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Pneumologia

Rare lung tumours – possibilities and limits of diagnosis

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Abstract

English:

Considering the wide range of both histological and imaging types found in a small group of tumours as an incidence, they can pose real problems in both diagnosis and therapeutic conduct, being difficult to differentiate clinically, imagistically, or histologically from lung tumours commonly found in the clinic (1). Adenocarcinoma, squamous cell carcinoma, and small cell carcinoma together account for approximately 95% of all lung tumours, but the lung is the site of many other types of tumours that may be of epithelial, mesenchymal, neuroendocrine, or lympho-haematopoietic origin, and these latter together account for approximately 5% of all pulmonary tumours (2,3). With a few exceptions, both the clinical manifestations and the imaging aspect are nonspecific, many of them having features in common with the other tumours with high incidence (3). The present study was performed on a group of 82 patients diagnosed with low-incidence lung tumours, aiming at presenting the main epidemiological, clinical, and paraclinical features as well as the difficulties in diagnosing this heterogeneous group of tumours (4,5). The ratio of patients who presented with benign tumours was close to that of the patients who presented with malignant tumours. Age, male sex, smoking, and occupational exposure were not included as risk factors for any tumour nature. Significantly more patients in urban areas have developed both benign and malignant tumours. Patients with malignant tumour pulmonary development presented to the hospital with symptoms in a significantly higher number, compared to those diagnosed with benign tumour. The location of benign tumours was mostly peripheral. Peripheral location of benign tumours required surgery to obtain the histopathological type, having a curative visa in some cases. About a third of those with malignant tumours had secondary lung tumours, or distant metastases.

Keywords

lung tumours • low incidence • nonspecific appearance • diagnosis difficulties • histological aspect • heterogeneous group

Tumori pulmonare rare - Posibilitati si limite de diagnostic

Rezumat

Romanian:

Data fiind multitudinea de forme atat histologice cat si imagistice intalnite in cadrul unui grup restrans de tumori ca si incidenta, acestea pot pune reale probleme atat de diagnostic cat si de conduita terapeutica fiind greu de diferentiat clinic, imagistic sau histologic de tumori pulmonare des intalnite in practica medicala. Adenocarcinomul, carcinomul scuamos si carcinomul cu celule mici reprezinta aproximativ 95% din totalul tumorilor pulmonare, insa plamanul reprezinta sediul a numeroase tipuri de formatiuni tumorale care pot avea origine epiteliala, mezenchimala, neuroendocrina, limfo-hematopoietica si care reunesc aproximativ 5% din totalul tumorilor pulmonare. Cu mici exceptii, atat manifestarile clinice cat si aspectul imagistic, sunt nespecifice, multe din ele avand caractere comune cu celelalte tumori cu incidenta ridicata. Studiul a fost realizat pe un lot de 82 de pacienţi diagnosticaţi cu tumori pulmonare cu incidenta scazuta, avand ca scop prezentarea principalelor caracteristici epidemiologice, clinice si paraclinice cat si dificultatile aparute in diagnosticul acestui grup heterogen de tumori. Varsta, pacientii de sex masculin, istoricul tabacic, expunerea profesionala, nu fost identificate ca fiind factori de risc in aparitia a nici unei forme tumorale incluse in studiu. Semnificativ, pacientii din mediul urban au avut o incidenta mai mare a aparitiei patologiei tumorale pulmonare, atat de natura maligna cat si benigna. Pacientii diagnosticati ulterior cu tumori pulmonare de natura maligna au fost simptomatici la momentul prezentarii, într-un număr semnificativ mai mare, comparativ cu cei diagnosticaţi cu tumori de natura benigna. Localizarea tumorilor benigne a fost în mare parte periferică. Localizarea periferică a tumorilor benigne, a necesitat intervenţie chirurgicală pentru obţinerea tipului histopatologic, având viza curativă în unele cazuri. Aproximativ o treime dintre cei cu tumori maligne au avut tumori pulmonare secundare sau metastaze la distanta.

