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THE CHALLENGES OF EARLY DIAGNOSIS OF LUNG CANCER

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Abstract: Lung cancer is one of the most common tumors in the Brazilian population, with a high mortality rate. The survival rate for a patient with this disease is about 5 years. Smoking is directly associated with this disease, but etiological factors such as family history, occupational risks, and exposure to air pollution can contribute to the onset of lung cancer. According to data from the National Cancer Institute (INCA), estimates for 2020 point to 30,200 new cases of tumors of the trachea, bronchi, and lung in the country. Adenocarcinoma was the most common histological type found in the patients surveyed. The Brazilian anti-smoking legislation is a world reference and has proven to be an important factor in the reduction of smoking in recent years. Thus, this review sought to observe which factors lead to a late diagnosis of lung cancer through the analysis of various existing literature and public data.
Keywords: Lung cancer, Early diagnosis, Challenges.

INTRODUCTION

According to the World Health Organization (OMS), 1.6 million deaths per year are attributed to malignant neoplasms of the lung. About 60% of new cases are registered in Africa, Asia, Central and South America, affecting mainly the elderly. In 2020, lung cancer was the fourth most common type of cancer in the Brazilian population (IARC, 2020), with a high lethality in relation to other malignant tumors, with the occurrence of 26.6 deaths per 100,000 inhabitants and a survival rate around 5 years. Among the etiological factors, we have genetic alterations associated with family inheritance and exposure to environmental carcinogens (radon, cadmium, air pollution and tar), with smoking being responsible for about 50% of cases in Brazil (ARAUJO et al., 2018).

Several factors interfere with early diagnosis. Access to health systems is a key factor. A 2018 OMS estimate estimated that by the year 2020 the public network would be responsible for 73% of care and the private network for 27% (ARAUJO et al., 2018). This assistance, according to a study carried out by the Oswaldo Cruz Foundation (FIOCRUZ) and the National Cancer Institute (INCA) in 2017, generates annual expenditures to the public coffers of approximately R$56.9 billion in medical costs with the treatment of lung cancer and loss of productivity (FIOCRUZ&INCA., 2017).

The absence of symptoms in the early stages of the disease is also related to late diagnosis, as well as the incorrect identification due to the symptomatology being comprehensive and not very specific at the beginning of this pathology, such as shortness of breath, chest pain, wheezing. and hemoptysis (GOEBEL et al., 2019).

The delay in performing tests also contributes to late diagnosis, with about 70% of patients being diagnosed with a locally advanced tumor or in a metastatic state. In general, access to the various diagnostic tools is greater in the South and Southeast regions, where about 89% of patients are diagnosed by chest X-ray, while only 20% of patients were diagnosed with computed tomography (TC) scans (ARAUJO et al., 2018). A study carried out in 2009 by the Organization for Economic Co-operation and Development (OECD) showed that Brazil performed about ten times fewer TC exams per 1,000 inhabitants when compared to several countries. (Australia, South Korea, Denmark, Iceland, the Netherlands, Czech Republic, Slovakia, Luxembourg, Turkey, Canada, Estonia, France, Israel, Chile, and the United States) and 20 times fewer TC scans when compared to the United States (SANTOS et al., 2014).

Access to molecular tests is also important

for the reduction of diagnosis time, since it allows the evaluation of the gene expression profile, helping in tumor subtyping. A study conducted in the first half of 2014 pointed out that of the 1700 cases of malignant lung tumors in the country, less than half of the patients underwent testing for mutations in the Epidermal Growth Factor Receptor Receptor Gene (EGFR), with the SUS taking a third of these diagnoses (ARAUJO et al., 2018).

For assertive and early diagnosis of malignant lung neoplasia to also occur through health service facilities, some essential standards need to be followed such as access to specialized care, timeliness of care, educational training to health professionals, patients and their caregivers, and quality assurance of services provided (ERS, 2018).

OBJECTIVES

GENERAL OBJECTIVE

- Address the main factors that lead to late diagnosis of lung cancer in Brazil.

SPECIFIC OBJECTIVES

- To characterize the anatomy, pulmonary physiology and the etiological factors of malignant lung cancer;
- Describe the epidemiological profile worldwide and nationally;
- Present the histological changes indicative of malignant lung tumor;
- Discuss the diagnosis of lung cancer in Brazil.

METHODOLOGY

This project is an integrative review that comprises the analysis of conceptualized research that provides a basis for decision making and the improvement of clinical practice, enabling the synthesis of the state of knowledge on a given topic, in addition to demonstrating gaps in knowledge that need to be filled with new studies (MENDES, SILVEIRA, GALVÃO, 2008). For the development, 6 methodological steps were used, which are Definition of the research question; literature search; ca-tegorization of the studies; categorization of the articles included in the review; the interpretation of the results obtained and the presentation of the review.

The first stage consisted of the elaboration of the guiding question. This is considered the most important step because it determines the subject to be researched, which directs all subsequent steps. The guiding question was: What are the factors that lead to the late diagnosis of lung cancer?

The second phase was the literature search. In this phase we defined the following descriptors: Lung cancer, Biomedical, diagnosis and treatment. The search for articles in the Scientific Eletronic Library Online (SCIELO), Latin American andCaribbean Health SciencesLiterature (LILACS), Medical LiteratureAnalysisandRetrieval System Online (MEDLINE) and PUBMED databases was carried out.

The third phase corresponded to the collection of data from other researches that were relevant to the construction of this project. The inclusion factors were: articles published between 2010 and 2021, with full texts available in Portuguese, Spanish, English and German. The exclusion criteria were: articles that did not meet the inclusion criteria.

The fourth phase was the critical evaluation of the articles included in the previous step. We categorized and evaluated the data provided by the articles selected for study in order to group the knowledge on the theme.

The fifth phase corresponded to the summary of the information obtained during the thematic analysis; in this phase we will talk about our interpretation and conclusion.

The sixth phase referred to the presentation of the review itself. It is the con-cretization of all the steps previously followed.

REVIEW OF THE LITERATURE

LUNG ANATOMY AND PHYSIOLOGY

The respiratory system comprises all the structures that conduct air to the lungs and vice-versa, and perform the gas exchange between the ambient air and the blood, being divided into upper and lower respiratory tracts. The upper portion (nose, nasal cavity, sinuses, and pharynx) filters, warms, and humidifies the inhaled air, while the lower portion (larynx, trachea, bronchi, and right and left bronchioles) conducts air into and out of the lung alveoli exchange surfaces **(Figure 1).**

The lungs have a pyramidal shape, containing an apex in the upper part, a base in the lower part, and 3 faces: costal face (which is related to the ribs), diaphragmatic face (lower part of the lung), and the mediastinal face (where the hilum is located). The hilum is the lung structure where the blood vessels and nerves pass. The lungs are distinct because of their shape and the irregular location of the heart. The right lung is divided into three lobes and the left lung into two. In the right lung we have the oblique fissure that runs from the middle of the costal face forward and downward, forming the upper and lower lobes, and the horizontal fissure that runs from the middle of the oblique fissure forward, forming the middle lobe. In the left lung we have the oblique fissure that divides it into an upper and lower lobe.

The lungs are surrounded by a serous membrane called pleura, which is divided into visceral (in contact with the lung) and parietal (in contact with the chest wall), with the pleural cavity between them (ZIERI, 2014).

