LATE DIAGNOSIS OF LUNG CANCER: ANALYSIS OF BRONCHOSCOPIES IN A QUATERNARY HOSPITAL

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ABSTRACT

Introduction: Lung cancer is the leading cause of death from malignant disease in the world, and the WHO estimates that the rate of appearance of new cases tends to increase, especially due to the increase in tobacco consumption. In general, patients with early-stage lung cancer are asymptomatic or oligosymptomatic, and for this reason most lung neoplasms are diagnosed at advanced stages. It is known that early diagnosis is a predictive factor of better prognosis and efficacy in treatment. **Objective:** To identify lung cancer diagnoses in bronchoscopies performed in 2019 and to relate the degree of staging of the neoplasms. **Method:** A retrospective, cross-sectional, observational study was conducted by collecting data from the medical records of 226 fiberoptic bronchoscopy

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examinations with transbronchial biopsy performed in 2019. Chest CT scan reports of positive malignancy tests were surveyed and classified according to the degree of staging at the time of diagnosis. Patients whose medical records lacked information on histological type or did not have sufficient data for classification in the chest CT scan report were excluded from the study. Results: Of the 129 patients diagnosed with cancer, 73 were men and 56 women (ratio 1.3:1, respectively). The mean overall age of the patients at diagnosis was 64.8 years. Regarding non-small cell tumors, 72.9% of the total had an advanced stage that was inoperable at the time of diagnosis (IIIB-IV), compared to the early stages (IA-IIIA) **Conclusion:** The majority of patients with lung cancer had their diagnosis established at an advanced stage and inoperable (stages IIIB-IV). However, even with well-established and up-to-date guidelines for screening lung neoplasms, early diagnosis is still a challenge to promote treatments with a higher expectation of cure.

Keywords: Lung neoplasms. Diagnosis of the Health Situation. Tracking Programs.

INTRODUCTION

Lung cancer is the leading cause of death from malignant disease in the world in the male population, with more than two million new cases and more than one million deaths annually, both in men and women (BRAY et al., 2018; SIEGEL; MILLER; JEMAL, 2020).

In Brazil, lung cancer is also the leading cause of cancer death, with its incidence and survival rates being very close to global rates (TSUKAZAN et al., 2017). In recent decades, there has been a greater relative increase in the female population than in the male population (approximately 70% more). It is suspected that this increase has as its main explanation a change in smoking habits and prevalence in women (ARAUJO et al., 2018).

Smoking is the main representative of the group of etiological environmental agents and corresponds to more than 80% of the etiology of lung cancer in the United States; of which smokers, in general, are 20 times more likely to develop lung cancer than non-smokers (ALBERG et al., 2013; ARAUJO et al., 2018; BRENNER et al., 2012; SIEGEL; MILLER; JEMAL, 2020).

Patients with early-stage lung cancer are usually asymptomatic or oligosymptomatic. Bronchopulmonary symptoms such as cough, hemoptysis, dyspnea, and chest pain are the main clinical findings. (HYDE; HYDE, 1974).

Among the main complementary tests that are important for diagnosis, fiberoptic bronchoscopy, the gold standard in bronchogenic carcinoma, with the possibility of transbronchial biopsy for surgical planning and tumor staging; and percutaneous transcutaneous biopsy, which, if associated with chest tomography, can reach sensitivity of up to 65% (ANDOLFI et al., 2016).

Patients classified as stage I have five-year survival ranging from 92 to 68%. Patients classified as stage II, survival ranges from 65 to 53%; in stage III, from 41 to 12%; and there is no five-year survival expectancy for stage IV patients (DETTERBECK et al., 2017; GOLDSTRAW et al., 2016). It can be established that stages I to III comprise tumors with no metastases, and this classification is of fundamental importance to define the type of treatment of the patient with lung cancer (DETTERBECK et al., 2017).

Patients with non-small cell carcinoma classified as stages I and II are candidates for tumor resection surgery, and approximately one-third of patients in stage IIIa may also benefit from surgery (CERSOSIMO, 2002; DETTERBECK et al., 2017; LIM et al., 2018).

METHOD

This is an observational, analytical, and retrospective study, which involved the analysis of medical records of patients who underwent fiberoptic bronchoscopy performed in 2019 by the Thoracic Surgery Service of Hospital do Rocio, in Campo Largo, Paraná.

The beginning of data collection was characterized by data from the medical records of patients over 18 years of age who underwent fiberoptic bronchoscopy in 2019 and who had material collected through transbronchial biopsy and sent for histopathological analysis. Based on this, all the anatomopathological reports of these medical records were analyzed and, for statistical purposes, the reports were divided into five main subgroups: adenocarcinoma, squamous cell carcinoma, small cell carcinoma and others; the latter comprises infectious diseases and acute and chronic inflammatory diseases.

