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## **Elevated serum NSE in inoperable non-small-cell lung carcinoma (NSCLC) is associated with a better response but worse prognosis**

### **Abstract**

The aim of the study was to evaluate the predictive and prognostic values of elevated serum levels of selected cancer markers (NSE, Cyfra 21-1, CEA, ferritin, free beta-hCG, LDH) in patients with inoperable non-small-cell lung cancer (NSCLC). We investigated a group of 79 patients (49 men and 30 women) with NSCLC. Multivariate regression analysis showed response in patients with NSE > 12.5 ng/ml ( $p = 0.002$ ), good performance status ( $p = 0.007$ ) and elderly patients ( $p = 0.005$ ). However, elevated NSE adversely affected the prognosis. Median survival in patients with NSE < 12.5 ng/ml, 12.5–20.0 ng/ml and > 20.0 ng/ml was 13.3, 11.3 and 6.7 months, respectively ( $p = 0.004$ ). The negative effect of elevated NSE was independent of the response category. Univariate regression analysis showed that the following factors had a significantly negative effect on the prognosis: performance status, stage IIIB or IV, weight loss of > 10%, NSE > 20 ng/ml, Cyfra 21-1 > 10 ng/ml, CEA > 3 ng/ml, ferritin ratio > 1 and LDH > 480 IU/l. Multivariate analysis showed an independent adverse prognostic effect of stage IIIB or IV and elevated ferritin.

**Key words:** neuron specific enolase, non-small-cell lung cancer, prognosis, response to treatment

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### **Introduction**

Elevated serum neuron specific enolase (NSE) in patients with non-small-cell lung carcinoma (NSCLC) has been reported in 12–57% of the cases [1–6], although the clinical relevance of this phenomenon remains unknown.

The aim of the study was to evaluate the relationship of elevated serum NSE and other tumor markers on the type of treatment response and on the prognosis in patients with inoperable NSCLC.

### **Material and methods**

We investigated a group of 79 patients (49 men and 30 women) with NSCLC. The median age was 60 years (range, 42–73 years). All the subjects had been referred to the Institute of Tuberculosis and Lung Diseases, Warsaw, Poland in 2000–2002. The diagnosis of NSCLC was established histopathologically in accordance with the WHO classification [7]. Adenocarcinoma was present in 38 (48%) patients, squamous cell carcinoma in 26 (33%) patients and the histologic subtype could not be de-

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**Table 1. Tumour markers concentration according to histological subtype of NSCLC**

| Histological type   | No of pts | NSE [ng/ml]<br>Median (range)    | Cyfra 21-1 [ng/ml]<br>Median (range) | CEA [ng/ml]<br>Median (range) | LDH [U/l]<br>Median (range) |
|---------------------|-----------|----------------------------------|--------------------------------------|-------------------------------|-----------------------------|
| Adenocarcinoma      | 38        | 10.6<br>(6.7–142)                | 4.7<br>(0.1–254.4)                   | 2.55<br>(0.6–163.2)           | 326.5<br>(204–1424)         |
| Squamous            | 26        | 11.4<br>(4.6–358)                | <b>8.99*</b><br><b>(0.1–186.7)</b>   | 1.5<br>(0.5–200)              | 359<br>(145–2293)           |
| Subtype not defined | 15        | <b>33.1*</b><br><b>(9.1–188)</b> | 3.12<br>(0.6–29.05)                  | 2.1<br>(0.6–156.4)            | 413<br>(243–1768)           |
| Total               | 79        | 11.9<br>(4.6–358)                | 4.95<br>(0.1–254.4)                  | 1.8<br>(0.5–200)              | 339<br>(145–2293)           |

\*p < 0.05; NDRP — neuron specific enolase; CEA — carcino-embryonic antigen; LDH — lactate dehydrogenase

terminated in 15 (19%) patients. The performance status (PS) was evaluated on the ECOG/WHO/Zubrod scale [8]. The study population consisted of 4 patients with PS 0 (5%), 25 with PS 1 (31%), 33 with PS 2 (42%), 10 with PS 3 (13%) and 7 with PS 4 (9%). Patients with PS 3 or 4 were qualified for the treatment only if their poor performance status resulted from such reversible factors as dyspnoea caused by pleural effusion, atelectasis or bone metastasis.