Gas exchange occurs at the alveolar level, with each lung having approximately 150 million alveoli, which form clusters, like grape bunches. This process of gas exchange is called respiration, and is related to two processes: pulmonary and cellular respiration. Pulmonary respiration is responsible for the exchange of oxygen and carbon dioxide between the body tissues and the environment. Its purpose is to meet the respiratory demands of the cells. Cellular respiration comprises the absorption of oxygen and the release of carbon dioxide by the cells. Biochemical pathways are considered to be responsible for oxygen consumption and carbon dioxide production. The process of lung ventilation is influenced by pressure changes within the pleural cavities. The movements of the diaphragm muscle and the lateral walls of the thoracic cavity change the volume of the thoracic cavity, promoting changes in lung volume. This changes the thoracic cavity by expanding or compressing the lungs, thus changing the air pressure inside the airways. The onset of breathing causes the chest cavity to keep the internal and external pressures equal, so that no air enters or leaves the lungs. The air goes from an area of higher pressure to an area of lower pressure. When the rib cage increases its volume during inhalation, the pressure decreases inside the lungs and the air goes in. Whereas when the rib cage reduces in volume during expiration, the pressure inside the lungs increases, causing air from inside the lungs to go out of the respiratory system (Figures 4 and 5).

WORLDWIDE AND NATIONAL LUNG CANCER EPIDEMIOLOGY

Lung cancer (CP) is one of the most prevalent malignant tumors in the world, being the leading cause of cancer death in men and the second in women (after breast cancer). A study in 2012 found that 1.8

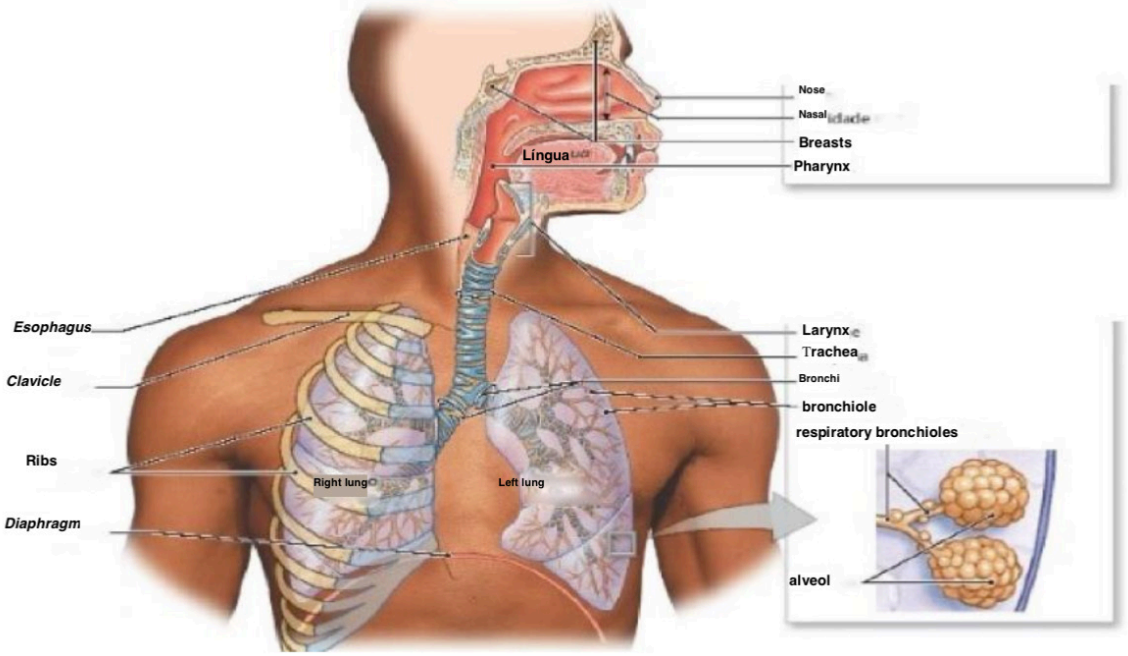

Figure 1- Structure of the respiratory system

Source: Martini et al.(2015).

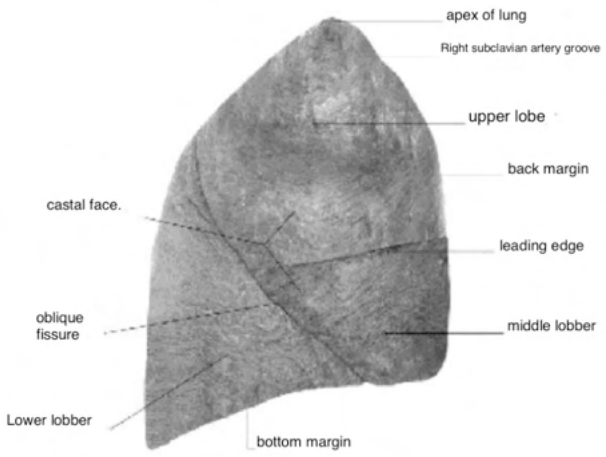

Figure 2 - Lateral view of the right lung

Source: Colicgyno (2009, p. 183).

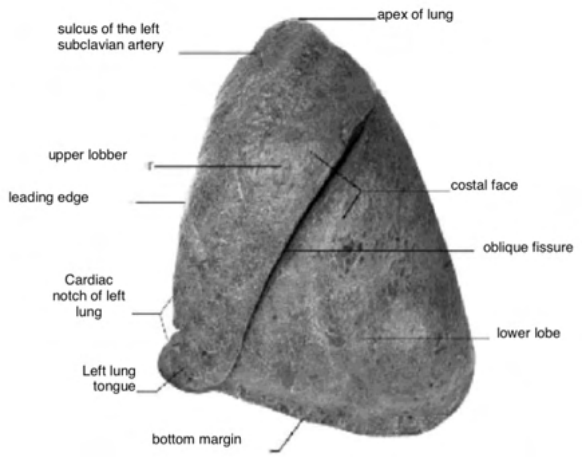

Figure 3 - Lateral view of the left lung

Source: Colicgyno (2009, p. 183)

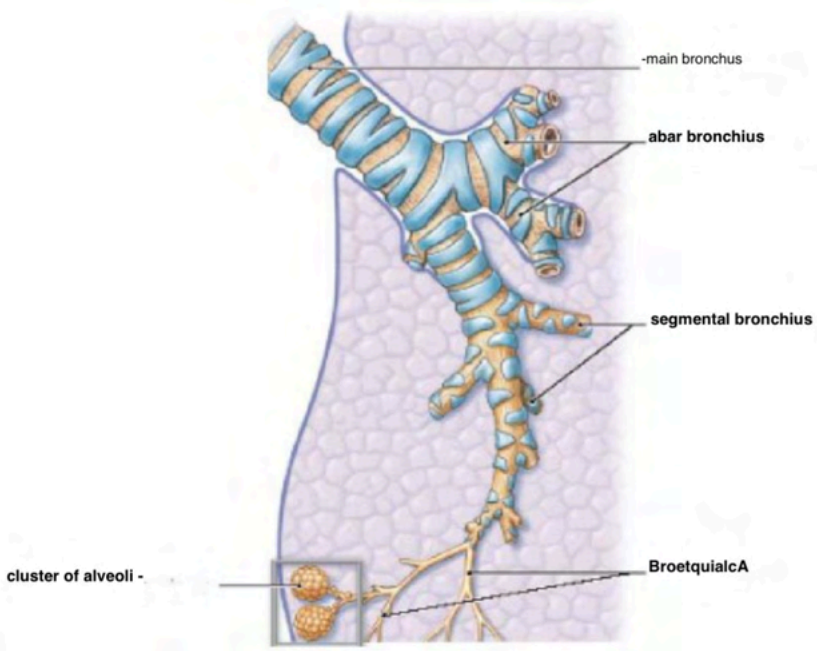

Figure 4- Gas exchange process

Source: Martini et al. (2015).

