

Original Article

Early diagnosis of lung cancer: the great challenge. Epidemiological variables, clinical variables, staging and treatment*

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ABSTRACT

Objective: To evaluate confirmed cases of lung cancer, reviewing epidemiological variables, clinical variables, staging and treatment. **Methods:** The cases of 263 patients were studied. All of the patients had been treated at the Universidade Federal do Paraná (Federal University of Paraná) Hospital de Clínicas or at the Hospital Erasto Gaertner, two institutions that, together, serve a significant portion of the patients seeking treatment in the city of Curitiba, located in the state of Paraná. This was a retrospective study, involving the administration of questionnaires. The descriptive analysis of the data obtained was performed using the Epi-Info program. **Results:** There was a predominance of male patients (76%). At the time of diagnosis, the majority of patients (90%) were smokers or former smokers. In 87% of the cases, there was no history of lung disease. The most common initial symptoms were cough (142 cases) and chest pain (92 cases). Non-small cell lung cancer was found in 87% of the patients, and the most common histological type was spinocellular carcinoma, which was found in 49% of all of the patients. Smoking was found to be the most significant predisposing factor. **Conclusion:** The characteristics of lung cancer progression, such as the nonspecificity of the initial symptoms, the duration of tumor growth and the course of the tumor, together with the lack of tracking programs, are the principal factors that hinder the early detection of lung cancer, making it difficult to treat lung cancer patients and to increase their survival.

Keywords: Lung neoplasms/diagnosis; Lung neoplasms/epidemiology; Lung neoplasms/surgery; Early diagnosis; Neoplasms staging

*Study carried out at the Hospital de Clínicas of the Universidade Federal do Paraná (UFPR, Federal University of Paraná) and the Hospital Erasto Gaertner - Curitiba, Paraná, Brazil.

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INTRODUCTION

Lung cancer is currently the most common neoplasm and has the highest mortality rate.⁽¹⁻³⁾ According to the 2003 National Cancer Institute (Ministry of Health) estimates of cancer incidence and mortality, from 1979 to 2000, mortality due to lung cancer rose from 7.73/100,000 to 12.13/100,000 among men (a relative increase of 57%), compared with an increase from 2.33/100,000 to 5.33/100,000 (134%) among women. The number of lung cancer deaths predicted for 2003 in Brazil was 11,315 for men and 4915 for women. The absolute number of deaths predicted for 2003 corresponds to gross mortality rates of 13.00/100,000 among men and 5.45/100,000 among women.

Data provided by the National Cancer Institute demonstrate that lung cancer is the most common of all malignant tumors worldwide, presenting a global increase of 2% per year and accounting for approximately 1.2 million new cases annually.⁽⁴⁾

Most of the cases affect individuals between the ages of 50 and 70. In industrialized countries, lung cancer was initially an epidemic disease among men. However, it has become increasingly more common among women. The principal risk factor is smoking, which confers a 10- to 30-times greater risk of developing a lung neoplasm. Other traditionally accepted factors are as follows: preexisting pulmonary disease; occupational exposure (asbestos, uranium, chromium, alkylating agents, etc.); family history of lung cancer; and previous pulmonary neoplasm.^(1,5-9)

Most diagnoses are confirmed when the disease has become advanced, locally or disseminated, since early-stage tumors do not usually produce symptoms that warrant investigation. This indicates that early detection measures are particularly important, since surgical resection, which constitutes the only therapeutic approach that offers a potential cure, is effective only in early clinical stages.

The objective of this study was to present epidemiological characteristics found in a sample of patients with lung cancer treated at two referral centers in the city of Curitiba (located in the state of Paraná, Brazil) in the 1990s, as well as to conduct a review of early signs and symptoms, histological subtypes, staging, and types of treatment used.

METHODS

A retrospective study, comprising 263 patients definitely diagnosed with lung cancer, was carried out from January of 1991 to December of 1997. Data were collected from medical charts of the Hospital de Clínicas of the Federal University of Paraná and of the Hospital Erasto Gaetner, both of which are located in Curitiba.

