

Prognostic Value of the Carcinoembryonic Antigen Found in Pleural Lavage Fluid From Patients With Lung Carcinoma

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OBJECTIVE: To detect the tumor marker carcinoembryonic antigen (CEA) in pleural lavage fluid taken during surgery from patients with pulmonary carcinoma without associated pleural effusion and assess its possible prognostic implications.

PATIENTS AND METHODS: A prospective, observational study was undertaken to include consecutive patients who underwent surgical treatment for lung carcinoma in which pleural lavage was performed prior to closure of the thoracic cavity (study group). The same techniques and measurements were used in patients undergoing thoracotomy for benign disease (control group). The preoperative blood level of CEA was also quantified.

RESULTS: In the study group, the median CEA levels in blood and pleural lavage fluid were 2.90 ng/mL and 0.40 ng/mL respectively; these figures are higher than those corresponding to the control group. A CEA level of 0.30 ng/mL in pleural lavage fluid was established as a cutoff point, based on the corresponding receiver operating characteristic curve, with a sensitivity of 68.4% and a specificity of 35.7%. A graph of survival in relation to this cutoff point revealed a statistically significant effect ($P < .05$).

CONCLUSIONS: It is possible to detect CEA in pleural lavage fluid from the thoracic cavity of patients with lung carcinoma. The values obtained are higher than those found in fluid from patients without neoplastic disease, and this parameter functions as an independent predictor of disease course.

Key words: *Carcinoembryonic antigen. Pleural lavage. Pulmonary carcinoma.*

Valor pronóstico del antígeno carcinoembrionario hallado en lavados pleurales de pacientes con carcinoma pulmonar

OBJETIVO: Detectar el marcador tumoral antígeno carcinoembrionario (CEA) en lavados pleurales de pacientes con carcinoma pulmonar sin derrame pleural asociado, en el momento de la cirugía, a fin de estudiar sus posibles implicaciones pronósticas.

PACIENTES Y MÉTODOS: Se trata de un estudio observacional prospectivo que recoge de forma consecutiva a los pacientes intervenidos de carcinoma pulmonar a los que se realizó lavado pleural de la cavidad torácica al finalizar su apertura (grupo de estudio). Se practicaron la misma técnica y medición en pacientes toracotomizados por enfermedades benignas (grupo control). También se cuantificó el valor del CEA sanguíneo preoperatorio.

RESULTADOS: El CEA (mediana) sanguíneo en el grupo de estudio fue de 2,90 ng/ml y en el lavado pleural de 0,40 ng/ml, cifras superiores a las correspondientes del grupo control. Se estableció como punto de corte del CEA en el lavado pleural el valor de 0,30 ng/ml, establecido según la curva de eficacia diagnóstica correspondiente, con una sensibilidad del 68,4% y una especificidad del 35,7%. La gráfica de supervivencia en función de este punto de corte mostró significación estadística ($p < 0,05$).

CONCLUSIONES: Es posible detectar CEA en lavados pleurales de la cavidad torácica en pacientes con carcinoma pulmonar, con valores superiores a los encontrados en pacientes sin enfermedad neoplásica. La medición de dicho valor es un factor pronóstico independiente en la evolución de la enfermedad.

Palabras clave: *Antígeno carcinoembrionario. Lavado pleural. Carcinoma pulmonar.*

Introduction

Lung cancer is the most common cause of death due to neoplastic disease in developed countries. Prognosis is poor, and the 5-year survival rate of less than 15% is

attributed to the lack of early detection and the impossibility of cure in patients with extensive disease.