Staging was performed in accordance with the TNM classification [9] with stage IIIA disease being observed in 14 (18%) patients, stage IIIB in 32 (40%) patients and stage IV in 33 (42%) patients. All the patients received cisplatin-based chemotherapy (2–6 cycles). Patients with stage III disease received radiotherapy to the tumour and the mediastinum after 2–3 chemotherapy cycles. Treatment response was evaluated before the third chemotherapy cycle with complete response (CR) being observed in 1 patient, partial response (PR) in 21 patients, minimal response (MR) in 13 patients, stabilisation of the disease (SD) in 21 patients and progression of the disease (PD) in 23 patients.

Blood was sampled before the treatment into serum separator tubes and the serum obtained by centrifugation was stored until measurements were performed at –20°C. NSE was determined by radioimmunoassay (Pharmacia NSE RIA). Cyfra 21-1 and ferritin were measured by electrochemiluminescence (Elecsys System 1010/2010, Roche). Free beta-hCG (fbhCG) was measured by radioimmunology (ELSA, Schering CIS Biointernational). Carcinoembryonic antigen (CEA) was measured by radioimmunology (CEA-IRMA, Polatom, Świerk). Serum LDH was measured automatically using the biochemistry system Hitachi 911. The following values were considered abnormal: NSE > 12.5 ng/ml, Cyfra 21-1

> 3.3 ng/ml, CEA > 3 ng/ml, fbhCG > 0.22 ng/ml, LDH > 480 IU/l. The upper limit of norm for ferritin is different in men and in women (400 ng/ml and 150 ng/ml, respectively) and to avoid this difference in our study we used ferritin index (Fer) instead (a ratio of actual ferritin and upper limit of norm for a given sex). Fer > 1 was considered abnormal.

The statistical analysis was performed using the SPSS statistical software package. The median concentrations of tumour markers in the various patient groups were compared using the Kruskal-Wallis test. Univariate and multivariate regression analysis was used to evaluate the effects of selected parameters on the response to treatment.

## Results

Serum NSE > 12.5 ng/ml was observed in 38 patients (48%), NSE > 20 ng/ml in 20 (25%), Cyfra 21-1 > 3.3 ng/ml in 48 (61%), Cyfra 21-1 > 10 ng/ml in 23 (29%), CEA > 3 ng/ml in 30 (38%), fbhCG > 0.22 ng/ml in 9 (11%), LDH > 480 ng/ml in 18 (23%) and Fer > 1 in 27 patients (34%).

The tumour marker levels depending on the histological subtype of NSCLC are presented in Table 1. Median NSE levels were significantly higher in patients with undefined histology than in those with adenocarcinoma or squamous cell carcinoma. Median Cyfra 21-1 levels were the highest in patients with squamous cell carcinoma and median CEA levels were found to be the highest in patients with adenocarcinoma.

Treatment response (CR + PR) was achieved more commonly in patients with NSE > 12.5 ng/ml versus those with NSE below this level (38% v. 19%). Univariate analysis (Table 2) showed that a favourable treatment response (positive predictive value) may be expected in patients

**Table 2. Influence of clinical parameters and serum tumour marker concentration on the response to chemotherapy (univariate regression analysis) in 79 NSCLC pts**

| Parameter                  | No of pts | Regression coefficient | (SE)         | p            |
|----------------------------|-----------|------------------------|--------------|--------------|
| <b>PS</b>                  | 79        | <b>0.573</b>           | <b>0.27</b>  | <b>0.037</b> |
| Stage                      | 79        | 0.08432                | 0.114        | 0.463        |
| <b>Age</b>                 | 79        | <b>-0.01488</b>        | <b>0.007</b> | <b>0.039</b> |
| Sex                        | 79        | -0.06939               | 0.116        | 0.553        |
| Weight loss > 10%          | 79        | 0.07298                | 0.124        | 0.559        |
| <b>NSE &gt; 12.5 ng/ml</b> | 79        | <b>-0.489</b>          | <b>0.263</b> | <b>0.06</b>  |
| fbHCG > 0.22 ng/ml         | 79        | -0.127                 | 0.178        | 0.477        |
| Cyfra 21-1 > 3.3 ng/ml     | 79        | -0.03898               | 0.116        | 0.737        |
| CEA > 3 ng/ml              | 79        | 0.01565                | 0.117        | 0.894        |
| Fer coefficient > 1        | 79        | 0.167                  | 0.118        | 0.161        |
| LDH > 480 U/l              | 76        | 0.262                  | 0.302        | 0.389        |

