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## Prognostic value of serum C-reactive protein (CRP) and cytokeratin 19 fragments (Cyfra 21-1) but not carcinoembryonic antigen (CEA) in surgically treated patients with non-small cell lung cancer

Znaczenie rokownicze surowiczego stężenia białka C-reaktywnego (CRP) i fragmentów cytokeratyny 19 (Cyfra 21-1), ale nie antygenu rakowopłodowego (CEA) u chorych leczonych operacyjnie z powodu niedrobnokomórkowego raka płuca

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### Abstract

**Introduction:** The aim of the study was to assess the prognostic value of cytokeratin 19 fragments (Cyfra 21-1), carcinoembryonic antigen (CEA) and C-reactive protein (CRP) in surgically treated NSCLC patients.

**Material and methods:** 50 NSCLC patients (25 adenocarcinoma, 21 squamous cell and 4 adenosquamous), clinical stages I and II, age 42–89 years, entered the study. CEA, Cyfra 21-1 and CRP concentrations were measured in serum taken before surgery, CEA and Cyfra 21-1 in 50 patients, CRP — in 46 patients. The survival was calculated from the date of surgical treatment until death or until the end of the observation time. The results were expressed as medians (95%CI).

**Results:** Cyfra 21-1 concentration was 2.1 (0.7–14.5) ng/mL. Survival time in the patients with Cyfra 21-1 ≤ 2 ng/mL, and > 2 ng/mL was 79 (14.85–88.2) and 29 (5.7–87.6) months, (p < 0.026). CEA concentration was 2.68 (0.87–72.7) ng/mL, significantly higher in adenocarcinoma than in squamous cell lung cancer — 4.38 ng/mL (1.67–41.35) vs. 2.2 ng/mL (1.0–6.1), p = 0.002. CRP concentration was 5.45 (0–122.6) mg/L. Significant dependence was found between CRP and pathological tumour size (pT). Median CRP values in pT1, pT2 and pT3+4 tumours were: 2.8 mg/L, 6.9 mg/L and 23.5 mg/L, respectively. Survival time of the patients with CRP ≤ 10 mg/L and CRP > 10 mg/L was 79 (14.85–88.2) and 29.5 (5.7–87.6) months, respectively (p = 0.045). CRP > 10 mg/L and Cyfra 21-1 > 2 ng/mL were the only significant preoperative prognostic indicators (HR 2.08 and 2.04, respectively). Among the postoperative parameters, pathological stage of disease (p-stage) and pT were the significant prognostic indicators (HR 2.1 and 2.42, respectively).

**Conclusions:** In the present study, concerning surgically treated NSCLC patients, preoperative CRP > 10 mg/L and Cyfra 21-1 > 2 ng/mL were the only negative prognostic indicators, while pT and p-stage were significant postoperative prognostic indicators.

**Key words:** non-small cell lung cancer, prognosis, cytokeratins, carcinoembryonic antigen, c-reactive protein, surgical treatment

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## Streszczenie

**Wstęp:** Celem pracy była ocena znaczenia rokowniczego przedoperacyjnych stężeń : fragmentów cytokeratyny 19 (Cyfra 21-1), antygenu rakowo-łagodowego (CEA) i białka C-reaktywnego (CRP) w surowicy u chorych operowanych z powodu NDRP.

**Materiał i metody:** Badaniem objęto 50 chorych, w wieku 42–89 lat, w I i II klinicznym stadium zaawansowania NDRP, 25 chorych na gruczolakoraka, 21 na raka płaskonabłonkowego i 4 na raka gruczolowo-płaskonabłonkowego. Stężenie CEA, Cyfra 21-1 i CRP oceniano w surowicy pobranej przed zabiegiem operacyjnym: CEA i Cyfra 21-1 — u 50 chorych, CRP — u 46 chorych. Czas przeżycia mierzono od daty zabiegu do zgonu lub do końca obserwacji. Wyniki podawano jako mediany (95%CI).

