# Clinical Significance of the Tumor Markers CYFRA 21-1 and Neuron-Specific Enolase in Lung Cancer

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The diagnostic validity of CYFRA 21-1 and neuron-specific enolase is assessed in patients with lung cancer. Serum contents of CYFRA 21-1 and neuron-specific enolase are increased, respectively, in 74 and 67% of patients with various histological variants of lung cancer. Diagnostic sensitivity of CYFRA was 77.2% in lung cancer other than the small cell variant and 76% in small cell lung cancer. A correlation between the CYFRA content and the tumor size in patients with squamous and other than small cell lung cancer is demonstrated. In patients with spread small cell cancer, serum enolase content tends to increase compared with that in patients with localized small cell cancer. Both CYFRA and enolase are sensitive lung tumor markers in the diagnostics and evaluation of the extent of tumor spread.

**Key Words:** *tumor markers; CYFRA 21-1; neuron-specific enolase; lung cancer*

Lung cancer is the major problem of modern oncology, since its incidence progressively increases both in men and women, while the diagnostics and therapy of this disease are not always adequate. Timely differential diagnosis of small cell and other histological variants of lung cancer is important for the correct choice of therapy. Tumor markers which have been used for differential diagnosis of small cell lung cancer [2,4,7] have low specificity and sensitivity.

The new lung cancer marker CYFRA 21-1 (CYFRA) is the cytokeratin fragment 19 (a cytoskeleton component of bronchial epithelial cells) with high diagnostic sensitivity and specificity in lung cancer, primarily in squamous cell neoplasms [7,9]. In contrast to structural cytokeratins employed for immunohistochemical typing of malignant tumors, CYFRA is a circulating marker, i.e., it is dissolved in biological fluids. A new method of immunoenzyme analysis with the use of two monoclonal antibodies was developed in 1993 by Boehringer Mannheim company [1]. Neuron-specific enolase (NSE) is a neuroendocrine tumor marker used in the diagnostics and monitoring of small-cell lung cancer (SCLC). It is an isoenzyme of the glycolytic enzyme enolase typical of neuroendocrine cells of the central and peripheral nervous systems [6,8]. A highly sensitive immunoenzyme test based on two monoclonal antibodies reacting with different epitopes of the γ-subunits of NSE was developed by Boehringer Mannheim in 1995. This test allows the determination of two NSE isoforms in blood serum. In the present study we assessed the diagnostic validity of CYFRA 21-1 and NSE in lung cancer.

## MATERIALS AND METHODS

The study included 55 untreated patients with the following variants of lung cancer: squamous cell (25), adenocarcinoma (17), and SCLC (13). Control group

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TABLE 1. Serum Contents of CYFRA 21-1 and NSE in Lung Cancer ($X \pm m$)

| Tumor marker, ng/ml | Control group ($n$=10) | Small cell lung cancer ($n$=13) | Squamous cell cancer and adenocarcinoma ($n$=42) |
|---|---|---|---|
| CYFRA 21-1 | 1.2±0.3 (0—3.1) | 3.6±0.6 (2.7—4.8)* | 9.3±1.3 (1.6—41.0)*** |
| NSE | 12.0±0.8 (9.7—13.6) | 62.3±17.6 (41.1—97.4)** | 16.2±1.19 (6.9—36.7)* |

Note. *$p$<0.01, **$p$<0.02, ***$p$<0.001 compared with the control. Here and in Table 2: variation range is given in parentheses.

TABLE 2. Serum Contents of CYFRA 21-1 and NSE in Various Histological Variants of Lung Cancer ($X \pm m$)

| Tumor marker, ng/ml | Squamous cell lung cancer ($n$=25) | Adenocarcinoma ($n$=17) | Small cell lung cancer ($n$=13) |
|---|---|---|---|
| CYFRA 21-1 | 9.8±2.0 (1.6—41.0) | 7.3±1.4 (1.9—21.6) | 3.6±0.6 (2.7—4.8) |
| NSE | 15.6±1.8 (7.3—36.7) | 15.8±1.6 (6.9—34.3) | 62.3±17.6 (41.1—97.4) |

consisted of 10 healthy individuals and patients with nonmalignant pulmonary diseases. According to the manufacturer's recommendations, blood samples collected from the cubital vein after an overnight fast were processed within 1 h to prevent NSE release from the formed elements. Sera with the signs of hemolysis were not analyzed. Serum contents of CYFRA and NSE were determined by heterogeneous two-step immunoenzyme analysis based on the streptavidin technology (Enzymun-Test, Boehringer Mannheim). The measurements were carried out in an ES-300 automatic analyzer (Boehringer Mannheim).