SE — standard error, PS — performance status, NSE — neuron specific enolase, fbHCG — free beta HCG, CEA — carcino-embryonic antigen, LDH — lactate dehydrogenase

**Table 3. Influence of selected parameters on the response to chemotherapy in 76 NSCLC pts (multivariate regression analysis)**

| Parameter        | No of pts | Regression coefficient | (SE)  | p     |
|------------------|-----------|------------------------|-------|-------|
| PS               | 76        | 0.347                  | 0.125 | 0.007 |
| Age              | 76        | -0.046                 | 0.016 | 0.005 |
| NSE > 12.5 ng/ml | 76        | -0.809                 | 0.256 | 0.002 |

PS — performance status, SE — standard error, NSE — neuron specific enolase

with good performance status (PS 0/1 v. 2 v. 3,  $p = 0.04$ ) and in elderly patients (assessed as a continuous function,  $p = 0.04$ ) and in patients with NSE > 12.5 ng/ml ( $p = 0.06$ ). The remaining tumour markers we investigated did not prove helpful in predicting the type of treatment response. Multivariate analysis (Table 3) confirmed the independent positive predictive value of the following factors: NSE > 12.5 ng/ml ( $p = 0.002$ ), better PS ( $p = 0.007$ ) and more advanced age ( $p = 0.005$ ).

Elevated NSE was a poor prognostic factor (Fig. 1). Median survival rates in patients with NSE < 12.5 ng/ml, NSE between 12.5 ng/ml and 20 ng/ml and NSE > 20 ng/ml were 13.3, 11.3 and 6.7 months, respectively ( $p = 0.004$ ). The negative prognostic significance of elevated NSE was observed independently of the type of treatment response (Fig. 2). In patients who had favourably responded to chemotherapy (CR + PR + MR), the median survival was 11 months in patients with NSE > 12.5 ng/ml and 19.6 months in patients with NSE ≤ 12.5 ng/ml ( $p = 0.047$ ). In the case of stabilisation of the disease (SD) the medians were

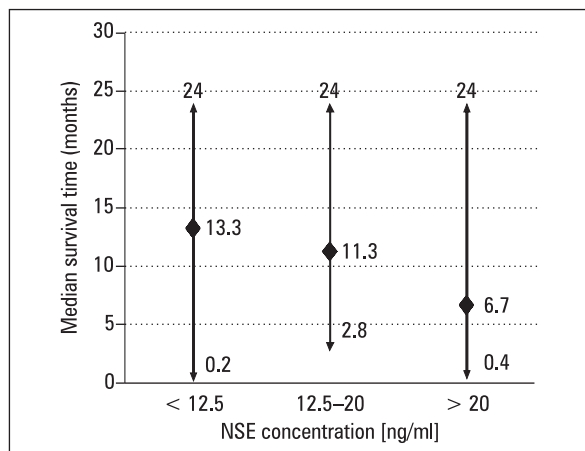
10.5 and 13.3 months, respectively, and in the case of progression of the disease (PD) 2.6 and 7.7 months, respectively ( $p = 0.039$ ).

Univariate analysis revealed poor performance status, higher stage, weight loss of > 10%, NSE > 20 ng/ml, Cyfra 21-1 > 10 ng/ml, CEA > 3 ng/ml, Fer > 1 and LDH > 480 IU/l as being the poor prognostic factors (Table 4).

Multivariate analysis showed an independent and negative prognostic significance of ferritin ratio and the highest stage of NSCLC (Table 5).

## Discussion

Attempts at identifying neuroendocrine lung tumours (carcinoid, small-cell lung carcinoma, large-cell neuroendocrine carcinoma) as a separate histologic group have been made for the past several years [10]. They are characterised by the typical morphological features revealed by the light microscopy, presence of neuroendocrine granules under the electron microscope and positive immunohistochemical reactions with neuroendocrine markers.



**Figure 1.** Median survival time according to NSE concentration in 79 NSCLC pts (♦ median, — range)

Furthermore, some of the non-small-cell carcinomas (especially adenocarcinomas) show a positive immunohistochemical reaction with neuroendocrine markers (chromogranin A, synaptophysin, Leu 7) in the absence of the morphological features of neuroendocrine activity [11–17]. Neuroendocrine markers were found in 22% of the 237 cases analysed by Linnoil et al. [13]. Theoretically, tissue expression of NSE plays a less important role in the diagnosis of neuroendocrine activity due to the lower specificity of this marker. However, many authors have demonstrated NSE in the tissue of NSCLC in combination with other neuroendocrine markers [11–15]. Ruibal et al. [18] found that elevated levels of cytosolic NSE in squamous cell carcinoma correlated with a low degree of tumour differentiation, aneuploidy and an increased number of cells in the S phase of the cell cycle.