Cuvinte-cheie

tumori pulmonare • incidenta scazuta • aspect nespecific • dificultati de diagnostic

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Introduction

Rare lung tumours are limited in number and constitute a special category in tumour pathology. Several types of tumours can have their origin at the pulmonary level, and these could be of the epithelial or mesenchymal type or have their origin in the lymphohematopoietic system (5–7). In the current context, this study aims at performing an analysis of the types of clinical presentation, and the features and methods of diagnosis of low-incidence lung tumours, malignant and benign, diagnosed at the Marius Nasta Institute, between 2015 and 2018.

Methods

The study was performed in a group of 82 patients diagnosed with rare lung tumours. The objectives of the study were to obtain descriptions of the following aspects:

- the epidemiological features of the studied group;
- the histopathological types of rare tumours
- the associated risk factors;
- the diagnosis methods performed; and
- the types of treatment applied.

From a statistical point of view, the study is retrospective, non-interventional, and transversal. A batch of 82 consecutive patients diagnosed with lung tumours with rare malignant or benign histology was addressed to the pulmonology or thoracic surgery departments of the Marius Nasta Institute, Bucharest, for diagnosis and/or treatment, between 2015 and 2018.

The study collected data on: addressing symptoms, history of smoking and/or occupational exposure as well as its type, demographic elements (age, sex, origin), tumour location (central/peripheral), their distribution in the lungs, the type of diagnosis or therapeutic surgery (where appropriate), the histological type, and the occurrence of metastasis.

A general descriptive statistic of patients with low-incidence tumours was performed. The clinical characteristics, demographic, location, and type of diagnosis or therapeutic intervention for this group of patients were summarised. In order to collect the data, the patients' observation sheets were analysed, maintaining their privacy.

After selecting the valid files, an analysis of 82 cases was performed, of which 38 patients (46.3%) were found to have a benign tumour and another 44 patients (46.3%) were found with an unusual malignant form of lung tumour. The ratio of the two types of tumours was similar in the cases studied, and there was no statistically significant difference (Table 1).

Table 1. Histological distribution of tumours.

Tumour type	Number	Percentage	*P* – statistically significant
Benign	38	46.3	0.07
Malignant	44	53.7	

The median age for these patients was 52.47 ± 14.28 years (range, 25–76 years) for patients with benign tumours, and 55.34 ± 16.37 years (range, 18–80 years) for patients in whom a rare pulmonary neoplasm was identified. There was no statistically significant difference between the two groups, benign and malignant. This may be due to a significantly lower incidence of rare histological tumours, regardless of their nature.

Among the patients diagnosed with benign tumours, there were 25 (65.8%) male patients and 13 (34.2%) female patients. Among the patients diagnosed with the unusual malignant type of lung tumour, 24 (54.5%) were men and 20 (45.5%) were women. If, theoretically, regarding benign tumours with low incidence, the male sex were to be considered a risk factor, no such inference could be demonstrated as viable in our study, because in the group of patients studied, there was no statistically significant difference concerning their sex. The statistical importance was measured between the incidence of benign tumours, compared to malignant tumours, for men and for women, and the results yielded an absence of statistical significance ($P = 0.88$ and $P = 0.22$, respectively).

There were significantly more patients who developed benign lung tumours in urban areas compared to a rural environment – 10 patients (26.3%) vs 28 patients (73.7%). Concerning the same aspect, when we refer to patients diagnosed with the rare lung neoplasm, we found that most of them, 31 patients (70.5%), were from an urban area, contrasting with the number of patients hailing from a rural environment, 13 patients (29.5%). There are statistically significant differences between the types of provenance for each tumour form, in favour of the urban environment. Thus, it can be considered that urbanisation creates a favourable framework in tumour embryogenesis, regardless of the nature of the cells.

Among the patients assessed, out of the total of 38 patients diagnosed with benign tumours, a smoking history was identified in 16 patients (42.1%). Among patients belonging to the category of the malignant form of tumour, those with a smoking history amounted to 23 patients (52.3%), and those without to 21 patients (47.7%); and these results can be said to demonstrate statistical significance (Table 2).

