Epidemiological profile and prognostic factors in patients with lung cancer

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Summary

Objective: To describe the epidemiological profile of patients with lung cancer treated at a public tertiary referral hospital specializing in oncology, and to explore variables that may be related to the overall survival (OS) of these patients.
Method: Data from the medical records of all patients with invasive lung cancer consecutively seen at the Oncology Department of Hospital Estadual Mário Covas between August 2008 and December 2013 were extracted. The information obtained was submitted to statistical analysis.
Results: Of the total 210 patients, 39 were excluded from analysis due to lack of information in the medical record. The most common histological type was adenocarcinoma, representing 39.41% of the sample, followed by squamous cell carcinoma with 25.29% and small-cell carcinoma with 13.53%. Other histological types were responsible for the remaining 21.76%. There was a statistically significant association between Karnofsky performance status (KPS) ≤ 70%, palliative chemotherapy lines performed and stage at diagnosis, and OS. Additionally, administration of target therapy to patients with *EGFR* mutation was associated with significantly better overall survival. However, analysis of laboratory variables (hemoglobin, albumin and LDH) as possible prognostic factors for survival showed no statistically significant relationship. Among patients with stage III and IV, the median OS was 10.1 months.
Conclusion: The risk factors for shorter OS were KPS score ≤ 70%, less than two lines of palliative chemotherapy, and stage III and IV at diagnosis. The implementation of CT screening for risk patients may allow earlier diagnosis of cases and improve these results.

Keywords: lung neoplasms, epidemiology, survival, prognosis, risk factors.

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Introduction

Lung cancer was considered a rare disease until the early twentieth century.[1] Since then, its occurrence increased rapidly and is currently one of the most prevalent cancers in Brazil and in the world, with high mortality rate and increasing incidence especially among women. In Brazil, for 2014, according to the National Cancer Institute (Instituto Nacional do Câncer, INCA), 16,400 new cases of lung cancer are estimated among men and 10,930 among women. These numbers correspond to an estimated risk of 16.79 new cases per 100,000 men and 10.75 per 100,000 women.[1] The US estimate far exceeds the Brazilian; for 2014, just over 222,000 new cases of lung cancer are expected.[2,3] It is responsible for the highest percentage of mortality from malignant neoplasms, approaching 30% of total deaths,[2] so that only 16.6% of patients will be alive 5 or more years after diagnosis.[4]

Although genetic and environmental factors are involved in the pathogenesis, smoking persists as the primary trigger for most cases.[4,5] Other risk factors include exposure to asbestos, arsenic, chromium, nickel, cadmium and silica.[6,7]

The main histologic types of lung cancer are squamous cell carcinoma, adenocarcinoma, small-cell carci-

noma (oat-cell), and large-cell carcinoma. During the last decades there has been a decrease in squamous cell carcinomas, while adenocarcinomas increased. This is probably due to changes in the composition of tobacco products, as well as the change in people's behavior regarding smoking.[1]

In the last decade there has been a revolution in the understanding of this cancer's pathogenesis, molecular biology and treatment. Several gene mutations have been discovered (e.g. *EGFR* and *EML4-ALK*), culminating in the development of the so-called molecularly targeted drugs.[8] The treatment, which for many years drew heavily on platinum-based chemotherapy has been incremented by adding such drugs, which caused an increase in response rate, improved quality of life, a more favorable toxicity profile, and longer progression-free survival.[9-12]

Despite the current staging system and new technologies developed in recent years, most patients (75 to 80%) are still diagnosed with advanced or metastatic disease, and even those treated with curative intent (stages I to III) develop distant metastases during disease progression. Some factors such as old age, performance status, and stage at diagnosis are directly related to overall survival (OS).[13]

Our study aims to trace the epidemiological profile of patients with lung cancer treated at a public tertiary referral hospital specializing in oncology, as well as explore some prognostic variables that may be involved with OS.

Method

This is a single-center retrospective epidemiological study that included data from the medical records of all patients with invasive lung cancer consecutively seen at the Oncology Service of Hospital Estadual Mário Covas (HEMC) in August 2008 to December 2013. The HEMC is the largest referral center for oncology in the Greater ABC Area in São Paulo, treating only patients of the public Unified Health System.

