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Prognostic assessment of tumor markers in lung carcinomas

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SUMMARY

BACKGROUND: Serum tumor markers are molecules that are secreted by tumor cells and may be present in small amounts in the serum of healthy individuals. Their role as prognostic factors in lung cancer remains controversial.

OBJECTIVE: To assess the prognostic role of CEA, CA 19-9, CA 15-3, and CA 125 in non-squamous non-small cell lung cancer.

PATIENTS AND METHODS: A total of 112 patients with non-squamous non-small cell lung cancer from two Oncology Centers were retrospectively analyzed. Tumor marker levels were measured prior to treatment. Data regarding clinical characteristics and overall survival were collected.

RESULTS: Median overall survival of all patients was 15.97 months. Pre-treatment elevations of CA 125 and CA 15-3 were associated with shorter overall survival (p=0.004 and p=0.014, respectively). Single CEA and CA 19-9 elevations were not associated with a worse prognosis. Patients with two or more elevated markers had a statistically significant decrease in overall survival (p=0.008). In the multivariate analysis, smoking status and number of positive tumor markers at diagnosis were independently associated with a worse prognosis.

CONCLUSION: High pre-treatment levels of tumor markers were correlated with decreased survival in patients with non-squamous non-small cell lung cancer.

KEYWORDS: Lung neoplasms. Carcinoembryonic antigen. CA-19-9 antigen. Mucin-1.

INTRODUCTION

Lung cancer is the most lethal neoplasm worldwide[1]. Despite recent therapeutic advancements, the life expectancy of these patients remains short, since approximately 80% of cases are diagnosed at an advanced stage. Clinical and/or pathological staging is considered the main prognostic factor. Other important factors are performance status, weight loss, smoking status, and some histopathological and molecular traits[2-4].

Tumor markers are molecules, usually peptides, which are secreted by tumor cells. Their role as a prognostic or therapeutic response monitoring tool in other neoplasms is already widely known. In lung cancer, their use is not routinely recommended by oncology societies[5,6], and hence, in general, they are scarcely employed.

In view of the differing conclusions published on the prognostic value of tumor markers in lung cancer, conducting a new study on the subject could contribute to better understanding the topic.

This study aims to assess the importance of CEA, CA 19-9, CA 15-3, and CA 125 markers as prognostic factors in patients with non-squamous non-small cell lung cancer (NSCLC).

METHODS

This is a retrospective cohort study based on the data collected from medical records in two different institutions. The population comprised 112 patients with non-squamous NSCLC, diagnosed between May 2002 and July 2019. Samples containing the markers were collected from the patients before starting the treatment for cancer.

The following data were collected: name, age, sex, duration of survival, clinical or pathological stage of the neoplasm, histological type, smoking status, and the number of positive markers at diagnosis.

Patients from *Clínica São Germano* had their samples collected at different laboratories located in the State of São Paulo. The following marker level values were considered "positive": CEA>5 ng/mL, CA 19-9>37 UI/mL, CA 125>35 UI/mL, and CA 15-3>30 UI/mL. For patients from *Santa Casa de Misericórdia*, the samples were collected by the institution laboratory, and the following marker level values were considered "positive": CEA>5 ng/mL, CA 19-9>37 UI/mL, CA 125>35 UI/mL, and CA 15-3>25 UI/mL.

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Inclusion criteria

- Histologically documented diagnosis of non-squamous NSCLC;
- Age³18 years;
- Having had at least one of the four markers dosed before starting treatment;
- Patients diagnosed with another localized malignant neoplasm prior to lung cancer were allowed, as long as they had received treatment and showed no evidence of relapse for at least 5 years.

Exclusion criteria

- Incomplete data in medical records;
- Diagnosis of another metastatic malignant neoplasm (synchronous or prior to the lung cancer diagnosis);
- Refusal to sign the VICF.

Statistical analysis

The duration of overall survival (OS) was calculated as the time from the date of diagnosis until the date of death from any cause. Data were collected until May 2020.