Regarding the occupational aspect, whether we are referring to the benign or malign pathology, most patients did not present any form of exposure that could have caused the

appearance of these tumours. We found that, out of the 38 patients who were diagnosed with benign lung tumours, only 10 patients (26.3%) had a history of professional exposure, while only 13 patients (29.5%) with malignant tumours were exposed to any contaminant. This allows us to infer that those who developed malign or benign lung tumours were not professionally exposed. Thus, the causal link between the two categories is not proven and we can say that occupational exposure to various inhalants is not an eloquent risk factor in the occurrence of rare neoplastic forms of tumour in the lungs.
The incidental discovery is attributed to the diagnosis of benign tumours, made either during routine examinations or after completing an assessment for other conditions. Clinically (variable over time), patients are asymptomatic. The creation of the mass effect on the neighbouring structures/organs determines the appearance of the manifestations.
In the case of the patients with the benign form of lung tumours studied, the proportion of symptomatic patients was equal to that of asymptomatic patients: 19 cases. Therefore, half of the patients had a higher benign tumour cell turnover. Thus, the appearance of symptoms depends, most likely, on the coexistence of genetic and environmental factors, which contribute to the emergence of clinical manifestations.
Regarding patients with malign pathology, the majority of them, 43 patients (97.7%), were symptomatic at the time of first medical encounter. This was to be expected, as malignant tumours, regardless of their histological nature, whether classical or low incidence, lead in the vast majority of cases to the onset of symptoms. Whether we are talking about the manifestations with a pulmonary starting point (dyspnoea, haemoptysis, pleural pain), general symptoms (weight loss, loss of appetite, fatigue, anaemia), or those generated by local-regional extension, all these create a significant accumulation of symptoms, which put the patient in a position to report to the hospital.
Tumour location is an extremely important element in the diagnostic management of these rare forms of lung tumour, whether we refer to benign or malignant type. In cases with benign tumours, the predominant form was the peripheral one, in 25 patients (65.8%), followed by central lesions, nine patients (23.7%), and only four patients (10.5%) were unspecified cases. Among patients with malignant tumours, the lesion was central in 21 patients (47.7%) and peripheral in 18 patients (40.9%). The location is subdivided into central and peripheral, the difference being defined by the accessibility involved in using the fibrobronchoscope (limit: segmental–subsegmental bronchi). It is noted that in a small number of cases, the location could not be clearly objectified when analysing the observation sheet, and this factor constituted the reason why performing fibrobronchoscopy had to be ruled out. The frequency of central location was statistically significantly higher in rare malignant tumours than in benign ones in our group of patients (Figure 1). Regarding the distribution of these tumours in the lung, benign or malign, the left upper lobe was the main site – 12 patients (31.6%) vs 11 patients (25%) for benign and malign categories, respectively (Figure 2).
For the patients studied, histological diagnosis was identified using the following: thoractotomy followed by lobectomy, bilobectomy, pneumonectomy, bronchial biopsy fibrobronchoscopy, mediastinoscopy, and atypical resections (Table 3).
Taking into account the above, patients were divided into diagnosis categories, such as:

- surgical diagnosis: thoracotomy followed by lobectomy, bilobectomy, and atypical resections;
- fibrobronchoscopy with bronchial biopsy; and
- mediastinoscopy.

Analyses of these cases led us to the discovery that, for rare benign lung tumours, the mediastinoscopy method had not been used in any of the cases. This phenomenon was to be expected, as mediastinal lymph node involvement is

Table 2. Distribution related to smoking status, according to tumour type.

Smoking status	Benign		Malignant	
	Number	Percentage	Number	Percentage
Smoker	16	42.1	23	52.3
Non-smoker	22	57.9	21	47.7
P – statistically significant	0.33		0.76	

Table 3. Diagnosis methods by tumour type.

Diagnosis methods	Benign		Malignant		*P* – statistically significant
	Number	Percentage	Number	Percentage	
Fibrobronchoscopy with bronchial biopsy	12	31.58	12	27.27	0.02
Surgical	26	68.42	23	52.27	
Mediastinoscopy	0	0	9	20.45	
P – statistically significant	0.006		0.63		

not encountered, since there is no benign cell spread in the locoregional lymph nodes (Table 3).