**Wyniki:** Stężenie Cyfra 21-1 wynosiło 2,1 (0,7–14,5) ng/ml. Czas przeżycia chorych z Cyfra 21-1  $\leq$  2 ng/ml i  $>$  2 ng/ml wynosił odpowiednio: 79 (14,85–88,2) i 29 (5,7–87,6) miesięcy,  $p < 0,026$ .

Stężenie CEA wynosiło 2,68 (0,87–72,7) ng/ml, i było istotnie wyższe u chorych na gruczolakoraka w porównaniu z chorymi na raka płaskonabłonkowego — 4,38 (1,67–41,35) v. 2,2 (1,0–6,0) ng/ml,  $p = 0,002$ .

Stężenie CRP wynosiło 5,45 (0–122,6) mg/l. Stwierdzono zależność pomiędzy CRP a patologicznym wymiarem guza. Mediana stężenia CRP w grupach pT1, pT2 i pT3+4 wynosiła odpowiednio: 2,8 mg/l, 6,9 mg/l and 23,5 mg/L ( $p < 0,05$ ). Czas przeżycia chorych ze stężeniem CRP  $\leq$  10 mg/l i  $>$  10 mg/l wynosił odpowiednio: 79 (14,85–88,2) i 29,5 (5,7–87,6) miesięcy ( $p = 0,045$ ). CRP  $>$  10 mg/l i Cyfra 21-1  $>$  2 ng/ml były jedynymi przedoperacyjnymi parametrami o istotnym znaczeniu rokowniczym (HR odpowiednio 2,08 i 2,42). Wśród parametrów pooperacyjnych istotne znaczenie rokownicze posiadały: stopień zaawansowania patologicznego NDRP i wymiar guza w badaniu patologicznym (HR 2,1 i 2,42).

**Wnioski:** W badanej grupie chorych na NDRP, spośród parametrów przedoperacyjnych tylko CRP  $>$  10 mg/l i Cyfra 21-1  $>$  2 ng/ml były negatywnymi czynnikami rokowniczymi, spośród parametrów pooperacyjnych — wymiar guza i stopień zaawansowania patologicznego NDRP.

**Słowa kluczowe:** rak niedrobnokomórkowy, rokowanie, cytokeratyny, antygen rakowo-łagodowy, białko C-reaktywne, leczenie operacyjne

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## Introduction

Surgical treatment in the early stage of non-small cell lung cancer (NSCLC) is associated with the best prognosis. Current 5-year survival rates are 50–70% in pathological stage I of the disease and 43–61% in stage II [1]. Despite extensive preoperative evaluation, still a significant proportion of the patients are diagnosed with pathological stage III disease after surgery. Such a finding is combined with substantially worse survival (5-year survival rates — 10–30%), even with the use of adjuvant therapy [2].

Stage of the disease is the strongest prognostic indicator; nevertheless, other prognostic factors such as age, tumour histology, lymphatic and blood vessels involvement are described in the literature [3, 4].

The role of preoperative assessment of tumour markers and inflammatory proteins as prognostic indicators is still not established.

The aim of the present study was to assess the value of preoperative tumour markers [cytokeratin 19 fragments (Cyfra 21-1), carcinoembryonic antigen (CEA)] and C-reactive protein (CRP) in predicting long-term survival in surgically treated non-small cell lung cancer patients.

## Material and methods

Fifty consecutive NSCLC patients referred in 2004 to the Department of Thoracic Surgery of the National Institute of Tuberculosis and Lung Diseases were prospectively enrolled into the study group. Written consent for participation in the study was obtained in all of them. The group included 38 males and 12 females, and median age was 65 years (range 42–89 years). Histological types of tumours, according to WHO classification from 2004 [5], were as follows: adenocarcinoma — in 25 patients, squamous cell lung cancer — in 21, adenosquamous lung cancer — in 4 patients. Preoperative staging was based on chest and upper abdomen computed tomography (CT), fibre-optic bronchoscopy and abdomen ultrasonographic examination. Brain CT scan was performed in four patients due to clinical suspicion of CNS metastases — the results were negative in all of them. Mediastinoscopy was performed in six patients with the suspicion of N2 disease based on chest CT (mediastinal lymph nodes enlargement  $>$  1 cm in the short axis). The results were negative in all of them. The clinical staging (including the negative result of mediastinoscopy), according to WHO sixth edition [6],

was: Ia in 12 patients, Ib in 26 patients, IIa in 3 patients and IIb in 9 patients.