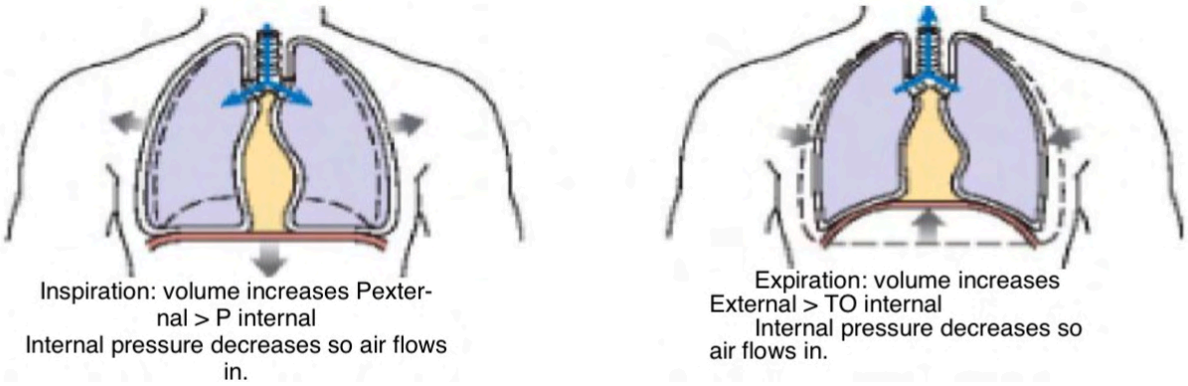

Figure 5- Physiology respiratory

Source: Martini et al. (2015).

million cases of CP were diagnosed in the world that year, representing 12.9% of the total global cancer incidence. The geographical distribution of lung malignancies in the world shows relevant regional variation, with the most significant incidence rates in men being seen in Central and Eastern Europe (53.5 per 100,000 population) and East Asia (50.4 per 100,000 population). For women, the incidence rates are generally lower and the geographic pattern is more related to different exposures to tobacco use. Thus the highest rates are seen in North America (33.8 per 100,000 population), Northern Europe (23.7 per 100,000 population), and East Asia (19.2 per 100,000 population) (MAO et al., 2016).

The national territory has been showing steady increases when compared to developed countries, where cases of CP increased until 1990 and decreased thereafter. Age-adjusted rates of CP mortality in the national territory show an increase from 10.6 per 100,000 population to 13.1 per 100,000 population among men and from 3.0 per 100,000 population to 5.4 per 100,000 population among women from 1979 to 2004 (DE SÁ et al., 2016).

According to data from INCA, the 2020 estimates pointed to the occurrence of 30,200 new cases of cancer of the trachea, bronchi and lung, being in men 17,760 and 12,440 for women. In men this group of malignant tumors is the third most frequent, representing 7.9% of the cases, after prostate cancer (29.2%) and colon and rectum cancer (9.1%). In the female population, this same group of pathologies is the fourth most frequent, accounting for 5.6% of cases, behind breast cancer (29.7%), colon and rectum (9.2%) and cervical cancer (7.5%). These figures do not consider non-melanoma skin tumors **(Table 1)**.

By analyzing the INCA estimates by state of new cases of tracheal, bronchial, and lung cancer for 2020, we can calculate the incidence rate per 100,000 inhabitants.According to these data, we see that the southern region has the highest incidence of tracheal, bronchial, and lung cancer per 100,000 inhabitants in the country **(Chart 1)**.

Primary Location	Cases	%			Primary Location	Cases	%
Prostate	**65.840**	**29,2%**			**Female Breast**	**66.280**	**29,7%**
Colon and Rectum	**20.520**	**9,1%**	**Homens**	**Mulheres**	**Colon and Rectum**	**20.470**	**9,2%**
Trachea, Bronchus and Lung	**17.760**	**7,9%**			**Cervix**	**16.590**	**7,4%**
Stomach	**13.360**	**5,9%**			**Trachea, Bronchus and Lung**	**12.440**	**5,6%**
Oral Cavity	**11 180**	**5.0%**			**Thyroid Gland**	**11.950**	**5,4%**
Esophagus	**8.690**	**3,9%**			**Stomach**	**7.870**	**3.5%**
Bladder	**7.590**	**3,4%**			**Ovary**	**6.650**	**3,0%**
Non-Hodgkin Lymphoma	**6.580**	**2,9%**			**Body of the uterus**	**6.540**	**2,9%**
Lannge	**6.470**	**2,9%**			**Non-Hodgkin Lymphoma**	**5.450**	**2.4%**
Leukemias	**5920**	**2,6%**			**Central Nervous System**	5.220	2,3%

Table 1- 2020 estimates of new cancer cases by sex, except non-melanoma skin.

Source: INCA (2019).

State	Population Estimation 2020 (IBGE)	Estimated new cases of CA of the trachea, bronchus and lung (INCA)	Cases of CA of the trachea, bronchus and lung per 100,000 population
Acre	894.470	100	11,17
Amapá	861.773	50	5,80
Amazonas	4.207.714	320	7,60
Pará	8.690.745	560	6,44
Rondônia	1.796.460	180	10,01
Roraima	681.181	30	4,75
Tocantins	1.590.248	220	13,83
Alagoas	3.351.543	250	7,45
Bahia	14.930.684	1.170	7,83
Ceará	9.187.103	1.290	14,04
Maranhão	7.114.598	470	6,60
Paraíba	4.039.277	490	12,13
Pernambuco	9.616.621	1.120	11,64
Piauí	3.281.480	320	9,75
Rio Grande do Norte	3.534.165	420	11,88
Sergipe	2.318.822	230	9,91
Distrito Federal	3.055.149	420	13,74
Goiás	7.113.540	940	13,21
Mato Grosso	3.526.220	320	9,07
Mato Grosso do Sul	2.809.394	460	16,37
Espírito Santo	4.064.052	530	13,04
Minas Gerais	21.292.666	2.990	14,04
Rio de Janeiro	17.366.189	2.930	16,87
São Paulo	46.289.333	6.890	14,88
Paraná	11.516.840	1.990	17,27
Rio Grande do Sul	11.422.973	3.740	32,74
Santa Catarina	7.252.502	1.170	24,40

Chart 1- Incidence of new cases of cancer of the trachea, bronchus, and lung per 100,000 population.

Source: Prepared by the author based on INCA (2019) and IBGE(2020).

ETIOLOGY

The control of tobacco consumption is the main measure of prevention of CP, since the risk of active smokers developing this disease is 20 to 50 times higher when compared to nonsmokers. Although cigarettes are the most widely consumed tobacco product in the world, studies have shown that the use of cigars, cigarillos and pipes are equally associated with the risk of CP, demonstrating that regardless of how tobacco is manufactured, its damage to health is equally harmful. Besides tobacco, other etiologic factors include dietary intake, chronic lung diseases, chronic inflammation from infections, occupational exposures (ionizing radiation, uranium, radium, and radon gas), air pollution, family history, and genetic predisposition (MALHOTRA et al., 2016).

Regarding diet, a meta-analysis (GNAGNARELLA et al., 2017) found a 24% increased risk of developing CP in non-smokers who consumed high amounts of red meat. This is due to the presence of chemicals such as nitrates, which are classified as potentially carcinogenic elements, and saturated fat, which in amounts above 22.2g per day can cause increased body fat and trigger a chronic inflammatory state. In addition, the exacerbated consumption of lipids may also be associated with a higher risk for this disease since these molecules cause changes in the metabolism of sex hormones such as estrogen, progesterone and androgens (like testosterone), which induce cell proliferation, and this high rate of mitoses is associated with a higher risk of mutations that can lead to cancer cells (BADE and DELA CRUZ, 2020).

Chronic lung diseases have been associated with a high risk for the emergence of CP, being chronic obstructive pulmonary disease (COPD) the most correlated, because it is a pathology characterized by chronic inflammation of tissues, which favors an increase in the rate of DNA errors during the replication process, due to the constant need for cell replacement. There is still disagreement in the literature about the role of certain infections as a risk factor for CP. An example of this disagreement involves the human papilloma virus (HPV), which was detected in bronchial squamous cell lesions in an Asian study (KLIGERMAN; WHITE, 2011), but did not play a significant role in another study conducted in Western Europe (SIMEN-KAPEU et al., 2010)(BARTA et al., 2019). Tuberculosis, on the other hand, caused by Mycobacterium tuberculosis and its epidemiological relationship with CP is well documented in preclinical and clinical evidence, although the molecular mechanism of this relationship is unknown. The main hypothesis of this association is also linked to constant inflammatory processes and the need for cellular repair (MOLINA-ROMERO et al., 2019).