The use of fibrobronchoscopy prevailed in the case of a positive diagnosis of benign tumours, which is expected given their predominant peripheral location. The frequency of use of the surgical approach in order to establish the diagnosis was significantly higher than the frequency corresponding to use of the fibrobronchoscope for the same purpose (P = 0.025). Checking the statistical importance associated with the surgically accessible diagnosis method, for the two tumour types (malignant and benign), we have not found any difference (Table 3).

Regarding the cases that required surgical intervention, in the group of rare benign lung tumours, we observed that lobectomies (17 patients) and bronchial biopsies (12 patients) were the most common. Apart from these, atypical resections (five patients), pneumonectomies (two patients), and bilobectomies (two patients) have been made. The explanation for the extent of the resection performed in cases of benign tumour was that the tumour size was significant, exerting compressive phenomena with clinical impact on neighbouring organs, or that the tumour's location and extension (e.g. typical bronchial carcinoid with central location) required such type of resection. Also, in the patients

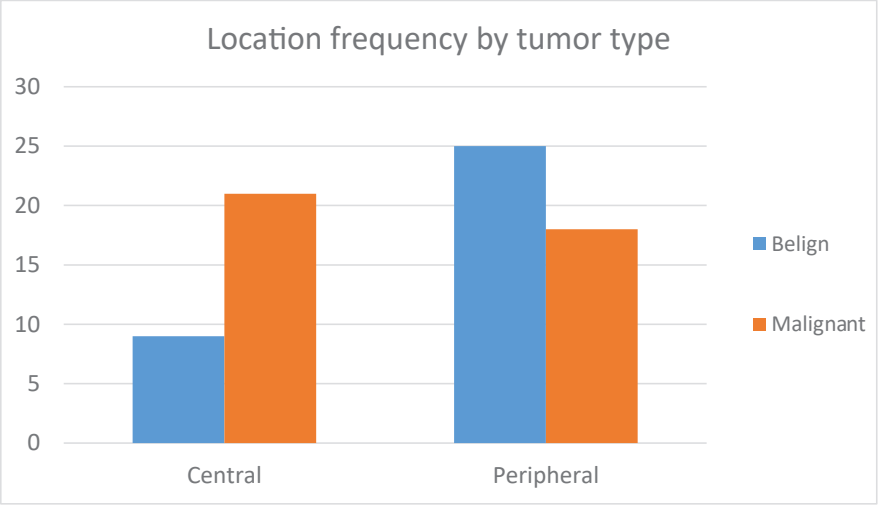


Figure 1. Location frequency by tumour type.

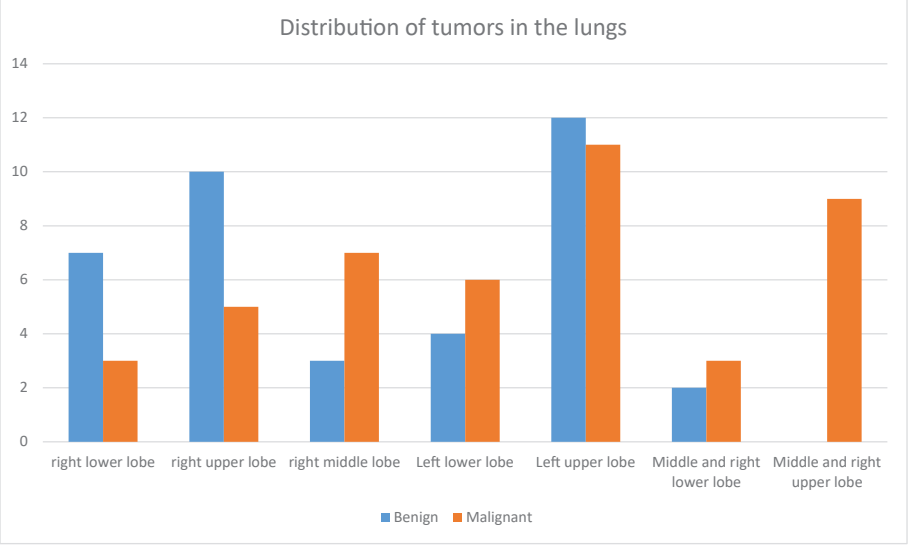


Figure 2. Distribution of tumours in the lung.

