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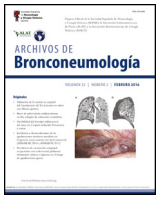

Original Article

# Utility of CEA and CA 15-3 Measurements in Non-Purulent Pleural Exudates in the Diagnosis of Malignancy: A Single-Center Experience☆

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ABSTRACT

*Objective:* To establish the diagnostic accuracy of pleural fluid (PF) CEA and CA 15-3 in identifying malignancy, and to determine the additional value of these markers in patients with malignant pleural effusions (MPEs) with false negative results from cytological fluid examination.
*Methods:* PF concentrations of CEA and/or CA 15-3 were determined in 1575 patients with non-purulent exudates, 549 of whom had confirmed MPEs, 284 probable MPEs, and 742 benign effusions. Tumor marker cut-off points were set to ensure 100% specificity for malignant effusion.
*Results:* The 41%, 40% and 60% of MPE patients had high PF levels of CEA (>45 ng/mL), CA 15-3 (>77 UI/l) or both, respectively. These percentages were 30%, 19% and 41% in MPEs with positive pleural biopsy and negative PF cytology; and 24%, 13% and 35% in clinical MPEs without histocytological confirmation. Tumor markers were of no value in lymphomas and mesotheliomas. The area-under-the-curve for CEA was 0.819 (95% CI: 0.793–0.845) and for CA 15-3, it was 0.822 (95% CI: 0.796–0.847). The use of tumor markers compared to cytology alone, increased the diagnosis of malignancy by 14%.
*Conclusions:* Measurements of PF CEA and CA 15-3 may complement pleural cytology in the identification of MPEs.



## Utilidad de la medición de CEA y CA 15-3 en los exudados pleurales no purulentos para diagnosticar malignidad: experiencia de un único centro

*Palabras clave:*
Derrame pleural maligno
CEA
CA 15-3
Marcadores tumorales
Líquido pleural

RESUMEN

*Objetivo:* Establecer la rentabilidad diagnóstica de la medición de CEA y CA 15-3 en el líquido pleural (LP) para identificar malignidad, así como el valor adicional de estos marcadores en pacientes con derrame pleural maligno (DPM) y citología pleural falsamente negativa.
*Método:* Se determinaron las concentraciones de CEA o CA 15-3 en el LP de 1.575 pacientes con exudados no purulentos, de los que 549 tenían DPM demostrados, 284 derrames probablemente malignos y 742 derrames benignos. Se buscaron puntos de corte 100% específicos para dichos marcadores, de forma que no pudieran ser superados por ningún derrame benigno.

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*Resultados:* El 41%, 40% y el 60% de los pacientes con DPM tenían concentraciones pleurales elevadas de CEA (>45 ng/mL), CA 15-3 (>77 UI/l), o de alguno de los anteriores, respectivamente. Estos porcentajes fueron del 30%, 19% y 41% en los DPM con biopsia pleural positiva y estudios citológicos del LP negativos; y del 24%, 13% y 35% en los derrames considerados clínicamente malignos, pero sin demostración citohistológica. Los marcadores tumorales no tuvieron utilidad en linfomas ni mesoteliomas. El área bajo la curva de eficacia diagnóstica (AUC) del CEA fue de 0,819 (IC 95%: 0,793–0,845) y la del CA 15-3 de 0,822 (IC 95%: 0,796–0,847). Globalmente, el uso adicional de los marcadores tumorales incrementó el diagnóstico de malignidad un 14% respecto a la citología pleural de forma aislada.
*Conclusiones:* La determinación de CEA y CA 15-3 en LP puede complementar a la citología pleural en la identificación de los DPM.


## Introduction

The easiest way of diagnosing malignant pleural effusion (MPE) is to demonstrate the presence of tumor cells in the cytological examination of pleural fluid (PF).[1] Unfortunately, pleural cytology has a maximum yield of around 60%, and figures are much lower in some tumor types, such as squamous cell lung cancer or mesothelioma (25%–30%).[2] For this reason, extensive research has been conducted into obtaining a diagnosis of malignancy in patients with false negative results on pleural cytology, without the need to resort to invasive procedures such as biopsy by thoracoscopy. In this respect, measuring the concentrations of certain conventional tumor markers in pleural fluid is an attractive option, as this specimen is easy to obtain in clinical practice. However, there is no consensus on the most useful tumor markers and the most appropriate cutoff points to use.

