

# The prognostic value of carcinoembryonic antigen levels in blood and intraoperative pleural lavage fluid in non-small-cell lung cancer



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## Abstract

**Introduction:** There is no specific marker for lung cancer, but, in some lung cancer types, carcinoembryonic antigen (CEA) can reach high levels in the blood and pleural fluid.

**Aim:** This study investigated the relationship of CEA levels in blood (CEA<sub>b</sub>) and intraoperative pleural lavage fluid (CEA<sub>p</sub>) in non-small-cell lung cancer (NSCLC) with the type, stage, and extent of lung cancer.

**Material and methods:** A total of 50 patients, who underwent surgery at our clinic due to NSCLC (group I) or benign lung pathology (group II), were assessed. For this prospectively designed study, 25 consecutive patients were included in each group, and their CEA<sub>b</sub> and CEA<sub>p</sub> levels were investigated.

**Results:** When the levels of CEA<sub>p</sub> were compared, the average value of group I (1.35 ng/ml) was significantly higher than the average value of group II (0.04 ng/ml) ( $p = 0.027$ ). When CEA levels were examined separately, and average values were taken according to surgical pathology results, both CEA<sub>b</sub> and CEA<sub>p</sub> levels of adenocarcinoma patients were found to be higher than those of the other groups. This difference was only significant for the level of CEA<sub>p</sub> ( $p = 0.026$ ).

**Conclusions:** Although the average CEA<sub>b</sub> levels of patients with adenocarcinoma were higher than those of patients with other histopathological types, this difference was not statistically significant. However, we found that CEA<sub>p</sub> levels were significantly higher in patients with adenocarcinoma. These results have led us to consider that CEA<sub>p</sub> elevation is a more sensitive marker than the elevation of CEA<sub>b</sub>.

**Key words:** carcinoembryonic antigen, non-small-cell lung cancer, pleural lavage.

## Introduction

Lung cancer is the most common type of cancer, resulting in the death of men and women in Turkey and throughout the world. Globally, each year about one million men and 400 thousand women develop lung cancer, and 1.2 mil-

## Streszczenie

**Wstęp:** Nie istnieje, co prawda, specyficzny marker dla raka płuc, jednak przy niektórych rodzajach raka płuc antygen rakowo-płodowy (CEA) może osiągać wysokie wartości w krwi oraz w płynie opłucnowym.

**Cel:** Analiza związków stężenia CEA w krwi (CEA<sub>b</sub>) oraz w płynie ze śródoperacyjnego płukania opłucnej (CEA<sub>p</sub>) w niedrobnokomórkowym raku płuca (NSCLC) z rodzajem, stadium oraz rozległością raka płuca.

**Materiał i metody:** Przebadano grupę 50 pacjentów poddanych zabiegom chirurgicznym w naszym ośrodku z powodu NSCLC (grupa I) lub łagodnych zmian płucnych (grupa II). Dla celów przedstawionego poniżej prospektywnego badania każda z grup składała się z 25 kolejnych pacjentów; oznaczono stężenia antygeny w krwi i w płynie opłucnowym.

**Wyniki:** Porównanie stężeń CEA<sub>p</sub> wykazało, że średnia ich wartość w grupie I (1,35 ng/ml) była znacząco wyższa niż średnia wartość w grupie II (0,04 ng/ml) ( $p = 0,027$ ). Kiedy stężenia CEA oznaczono odrębnie, a średnie wartości przeanalizowano w stosunku do wyników badań patomorfologicznych, okazało się, że wartości zarówno CEA<sub>b</sub>, jak i CEA<sub>p</sub> u pacjentów z rakiem gruczołowym były wyższe niż w pozostałych grupach. Różnica ta była istotna statystycznie jedynie w przypadku CEA<sub>p</sub> ( $p = 0,026$ ).

**Wnioski:** Średnie stężenie CEA<sub>b</sub> u pacjentów z rakiem gruczołowym było większe niż u pacjentów z innymi typami histopatologicznymi; różnica ta nie była jednak istotna statystycznie. Niemniej stężenie CEA<sub>p</sub> u tych pacjentów było istotnie większe. Wyniki sugerują, że CEA<sub>p</sub> może być czulszym markerem niż CEA<sub>b</sub>.

