RESEARCH ARTICLE

Clinical Observations on the Association Between Diagnosis of Lung Cancer and Serum Tumor Markers in Combination

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Abstract

Objective: To evaluate the association of a diagnosis of lung cancer and combined detection of serum carcinoembryonic antigen (CEA), carbohydrateantigen 19-9 (CA19-9), neuron specific enolase (NSE) as well as the cytokeratin 19 fragment (CYFRA21-1). Methods: Serum CEA, CA19-9, NSE and CYFRA21-1 were assessed in 150 patients with lung cancer, 100 patients with benign lung disease and 100 normal control subjects, and differences of expression were compared in each group, and joint effects of these tumor markers in the diagnosis of lung cancer were analyzed. Results: Serum CEA, CA19-9, NSE and CYFRA21-1 in patients with lung cancer were significantly higher than those with benign lung disease and normal controls (p<0.01). It is suggested that these four tumor markers combined together could produce a positive detection rate of 90.2%, significantly higher than that of any single test. Conclusion: Combination detection of CEA, CA19-9, NSE and CYFRA21-1 could significantly improve the sensitivity and specificity in diagnosis of lung cancer, and could be important in early detection.

Keywords: Lung cancer - CEA - CA199 - NSE - CYFRA21-1

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Introduction

Lung cancer is one of the most common malignant tumors, with high mortality rate worldwide, and still demonstrating a rising trend yearly (Parkin et al., 2005; Liu et al., 2013; Lu et al., 2013). In China, lung cancer is more common than stomach and liver cancer, and is the first cause of death from malignant tumors (Hu et al., 2013). However, conventional disgnositc methods, eg., imaging, fiber bronchoscope, cytology and histopathologic is difficult for early detection of lung cancer (Malik et al., 2013). Recently, tumor markers is suggested to be a usefull tool in this setting, especially in early diagnosis of lung cancer (Buccheri et al., 2002; Schneider et al., 2002; Kav et al., 2012). On this background, we developed a method of joint detection of serum carcinoembryonic antigen (CEA), carbohydrateantigen 19-9 (CA19-9), neuron specific enolase (NSE) as well as cytokeratin 19 fragment (CYFRA21-1). The current study is to test our hypothesis that this method is superior to conventional methods.

Materials and Methods

Study subjects

From March 2011 to February 2013, 150 patients with lung cancer were retrospectively recruited. Among these patients 89 were male, 61 were female; aged 38-69 years, average 54.8 years. All lung cancer patients were by pathologically or cytologically confirmed. Patients with lung benign disease were diagnosed with pulmonary tuberculosis, pneumonia and bronchiectasis, totally 100 patients. Among these patients with non-cancer benign disease, 58 were male, 42 female, aged 24 to 72 years. Control group was consisted by 100 subjects (59 male and 41 female, aged 9-22 years) who underwent healthy physical examination.

Study materials and methods

Peripheral morning fasting blood were obtained from all study subjects. To isolate serum for subsequent testing, centrifugation was set as 2000 turn/RPM for 15 minutes. Chemiluminescence immunoassay was used to electrochemically detect CEA, CA19-9, NSE and CYFRA21-1, and all experiment operating was in strict accordance with the instructions authorised by instrument and reagent kit.

Evaluation

Negative testing was set if CEA < 5.0 ng/ml, CA19-9 < 37 U/ml, NSE < 15.0 ng/ml, and CYFRA21-1 < 3.3 ng/ml, otherwise positive if specimen serum tumor markers detected equal to or greater than the upper limit of above mentioned value.

Statistical analysis

SPSS13.0 statistical software was used for statistical analysis. Enumeration data was expressed as $\overline{\chi}\pm s$;

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Table 1. Comparison of CEA, CA199, NSE and CYFRA21-1 in Different Groups ($\bar{\chi}$±s, %)

Groups	Number of patients	CEA (ng/ml)	CA199 (U/ml)	NSE (ng/ml)	CYFRA21-1 (ng/ml)
Lung cancer	150	45.56±21.68	65.82±15.36	28.52±15.53	23.55±13.86
Lung benign disease	100	5.13±3.14	21.71±9.84	13.86±9.74	3.35±1.46
Normal control	100	4.45±2.78	19.89±7.23	11.85±7.59	2.99±1.86

Table 2. Comparison of CEA, CA199, NSE and CYFRA21-1 in Normal Control and Lung Cancer Patients with Different Stages ($\bar{\chi}$±s, %)