Variables were analyzed descriptively. For quantitative variables, this analysis was performed by observing the minimum and maximum values and calculating means, standard deviations, and medians. For qualitative variables, absolute and relative frequencies were calculated.

To test the homogeneity among proportions, the chi-square test or Fisher's exact test was used. To study the association of markers with survival time, the Kaplan–Meier survival curve and the univariate Cox regression model were used. The multivariate study was performed by using the multivariate Cox model. Variables with $p<0.10$ in the univariate analysis were selected. A "stepwise" selection process was applied in order to produce the final model. The significance level used for the tests was 5%. The software program used in the analyses was SPSS 17.0.

RESULTS

Altogether, 112 patients aged between 28 and 91 years (mean of 66.19 years with a standard deviation of 12.02 years and a median of 66.50 years) were evaluated. Other clinical characteristics of the population are described in Table 1.

CEA was measured in 109 patients. Of these, 64.2% showed an increased level of the marker. The CA 19-9 level, in turn, was measured in 97 patients and found to be high in 30.9% of them. The CA 125 marker level was measured in 97 individuals and found to be increased in 56.7% of them. The CA 15-3 level was measured in 91 cases and tested positive in 50.6% of patients (Table 1).

Overall survival ranged from 25 days to 137 months (mean of 27.08 months with a standard deviation of 28.66 months and a median of 15.97 months). At the time of analysis, 83 patients (74.1%) had died.

Table 2 shows the "Hazard Ratio" values for survival according to the univariate Cox model. Smoking status, staging, high CA 125 levels, high CA 15-3 levels, and two or more of the four increased markers were the factors associated with worse survival. The median OS of patients with a negative CA 125 and a positive CA 125 were 18.84 months and 11.93 months ($p=0.004$), respectively. In patients with normal CA 15-3 level, the median OS was 18.57 months; however, in patients with a higher marker level ($p=0.014$), the median OS was 13.44

Table 1. Patients' clinical traits.

	%
Sex	
Male	50.0
Female	50.0
Histological subtype	
Adenocarcinoma	99.1
Large cell carcinoma	0.9
Staging	
I	5.4
II	6.3
IIIA	8.9
IIIB	10.7
iv	68.8
Smoking status	
No	38.9
Yes	61.1
Marker positivity frequency	
CEA	64.2
CA19-9	30.9
CA125	56.7
CA15-3	50.6
Number of positive markers	
None	19.1
One	21.4
Two	20.2
Three	23.8
Four	15.5

months. The increase in CEA and CA 19-9 levels alone did not correlate with a worse prognosis (p=0.072 and p=0.154, respectively). All four marker levels were collected in 84 patients. The median OS in patients with no positive marker was 28.53 months. The median OS in patients with one positive marker was 19.55 months, and it was 12.80 months in the group with two or more positive markers (p=0.008).

The variables such as smoking status, staging, CEA level, CA 125 level, CA 15-3 level, and the number of positive markers were used in the multivariate Cox model. The variables selected by the stepwise method were smoking status and the number of positive markers (Table 3).

The risk of death was twice as high among smokers (p=0.017). Patients with two or more high marker levels also had an approximately twofold increase in the risk of death when compared to patients with no positive marker (p=0.024).

DISCUSSION

In this work, we assessed the tumor markers CEA, CA 19-9, CA 125, and CA 15-3 in non-squamous NSCLC. The prognostic value of tumor markers in lung cancer is controversial. The most studied one is CEA, followed by CA 125. CA 15-3 and CA 19-9 have been very poorly assessed in this context.

We found that CA 125 and CA 15-3 were correlated with shorter OS in the univariate analysis.

CA 125 was positive in 56.7% of patients. Several publications report sensitivities between 31.7 and 55%[7-11]. In our patients, having high CA 125 levels before treatment was a negative prognostic factor. Other authors have obtained similar results in both early and advanced diseases. Of the four markers studied, CA 125 was the one with the most consistent results in the literature regarding its prognostic role[10,12].

