„CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

SUMMARY

PhD. THESIS

POSSIBILITIES AND LIMITATIONS IN THE DIAGNOSIS OF RARE LUNG TUMORS

COORDINATOR

PROF.UNIV.DR. MIRON ALEXANDRU BOGDAN

PhD. STUDENT

DR. GEAMBAȘU CĂTĂLIN

2013

LIST OF SCIENTIFIC PAPERS PUBLICATED

PAPERS PUBLICATED:

- **Cătălin Geambașu**, Marius Sava, Cătălina Elena Ene, Ionela N. Belaconi, Miron Alexandru Bogdan.
  Rare pulmonary tumours: a histological and radiological overview. Pneumologia, 10.2478/pneum-2020-0004 • 69 • 2020 • 11-16. www.Sciendo.com

- **Cătălin Geambașu** , Marius Sava, Cătălina Elena Ene , Ionela Nicoleta Belaconi , Stefan Dumitrache-Rujinski , Claudia Toma , Miron Alexandru Bogdan. Pneumologia, 10.2478/pneum-2023-0008 • 70 • 2021 • 1-8. www.Sciendo.com

PAPERS PRESENTED AT MEDICAL CONGRESSES:

- "Rare lung tumors - statistical data carried out in the Institute of Pneumology Marius Nasta - Bucharest". Cătălin Geambaşu. The Monthly Session of Scientific Communications with the theme "Notice in the classification and therapy of bronchopulmonary neoplasm - the appearance of the new edition of the TNM classification" - February 22, 2017.

- "Difficulties and limits in the diagnosis of lung tumors with low incidence". Cătălin Geambaşu. "Notice in Molecular Biology and Bronchopulmonary Neoplasm Therapy" - Bucharest - September 26, 2018.

- "Clinical-imaging approach in rare lung tumors". Cătălin Geambașu, Miron Alexandru Bogdan. The National Conferences of the Sections of the Romanian Society of Pneumology, Bucharest – November 13-15, 2019.

Contents

INTRODUCTION

Lung tumors are entities of great histopathological variety; the vast majority are lung adenocarcinoma, squamous cell carcinoma, and small cell carcinoma. However, there is a wide variety of both malignant and benign tumors that can primarily affect the lung, causing many difficulties in the clinical-imaging and histopathological diagnosis. This includes tumors of an epithelial nature (adenomas, papillomas), soft tissue tumors, vascular connective tumors as well as tumors of uncertain nature (inflammatory pseudotumors, hamartomas). Over time, given the paradigms as well as the numerous implications in the diagnosis, evolution and treatment of these entities, the classification of lung tumors has undergone numerous changes; the most important changes being: (1) the new immunohistochemical approach, (2) the involvement of genetic studies with implications in personalized therapy for advanced forms of neoplasia, (3) the reclassification of large cell lung carcinoma, (4) the classification of squamous cell carcinoma into keratinized cell carcinoma, nonkeratinized and with basaloid cells, (5) the grouping of the multiple entities of neuroendocrine tumors in a single category, (6) the inclusion in a separate category of lung tumors of ectopic origin - germ cell tumors, melanoma and meningioma with pulmonary localization and intrapulmonary thymoma.

In cases of low-incidence lung tumors, we are talking about both malignant and benign entities; the incidence being below 1% in the case of benign formations and 2-3% in the case of malignant ones, but there are a number of histological types, initially benign in nature that can undergo malignant transformation and secondarily the possibility of metastasis - for example adenoma/ atypical carcinoid tumor.

The location of these tumors can be both central and peripheral, this aspect having clinical and imaging relevance, influencing subsequent diagnostic and therapeutic management.

The symptomatology is most often non-specific, similar to that determined by lung neoplasms frequently encountered in clinical practice (persistent non-productive cough, hemoptysis, wheezing, dyspnea), as well as particular symptoms and signs found only in the case of distinct entities (the presence of purpuric syndromes found elsewhere in primary lung lymphoma). The evolution is closely related to the histological nature of the tumor formation - frequently without clinical and evolutionary impact in the case of

hamartoma; progressive and trailing symptomatology, with increased ability to metastasize and rapid evolution in the case of large cell neuroendocrine carcinoma.

We considered it necessary to carry out a retrospective and partially prospective study with patients diagnosed in our clinic with low-incidence lung tumors, given the heterogeneous nature, of a wide histopathological variety, with multifactorial etiopathogenesis, often with atypical clinical and imaging aspects, characteristics that cause diagnostic difficulties.

In short, malignant pathology is common in adult smoking patients, the most common histological types being represented by: epidermoid (squamous) carcinoma, adenocarcinoma, microcellular carcinoma and non-microcellular carcinoma (large cells). Thus, the rest of the pathology of a malignant nature (for example: sarcomas, primary lung lymphomas, carcinoid tumors) are much less common, often not being related to the smoking history.

Benign tumors are most frequently represented by: hamartomas, bronchogenic cysts, hemangiomas, lipomas.

Frequently, the intraparenchymal/bronchial development of lung tumors is asymptomatic, because the lung parenchyma does not hurt. This happens until the patient presents himself to the hospital in the context of the appearance of: hemoptysis, chest pain due to the involvement of the parietal pleura, the costal grid, or the vertebral bodies (direct or metastatic involvement). Primary manifestations can also be represented by distant ones, either through the presence of metastases (cerebral, liver, bone, adrenal), or paraneoplastic syndromes (rheumatoid syndrome, hematological anomalies, neurological anomalies, Pierre Marie-Bamberger syndrome).

The investigations carried out with the aim of determining the positive histological diagnosis are represented by: standard chest X-ray, Computer Tomography (CT) examination of the chest with contrast material, completed with head and abdomen for TNM classification, fibrobronchoscopy with bronchial biopsy. Bronchoalveolar lavage is performed when the tumor has a peripheral location: distal to the subsegmental bronchi inaccessible to the fibrobronchoscope, ultrasound- or CT-guided punctures (for tumors in contact with the chest wall), or tumor biopsy through thoracotomy. In the case of mediastinal nodal determinations, mediastinoscopy or ultrasound-guided transbronchial punctures (EndoBronchialUltraSound guided biopsy - EBUS) are used.

Not in all cases the investigations mentioned above manage to accurately differentiate between the malignant or benign nature of a lung tumor, especially in the absence of a tissue fragment for a histopathological examination. There are, however, certain "patterns" that guide the diagnosis, such as: eggshell calcifications, the appearance of a popcorn like aspect, the well-defined contour of the imaging-detected formation or the appearance of the pulmonary structure with digitiform extensions, etc. In these situations of uncertainty, delaying semi-invasive or invasive investigations that can provide enough tissue for the purpose of a histopathological examination, can have dire consequences. This is all the more important in the case of lung tumors with histology rarely encountered in current clinical practice, in order to establish an optimal therapeutic attitude.

