Original Article

Diagnostic value of CYFRA 21-1, CEA, and CA125 for bone metastasis of lung cancer

Jian-jun He[1], Ke Zhi[2], Guo-feng Liu[3], Hai-Yan Zhang[4]

ABSTRACT

Objective: To evaluate the sensitivity, specificity, and accuracy of the serum tumor markers cytokeratin 19 fragment (CYFRA 21-1), carcinoembryonic antigen (CEA) and cancer antigen 125 (CA125) in the diagnosis of bone metastases in patients with lung cancer.

Methodology: A total of 134 patients with lung cancer, diagnosed by pathological examination or bronchoscopic biopsy, as well as 105 healthy subjects, were enrolled in the study. The cancer patients were divided into a metastasis-negative group, a localized metastasis group (1 to 2 metastases), and an extensive metastasis group (3 or more metastases). Serum levels of CYFRA 21-1, CEA, and CA125 were measured in each subject. The diagnostic efficiency of three tumor markers, used alone or in combination, was assessed using ROC analysis and compared with that of X-ray, CT, and emission computed tomography (ECT).

Results: The levels of CYFRA 21-1, CEA, and CA125 were highest in patients with extensive metastasis, and lowest in patients without metastasis. The optimal cutoff value of CYFRA 21-1, CEA, and CA125 for diagnosing bone metastasis of lung cancer was 42.59 ng/ml (AUC: 0.908), 36.35 ng/ml (AUC: 0.854) and 36.21 U/ml (AUC: 0.786), respectively. The combined use of CYFRA 21-1, CEA, and CA125 was more sensitive than X-ray and more specific than CT.

Conclusions: Combined determination of CYFRA 21-1, CEA, and CA125 can significantly improve accuracy and positive rates of diagnosis of bone metastasis in patients with lung cancer. Compared with imaging methods, serological detection is simple, rapid, and highly cost-effective.

KEY WORDS: Bone metastasis of lung cancer, CYFRA 21-1, carcinoembryonic antigen, CA125 antigen.

Pak J Med Sci January - March 2012 Vol. 28 No. 1 175-178

How to cite this article:

He JJ, Zhi K, Liu GF, Zhang HY. Diagnostic value of CYFRA 21-1, CEA, and CA125 for bone metastasis of lung cancer. Pak J Med Sci 2012;28(1):175-178

INTRODUCTION

Bone metastasis (BM) commonly occurs in lung cancer. Early detection and treatment of bone metastases can not only improve the quality of life of these patients, but also significantly reduce mortality.[1-3] However, in current practice, bone metastasis is primarily diagnosed through imaging modalities. X-rays have high specificity but low sensitivity, and thus positive results can be obtained only when over 50% of the trabecular structure has been destroyed and the diameter of the lesions exceeds 1cm. In contrast, computed tomography (CT) has high sensitivity but relatively low specificity. Emission computed tomography (ECT) is currently the gold standard for the diagnosis of bone metastases. Detecting the selective deposition of radioisotope tracers in the metastasis, ECT is capable of identifying lesions with a diameter as small as 2mm, allowing them to be diagnosed 3 to 6 months earlier than using X-rays. Unfortunately, ECT is quite expensive to perform on a large-scale

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* Received for Publication: November 15, 2010
* Revision Received: October 20, 2011
* Revision Accepted: November 25, 2011

basis.[4,5] Hence, there exists a pressing need to find cheaper yet equally useful diagnostic alternatives for detecting bone metastasis of lung cancer.

Cytokeratin 19 (CYFRA 21-1) is a type-I acidic keratin with a molecular weight of approximately 40,000. In malignant epithelial cells, activated proteases accelerate cellular degradation, releasing an abundance of cytokeratin fragments into the circulation. Previous studies have established that CYFRA 21-1 is highly expressed in malignant lung cancers, particularly squamous cell carcinoma. Accumulating evidence has confirmed that CYFRA 21-1 is of great value in the diagnosis of lung cancer, especially for non-small cell lung cancer (NSCLC). Carcinoembryonic antigen (CEA) is a glycoprotein normally produced during fetal development, with serum levels normally very low in healthy adults.