Surgical treatment consisted of the following: lobectomy in 42 patients, bilobectomy in 1 pt and pneumonectomy in 7 patients.

Pathological stage of the disease was as follows: Ia in 13 patients, Ib in 20, IIb in 9 patients, IIIa in 4, IIIb in 3 and IV (metastases to the other lobe) in 1 pt. Pathological tumour size (pT) was: pT1 in 13 patients, pT2 in 32, pT3 in 2, and pT4 in 3 patients.

The degree of differentiation of lung cancer was determined in 47 tumours: 14 were poorly differentiated (G3), 29 were moderately differentiated (G2) and 4 were well differentiated (G1). Mean ( $\pm$  SD) and median (95%CI) percentage of necrotic cells were  $21.74\% \pm 16.9\%$  and 20% (0–80)%, respectively.

The patients in whom pathological stages IIIa–IV of NSCLC were recognised after surgical treatment received adjuvant therapy (chemo  $\pm$  radiotherapy).

Carcinoembryonic antigen (CEA) and cyto-keratin 19 fragment (Cyfra 21-1) concentrations were measured in serum taken before surgery and before mediastinoscopy. Cobas Core immunoassay was used. The cut-off values provided by the assay's manufacturer were applied: 5 ng/mL for CEA and 3.3 ng/mL for Cyfra 21-1. Serum CRP was assessed in 46 patients by Hitachi analyser. The cut off value was 5 mg/L. The CEA, Cyfra 21-1 and CRP values with highest prognostic significance were identified with the use of ROC curves.

The survival time was calculated from the date of surgical treatment until death or until the end of observation time (five years).

Kruskal-Wallis one-way analysis of variance (on ranks) was used to compare marker values in different subgroups of patients. Death hazard ratio

(HR) was assessed with single and multiple regression analysis.  $P < 0.05$  was considered significant.

## Results

Median survival in the presented group of patients was 72.5 (4–108) months. The percentages of 1-, 2-, 3-, 4- and 5-year survival were: 88%, 72%, 60%, 54% and 54%, respectively.

Median preoperative serum Cyfra 21-1 concentration was 2.1 (95%CI 0.7–14.5) ng/mL. In 16/50 patients (32%) Cyfra 21-1 values exceeded 3.3 ng/mL. A tendency towards higher Cyfra 21-1 values in the patients with higher pathological stages of the disease, comparing to the patients with lower stages of the disease, was found (Table 1). Median Cyfra 21-1 in stages Ia–IIb was 2.03 (95%CI 1–6.76) ng/mL, and in stages III–IV it was 3.6 (95%CI 1–14.5) ng/mL ( $p = 0.1$ ). The values of Cyfra 21-1 did not correlate with the histological type of tumour (Table 2) nor with the percentage of tumour necrosis. According to ROC analysis, the Cyfra 21-1 value with optimal prognostic significance was 2 ng/mL. Median survival times in the patients with Cyfra 21-1  $\leq 2$  ng/mL (23 patients) and  $> 2$  ng/mL (27 patients) were 79 (95%CI 14.85–88.2) months and 29 (95%CI 5.7–87.6) months, respectively ( $p < 0.026$ ). The survival curves of the patients with Cyfra 21-1  $\leq 2$  ng/mL and  $> 2$  ng/mL are presented in Figure 1.