In the current context, the present work aims to carry out an analysis of the types of clinical presentation, the particularities and positive diagnosis methods of malignant or benign lung tumors with unusual histology, diagnosed in the Marius Nasta Pneumology Institute, in the period 2015-2018 . We considered it necessary to carry out a retrospective and partly prospective study with patients diagnosed in our clinic, with low-incidence lung tumors, given the heterogeneous nature, of a wide histopathological variety, with multifactorial etiopathogenesis, often atypical clinical and imaging aspects, characteristics which causes diagnostic difficulties.

GENERAL REVIEW

1. CLASSIFICATION

In 2015, a new classification of lung, pleural, thymic and cardiac tumors is published by the World Health Organization, representing the improved version of the one from 2004. The major changes are:

• The use of immunohistochemistry: although it was introduced in the WHO classification in 1999, as well as in that of 2004, immunohistochemical diagnosis found its use for several tumor pathologies: large cells neuroendocrine carcinomas, sarcomatoid carcinomas and in the differential diagnosis between carcinomas and malignant mesothelioma. In previous classifications, lung tumor diagnosis was based on the interpretation of microscopic slides, along with standard hematoxylin-eosin staining. Today, immunohistochemistry is routinely recommended following biopsy, cytological sampling and resected tumor fragments. For example, a tumor fragment in stage G4 (poorly differentiated), analyzed under the optical microscope, does not provide a precise description of the slide, which is why immunohistochemistry is recommended to clarify the diagnosis, as it can preserve enough tissue for molecular testing as well.

• A new diagnostic criteria for lung tumors was based on biopsies (bronchoscopy, aspiration) and cytology. Their existence has also acquired an important role in: screening, achieving a precise pathological classification and in the management of molecular testing. Many tumors can be classified using markers such as: mucin, TTF-1 (these being mainly used for glandular differentiation), p40, p63 (these being mainly used for squamous differentiation). For non-small cell carcinomas (NSCC - non-small cell carcinoma) that cannot be classified as adenocarcinoma or squamous cell carcinoma and that do not respond to immunohistochemical markers, the name non-small cell carcinoma not otherwise specified (NSCC NOS - non- small cell carcinoma not otherwise specified). This category has a limited immunohistochemical panel (cytokeratin, CD45, S100) to confirm carcinoma features. However, for the tumor categories that respond immunohistochemically to both TTF-1 and P63, it raises the possibility of an adenosquamous carcinoma, but the clear diagnosis can only be made on the resection of the piece;

Epithelial lung tumors	Adenocarcinoma		
	Squamous cell carcinoma		
	Neuroendocrine tumors	Small cell carcinoma	
		Large cell carcinoma	
		Large cell neuroendocrine carcinoma	
		Preinvasive lesions	
		Carcinoid tumors	Typical
			Atypic
		Adenosquamous carcinoma	
		Sarcomatoid carcinoma	Pleomorphic carcinoma
			Spindle cell carcinoma
			Giant cell carcinoma
			Carcinosarcoma
			Pulmonary blastoma
		Unclassified carcinomas	
		Tumors of the salivary gland type	
	Papilloma	Squamous cell papilloma	Exophytic
			Inverted
		Glandular papilloma	
		Mixed papilloma	
	Adenoma	Sclerosing pneumocytoma	
		Alveolar adenoma	

		Papillary adenoma		
		Mucinous cystadenoma		
		Mucous glandular adenoma		
Mesenchymal tumors	Pulmonary hamartoma			
	Chondroma			
	PEComa tumors			
	Congenital myofibroblastic peribronchial tumors			
	Diffuse pulmonary lymphangiomatosis			
	Inflammatory myofibroblastic tumors			
	Epithelioid hemangioendothelioma			
	Pleuropulmonary blastoma			
	Synovial sarcoma			
	Pulmonary arterio-intimal sarcoma			
	Pulmonary myxoid sarcoma with EWSR1-CREB1 translocation			
	Myoepithelial tumors	Myoepithelial tumors		
		Myoepithelial carcinoma		
Lymphohistiocytic tumors	Extranodal marginal lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)			
	Diffuse large cell lymphoma			
	Lymphomatoid granulomatosis			
	Intravascular large B-cell lymphoma			
	Lung histiocytosis with langerhans cells			
	Erdheim+Chester Disease			
	Germ cell tumors	Teratoma	Mature	

Tumors of ectopic origin			Immature
	Intrapulmonary thymoma		
	Melanoma		
	Meningioma		
Metastatic tumors			

Table 1 Lung tumor classification. [1]

2. GENERAL ASPECTS

Adenocarcinoma, squamous carcinoma and neuroendocrine carcinoma represent over 98% of all tumor formations with pulmonary localization; benign tumors with lung localization represent less than 1%, while malignant lesions other than the three mentioned are between 3-5%. [1]

The symptomatology determined by both benign and malignant lesions varies greatly. Most of the patients may be asymptomatic at the time of presentation, even if the pulmonary extension is extensive, while other patients with limited lesions but most frequently with endobronchial localization, or chest wall invasion, may present a variety of symptoms. This may be nonspecific and may include: cough, hemoptysis, chest pain, dyspnea, wheezing, fever, symptomatology closely dependent on intrathoracic location. [2]

Some tumor formations (e.g. carcinoid tumor, adenoid cystic carcinoma) can frequently occur intratracheally or at the level of a primitive bronchus, which will cause coughing, wheezing or hemoptysis. Also, other tumor entities with endobronchial localization (papilloma, adenoma, primary pulmonary lymphoma) can start with this symptomatology. [3]

Large cell neuroendocrine carcinoma can present with hemoptysis, usually appearing about 4 months after the onset of symptoms, being determined by the invasion and formation of ulcerative areas in the bronchial mucosa. [4]

Tumors with intratracheal development (e.g. primary pulmonary neurofibroma) often cause an obstructive type of symptomatology, which advocates a misdiagnosis with asthma or other obstructive conditions. Endobronchial obstruction caused by any of these low-incidence lung tumors can lead to the formation of postobstructive pneumonias and

the appearance of infectious-type symptoms (fever, productive cough, sweating). Carcinoid tumors can cause endocrine manifestations with the appearance of Cushing-like symptoms and acromegaly, secondary to the ectopic production of ACTH, respectively GH and insulin-like growth factor 1. Frequently, this type of tumor can lead to the appearance of carcinoid syndrome characterized by the appearance of facial erythema, brochospasm, digestive manifestations - abdominal pain, diarrhea, hepatomegaly determined by the appearance of secondary liver determinations - cardiac damage secondary to valvular fibrosis. All this symptomatology has as its physiopathological mechanism, serotoninergic hyperproduction. [3]

Another manifestation is represented by the appearance of pulmonary hypertrophic osteoarthropathy and the appearance of hippocratism at the digitoplantar level.