From the collection of anatomopathological reports and classification among the different types of neoplasms found, the study sample was established, in a total of 129 medical records. The reports of all chest computed tomography (CT) scans performed by these patients during the same period of hospitalization in which they underwent bronchoscopy were collected, and CT scans were considered the imaging test of choice available at the service to be classified according to TNM staging.

Patients who had medical records with a lack of information and those who did not have a sample sent to the pathology laboratory were excluded from the study. Small cell carcinomas were not classified according to TNM staging, because this classification is rarely used for this type of cancer in clinical practice. However, the tumor size and epidemiological profile of patients with this type of cancer have been documented for statistical purposes.

The collected data were tabulated in Microsoft Excel® software. For data and epidemiological profile, simple statistics were used, and for comparative data analysis, Student's t-test and Fisher's exact test were used.

RESULTS

A total of 1514 bronchoscopies were documented during 2019, performed on an elective basis at the tertiary hospital, and 226 bronchoscopies presented suspicious imaging, with the recommendation of transbronchial biopsy. Of these, 83 were excluded from the study because they were non-neoplastic diseases, and 14 patients were discarded from the study because they did not have sufficient radiological examinations to stage the lesion, leaving 129 patients diagnosed with cancer at bronchoscopy.

EPIDEMIOLOGICAL EVALUATION

A total of 129 patients confirmed for cancer were analyzed, 73 men and 56 women (ratio 1.3/1). The mean overall age of the patients at diagnosis was 64.8 years. Among women, the age range analyzed was 35-89 years, with a mean of 63.7 years. For men, the spectrum was 22-84 years, with a mean of 65.7 years. The table below presents descriptive statistics of age according to gender and the p-value of the statistical test.

Table 1 – GENDER AND MEAN AGE

	N	Average	Minimum	Maximum	DP
Women	56	63,5	35	89	10,91
Men	73	65,7	22	86	10,98

P= 0.3058
SOURCE: The author (2021).
LEGEND: N=sample number; DP=Standard Deviation

EVALUATION OF THE HISTOLOGICAL TYPE ACCORDING TO AGE

Regarding the histological type of the tumor, five main types were observed: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, poorly differentiated carcinoma, and mixed carcinoma. The five types were analyzed according to their prevalence and age of the patients, with squamous cell carcinoma being the most prevalent in the study, with 45 patients, followed by adenocarcinoma with 40 patients, and the mean age in both groups was 64.1 and 65 years; respectively.

Table 2 – HISTOLOGICAL TYPES AND AGE

	N	Average Age (years)
Adenocarcinoma	40	65,8
C. céls. Squamous	45	64,1
C. of small cells.	21	63,7
C. Little differentiated	22	66
C. Mixed	1	54

SOURCE: The author (2021).
LEGEND: N=sample number; C= Carcinoma; Cells: Cells

EVALUATION OF THE HISTOLOGICAL TYPE ACCORDING TO SEX

Regarding the histological type of the tumor, data regarding each of them and their relationship with the gender and mean age of the patients at diagnosis were compared, Table 3 is presented below for the histological types: adenocarcinoma, squamous cell carcinoma and small cell carcinoma.

Table 3 – HISTOLOGICAL TYPE, SEX AND AGE

	N	Average age	DP
Adenocarcinoma	40	65,85	11,23
Women	25	62,2	11,186
Men	15	71,8	8,760
Squamous cell carcinoma	45	64,15	10,71
Women	14	62,8	11,587
Men	31	64,4	10,487
Small cell carcinoma	21	63,7	9,698
Women	9	63,4	9,875
Men	12	63,9	14,896

SOURCE: The author (2021).
LEGEND: N=sample number; DP=Standard Deviation

EVALUATION OF THE HISTOLOGICAL TYPE ACCORDING TO TUMOR SIZE

The histological types were compared with the tumor sizes on CT scans. The mean size for adenocarcinomas was 60.07 mm, for squamous cell carcinomas it was 64.5 mm, and 94.7 mm for small cell carcinomas. The table below compares the tumor size data on CT for small cell carcinomas, with a mean of 94.7 mm, and non-small cell carcinomas, with a mean of 61.63 mm, with a p for this association equal to 0.028.

Table 4 – TUMOR SIZE AND HISTOLOGICAL TYPES

	Average size (mm)	DP
C. Small cells.	94,7	39,73
C. Not small cells.	61,63	29,04

P=0.028.
SOURCE: The author (2021).
LEGEND: N=sample number; SD=Standard Deviation; C = Carcinoma.