For the entire sample, clinical, epidemiological and pathological characteristics were analyzed. However, variables considered as possible prognostic factors were analyzed only in patients with non-small cell lung cancer, having in mind that this entity has peculiarities if compared to small-cell tumors.

The qualitative variables were described as absolute and relative frequency, and the quantitative variables, since they do not have a normal distribution (Shapiro-Wilk, $p>0.05$), were presented as medians and confidence intervals, at 25 and 75 percentiles.

In order to analyze the association between qualitative variables, we used a chi-square test. The analysis of quantitative variables between two categories and between groups was performed using the Mann-Whitney and Kruskal-Wallis, respectively. As for OS analysis, we used Cox regression with log-rank test and Kaplan-Meyer curves; OS was defined as the time between diagnosis and death. We adopted a confidence level at 95% and data analysis was performed using Stata software, version 11.0. Statistical analyzes of prognostic factors were calculated only for non-small-cell tumors.

Results

From August 2008 to December 2013, 210 patients with invasive lung cancer were identified. Of these, 39 were excluded from the analysis due to lack of necessary information in the medical records or loss of follow-up. In 171 patients analyzed, the average age was 64 years, ranging from 33 to 90 years. As for gender, 114 (66.67%) were men and 57 (33.33%), women. 119 patients were smokers (69.59%), and the remaining 52 (30.41%), non-smokers.

Regarding histology, 67 (39.41%) had adenocarcinoma, 43 (25.29%) squamous histology, 37 (21.76%) had other histology types, and 23 (13.53%) small-cell carcinomas. Among the patients with adenocarcinomas, 15 samples were subjected to mutation analysis of the *EGFR* gene (epidermal growth factor receptor), with nine showing mutation and six wild-type *EGFR*. The other histological types included: carcinoid tumor, large-cell, unspecified or undefined non-small-cell, and undifferentiated carcinoma.

Most patients were diagnosed at stage IV (63.74%). The main metastatic site was the lung (35.09%), followed by the bones with 32.16%; noting that patients could have more than one metastatic site.

We observed that chemotherapy was the predominant type of treatment, given to 80.12% of patients. 11 patients (6.43%) were treated with palliative support alone. Targeted drugs were used in 11 patients, nine of them as first line, and two as second line medication (provided in the clinical research protocol).

The median follow-up was 9.9 months (range 4.2 to 20 months) and, by the end of the study, 80.12% of the patients died due to lung cancer. The median OS was 11.2 months for non-small-cell tumors, and 7.8 months for small-cell (oat-cell) tumors.

Patients in stages I and II presented median OS of 42.6 months, while stages III and IV had 10.1 months of median OS. Analyzing patients as staging subgroups (I and II *vs.* III and IV), there were statistically significant

differences in the OS with p=0.034. The corresponding Kaplan-Meier curves are shown in Figure 1.

Regarding Karnofsky performance status (KPS) 77 patients (45.03%) belonged to the ≥ 70% group, favored in the median OS, with hazard ratio of 0.32 (95CI 0.21-0.50) and p<0.001. Another finding was that patients who underwent more than two lines of palliative chemotherapy had longer OS, with p<0.001. The corresponding Kaplan-Meier curves are shown in Figure 2.

Three laboratory variables were analyzed (hemoglobin, albumin and lactate dehydrogenase – LDH). Hemoglobin is stratified into < 11 g/dL and > 11 g/dL, comprising 31.2 and 68.6% of patients, respectively. Albumin was stratified into < 3,0 g/dL and ≥ 3,0 g/dL, and included 26 and 47 patients, respectively. Last, we stratified the LDH variable into < 480 (U/L), which included 48 patients, and LDH ≥ 480 (U/L) found in 60 patients. However, we did not find any relationship between these variables and OS.

Multivariate analysis by Cox regression showed that KPS score < 70% is a risk factor for shorter OS and the use of targeted drugs is a protective factor for increased OS. Hazard ratio values and their respective confidence intervals are shown in Table 1.