Occupational risks can also influence the onset of CP, with mining being the oldest occupation associated with it, because the uranium, radium, and radon gas found in the soil of rocks and mines with variable concentrations, besides being radioactive elements, when inhaled are deposited deep in the lungs and, over time, generate decay to other by-products (each decay generates alpha radiation emission) up to lead, which has a half-life of 22 years and is harmful to the respiratory epithelium. When evaluating the role of urban centers in the increase of CP cases in the population, one study showed a 10% to 40% increase in CP deaths in urban centers, with carcinogens such as benzene, formaldehyde, and 1,3-butadiene being found in the air. Despite studies, it is still difficult to identify the role of these agents found in air pollution in urban centers as the only factor in

developing malignant lung neoplasia (SCHWARTZ and COTE, 2016).

From a genetic point of view, the inheritance of certain polymorphic genes (which have acquired variations in their DNA sequence), e.g.op53, p14ARF and FHIT are associated with higher risk of CP. These genes, in the absence of mutations, generate tumor suppressor proteins, essential to prevent carcinogenesis. A family history of CP, especially in members diagnosed under 60 years of age has been shown to be a predisposing factor, with a 2-fold increase in the risk of CP in smokers with family history, a high risk also for nonsmokers (BADE and DELA CRUZ, 2020).

CELLULAR CHANGES AND HISTOLOGICAL TYPES

Histological evaluation is fundamental for correct therapeutic determination. Adenocarcinoma, large cell carcinoma and squamous cell carcinoma are known as non-small cell lung cancer (NSCLC) because of their similarity in sensitivity to chemotherapy and radiotherapy when compared to small cell carcinoma which corresponds to small cell lung cancer (SCLC) (ISMAEL et al., 2010). Chart 2 shows the different histological types for lung cancer according to the OMS classification.

The incidence of adenocarcinoma has surpassed the occurrence of squamous cell carcinoma, becoming the most prevalent subtype of lung neoplasm in the world (OLIVEIRA et al., 2019). The observed decrease in the incidence of squamous cell PC and the increase in the number of adenocarcinomas may be related to the decrease in the number of smokers in the world since 1960, as well as the decrease in tar contents and introduction of filters in cigarettes, causing the smoker to increase the inhalation time thus absorbing small particles that will be deposited in the lung periphery, the most common site for the development of adenocarcinoma (TSUKAZAN et al., 2017).

The selection of lesions found for biopsy is usually decided by physicians, surgeons or interventional radiologists through different techniques such as bronchoscopy, fine needle aspiration biopsy and thoracotomy. Genetic analysis of a single biopsy sample may not cover the characteristics of the entire tumor, and multiple materials are required for heterogeneous confirmation of the tumor (KIM and TSAO., 2014).

Adenocarcinoma is characterized by having large, hyperchromatic cells, nuclei usually with irregular contours, and cytoplasm that varies in size. Squamous cell carcinoma, on the other hand, has keratinizing (intensely cornified, very dense nuclei with fusiform cytoplasm) and non-keratinizing (large, hyperchromatic nuclei and medium-sized cytoplasm) cells. Small cell lung cancer consists of small and medium-sized cells, possessing noticeably dense chromatin (ENGELS, 2020). And large cell carcinoma have cells in a solid and large arrangement being undifferentiated (THEEGARTEN and HAGER, 2016).

Both adenocarcinomas and large cell carcinomas are found in a peripheral nodular form or have damage that eventually compromise the regi-non of the pleura, not being so common metastasis to distal organs. (LAYFIELD et al., 2016).

Figures 6, 7, 8 and 9 can show some of the histological patterns of lung cancer.

TUMOR STAGING

The staging of CP is performed mainly based on the tumor-node-metastasis (TNM) system and its objective is to standardize the main oncologic treatment models for each stage, estimating the patient's prognosis and comparing the results of different therapies and their associations. TNM analyzes the

Adenocarcinoma
Editic Adenocarcinoma
Acinar Adenocarcinoma
Papillary Adenocarcinoma
Micropapillary Adenocarcinoma
Solid Adenocarcinoma
Invasive mucinous adenocarcinoma
Colloid adenocarcinoma
Fetal adenocarcinoma
Enteric adenocarcinoma
Minimally invasive adenocarcinoma
Squamous cell carcinoma
Neuroendocrine tumors
Carcinoid tumors
Typical carcinoid
Atypical carcinoid
Small cell carcinoid
Large cell neuroendocrine carcinoid
Large cell carcinoid
Adenosquamous carcinoid
Pleomorphic carcinoid
Giant cell carcinoid
Carcinosarcoma
Pulmonary blastoma
Other Carcinomas and unclassified
Lymphoepithelioma-like Carcinoma
NUT Carcinoma
Salivary gland type carcioma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Myoepithelial epithelial carcinoma
Mesenchymal tumors, lymphohistiocytic tumors, tumors of ketotic origin, and metastatic tumors

Chart 2 - Classification of the different histological types of lung cancer according to the W.H.O. (World Health Organization).

Source: Adapted from Zheng (2016).

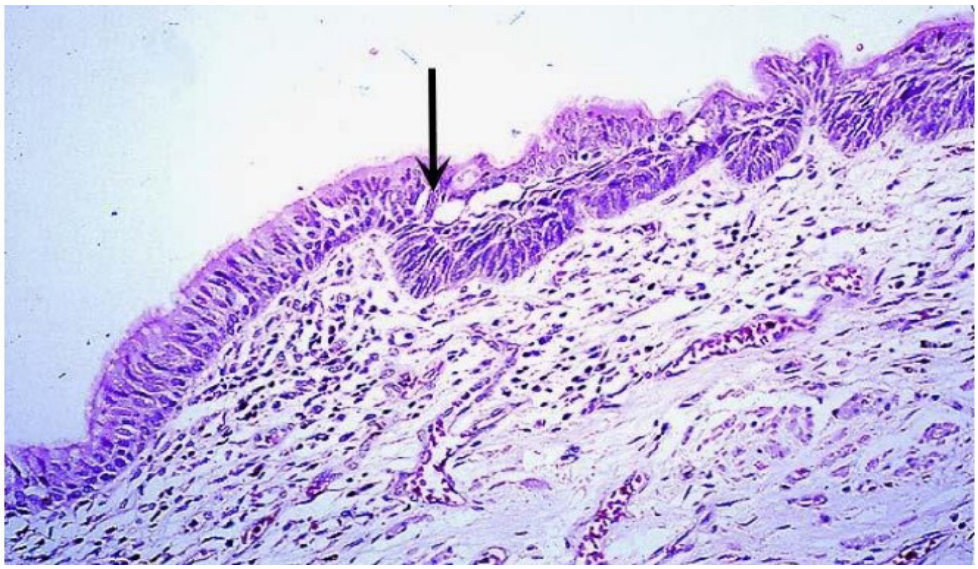

Figure 6 – Squamous cell carcinoma of the lung.

Source: UFSM ([200-]).