Information was obtained from the charts by filling out a previously defined study protocol. All of the variables analyzed were static. Patients were included in the sample only if their charts contained sufficient clinical information to fill out the protocol and if they had been diagnosed with bronchogenic carcinoma by at least one of the following methods: fiberoptic bronchoscopy with biopsy (endobronchial or transbronchial), sputum cytology, bronchoalveolar lavage and/or biopsy of other tissues (metastatic disease).

All cases of primary lung cancer other than bronchogenic carcinoma, cases that presented neoplasm in adjacent pulmonary tissues or pulmonary metastasis of primary neoplasms of other tissues, and cases whose medical charts contained insufficient clinical information, were excluded.

The descriptive analysis of the data was performed using the Epi Info program, and the results were compared with information from the medical literature and with data from national epidemiological surveys.

Individuals who had smoked less than 100 cigarettes during their lifetime were defined as nonsmokers. Those patients who had stopped smoking for at least one year prior to being diagnosed with lung cancer were defined as former smokers, and habitual tobacco users or former users who had stopped smoking for less than a year prior to diagnosis were defined as smokers.

RESULTS

Of the 263 patients analyzed, 238 (91.49%) had been treated at the Hospital Erasto Gaetner, and 25 (9.51%) had been treated at the Hospital de Clínicas of the Federal University of Paraná. Males accounted for 76% of the cases ($n = 200$), and only 24% were females ($n = 63$). The mean age was 60.9 years (range, 28-85 years).

Most of the patients (234 cases = 90%) were smokers or former smokers at the time of diagnosis (Table 1). There was a history of alcoholism in 107 cases (41%). Most of the patients in this study reported no history of pulmonary disease (87%), and among those who did, chronic obstructive pulmonary disease was the most frequent. There were 9 patients (3%) who had a history of extrapulmonary neoplasms. There was a family history of cancer in 73 cases (28%), 16 (6%) of which were cases of pulmonary neoplasm.

The most frequent initial symptoms were cough and chest pain (Figure 1). The diagnosis of lung cancer was suggested by chest X-ray in 233 cases (89%) and by computed axial tomography of the chest in 52 (20%). In 22 cases, both methods were required in order to confirm the diagnosis.

Non-small cell lung cancer (NSCLC) was found in 229 patients (87%), and small cell lung cancer (SCLC) was found in 34 (13%). The most frequent histological type was spinocellular carcinoma, with 49% (Table 2).

The assessment of the staging of NSCLC revealed 35 patients at a stage that was consistent with surgical treatment (15%): 5 patients with stage I (2%), 10 with stage II (4%) and 20 with stage

TABLE 1

Distribution of lung cancer cases by smoking habits

Category	Number of cases	%
Smokers	155	59%
Former smokers	79	30%
Nonsmokers	29	11%
Total	263	100%

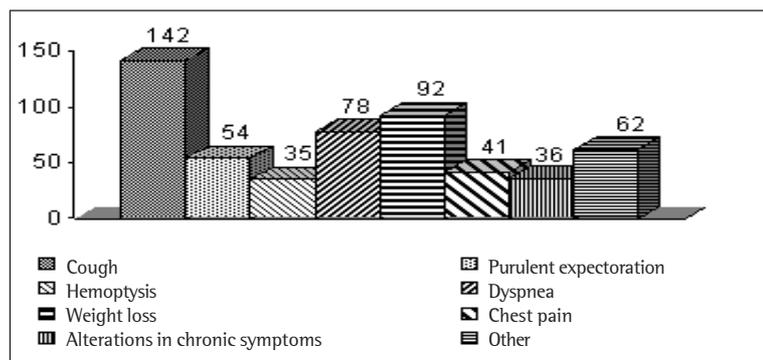


Figure 1 -Initial symptomatology reported by the patients

TABLE 2

Distribution of lung cancer cases by histological subtype

Histological type	Number of cases	%
Spinocellular carcinoma	130	49%
Adenocarcinoma	65	25%
Small cell carcinoma	34	13%
Large cell carcinoma	11	4%
Undifferentiated carcinoma	10	4%
Undetermined carcinoma	8	3%
Mixed cases	5	2%
Bronchoalveolar carcinoma	3	1%
Total	266	100%

