.40%) and ribs (12.16%). According to the number of BM sites, patients with BM can be divided into 3 subgroups: metastasis to 1 site (67.57%), metastasis to 2 sites (25.67%), and metastasis to 3 and more sites (6.76%).

3.3. Risk factors for bone metastasis in patients with colorectal cancer

In order to find out the risk factors for bone metastasis in patients with CRC, comparison was conducted for different variables between patients in bone metastasis and none bone metastasis groups (Table 3). For gender and tumor histopathological types,
there were no statistically significant differences between the 2 groups \((P=.830\) and \(P=.203\)). Also, no significant differences were found for serum calcium and hemoglobin between patients with and without BM \((P>.05\), respectively). However, patients with BM had higher concentrations of ALP, CEA, CA199, and CA125 than those without BM \((P<.001, P=.00, P<0.001,\) and \(P=.031\), respectively). Binary logistic regression analysis indicated that ALP \((\text{OR}=1.007, P<.001)\), CEA \((\text{OR}=1.001, P=.016)\), and CA125 \((\text{OR}=1.008, P<.001)\) were identified to be the independent risk factors for bone metastasis in CRC (Table 4).

### 3.4. The cut-off values, sensitivities, and specificities of risk factors for predicting bone metastases

Figure 1 and Table 5 show the accuracy, sensitivity, and specificity of the single-factor and multifactor for predicting the risk of developing BM in patients with CRC. It was found that ALP had the highest diagnostic accuracy for predicting the risk of BM \((\text{AUC}=0.829, P<.001)\), with a sensitivity and specificity of

**Table 4**

| Factors | \(\beta\) | OR | OR (95% CI) | \(P\) |
|---------|----------|----|-------------|------|
| ALP     | 0.007    | 1.007 | 1.004–1.010 | <.001|
| CEA     | 0.001    | 1.001 | 1.000–1.002 | .016 |
| CA199   | 0.000    | 1.000 | 0.999–1.001 | .836 |
| CA125   | 0.008    | 1.008 | 1.004–1.012 | <.001|
| HB      | 0.000    | 1.000 | 0.989–1.010 | .941 |

\(\beta=\) coefficient of regression, \(\text{ALP}=\) alkaline phosphatase, \(\text{CA125}=\) cancer antigen 125, \(\text{CA199}=\) cancer antigen 199, \(\text{CEA}=\) carcinoembryonic antigen, \(\text{CI}=\) confidence interval, \(\text{HB}=\) hemoglobin, \(\text{OR}=\) odds ratio.

Figure 1. The receiver operating characteristics (ROC) curves of single risk factor for diagnosing bone metastases in patients with colorectal cancer. (A) The ROC of ALP. (B) The ROC of CEA. (C) The ROC of CA125.
81.1% and 71.5%, respectively. And the cut-off values of ALP, CEA, and CA125 were 85.5 U/L, 6.9 mmol/L, and 16.8 mmol/L, respectively.

In combination with ALP, CEA, and CA125, it had the highest diagnostic value for identifying BM in patients with CRC (AUC = 0.874, P < .001) (Fig. 2).

| Factors         | Cutoff value | Sensitivity (%) | Specificity (%) | AUC     | 95% CI       | P     |
|-----------------|--------------|-----------------|-----------------|---------|--------------|-------|
| ALP             | 85.5 U/L     | 81.1            | 71.5            | 0.829   | 0.786–0.871  | <.001 |
| CEA             | 6.9 mmol/L   | 81.1            | 70.6            | 0.791   | 0.743–0.838  | <.001 |
| CA125           | 16.8 mmol/L  | 82.4            | 71.8            | 0.804   | 0.761–0.846  | <.001 |
| CEA + ALP       | 86.6         | 69.5            | 69.5            | 0.845   | 0.803–0.887  | <.001 |
| CEA + CA125     | 86.5         | 68.9            | 82.0            | 0.830   | 0.790–0.869  | <.001 |
| ALP + CA125     | 87.8         | 71.0            | 71.0            | 0.864   | 0.833–0.895  | <.001 |
| CEA + CA125 + ALP | 85.1      | 76.6            | 76.6            | 0.874   | 0.844–0.904  | <.001 |