with malignant lung tumours with non or limited extension, the most-used methods of diagnosis and treatment from a surgical point of view were lobectomies (15 patients) and bronchial biopsies (12 patients), followed by mediastinoscopies (nine patients), pneumonectomies (seven patients), and lymph node biopsy (laterocervical lymph node – one patient).

It is mentioned that pneumonectomies, or lobectomies, had a curative visa. Prior to the decision to perform these, an extemporaneous examination was performed, which specified the malignant nature of the tissue formation. In the case of laterocervical ganglion biopsy, the vocation was exclusively for histological specification of the type of malignancy.

In terms of the histological types of benign tumours, we identified that most cases were typical carcinoid, 17 patients (44.74%), followed by hamartoma, nine patients (23.68%); bronchial papilloma, seven patients (18.42%); and hemagioendothelioma, five patients (13.16%) (Figure 3).

Regarding the rare type of lung neoplasm, the most common was large cell lymphoma, 13 patients (29.55%), followed by atypical carcinoids, 10 patients (22.73%); large cell neuroendocrine carcinoma, eight patients (18.18%); primary sarcoma of lung, six patients (13.64%); lymphoid granulomatosis, five patients (11.36%); and malignant hemangioendothelioma, two patients (4.55%) (Figure 4).

Last but not least, secondary pulmonary determinations, or distant from the primary tumour, were found in a limited number of patients, so their presence did not create any statistically significant difference. Therefore, among the group

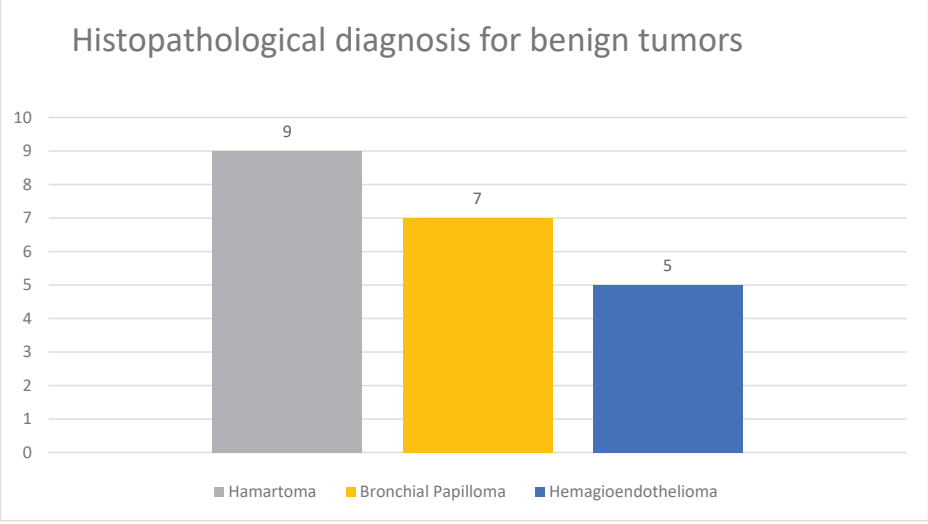


Figure 3. Distribution of histopathological diagnosis for benign tumours.

