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Original Article

Diagnostic value of CYFRA 21-1 and CEA for predicting lymph node metastasis in operable lung cancer

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Abstract: Tumour markers are used extensively for the management of lung cancer, including diagnosis, evaluating effectiveness of treatments, monitoring recurrence after therapy and for predicting prognosis. However, there exists a knowledge gap regarding potential quantitative correlations between tumour marker levels and the extents of lymph node involvement in primary lung cancer. The current study is comprised of 139 lung cancer patients scheduled to undergo surgical operation. Of the 139 patients, 107 were subsequently diagnosed with lung cancer without lymph node involvement and 32 were diagnosed with malignant disease with lymph node involvement by histological examination. Preoperative tumour marker levels were quantified in each patient. The median tumour marker levels were statistically higher in lung cancer patients with malignant lymph nodes than in those who suffered either benign lung disease or carcinoma *in situ* (Kruskal-Wallistest; $P = 0.001$). Tumour marker levels were significantly correlated with clinical stage (ANOVA; $P = 0.009$). When examined as a dichotomous variable (CYFRA 21-1 ≤ 5.0 and CEA ≤ 5.0 group and CYFRA 21-1 > 5.0 or CEA > 5.0 group), elevated tumour marker levels correlated strongly with the presence of positive lymph nodes (χ^2 test; $P = 0.000$). This correlation suggests that the tumour marker levels are clinical predictors for the malignant involvement of lymph nodes in operable lung cancer patients.

Keywords: CYFRA 21-1, CEA, lung cancer, lymph node, metastasis

Introduction

Lung cancer is among the most common malignancies and remains among the most difficult to treat. Defining the stage of a malignant disease is key for planning therapy, estimating prognosis and for comparison of studies. The extent of lymph node involvement in patients with lung cancer is the most important prognostic factor and influences therapeutic strategies [1, 2].

Currently, the status of lymph nodes is mainly based on extensive imaging (CT and PET scans). In some cases, this is sufficiently reliable, but in most cases, the initial lymph node staging must be confirmed with further tests [3].

Tumour markers are used extensively for the management of lung cancer, such as diagnosis, evaluating treatment effectiveness, monitoring recurrence after therapy and for predicting prognosis. Some studies have shown that tumour markers are highly correlated with stage groupings [4, 5]. Average scores of tumour markers showed a tendency to be increased in the more advanced stages of lung cancer. According to the TNM stage system, lymph node status affects the clinical stage grouping of lung cancer. Based on these considerations, we want to explore the potential quantitative correlation between tumour marker levels and lymph node involvement in primary lung cancer.

As serologic markers for lung cancer management, cytokeratin 19 fragments (CYFRA 21-1) and carcinoembryonic antigen (CEA) are commonly measured [6-9]. In the current study, CYFRA 21-1 and CEA levels of lung cancer patients with either lymph node involvement or carcinoma in situ were measured, and the diagnostic performance of the tumour marker levels in predicting lymph node dissemination was examined.

Table 1. Patient characteristics

	Benign lung disease (n = 15)	Lung cancer with negative lymph nodes (n = 107)	Lung cancer with positive lymph nodes (n = 32)
Gender			
Male	4 (26.7%)	51 (47.7%)	25 (78.1%)
Female	11 (73.3%)	56 (52.3%)	7 (21.9%)
Average age (years)	51.7	61.8	62.8
Stage			
I		104 (97.2%)	1 (3.1%)
II		2 (1.9%)	14 (43.8%)
III		1 (0.9%)	17 (53.1%)
Histology			
Adenocarcinoma		83 (77.6%)	20 (62.5%)
Squamous cell carcinoma		22 (20.6%)	11 (34.4%)
Adenosquamous carcinoma		2 (1.8%)	1 (3.1%)
Characteristics of benign lung diseases			
Benign sarcoidosis	3 (20.0%)		
Organizing pneumonia	2 (13.3%)		
Pulmonary tuberculosis	2 (13.3%)		
Pulmonary sclerosisng hemangioma	2 (13.3%)		
Hamartoma	1 (6.7%)		
Lymphadenitis	3 (20.0%)		
Other	2 (13.3%)		
CYFRA 21-1 (ng/mL)			
Mean	1.91	3.35	7.67
Range	0.96-2.52	0.73-16.43	1.50-68.99
CEA (ng/mL)			
Mean	1.32	3.06	9.62
Range	0.48-2.97	0.20-19.79	0.80-67.55

Table 2. Median tumour marker levels were higher in patients with lymph node involvement compared with patients without nodal involvement

	Benign lung disease	Node negative	Node positive
CFYRA 21-1 (ng/mL)	1.96[a]	2.80[a,b]	3.85[a,b]
CEA (ng/mL)	1.13[a]	2.34[a,b]	3.45[a,b]

Benign lung disease: patients with benign lung disease; Node negative: patients without nodal involvement carcinoma; Node positive: patients with nodal involvement carcinoma. [a]Kruskal-Wallis test was used to compare the difference of tumour markers between patients with different types of underlying lung disease; [b]Wilcoxon rank sum test was used to compare the difference of tumour markers between patients with lymph-node-negative invasive carcinoma, and lymph-node-positive invasive carcinoma, *P values* < 0.05 were considered statistically significant.