TNM classification is the principal guide to the prognosis of non-small cell lung cancer.¹ Prognosis can be influenced by many additional biological factors, of which the most notable are the circulating tumor markers in blood. Numerous studies indicate the particular relevance of carcinoembryonic antigen (CEA) in the diagnosis and management of patients with non-small cell lung cancer.²

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CEA was one of the first markers to be evaluated in lung cancer.³ Although it is also elevated in patients with adenocarcinoma of the gastrointestinal tract, CEA is found at increased concentrations in the blood of 40% to 80% of lung cancer patients, and the antigen acts as a sensitive indicator of adenocarcinomas and advanced stages of the disease. In fact, the blood concentration of CEA has been correlated with the spread and/or progression of the primary disease.⁴

Analysis of tumor markers in serum has been applied to the diagnosis, prognosis, and follow up of patients with lung cancer. Although the possibility of early diagnosis has been considered, analysis of tumor markers is currently most useful for the evaluation of therapeutic efficacy and as an indicator of relapse or disease progression.⁵

Pleural fluid from patients with neoplastic pleural effusion is known to contain detectable levels of tumor markers, notably CEA.⁶ However, the literature does not contain descriptions of the detection of CEA in pleural lavage fluid from patients with lung carcinoma without concomitant pleural effusion. Thus, the aim of this study was to assess the possibility of isolating CEA in pleural lavage fluid, with the intention of establishing its possible significance as an independent prognostic variable.

Patients and Methods

Patient Characteristics

From January 2000 to January 2004, a total of 164 patients with potentially resectable lung carcinoma were identified for

TABLE 1
Patient Characteristics

Characteristics	Results
Sex	
Male/female	149/15
Age, years	63 (55-69)*
Procedure	
Atypical resection	14
Lobectomy	107
Pneumonectomy	36
No resection	7
Histology	
Adenocarcinoma	71
Squamous	77
Large cells	7
Others	9
Stage	
0	3
Ia	20
Ib	62
IIa	3
IIb	24
IIIa	26
IIIb	19
IV	7
Visceral pleura involvement	
Yes	49
No	115
Mean size of the tumor, cm	3.5 (2-4.5)*

*Data correspond to the median (25th-75th percentiles).

inclusion in a prospective study. A medical history was taken, and physical examination, complete laboratory workup (including preoperative CEA), radiography (chest radiograph, and computed tomography scan of the thoracic and abdominal region), and bronchoscopy were performed in all patients.

Inclusion criteria were as follows: *a*) presence of a primary lung tumor; *b*) thoracotomy performed with the aim of curing the cancer; *c*) determination of serum CEA levels on the morning of surgery; *d*) washings of the thoracic cavity performed following thoracotomy; *e*) absence of kidney failure; *f*) absence of positive cytology for malignancy in pleural lavage fluid; and *g*) determination of CEA levels in lavage fluid from the thoracic cavity.

Exclusion criteria were as follows: *a*) presence of pleural effusion (as determined by radiography and confirmed on opening the thoracic cavity), and *b*) presence of serosanguineous fluid in pleural washes.

Patients were assigned to 2 groups: a study group, comprising patients with lung neoplasms who met the specified criteria (n=164), and a control group, containing patients who underwent thoracotomy for nonneoplastic diseases and in whom pleural lavage was performed (n=30).

After the period for inclusion of subjects was closed on January 31, 2004, a follow up was undertaken to determine the condition of patients at 3 months (April 30, 2004), either by telephone interview or assessment of the patient's chart.

Pleural Lavage Technique

Washes of the pleural cavity were performed during surgery in all patients. The lavage procedure entailed the introduction of 200 mL of physiologic saline (isotonic solution of 0.9% sodium chloride, Braun-Dexon, Spangenberg, Germany) into the cavity, followed by recovery of 30 mL with a syringe after 2 to 3 minutes. Aliquots of the samples were placed in test tubes to be sent to the pathology department and hospital laboratory for cytology and determination of CEA levels.

Statistical Analysis

Since the quantitative variables displayed a nonparametric distribution, they are presented as the median and the 25th and 75th percentiles. Between-groups comparisons were performed using the Mann-Whitney U test.

To estimate the cutoff point for the use of CEA concentration in pleural lavage fluid as a prognostic marker, a receiver operating characteristic curve was constructed.

The Kaplan-Meier procedure was used to plot the survival curve, and between-groups comparisons of the functions were performed using the log-rank test.

Statistical significance for hypothesis testing was established at $P < .05$.