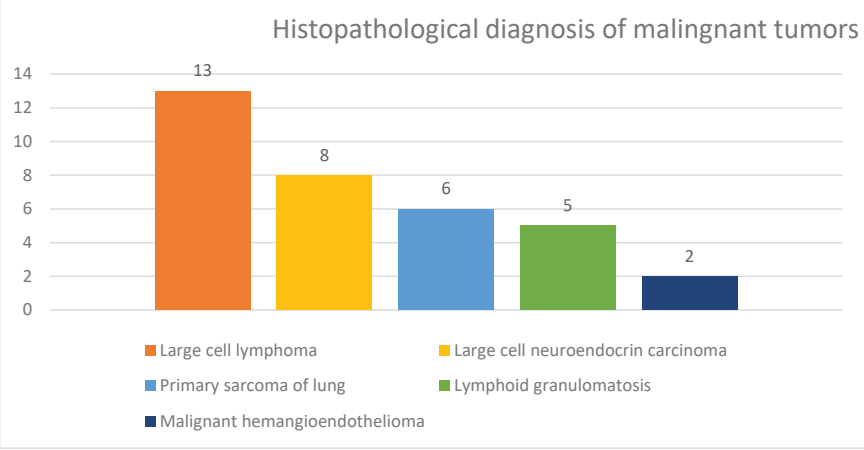


Figure 4. Distribution of histopathological diagnosis for malignant tumours.

of 82 total patients, including 44 patients who developed malignant tumours, only 14 patients reported the occurrence of metastases. Among them, we list contralateral pulmonary metastases, three patients (6.8%); contralateral and cerebral lung metastases, three patients (6.8%); ipsilateral pulmonary and cerebral metastases, two patients (4.5%); pleurisy and brain metastases, two patients (4.5%); ipsilateral pulmonary metastases, one patient (2.3%); pleurisy, one patient (2.3%); pleuropulmonary metastases, one patient (2.3%); and bilateral lung metastases, one patient (2.3%). Locoregional extension was found to be primary in cases of large cell neuroendocrine carcinoma and primary sarcoma of lung, while lymphoid tumours such as large cell lymphomas or lymphoid granulomatosis mainly extend at the level of hilar and mediastinal lymph nodes.

We can conclude that most of the patients did not have metastases at the time of evaluation. In the patients with locoregional extension, most metastases were present in the lung and pleura.

Discussion

Although the majority of lung tumours are described as adenocarcinoma, squamous cell carcinoma, or small cell carcinoma, there are numerous histological types of tumours, both benign and malignant, that pose important diagnostic problems given the nonspecific symptomatology and imaging appearance (4,8,9).

One of the purposes of this study was to observe the differences from the epidemiological, clinical, imagistic point of view as well as the diagnostic approach between the studied group and other published studies.

This study examined the records of 82 patients diagnosed with rare malignant or benign lung tumours over a 3-year period at the ‘Marius Nasta’ Institute of Pneumology, Bucharest. Of these, 39 patients (46.3%) developed benign tumours and 44 patients (53.7%) developed malignant tumours.

Age was not a risk factor for malignant aetiology with rare histology, contrary to the literature on classical histological types; and also, there were no statistically significant differences for mean age concerning tumour types. Accordingly, the average age for those with benign tumours was 52.47 ± 14.28 years, with extremes of 25–76 years, respectively, for the youngest and oldest patient. The average age for those with malignant tumours was 55.34 ± 16.37 years, with extremes of 18–80 years, respectively, for the youngest and oldest patient.

Contrary to expectations, for the group of patients studied, the male sex did not represent a risk factor for any tumour nature, with no statistically significant difference for any category. Among those diagnosed with benign tumours, 13 were women (34.2%) and 25 were men (65.8%). Among those diagnosed with malignant tumours, 20 were women (45.5%) and 24 were men (54.5%), an observation that offers a prominent contrast with the inferences that can be drawn from the prevalent literature, according to which predominance is asserted for the male sex in the incidence of lung tumours, especially in cases of malignance. Classical risk factors, including smoking history and occupational exposure, were not defining precipitating elements in the development of malignant tumours with rare histology. Concerning smoking history, among those with benign tumours, it is present in 16 patients (42.1%) and absent in 22 patients (57.9%), without a statistically significant difference; and among those with rare neoplasms, 23 smokers (52.3%) and 21 non-smokers (47.7%) were identified, again with no statistically significant difference. Occupational exposure was identified in a significantly lower percentage, in the categories of both benign and malignant tumours. Also, there was no statistical gap between the absence of occupational exposure for the two classes, malignant and benign.