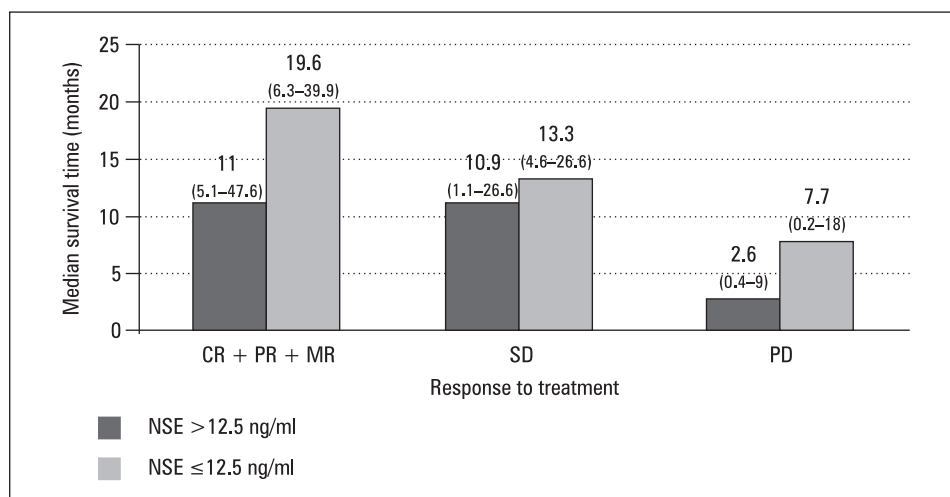
Many authors have studied the relationship between elevated serum levels of NSE and the clinical course of NSCLC but their results have been inconclusive.

We found serum NSE levels exceeding 12.5 ng/ml in 48% of the patients. Other authors have observed elevated NSE levels in 12–57% [1–6]. This discrepancy is probably associated with the various methods of NSE determination, various cutoff values (12.5–21.3 ng/ml) and the histologic variability of the NSCLC study groups [1, 4, 5, 19, 20].

In our study, the group with elevated serum NSE showed a significantly higher incidence of tumours with the NSCLC morphology compared to the other patients, although the histologic subtype could not be established. This suggests that elevated serum NSE may be a marker of lower-grade NSCLC.

If the biology of NSE-secreting NSCLC were similar to small-cell lung carcinoma, we would expect such tumours to show a higher susceptibility to chemotherapy [5]. We observed favourable response (CR + PR) in 38% of the patients with elevated serum NSE and in only 19% of patients with normal NSE values. NSE values exceeding 12.5 ng/ml, older age and good performance status were independent positive predictive factors for treatment response. The chemosensitivity of NSE-secreting NSCLC has been reported by Zandvijk et al. [5] and Zych et al. [6] although no correlation between NSE levels and the type of treatment response has been demonstrated by Maeda et al. [21] or Nisman et al. [19].

The survival of patients with NSCLC managed with chemotherapy is longer if they respond to treatment [22–24]. Taking this fact into account, the



**Figure 2.** Median survival time according to NSE concentration and type of response to chemotherapy in 79 NSCLC pts

**Table 4. Prognostic significance of clinical parameters and tumour marker levels (univariate regression analysis) in 79 NSCLC pts**