IIIa (9%). We observed that 194 patients (85%) presented advanced disease: 46% with stage IIIb and 39% with stage IV (Table 3). Among the patients with SCLC, 7 (20%) presented limited disease at the time of diagnosis (20%), and 27 (80%) presented advanced disease.

A total of 140 patients (53%) were submitted to radiotherapy, 66 (25%) received chemotherapy, and 23 (9%) were submitted to surgical treatment. Another 45 patients (16%) received only supportive treatment, and 12 abandoned the treatment (5%).

The patients submitted to radiotherapy and chemotherapy were those who presented SCLC, as well as those with NSCLC of a histology that was susceptible to these treatments. The cases of stage III or II NSCLC, together with some selected cases of stage IIIa, were submitted to surgical procedures. At NSCLC stages IIIa, IIIb, and IV, the treatment chosen varied among radiotherapy, chemotherapy and supportive treatment, on a case-by-case basis.

TABLE 3

Staging of non-small cell lung cancer

Stage	Number of cases	Total
I	5 - 2%	15%
II	10 - 4%	
IIIa	20 - 9%	
IIIb	105 - 46%	85%
IV	89 - 39%	
Total	229	100%

DISCUSSION

According to the National Cancer Institute, lung cancer is still the most common neoplasm in the world (accounting for 12.3% of all new cases of cancer), and it is also the most frequent cause of death by cancer. It has surpassed breast cancer in the USA and is the leading cause of death by neoplasm among women.^(3,10) In Brazil, data from the Ministry of Health reveal that lung cancer is the leading cause of death by cancer among men and the second leading cause among women. According to the National Cancer Institute (2003), the highest mean annual rates of incidence adjusted for age/100,000 people, for men and women respectively, were as follows: 1993-1997: 54.9 and 16.1 in Porto Alegre (in the state of Rio Grande do Sul); 1997-1998: 39.2 and 12.6 in São Paulo (São Paulo); 1996-1998: 34.2 and 14.8 in the Distrito Federal. The lowest rates (11.2 and 2.3) were observed in João Pessoa (Paraíba) in the 1999-2000 period.

Of the cases of lung neoplasm, 13% to 27% result from occupational factors, principally if accompanied by smoking.⁽¹⁾ The following factors are also included: arsenic, asbestos, minerals, alkylating agents, nickel, chromates and carcinogenic polyhydrocarbons. Smoking has an additive or multiplicative effect on some of these agents.⁽¹²⁾ Excessive exposure to asbestos represents an approximately 5-fold greater risk of lung cancer among smokers.⁽¹³⁾ In this study, 27% of the cases presented exposure to occupational factors. A total of 89% of the patients had previously lived in a rural environment. For all age brackets, the percentage of smokers in rural zones is greater than that of smokers in urban zones.⁽¹⁴⁾

Smoking is the most significant predisposing factor for lung cancer. The relative risk of developing lung cancer is 20- to 30-fold greater among smokers than among people who have never smoked.⁽²⁾ It is estimated that 80% to 90% of the cases of lung cancer occur among smokers. This fact is corroborated by the results of the present study (Table 1).^(1,2,6) The risk is related to the number of cigarettes smoked per day, the age at which the smoking habit was acquired, the duration of the smoking habit, and how deeply the individual inhales. Passive exposure to cigarette smoke also plays an important role, since passive

smoke contains a complex mixture of various mutagenic and carcinogenic agents.^(2,6,9,12)

Smoking is increasing, principally among young women. There is a predominance of women and a greater incidence of adenocarcinoma among young individuals who develop lung cancer. It has been postulated that endogenous and exogenous estrogens play a role in the development of adenocarcinoma.^(10,15-16)

A significant increase in the number of lung cancer cases occurs between the ages of 50 and 80.^(1,3,8,11,17) In the present study, the mean age at diagnosis was 60.9 years.