Significantly more patients presented to the hospital for symptoms in the case of those diagnosed with malignant tumours, as compared to those with benign tumours; and in the latter category, the proportion between symptomatic and asymptomatic patients was equal.

Tumour location has created some statistically significant differences. Several benign tumours were detected peripherally. The central arrangement is predominant in malignant tumours, as compared to benign ones.

Thus, the peripheral location, due to the inaccessibility of the fibrobronchoscopic approach, required surgery of lesser or greater magnitude, in order to obtain the histopathological type, having in some cases the intention of radicality/curative visa.

Regarding the distribution of tumours in the lungs, there was a global difference, statistically significant between benign and malignant tumours. Both in benign and malignant tumours, the main distribution according to location was at the level of the left upper lobe and the right upper lobe.

Surgical methods used in the positive diagnosis histologically (with a curative visa in some cases) were dominant for both tumour groups. These include 32 lobectomies, nine pneumonectomies, five atypical resections, and two bilobectomies.

It is mentioned that pneumonectomies, or lobectomies, had a curative visa. Prior to the decision to perform these, an extemporaneous examination was performed, which specified the malignant nature of the tissue formation.

Fibrobronchoscopy with bronchial biopsy (a total of 24 patients) and mediastinoscopy (nine patients; performed only in the case of malignant tumours) were the other histologically positive diagnosis methods. Laterocervical ganglion biopsy (one patient) had as its exclusive vocation the confirmation of the histological type of the respective tumour.

The explanation for the extent of the resection performed in cases of benign tumour was that the tumour size was significant, exerting compressive phenomena with clinical impact on neighbouring organs, or that the tumour's location and extension (e.g. typical bronchial carcinoid with central location) required such type of resection.

No recently introduced methods, such as computer-guided or ultrasound-guided transthoracic punctures, have been used to diagnose peripherally located tumours that were inaccessible to the fibrobronchoscopic approach.

In terms of the histological types of benign tumours, we identified that most cases were typical carcinoid, 17 patients (44.74%), followed by hamartoma, nine patients (23.68%); bronchial papilloma, seven patients (18.42%); and hemagioendothelioma, five patients (13.16%).

Regarding the rare type of lung neoplasm, the most common was the large cell lymphomas, 13 patients (29.55%), followed by atypical carcinoids, 10 patients (22.73%); large cell neuroendocrine carcinoma, eight patients (18.18%); primary sarcoma of lung, six patients (13.64%); lymphoid granulomatosis, five patients (11.36%); and malignant hemangioendothelioma, two patients (4.55%). This information correlates with the rest of the published studies, especially in the case of rare pulmonary neoplasms, where we find that lymphoid types of tumours occupy the first place in term of incidence. In some studies published, the most common tumour was large cell neuroendocrine carcinoma, but also in our cohort, this histological type had a high incidence (10–12).

Last but not least, secondary lung determinations, or distant from the primary tumour, were found in a small number of patients, so their presence did not create any statistically significant difference. Therefore, out of a total of 82 patients, among whom 44 patients developed malignant tumours, only 14 patients reported metastases, most of them being located at the pleuropulmonary level, compared with other studies in which the presence of metastases was more common, predominantly in the case of large cell neuroendocrine carcinoma, primary sarcoma of lung, or atypical carcinoid, and often with extrapulmonary locations (brain, liver, adrenal, or even in a musculoskeletal site) (13–15).

Conclusions

Rare lung tumours represent a distinctive group in respiratory pathology, given the multiple difficulties that can arise in diagnosis as well as in differentiation from other primary lung tumours (16).

In the current study, we tried to evaluate as many patients as possible with this pathology and endeavoured to find the missing links that could facilitate the diagnostic approach, from aspects of symptomatology (nonspecific), to imaging/histological aspects of differentiation compared to other primary pulmonary masses and also epidemiological elements that could provide specificity to this pathology.