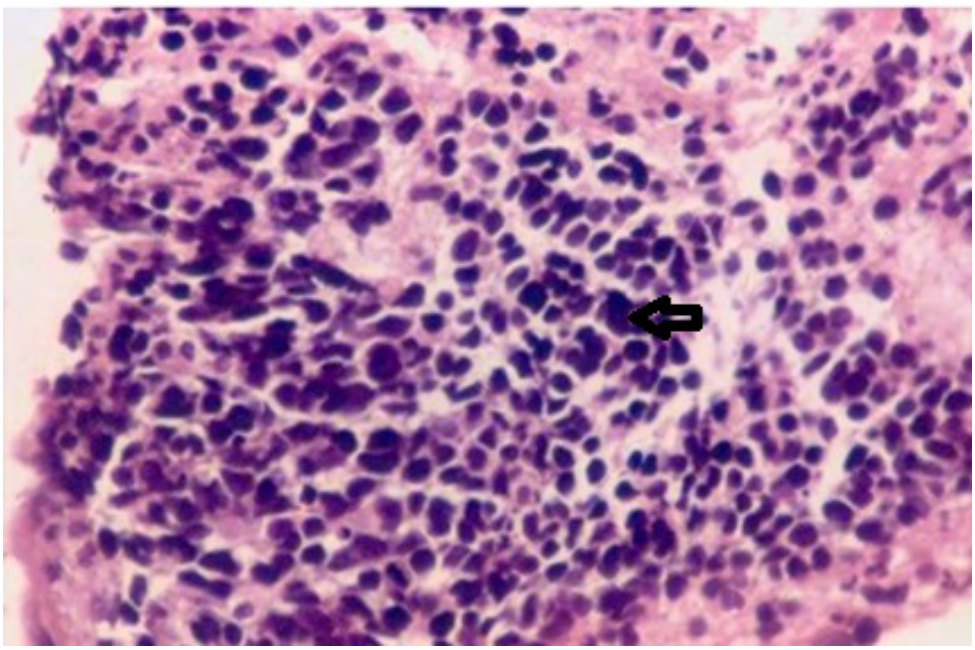

Figure 7 – Small cell carcinoma.

Source: UFSM ([200-]).

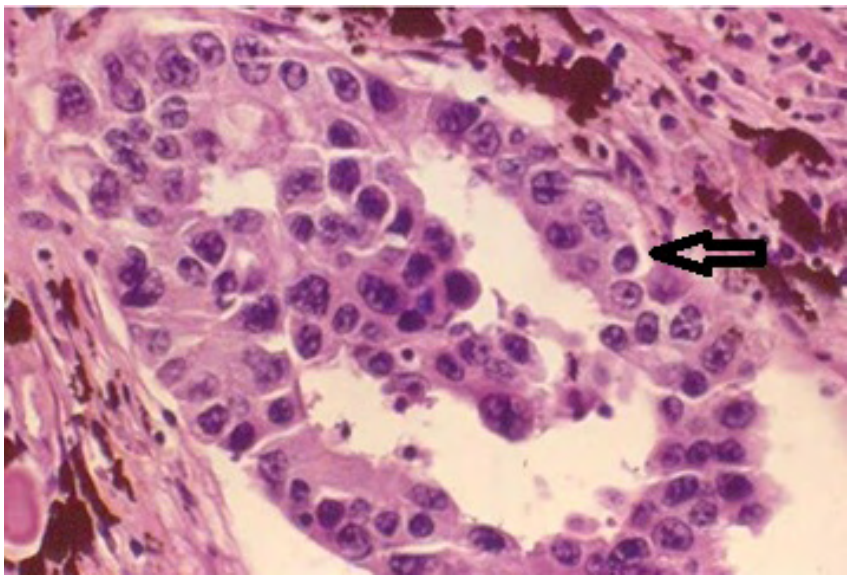

Figure 8 – Adenocarcinoma of the lung.

Source: UFSM ([200-]).

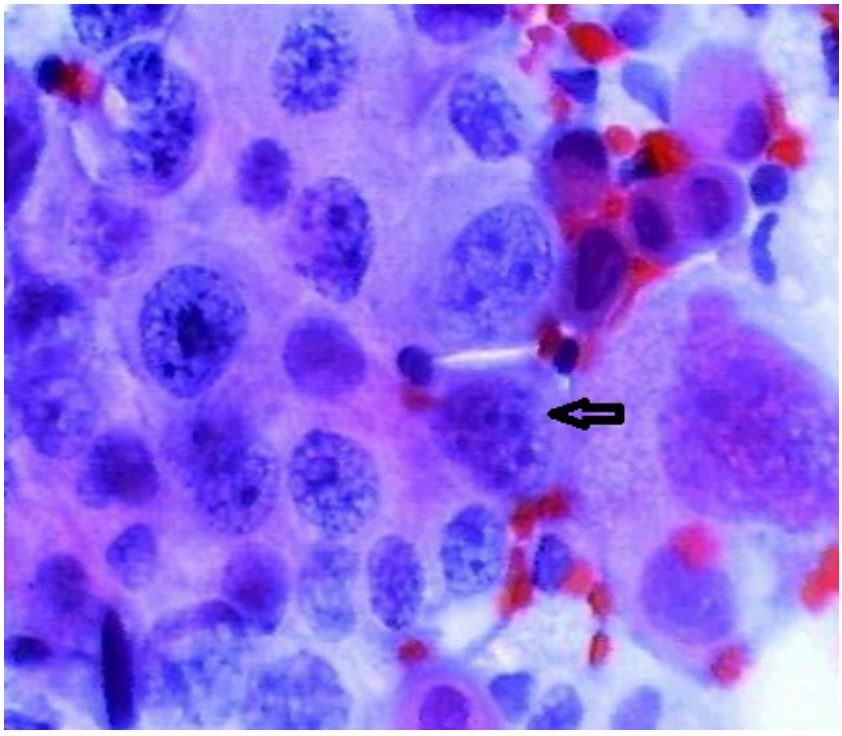

Figure 9 – Large cell carcinoma.

Source: UFSM ([200-]).

degree of tumor extension, starting with the primary lesion in the lung (T), the involvement of lymph nodes (N), and the dissemination of lesions in the same organ or in others, also called metastasis (M).It is commonly classified into initial or early stage (I and II), locally advanced (III), and advanced or metastatic (IV).Knowing the staging of CP is necessary to improve programs to combat smoking, as well as the tracking of cases, whether in diagnosis or in oncologic treatment nationwide by the public and private sectors. Analyzing the average percentage of staging between 2000 and 2014 in Brazil, early staging was 13.3%, locally advanced 33.2%, and advanced/metastatic 53.4% of cases.In the United States early staging corresponded to 15.9%, locally advanced 22.0% and advanced/metastatic 57.0% and in the United Kingdom about 87% of cases are diagnosed in stages III and IV (COSTA et al., 2020). According to INCA (2019), staging can be divided into clinical and pathological, the former being determined from the data of the physical examination and complementary exams of the case (CT, MRI, radiographic exam) and the latter established through surgical findings and anatomopathological exams.

The Brazilian Society of Clinical Oncology (SBOC) has several guidelines for the use of diagnostic methods for CP according to histological classifications, which are adenocarcinoma, squamous cell carcinoma, small cell carcinoma and large cell carcinoma. For small cell carcinomas, the clinical history must be collected and a complete physical exam must be performed, as well as laboratory tests such as complete blood count, liver profile and function, renal function and electrolytes, imaging exams such as TC of the Thorax, Abdomen/Pelvis with liver and adrenal evaluation, Magnetic Resonance Imaging (RM) or TC of the Skull, Bone Scintigraphy and PET/CT if available to rule out extensive disease. If the latter is performed, bone scintigraphy, chest TC, and abdominal/pelvis TC can be dispensed with. In cases of non-small cell disease where the disease is localized or locally advanced, contrast-enhanced TC of the chest and total abdomen, MRI of the skull, PET/CT, invasive mediastinal evaluation through transcutaneous fine needle biopsy or endoscopic transbronchial needle aspiration, among others (when the tumor is central > 3 cm or there is suspicion of mediastinal lymph node involvement seen on TC Chest or PET/CT) must be used, scintigraphy (in symptomatic bone cases or for suspected skeletal involvement), laboratory tests such as complete blood count and renal and hepatic functions and serology for hepatitis B, C, HIV and evaluation of hormonal profile for patients who are candidates for immunotherapy, pulmonary function test for patients eligible for surgery and diagnostic thoracocentesis and/or pleuroscopy for patients with pleural effusion where it is suspected to have been affected by neoplasia. In cases where the disease is advanced, PET/CT is recommended (if not available, replace with TC of the Thorax, Abdomen and Pelvis and Bone Scintigraphy), MRI of the Skull, laboratory tests such as complete blood count, liver function, kidney function with electrolytes, blood glucose, and if immunotherapy is used: TSH, free T4, ACTH, serologies for HIV and hepatitis, amylase and lipase, pathological examination for EGFR mutation research,ALK fusion, BRAF, ROS, NTRK in all patients with non-squamous histology and PD-L1 for all non-small cell lung cancers and if available, perform gene sequencing panel to evaluate other mutations (SBOC, 2021).