Median preoperative serum CEA concentration was 2.68 (95%CI 0.87–72.7) ng/mL. CEA exceeding 5 ng/mL was found in 11/50 patients (22%). CEA serum concentration depended on the histological type of tumour (Table 2). Significantly higher median serum CEA was found in the patients with adenocarcinoma, comparing to the patients with squamous cell lung cancer — 4.38

**Table 1. Cyfra 21-1, CEA and CRP according to the pathological stage of the disease in 50 NSCLC patients treated with surgery**

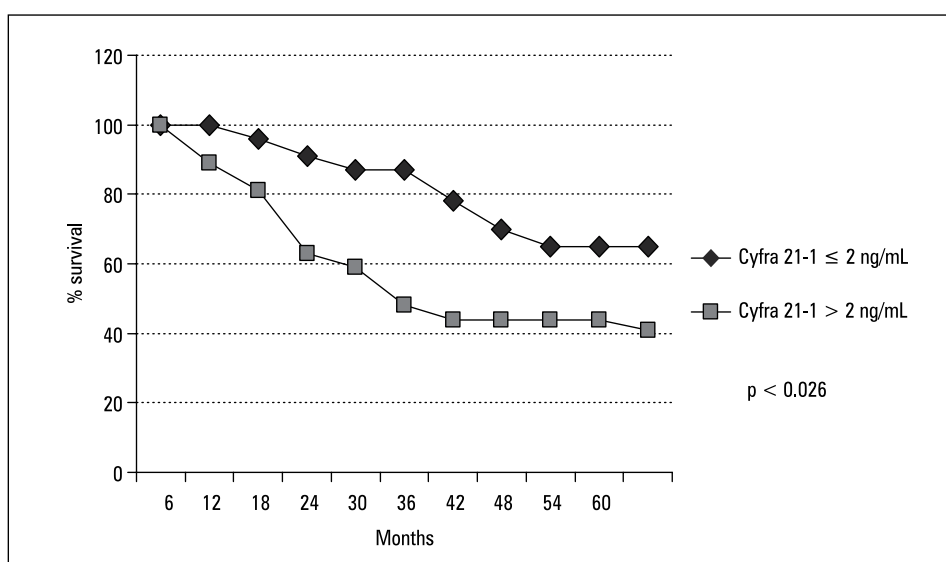
Factor	No	Cyfra 21-1 (ng/mL) Median (95%CI)	CEA (ng/mL) Median (95%CI)	CRP (mg/L)* Median (95%CI)
p-stage				
Ia	13	1.8 (0.75–3.5)	2.8 (1.4–15.02)	2.8 (0.06–60.99)
Ib	20	2.16 (1–10.45)	2.58 (0.94–24.4)	9.4 (1.49–74.78)
IIb	9	1.93 (1.3–5.77)	2.6 (1–72.7)	12.4 (0.2–86.3)
IIIa	4	4.6 (1–7.1)	2.77 (1.8–4.3)	0.1 (0–23.5)
IIIb	3	2.9 (1.8–14.5)	1.5 (1–3.3)	50.8 (2.4–122.6)
IV	1	2.61	9.57	6.9
Ia–IIb	42	2.03 (1–6.76)	2.68 (1–30.18)	5.45 (0.36–76.1)
III–IV	8	3.6 (1–14.5)	2.72 (1–9.57)	4.65 (0–122.6)
p		0.1	0.54	0.5

\*In 46 patients; p-stage — pathological stage of disease; CEA — carcinoembryonic antigen; CRP — C-reactive protein; NSCLC — non-small cell lung cancer

**Table 2. Cyfra 21-1, CEA and CRP according to the histological type of tumour in 50 NSCLC patients**

Histology	No patients	Cyfra 21-1 (ng/mL) Median (95%CI)	CEA (ng/mL) Median (95%CI)	CRP (mg/L)* Median (95%CI)
Adeno	25	2.0 (1–5.22)	4.38 (1.67–41.35)	4.7 (0.42–83.99)
SCC	21	2.35 (1.1–13.8)	2.2 (1–6.1)	17.15 (0–99.88)
Others	4	3.43 (0.7–7.1)	3.22 (1.4–4.49)	1.3 (0.2–23.5)
p		0.27	0.002	0.112