| Parameter                       | No of pts | Regression coefficient | (SE)         | p            |
|---------------------------------|-----------|------------------------|--------------|--------------|
| <b>PS</b>                       | <b>79</b> | <b>-4.024</b>          | <b>1.122</b> | <b>0.001</b> |
| <b>Stage</b>                    | <b>79</b> | <b>-5.737</b>          | <b>1.507</b> | <b>0.001</b> |
| Age                             | 79        | 0.085                  | 0.155        | 0.584        |
| Sex                             | 79        | 1.563                  | 2.474        | 0.529        |
| <b>Weight loss &gt; 10%</b>     | <b>79</b> | <b>-6.767</b>          | <b>2.535</b> | <b>0.009</b> |
| NSE > 12.5 ng/ml                | 79        | -4.237                 | 2.36         | 0.077        |
| <b>NSE &gt; 20 ng/ml</b>        | <b>79</b> | <b>-5.427</b>          | <b>2.699</b> | <b>0.048</b> |
| fbHCG > 0.22 ng/ml              | 79        | -4.177                 | 3.445        | 0.229        |
| fbHCG > 1 ng/ml                 | 79        | -9.952                 | 5.372        | 0.068        |
| Cyfra 21-1 > 3.3 ng/ml          | 79        | -3.328                 | 2.488        | 0.185        |
| <b>Cyfra 21-1 &gt; 10 ng/ml</b> | <b>79</b> | <b>-7.124</b>          | <b>2.272</b> | <b>0.002</b> |
| <b>CEA &gt; 3 ng/ml</b>         | <b>79</b> | <b>-5.508</b>          | <b>2.4</b>   | <b>0.024</b> |
| <b>Fer coefficient &gt; 1</b>   | <b>79</b> | <b>-8.953</b>          | <b>2.324</b> | <b>0.001</b> |
| <b>LDH &gt; 480 U/l</b>         | <b>76</b> | <b>-9.303</b>          | <b>2.3</b>   | <b>0.001</b> |

SE — standard error, PS — performance status, NSE — neuron specific enolase, fbHCG — free beta HCG, CEA — carcino-embryonic antigen, LDH — lactate dehydrogenase

**Table 5. Prognostic significance of selected clinical parameters and tumour marker levels (multivariate regression analysis) in 76 NSCLC pts**

| Parameter                     | No of pts | Regression coefficient | (SE)         | p            |
|-------------------------------|-----------|------------------------|--------------|--------------|
| PS                            | 76        | -1.208                 | 1.273        | 0.346        |
| <b>Stage</b>                  | <b>76</b> | <b>-3.714</b>          | <b>1.57</b>  | <b>0.021</b> |
| Weight loss > 10%             | 76        | -4.08                  | 2.464        | 0.102        |
| NSE > 20 ng/ml                | 76        | -0.911                 | 2.601        | 0.727        |
| Cyfra 21-1 > 10 ng/ml         | 76        | -2.379                 | 2.625        | 0.368        |
| CEA > 3 ng/ml                 | 76        | -0.783                 | 2.375        | 0.742        |
| <b>Fer coefficient &gt; 1</b> | <b>76</b> | <b>-6.513</b>          | <b>2.378</b> | <b>0.008</b> |
| LDH > 480 U/l                 | 76        | 0.464                  | 2.91         | 0.874        |

SE — standard error, PS — performance status, NSE — neuron specific enolase, CEA — carcino-embryonic antigen, LDH — lactate dehydrogenase

group of patients with elevated NSE and good response to treatment should attain longer survival. However, in the study group, the discovery of NSE > 12.5 ng/ml, especially > 20 ng/ml, was associated with a significant deterioration of prognosis compared to patients with NSE ≤ 12.5 ng/ml. If we were to assume that NSE-secreting tumours are characterised by a lower degree of differentiation than the other NSCLC, and therefore by a higher growth dynamics and a more aggressive clinical course, then it is not surprising that despite the higher susceptibility to chemotherapy, they would be associated with a poorer prognosis. These findings are consistent with the other studies which investigated the prognostic significance of serum

NSE in inoperable NSCLC [4, 5, 19, 25, 26]. Foa et al. [27] and Reinmuth et al. [28], who studied a population of patients undergoing surgery for NSCLC, did not show any correlation between NSE levels and survival.

The negative impact of elevated NSE levels on survival observed in our study was independent of the type of treatment response. We showed a significantly shorter survival in responders with elevated NSE levels compared to responders with normal serum NSE levels (11 and 19.6 months, respectively). The same relationship could be observed in patients with disease progression, where median survival was 2.2 and 7.7 months, respectively.



## Conclusions

1. Elevated serum NSE was a marker of low-grade non-small-cell lung carcinoma characterised by a higher susceptibility to chemotherapy but a worse prognosis.
2. The other tumour markers (Cyfra 21-1, CEA, LDH) did not have any predictive significance, although we did show a negative prognostic significance of their elevated levels, which was most likely dependent on the tumour mass.
3. Elevated ferritin levels was associated with a negative prognostic significance in an independent manner.

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