**Słowa kluczowe:** antygen rakowo-płodowy, niedrobnokomórkowy rak płuca, płukanie opłucnej.

lion people die as a result. This number represents 17% of cancer-related deaths; the number of lung cancer deaths is higher than the combined number of patients who die due to colon, breast, and prostate cancer [1].

Tumor markers are produced by related tumors or tissues at supraphysiological levels; they can be found in hor-

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none, enzyme, metabolite, immunoglobulin, and protein structures and can be measured quantitatively in the tissue, blood, or other body fluids of patients with the use of biochemical or immunochemical methods. Specific tumor markers can be identified according to the type and prevalence of the tumor. Tumor markers are used for risk identification, early cancer screening, and confirmation of diagnosis; they are also used to determine prognosis, select optimal therapy, and predict disease recurrence or progression during the follow-up period. They can thus provide insights into many aspects of the disease [2].

There is no specific marker for lung cancer in the strictest sense; notwithstanding, an oncofetal antigen known as carcinoembryonic antigen (CEA) can reach high levels in some types of lung cancer, even though it is not specific to lung cancer [3, 4]. While it has been reported that various levels of this antigen can be detected in the pleura in the presence of malignancy, there is no consensus on the subject [5, 6].

### Aim

This study investigated the relationship of CEA levels in blood (CEA<sub>B</sub>) and intraoperative pleural lavage fluid (CEA<sub>P</sub>) in non-small-cell lung cancer (NSCLC) patients with the type, stage, and extent of lung cancer; it also examined the differences in CEA levels between malignant patients and benign patients. Accordingly, the usefulness of CEA levels as a guide in the treatment of lung cancer was evaluated.

### Material and methods

A total of 50 patients were assessed between December 2011 and October 2012; all subjects were selected from among the patients who were admitted to our clinic and underwent surgery due to non-small-cell lung carcinoma (NSCLC) (group I – study group) or benign lung pathology (group II – control group). For this prospectively designed study, 25 consecutive patients were included in each group. The levels of CEA<sub>B</sub> and CEA<sub>P</sub> were investigated in a total of 50 patients. Patients undergoing videothoroscopic surgery who had additional malignancies other than NSCLC were not included in this study.

The patients in both groups were evaluated using blood biochemistry tests, electrocardiography, respiratory function tests, arterial blood gas tests, PA and lateral chest X-ray, and computed tomography. When needed, positron emission tomography (PET) and magnetic resonance imaging (MRI) examinations were performed. To obtain a diagnosis, one or more of the following methods were applied: sputum cytology, transthoracic fine needle aspiration (FNA), bronchoscopic intervention (lavage, brushing, biopsy). Mediastinoscopic lymph node biopsies were conducted when required. The classification of patients in group I was made in accordance with the international lung cancer classification accepted in 2009 by the International Association for the Study of Lung Cancer (IASLC). Histopathological typing was in accordance with the World Health Organization classification from 2004 [7, 8].

After thoracotomy, lavage of the pleural cavity was conducted with 100 ml of saline fluid without any manipulation. Measurement of CEA in lavage fluid was done using the electrochemiluminescence immunoassay (ECLIA) method (Modular Analytics, E170, Roche Diagnostics GmbH, D-68298 Mannheim, Germany). The measuring range was determined to be 0.2–1000 ng/ml, and the lower limit was 0.2 ng/ml.

### Statistical analysis

For the comparison of blood and fluid CEA levels between the two groups, the Mann-Whitney *U* test was used. To calculate the relationships between CEA levels and age, gender, smoking history, comorbidity, stage of the disease, and surgical pathology, the  $\chi^2$  test, Fisher's exact test and Kruskal-Wallis analysis were used. Values of  $p < 0.05$  were considered significant in all tests.