Endocrine damage can also be found in germ cell tumors, especially in lung choriocarcinoma. This entity with primary pulmonary localization is characterized by variations in the level of beta-HCG (human chorionic gonadotropin); a clear distinction can be made by immunohistochemical determinations, highlighting the thyroid transcription factor thus determining the pulmonary origin. [2]

3. DIAGNOSTIC MANAGEMENT IN RARE LUNG TUMORS

3.1 ESTABLISHING THE RISK OF MALIGNANCY

3.1.1 PATIENT CHARACTERISTICS

The average age of appearance of malignant tumor formations is ~ 70 years. Over the age of 50, the risk of the disease is twice as high. Perhaps the greatest risk factor associated with the occurrence of lung neoplasm is represented by smoking. This aspect was first stated in 1950 by Doll and Hill in the UK and by Wynder and Graham in the USA. In 1964, at the Conference of the Association of Surgeons in the USA, the consequences of smoking on health were presented and how this vice influences the appearance of some forms of neoplasia, especially with pulmonary localization [5]. Since then, the hypothesis that heavy smokers have the highest risk of developing certain forms of lung cancer has been maintained, while those who have quit smoking for more than 15 years, regardless of the dose to which they were exposed, presents a much lower risk [6] .

3.1.2 COMPUTER TOMOGRAPHY

It represents the basic imaging investigation in the diagnosis of a nodular lesion, being able to identify the dimensions, edges, location and densities of the lesion using Hounsfield Units (UH). The use of computer tomography associated with the administration of iodinated contrast substance allows visualization and characterization of heterogeneity as well as vascular aspects. [5].

3.1.3 POSITRON EMISSION TOMOGRAPHY USING FLUORODEOXYGLUCOSE

It represents a highly accurate imaging investigation, used to visualize large nodular lung lesions, based on the increased capacity of malignant formations to capture fluorodeoxyglucose. PET frequently shows false negative results in nodules <1cm. At the same time, false positive results may occur in the case of active inflammatory lesions. The uptake capacity of fluorodeoxyglucose can be measured qualitatively or quantitatively. To qualitatively evaluate the capture capacity, the terms "negative/positive" or "weak/moderate/intense" are used, while the quantitative evaluation of the capture uses measurements of the type "SUVmax/mean-intensity at the level injury". Currently, most experts do not recommend performing PET if the nodular lesion measures <10mm in diameter. Fig. 4.2 [6].

3.2 DIAGNOSTIC MANAGEMENT

The first diagnostic management of pulmonary nodule was published by the ACCP (American College of Clinical Pharmacy) in 2003. Since then, a whole series of guidelines and updates have been published with the aim of establishing as precisely as possible a method of diagnostic. Among these, the most used are: the BTS (British Thoracic Society) Guide published in 2015 and the RADS (Reporting and Data Systems) Guide designed by the Fleischner Society and the ACR Guide (. The guide published by the Fleischner Society in 2017 proposes the evaluation of the lung nodule according to the solid, subsolid, multisolid, subcentimeter character, as well as if it has a "ground glass" appearance [7].

3.2.1 DIAGNOSIS OF LUNG TUMORS SUGGESTIVE OF BEING NEOPLASTIC

Like the histopathological types of lung neoplasm, frequently encountered in medical practice (adenocarcinoma, squamous cell carcinoma, small cell neuroendocrine carcinoma), also lung tumors with low incidence, of a malignant nature (large cell neuroendocrine carcinoma, primitive lung lymphoma) but also benign (carcinoid tumors) can present both clinical manifestations and imaging appearance suggestive of a proliferative condition, which is why the diagnostic approach will be a common one with the main aim of histopathological confirmation [8].

The malignant potential of a tumor is initially assessed according to the patients' risk factors and the imaging appearance. The diagnostic approach will be based on these two elements.

There are a number of elements that raise the suspicion that a lung nodule is malignant : age, smoking history, history of neoplasia, location of the nodule, aspects of the nodule. Depending on these elements, the British Thoracic Society stratifies pulmonary nodules into three categories according to risk: low, moderate, high). However, there is disagreement between American and British clinicians regarding the percentage of risk that a nodule is malignant. In the US, a percentage of <5% is considered low risk, moderate between 5%-65% and high risk >65%. The British Thoracic Society uses the same terminology but presents different percentages, considering low risk to be <10%, intermediate between 10%-70% and high >70%. At the same time, the volume and doubling time of the nodule were considered important to measure; a nodule with low volume (<250mm3) and low doubling time (>500 days) was considered to have a low risk of malignancy. Pulmonary nodules that present a low risk of being malignant can remain in the clinician's attention only through periodic imaging evaluations, while in the case of the other two categories, the diagnostic management will be totally different. [6]

The first stage refers to carrying out the necessary investigations to establish a diagnostic approach as accurate as possible. Most of the time, at the time when the suspicion was raised, an imaging investigation has already been performed, most of the time a chest CT exam, then the multimodal approach will include the performance of PET CT, the invasive study of the mediastinum in order to staging or performing brain imaging investigations to establish the presence of distant dissemination. If no distant secondary findings are identified, evaluation for invasion of hilar and mediastinal lymph node stations

is necessary. In case of lack of extension from this level, the lung nodule considered suspicious should be either resected or biopsied [6]

The second stage consists in the choice by the clinician of the most effective diagnostic methods, limiting as much as possible the number and invasive nature of the chosen procedures. The ideal situation is that in which both diagnosis and staging are done during the same procedure. [6].

The third stage refers to the principle according to which, in most cases in which a lung neoplasm is suspected, histopathological confirmation is absolutely necessary before initiation of treatment. Histopathological confirmation may occur separately or at the same time as initiation of treatment. In certain situations, the diagnosis will precede the therapeutic decision, for example in the case of a tumor associated with mediastinal adenopathies. In this case, the biopsy of the adenopathies should be performed before establishing the definitive treatment, given the importance of the mediastinal status regarding the optimal treatment option. Another situation is when the diagnostic and treatment procedures are done through a single surgical maneuver. The rarest situation is that in which the treatment is initiated without a histopathological confirmation (tumor with high risk of being malignant, in which surgical intervention is contraindicated and in which the result of the biopsy obtained by puncture - transthoracic biopsy is non-diagnostic, it can be decides to initiate stereotactic body radiotherapy) [9].

