JBUON 2017; 22(6): 1390-1394
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Carcinoembryonic antigen and carbohydrate antigen 19-9 serum levels in non-small cell lung cancer

Nikolaos Tsoukalas[1]*, Ioannis D. Kostakis[2]*, Constantinos Giaginis[3], Maria Tolia[4], Michail Galanopoulos[5], Maria Kiakou[5], Eleni Aravantinou-Fatorou[6], Konstantinos Tsapakidis[7], Panagiotis Baxevanos[1], Ioannis Litos[7], Vasiliki Tzouda[8], Alexandros Tzovaras[8], George Kyrgias[4], Evangelos Tsiambas[1], Stamatios Theocharis[3]

[1]Department of Oncology, Veterans Hospital (NIMTS), Athens, Greece; [2]Second Department of Propedeutic Surgery, "Laiko" General Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece; [3]First Department of Pathology, National and Kapodistrian University of Athens, Medical School, Athens, Greece; [4]Department of Radiotherapy-Radiation Oncology, University of Thessaly, Medical School, Larissa, Greece; [5]Department of Oncology, "401" General Military Hospital, Athens, Greece; [6]Department of Oncology, "251" Air Force Hospital, Athens, Greece; [7]Department of Oncology, University of Thessaly, Medical School, Larissa, Greece; [8]Department of Oncology, "Saint Savvas" Anticancer Hospital, Athens, Greece

*These authors contributed equally to this work

Summary

Purpose: *To investigate the potential diagnostic and prognostic role of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) serum levels in non-small cell lung cancer (NSCLC).*

Methods: *One hundred consecutive patients with newly diagnosed primary NSCLC were included in this study (88 men and 12 women). Blood was drawn before any kind of treatment and the collected serum was processed using chemiluminescence in order CEA and CA 19-9 levels to be measured.*

Results: *No significant associations between CEA or CA 19-9 levels and any tested clinical and pathological parameter were detected. Moreover, CEA levels did not seem to affect survival. On the other hand, patients with high CA 19-9 values (≥37 IU/ml) (median survival: 8 months) had a shorter overall survival than patients with low CA 19-9 values (<37 IU/ml) (median survival: 13 months) (p=0.026). However, CA 19-9 levels did not remain an independent prognostic factor in the multivariate survival analysis (p=0.114).*

Conclusion: *CEA and CA 19-9 serum levels do not seem to have any diagnostic role in NSCLC. With regard to their prognostic role, CEA values do not seem to affect the prognosis in NSCLC. However, high CA 19-9 values are associated with worse prognosis.*

Key words: *carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), lung cancer*

Introduction

Lung cancer is the primary cause of cancer-related mortality worldwide [1]. There are four main histological types of lung cancer. Squamous cell carcinoma, adenocarcinoma and large cell carcinoma form the group of non-small cell lung carcinomas (NSCLCs), into which most cases fall, whereas small cell lung carcinomas constitute a different category [2,3]. Although no biomarker has been included in surveillance guidelines yet, there are a number of biomarkers that have been tested in NSCLC providing promising results regarding diagnosis and/or prognosis of this disease [4]. Our aim was to investigate the potential diagnostic and prognostic role of CEA and CA 19-9 serum levels in NSCLC.

Correspondence to: Nikolaos Tsoukalas, MD, MSc, PhD. 10-12 Gennimata Street, Ampelokipi, 11524, Athens, Greece.
Tel: +30 6977366056, E-mail: tsoukn@yahoo.gr
Received: 15/05/2017; Accepted: 06/07/2017

Methods

Patients

One hundred consecutive patients with newly diagnosed primary NSCLC were included in this study [88 men and 12 women, mean age ± SD: 68.4 years ± 10.8, median age (range): 70 years (36-92)]. No patient had received any treatment previously. We reviewed their medical records in order to gather data about the following parameters: age, gender, smoking habits, alcohol consumption, ECOG performance status, histological type of cancer [adenocarcinoma, squamous, large cell or not otherwise specified (NOS)], stage (according to the 7th edition of the TNM classification of UICC/AJCC), T stage (T), N stage (N), presence of distant metastases (M), histological grade, presence of lymphovascular invasion, inflammation, necrosis and fibrosis and overall survival. Patients' data are listed in Table 1. All the participants gave informed consent and the study conformed to the Declaration of Helsinki and was approved by the Ethics Committees of our institutes.