DIFFERENTIAL DIAGNOSIS

The main aspect of CP is the late onset of symptoms, therefore the use of advanced techniques is extremely important for the

Tumor
Tx - Primary tumor cannot be accessed; presence of malignant cells in sputum or bronchial lavage, but the tumor is not visualized on imaging or bronchoscopy. **TO** - No evidence of primary tumor. **Tis** - carcinoma in situ. **TI** - Tumor < 3 cm in diameter, surrounded by lung or visceral pleura, without invasion more proximal than the bronchio- quiolobar. **Tlmi**- Minimally invasive adenocarcinoma. **T1a** - Tumor < 1 cm in diameter. **T1b** - Tumor > 1 and ≤ 2 cm in diameter. **T1c** - Tumor > 2 and < 3 cm in diameter. **T2** - Tumor > 3 cm and <5 cm in diameter or of any size with one of the following characteristics: • It affects the main bronchus, but does not involve the carina; • Invades the visceral pleura; • Associated with atelectasis or obstructive pneumonitis extending to the hilum or involving the entire lung. **T2a** - Tumor > 3 cm and < 4 cm in diameter. **T2b** - Tumor > 4 cm and < 5 cm in diameter. **T3** - Tumor > 5 cm and ≤ 7 cm in diameter or of any size with one of the following characteristics: • Direct invasion of any of the following structures: chest wall, phrenic nerve, parietaL pericardium • Separate tumor nodules in the same lobe. **T4** - Tumor > 7 cm or invading any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral bodies, carina or with separate nodules in another ipsilateral lobe.
Linfonodos
NO - No metastases to regional lymph nodes. **N1** - Metastasis to peribronchial, hilar or intrapulmonary lymph nodes on the same Side or both, including direct extension. **N2** - Metastasis to mediastinal lymph nodes on the same Side and/or to subcarinal lymph nodes. **N3** - Metastasis to contralateral mediastinal, contralateral hilar, supraclavicular or pre-scalar lymph nodes on the same Side or contralateral.

Metastasis
MO - No known distant metastases. **M1** - Distant metastases present. **M1a**- Nodule(s) in contralateral lobe, pleural nodules, pleural or pericardial effusion malignant **M1b** - Extrathoracic metastases. **M1c** - multiple extrathoracic metastases

Figure 10 - TNM classification for lung cancer

Source: Frank C. Detterbeck. The 8th editionLungCancerStageClassification, CHEST (2016).

diagnosis, assertive staging and choice of the best therapeutic strategy. The introduction of advanced tools and techniques such as the use of biomarkers, radiogenomics and artificial intelligence, which are being widely used nowadays, demonstrates their great potential to complement/replace basic diagnostic techniques.Biomarkers are naturally occurring molecules, being genes or other biological agents that can undergo changes during a given disease condition, and thus can be used to detect abnormal cellular functions in cancer patients. According to their characteristic they can be classified as imaging biomarkers (used in conjunction with low-dose TC and PET/CT) and molecular biomarkers (based on miRNA-like genes, peptides, and proteins), and depending on their application we have diagnostic, prognostic, and predictive. Diagnostic biomarkers help detect specific disease, prognostic biomarkers help evaluate disease recurrence, and predictive biomarkers help predict disease before symptoms are observed. Molecular biomarkers (examples: BRAF - mutation and amplification, PTEN - de-lection, EGFR - mutation, ALK - rearrangement, ROS1 - rearrangement and KRAS - mutation) are used for the detection of CP and immunotherapy markers include cytotoxic T-lymphocyte associated antigen and the programmed death ligand receptor expressed on inflammatory cells and immunological white blood cells present in the blood that infiltrate the tumor tissuebeing within the group of predictive biomarkers(PRABHAKAR et al, 2018).

For the detection of tumor biomarkers we can use several methods such as cytochemistry, histochemistry, immunocytochemistry, ELISA, flow cytometry and immunohistochemistry. One of the most widely used techniques is the immunohistochemistry technique that comprehends in the detection of antigens in tissue sections through specific antibodies. Its unique advantage over other methods of protein detection is the ability to correlate the presence of an antigen with its location in a particular tissue or cell. The fixation of the tissue depends on the type of antigen to be detected, for example, some antigens will become undetectable after fixation in formaldehyde and the tissues must be frozen or fixed with fixative other than formaldehyde which is the gold standard fixative for immunohistochemistry. The goal of immunohistochemistry is to detect the maximum amount of antigen with as little sample as possible (RAMOS-VARA, 2017).

Biosensors are an analytical tool that converts chemical signals into an electronic response and is a mechanism used to detect and quantify biomarkers. The device consists of a bioreceptor surface (enzymes, nucleic acids, receptors, antigens, proteins or antibodies) and these are immobilized on the biosensor substrate so that the analyte contained in the sample when in contact with the immobilized bioreceptor produces physical-chemical change (change in temperature, resistance and capacitance) that can be recognized by an electrical transducer, thus showing the user if the analyte is present in the clinical sample. The conductive surface on which the bioreceptor element is immobilized must be transparent so that the result obtained can be visually analyzed and confirmed. Biosensors are useful in diagnosis because they are minimally invasive for the patient and provide accurate results.

The process of tumor detection using radiogenomics involves four steps: image retrieval and restoration (1), distribution of the desired region (2), feature extraction and amplification of the results (3), and model making (4). The images are converted into 3D structures in the computer and through these

the physician can use the com-puter program to simulate different surgical techniques of the area to be operated, thus promoting a previous knowledge of the risks and steps that must be adopted in the surgical act **(Figures 11 and 12).**

Finally, there is artificial intelligence that makes use of various computer-based models and intelligent behavior with minimal human intervention. In healthcare artificial intelligence has created a distinct position for itself, ranging from wearable medical devices to automated diagnostic techniques, reducing errors, promoting faster and more efficient results, and demonstrating that the current trend is towards using less invasive methods and patient compliance without compromising diagnostic accuracy (PRA-BHAKAR et al, The company Viziomed has created several artificial intelligence platforms for the diagnosis of pathologiesdetected through diagnostic imaging.It uses the image storage base of the Pacs (Picture Archivingand Communication System) system that clinics and hospitals have,transferring these images to the viziobot system that filters them and hides patient information before sending them for analysis. Subsequently the viziobot system directs this data to the viziomed platform which uses the various artificial intelligences for diagnosis (for example for the diagnosis of chest TC the platform uses the Imbio LTA - Lung Texture Analysis, Imbio LDA - Lung Density Analysis and ImbioLDAi - Lung Density Analysis at inspiration). After the pre-report the information returns to the viziobote platform then to the Pacs system (VIZIOMED, 2021) (**Figure 13**).