The fourth stage refers to the participation that the patient must have in decision-making during the diagnostic management and the development of the treatment. Put in the situation of suffering from a neoplastic condition, but also the multiple investigations required, make the patient suffer from anxiety and depression of varying intensity. During this period, but also after the initiation of treatment, it is essential for the patient to participate in the diagnostic approache and therapeutic decisions, becoming an active part of the process [10].

PERSONAL CONTRIBUTIONS

INTRODUCTION

Pulmonary tumor pathology is a frequent reason for presenting patients to the pneumology/thoracic surgery clinic. The diagnostic approach in order to specify the histological type depends on the location of the tumor (central, peripheral, mediastinal) and is dependent on the equipment/techniques used in the respective clinic, as well as on the patient's clinical condition.

Lung tumors with rare histology, benign or malignant, represent an area of interest, given the fact that the risk factors, age of onset, diagnostic/therapeutic approach and prognosis are different compared to the commonly encountered tumor pathology.

Although there is no clear evidence of the prevalence of rare lung tumors, data from the literature point to a frequency of less than 1% in the case of benign tumors and 2-3% in the case of malignant tumors.

The evaluation of the etiology of rare lung tumors, histological type and diagnostic modality is a current topic in lung tumor pathology.

4. OBJECTIVES

The main objective of the paper is the analysis of diagnostic methods, invasive and semi-invasive, used for diagnostic/curative purposes in the case of lung tumors with rare histology.

The secondary objectives resulting from the analysis of the files of patients diagnosed with rare lung tumors were:

- Classification into categories according to tumor type: malignant, benign or with intermediate evolutionary risk.
- The contribution of risk factors (age, smoking, professional exposure) to belonging to one of the categories mentioned above.
- Descriptive analysis of the main characteristics of patients from the categories mentioned above (age, sex, origin – urban/rural, initial clinical presentation).

5. MATERIAL AND METHOD

The study carried out is a retrospective, observational, transversal one, carried out between 2015-2018, on consecutive patients, addressed to the Marius Nasta Institute of Pneumoftisiology Bucharest, for the diagnosis/treatment of pulmonary tumors, discovered incidentally or in the context of general or respiratory symptoms.

The aria of resection (atypical resection, lobectomy, pneumonectomy, mediastinal or bronchial biopsy) sent to the morphological laboratory were analyzed macroscopically and microscopically by classical methods (hematoxylin-eosin staining).

5.1 INCLUSION CRITERIA:

• Patients over 18 years;

• Obtaining informed consent regarding data processing for scientific purposes with maintaing of anonymity;

• The existence in the patients' files of the information/data that were the subject of the analysis of the above-mentioned criteria as well as of the histological result of the resected pieces;

5.2 EXCLUSION CRITERIA:

• patiens younger than 18;

• Lack of essential information/data from patient files, which were the subject of the analysis;

5.3 STRUCTURE OF THE STUDY TRIAL ANALYZED

The patients were grouped into three main groups, depending on the type of the tumor:

A. Patients with benign tumors

B. Patients with tumors with intermediate potential evolutive risk

C. Patients with malignant tumors

Group B (intermediate potential evolutive risk) consists of those patients in whom, following the histopathological diagnosis, the rate of cell proliferation/constitutive cell multiplication is conventionally considered to be below the threshold that defines the

malignant character. It should be noted that this aspect can evolve over time, influenced by environmental factors, professional exposure, age, smoking.

Within the three group studied, as well as globally, the elements described in the "Main and secondary objectives" section were analyzed, with the analysis of the statistical significance of the correlations between the studied parameters.

5.4 STATISTICAL DATA ANALYSIS

SPSS version 26 was used for the statistical analysis of the data:

- Results were expressed as mean values ± standard deviations, medians, or as absolute numbers/percentages.
- The Kolmogorov-Smirnov test was used to analyze the distribution of variables.
- The relationship between certain categorical variables was assessed using the Chi-Square test and statistical significance was considered at a p value<0.05.
- The diagrams are tree type (hierarchical), table type, pie and bar type (pie and bar).

The study carried out had the approval of the Ethics Council of the Marius Nasta Institute of Pneumoftisiology Bucharest and of the Doctoral School within the,, Carol Davila,, University of Medicine and Pharmacy Bucharest, in order to publish the analyzed data for scientific purposes, with the obligation to preserve anonymity.

5.5 RESULTS

The gender structure was as follows:

- 61 men (59.8%)
- 41 women (40.2%)

Related to age, it has been observed that the incidence of this particular group of lung tumors increases with age, the peak of incidence being between 61 and 70 years.

Average age for those diagnosed with:

- benign tumors - it was 53.47 years ± 12.28 years (extreme: 25-76 years);
- intermediate tumors – it was 52.41 years ± 13.17 (extreme: 32-80 years);

• malignant tumors - it was 53.85 years ± 14.37 years (extreme: 18-80 years).

From the environment point of view, the patients were distributed as follows:

• Urban - 71 (69.60%)

• Rural – 31 (30.40%)

Patients who came from the urban environment had the highest incidence of lung tumors with rare histology, either benign, intermediate or malignant.

From the point of view of smoking status, the patients were divided into three categories:

• Non-smokers - 49 (48%)

• Smokers - 40 (39.2%)

• Former smokers – 13 (12.7%)

Regarding benign and malignant tumors, most patients, 15 (68.2%), respectively 26 (65%), had a history of smoking; at the opposite pole are the patients diagnosed with lung tumors with intermediate potential evolutive risk, in their case, only 12 (30%) of the patients have a history of smoking.

Related to exposure to noxes, as a risk factor involved in the pathogenesis of lung tumors with rare histology, it was observed that it did not represent a statistically significant risk factor (p=0.9):

• Patients without professional exposure - 69 (67.60%)

• Patients with professional exposure – 33 (32.40%)

From the point of view of the initial clinical presentation, of the 102 patients diagnosed with rare lung tumors, 79 (77.46%) were symptomatic at the time of evaluation, with a directly proportional increase in the number of symptomatic patients starting from group A – the cases of benign tumors, up to group C – cases diagnosed with malignant lung tumors with rare histology. The main diagnostic methods used in tumor histological confirmation were:

• Classic lung resections – 50 (49%)

• Fibrobronchoscopy – 31 (30.40%)

• Mediastinoscopy – 11 (10.80%)

• Video-assisted thoracic surgery – 10 (9.80%)