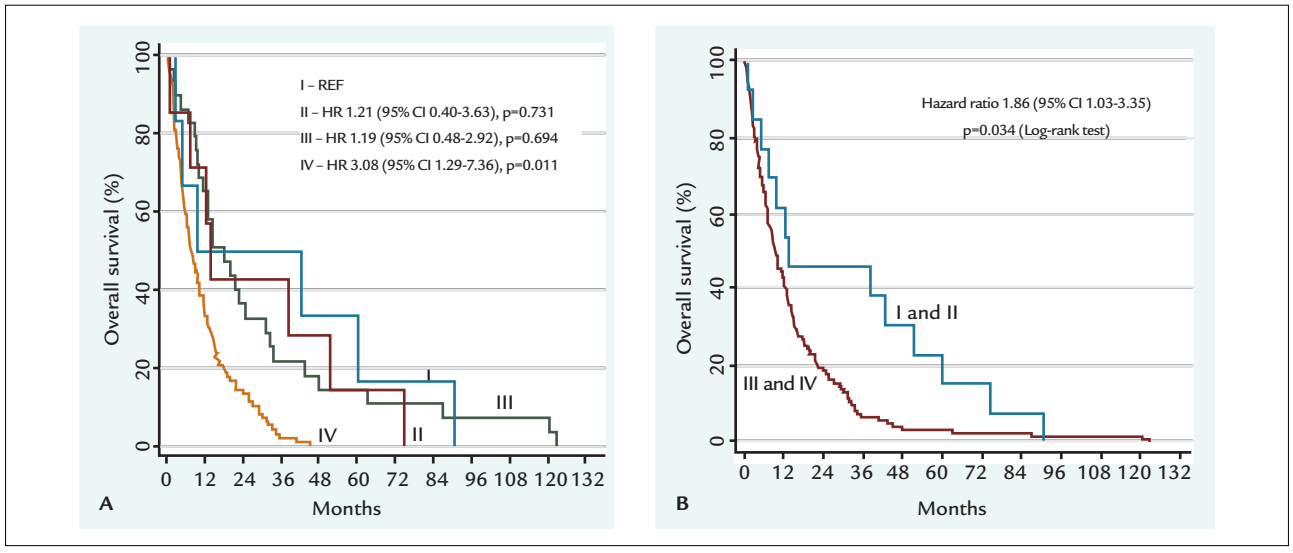

FIGURE 1 Kaplan-Meier curves. (A) Overall survival for individual staging, and (B) Overall survival grouped by stage I and II *versus* III and IV. HR: hazard ratio.

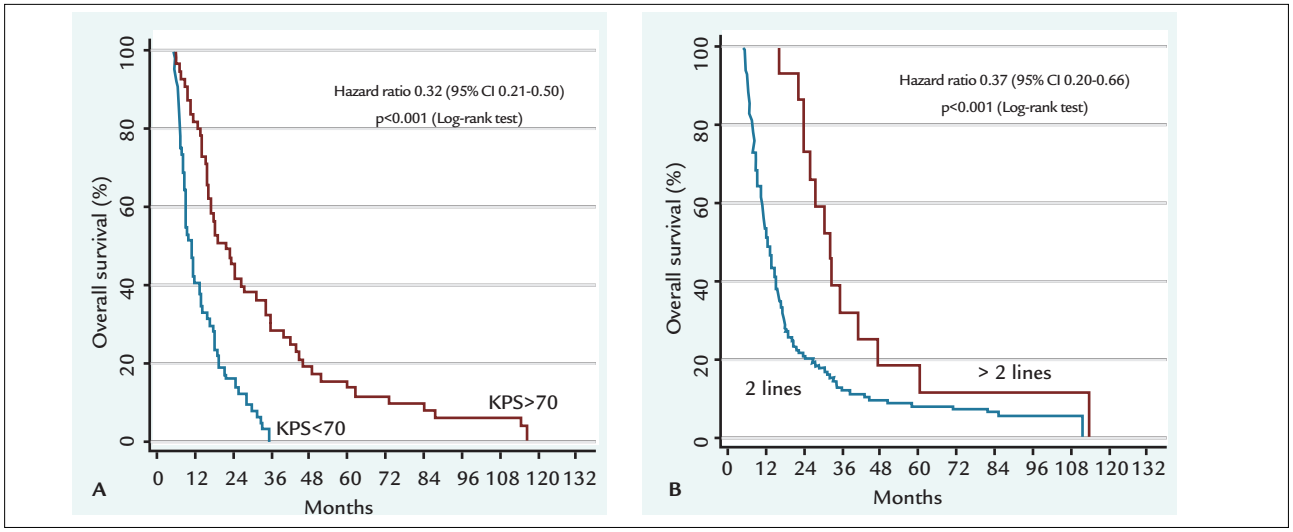

FIGURE 2 Overall survival curves divided by KPS score (A) and by palliative treatment lines (B).