Measurement of CEA and CA 19-9 serum levels

Three ml of blood were drawn from each patient and put in serum-separating tubes before the application of any kind of treatment. Blood was allowed to clot for at least 30 min at room temperature. Subsequently, the serum-separating tubes were centrifuged for 15 min at 2500 rpm. The collected serum was processed using chemiluminescence in order CEA and CA 19-9 levels to be measured within 2 hrs. The normal values according to the used assays were <10 ng/ml for CEA and <37 IU/ml for CA 19-9.

Statistics

Assessment of normal data distribution was done using the Shapiro-Wilk test. T-test and Mann-Whitney U test were used to compare two groups according to whether values followed normal distribution or not, respectively. One way analysis of variance (ANOVA) with the Bonferroni correction and Kruskal-Wallis test were used for comparisons among three or more groups according to whether values followed normal distribution or not, respectively. Correlations between two quantitative variables were estimated using the Spearman's rank correlation coefficient.

For the assessment of overall survival, the patients were divided into four groups, according to the levels of CEA and CA 19-9: group 1: ≤25th percentile; group 2: >25th and ≤50th percentile; group 3: >50th and ≤75th percentile; and group 4: >75th percentile. In addition, the patients were also divided into two groups, according to whether CEA and CA 19-9 levels were within normal range. Overall survival was estimated using the Kaplan-Meier method and the log-rank test was used for the comparison of overall survival between different groups. Cox regression analysis was performed for the multivariate survival analysis.

All the tests were two-tailed. The results were considered statistically significant if $p<0.05$.

Table 1. Patient and disease characteristics

Parameter	*Number*
Gender	
Male	88
Female	12
Age, years	
Mean ± SD	68.4 years ± 10.8
Median (range)	70 years (36 – 92)
<70	49
≥70	51
Smoking	
Yes	93
No	7
Alcohol consumption	
Yes	59
No	41
Performance status	
0	29
1	52
2	19
Histological type	
Squamous cell carcinoma	36
Adenocarcinoma	42
Large cell carcinoma	8
Unspecified NSCLC	14
T	
T1	15
T2	39
T3	24
T4	22
N	
N0	9
N1	28
N2	51
N3	12
M	
M0	58
M1	42
Stage	
I	5
II	21
III	32
IV	42
Histological grade	
I	11
II	41
III	48
Lymphovascular invasion	
Yes	27
No	73
Inflammation	
Yes	14
No	86
Necrosis	
Yes	37
No	63
Fibrosis	
Yes	11
No	89
Survival	
Alive	4
Dead	96
Mean ± SD	15.7 months ± 13.6
Median (range)	12 months (1–73)
CEA serum levels	
Normal (<10 ng/ml)	70
Increased (≥10 ng/ml)	30
CA 19-9 serum levels	
Normal (<37 IU/ml)	76
Increased (≥37 IU/ml)	24

T: primary tumor infiltration, N: infiltrated regional lymph nodes, M: distant metastasis, CEA: carcinoembryonic antigen, CA 19-9: carbohydrate antigen 19-9

Results

Associations between CEA levels and various clinicopathological parameters

There were no significant associations between CEA levels and any tested parameter, namely age (younger or older than 70 years) (p=0.896), gender (p=0.379), smoking (p=0.962), alcohol consumption (p=0.549), ECOG performance status (p=0.952), histological type (p=0.943), T (p=0.24), N (p=0.702), M (p=0.574), TNM stage (p=0.412), grade (p=0.89), presence or absence of lymphovascular invasion (p=1), inflammation (p=0.135), necrosis (p=0.572) and fibrosis (p=0.361).

Associations between CA 19-9 levels and various clinicopathological parameters

No significant associations were detected between CA 19-9 levels and any tested parameter, namely age (younger or older than 70 years) (p=0.424), gender (p=0.247), smoking (p=0.32), alcohol consumption (p=0.512), ECOG performance status (p=0.743), histological type (p=0.155), T (p=0.739), N (p=0.508), M (p=0.238), TNM stage (p=0.443), grade (p=0.408), presence or absence of lymphovascular invasion (p=0.404), inflammation (p=0.813), necrosis (p=0.197) and fibrosis (p=0.839).