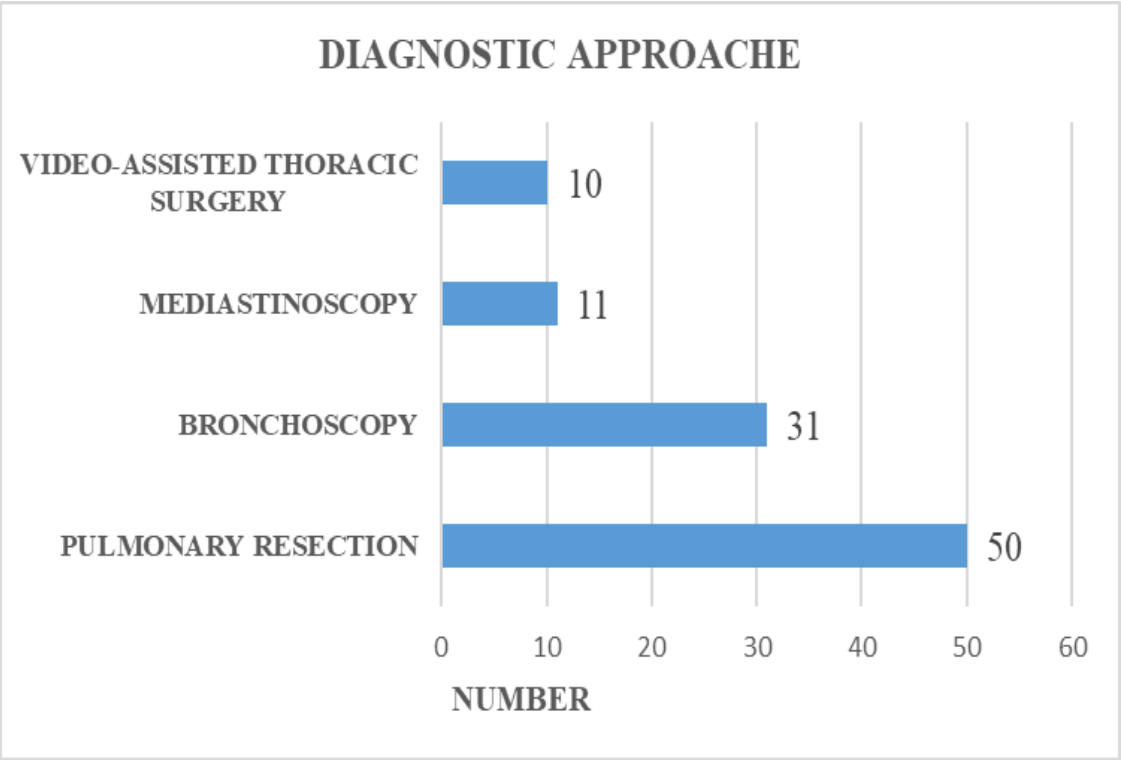

Fig.1 Rare lung tumors - Diagnostic approache used

Classical lung resection techniques were used in 50 (49%) of cases subsequently confirmed with rare lung tumors. Of these, 11 (50%) were represented by cases diagnosed with benign tumors, with the following histological distribution: pulmonary hamartoma – 7 (58.3%), inflammatory pseudotumor – 2 (66.6%) , pulmonary lipoma – 2 (100%).

In the case of lung tumors with an intermediate evolutive risk, classic lung resection techniques were used in 23 (57.5%) of the patients confirmed with this type of tumor, having the following histological distribution: typical carcinoid tumor – 10 (50%), tumor atypical carcinoid – 8 (66.6%) and pulmonary hemangioendothelioma – 5 (62.5%).

Similar to tumors of a benign nature and with an intermediate evolutive risk, in the case of malignant tumors with rare histology, the main method of confirmation/curative surgical therapy used was classical lung resection. Thus, lung resections were used in 16 (40%) of the patients subsequently confirmed to have malignant lung tumors . The histological distribution of these cases was as follows: large cell neuroendocrine carcinoma – 8 (66.6%), primary pulmonary sarcoma – 3 (75%), pulmonary angiosarcoma – 2 (100%), pulmonary lymphoma – sclerosing type – 2 (40%), large cell lung lymphoma – 1 (5.88).

As for benign lung tumors, by classical bronchological methods, 5 patients (22.73%) were diagnosed, and the confirmed cases were as follows: bronchial papilloma – 3 (100%), bronchial fibroma – 2 (100%).

In cases of lung tumors with intermediate evolutive risk, bronchoscopy was used in 13 cases (32.50%), with the following distribution: typical carcinoid tumor – 10 cases (50%) and atypical carcinoid tumor – 3 cases (25%).

Similar to lung tumors with intermediate evolutive risk, and in cases of malignant tumors, 13 patients (32.50%) were confirmed by classic bronchoscopic methods, with the following histological distribution: large cell lung lymphoma – 6 (35, 3%), large cell neuroendocrine carcinoma – 4 (33.3%), pulmonary lymphoma – sclerosing type – 2 (40%) and primary pulmonary sarcoma – 1 (25%).

Mediastinoscopy, being an important procedure for lung tumors with lymph node extension, was used in the case of 11 (10.8%) of the patients included in the studied group, representing 27.5% of the total cases of rare malignant tumors evaluated. The distribution of these cases according to histological type was as follows: pulmonary large cell lymphoma – 10 (58.8%), pulmonary lymphoma – sclerosing type – 1 (20%).

Video-assisted thoracic surgery was used in the diagnosis of 10 (9.8%) of evaluated cases; 6 (27.27%) of this cases were confirmed with benign tumors with the following histological subtypes: hamartoma – 5 (41.6%) and inflammatory pseudotumor – 1 (33.3%).

Through video-assisted thoracic surgery, 4 (10%) cases of lung tumors with intermediate evolutive risk were diagnosed, with the following histological type: pulmonary hemangioendothelioma – 3 (37.5%) and atypical carcinoid tumor – 1 (8.3%) .

From the point of view of the histological type, analyzing the three groups, the following were observed:

In the case of group A, consisting of patients with benign lung tumors, the most common histological type was pulmonary hamartoma - 12 patients (54.50%), followed by inflammatory pseudotumor and bronchial papilloma - 3 cases each (13.60%). bronchial fibroma – 2 cases (9.10%) and pulmonary lipoma – 2 cases (9.10%).