TABLE 1 Multivariate analysis of factors associated with overall survival.

Variable	HR (95CI)	p*
KPS < 70%	2.53 (1.17 – 5.47)	0.018
Use of targeted drugs	0.91 (0.01 – 0.86)	0.036
Advanced stages	4.88 (0.99 – 23.96)	0.051
Albumin < 3.0 g/dL	1.70 (0.89 – 3.28)	0.110
Non-smoker	0.72 (0.32 – 1.60)	0.420

KPS: Karnofsky performance status; HR: hazard ratio; 95CI: 95% confidence interval; *Logistic regression.

Discussion

Our study is a retrospective, observational and epidemiological analysis of cases of lung cancer in a Brazilian oncological reference hospital in the public health system, as well as its relationship to the literature. The Brazilian estimate for the number of cases of lung cancer is very low compared to global and US epidemiology. It is worth mentioning that US statistics include more than 224,000 new cases of lung cancer in 2015, while Brazilian statistics for 2014 predicted only 27,330 new cases. This reveals strong discrepancy comparing the total population of the two countries.[1,2]

According to data released by the National Cancer Comprehensive Network (NCCN),[4] 85% of lung cancers belong to the class of non-small-cell tumors (NSCLC) and the remaining 15% to the group of tumors known as small-cell or oat-cell lung carcinoma (SCLC). This result was similar to that found in our study, which detected 86.47% of non-small-cell tumors and 13.53% of small-cell carcinomas. As for histological subtype, 39.41% of adenocarcinomas, 25.29% of squamous cell carcinomas, 13.53% of small-cell tumors and 21.76% of unspecified non-small-cell tumors were detected, which is in line with the literature with respectively 38, 20, 13 and 18%.[14] In a study published by Caires-Lima et al.,[15] conducted at Instituto do Câncer do Estado de São Paulo, also a referral center for oncology, epidemiology of 232 patients pointed out the adenocarcinoma subtype with 61% of cases, followed by squamous cell carcinoma and large-cell carcinoma, with 30 and 2%, respectively. In 7% of patients determining the subtype was not possible, and 7.6% represented small-cell tumors.[15]

As the study was conducted in a service that works with the public Unified Health System exclusively, only 22% of patients with adenocarcinoma underwent mutation analysis of the *EGFR* gene, which was possible after inclusion of patients in clinical research protocols. Of the patients tested, 60% had mutations of the *EGFR* gene, a number well above that found in the literature, which is around 10 to 30% for the general population, but reaching levels of up to 60% among non-smoking Asian women.[16-18] Therefore, the higher prevalence of *EGFR* mutation observed in our study might be due to bias in the selected patients, once the majority of them were treated in the context of international clinical trials with rigid inclusion criteria.

NSCLC is usually diagnosed in advanced stages of the disease, rarely in early stages. Even in developed countries like the US, only 15% of patients have cancer stages I and II at diagnosis, according to the SEER (Surveillance, Epidemiology, and End Results).[2] Statistics for stage III and IV are 22 and 57%, respectively; the other 6% are unknown.[2] Our data were similar to those observed in the literature, for example the stage IV, which was present in 63.74% of our sample, similar to the data observed in the study of Caires-Lima et al., in which 71% of patients were diagnosed in stage IV.[15]

With the exception of rare oligometastatic cases, patients diagnosed with NSCLC stage IV typically die of this disease, and have a median OS of 10 to 12 months,[19,20] which is corroborated in our study. The five-year survival rate of patients in advanced stages of disease is around 2%.[20]