\*In 46 patients; CEA — carcinoembryonic antigen; CRP — C-reactive protein; NSCLC — non-small cell lung cancer; adeno — adenocarcinoma; SCC — squamous cell lung cancer

**Figure 1.** Prognostic significance of preoperative serum Cyfra 21-1 in 50 non-small cell lung cancer patients

ng/mL (95%CI 1.67–41.35) vs. 2.2 ng/mL (95%CI 1.0–6.1),  $p = 0.002$ . No correlation was found between serum CEA and pathological stage of the disease (Table 1). ROC analysis failed to indicate an optimal prognostic CEA value.

Median serum CRP was 5.45 (95%CI 0–122.6) mg/L. Values exceeding 5 mg/L were found in 26/46 patients (60%). Significant dependence was found between serum CRP and pathological tumour size (pT). Median CRP values in pT1, pT2 and pT3+4 tumours were: 2.8 mg/L, 6.9 mg/L and 23.5 mg/L, respectively ( $p < 0.05$ ) (Table 3).

ROC analysis revealed that CRP > 10 mg/L was the optimal prognostic cut-off value. Median survival time of 28 patients with CRP ≤ 10 mg/L was 79 (14.85–88.2) months, and for 18 patients with CRP > 10 mg/L it was 29.5 (5.7–87.6) months ( $p = 0.046$ ). Survival curves of the patients with serum CRP ≤ 10 mg/L and > 10 mg/L are presented in Figure 2.

Univariate analysis revealed that out of the factors known before lung surgery, only serum CRP > 10 mg/L and Cyfra 21-1 exceeding 2 ng/mL

were significant prognostic indicators. No prognostic significance for patient age, sex, histological type of tumour and clinical stage of disease was found (Table 4). Among the parameters known after surgical treatment, pathological stage of the disease and pT value were significant prognostic indicators (Table 4). No prognostic significance of the percentage of necrotic tumour cells and the degree of tumour differentiation was found.

Multivariate analysis taking into account only pretreatment prognostic parameters (Cyfra 21-1 > 2 ng/mL and CRP > 10 mg/L) revealed that none of the markers was an independent prognostic factor. Multivariate analysis taking into account all significant prognostic variables, both pretreatment and post-treatment, revealed that only pathological stage of disease was an independent prognostic indicator (Table 4).

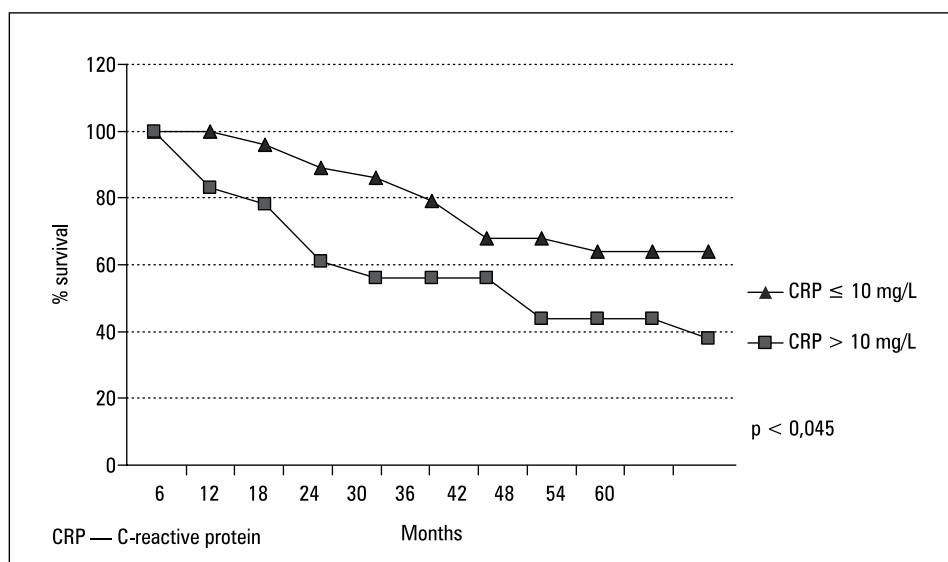
## Discussion

CRP is a marker of inflammation and tissue damage. Its prognostic significance is well esta-