It is clear that the lack of risk factor (age, sex, smoking, or environmental factors), as well as the absence or presence of symptoms and the imaging appearance, should not delay the diagnostic approach. At the same time, more studies carried out on lung tumours with low incidence would provide more and more information necessary to establish the diagnosis as quickly and accurately as possible.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Disclosure

Data of this study were comunnicated as an oral presentation at the National Conferences of Romaninan Society of Pneumology Sections, held in Bucharest between November 13 - 15th.

References

1. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *Journal of Thoracic Oncology*. 2015;10(9): 1243–1260.
2. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International association for the study of lung cancer/American thoracic society/European respiratory society international multidisciplinary classification of lung adenocarcinoma. *Journal of Thoracic Oncology*. 2011;6(2): 244–285.
3. Brady P, McCreary C, O'Halloran KD, Gallagher C. Squamous papilloma causing airway obstruction during conscious sedation. *Anesthesia Progress*. 2017;64(3): 168–170.
4. Fortes HR, von Ranke FM, Escuissato DL, Araujo Neto CA, Zanetti G, Hochhegger B, et al. Recurrent respiratory papillomatosis: a state-of-the-art review. *Respiratory Medicine*. 2017;126: 116–121.

5. Yabuki K, Matsuyama A, Obara K, Takenaka M, Tanaka F, Nakatani Y, et al. A unique case of a huge mixed squamous cell and glandular papilloma of non-endobronchial origin with a peripheral growth. *Respiratory Medicine Case Reports*. 2018;24: 108–112.
6. Mlika M, Anjum F, El Mezni F. *Pulmonary papilloma*. Treasure Island (FL): StatPearls; 2020.
7. Miyoshi R, Menju T, Yoshizawa A. Expression of $p16^{Ink4a}$ in mixed squamous cell and glandular papilloma of the lung. *Pathology International*. 2017;67(6): 306–310.
8. Mitsumoto GL, Bernardi FDC, Paes JF, Villa LL, Mello B, Pozzan G. Juvenile-onset recurrent respiratory papillomatosis with pulmonary involvement and carcinomatous transformation. *Autopsy & Case Reports*. 2018;8(3): e2018035.
9. Lin D, Jiang Y, Wang J, Ding L, Xin F, Zhao H, et al. Pulmonary mixed squamous cell and glandular papilloma mimicking adenocarcinoma: a case study and literature review. *Journal of Thoracic Disease*. 2013;5(4): E129–E132.
10. Caplin ME, Baudin E, Ferolla P, Filosso P, Garcia-Yuste M, Lim E, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Annals of Oncology*. 2015;26(8): 1604–1620.
11. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of Clinical Oncology*. 2008;26(18): 3063–3072.
12. Fasano M, Della Corte CM, Papaccio F, Ciardiello F, Morgillo F. Pulmonary large-cell neuroendocrine carcinoma: from epidemiology to therapy. *Journal of Thoracic Oncology*. 2015;10(8): 1133–1141.
13. García-Yuste M, Matilla JM, Alvarez-Gago T, Duque JL, Heras F, Cerezal LJ, et al. Prognostic factors in neuroendocrine lung tumors: a Spanish Multicenter Study. Spanish Multicenter Study of Neuroendocrine Tumors of the Lung of the Spanish Society of Pneumonology and Thoracic Surgery (EMETNE-SEPAR). *The Annals of Thoracic Surgery*. 2000;70(1): 258–263.
14. Akata S, Okada S, Maeda J, Park J, Yoshimura M, Saito K, et al. Computed tomographic findings of large cell neuroendocrine carcinoma of the lung. *Clinical Imaging*. 2007;31(6): 379–384.
15. Chen LC, Travis WD, Krug LM. Pulmonary neuroendocrine tumors: what (little) do we know? *Journal of the National Comprehensive Cancer Network*. 2006;4(6): 623–630.
16. Chaves E, Pessoa Toão, Campobasso O, Chrétien J, Hochholzer L, Kreyberg L, et al. Histological Typing of Lung Tumours. *Tumori*. 1981;67(4): 253–272.