Survival analysis according to CEA levels

CEA levels did not seem to affect survival. No significant differences were detected regarding overall survival either in the comparison among the four groups according to CEA levels (p=0.456) or in the comparison between patients with normal (<10 ng/ml) and increased CEA levels (≥10 ng/ml)(p=0.942) (Figure 1).

Survival analysis according to CA 19-9 levels

CA 19-9 levels seemed to affect survival. Specifically, patients with high CA 19-9 levels (>75th percentile:>34.1 IU/ml) (median survival: 9 months, SE: 1.5 months, 95% CI: 6.1-11.9 months) had shorter overall survival than patients with low CA 19-9 levels (≤75th percentile) (median survival: 13 months, SE: 0.7 months, 95% CI: 11.7-14.3 months) (p=0.036). This finding coincided with the shorter overall survival of patients with increased CA 19-9 levels (≥37 IU/ml) (median survival: 8 months, SE: 1.6 months, 95% CI: 4.8-11.2 months) with that of patients with normal CA 19-9 levels (<37 IU/ml) (median survival: 13 months, SE: 0.7 months, 95% CI: 11.7-14.3 months) (p=0.026; Figure 2). However, increased CA 19-9 levels did not remain an independent prognostic factor in the multivariate survival analysis, either with the categorization according to percentiles (p=0.114) or with the categorization according to the presence of normal or abnormal values (p=0.114). On the contrary, worse performance status (p=0.04), higher histological grade (p=0.038) and higher stage of disease (p=0.005) were found to be independent prognostic factors predicting worse outcomes.

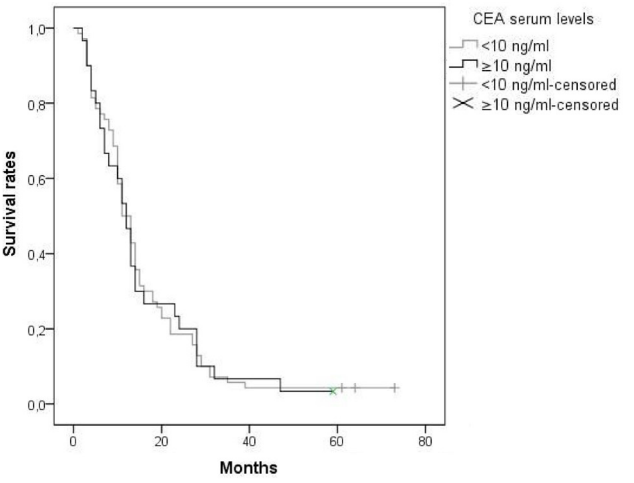

Figure 1. Kaplan – Meier curves of overall survival according to CEA serum levels.

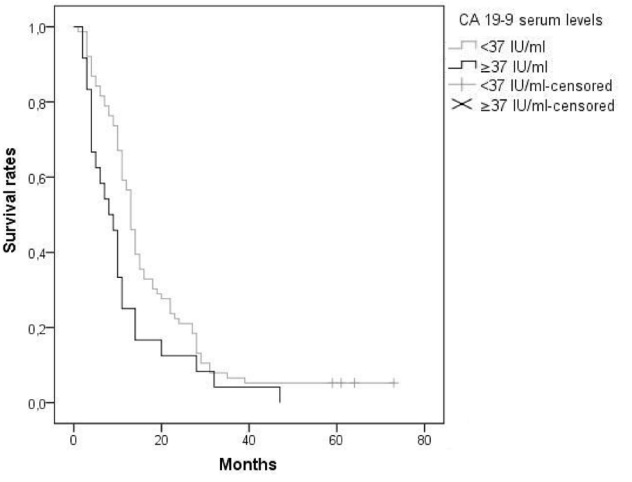

Figure 2. Kaplan – Meier curves of overall survival according to CA 19-9 serum levels.