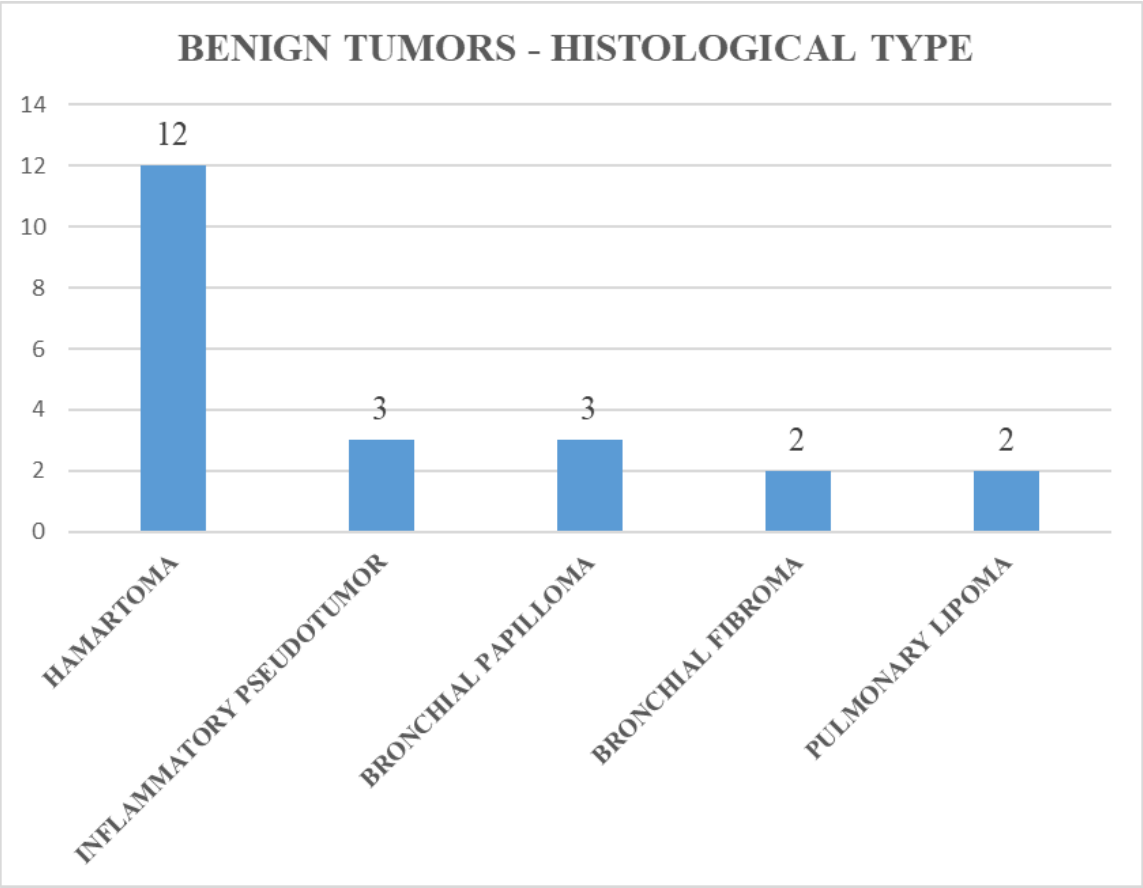

Fig.2 Benign lung tumors - Histological type

In the case of group B, consisting of lung tumors with an intermediate potential evolutive risk, most cases were of carcinoid tumors, with the two subtypes: typical carcinoid – 20 cases (50%), atypical carcinoid – 12 cases (30%) and hemangioendothelioma pulmonary – 8 cases (20%).

In the case of group C, consisting of malignant lung tumors with rare histology, included in group C, the most cases were those of large cell lung lymphoma – 17 (42.50%), followed by large cell neuroendocrine carcinoma – 12 patients (30%), pulmonary lymphoma – sclerosing type – 5 (12.50%) and primitive pulmonary sarcoma with the two subtypes: pulmonary sarcoma – 4 (10%) and pulmonary angiosarcoma – 2 (5%).