Results

In all of the patients included in the study, the macroscopic appearance of the pleural lavage fluid was clear, with no evidence of blood contamination.

Table 1 shows the characteristics of the patients studied. Neoadjuvant treatment was performed with chemotherapy in 28 patients and with radiotherapy in 3 patients.

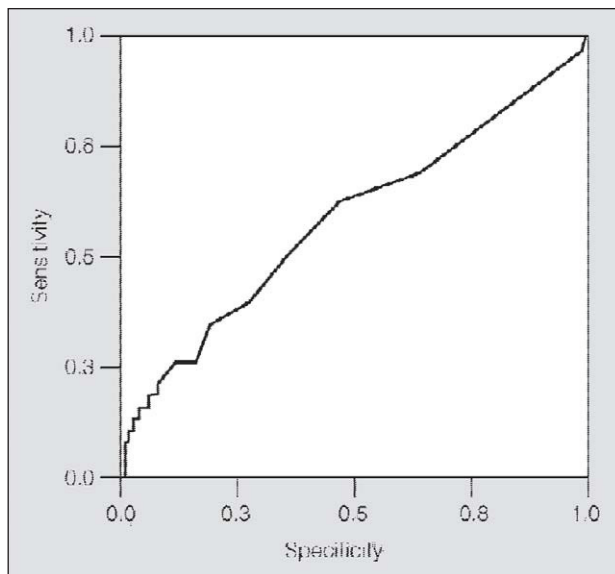


Figure 1. Receiver operating characteristic curve to define the cutoff point for carcinoembryonic antigen in pleural lavage fluid from the study group.

In the study group, the median CEA levels in blood and pleural lavage fluid were 2.90 ng/mL and 0.40 ng/mL, respectively; the concentrations found in the study group were higher than those corresponding to the control group (0.85 ng/mL and 0.20 ng/mL, respectively). A CEA level of 0.30 ng/mL in pleural lavage fluid was established as a cutoff point, based on the corresponding receiver operating characteristic curve, with a sensitivity of 68.4% and a specificity of 35.7% (Table 2). The survival curves for the study group (Figure 2) revealed survival to be significantly different above and below the cutoff point ($P=.044$).

The median time until patient death was 9.7 months (25-75 percentiles: 13.3-26.5) for the group in which the CEA concentration in pleural lavage fluid was 0.30 ng/mL or higher, and 23.9 months (25-75 percentiles: 13.3-26.5) in the group in which the level was less than 0.30 ng/mL.

Univariate analysis (Table 3) did not show statistically significant relationships between CEA level in pleural lavage fluid and either involvement of the visceral pleura, tumor stage (initial stages [I and II] or advanced stages [III and IV]), mediastinal node involvement (grouping N0-N1 or N2 involvement), histologic type, or size of the tumor (<5 cm or \geq 5 cm).

Discussion

In the literature, more than 150 prognostic factors based on characteristics of the tumor or patient, or on the therapeutic interventions have been identified as associated with lung carcinoma.⁷ Analysis of tumor markers in serum has been applied to the diagnosis, prognosis, and treatment of patients with lung tumors. Furthermore, pleural fluid from patients with neoplastic

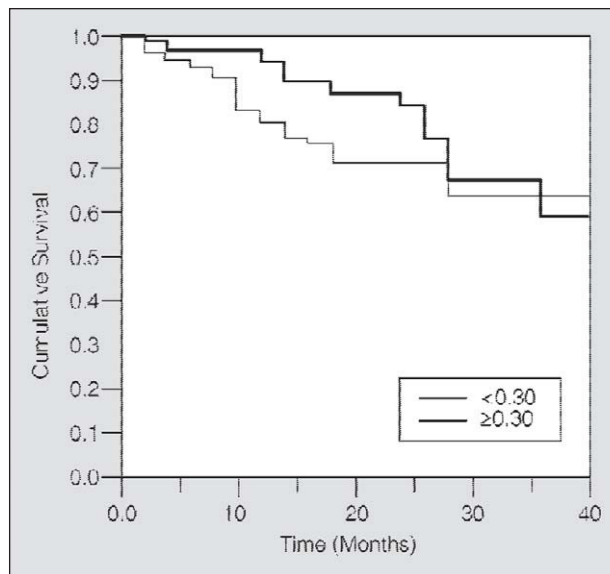


Figure 2. Survival curve according to the concentration of the carcinoembryonic antigen in pleural lavage fluid (<0.30 ng/mL or \geq 0.30 ng/mL; $P=.044$). Kaplan-Meier survival analysis. Between-groups comparisons of the plots performed using the log-rank test.