EVALUATION OF NON-SMALL CELL CARCINOMAS AND STAGING

Non-small cell tumor data were staged at the time of diagnosis, 14 patients (35%) with adenocarcinoma were diagnosed in stage I to IIIA, the rest in stage IIIB to IV; Regarding the patients with squamous cell carcinoma, nine (20%) were in stage I to IIIA, and 36 (80%) were in stage IIIB-IV.

Table 5 – NON-SMALL CELL CARCINOMA AND CLINICAL STAGE

	I – IIIA	IIIB – IV
Adenocarcinoma	14 (35%)	26 (65%)
C. céls. Squamous	9 (20%)	36 (80%)

P=0.028.
SOURCE: The author (2021).
LEGEND: N=sample number; C= Carcinoma; Cells: Cells

DISCUSSION

Lung cancer is one of the main malignant diseases today and its late diagnosis is extremely frequent. The surveys of the present study are in line with the data in the

literature: a total of 72.09% of non-small cell neoplasms found in stages IIIB and IV were observed, characterizing a disease that was inoperable at the time of diagnosis. Data from the Cancer Institute (INCA) from 2019 reveal a similar percentage: 86.2% of lung neoplasms are diagnosed at a late stage in Brazil, with 70% being the average prevalence of neoplasms at an advanced stage (BRAZILIAN MINISTRY OF HEALTH, 2019).

In a 2011 prospective study conducted in Canada (ELLIS; VANDERMEER, 2011), the researchers also raised a delay in the diagnosis of the patients studied: approximately 70% of the study participants were diagnosed in stages IIIB and IV, and the average age at diagnosis was 68 years. The authors also related the time elapsed from the onset of symptoms to the start of definitive treatment, which was an average of 138 days.

The United Kingdom, which has a health system very similar to Brazil's, faces similar scenarios. Salomaa and collaborators (SALOMAA et al., 2005) in a retrospective study, found a total of 67% of lung neoplasms already diagnosed in stage IIIB-IV; while Walter and collaborators (WALTER et al., 2015), in a British study by the University of Cambridge that involved 5092 patients, surveyed 68% of cases of lung cancer diagnosed at an advanced stage.

No statistical difference was observed in relation to the degree of staging and the two main types of non-small cell cancer (adenocarcinoma and squamous cell carcinoma). The p-value found (p=0.060) demonstrates a statistical tendency for squamous cell carcinoma to have more cases diagnosed in the late stage – stages IIIB-IV – compared to adenocarcinomas, but data in the literature are scarce to be compared.

Regarding epidemiology, this study found a mean age of 64.8 years, which is consistent with the main epidemiological studies on lung cancer, which present rates ranging from 60 to 70 years at the time of diagnosis (ALBERG et al., 2013; ELLIS; VANDERMEER, 2011; LIM et al., 2018; MINISTRY OF HEALTH (BRAZIL), 2019; SIEGEL; MILLER; JEMAL, 2020).

In addition, there was a higher number of cases in men than in women (56.5% vs 43.4%, respectively), with no statistically significant difference in age (p=0.305); values very close to and within the incidence of the American (50.8% vs 49.2%) and world (65.3% vs 34.6%) values, separated by sex (BRAY et al., 2018; SIEGEL; MILLER; JEMAL, 2020). No statistically significant difference was observed between the mean ages in relation to the sexes of the patients in the study, therefore, it can be said that cancer was diagnosed at similar ages for both sexes.

The main screening test for lung cancer is chest tomography (low-dose tomography when available) and is indicated in smokers with a high smoking history (at least 30 pack-

years) aged between 55 and 74 years. Suspicious findings on other imaging tests – such as simple chest X-rays – combined with respiratory symptoms such as cough, ventilatory-dependent chest pain, or dyspnea, are also frequent reasons for imaging and follow-up if a suspicious pulmonary nodule is found.

This follow-up tends to be more frequent if the nodule has malignant characteristics or presents a considerable increase in size in a short period of time (MIDTHUN, 2011). In the present study, the test of choice for staging was chest tomography, and its reports were important for meeting all the criteria necessary to classify and stage lung cancer.

Article published in 2011 by *New England Journal of Medicine* confirms the importance of chest tomography, both in patient adherence to the examination and in the sensitivity of detecting small nodules, in comparison with plain chest X-rays (24.2% vs 6.9%, respectively) (ET AL LON S. SCHNEIDER, 2011).

Notwithstanding, another article from 2020 published by the same journal, based on the clinical trial *Dutch-Belgian Lung Cancer Screening trial (NELSON)*, again highlights the need for early diagnosis by means of imaging tests, especially chest tomography. The clinical trial involved approximately 15,000 participants during a 10-year follow-up, in which the incidence and early detection of lung cancer with chest computed tomography at 0, 1, 3, and 5.5 years was evaluated. (DE KONING et al., 2020).