However, cancer cells, which have lost polarity, secrete CEA into the blood and lymph circulation, resulting in elevated CEA levels in the blood. As a result, testing of serum CEA levels plays an important role in judging efficacy, monitoring progression, and predicting prognosis in lung cancer patients. Cancer antigen 125 (CA125) was first identified through the immunological detection of epithelial ovarian carcinoma, and is known to bind to monoclonal antibody OC125. CA125 is not a specific marker for ovarian cancer, as its levels may increase in fallopian tube adenocarcinoma, endometrial cancer, cervical cancer, pancreatic cancer, intestinal cancer, breast cancer, and lung cancer. CYFRA 21-1, CEA, and CA125 are often used together for lung cancer diagnosis. Studies have shown that CYFRA 21-1 and CEA levels are closely correlated with the development, course, and stage of lung cancer.[6-8]

The purpose of the current study was to investigate the potential correlation between levels of the tumor markers CYFRA 21-1, CEA, and CA125 and the presence and extent of bone metastasis in patients with lung cancer, and to compare their specificity and sensitivity, when used alone and in combination, with the imaging modalities conventionally used to diagnose this condition.

METHODOLOGY

Subjects: A total of 134 patients with lung cancer were enrolled in the study (78 men and 56 women; age range, 42–78 y), including 26 localized metastasis cases (18 men and 8 women; age range, 44–76 y), 40 extensive metastasis cases (28 men and 22 women; age range, 49–78 y) and 68 Non-Metastasis cases (45 men and 23 women; age range, 42–74y). All lung cancer patients were diagnosed by bronchoscopic biopsy or postoperative pathological examination. The control group included 105 healthy subjects (67 men and 38 women; age range, 40–79y) who underwent a routine physical examination at our institution. Primary bone disease, breast cancer, renal cancer, prostate cancer, and other diseases potentially predisposing to bone metastasis were excluded in all participants. All subjects provided informed consent, and the study protocol was approved by the ethnical committee of Central South University (Changsha, China).

Methods:

Measurement of CYFRA 21-1, CEA, and CA125 serum levels: Serum levels of CYFRA 21-1, CEA, and CA125 were determined using an automatic electrochemical analyzer (Cabas®6000, Roche, Germany). All fasting blood samples were collected between 7:30 a.m. and 8:30 a.m., and were centrifuged 30 to 45 min after collection. All tests on the sera were completed before 12:00 a.m. on the day of sampling, and no hemolysis occurred. All reagents underwent stringent quality control testing.

Diagnosis of bone metastases: A whole-body radionuclide bone scan was performed 3 –5 h after intravenous administration of 555–740 MBq of 99mTC-MDP (15–20 mCi) (Chengdu Gaotong Isotope Corporation, Chengdu, Sichuan, China) using a SkyLight variable-angle dual-head SPECT nuclear camera (Philips Healthcare, Andover, MA, USA). The diagnosis of BM was established by a combination of X-rays, computed tomography (CT) scans, and follow-up results.

Statistical Analysis: Measurement data are presented as mean ± standard derivation. Comparison of mean values between different

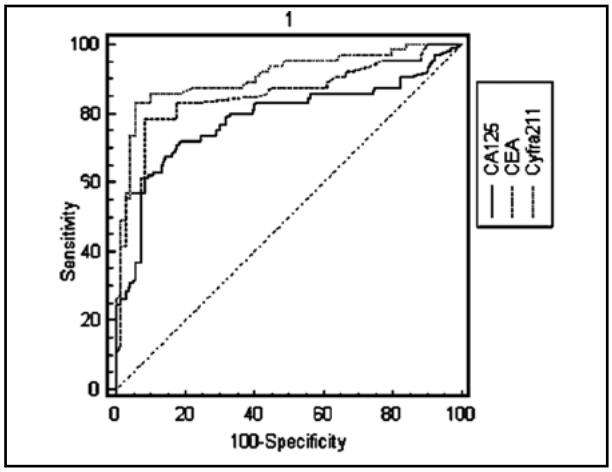

Fig.1. Sensitivity, specificity, and AUC area of CYFRA 21-1, CEA, and CA125 in the diagnosis of lung cancer bone metastases.