### Results

The average age of group I (study group) was 59.90  $\pm$  7.90 years (range: 33–73), and only 1 patient was female. Three (12%) patients were under the age of 55. All patients underwent anatomic lung resection; in 14 (56%) of these patients, the lesion was on the right side. Histopathological examinations revealed the following conditions: 11 squamous cell carcinomas (44%), 10 adenocarcinomas (40%), 1 carcinoid tumor (0.4%), 1 neuroendocrine tumor, 1 mucoepidermoid carcinoma, and 1 pulmonary blastoma. The CEA<sub>B</sub> was at measurable levels in all cases, while the CEA<sub>P</sub> level of 15 patients could not be measured as it was under 0.2 ng/ml. The clinical stages of the patients were as follows: IA: six, IB: nine, IIA: three, IIB: one, IIIA: six. Altogether, 15 (60%) patients had comorbidities accompanying the lung cancer, which included: hypertension (HT), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), coronary artery disease (CAD), and cerebrovascular accident (CVA). Only 4 (16%) patients in group I did not have a history of smoking. No early postoperative mortality was observed, while morbidity was noted in 5 (20%) patients: chylothorax and arrhythmia in 2 patients each and pneumonia in 1 patient (Tab. I).

The average age of group II (control group) was 44.04  $\pm$  12.89 years (range: 24–62), and it included 13 (52%) male and 12 (48%) female patients. Diagnoses of the patients in this group were as follows: 7 hydatid cysts, 6 bronchiectases, 4 mediastinal cysts, 2 organizing pneumonias, 2 solitary fibrous tumors, 2 bullous lung diseases, 1 fibrous rib dysplasia, and 1 hamartoma. It was impossible to measure the CEA<sub>B</sub> level in only 1 patient; in turn, the CEA<sub>P</sub> level was measurable (over 0.2 ng/ml) in only 4 cases. In this group, 12 (48%) patients did not have a smoking history. There was no postoperative mortality; morbidity developed in 5 (20%) patients: hemorrhage requiring blood and blood product replacement in 4 patients and pneumothorax in 1 patient (Tab. I). Patients in both groups were examined in two categories: 55 years of age or older and under 55 years. In group I, there were only three patients under

Tab. I. Demographic data

Parameter		Group I	Group II	P-value
Age	< 55	3 (12%)	18 (72%)	< 0.01
	≥ 55	22 (88%)	7 (28%)	
Sex	Male	24 (96%)	13 (52%)	< 0.01
	Female	1 (4%)	12 (48%)	
Smoking	+	21 (84%)	13 (52%)	0.032
	-	4 (16%)	12 (48%)	
Complication	Chylothorax	2	-	0.948
	Arrhythmia	2	-	
	Pneumonia	1	-	
	Blood product replacement	-	4	
	Pneumothorax	-	1	
	Total	5	5	
Histology	AC	10	-	
	SCC	11	-	
	Other malign	4	-	
	Hydatid cyst	-	7	
	Bronchiectasis	-	6	
	Mediastinal cyst	-	4	
	Bullous emphysema	-	2	
	Other benign	-	6	
Stage	1-A	6	-	
	1-B	9	-	
	2-A	3	-	
	2-B	1	-	
	3-A	6	-	
Concomitant diseases	Hypertension	5	7	
	COPD	5	2	
	CAD	2	-	
	DM	2	3	
	CVE	1	-	
	Asthma	-	3	
	Total	15	15	0.985

AC – adenocarcinoma, SCC – squamous cell carcinoma, COPD – chronic obstructive pulmonary disease, CAD – coronary artery disease, DM – diabetes mellitus, CVE – central vascular event.

55 years, while group II included 18 patients under the age of 55. Most of the group II patients in whom malignant disease was established were over 55 years of age. As lung malignancies can be seen more often in older age groups, this situation was consistent with the literature.

### Average CEA levels

When CEA<sub>b</sub> levels were evaluated, the lowest value in group I was 0.77 ng/ml, and the highest value was 139.3 ng/ml (average: 4.12 ng/dl). In turn, the lowest value in group II was < 0.2 ng/ml, and the highest value was measured as

**Tab. II.** CEA levels in blood and pleural lavage fluid

Variable	Group	N	Average	Std. deviation	Min.	Max.	P-value
CEA <sub>B</sub>	I	25	14.13	34.51	0.77	139.30	0.001
	II	25	1.70	0.92	0.54	3.42	
CEA <sub>p</sub>	I	25	1.35	3.17	0	14.35	0.027
	II	25	0.04	0.10	0	0.38	

CEA<sub>B</sub> – blood, CEA<sub>p</sub> – pleural lavage fluid.