Carcinoembryonic antigen (CEA) has been by far the most widely studied marker in PF, followed by others such as CYFRA 21-1 and carbohydrate antigen 15-3 (CA 15-3). Although evidence has shown that these markers can offer valuable information in some situations, neither the British[3] nor the Spanish[1] guidelines recommend their routine use in PF.

This study reports the largest single-center series published to date on the potential utility of determining CEA and CA 15-3 in PF for identifying malignancy in the context of non-purulent exudate. This validates our previous experience[4] and shows the added value of determining these tumor markers in addition to pleural cytology.

## Materials and Methods

A retrospective review was conducted of all consecutive patients with pleural effusion referred by their treating physician to the Pleural Medicine Department of our hospital between August 2003 and August 2016 to undergo diagnostic thoracentesis with determination of CEA or CA 15-3 in the PF. The study was approved by the local ethics committee (CEIC-1713).

### *Diagnostic Variables and Criteria*

Demographic data, results of the PF analysis, pathology studies and the final diagnosis of each patient were collected. Pleural effusion was defined as malignant if malignant cells were found in PF or in a pleural biopsy. Probably malignant pleural effusion (PMPE) was considered if 2 of the following conditions were met: (a) evidence of a primary tumor or extrapleural metastases, and (b) existence of a pleural exudate with negative cytological studies, not explained by causes other than tumor invasion of pleura, after performance of the clinical tests considered relevant by the treating physician and a sufficient follow-up period. Histological confirmation was always required for the diagnosis of pleural mesothelioma. Generally accepted criteria were used for diagnosing benign pleural effusion (BPE).[5]

### *Measuring Tumor Markers in Pleural Fluid*

CEA and CA 15-3 in PF were measured in an Electsys Roche electrochemiluminescence analyzer with a commercially available kit (Roche Diagnostics, Mannheim, Germany), according to the instructions of the manufacturer. Analyses were performed within hours of extraction of the PF specimen. In our laboratory, normal serum values are 0.2–5 ng/mL for CEA, and 1–30 IU/mL for CA 15-3.

### *Statistical Analysis*

Data were expressed as number and percentage with their corresponding 95% confidence intervals (CI), or a median and 25%–75% quartiles. An analysis of the diagnostic efficacy curves (ROC) determined the yield of the tumor markers for identifying malignancy, seeking cutoff points with 100% specificity (i.e., no BPE above this threshold); these calculations were obtained excluding PMPE. Qualitative and quantitative variables between patients with MPE, PMPE, and BPE were compared using the Kruskal–Wallis and chi-squared tests, respectively. The frequency of elevated tumor markers among the different tumor types was compared using the chi-squared test with subsequent analysis of standardized residuals. Sensitivity and odds ratios were calculated using a $2\times2$ table. Calculations were performed using the SPSS statistical package, version 22.0.

## Results

### *Study Population*

During the study period, 2580 patients referred for CEA or CA 15-3 determinations in PF were identified. After exclusion of 191 empyemas (gross pus) and 814 individuals who met Light's criteria for transudate,[6] the study population consisted of 1575 patients with non-purulent pleural exudates. Of these, 549 had cytologically demonstrated MPE, 284 had PMPE, and 742 had BPE (Table 1).

### *Diagnostic Efficacy of Tumor Markers in Pleural Fluid*

Median concentrations of CEA and CA 15-3 in PE were significantly higher in MPE than in the other groups, and also significantly higher in PMPE than in BPE (Table 2).

ROC analysis of the MPE and BPE populations established pleural concentrations of CEA>45 ng/mL and CA 15-3>77 IU/mL as 100% specific cutoff points. In 41% (95% CI: 37–45) and 40% (95% CI: 36–44) of subjects with MPE, respectively, levels of these markers were above these limits. Moreover, 60% (95% CI: 56–64) of MPE patients had elevated levels of either of the 2 markers. Although elevated markers in PF was a definitive factor for confirming MPE (infinite positive probability ratios), their absence did not substantially modify the probability of cancer (negative probability ratios of 0.59 and 0.60 for CEA and CA 15-3, respectively, implying