Table-I: Serum levels of tumor markers CYFRA 21-1, CEA, and CA125 in lung cancer patients and healthy subjects.

Serum marker	*Control group (n = 105)*	*Metastasis-negative group (n = 68)*	*Localized metastasis group (n = 26)*	*Extensive metastasis group (n = 40)*
CYFRA 21-1 (ng/ml)	4.93 ± 0.25	29.20 ± 17.10*	65.10 ± 16.80*,**	85.10 ± 23.80*, **,***
CEA (ng/ml)	4.32 ± 0.27	16.99 ± 4.13*	31.70 ± 15.09*,**	50.70 ± 15.09*,**,***
CA125 (U/ml)	14.32 ± 6.35	28.61 ± 19.12*	39.64 ± 18.11*,**	69.64 ± 24.11*,**,***

Note: * $p < 0.05$ compared to control group; ** $p < 0.05$, localized metastasis group compared to metastasis-negative group; *** $p < 0.05$, extensive metastasis group compared to localized metastasis group, $p<0.05$

groups was performed using the unpaired t test. P values less than 0.05 were considered to be statistically significant. ROC curves were constructed using Medcalc for Windows (version 8.0.1.0; MedCalc Software, Mariakerke, Belgium), and the area under the ROC curve was calculated.

RESULTS

Serum levels of the tumor markers CYFRA 21-1, CEA, and CA125 in healthy subjects and in lung cancer patients with extensive, localized, or no bone metastases: As shown in Table-I, the mean serum levels of CYFRA 21-1, CEA, and CA125 were significantly lower in healthy subjects than in lung cancer patients. Among the three subgroups of lung cancer patients, the serum levels of each of the three tumor markers were lowest in patients with no metastasis and highest in patients with extensive metastases. The most pronounced such increase was observed in the average serum levels of CYFRA 21-1, which showed a nearly 18-fold increase in patients with extensive metastases compared to healthy controls (85.10 ± 23.80 vs. 4.93 ± 0.25, respectively).

Sensitivity, specificity, and AUC area of CYFRA 21-1, CEA, and CA125 for diagnosis of bone metastasis of lung cancer using ROC analysis: ROC curves were generated by setting CYFRA 21-1, CEA, and CA125 as the test variables, Disease State as the state variable, and defining the value of the state variable as one. The upper-left-most point on the curve was defined as the optimal cutoff point, which was used to calculate the sensitivity, specificity, and AUC area of the three serological markers. The results of ROC analysis are presented in Table-II and Fig.1.

Of the three serum markers, CYFRA 21-1 had the highest diagnostic value, with a sensitivity of 83.08% and a specificity of 94.20% at the optimal cutoff value of 42.59 ng/ml. In contrast, the sensitivity and specificity of CA125 at its optimal cutoff were 72.31% and 81.16, respectively, which were the lowest among the three serum markers.

Diagnostic efficiency of CYFRA 21-1, CEA, and CA125 for bone metastasis of lung cancer when used alone versus in combination: The diagnostic value of the three serum markers when used in combination was superior to that of any of the three used alone, yielding a sensitivity of 92.05% and a specificity of 92.80% (Table-III).

Comparison of diagnostic efficiency between X-ray, CT, and ECT and the combined use of CYFRA 21-1, CEA, and CA125: Combined use of the three serum markers was much more sensitive than X-ray and much more specific than CT. The diagnostic efficiency of the combination of the three serum tumor markers approached that of ECT, the method currently preferred for diagnosing bone metastases (Table-IV).