Groups	Number of patients	CEA (ng/ml)	CA199 (U/ml)	NSE (ng/ml)	CYFRA21-1 (ng/ml)
Normal control	100	3.42±1.78	12.89±7.23	11.15±7.09	2.55±1.86
StageI-II	53	23.51±11.63	43.54±17.62	21.26±10.08	11.55±6.46
Stage III-IV	38	75.42±17.72	88.19±21.63	37.87±14.19	35.98±11.48

Table 3. Sensitivity and Specificity (%) of Tumor Marker and Its Combinations in Detecting Patients with Lung Cancer

Tumor Marker	Sensitivity (%)	Specificity (%)
CEA	39.45	73.53
CA199	43.76	78.34
CYFRA21-1	58.42	91.52
NSE	52.78	84.52
CEA + CA199 + CYFRA21-1	86.67	83.24
CEA + CA199 + NSE	76.28	79.61
CA199 + CYFRA21-1 + NSE	82.75	87.92
CEA + CA199 + CYFRA21-1 + NSE	90.16	75.64

comparison between groups was conducted using univariable analysis of variance. Statistically significant difference is defined when p value < 0.05.

Results

Serum level of CEA, CA19-9, NSE and CYFRA21-1 in patients with lung cancer were significantly higher than those with lung benign disease or control (p< 0.01). This difference was not detected betweeen subjects with lung benign disease and healthy controls (p> 0.05) (Table 1).

Compared with lung cancer patients in stage Ior II, patients staged III or IVdemonstrated significantly higher CEA, CA19-9, NSE and CYFRA21-1 level (P < 0.01) (Table 2).

The sensitivity of these four serum tumor markers was different when seperately conducted in the diagnosis for lung cancer, rank from high to low, CYFRA21-1 > NSE > CA199 > CEA; regarding specificity, from high to low, CYFRA21-1 > NSE > CA199 > CEA. In terms of joint detection, CEA + CA19-9 + NSE + CYFRA21-1 suggested to be a combination with highest sensitivity (90. 16%), followed by CEA + CA19-9 + CYFRA21-1 (86. 67%), and CA199 + CYFRA21-1 + NSE (82. 75%) (Table 3).

Discussion

Lung cancer is one of the most common malignant tumors, with high mortality rate worldwide, and still demonstrating a rising trend yearly (Liu et al., 2013; Lu et al., 2013). Early detection of lung cancer, and early treatment could significantly improve the response rate, and prolong survival time of patients (Parkin et al., 2005). Tumor markers, that are produced by tumor cells and released into blood or body fluids are considered to be associated with the process of tumorigenesis and tumor development (Cho et al., 2009; Hu et al., 2013; Lu et al., 2013). Detection of tumor markers is reported to be an useful tool in the diagnosis of lung cancer and could be an indicator for mornitoring curative effect as well as prognosis for patients with lung cancer. This study suggests that a number of tumor markers might associated with lung cancer, and a single test could result in misdiagnosis. Therefore, our purpose is to develop a diagnostic system to improve sensitivity, and specificity on lung cancer screening.

At present CEA is mainly used in the diagnosis of gastrointestinal cancer, however, it is reported that the sensitivity of CEA is around 35% to 77% (Ramshankar et al., 2013), our study suggested that the sensitivity of CEA in detecting lung cancer was 39.45%, and the specificity was 73.53%, that is in accordance with previous reports. Another finding of our study is that serum CEA in patients with lung cancer were significantly higher than those with benign disease and healthy controls (p< 0.05), indicating that CEA could be used in early diagnosis of lung cancer.

CA19-9 tumor associated antigen is commonly used in patient with pancreas, liver, and colorectal cancers .Now, it is confirmed that CA199 is an important marker in diagnosis of lung cancer, and the sensitivity in detecting lung cancer was 43.76%, specificity was 78.34% (Bilgin et al., 2013). In this study, serum CA199 in patients with lung cancer were significantly higher than those with lung benign disease and healthy controls (p< 0.05), suggesting CA199 is of importance in the diagnosis of lung cancer.

CYFRA21-1 is mainly distributed in monolayer and stratifiedepithelium and in the cytoplasm of tumor cells. The sensitivily of CYFRA21-1 was 55% - 70% for lung cancer , and the specificity was 70% - 80%. Therefore it is considered to be the best tumor marker in detection of lung squamous cell carcinoma (Ardizzoni et al., 2006). Our study demonstrated that the sensitivity of CYFRA21-1 in detecting lung cancer was 58.42%,the specificity was 91.52%.Level of CYFRA21-1 in serum of patients with lung cancer were significantly higher than those with lung benign disease and healthy controls suggesting the CYFRA21-1 is important in early diagnosis of lung cancer.

