Original Article

Lung cancer: histology, staging, treatment and survival*

Câncer de pulmão: histologia, estádio, tratamento e sobrevida

Fabiola Trocoli Novaes[1], Daniele Cristina Cataneo[2], Raul Lopes Ruiz Junior[2], Júlio Defaveri[3], Odair Carlito Michelin[4], Antonio José Maria Cataneo[5]

Abstract

Objective: To analyze principal histological types of lung cancer, as well as the staging, treatment and survival of lung cancer patients. **Methods:** This was a retrospective study based on the analysis of medical charts of patients treated at the Botucatu School of Medicine *Hospital das Clínicas* over a six-year period. **Results:** From January of 2000 to January of 2006, 240 patients with lung cancer, most (64%) of whom were male, were treated. The most common histological type was squamous cell carcinoma (37.5%), followed by adenocarcinoma (30%), neuroendocrine carcinoma (19.6%) and large cell carcinoma (6.6%). Only 131 patients (54.6%) were treated. Of those, 52 patients (39.7%) received only chemotherapy, 32 (24.4%) were treated with chemotherapy combined with radiotherapy, and 47 (35.9%) were submitted to surgery alone or surgery accompanied by chemotherapy, with or without radiotherapy. Only 27 patients (20.6%) were submitted to surgery alone. Concerning staging, 34.4% presented stage IV at the time of diagnosis, 20.6% presented stage IIIB, 16.8% presented stage IIIA, and the remaining 28.2% were classified as stage I or II. Five-year survival was 65% for those in stage I and 25% for those in the remaining stages. **Conclusions:** Of the various histological types, the most common was squamous cell carcinoma and the least common was large cell carcinoma. Most cases presented advanced stages at the moment of diagnosis, and less than 30% of the cases presented early stages. This accounts for the low survival rate and the small number of patients submitted to surgical treatment alone, the majority being submitted to chemotherapy alone.

Keywords: Carcinoma, bronchogenic; Lung neoplasms/histology; Lung neoplasms/drug therapy; Lung neoplasms/radiotherapy; Surgery; Survival.

Resumo

Objetivo: Analisar os principais tipos histológicos, estádio, tratamento e sobrevida dos portadores de câncer de pulmão. **Métodos:** Estudo retrospectivo a partir da análise dos prontuários de pacientes acompanhados no Hospital das Clínicas da Faculdade de Medicina de Botucatu, num período de seis anos. **Resultados:** De janeiro de 2000 a janeiro de 2006, foram acompanhados 240 doentes com câncer de pulmão, com predominância do sexo masculino (64%). O tipo histológico mais freqüente foi o carcinoma escamoso (37,5%), seguido pelo adenocarcinoma (30%), carcinoma neuroendócrino (19,6%) e carcinoma de grandes células (6,6%). Apenas 131 pacientes (54,6%) foram tratados. Destes, 52 pacientes (39,7%) foram submetidos à quimioterapia exclusiva, 32 (24,4%) realizaram quimioterapia associada à radioterapia e 47 (35,9%) foram submetidos à cirurgia associada ou não à quimioterapia exclusiva e/ou radioterapia. Somente 27 pacientes (20,6%) foram submetidos à cirurgia exclusiva.Em relação ao estadiamento, 34,4% apresentavam, no momento do diagnóstico, estádio IV, 20,6% estádio IIIB, 16,8% estádio IIIA e os outros 28,2% pertenciam aos estádios I e II. A sobrevida em cinco anos foi de 65% para o estádio I e 25% para os estádios remanescentes. **Conclusões:** O tipo histológico predominante foi o carcinoma escamoso e o de menor freqüência foi o carcinoma de grandes células. A maioria se encontrava em estádio avançado ao diagnóstico, estando nos estádios iniciais menos de 30% dos casos. Isto justifica a baixa sobrevida e a pequena quantidade de pacientes submetidos ao tratamento cirúrgico exclusivo, em comparação à maioria que foi submetida à quimioterapia exclusiva.

Descritores: Carcinoma broncogênico; Neoplasias pulmonares/histologia; Neoplasias pulmonares/quimioterapia; Neoplasias pulmonares/radioterapia; Cirurgia; Sobrevivência.