pleural effusion is known to contain detectable levels of tumor markers.

Tumor markers can be defined as substances or cellular changes associated with the process of neoplastic transformation.⁸ It would be desirable to

TABLE 2
Patients Alive and Dead at the End of the Study, by Carcinoembryonic Antigen (CEA) Concentration in Pleural Lavage fluid: Cutoff Point 0.30 ng/mL

	CEA in Pleural Lavage Fluid (ng/mL)	
	≥ 0.30	<0.30
Dead (n=38)	68.4% (n=26)	31.6% (n=12)
Living (n=126)	64.3% (n=81)	35.7% (n=45)
Total (n=164)	107	57

TABLE 3
Univariate Analysis*

Parameter	Pleural Lavage Fluid	P
Histology		.642
Squamous	0.4 (0.200-0.500)	
Adenocarcinoma	0.3 (0.200-0.600)	
Staging		.268
Stages I-II	0.3 (0.200-0.600)	
Stages III-IV	0.4 (0.200-0.700)	
Visceral pleura involvement		.57
No (n=115)	0.350 (0.200-0.575)	
Yes (n=49)	0.450 (0.200-1.125)	
Node involvement		.57
N0-N1 (n=132)	0.3 (0.200-0.600)	
N2 (n=32)	0.4 (0.200-0.700)	
Size of the tumor, cm		.193
<5 (n=124)	0.3 (0.200-0.600)	
\geq 5 (n=40)	0.4 (0.200-0.700)	

*Values are shown as the median concentration of carcinoembryonic antigen (ng/mL) obtained in pleural lavage fluid (25th-75th percentiles, weighted average).

begin to use all of this biological information to complement the prognostic capacity of the anatomic TNM staging.⁹ In addition, malignant cells can be detected in pleural fluid, with a diagnostic yield of around 60%.¹⁰ Some studies have taken a step further and assessed the value of cytologic findings in pleural lavage fluid from patients without associated pleural effusion.^{11,12} However, no data has been published on the detection and value of tumor markers in pleural lavage fluid, the objective of this study.

CEA encompasses a heterogeneous group of proteins that circulate at high concentration in the blood of patients with certain malignant tumors, especially those of epithelial origin. Although the sensitivity and specificity for the diagnosis of lung tumors is low, elevated levels of this marker at the time of diagnosis are associated with poor prognosis,¹³ even after presumably curative surgical excision of the tumor. This conclusion has also been extended to the measurement of CEA in pleural fluid, where it achieves a sensitivity of 49% and a specificity of 98%.¹⁴ In addition, patients with malignant pleural effusion have been demonstrated to present higher levels of CEA in pleural fluid than patients with other pleural exudates.¹⁵

In this study, we found higher CEA levels in pleural lavage fluid from patients with lung carcinoma than in a control group of patients undergoing thoracotomy for nonneoplastic disease.

Blood contamination of the chest cavity was avoided following thoracotomy, and serosanguineous pleural lavage fluid was discarded. Furthermore, the finding that preoperative blood CEA levels (determined on the day of surgery) differed from those of pleural lavage fluid reinforces the conclusion that there was no blood contamination of the samples.

One of the criteria for inclusion of patients was negative cytology of pleural lavage fluid. We decided to include this criterion in order to avoid additional complicating factors whilst making the study group as homogeneous as possible.