NSE is an important tumor marker for neuroblastoma and small cell lung cancer (Bilgin et al., 2013). Current study suggested that the sensitivity of NSE in detection of lung cancer was 52.78%, and the specificity was 84.52%. Its content in serum of patients with lung cancer

were significantly higher than those with lung benign disease and healthy controls ($p< 0.05$), suggesting that it is important in the diagnosis of lung cancer,especially small cell lung cancer.

Clinical and pathological research found that lung cancer is heterogeneous (Oguz et al., 2013). To improve the diagnostic sensitivity and specificity, severed tumor markers, combined together could be more effective in the diagnosis of lung cancer. Our results showed that CEA, CA19-9, NSE and CYFRA21-1 as a single detection of lung cancer, CYFRA21-1 is a marker bearing the highest sensitivity with positive rate of 58.42%. When CEA, CA199 and CYFRA21-1 combined together, the sensitivity was 86.67%, and specificity 83.24%; instead, if CEA, CA199 and NSE combined together, the sensitivity was 76.28%, specificity 79.61%; most high sensitivity was 90.16% after a joint of CEA, CA199,NSE and CYFRA21-1 together, and the specificity was 75.64%.

In summary, single measurement of CEA and CA19-9, CYFRA21-1 and NSE is of diagnostic value in the diagnosis of lung cancer, and a joint detection of these four tumor markers, could greatly improve the sensitivity of diagnosis on lung cancer. Thus is helpful for the differential diagnosis of lung cancer and lung benign disease. However, this method should be confirmed by further randomized clinical trials.

References

Ardizzoni A, Cafferate MA, Tiseo M, et al (2006). Decline in serum carcinoembryonic antigen and cytokeratin 19 fragment during chemotherapy predicts objective response and survival in patients with advanced nonsmall cell lung cancer. *Cancer*, **107**, 2842-9.

Bilgin E, Dizdar Y, Serilmez M, et al (2013). For which cancer types can neuron-specific enolase be clinically helpful in Turkish patients? *Asian Pac J Cancer Prev*, **14**, 2541-4.

Buccheri G, Eerrigno D (2002). Lung tumor markers in oncology practice: a study of TPA and CA125. *Br J Cancer*, **87**, 1112-8.

Cho JY, Sung HJ (2009). Proteomic approaches in lung cancer biomarker development. *Expert Rev Proteomics*, **6**, 27-42.

Fletcher CD, Berman JJ, Corless C, et al (2002). Diagnosis of gastrointestinal stromal tumoes: a consensus approach. *Hum Patnol*, **33**, 459-65.

Hu LA, Fu Y, Zhang DN, et al (2013). Serum IL-33 as a diagnostic and prognostic marker in non- small cell lung cancer. *Asian Pac J Cancer Prev*, **14**, 2563-6.

Kav S, Tokdemir G, Tasdemir R, et al (2012). Patients with cancer and their relatives beliefs, information needs and information-seeking behavior about cancer and treatment. *Asian Pac J Cancer Prev*, **13**, 6027-32.

Liu YC, Zhou SB, Gao F, et al (2013). Chemotherapy and late course three dimensional conformal radiotherapy for treatment of patients with Stage III non-small cell lung cancer. *Asian Pac J Cancer Prev*, **14**, 2663-5.

Lu YY, Huang XE, Xu L, et al (2013). Potential predictors of sensitivity to pemetrexed as first-line chemotherapy for patients with advanced non-squamous NSCLCs. *Asian Pac J Cancer Prev*, **14**, 2005-8.

Malik PS, Sharma MC, Mohanti BK, et al (2013). Clinico-pathological profile of lung cancer at AIIMS: a changing paradigm in India. *Asian Pac J Cancer Prev*, **14**, 489-94.

Oguz A, Unal D, Tasdemir A, et al (2013). Lack of any association between blood groups and lung cancer, independent of histology. *Asian Pac J Cancer Prev*, **14**, 453-6.

Pan JB, Hou YH, Zhang GJ (2013). Correlation between EGFR mutations and serum tumor markers in lung adenocarcinoma patients. *Asian Pac J Cancer Prev*, **14**, 695-700.

Parkin DM, Brary FB, Pisani P (2005). Global cancer statistics. *Cancer J Clin*, **55**, 74-108.

Ramshankar V, Krishnamurthy A (2013). Lung cancer detection by screening - presenting circulating miRNAs as a promising next generation biomarker breakthrough. *Asian Pac J Cancer Prev*, **14**, 2167-72.

Schneider J, Bitterlich N, Velcovsky HG, et al (2002). Fuzzy logic based tumor marker profiles improved sensitivity in the diagnosis of lung cancer. *Int J Clin Oncol*, **7**, 145-51.