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* Study carried out by the Multidisciplinary Study Group on Lung Cancer of the *Universidade Estadual Paulista* – UNESP, São Paulo State University – Botucatu School of Medicine, Botucatu, Brazil.

1. Resident Physician in the Department of Surgery. *Universidade Estadual Paulista* – UNESP, São Paulo State University – Botucatu School of Medicine, Botucatu, Brazil.
2. Assistant Professor in the Department of Surgery. *Universidade Estadual Paulista* – UNESP, São Paulo State University – Botucatu School of Medicine, Botucatu, Brazil.
3. Adjunct Professor in the Department of Pathology. *Universidade Estadual Paulista* – UNESP, São Paulo State University – Botucatu School of Medicine, Botucatu, Brazil.
4. Assistant Professor in the Oncology Section of the Department of Clinical Medicine. *Universidade Estadual Paulista* – UNESP, São Paulo State University – Botucatu School of Medicine, Botucatu, Brazil.
5. Adjunct Professor in the Department of Surgery. *Universidade Estadual Paulista* – UNESP, São Paulo State University – Botucatu School of Medicine, Botucatu, Brazil.

Correspondence to: Antônio José Maria Cataneo. Rua Silva Jardim, 420, Vila São Lúcio, CEP 18603-770, Botucatu, SP, Brasil.
Tel 55 14 3882-2654/3811-6091. Fax 55 14 3815-7615. E-mail: acataneo@fmb.unesp.br
Submitted: 3 September 2007. Accepted, after review: 7 December 2007.

Introduction

Worldwide, lung cancer is currently the malignant tumor with the highest mortality rate in men and the second highest mortality rate in women, ranking lower only in relation to breast cancer.[1] In Brazil, estimates for 2008, as well as for 2009, are that 27,000 people will be affected (18,000 males and 9,000 females).[2] In the United States, where the population is approximately twice as large as that of Brazil, 170,000 new cases are currently reported per year.[3] Despite being more common in male individuals, its incidence in men has stabilized or decreased, whereas, in women, it has drastically increased in recent decades.[4-6] Only 20% of the cases are diagnosed in the early stages. The diagnosis is usually delayed and is made only when the disease is already in the advanced stages, which precludes curative treatment.

In clinical practice, lung carcinomas are classified as small cell carcinoma or non-small cell carcinoma. The latter includes squamous cell carcinoma, adenocarcinoma, and undifferentiated large cell carcinoma. Pathologists have preferred the World Health Organization classification published in 1999, according to which there are seven major types of lung cancer: squamous cell carcinoma; small cell carcinoma; adenocarcinoma; large cell carcinoma (neuroendocrine and non-neuroendocrine); adenosquamous carcinoma; pleomorphic sarcomatoid carcinoma; and carcinoid tumor. In clinical studies, the previous classification is most often used, and neuroendocrine large cell carcinoma is classified together with small cell carcinoma due to the fact that the former is as aggressive as the latter. Despite being neuroendocrine, typical and atypical carcinoid tumors have a much better prognosis and deserve to be classified separately.

Lung cancer staging using the tumor-node-metastasis system has undergone modifications since 1970. The current system was published in 1997 after a multicenter study involving more than 5,000 cases of lung cancer.[7,8] The treatment for lung cancer, when the tumor is still localized, without dissemination outside the lungs, is surgery. Tumors restricted to the lungs, in stages I and II, should be removed surgically.[9] In such cases, chances for cure are high, five-year survival being 67, 57, 55, and 39%, respectively, for those in stages IA, IB, IIA, and IIB.[7] Some clinical trials have shown that (adjuvant) chemotherapy used in the postoperative period improves survival even in cases of complete resection.[10-13] Preoperative (neoadjuvant or induction) chemotherapy can be used in patients in stage III and complemented in the postoperative period.[9,10,14,15] However, previous chemotherapy has been shown to increase postoperative morbidity in such patients.[10] Surgical rescue can be attempted even in those in the most advanced stage (stage IV). Single metastases, which can occur in the brain and in the adrenal glands, can be resected, and the primitive lung tumor can also be extirpated. However, the expected mean survival for most patients in the advanced stages is quite low.