TOBACCO LEGISLATION AND TOBACCO CONTROL

On July 15, 1996, Law 9294 was instituted, which prohibited the use of cigarettes, cigarillos, cigars, pipes or any other smoking product derived or not from tobacco in closed places, private or public, being, therefore, prohibited to use them in aircraft and public transportation vehicles. It was also established that the packaging of these products must contain warning messages about the harmful effects of smoking, accompanied by images or figures to illustrate the meaning of the message. Article 3 of this law determined that commercial advertisements for cigarettes, cigarillos, cigars, pipes or any other smoking product were prohibited throughout Brazil, with the exception of these products in points of sale, provided they were accompanied by warning clauses (BRAZIL, 1996).

The Ministry of Health, on February 9, 2006, created the Ordinance Nº 300 which instituted the program "Tobacco Free Health Ministry", with the purpose of elaborating and implementing educational and curative actions aimed at raising the awareness of employees and visitors to the institution in relation to the harm caused by the use of tobacco. In its article 2, the Ministry determines the faithful observance in all dependencies of the Ministry of Health, both in the Federal District and in the States and Municipalities, of the provisions of Law number 9.294, 1996, which prohibits the use of cigarettes, cigarillos, cigarette butts, pipes or any other smoking product, whether or not derived from tobacco (BRAZIL, 2006).

Another measure adopted to discourage the use of tobacco products came through Law Nº 12,546 of December 14, 2011, which determined the minimum retail price of cigarettes nationwide, below which their sale is prohibited. It was also determined that the warning messages would be used sequentially, simultaneously or in rotation, and in the latter case must vary at most every 5 months, inserted legibly and prominently displayed on 100% of its back face and one of its sides (BRAZIL, 2011).

Law Nº 8,262 of May 31, 2014 included

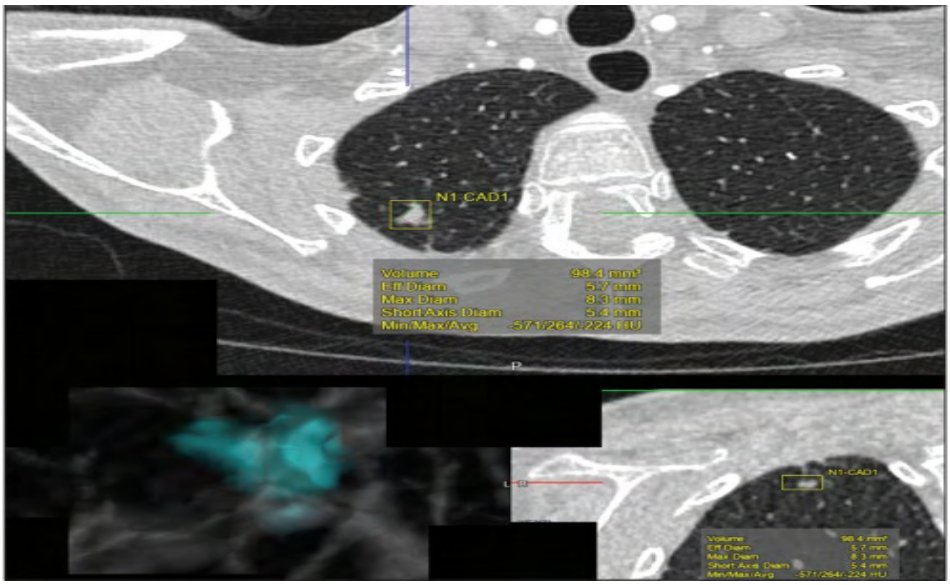

Figure 11- Use of radiogenomics for the detection of pulmonary nodules by providing quantitative and three-dimensional information about the nodule

Source: Santos et al. (2019).

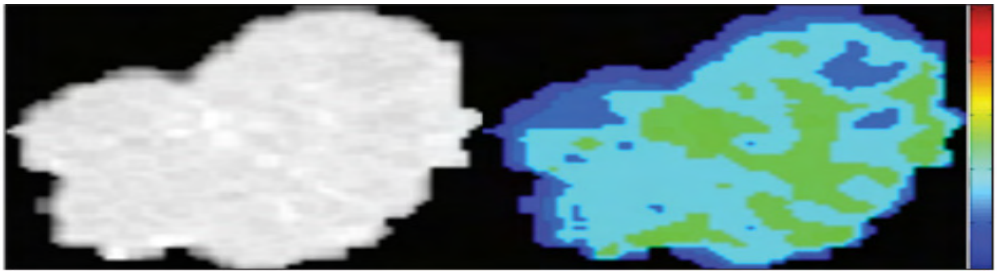

Figure 12 -Quantification of intratumoral heterogeneity of a lung adenocarcinoma on TC scan of the chest, for radiomic/radiogenomic evaluation. The color scale refers to an attribute extracted from the image reflecting the tissue and genetic subregions of the tumor.

Source: Santoset al. (2019).

Figure 13 – Initial panel with quantification and grouping of exams by pathologies diagnosed by the Viziomed platform

Source:Viziomed (2021).

shisha among the smoking products prohibited in enclosed public places. Excluded from the prohibition were places of religious worship whose rituals include the use of tobacco products, whether or not derived from tobacco, establishments specifically for the sale of tobacco products, whether or not derived from tobacco, provided that this condition is clearly announced at the entrance and provided that the place reserved for the experimentation of products has isolation, ventilation, or air exhaustion conditions that prevent the contamination of other environments. The shisha was included with the prohibition of commercial advertising of tobacco products, whether or not derived from tobacco, with the exception only of the exhibition of such products in places of sale (BRAZIL, 2014).

CHALLENGES OF EARLY DIAGNOSIS

Access to the Single Health System

The population's access to the Unified Health System is a relevant factor for the late diagnosis of CP, especially in relation to the population with a lower socioeconomic level. Data from the 2013 National Health Survey (PNS) conducted by the Ministry of Health in partnership with the IBGE showed that 18.1% of the Brazilian population had precarious access to health services (defined as having no service the last time the interviewee needed the service and not having made a new attempt at service due to lack of accessibility), with the North region being the most affected (31.1%). The profile of people with precarious access to the health system included mainly those with no schooling, aged 18-24 years, black and brown, smokers and with excessive consumption of alcohol (**Table 2**).

In the second edition of the PNS, it was found that 60% of Brazilian households (44 million) were registered in a family health unit, which represents an increase of 6.7% when compared to the previous survey, where in 2013, 34.6 million Brazilian households were registered in a family health unit, thus demonstrating that about 40% of households (29.3 million) are outside the basic health register. The Northeast region had the highest number of registered homes (64.8%), followed by the South (64.8%), North (60%), Center-West (58.6%), and Southeast (51.9%). Of the households registered for at least one year or more in a family health unit, it was found that only 38.4% of Brazilian households received a monthly visit by a community agent or member of the family health team in 2019,corresponding to 15.4 million households, showing a drop when compared to 2013, which corresponded to 47.2%, being one of the hypothesesle-vantadas ade that the increase in households ended up being higher than the increase in monthly visits to households. Also in 2019 it was observed that among the households registered nationwide, 23.8% or 9.5 million households never received a visit from a community health agent or a member of the family health team, representing an increase of 6.1% when compared to 2013 (IBGE., 2019).

Late symptoms of CP

CP is a pathology that lacks specific signs and symptoms for this disease, especially in its early stages, which hinders its early identification. In general, patients with CP who are active smokers and with an initial presentation present symptoms that are similar to those already presented throughout their lives, such as cough and shortness of breath, and are not very specific. In addition, since the lung has a large surface area, small lesions do not usually alter lung function. Another factor that contributes to the late diagnosis of CP is the fact that many smokers end up delaying medical attention because of the feeling of guilt that they may have been responsible

Variables.	Prevalence (96) (N - 12.435)
Poor Access	**18,1**
Region	
Southeast	**12.9**
South	**1 1.2**
Center-West	**24.5**
Northeast	**27.0**
North	**31,1**
Skin Color	
Other	**12.9**
Black and mixed race	**23.3**
Age (years)	
18-24	**19.8**
25-39	**18.5**
40-59	**19.3**
60 Age (years)	**15.2**
Education	
No schooling	**38.4**
Primary	**19.4**
Medium	**17.2**
Education	
No schooling	**30.4**
Fundamental	**19.4**
Medium	**17.2**
Higher or more	**9,2**
Smoking	
Never smoked	**16,8**
Smoker	**24,7**
Ex-smoker	**17.7**
Alcohol use	
Does not drink	**18.1**
Moderate drinking	**17.1**
Drinking excessively	**20.3**

Table 2 – Poor access to health services according to socioeconomic and health variables among the Brazilian adult population. National Health Survey.