Following analysis of the concentration of CEA in pleural lavage fluid, we established a cutoff point of 0.30 ng/mL (Figure 1). Comparison of the survival curves (Figure 2) for the 2 groups included in the study (CEA levels in pleural lavage fluid of ≥ 0.30 ng/mL or < 0.30 ng/mL) revealed a statistically significant difference.

At the end of the study, 126 patients were alive and 38 had died as a result of neoplastic lung disease. In the patients who had died, the median concentration of CEA in pleural lavage fluid was 0.916 ng/mL, compared with 0.556 ng/mL in the living patients.

We believe that the CEA obtained in pleural lavage fluid from patients with lung carcinoma functions as

additional objective data that is useful in establishing a more accurate prognosis of the neoplastic disease.

We have demonstrated that it is possible to detect CEA in pleural lavage fluid from the thoracic cavity of patients with pulmonary carcinoma, and that the values obtained are higher than those found in patients without neoplastic disease. This parameter functions as an independent predictor of disease course.

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REFERENCES

1. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest*. 1997;111:1710-7.
2. Nisman B, Amir G, Lafair J, Heching N, Lyass O, Peretz T, et al. Prognostic value of cyfra 21-1, TPS and CEA in different histologic types of non-small cell lung cancer. *Cancer Res*. 1999;19:3549-52.
3. Niklinski J, Furman M. Clinical tumour markers in lung cancer. *Eur J Cancer Prev*. 1995;4:129-38.
4. Hotta K, Segawa Y, Takigawa N, Kishino D, Saeki H, Nakata M, et al. Evaluation of the relationship between serum carcinoembryonic antigen level and treatment outcome in surgically resected clinical-stage I patients with non-small-cell lung cancer. *Cancer Res*. 2000;20:2177-80.
5. Villena V, López Encuentra A, Echave J, Martín P, Ortuño B, Estenez J. Diagnostic value of CA 549 in pleural fluid. Comparison with CEA, CA 15.3 and CA 72.4. *Lung Cancer*. 2003;40:289-94.
6. Salama G, Miédougué M, Rouzaud P, Mauduyt MA, Pujazon M, Vincent C, et al. Evaluation of pleural cyfra 21-1 and carcinoembryonic antigen in the diagnosis of malignant pleural effusions. *Br J Cancer*. 1998;77:472-6.
7. Hirsch F, Franklin WA, Gazdar AF, Bunn P. Early detection of lung cancer: clinical perspectives of recent advances in biology and radiology. *Clin Cancer Res*. 2001;7:5-22.
8. Hernández Hernández JR. Importancia y significado de los marcadores tumorales en neumología. *Arch Bronconeumol*. 1997;33:485-7.
9. Díez M, Torres A, Maestro ML, Ortega MD, Gómez A, Pollán M, et al. Prediction of survival and recurrence by serum and cytosolic levels of CEA, CA 125 and SCC antigens in resectable non-small-cell lung cancer. *Br J Cancer*. 1996;73:1248-54.
10. Maskell NA, Butland RJA. BTS guidelines for the investigation of a unilateral pleural effusion in adults. *Thorax*. 2003;58 Suppl 2:17-23.
11. Dresler CM, Fratelli C, Babb J. Prognostic value of positive pleural lavage in patients with lung cancer resection. *Ann Thorac Surg*. 1999;67:1435-9.
12. Okada M, Tsubota M, Miyamoto Y, Maniwa Y. Role of pleural lavage cytology before resection for primary lung carcinoma. *Ann Surg*. 1999;229:579-84.
13. Rubins JB, Dunitz J, Rubins H, Maddaus MA, Niewoehner DE. Serum carcinoembryonic antigen as an adjunct to preoperative staging of lung cancer. *J Thorac Cardiovasc Surg*. 1998;116:412-6.
14. Hernández L, Espasa A, Fernández C, Candela A, Martín C, Romero S. CEA and CA 549 in serum and pleural fluid of patients with pleural effusion. *Lung Cancer*. 2002;36:83-9.
15. Ferrer Sancho J. Marcadores tumorales en líquido pleural. *Arch Bronconeumol*. 2000;36:295-7.