The conclusion of the study was highly anticipated by the scientific community, as it confirmed the benefit of chest tomography in the possibility of detecting lung neoplasms at an early stage by this screening method and showed a reduction of 25% or more in the mortality rate in this population, through the early diagnosis of malignancy.

For anatomopathological reports confirming the cell type corresponding to each neoplasm, fiberoptic bronchoscopy is still the main invasive test for the diagnostic evaluation of lung cancer in Brazil; it is a fast method with a low complication rate; It is important for the first moment of defining the histological type of the tumor. This is due to the possibility of performing bronchoalveolar lavage (useful mainly in the detection of infections and hematological diseases) and transbronchial biopsy (FERNANDEZ; JATENE; ZAMBONI, 2002).

Requires minimal sedation, which makes fiberoptic bronchoscopy acceptable and safe; In addition, it is capable of evaluating all lung segments, including the color and appearance of the mucosa of the bronchial tree. More than 70% of lung neoplasms can be diagnosed by this test, and if the lesion is in the central region of the bronchial tree, this percentage can reach up to 90%, depending on the experience of the examiner (HERTH, 2011).

And yet, in the face of well-established and effective screening programs and methods for early diagnosis of lung cancer, why does the high rate still remain prevalent in our environments? Should there be an adjustment in the Brazilian guidelines so that we observe a greater appearance of early stages at the time of diagnosis?

Some studies question and raise hypotheses about possible explanations for the high incidence of late diagnosis of lung cancer today. In 2019 systematic review (CASSIM et al., 2019), the authors divided the factors into three main groups: factor related to the health system and health professionals, patient-related factors, and disease-related factors.

Among the main factors related to the health system, the doctor-patient relationship was often unsatisfactory, as well as difficulty in accessing health and continuity of treatment (ineffective general guidelines, delay in consulting specialists). The patient-related factor ranges from socioeconomic aspects to demographic and cultural aspects inherent to the individual. Regarding the disease factor, it was observed that the presence or absence of symptoms exerts a significant influence on the delay in detection and allows the tumor to grow often unnoticed.

This discussion is based on a 1995 model titled *"The General Model of Total Patient Delay"*, proposed by Barbara L. Andersen and popularly called "*The Andersen Model*", in a British article published at the time (ANDERSEN; CACIOPPO, 1995). The original study proposes five different stages in which there may be a delay in the diagnosis of cancer, namely *"Appraisal delay", "Illness delay", "Behavioural delay", "Scheduling delay" and "Treatment delay".*

Simplified, it can be said that the theory addresses five main components that are "key pieces" from the initial assessment (*Appraisal*), to the appearance of symptoms (*Illness/Behavioural*), leading the patient to seek medical assistance and initiate the diagnosis and definitive treatment (*Sheduling/Treatment*). If there is a failure in the initial components of this trajectory, the diagnosis will be delayed.

Currently, other theories have been proposed with the objective of updating the initial model, adapting and adapting it to the new realities, as is the example of the systematic review on the applicability of Andersen's model, proposed by Walter et al. (WALTER et al., 2012). The onset and appearance of symptoms was considered the main factor of delay, followed by perception of the severity of the problem and first contact with health services, in the patient's path from diagnosis to the search for definitive treatment.

Models like this help to understand and raise possible hypotheses for the global problem of delay in the diagnosis of lung cancer. It is known that protocols for screening diseases, especially those that are better studied and relevant to public health – such as

lung cancer – are created and updated based on the most recent studies and improved based on previous guidelines (ANDRADE; RAMOS-BARBOSA; PEREIRA-SILVA, 2002).

Brazil follows updated international recommendations for lung carcinoma screening, adjusted to the reality and resources available in the national territory. It is up to physicians to improve efforts to improve the doctor-patient relationship and minimize problems regarding the individual's understanding and severity of the disease, seeking to shorten, as far as possible, the path to be taken from initial suspicion to definitive treatment.

The main limitations for this study were the lack of data available at the time of collection, inherent to retrospective studies. A very relevant piece of data for the study, but which was not found in some of the medical records of the study, was about smoking and smoking history of the patient studied. Because this is the main risk factor for the development of lung cancer, the authors believe that the epidemiological statistics on smoking in this study follow values that are very close to those found in the Brazilian and international literature.

CONCLUSION

Most patients with lung cancer had their diagnosis established at an advanced and inoperable stage (stages IIIB-IV). However, even with well-established and up-to-date guidelines for screening lung neoplasms, their clinical characteristics associated with the patient's profile and delays related to health services, are still challenges to promote more effective measures for early diagnosis and the possibility of treatment with a higher expectation of cure.

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