The objective of this study was to analyze the principal histological types of lung cancer, as well as to evaluate the staging, treatment, and survival of lung cancer patients treated at a tertiary care center located in the state of São Paulo.

Methods

After being approved by the Ethics in Human Research Committee of the institution, this retrospective study was performed based on the analysis of medical charts of patients with bronchial carcinoma treated at the Botucatu School of Medicine *Hospital das Clínicas* in the period from January of 2000 to January of 2006. All patients with a histopathological diagnosis of lung cancer treated during this period were included. Aiming at minimizing losses, when individual medical chart review revealed that a patient did not attend follow-up visits anymore, we contacted the patient or the family members by phone in order to determine whether the patient was still alive.

Gender, age, tobacco intake in pack-years (number of packs of cigarettes smoked per day multiplied by the number of years of smoking), histological type, staging, treatment modality, and survival were analyzed based on the information from the medical charts.

For the description of the categorical variables (gender, smoking, staging, and treatment), distribution of frequencies was used. For the continuous or numerical variables (age and tobacco intake), measurements of central tendency and of variability were performed.

Overall survival was obtained using the Kaplan-Meier method.[16] Survival stratified by staging, histological type, and gender was also obtained. The differences among the survival curves were determined using the log-rank test, and the level of significance was set at 5%. The analyses were performed using the SAS program for Windows, version 8.02 (Statistical Analysis System, Cary, NC, USA).[17]

Results

From January of 2000 to January of 2006, 240 patients with lung cancer, 64% of whom were male, were treated. Those patients were monitored until January of 2007, when this study was ended. A total of 4.2% of the patients were lost to follow-up due to the fact that telephone contact was unsuccessful. Seventy-seven (32%) of the patients were over 70 years of age. Among men, the mean age was 64 years, and, among women, it was 59 years. Smoking was found in 89.4% of the cases evaluated, and the mean tobacco intake was 47.02 pack-years. Among men, the prevalence of smoking was 97.36%, and the mean tobacco intake was 52.25 pack-years. Among women, the values were 72.97% and 33.64 pack-years. The histological pattern with the highest incidence was squamous cell carcinoma, followed by adenocarcinoma (Table 1).

Of the 240 patients studied, only 131 (54.6%) received some type of treatment for the tumor. At the time of diagnosis, 94 (71.8%) presented stages III or IV and the remaining 37 (28.2%) were classified as stages I or II (Table 2). Among the 109 patients who received no treatment, poor performance status was seen in 71 (65%), of whom 18 died immediately after diagnosis, 18% were over 80 years of age, and 17% refused any type of treatment.

Concerning treatment, 52 patients (39.7%) received only chemotherapy, 32 (24.4%) were treated with chemotherapy combined with radiotherapy, and 47 (35.9%) were submitted to surgery alone or surgery accompanied by chemotherapy, with or without radiotherapy. Only 27 patients (20.6%) were submitted to surgery alone. Among those who received only chemotherapy, the most common histological type was adenocarcinoma, and, among those submitted to surgery alone, the principal histological type was squamous cell carcinoma. The initial stages (stages I and II) were found mainly among those submitted to surgical treatment alone. Those treated with chemotherapy, with or without radiotherapy, presented more advanced stages (stage IIIA, IIIB, or IV) at the time of diagnosis.

Of the 131 patients treated, 45 (34.4%) presented metastases at the time of diagnosis, and several of those presented multiple organ involvement. In order of frequency, the principal sites of metastases were as follows: lungs (23.6%); brain (16%); bones (13.7%); and liver (13%). Five-year survival was 25% (Figure 1), and, by staging, it was 65% for those in stage I and 42.7% for those in stage II. For those in stage III and those in stage IV, two-year survival was, respectively, 19.4 and 11.8% (Figure 2). The patients treated survived, on average, 4 months after the diagnosis.

In terms of histological type, there was no difference in survival (p = 0.9634). Although survival was higher among women than among men, this difference was not significant (p = 0.1124).