Discussion

CEA has been tested as diagnostic and prognostic biomarker in NSCLC in several studies, but with controversial results. Wang et al. [5], Asmitananda et al. [6] and Mumbarkar et al. [7] reported that serum CEA is higher in lung cancer than in benign lung diseases, but it is not accurate enough in differentiating lung cancer from them. Molina et al. [8] also detected abnormal CEA serum levels only in a portion of patients with NSCLC (61.9%). They also reported that CEA values are more frequently increased in stage IV

NSCLC than in NSCLC of earlier stages, with this difference being more apparent in adenocarcinomas than in squamous cell carcinomas [8]. In addition, Tomita et al. [9] and Salgia et al. [10] found increased levels of CEA in patients with stage III or IV disease. On the contrary, Mumbarkar et al. [7] stated that CEA serum levels are higher in stage II NSCLC than in NSCLC of later stages. In addition, Lee et al. [11] suggested that CEA values in serum are increased in patients with T3 and T4 tumors, as well as in patients with N2 and N3 tumors. However, Tomita et al. [9,12] did not confirm this, reporting that there is no significant difference between T3 and T4 tumors on the one hand and T1 and T2 tumors on the other. Pollan et al. [13], on the other hand, did not detect any differences among tumors of different T stages, but reported that N2 tumors are more likely to have abnormal CEA values. Moreover, Asimtananda et al. [6], Molina et al. [8], Lee et al. [11] and Salgia et al. [10] found that CEA serum levels are more likely to be elevated in adenocarcinomas in comparison with the other subtypes of NSCLC. On the contrary, Pollan et al. [13] did not detect any significant differences in CEA values among different histological types.

With regard to its potential prognostic role, Cai [14], Ozeki et al. [15] and Pollan et al. [13] found that patients with NSCLC and normal CEA serum levels have longer overall and disease-free survival than those with abnormal CEA serum levels. The worse prognosis of patients with NSCLC and abnormal CEA values in serum was also confirmed by Takahashi et al. [16] and Tomita et al. [17] Nonetheless, Tomita et al. [9] detected this worse prognosis of patients with abnormal CEA values only in adenocarcinomas and not in squamous cell carcinomas, whereas Liu et al. [18] did not detect any correlation between CEA serum levels and overall survival in patients with NSCLC. Two meta-analyses, conducted by Wang et al. [19] and Zhang et al. [20], have tried to address the issue of the potential prognostic role of CEA. They concluded that the elevated serum levels of CEA are associated with worse outcomes in NSCLC [19,20].

Concerning the potential diagnostic and/or prognostic role of CA 19-9 in NSCLC, there are fewer studies than those for CEA. Wang et al. [5] and Asmitananda et al. [6] reported that CA 19-9 in serum is higher in lung cancer than in benign lung diseases, but it is not accurate enough in differentiating lung cancer from them. Furthermore, Asmitananda et al. [6] did not find significant differences regarding CA 19-9 values among the different subtypes of lung cancer. Molina et al. [8] detected abnormal CA 19-9 serum levels only in a portion of patients with NSCLC (29%). They also reported that CA 19-9 values are more frequently increased in stage IV NSCLC than in NSCLC of earlier stages, with this difference being more apparent in adenocarcinomas than in squamous cell carcinomas [8].

Our results are added to the already existing controversial findings of the literature. According to our results, preoperative CEA serum levels do not seem to have any particular diagnostic or prognostic role in NSCLC, since they are not associated with histological type, stage, pathological features or survival. Moreover, preoperative CA 19-9 serum levels do not also seem to have any particular diagnostic role in NSCLC, due to the absence of significant associations with histological type, stage or pathological features, but they seem to possess prognostic role. We found that patients with abnormal preoperative CA 19-9 serum levels have shorter overall survival than patients with normal levels, although they did not remain an independent prognostic factor in multivariate survival analysis. In conclusion, preoperative CA 19-9 serum levels may predict worse prognosis when they are abnormal in patients with NSCLC. Further prospective cohort studies are strongly recommended in order to achieve more precise conclusions.

Conflict of interests

The authors declare no conflict of interests.