Other predisposing factors for lung cancer are preexisting pulmonary diseases and a family history of lung cancer. In the present study, 11% of the patients had chronic obstructive pulmonary disease. There is evidence of a 2- to 5-fold increase in the prevalence of the disease among close relatives of patients with lung cancer.⁽¹³⁾ Among the cases we studied, 6% had a family history of lung cancer, and over 20% presented a family history of other types of cancer.

Cough is the most common symptom.^(16,18) In this study, 54% of the patients reported cough as an initial manifestation of the disease. Although hemoptysis is common, it is rarely severe. Early dyspnea or chest discomfort affects 60% of the patients at the time of diagnosis.⁽³⁾

Among the cases evaluated in the present study, the first cancer manifestation was mucopurulent expectoration (in 21%) or bloody expectoration (in 13%). Dysphonia due to the involvement of the recurrent laryngeal nerve was reported as the initial manifestation of the disease in 4% of cases, which is in accordance with the findings of other authors who showed that this is the initial symptom of neoplasm in 3% to 13% of cases.⁽³⁾

Other symptoms found in our study were weight loss (16%) and fever (4%). Asthenia was reported by only 12 patients (5%), although, according to international consensus, it is present at the onset of the disease in 55% to 88% of cases.⁽³⁾

An increase in the intensity or frequency of the cough, qualitative and quantitative alterations in expectoration, and the intensification of pain or dyspnea were observed in the patients with a history of pulmonary diseases (14%). These suggestive signs call for a more elaborate investigation.

Squamous cell carcinoma (SCC, also known as epidermoid carcinoma) and SCLC, the most frequent histological subtypes, present as central expansive lesions of endobronchial growth. Since the SCC starts in the central bronchi, it is more likely to be detected early through sputum cytopathologic tests than are other types of carcinoma. However, SCLC, which presents a pattern of rapid growth and almost exclusively affects smokers, tends to cause extrinsic bronchial compression. The SCCs have a tendency to metastasize to the regional lymphatic ganglia, and approximately 10% of them form cavitations. Early metastatic dissemination is common in the SCLCs.^(3,5) Adenocarcinomas and large cell carcinomas usually present as peripheral nodes or lesions with pleural involvement, and exhibit similar clinical behavior. Their early detection through sputum testing is not possible, and they typically produce metastases in distant organs. Bronchoalveolar carcinoma, a low grade adenocarcinoma subtype (accounting for 2% of the cases of bronchogenic carcinoma), presents as nodes (single or multiple) or as alveolar infiltrate.⁽³⁾

In the past, the histological type most commonly found was SCC. However, in the past decade, it was surpassed by adenocarcinomas, which are more common among nonsmokers than in smokers, regardless of gender.^(1,3,19) In the present study, we also observed that SCC was the predominant histological type (50%), followed by adenocarcinoma (25%).

The tumor-node-metastasis staging was applied to the histopathological variables: SCC, adenocarcinoma, and large cell carcinoma. The SCLC was classified as limited disease (disease limited to the thorax, including pleural effusion) or advanced disease (extrathoracic).