ALP = alkaline phosphatase, AUC = area under curve, CA125 = cancer antigen 125, CEA = carcinoembryonic antigen, CI = confidence interval.
Bone metastasis is not common in CRC and early diagnosis is relatively difficult. The percentage of BM from patients with primary CRC was between 3.7% and 27%. Compared with previous studies, the incidence of BM from CRC in this study was a little low (2.8%). Vatandoust et al reported that signet ring cell cancer of CRC had a high rate of BM (up to 23.7%). But in this study, the rate of signet ring cell carcinoma was low (0.75%). The reason for it may be the number of patients with BM was small in our study. It was well-known that BM often suggested that the cancer had reached a late stage with a poor prognosis. After BM, patients usually suffer a lot of skeletal-related event (SRES), including bone pain, pathological fractures, and spinal cord compression. Thus, in order to dearly diagnose BM and could reduce the radiation from X-ray for BM, biomarkers as the risk factors for predicting BM from CRC, which was consistent with previous studies, the incidence of BM from CRC in this study was a little low (0.75%). The reason for it may be the number of patients with BM was small in our study. It was well-known that BM often suggested that the cancer had reached a late stage with a poor prognosis. After BM, patients usually suffer a lot of skeletal-related event (SRES), including bone pain, pathological fractures, and spinal cord compression. Thus, in order to dearly diagnose BM and could reduce the radiation from X-ray for BM, biomarkers as the risk factors for predicting BM from CRC, which was consistent with previous studies, the incidence of BM from CRC in this study was a little low (0.75%). The reason for it may be the number of patients with BM was small in our study. 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CA125 is a glycoprotein produced by normal epithelial tissue and is often found overexpressed in cancerous tissues. Serum CA125 level was mainly used for the diagnosis, treatment response monitoring, and cancer recurrence of ovarian cancer. Shi et al reported that serum CA125 could help diagnose liver metastases from pancreatic ductal adenocarcinomas and provided a suitable simultaneous resection protocol. CA125 could potentially predict the curability of gastric and cardia cancers, and it was the risk factor of distant metastasis from gastric and cardia cancers. However, to our knowledge, few studies analyzed the relationship between CA125 and bone metastasis in CRC. In this study, the concentration of CA125 > 16.8 mmol/L was identified to be one of risk factors for diagnosing BM from CRC, which indicated that CRC patients with the serum CA125 level > 16.8 mmol/L were more likely to develop BM.

Although several risk factors were successfully identified in our study, there were still some limitations in it. First, this was a retrospective study, and the data of patients was just obtained from a single medical institution. Second, some data were lost in our study, such as survival duration and the time to BM. And some data were not reported in the medical reports, including the grade of CRC, intervention, and lymph node metastasis, which would affect the clinical results of this study. Third, the sample size of this study was not large enough. A larger sample patient and multicenter study is helpful to verify the results of our study.

In summary, based on a large population analysis, we successfully identified high serum concentrations of ALP, CEA, and CA125 as the potentially independent risk factors for detecting BM from CRC patients. The specificity of ALP, CEA, and CA125 for detecting BM were 71.5%, 70.6%, and 71.8%, respectively. And the accuracy of ALP, CEA, and CA125 for diagnosing BM were 82.9%, 79.1%, and 80.4%, respectively. MICI/GDF15 as a bone metastasis biomarker, the specificity of it for detecting bone metastasis from prostate cancer, breast cancer, lung cancer, and CRC was 90%, and the accuracy for detecting bone metastasis was 87%, which was higher than our outcome of single factor. But, combined ALP, CEA, and CA125, the specificity and accuracy for diagnosing BM from CRC can also reach 76.6% and 87.4%, respectively. Combined ALP, CEA, and CA125 have the highest specificity and accuracy for diagnosing BM from CRC. Thus, for a newly diagnosed CRC patient with ALP > 85.5 U/L, CEA > 6.9 mmol/L, and CA125 > 16.8 mmol/L, physicians should pay attention to the BM of them. Because of the limitations in this study, a large sample patients and multicenter study is useful to validate these results.
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