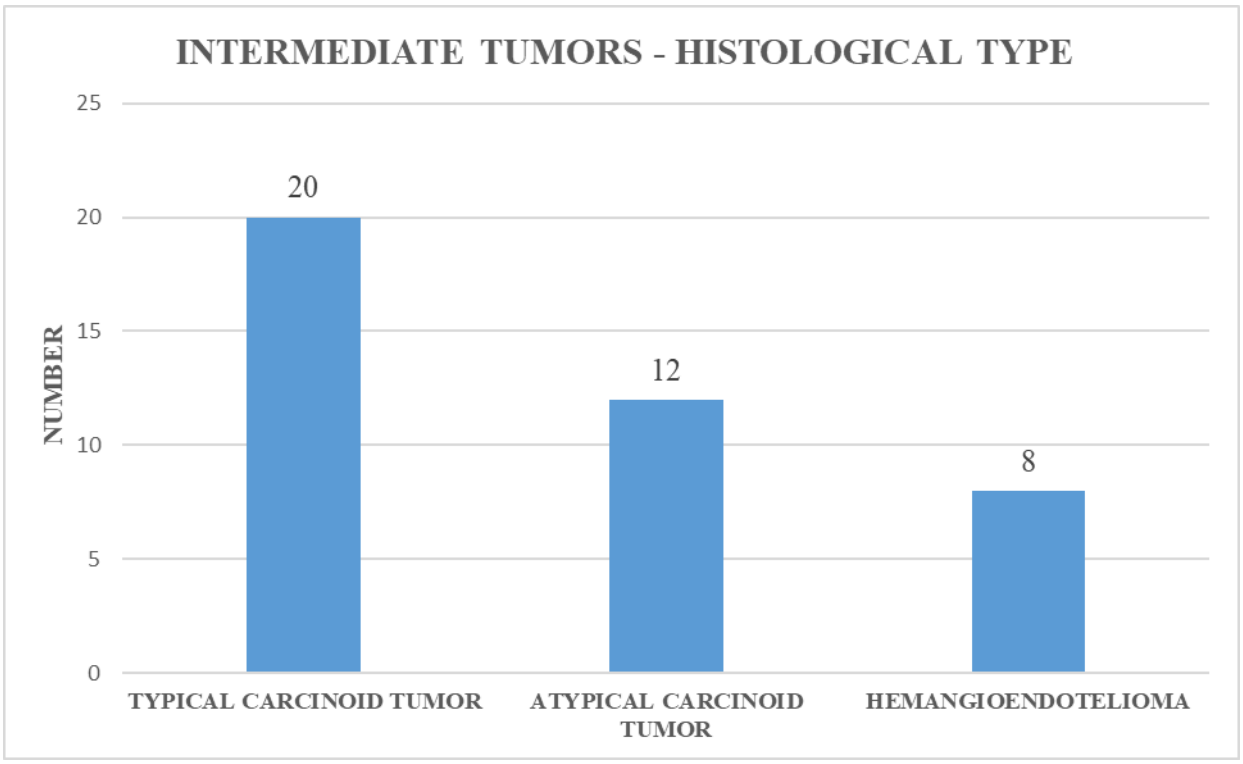

Fig.3 Intermediate lung tumors - Histological type

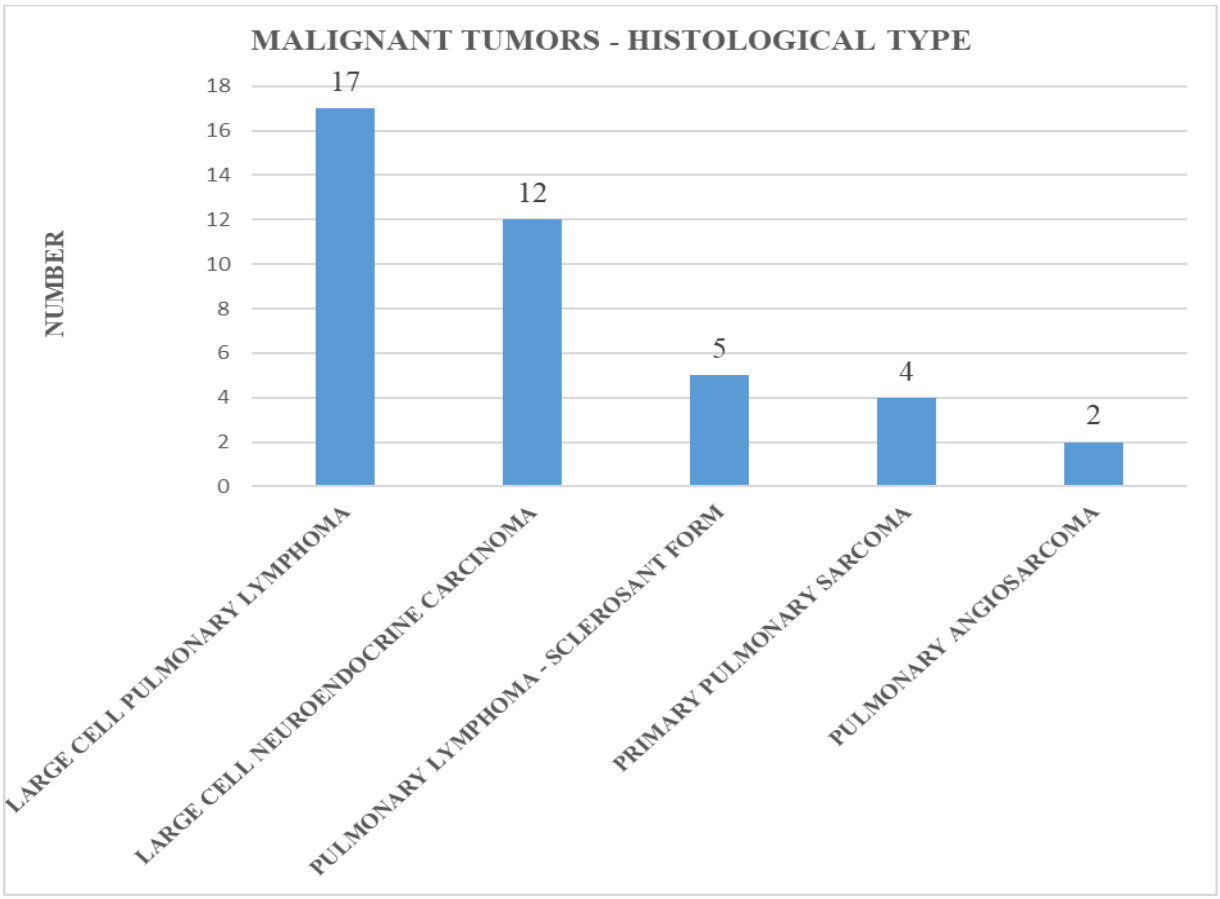

Fig.4 Rare malignant lung tumors - Histological type

Regarding tumor location, central or peripheral, lung tumors classified in groups B (intermediate tumors) and C (malignant tumors), presented a predominantly central location but without statistical relevance, while cases classified in group A (lung tumors benign) were mostly peripheral - 19 (86.40%).

The differentiation between central and peripheral localization was made according to the endobronchial approach (limit - segmental-subsegmental bronchi).

From the point of view of distribution at the level of the lung lobes, we observe a tendency of most tumor with rare histology to develop in the upper lung areas, an aspect existing mainly in the case of benign and malignant lung tumors.

Regarding the metastatic potential, the prerogative of malignant lung tumors, almost half of the cases, 19 (47.50%), did not present secondary determinations at the time of the initial evaluation. Among the cases in which local or distant metastases were detected, the majority of locations were pulmonary, ipsi- or contralateral and cerebral. An observed and extremely important aspect that could be the subject of future research is the brain metastatic potential of large cell neuroendocrine carcinoma.