**Table 3. CRP according to pathological size of tumour in 46 NSCLC patients**

Factor	No patients	Median CRP mg/L	Range mg/L	CRP > 10 mg/L
pT1	12	2.8*	0.06–60.99	2/12
pT2	29	6.9*	0–83.17	12/29
pT3+4	5	23.5*	2.4–122.6	4/5

\*p < 0.05; CEA — carcinoembryonic antigen; CRP — C-reactive protein; NSCLC — non-small cell lung cancer; pT — pathological tumour size



**Figure 2.** Prognostic significance of preoperative serum C-reactive protein in 46 non-small cell lung cancer patients

blished in cardiovascular diseases [7]. Shields et al. found that inflammation score assessed by CRP, b-cell attracting chemokine 1 (macrophage-derived chemokine) and interleukin 1 receptor antagonist provided good separation in 10-year lung cancer cumulative risk among current and former smokers and was of prognostic significance [8].

A large epidemiological study of 33,567 participants with various neoplastic diseases conducted by Ko et al. [9] indicated that CRP ≥ 3 mg/L was associated with higher mortality in lung cancer.

In the present study, preoperative serum CRP concentration > 10 mg/L was of prognostic significance, and the risk of death was twice as high in the group of patients with CRP > 10 mg/L comparing to the others. A similar observation concerning CRP prognostic value was made by O’Dowd et al. [10], who found significantly worse survival in patients with CRP exceeding 10 mg/L comparing to those with CRP equal to or lower than 10 mg/L (26.2 months and 75.9 months, respectively). Hara et al. [11] found the prognostic

significance of CRP > 5 mg/L in 203 patients who had undergone a curative resection of NSCLC. Tomita et al. [12] found in 301 resectable NSCLC patients that combined use of CRP and neutrophil-to-lymphocyte index could discriminate the groups with different 5-year survival rates (74.18% in case of both values low vs. 20% in case of both values high). Alifano et al. [13] found preoperative CRP exceeding 20 mg/L to be a significant prognostic indicator in 300 stage I or II NSCLC patients treated with surgery.

Searching for a possible reason for the prognostic significance of CRP in NSCLC, we found in the present study a significant dependence between serum CRP and the pathological size of the tumour. Lee et al. [14] found a correlation between CRP and pathological tumour diameter, as well as between CRP and the signs of lymphovascular invasion, in 102 patients who underwent pulmonary resection. Alifano et al. found in lung cancer patients a correlation between serum CRP and the presence of chronic bronchitis, hypoalbuminaemia, pathologic stage of the disease and peritumoural vascular emboli.

**Table 4. Prognostic significance of different variables in 50 NSCLC patients (univariate and multivariate analysis)**

Univariate analysis	HR	p
<b>CRP*</b>	<b>2.339</b>	<b>0.024</b>
CRP > 10 mg/L*	2.08	0.043
CRP > 20 mg/L*	2.137	0.038
Cyfra 21-1	1.402	0.167
Cyfra 21-1 > 2 ng/mL	2.04	0.046
CEA	1.17	0.25
CEA > 5 ng/mL	0.46	0.647
C-stage	0.86	0.39
P-stage Ia–IIb vs. III–IV	2.7	0.009
P-stage Ia, Ib vs. IIb vs III–IV	2.1	0.04
P-stage	2.1	0.041
p-T	2.42	0.019
Histological type	1.39	0.17
Age	0.74	0.46
Gender	1.17	0.248
% of tumour necrosis	0.37	0.7
G1 vs. G2 vs. G3	0.275	0.785
<b>Multivariate analysis (preoperative factors)*</b>	HR	p
CRP > 10 mg/L	1.39	0.173
Cyfra 21-1 > 2 ng/mL	1.52	0.136
<b>Multivariate analysis (all prognostic factors)*</b>	HR	p
CRP > 10 mg/L	1.73	0.09
Cyfra 21-1 > 2 ng/mL	1.03	0.31
p–Stage Ia–IIb vs. III–IV	2.65	0.01