Source: Dantas et al., (2021).

for the origin of the disease. This difficulty in expressing the signs and symptoms, even if diffuse, is one of the challenges to early diagnosis, since the ability to verbalize a feeling is crucial to its inter-pretation by public health system professionals, who must therefore be attentive to any sign or symptom reported by the patient (BERNHARDSON et al., 2021).

Delayed time to imaging and access to molecular testing

The initial diagnostic evaluation of CP is paramount for understanding the pathogenesis of the disease, defining prognosis and determining an individualized therapeutic plan based on predictive biomarkers, since it is an extremely heterogeneous disease. Brazil has many difficulties in expanding access to molecular pathology diagnostics and to health technology in general. An example that portrays this reality is that only half of patients with non-small cell lung cancer undergo testing for mutations in the EGFR gene, which impacts survival rates, which is around 14.2 months for individuals with stage IV adenocarcinoma undergoing genotyping and 8.5 months for those who do not undergo this testing (JUNIOR et al., 2019).

The amount of molecular testing performed in Brazil falls short of the current recommendation of the US National Cancer Network guidelines, which directs that all patients with CP with advanced disease must undergo molecular testing. In addition, there is also a disparity between access to tests performed in public and private services, with more than 2/3 of these tests being performed in the private sector. One factor that partially explains this disparity is that testing was initially done by pharmaceutical companies focused primarily on the private sector (PALACIO et al., 2018).

Similarly, access to imaging tests such as TC in the public network is substantially lower than in the private sector, where the average use of TC is 9.4% in the SUS, which especially affects the low-income population, since the public sector corresponds to 80% of the care to the Brazilian population. It is necessary to increase the supply of tomography scanners in the public health service, thus allowing the early diagnosis of malignant lung neoplasia (SANTOS et al., 2014).

Qualification of Healthcare Professionals

The qualification of health professionals can help or delay the diagnosis of CP. Studies with nurses in primary care units have shown that they do not receive specialized training in cancer screening, which contributes to inadequate screening. The lack or inadequate continuing education of professionals, especially those who are part of primary care, since this is considered the gateway to more complex and specialized health services, makes them insecure, especially about the protocols used in patient care and the correlation of signs and symptoms presented in CP. Another factor of the importance of the qualification of health professionals is in raising their awareness about the need for early diagnosis through their own qualification and also through training within their work processes, thus promoting the continuity of the qualification of new professionals (LOMBARDO, 2019).

According to Gomes et al. (2012), the main problems linked to the training of health professionals are in the disconnection theory-practice, disorder of the basic-scientific cycles, opposition between clinical and collective health, specialist versus generalists, lack of training to act facing most of the patients' problems and dehumanization.To overcome this problem, professional training in primary health care must be encouraged through programs for strengthening and reorientation

of the training and qualification process in the health area, such as the National Program for the Reorientation of Professional Training in Health and the Education for Health Work Program, which aim at the inclusion of teaching-service-community through the insertion of teachers and students of the public higher education network in the public health network, aiming at professional training with a complete interpellation of the health-disease process with emphasis on primary care (OLIVEIRA et al, 2016).

DISCUSSION

Lung cancer is one of the most lethal tumor types, accounting for one in every five cancer deaths (JUNIOR et al., 2019). Malignant tumors of the respiratory tract are associated with a high risk of death and depend on preventive actions and measures to avoid them. Along with trachea and bronchus tumors, CP is the second most prevalent among men and fourth among women, excluding non-melanoma skin cancer, in Brazil (SECRETARIA DE ESTADO DE SAÚDE DO GOVERNO DE GOIÁS, 2020).

Adenocarcinoma was shown to be the most prevalent histological type in CP being observed the decrease in the incidence of squamous cell carcinoma, due to the introduction of filters in cigarettes and the reduction in the number of smokers in the world (TSUKAZAN et al., 2017; OLIVEIRA et al., 2019).

The analysis of the literature shows that the symptomatology of CP happens most often late in life. According to INCA, such symptoms usually manifest themselves when the cancer is in an advanced stage, but some people present persistent cough, bloody sputum, and worsening shortness of breath in the early stage of the disease, being of great importance the early detection of malignant lung neoplasia, allowing greater possibilities of treatment and cure.

The SBOC protocols several guidelines for the use of diagnostic methods for CP, such as the test for mutation research of the epidermal growth factor receptor (EGFR) that is considered a therapeutic target for the choice of target therapy in patients with adenocarcinoma, the ALK fusion test that ultimately promotes survival and tumor growth, chest TC, PET/CT, transcutaneous fine needle biopsy or endoscopic transbronchial needle aspiration, among others (SBOC, 2021).

The difficult access of the population to health services associated with delays in imaging exams and molecular tests have been shown to be factors that can contribute to the late diagnosis of CP. According to the IBGE, 29.3 million households in Brazil were not registered in a basic health unit, which affects the access of this population to the network of care and diagnosis. In addition, according to the Institute of Applied Economic Research, one of the most frequent problems of the SUS are the delay in care in posts, health centers or hospitals, and the delay in getting to consult with a specialist (ALMEIDA 2013; IBGE, 2019).

Since 1986, Brazil has sought to establish a policy to combat smoking, being an international reference in this area. It began this process through the creation of the National Program to Combat Smoking and also the establishment of the Day to Combat Smoking.In 1996, Law 9.294 was created, which prohibited the advertising of smoking products in Brazil and also established the prohibition of these products and their derivatives in closed public and private places. In addition, the Ministry of Health Ordinance No. 1.035/2004 expanded the treatment of smoking in SUS. And between 2006 and 2016, Law 12,546/2011 and Decree 8,262/2014 were created, which ended the use of smoking

rooms by smokers and the prominence of warnings on cigarette packs. These policies have significantly reduced the number of smokers in the last 30 years (PORTELES et al., 2018).

The qualification of professionals involved in primary health care is essential for a correct identification of the symptoms presented, especially in the initial phase of CP. In addition, the Ministry of Health Ordinance No. 1.035/2004 expanded the treatment of smoking in SUS. And between 2006 and 2016, Law 12,546/2011 and Decree 8,262/2014 were created, which ended the use of smoking rooms by smokers and the prominence of warnings on cigarette packs. These policies have significantly reduced the number of smokers in the last 30 years (PORTELES et al., 2018).

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The qualification of professionals involved in primary health care is essential for a correct identification of the symptoms presented, especially in the initial phase of CP. Investment and promotion in training in evidence-based continuing education of health professionals, especially basic health professionals is of paramount importance for the correct identification of suspected cases, thus directing to an earlier and quality diagnosis(LOMBARDO, 2019).

CONCLUSION

As we have seen, several factors make early diagnosis of CP difficult, such as late and nonspecific manifestations of symptoms, limited access to health services (mainly primary care), and delays in imaging exams

and molecular tests, which directly impact patient survival. Therefore, it is necessary to invest more in public information policies that address the main forms of prevention and the most common signs and symptoms of this disease, so that the population seeks professional help as soon as possible, since survival increases if the tumor is diagnosed in early stages. In addition, we need to expand the supply of imaging exams, molecular tests, and ensure the continuing education of the professionals involved, thus reducing the waiting time for diagnosis, which enables a less aggressive and most often more effective therapeutic approach.

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