3.42 ng/ml (average: 1.69 ng/ml). The upper limit of normal CEA<sub>B</sub> value was defined as 5 ng/ml: the average CEA<sub>B</sub> values in both group I and group II were under this limit. The intergroup difference between the average values of CEA<sub>B</sub> was statistically significant ( $p < 0.05$ ). When CEA<sub>p</sub> levels were compared, the average value in group I was found to be higher than that of group II, and this difference was statistically significant ( $p = 0.027$ ) (Tab. II).

### Surgical pathology – CEA level

The histopathological diagnosis of patients in group I was studied under six headings. As pathologies other than adenocarcinoma and squamous cell carcinoma were very rare, they were collected under the common heading 'other'. When CEA levels were examined separately and average values were considered with regard to surgical pathology results, both the CEA<sub>B</sub> and CEA<sub>p</sub> levels were found to be higher in patients diagnosed with adenocarcinoma than in the other groups. Statistical analysis demonstrated that this difference was only significant for the level of CEA<sub>p</sub> ( $p = 0.026$ ) (Tab. III).

### Stage – CEA level

When the disease stages were assessed, the highest average values of CEA<sub>B</sub> and CEA<sub>p</sub> were seen in stage III patients. But when this elevation was compared with patients in other stages, statistical significance was not detected. When stage I was compared with the other stages, CEA levels were shown to be lower in stage I than in more advanced stages, but this was also not statistically significant.

## Discussion

Since the importance of early stage cancer detection was understood, many studies have been conducted in the search for a simple technique to facilitate early detection of all types of cancer, including lung cancer. Tumor marker analysis is straightforward and particularly useful in this context. After carcinoembryonic antigen (CEA) was first defined in 1965, many studies were published on the value of this marker for the diagnosis of various organ cancers, including lung cancer. Based on these studies, it has been established that CEA cannot be used alone for lung cancer detection, but it can be beneficial for guidance [9, 10]. Larger quantities of CEA are released in advanced lung cancer, and it has been asserted that, in lung cancer, CEA can be a serum marker with staging potential [11]. In various clinical studies, lower CEA levels were detected in

**Tab. III.** CEA level relation in subtypes of group I cases

Parameter	CEA <sub>B</sub> (min.–max.)	CEA <sub>p</sub> (min.–max.)	
Age	< 55	39.64 (0.77–116.20)	4.88 (0–14.35)
	≥ 55	10.64 (1.21–139.30)	0.86 (0–5.77)
	P-value	0.558	0.257
Smoking	+	10.46 (0.77–139.30)	0.92 (0–5.77)
	–	33.37 (1.87–116.20)	3.58 (0–14.35)
	P-value	0.767	0.802
Histology	AC	29.70 (1.21–139.30)	2.99 (0–14.35)
	SCC	4.26 (0.77–13.50)	0.31 (0–3.14)
	Other malign	2.31 (1.97–2.82)	0.77 (0–1.34)
	P-value	0.176	0.026
Stage	IA + IB	3.61 (0.77–11.16)	0.41 (0–4.54)
	IIA + IIB + IIIA	29.89 (1.56–139.30)	2.74 (0–14.35)
	P-value	0.149	0.210
Concomitant diseases	+	13.32 (1.56–139.30)	0.75 (0–5.77)
	–	15.32 (0.77–116.20)	2.24 (0–14.35)
	P-value	0.739	0.316

CEA<sub>B</sub> – blood, CEA<sub>p</sub> – pleural lavage fluid, AC – adenocarcinoma, SCC – squamous cell carcinoma.

asymptomatic patients in comparison with symptomatic patients [12]. However, since the marker can be detected at high levels in smokers and COPD patients, as well as cancer patients, Dent *et al.* reported that CEA was not suitable for tumor screening [13].

Although it is not a specific marker for lung cancer, studies have been conducted to compare blood and pleural fluid CEA levels in different types of lung cancer and at different stages. Preoperative CEA elevation was found to be a poor prognostic sign [5, 14, 15]. Rubbins *et al.* [16] asserted that serum CEA levels could provide additional prognostic information independent of age, stage, histological type, and tumor size. Their statistical analysis demonstrated that elevated preoperative serum levels of CEA were associated with significantly decreased postoperative survival time. The study also reported that serum CEA levels provided

information additional to that obtained with conventional methods of preoperative lung cancer staging.