## RESULTS

In patients with lung cancer, serum contents of CYFRA and NSE were significantly higher than in the control group and varied in a wide range (Table 1). In control subjects, the variability of CYFRA and NSE serum contents was lower than that in the patients. Based on the variation range for the tumor markers and the manufacturer's recommendations, we have chosen the following borderline values: 3.3 ng/ml for CYFRA and 12.5 ng/ml for NSE.

In all patients with lung cancer, serum contents of CYFRA and NSE were higher than the borderline values. Serum CYFRA content was the highest in patients with squamous cell cancer (1.6-41.0 ng/ml), it was lower in patients with adenocarcinoma (1.9-21.6 ng/ml), while in patients with SCLC it was slightly higher than the borderline value (2.7-4.8 ng/ml, Table 2). The mean CYFRA contents in patients with squamous lung cancer and adenocarcinoma were significantly higher than in patients with SCLC ($p$<0.01). Patients with SCLC had the highest serum content of NSE (41.1-97.4 ng/ml). The mean NSE content in these patients was significantly higher ($p$<0.01) than that in patients with adenocarcinoma and squamous cell cancer. Thus, serum contents of CYFRA and NSE in patients with SCLC were significantly different ($p$<0.01) from those in patient with other histological variants of lung cancer.

An increase in serum CYFRA and NSE contents was observed in 74 and 67% of patients, respectively. In relation to histological variant of lung cancer, CYFRA and NSE contents were increased, respectively, in 79.2 and 34.8% of patients with squamous cell cancer, in 68.8 and 43.8% of patients with adenocarcinoma, and in 43 and 76% of patients with SCLC. With the chosen borderline values (3.3 ng/ml for CYFRA and 12.5 ng/ml for NSE), the diagnostic sensitivity of CYFRA for adenocarcinoma and squamous cell lung cancer was 77.2%, and the sensitivity of NSE for SCLC was 76%.

TABLE 3. Serum Contents of CYFRA 21-1 in Relation to the Spread of Squamous Cell Cancer and Lung Adenocarcinoma

| CYFRA, ng/ml | Tumor size | | | Stage of development | | | |
|---|---|---|---|---|---|---|---|
| | T2 ($n$=8) | T3 ($n$=17) | T4 ($n$=10) | II ($n$=6) | IIIa ($n$=6) | IIIb ($n$=15) | IV ($n$=15) |
| $X \pm m$ | 5.5±2.2 | 12.7±2.6* | 8.9±1.3** | 3.6±1.3 | 5.2±1.3 | 10.5±2.1* | 9.5±2.5** |
| Median | 3.7 | 11.3 | 7.8 | 3.6 | 4.4 | 7.8 | 7.6 |
| Interval | 2.3—4.1 | 2.4—41.0 | 1.9—15.7 | 2.3—4.8 | 2.7—11.3 | 2.3—11.3 | 1.6—41.0 |

Note. *$p$<0.02, **$p$<0.05 compared with T2; *$p$<0.02, **$p$<0.05 compared with stage II.

Analysis of serum CYFRA and NSE contents in relation to the extent of tumor spread revealed a statistically significant relationship between serum content of CYFRA and size of tumor and stage of its development. Serum CYFRA content correlated with the extent of the tumor spread in all patients: it increased in patients with T2 and T4 tumors (TNM classification, WHO, 1987) and differed significantly in patients with T2 and T3-T4 tumors (Table 3). The diagnostic sensitivity of CYFRA was higher in T3 (81-83%) and T4 (90-100%) than in T2 (66-75%) squamous cell cancer and adenocarcinoma.

It should be noted that serum CYFRA content increased in patients with generalized squamous cell cancer and adenocarcinoma (Table 3). It was higher in patients with spread cancer (IIIb-IV) than in patients with localized process (II-IIIa). Moreover, the sensitivity of CYFRA was higher in patients with remote metastases (80-87%) than in patients with metastases into the regional lymph nodes (66-83%). A tendency toward an increase in serum NSE content was observed in patients with spread SCLC. However, there was not statistically significant difference between serum NSE contents in patients with spread and localized SCLC probably due to a small number of patients.

Our results show that serum contents of CYFRA 21-1 and NSE are markedly increased in patients with lung cancer and depend on the tumor size and stage of tumor development. These findings agree with the published data [2,3,5,7,9], and indicate that both CYFRA and NSE are sensitive tumor markers that can be employed in the diagnostics and evaluation of the extent of the lung cancer spread.

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