Materials and methods

Ethics statement

The study was approved by the Human Research Ethics Committee of the Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, and written informed consent was provided by all patients.

Patients

In this study, the clinical records of 139 newly diagnosed and previously untreated primary lung cancer patients and 15 benign lung disease patients were screened for inclusion in this study. All patients underwent a segmentectomy, lobectomy or wedge resection with systematic lymph node dissection to determine the status of lymph nodes at the Department of Thoracic Surgery, Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CAMS), between January and December 2013. Clinical, laboratory, pathological and follow-up data for these

Table 3. Relationship between tumour marker levels and clinical stage

Clinical Stage Group	No. of Patients	Mean CYFRA 21-1 (mg/mL)	Mean CEA (mg/mL)
Stage I	105	3.22*	3.10*
Stage II	16	5.11*	3.88*
Stage III	18	10.26*	13.75*

*ANOVA results for differences between groups; CYFRA 21-1: $P = 0.000$; CEA: $P = 0.000$. P values < 0.05 were considered statistically significant. There were no stage IV patients.

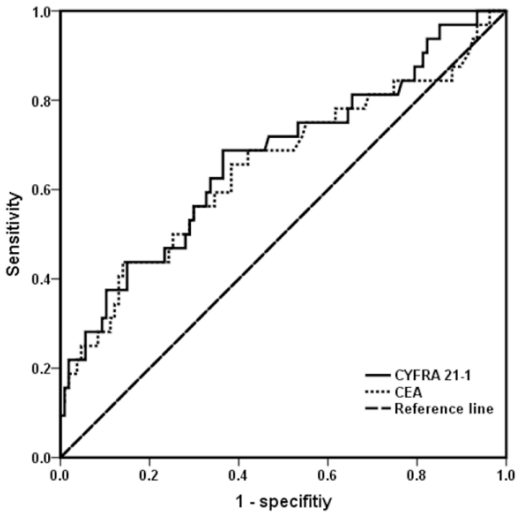

Figure 1. Area under the receiver operating characteristic curve values used for predicting lymph node involvement. CYFRA 21-1: AUC, 0.671 (95% CI, 0.557-0.784), $P = 0.003$; CEA: AUC, 0.651 (95% CI, 0.531-0.770), $P = 0.01$.

patients were acquired from electronic oncology registries.

Measurement of tumour markers

Blood samples were collected upon initial (pretreatment) diagnosis, prior to surgical treatment. Whole blood was collected by taking a 3-mL venous blood sample into a blood collection tube. Serum CYFRA 21-1 and CEA levels were detected with a CYFRA 21-1 and CEA test kit (Roche Diagnostics Corp, China) using a cobas e601 analyzer. The standard cut-off values were set at 3.3 ng/mL for CYFRA 21-1 and 5.0 ng/mL for CEA, for 95% specificity, as recommended by the manufacturers of the assay kits. The standard cutoff values were set based on the information obtained from healthy adults.

Histopathological characterisation and clinical staging

After surgical operation, diagnosis of lung cancer and benign lung disease were confirmed by histological examination. The lung cancer diagnosis was established in accordance with the revised World Health Organization classification of lung tumours and was staged in accordance with the revised staging for lung cancer [3, 10].

Statistical analysis

A Kruskal-Wallis test was used to compare the difference of tumour markers between patients with lymph-node-negative invasive carcinoma, and lymph-node-positive invasive carcinoma. ANOVA was used for investigating the differences between clinical stage groups. Relationships between categorical variables were compared using χ^2 tests. P values < 0.05 were considered statistically significant. Statistical analysis was carried out using SPSS (Statistical Package for the Social Sciences) 21.0 software.

Results

Patient characteristics

Patient characteristics are shown in **Table 1**. A total of 154 patients enrolled in the study. Of the patients enrolled, 15 patients had a diagnosis of benign lung disease. One hundred and seven patients were diagnosed with lung cancer without lymph node involvement, and 32 patients were diagnosed with lung cancer with involved lymph nodes.

Median tumour marker levels were higher in patients with lymph node involvement compared with patients without nodal involvement.