Shoji *et al.* [17] reported a positive correlation between serum CEA elevation and EGFR mutation and recurrence. Stokes *et al.* [18] suggested that routine CEA measurements before surgery could define the small patient group with metastatic disease, and that general research in this patient group should be conducted. Furthermore, their study noted early metastasis in all patients with high preoperative serum CEA levels. Salgia *et al.* [3] investigated the role of CA 125 and CEA in NSCLC. The researchers compared patients with early stage disease and patients with unresectable or metastatic disease, observing that the CA 125 and CEA levels were lower in the early stage group and that the serum CEA level was higher in patients with adenocarcinoma. They also noted that the CEA and CA 125 levels were decreased after chemotherapy. With these findings, they concluded that CA 125 and CEA levels could be a marker for disease progression and response to treatment in lung cancer patients.

In our study, the detected level of CEA<sub>p</sub> was statistically higher in cases of adenocarcinoma, and the level of CEA<sub>b</sub> was higher in patients with lung adenocarcinoma, but statistical significance was not achieved. In similar studies conducted to investigate this subject, CEA<sub>b</sub> was described as the most sensitive (75.7%) tumor marker for the diagnosis of adenocarcinoma; it was also determined that the elevation of this marker was more pronounced in adenocarcinoma in comparison with other lung cancer types [3, 4, 16]. Tomita *et al.* [19] published a comprehensive study assessing patients with adenocarcinoma; they reported that there was no correlation between positive pleural cytology and blood CEA levels, but there was a correlation between CEA<sub>b</sub> and CEA<sub>p</sub> levels. Moreover, correlations were detected between the stage of the disease and the increase of the CEA level. The authors emphasized that the level of CEA<sub>p</sub> could be a prognostic indicator in patients with N1-2 lymph node involvement. The levels of CEA<sub>p</sub> and CEA<sub>b</sub> in our study were high in patients with more advanced stages and N2 involvement, but statistical significance was not detected.

Takamochi *et al.* demonstrated that NSCLC patients with a tumor diameter of less than 20 mm had significantly lower CEA levels, but there was no directly proportional elevation with the increase of tumor diameter. On the other hand, the researchers reported that CEA<sub>b</sub> levels are more valuable than lymph node size on CT when determining mediastinal N2 involvement. In the same study, pN2 was detected in 33% of the patients whose CEA<sub>b</sub> level exceeded 5 ng/dl and whose tumor diameter exceeded 20 mm; based on these data, mediastinoscopy was recommended for patients with high CEA levels and tumor diameter of 20 mm or more [20]. A similar study demonstrated that cN2, tumor size, adenocarcinoma histology, and high CEA<sub>b</sub> level are markers of pN2 which can be used to preoperatively determine the mediastinal spread of the disease in lung cancer patients in whom N2 disease was not detected with thoracic CT. The authors

concluded that mediastinoscopy is unnecessary in 80% of patients with clinical NO-1 disease [21].

Most studies on the value of CEA for the diagnosis of lung cancer analyzed the blood levels of this marker. In recent years, there were also studies that investigated CEA<sub>p</sub> levels and compared them with lavage cytology [6]. We believe that results with high statistical significance can be achieved by increasing the number of studies and conducting a meta-analysis.

It is well known that CEA<sub>b</sub> levels are high in patients with adenocarcinoma. Although the average CEA<sub>b</sub> level in our study was higher in adenocarcinoma patients than in patients with other histopathological types, this difference was not statistically significant. In turn, the CEA<sub>p</sub> levels were found to be significantly higher in patients with adenocarcinoma. These findings have led us to consider that CEA<sub>p</sub> may be a more sensitive marker than CEA<sub>b</sub>. Furthermore, they have shown us that CEA<sub>p</sub> levels should be examined even in patients with low CEA<sub>b</sub> levels. Given the increasing proportion of adenocarcinoma in the pathological types of lung cancer, we think that the level of CEA in blood and/or pleural lavage fluid could be used to guide the diagnosis, staging, postoperative treatment planning, and determination of prognosis in adenocarcinoma. Therefore, we believe that a multicenter prospective study should be conducted on the subject.

### Ethical board approval

The study protocol has been approved by the Institutional Review Board of Ege University Medical School (decision no. 1462/369), and the study has been performed in accordance with the ethics standards laid down in the 1964 Declaration of Helsinki and its later amendments.

### Informed consent

Informed consent was obtained from each participant included in the study.

### Disclosure

Authors report no conflict of interest.

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