DISCUSSION

In patients with lung cancer, it is critical to diagnose bone metastases as early as possible. Identifying one or more serum biomarkers more sensitive than imaging examinations would allow earlier and more effective treatment, and improve the prognosis of these patients. During the development and progression of lung cancer, changes in serum CYFRA 21-1 levels often precede both the onset of clinical symptoms and the emergence of detectable lesions on imaging

Table-II: Sensitivity, specificity, and AUC area of CYFRA 21-1, CEA, and CA125 for diagnosis of bone metastasis of lung cancer

Serum marker	*Optimal cutoff value*	*Sensitivity*	*Specificity*	*Positive likelihood ratio*	*Negative likelihood ratio*	*Positive predictive value*	*Negative predictive value*	*AUC area*
CYFRA 21-1	42.59	83.08	94.20	14.33	0.18	93.1	85.5	0.908
CEA	36.35	78.46	91.30	9.02	0.24	89.5	81.8	0.854
CA125	36.21	72.31	81.16	3.84	0.34	78.3	75.7	0.786

Table-III: Diagnostic efficiency of CYFRA 21-1, CEA, and CA125 used alone or in combination for bone metastasis of lung cancer

Serum marker	*Cutoff value*	*Sensitivity*	*Specificity*
CYFRA 21-1	42.59 ng/ml	83.08	94.20
CEA	36.35 ng/ml	78.46	91.30
CA125	36.21 U/ml	72.31	81.16
CYFRA 21-1+CEA+CA125		92.05	92.80

Note: when CYFRA 21-1, CEA, and CA125 were used in combination for diagnosis, a positive diagnosis was defined as either CYFRA 21-1 or CEA or both giving a positive result.

examinations.[8] Monitoring serum CYFRA 21-1 levels also allows the clinician to evaluate a patient's response to treatment.[6] For example, a precipitous decrease in CYFRA 21-1 levels, or a return to the normal serum range, is a reliable indicator of effective treatment, whereas persistently elevated levels of this marker can indicate either incomplete removal of a tumor or the possible presence of multiple lesions. Despite this, few studies have thus far assessed the diagnostic and prognostic value of CYFRA 21-1 and the related markers CEA and CA125 for bone metastasis of lung cancer.[9]

In the current study, we measured the serum levels of CYFRA 21-1, CEA, and CA125 in 134 patients with lung cancer and 105 healthy subjects. Our results showed that serum levels of CYFRA 21-1, CEA, and CA125 are each significantly higher in lung cancer patients than in healthy controls. In addition, serum levels of CYFRA 21-1, CEA, and CA125 all tended to increase with disease severity, with the highest levels found in patients with extensive metastases and the lowest levels in patients with no metastases. Together, these data suggest that the extent of bone metastases is positively correlated with the serum levels of CYFRA 21-1, CEA, and CA125.

ROC analysis demonstrated that CYFRA 21-1 and CEA were each highly accurate in diagnosing bone metastasis of lung cancer, the AUC of both exceeding 0.85. Both CYFRA 21-1 and CEA yielded high positive and negative predicative values at their respective optimal cut-off values. In contrast, measurement of serum CA125 failed to accurately diagnose bone metastases in these patients.

The combined use of tumor markers has been demonstrated to improve diagnostic efficiency. Therefore, we compared the sensitivity of CYFRA 21-1, CEA, and CA125, used alone or in combination. We found that using a combination of CYFRA 21-1, CEA, and CA125 improved the sensitivity, while retaining good specificity for diagnosing bone metastases in these patients. This combination of three markers outperformed X-ray in sensitivity and CT in specificity. Hence, use of these three serum markers in combination may offer a more economical, rapid, reproducible, and cost-effective diagnostic algorithm for lung cancer bone metastases compared to the currently used imaging modalities. In conclusion, the serum tumor markers CYFRA 21-1, CEA, and CA125 appear to be of high clinical value for early diagnosis of lung cancer bone metastases. The combined use of CYFRA 21-1, CEA and CA125 is useful for early diagnosis, the design and timing of treatment, and the reduction of both surgical pain and the medical expenses associated with bone metastases from lung cancer.

Table-IV: Comparison of diagnostic efficiency of the combination of CYFRA 21-1, CEA, and CA125 versus X-ray, CT, and ECT.

Diagnostic method	*Sensitivity*	*Specificity*
CYFRA 21-1+CEA+CA125	92.05	92.80
X-ray	34.50	92.20
CT	89.50	42.50
ECT	95.30	94.60

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