\*in 46 patients; c-stage — clinical stage of disease; p-stage pathological stage of disease; p-T — pathological tumour size; G1–G3 degree of tumour differentiation; CEA — carcinoembryonic antigen; CRP — C-reactive protein; NSCLC — non-small cell lung cancer

The other prognostic indicator found by our group was preoperative serum Cyfra 21-1 exceeding 2 ng/mL. Median survival in the groups with Cyfra 21-1 < 2 ng/mL and > 2 ng/mL were 79 (95%CI 14.85–88.2) months and 29 (95%CI 5.7–87.6) months, respectively ( $p < 0.026$ ). Univariate analysis revealed that the risk of death in the patients with serum Cyfra 21-1 > 2 ng/mL was twice as high as for those with Cyfra 21-1  $\leq$  2 ng/mL.

The prognostic value of Cyfra 21-1 was investigated by many authors, and most of them confirmed the negative prognostic significance of abnormal Cyfra 21-1 value [15–20] (Table 5). In the reports concerning early-stage NSCLC treated

with surgical resection, Cyfra 21-1 cut-offs used for assessment of prognosis were usually 2–2.8 ng/mL [18, 19], and so were comparable to our cut off value of 2 ng/mL. The prognostic cut off value of Cyfra 21-1 in unresectable NSCLC was found to be much higher (4–18 ng/mL) [21, 22].

Cyfra 21-1 was previously described as a marker of squamous cell lung cancer (SCC) [23]. Subsequently, an elevated level of the marker was also found in serum of patients with adenocarcinoma and small cell lung cancer [22]. Similarly, in the present study we did not demonstrate significant differences between adenocarcinoma and SCC with respect to Cyfra 21-1 serum levels.

An interesting study concerning the origin of Cyfra 21-1 in serum was presented Kosacka et al. [24], who compared tumour cytokeratin 19 immunostaining with Cyfra 21-1 value in serum in each of the studied patients. The authors found that the lower the Cyfra 21-1 in tumour tissue, the higher it was in serum. This finding confirms early observations that Cyfra 21-1 is released into circulation from necrotic tumour cells. Hanada et al. [25] found that the combination of weak cytokeratin 19 tumour expression and high serum Cyfra 21-1 levels was a predictor of poorer prognosis in 107 SCC patients.

These data may indicate that Cyfra 21-1 serum level reflects mainly the degree of tumour necrosis. Nevertheless, we could not demonstrate a correlation between serum Cyfra 21-1 and the percentage of tumour necrotic cells in the presented group of patients.

In the present study, we did not find the prognostic significance of preoperative serum CEA. One of the reasons was that elevated CEA was found also in the patients with early-stage tumours (mainly of adenocarcinoma histology), who survived five years from surgical resection without a relapse. The other reason for the lack of prognostic significance of CEA in our study was probably the small number of patients enrolled.

Most published data indicate the prognostic significance of CEA (Table 6) [26–33], but the majority of reports concern groups of patients with adenocarcinoma [28, 32] or with substantial adenocarcinoma predominance [18, 29, 31]. The authors of recently published articles have found that increased CEA concentration is a significant predictor of pN2 disease [1], tumour diameter and visceral pleural invasion [34], as well as recurrence after surgery [35]. Tomita et al. [36] described the combination of high CEA and SUV max > 6.6 on PET-CT scan as a prognostic variable.