Of the 34 cases of SCLC, 79.4% were extensive. Of the 194 patients with NSCLC (SCC, adenocarcinoma and large cell carcinoma), 84.7% presented extensive staging (IIIb or IV). This corroborates the data in the literature, according to which, at the time of diagnosis, approximately 50% of patients with lung cancer are at stage IV, 30% in stage III and 10% in both stages I and II.⁽²⁰⁾

The treatment of choice for initial pulmonary carcinoma is surgical resection. Radiotherapy and chemotherapy are the treatments of choice in cases of SCLC. However, for the other histological

subtypes, these treatments are palliative and constitute the first choice only in more advanced stages of the disease.⁽¹⁾ The selection of patients who can undergo surgery includes those in clinical stages I and II (a/b). Most of the patients in our study presented the advanced stages. Therefore, the treatment most often used was radiotherapy, in 140 patients (53%). Chemotherapy was used in 66 cases (25%), and surgical treatment was used in 23 patients (9%). Supportive measures were used in 16% of the cases, and 12 patients (5%) did not comply with the treatment. The five-year survival rates for patients submitted to surgical intervention were in accordance with the data in the literature, from 50% to 80% for stage I patients and from 35% to 50% for stage II patients. Due to the restricted possibility of cure through the treatment used, survival is determined by age, morphology, and staging of the disease.⁽²¹⁾

In most of the cases, the presumptive diagnosis of the disease was made by chest X-ray, an exam that can be easily carried out, is relatively inexpensive, and without relative morbidity risk. However, its sensitivity is only approximately 70%, and its specificity is between 89% and 99%.⁽¹⁾ The use of chest X-ray in asymptomatic patients at risk for lung cancer or with early suggestive symptoms (weight loss, persistent cough, habitual cough, or unusual cough pattern) seems to be of considerable value.^(1,3,8,22)

Despite its high relative cost, computed axial tomography of the chest was used in the presumptive diagnosis of practically one-fifth of the sample. Useful in staging, computed axial tomography of the chest presents sensitivity and specificity that are greater than those of the simple chest X-rays and should be ordered in the cases in which the chest X-ray results are inconclusive.⁽¹⁷⁾

In most cases, the diagnosis was confirmed through fiberoptic bronchoscopy. This method is very useful since it makes it possible to perform both endobronchial and transbronchial biopsies, bronchoalveolar lavage, and bronchial brush. When the lesions are visible through fiberoptic bronchoscopy, they are diagnosed through the use of the aforementioned methods in over 90% of the cases, as opposed to 40% to 80% of histological confirmation of peripheral lesions that are not visible through the use of fiberoptic bronchoscopy.^(3,15,17) Only 3% of the cases were diagnosed through sputum cytology.⁽²³⁾

In a study analyzing 222 cases,⁽²⁴⁾ the conclusion was that, although the majority of the individuals were diagnosed within one year (91.4%), among those who were not, the doctors were the principal cause of delay. Of those patients who were not diagnosed within one year, the majority presented adenocarcinoma (94.7%), and the principal reasons for the delay were as follows: diagnosis of inflammation or benign tumor by computed axial tomography resulting in a follow-up gap, or only in slight growth or no alteration in the initial lesion; suspicion of lung neoplasm, the malignancy of which was ruled out by a transbronchial biopsy; suspicion of lung cancer followed by the refusal of the patients to undergo a thoracoscopy or further investigation; and dropping out of follow-up treatment. In 2002, some authors⁽²⁵⁾ observed that, among patients diagnosed histologically with lung cancer, failure of the radiologist to recognize abnormalities was the most common reason (in 47%) for the diagnosis not being performed at the time of the assessment of the chest X-rays.

The evolutive characteristics of the lung neoplasm and factors associated with the doctor, health system, or patient, can be held responsible for the delayed diagnosis and inefficacy in increasing the survival of these patients.

Due to cultural factors, habitual smoking, and fear of a possible diagnosis, patients usually postpone seeking treatment. When they do, they are submitted to evaluation by a general practitioner, and are confronted with a saturated health system, resulting in a significant delay before they are referred to a pulmonologist.

For lack of effective and economically feasible tracking programs to detect the initial disease in its asymptomatic phase, as well as because the first symptoms generally reflect an advanced stage of the disease, lung cancer is still a great challenge in the medical area, since the therapeutic initiatives to improve the five-year survival of patients have failed.⁽²¹⁾

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