Few authors have studied CA 15-3 in lung neoplasms. In our survey, CA 15-3 was positive in 50.6% of cases, which is consistent with the findings published by other authors[8,14]. Regarding survival, we found that having high pretreatment CA 15-3 levels led to a statistically significant decrease in the median OS. Our findings differ from the results published by Gross et al. who found no relationship between CA 15-3 levels and duration of survival[14].

CEA was positive in 64.2% of our cases. This result is in accordance with the results of several publications in which the CEA sensitivity ranged from 41 to 77%[7-11,14]. Nevertheless, having increased CEA levels was not considered as a negative prognostic factor. Several researchers have already assessed the prognostic utility of CEA in lung neoplasm, in both early and advanced diseases, albeit with conflicting results[10,11,13,15-23].

Table 2. "Hazard ratio" values for survival: univariate Cox model.

Variable	Hazard ratio	95%CI	p
Age			
	1.01	(0.99; 1.02)	0.532
Sex			
Female	1.00	–	–
Male	1.35	(0.87; 2.10)	0.177
Institution			
CSG	1.00	–	–
HSC	1.23	(0.76; 1.99)	0.407
Smoking status			
Non-smoker	1.00	–	–
Smoker	2.02	(1.23; 3.31)	0.006
Staging			
I–II	1.00	–	–
IIIA	7.12	(1.51; 33.53)	0.013
IIIB	10.37	(2.33; 48.93)	0.002
IV	10.15	(2.47; 41.66)	0.001
CEA			
Negative	1.00	–	–
Positive	1.54	(0.96; 2.48)	0.074
CA 19-9			
Negative	1.00	–	–
Positive	1.44	(0.87; 2.38)	0.156
CA 125			
Negative	1.00	–	–
Positive	2.04	(1.25; 3.35)	0.005
CA 15-3			
Negative	1.00	–	–
Positive	1.87	(1.13; 3.10)	0.016
Number of positive markers			
None	1.00	–	–
One	1.15	(0.45; 2.91)	0.770
Two or more	2.56	(1.20; 5.48)	0.016

Table 3. "Hazard ratio" values for survival: multivariate Cox model.

Variable	Hazard ratio	95%CI	p
Smoking status			
Non-smoker	1.00	–	–
Smoker	2.01	(1.13; 3.58)	0.017
Number of positive markers			
None	1.00	–	–
One	1.25	(0.49; 3.18)	0.637
Two or more	2.41	(1.12; 5.15)	0.024

CA 19-9 was the marker that increased the least frequently in our study (30.9%). In the few analyses of the role played by CA 19-9 in lung cancer published in the literature, the sensitivity ranged from 9.3 to 31%[8,12,13,24]. In our sample, we found no association between high CA 19-9 levels and prognosis. For Ma et al., who found a sensitivity of only 5% for CA 19-9 in patients with stage I NSCLC, an increase in the levels of this marker did not interfere with survival[15]. In contrast, other authors were able to correlate higher levels of this marker with a worse prognosis[12,24].

Finally, we found that, in patients who had at least two markers whose levels were high, survival was significantly lower in the univariate analysis. This remained to be an independent prognostic factor in the multivariate analysis. Other authors, when evaluating different combinations of markers, have also reported similar data[11,12,14,25].

Our findings, however, have limitations. This is a retrospective analysis that considers only two institutions. Another limiting factor was the use of different laboratories for the collection of samples containing the markers. Since we used qualitative data, this bias could be mitigated. Another relevant issue was the lack of data on performance status in our study. Performance status is known to be one of the main prognostic factors in oncology. In our case, the information about performance status at diagnosis was not available in a sufficient number of cases; therefore, we decided not to collect such data.

CONCLUSION

Having high levels of tumor markers prior to treatment was considered a poor prognostic factor in non-squamous NSCLC.

AUTHORS' CONTRIBUTIONS

FBS: Study Design, Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Writing – Original Draft, Writing – Review and Editing. **RSJ:** Supervision, Validation, Writing – Review and Editing.

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