The median of tumour marker levels between patients with different types of underlying lung disease is shown in **Table 2**. There was a significant difference between tumour marker levels in those patients with benign lung disease, lymph-node-negative invasive carcinoma, and lymph-node-positive invasive carcinoma (Kruskal-Wallis test, CYFRA 21-1: $P = 0.000$, CEA: $P = 0.000$). There was a statistically significant difference between median tumour marker levels in patients having positive nodes compared

Table 4. Sensitivity and specificity of CYFRA 21-1, CEA and the combination of tumour markers for predicting the lymph node involvement

Tumor marker (ng/mL)	Sensitivity (%)	Specificity (%)
CYFRA 21-1 > 5.0	37.5	85.0
CEA > 5.0	37.5	86.9
CYFRA 21-1 > 5.0 or CEA > 5.0[a]	56.3	75.6

[a]In the CYFRA 21-1 > 5.0 or CEA > 5.0 group, positive patients were considered to be those having at least one marker above the cutoff level, while negative patients were considered to be those having all markers below the cutoff level.

Table 5. Correlation between elevated tumour marker levels and involved lymph nodes

Tumour marker level	No. of patients with involved lymph nodes		
	Negative	Positive	Total
CYFRA 21-1 ≤ 5.0 and CEA ≤ 5.0[a]	81	26	107
CYFRA 21-1 > 5.0 or CEA > 5.0[b]	14	18	32
Total	95	44	139

χ^2 test was used to assess the difference between the CYFRA 21-1 ≤ 5.0 and CEA ≤ 5.0 group and the CYFRA 21-1 > 5.0 or CEA > 5.0 group; $P = 0.0000$. P values < 0.05 were considered statistically significant. [a]In the CYFRA 21-1 ≤ 5.0 and CEA ≤ 5.0 group, positive patients were considered to be those having all markers below the cutoff level. [b]While in the CYFRA 21-1 > 5.0 or CEA > 5.0 group, positive patients were considered to be those having at least one marker above the cut-off level.

with those patients without nodal involvement (Wilcoxon rank sum test, Cyfra 21-1: $P = 0.003$, CEA: $P = 0.01$).

Tumour marker levels were higher in patients with late stage disease compared with those patients with early stage lung cancer

Because the involvement of lymph nodes affects the clinical stage, we rationalized that tumour marker levels may also correlate with the clinical stage. ANOVA testing was used to analyze the correlation between tumour marker levels and the clinical stage (**Table 3**). No patients were stage IV. There was a statistically significant difference in tumour marker levels based on clinical stage grouping (ANOVA test, CYFRA 21-1: $P = 0.000$; CEA: $P = 0.000$; **Table 3**).

Tumour marker levels can be used as a predictor for malignant involvement of lymph nodes in operable lung cancer patients

A receiver operating characteristic (ROC) curve for tumour markers in predicting lymph nodes involvement is shown in **Figure 1**. The area under curve (AUC) was 0.671 for CYFRA 21-1 and 0.651 for CEA. When the cutoff value was set at the standard level (3.3 ng/mL), CYFRA 21-1 had a sensitivity of 0.688 and specificity of 0.636. To increase the specificity, when setting the cutoff value of CYFRA 21-1 at 5.0 ng/mL, a higher specificity of 0.850 was observed, while the sensitivity was 0.375. When the cutoff value for CEA was set at the standard level (5.0 ng/mL), CEA had a sensitivity of 0.375 and specificity of 0.869. We then analyzed the sensitivity and specificity with the combination of positive CYFRA 21-1 and positive CEA at a cutoff value of 5.0 ng/mL. This resulted in a higher specificity (56.3%) but in a lower sensitivity (75.6%) compared with either CYFRA 21-1 or CEA alone (**Table 4**).

When examined as a dichotomous variable (CYFRA 21-1 ≤ 5.0 and CEA ≤ 5.0 group and CYFRA 21-1 > 5.0 or CEA > 5.0 group), elevated tumour marker levels correlated strongly with the presence of positive lymph nodes (χ^2 test, $P = 0.000$; **Table 5**).

Discussion

Treatment options for lung cancer patients were determined by lymph node status. Determining involvement of lymph node via standard lymph node dissection increases operative time, blood loss, and post-operative chest drainage.

Our study represents the first investigation of tumour marker level as a predicator for lymph node involvement in operable lung cancer patients. By being carried out in a specialized oncology hospital, our study comprised a large percentage of lung cancer patients at early stages of disease progression. Our data show that a significantly higher level of tumour markers were observed in lung cancer patients with lymph node involvement compared with patients without lymph node involvement. Therefore, elevated tumour markers levels may be predictors of the malignant involvement of lymph nodes in lung cancer patients.

Considering the sensitivity of using tumour marker levels as predictors of positive lymph node involvement, tumour marker levels in

combination with other predictive factors would create a powerful assessment of whether lymph node dissection is necessary, particularly in the dissection of mediastinal lymph nodes. Currently, mediastinal lymph node status is usually determined by CT scan. The sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis are approximately 0.55 and 0.81, respectively, confirming that CT scanning has limited ability to predict mediastinal metastasis [1].

In conclusion, our study shows that tumour marker levels may be useful tools for predicting lymph node status in operable lung cancer. Because tumour marker levels can be measured easily, combining tumour marker levels with other methods may allow accurate predictions of lymph node involvement in lung cancer.

Disclosure of conflict of interest

None.

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