Prognostic factors in lung cancer have been studied for a few decades, both in non-small-cell and small-cell tumors.[13,21] The SWOG (Southwest Oncology Group) analyzed data from 2,531 patients and found the following variables as predictive of treatment response: good performance status, female gender, small tumor volume, normal LDH levels, and hemoglobin higher than 11 g/dL.[22] Another study, conducted by a European group, examined 1,052 patients and found that low tumor volumes, a good KPS score (≥ 80), female gender and older age (≥ 70 years) were all associated with a more favorable treatment response.[23] Even in patients with stage III receiving definitive treatment with chemotherapy and radiotherapy, KPS score ≤ 70% has been shown to be an independent prognostic factor of OS.[24] Our study confirms that adverse prognostic factors for survival include low performance status (KPS ≤ 70%) and more advanced stages (III and IV), and these factors are also defined as predictive by Caires-Lima et al.[15] and Debiasi et al.[25]

Another significant result in our study was the number of palliative chemotherapy lines performed. Together, the patients who underwent one or two lines of chemotherapy accounted for 60% of the sample. This finding led us to stratify our patients into two groups: those treated with less than two lines, and those treated with two or more lines of chemotherapy. With a hazard ratio of 0.37 and $p<0.001$, patients undergoing more than two lines of

chemotherapy had longer OS. In line with the literature, there are studies that show OS benefit using second and third lines, especially with molecularly targeted drugs.[26-29]

As the laboratory variables, hemoglobin and LDH were related to survival in previous studies.[17,18] Our study did not establish this association as statistically significant; however, our sample is small compared with the literature and, also, we did not have data on all patients, and these factors may be responsible for any negative data. Albumin showed a small statistical trend as a prognostic factor, with a value of p=0.061 and may be related to another factor, the weight loss, which in a study by Hoang et al.[30] was defined as an adverse prognostic factor. The latter author also identified in a multivariate analysis other five independent factors of worse prognosis: cutaneous metastases, low performance status (ECOG 1 or 2), liver metastases, ≥ four sites of metastases, and absence of previous surgery.

Conclusion

Risk factors for shorter OS found in our study were KPS score ≤ 70%, less than two lines of palliative chemotherapy, and stage III and IV at diagnosis. Most of the patients treated in our service had tumors in advanced stages, which probably explains the large number of deaths.

With the advent of low-dose helical CT[31] for screening of smokers and those at high risk for developing lung cancer, we may have cases diagnosed earlier and with better clinical outcomes. Unfortunately, this procedure is not covered by our Public Health System, so that efforts in this direction, parallel to the anti-smoking campaigns should be undertaken if we are to reduce mortality from this devastating disease in our country.

Resumo

Perfil epidemiológico e fatores prognósticos em pacientes com câncer de pulmão

Objetivo: traçar o perfil epidemiológico de pacientes com câncer de pulmão atendidos em hospital público terciário de referência em oncologia e explorar variáveis que possam estar relacionadas com a sobrevida global (SG) desses pacientes.

Método: foram extraídos dados dos prontuários de todos os pacientes com câncer de pulmão invasivo, entre agosto de 2008 e dezembro de 2013, atendidos consecutivamente no Serviço de Oncologia do Hospital Estadual Mário Covas. As informações obtidas foram submetidas à análise estatística.

Resultados: do total de 210 pacientes, 39 foram excluídos da análise pela ausência de informações no prontuário. O tipo histológico mais frequente foi o adenocarcinoma, representando 39,41% da amostra, seguido do carcinoma espinocelular com 25,29% e de pequenas células com 13,53%. Outros tipos histológicos foram responsáveis pelos 21,76% restantes. Houve associação com significância estatística entre KPS ≤ 70%, linhas de quimioterapia paliativa realizadas e estágio ao diagnóstico com SG. A administração de terapia-alvo direcionada para pacientes com mutação do *EGFR* foi significativamente associada à melhor SG. A análise das variáveis laboratoriais (hemoglobina, albumina e desidrogenase lática – DHL) como possíveis fatores prognósticos de sobrevida não mostrou relação estatisticamente significativa. Entre os pacientes em estágio III e IV, a SG mediana foi de 10,1 meses.

Conclusão: os fatores de risco para menor SG foram KPS ≤ 70%, menos de duas linhas de quimioterapia paliativa e estágios III e IV ao diagnóstico. A implementação do rastreamento tomográfico de pacientes de risco poderá permitir o diagnóstico mais precoce e a melhora desses resultados.

Palavras-chave: neoplasias pulmonares, epidemiologia, sobrevida, prognóstico, fatores de risco.

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