**Table 5. Prognostic value of Cyfra 21-1 according to published data**

Author	Study group	Histology	Cyfra 21-1 cut off ng/mL	5 years survivors	p
Reinmuth 2002 [15]	67 NSCLC p-stage I–IIIa	31 SCC, 17 AD, 16 LA, 3 Oth	≤ 3.57 > 3.57	62% 33%	0.014
Mizuguchi 2007 [17]	272 NSCLC p-stage I–IV	164 AD, 99 SCC, 5 LA, 4 AD/SCC	≤ 2 > 2	Multivariate analysis HR 2.42	0.015
Suzuki 2007 [16]	101 NSCLC c-Stage I	AD 72, SCC 21, LA 7, Oth 1	< 3.5 ≥ 3.5	83.3% 50%	0.006
Matsuoka 2007 [18]	275 NSCLC p-stage I	AD 193, SCC 71, oth 11	≤ 2.8 > 2.8	79.3% 64%	0.0041
Hanagiri 2011 [19]	264 AD p-stage I		≤ 2 > 2	92.8% 75.4%	0.0001
Park 2013 [20]	298 AD p-stage I–III		< 1.95 ≥ 1.95	79.1% 58.4%	0.001

NSCLC — non-small cell lung cancer; p-stage — pathological stage of disease; c-stage — clinical stage of disease; AD — adenocarcinoma; SCC — squamous cell lung cancer; LA — large cell lung cancer; oth — others

**Table 6. Prognostic value of carcinoembryonic antigen (CEA) according to published data**

Author	Study group	Histology	CEA cut off ng/mL	5-years survivors	p
Suzuki 1999 [26]	365 NSCLC c-stage I	AD 267, oth 98	< 5 ≥ 5	78.5% 53%	0.005
Sawabata 2002 [27]	297 NSCLC c-stage I	AD 212, SCC 74, LA 4, oth 7	≤ 7 > 7	72% 49%	0.0001
Tomita 2004 [28]	271 AD p-stage I–III		≤ 5 > 5	77.6% 42.5%	0.001
Okada 2004 [29]	1000 NSCLC c-stage I	694 AD, 260 SCC, 18 LA, 28 Oth	≤ 5 > 5	75.2% 53.8%	0.0001
Fukai 2007 [30]	45 NSCLC p-stage II	64%AD, 29%SCC	< 5 ≥ 5	79.9% 33.2%	0.0015
Matsuoka 2007 [18]	275 NSCLC p-stage I	193 AD, 71 SCC, 11 oth	≤ 5 > 5	81.9% 59.8%	0.091
Kawachi 2009 [31]	815 NSCLC c-stage I	541 Ad, 188 SCC, 39 oth	< 5 5–30 > 30	76.7% 60% 31.3%	
Igai 2012 [32]	122 AD p-stage IA		< 5 ≥ 5	93.3% 33.3%	0.0001
Kato 2013 [33]	141 AD p-stage I		≤ 2.5 > 2.5	93% 59.4%	0.0001

NSCLC — non-small cell lung cancer; p-stage — pathological stage of disease; c-stage — clinical stage of disease; AD — adenocarcinoma; SCC — squamous cell lung cancer; LA — large cell lung cancer; oth — others

On the other hand, Takahashi et al. [37], who examined CEA in 649 surgically treated patients, found that 7 out of 28 patients with serum CEA > 30 ng/mL were long-term survivors (> 4 years). This is similar to our observation that 6/11 patients with CEA > 5 ng/mL survived 5 years or longer.

Important new data concerning the relation between high CEA serum concentration and the presence of EGFR mutation in adenocarcinoma

were published in 2007 by Shoji et al. [38] and were recently confirmed by Zhang et al. [39].

### Summary

In the present study, concerning surgically treated NSCLC patients with clinical stage I and II of the disease, a preoperative CRP value exceeding 10 mg/L and Cyfra 21-1 higher than 2 ng/mL were the only negative prognostic indicators. Patho-

logical tumour size and p-stage of disease were significant postoperative prognostic indicators.

### Conflict of interest

The authors declare no conflict of interest.

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