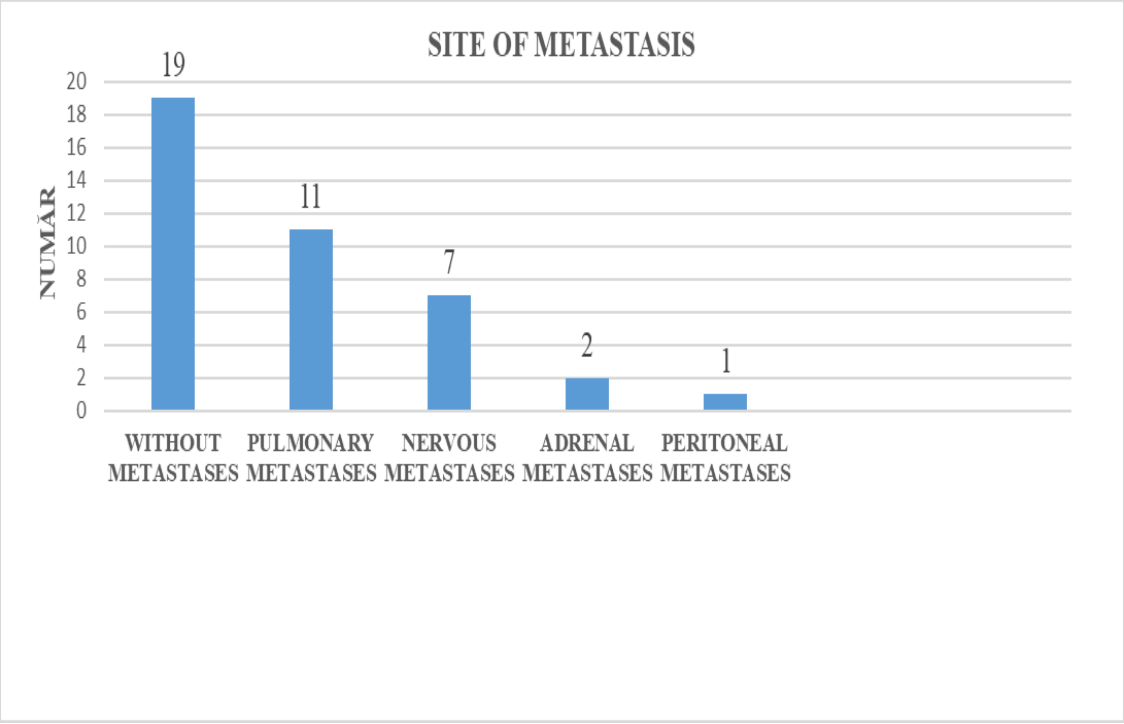

Fig.5 Site of metastases

Regarding the risk factors that can participate in lung tumor pathogenesis in general, the one with low incidence in particular, we found that the proportion of cases with smoking history was higher in group C, made up of confirmed cases with malignant lung tumors with low incidence, compared to that of patients with benign and intermediate tumors- (p=0.034). At the same time, it could not be demonstrated that exposure to noxes would have a statistically relevant influence on the occurrence of low-incidence lung tumors.

	NO.	BENIGN AND INTERMEDIATE TUMORS	MALIGNANT	TOTAL
NON-SMOKER	EVALUATED	35	14	49
	PREDICTED	29.8	19.2	49
FORMER SMOKER +EX SMOKER	EVALUATED	27	26	53
	PREDICTED	32.2	20.8	53
TOTAL	EVALUATED	62	40	102
	PREDICTED	62	40	102

Tabel 2. Comparative statistics between groups of cases with benign + intermediate/malignant tumors, related to smoking status

Related to the initial clinical presentation (with symptoms/without asymptoms), it was found that patients confirmed with rare malignant lung tumors, who were symptomatic at the time of presentation, were more numerous than those diagnosed with benign and intermediate tumors – p = 0.001.

	NO.	BENIGN AND INTERMEDIATE TUMORS	MALIGNANT	TOTAL
without symptoms	EVALUATED	22	1	23
	PREDICTED	14	9	23
with symptoms	EVALUATED	40	39	79
	PREDICTED	48	31	79
TOTAL	EVALUATED	62	40	102
	PREDICTED	62	40	102

Table 3 Comparative statistics between the groups of cases with benign + intermediate/malignant tumors, related to the way of clinical presentation

6. CONCLUSIONS/ LIMITATIONS OF THE STUDY AND FUTURE DIRECTIONS

Lung tumors represent an important chapter of lung pathology with which patients present in the pulmonology/thoracic surgery services, given the multiple difficulties that may arise in the diagnostic approach as well as in differentiation from other primary lung tumors.

A generally accepted definition of classifying a lung tumor as belonging to a rare histological type is that in which we are talking about a prevalence of less than 2% for benign lung tumors and between 2-3% for malignant ones.

In the present research, we tried to evaluate as many patients as possible diagnosed with rare tumor and to identify the missing elements that could facilitate the diagnostic approach, starting from the symptomatology (often non-specific), to the imaging/histological aspect in seeing the differentiation from other more common tumor types in current practice, and last but not least, the analysis of the epidemiological aspects that could provide specificity to this distinct group of tumors.

In the descriptive analysis of the studied group, it was observed that the proportion of patients with lung tumors with rare histology, benign was 22 (21.6%), intermediate - 40 (39.2%) and malignant - 40 (39, 2%).

The less common histological types present particularities in terms of clinical presentation, associated risk factors, diagnostic methods used, whether we are referring to tumors of a benign, intermediate or malignant type.

Lung resections were the main approache method of positive diagnosis in all types of tumors with rare histology, followed by classic bronchoscopy, mediastinoscopy and video-assisted surgery.

Regarding the risk factors involved in the pathogenesis of lung tumors with rare histology, we found that there were significantly more smokers in patients with malignant tumors compared to those diagnosed with benign and intermediate lung tumors ($p=0.0034$). At the same time, referring to the influence of occupational exposure in the pathogenesis of low-incidence lung tumors, we noticed that it was not relevant in any of the categories of cases studied (benign, intermediate or malignant) - $p=0.9$.

The clinical presentation at the time of the initial evaluation was statistically significant, given the fact that in the case of lung tumors with rare histology, there were

more patients with symptoms present at the initial evaluation, compared to those diagnosed with benign or intermediate tumors – p=0.001.

The newer semi-invasive methods used in the diagnosis of lung tumors (EBUS, radial EBUS and electromagnetic guided bronchoscopy) will facilitate the diagnostic approach and staging.

LIMITATIONS OF THE STUDY AND FUTURE DIRECTIONS

1. The retrospective nature of the study.
2. Lack of newly introduced methods in the diagnosis of lung tumors (CT/ultrasound-guided transthoracic puncture), classical and radial EBUS.
3. Absence of tumor immunohistochemistry subtyping for all patients.

REFERENCES

1. Travis, W.D., et al., *The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification.* J Thorac Oncol, 2015. **10**(9): p. 1243-1260.

2. Travis, W.D., et al., *International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma.* J Thorac Oncol, 2011. **6**(2): p. 244-85.

3. Yao, J.C., et al., *One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States.* J Clin Oncol, 2008. **26**(18): p. 3063-72.

4. Fasano, M., et al., *Pulmonary Large-Cell Neuroendocrine Carcinoma: From Epidemiology to Therapy.* J Thorac Oncol, 2015. **10**(8): p. 1133-41.

5. Baldwin DR, Callister ME. *The British Thoracic Society guidelines on the investigation and management of pulmonary nodules.* Thorax. 2015;70(8):794e798.

6. Horeweg N, Scholten ET, de Jong PA, et al. *Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers*. Lancet Oncol. 2014;15(12):1342e1350

7. Gould MK, Donington J, Lynch WR, et al. *Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer,* 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 suppl): e93See120S.

8. C E Engeler, J H Tashjian, S W Trenkner and J W Walsh. Ground-glass opacity of the lung parenchyma: a guide to analysis with high-resolution CT. American Journal of Roentgenology. 1993;160: 249-251. 10.2214/ajr.160.2.8424326

9. Renda Soylemez Wiener, MD, MPH, Daniel C. Wiener, MD, and Michael K. Gould, MD, MS. Risks of Transthoracic Needle Biopsy: How High?. Clin Pulm Med. 2013 Jan 1; 20(1): 29–35.

10. Jessica S Wang Memoli, MD,corresponding author Paul J. Nietert, PhD, and Gerard A. Silvestri, MD, FCCP. Meta-analysis of Guided Bronchoscopy for the Evaluation of the Pulmonary Nodule. Chest. 2012 Aug; 142(2): 385–393.