References

1. Didkowska J, Wojciechowska U, Mańczuk M, Łobaszewski J. Lung cancer epidemiology: contemporary and future challenges worldwide. Ann Transl Med 2016;4:150.
2. Gerber DE, Paik PK, Dowlati A. Beyond adenocarcinoma: current treatments and future directions for squamous, small cell, and rare lung cancer histologies. Am Soc Clin Oncol Educ Book 2015:147-62.
3. Petersen I. The morphological and molecular diagnosis of lung cancer. Dtsch Arztebl Int 2011;108:525-31.
4. Qi W, Li X, Kang J. Advances in the study of serum tumor markers of lung cancer. J Cancer Res Ther 2014;10:95-101.

5. Wang WJ, Tao Z, Gu W, Sun LH. Clinical observations on the association between diagnosis of lung cancer and serum tumor markers in combination. Asian Pac J Cancer Prev 2013;14:4369-71.
6. Li X, Asmitananda T, Gao L et al. Biomarkers in the lung cancer diagnosis: a clinical perspective. Neoplasma 2012;59:500-7.
7. Mumbarkar PP, Raste AS, Ghadge MS. Significance of tumor markers in lung cancer. Indian J Clin Biochem 2006;21:173-6.
8. Molina R, Auge JM, Escudero JM, et al. Mucins CA 125, CA 19.9, CA 15.3 and TAG-72.3 as tumor markers in patients with lung cancer: comparison with CYFRA 21-1, CEA, SCC and NSE. Tumour Biol 2008;29: 371-80.
9. Tomita M, Matsuzaki Y, Edagawa M, Shimizu T, Hara M, Onitsuka T. Prognostic significance of preoperative serum carcinoembryonic antigen level in lung adenocarcinoma but not squamous cell carcinoma. Ann Thorac Cardiovasc Surg 2004;10:76-80.
10. Salgia R, Harpole D, Herndon JE 2nd, Pisick E, Elias A, Skarin AT. Role of serum tumor markers CA 125 and CEA in non-small cell lung cancer. Anticancer Res 2001;21:1241-6.
11. Lee S, Lee CY, Kim DJ, Hong DJ, Lee JG, Chung KY. Pathologic correlation of serum carcinoembryonic antigen and cytokeratin 19 fragment in resected nonsmall cell lung cancer. Korean J Thorac Cardiovasc Surg 2013;46:192-6.
12. Tomita M, Matsuzaki Y, Shimizu T, Hara M, Ayabe T, Onitsuka T. Relationship between serum carcinoembryonic antigen level and T status in non-small cell lung cancer. Anticancer Res 2006;26:3845-8.
13. Pollán M, Varela G, Torres A et al. Clinical value of p53, c-erbB-2, CEA and CA125 regarding relapse, metastasis and death in resectable non-small cell lung cancer. Int J Cancer 2003;107:781-90.
14. Cai Z. Relationship between serum carcinoembryonic antigen level and epidermal growth factor receptor mutations with the influence on the prognosis of non-small-cell lung cancer patients. Onco Targets Ther 2016;9:3873-8.
15. Ozeki N, Fukui T, Taniguchi T et al. Significance of the serum carcinoembryonic antigen level during the follow-up of patients with completely resected non-small-cell lung cancer. Eur J Cardiothorac Surg 2014;45:687-92.
16. Takahashi N, Suzuki K, Takamochi K, Oh S. Prognosis of surgically resected lung cancer with extremely high preoperative serum carcinoembryonic antigen level. Gen Thorac Cardiovasc Surg 2011;59:699-704.
17. Tomita M, Shimizu T, Ayabe T, Onitsuka T. Prognostic significance of the combined use of preoperative platelet count and serum carcinoembryonic antigen level in non-small-cell lung cancer. Gen Thorac Cardiovasc Surg 2010;58:573-6.
18. Liu H, Gu X, Lv T et al. The role of serum carcinoembryonic antigen in predicting responses to chemotherapy and survival in patients with non-small cell lung cancer. J Cancer Res Ther 2014;10:239-43.
19. Wang XB, Li J, Han Y. Prognostic significance of preoperative serum carcinoembryonic antigen in non-small cell lung cancer: a meta-analysis. Tumor Biol 2014;35:10105-10.
20. Zhang ZH, Han YW, Liang H, Wang LM. Prognostic value of serum CYFRA21-1 and CEA for non-small-cell lung cancer. Cancer Med 2015;4:1633-8.