Discussion

We found a higher prevalence of lung cancer among males, with a 1.8:1 male/female ratio. This is in accordance with the literature, which shows a progressive increase in incidence in women as

Table 1 - Distribution by histological type.

Histological type	n (%)
SCC	90 (37.5)
AC	72 (30.0)
Neuroendocrine carcinoma (SCC and LCC)	39 (16.3)
LCC	16 (06.6)
Carcinoids	08 (03.3)
Mixed (SCC + AC)	02 (00.8)
Unspecified carcinoma	13 (05.4)

SCC: squamous cell carcinoma; AC: adenocarcinoma; SCC: small cell carcinoma; and LCC: large cell carcinoma.

Table 2 - Distribution by staging.

Staging	n (%)
IA	10 (07.6)
IB	15 (11.5)
IIA	00 (00.0)
IIB	12 (09.1)
IIIA	22 (16.8)
IIIB	27 (20.6)
IV	45 (34.4)

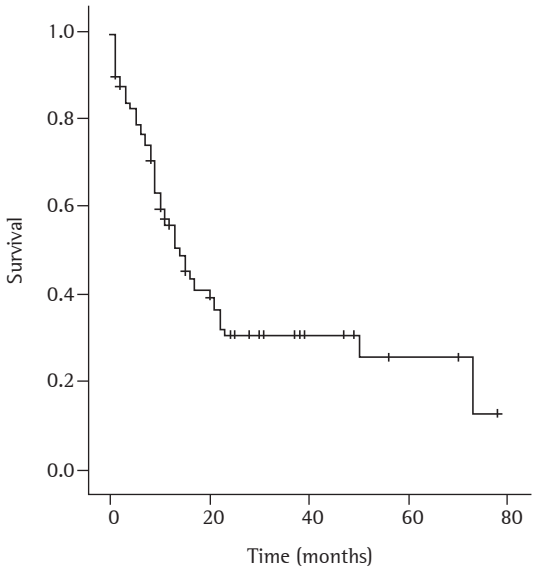

Figure 1 - Survival in months for all clinical stages.

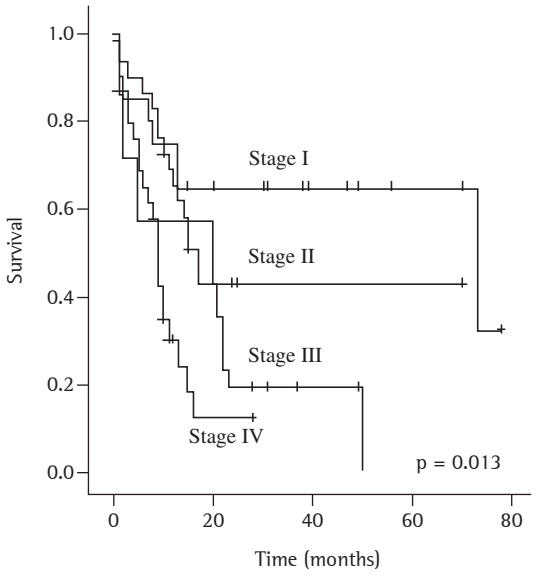

Figure 2 - Survival in months stratified by clinical stage.

compared to men.[6] In the mid-20th century, this ratio was 10:1. It is believed that this increase is related to the smoking habit, which has become increasingly common among women.[4,5] In the present study, the incidence of smoking was near 90%, similar to that of reports in the literature.[4] However, we could not determine, based on the data from the medical charts, whether the other patients were passive smokers, since it has been demonstrated that a nonsmoker whose spouse is a smoker is at increased risk of developing lung cancer, possibly due to passive tobacco exposure.[18] This information was missing from most of the medical charts evaluated, which made it difficult to analyze passive smoking. Over the past 20 years, the incidence of lung cancer in women has increased by 134%, making it the second leading cause of death from cancer among females, whereas it has increased by only 57% in men.[2] The literature indicates that, in the next two decades, lung cancer will be the neoplasia with the highest mortality rate among women in countries where the number of females who take up the smoking habit has been increasing.[5] Over the past 10 years, lung cancer mortality has stabilized or decreased among men, whereas it has increased among women,[4,6] surpassing breast cancer mortality in some countries.[1]

Analyzing the prognosis of lung cancer by gender, some studies have demonstrated a higher risk in female smokers, others have found that survival is higher in women, and still others have found no gender-related differences.[5,19-21] In our study, survival was higher among women than among men. However, this difference was small, presenting no statistical significance. In our sample, smoking and tobacco intake were lower in females than in males. It is likely that the prevalence of smoking in the population in our region is higher among men, as occurs nationwide in Brazil.[6] In addition, the male/female ratio of lung cancer found in the present study (1.8:1) was very similar to that found in other regions of Brazil (2:1).[2] Are women, when exposed to tobacco, more vulnerable to lung cancer than are men? Based on data in the literature, women seem to be at an increased risk for lung cancer. However, this conclusion cannot be drawn without further research on the topic.

Regarding histological type, there was a low incidence of large cell carcinoma, as shown in the literature.[4,14] In the past, the incidence of large cell carcinoma was higher, probably due to limitations in differentiating it under light microscopy only. This difficulty was overcome due to the advent of electron microscopy and, more recently, due to the use of immunohistochemistry. There has been an increase in the incidence of adenocarcinoma, which has surpassed that of squamous cell carcinoma.[3,22] According to Shields,[23] the distribution ranges from

20 to 35% for squamous cell carcinoma, from 30 to 50% for adenocarcinoma, from 15 to 35% for small cell carcinoma, and from 4.5 to 15% for large cell carcinoma. In our sample, squamous cell carcinoma ranked first over the 6-year study period, although, in a previous study conducted in 1996 and 1997,[24] adenocarcinoma was the most common histological type. Grouping all of those patients, squamous cell carcinoma is still the most common histological type, although its values are very close to those of adenocarcinoma, and the difference is not significant. Therefore, the impression that we had in 1997—that, in our region, adenocarcinoma had already surpassed squamous cell carcinoma—was not confirmed. Although tumor aggressiveness varies according to the histological type, there were no significant differences among the various types in terms of survival. In contrast, the high prevalence of advanced stages at the time of diagnosis reflects the late onset of symptoms and the high aggressiveness of certain histological types. In addition, it explains the reduced number of patients submitted to surgical treatment, which is indisputably indicated in the early stages and is indicated with restrictions in the more advances stages.[8,9] In the literature, only approximately 20% of the cases meet the operability criteria at the time of diagnosis, even in developed countries. In developing countries, this rate would be expected to be lower due to the fact that the underprivileged population has limited access to health care. This difference probably does not exist because the most frequent symptom, cough, is nonspecific, being common in smokers and in individuals with respiratory diseases,[25] and it does not motivate even individuals in the upper socioeconomic groups to seek medical attention. One study showed that the mean time to seeking medical attention is 110 days.[26] In our sample, the principal cause of lack of treatment was poor performance status, due to the fact that the disease was already advanced, and it seemed that the mean time to seeking or being referred to a specialized clinic was quite long. However, there have been no such studies in our region, and this supposition therefore cannot be confirmed.

In accordance with the literature, the comparison among the survival curves for each clinical stage revealed more aggressive behavior and more rapidly progressing disease in the more advanced stages. These results are in agreement with those presented in a review of lung cancer staging,[7] although some authors have shown better results for tumors that are still in stage I.[27] The overall survival curve obtained reflects the high aggressiveness of lung cancer, revealing a five-year survival of only 25%, but with much higher rates for the early stages of the disease. These data underscores the importance of early diagnosis of bronchial carcinoma, which provides a better prognosis, with a reasonable cure rate.

In conclusion, we found that, in the Botucatu region, the incidence of bronchial carcinoma remains higher among men. Of the various histological types, the most common was squamous cell carcinoma, and the least common was large cell carcinoma. Most cases presented advanced stages at the time of diagnosis. Patients in the early stages, for whom the possibility of surgical treatment exists, accounted for only a minority of the cases, whereas most cases required chemotherapy. Although the survival rate was good in the early stages, it was quite low in the advanced stages.

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