

THE IMPACT OF THE SARS-COV-2 PANDEMIC ON THE DIAGNOSIS OF LUNG CANCER PATIENTS

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Abstract

The SARS-COV-2 pandemic had an important impact on the diagnosis of all pathologies, including lung cancer. According to Global Cancer Observatory 2020, lung cancer is the leading cause of cancer death (18%).

The study aims are the comparative evaluation of lung cancer diagnosis and optimal identification of the factors that influenced the establishment of this diagnosis in the pre-pandemic and SARS-COV-2 pandemic periods. This retrospective study included patients >18 years-old, diagnosed with lung carcinoma on surgical specimens in „Marius Nasta” Institute of Pneumophtisiology, grouped in two cohorts: pre-pandemic (March 01, 2019 - February 29, 2020, N=370) and pandemic (March 01, 2020 - February 28, 2021, N=177).

Demographic, clinical, and paraclinical information have been collected from the Institute's database, and statistically analyzed (IBM SPSS Statistics 21). The number of newly diagnosed bronchopulmonary carcinoma decrease almost by half during the first year of the SARS-COV-2 pandemic. We noticed a significant increase in the number of patients with professional exposure ($p=0.040$), atypical resections ($p\leq 0.001$), and tumors that couldn't be completely resected ($p=0.001$), and an ascending trend of lung carcinoma diagnosis in women smokers, even though it wasn't statistically significant ($p=0.098$). The proportion of newly diagnosed women from rural medium significantly decreased, from 36.45% to 17.65% ($p=0.023$).

The SARS-COV-2 pandemic debut determined a significant under-diagnosis of lung cancer, with an increase in advanced tumors at the time of diagnosis. It is important to further analyze the situation in our country, given the fact that the literature review reported different results, depending on the geographic area.

Keywords: SARS-COV2 pandemic, impact, diagnosis, lung cancer, histopathology.



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Abstract

Pandemia SARS-COV-2 a avut un impact important asupra diagnosticului tuturor patologiilor, inclusiv al cancerului pulmonar. Potrivit Global Cancer Observatory 2020, cancerul pulmonar este principala cauză de deces prin cancer (18%).

Scopul studiului este evaluarea comparativă a diagnosticului de cancer pulmonar și identificarea factorilor care au influențat stabilirea acestui diagnostic în perioada pre-pandemică și în timpul pandemiei SARS-COV-2. Acest studiu retrospectiv a inclus pacienți >18 ani, diagnosticați cu carcinom pulmonar pe specimene chirurgicale în Institutul de Pneumoftiziologie „Marius Nasta”, grupați în două cohorte: pre-pandemie (01 martie 2019 - 29 februarie 2020, N=370) și pandemie (01 martie 2020 - 28 februarie 2021, N=177). Informațiile demografice, clinice și paraclinice au fost colectate din baza de date a institutului și analizate statistic (IBM SPSS Statistics 21).

Numărul de cazuri de carcinom bronhopulmonar nou diagnosticate a scăzut aproape la jumătate în primul an al pandemiei SARS-COV-2. Am observat o creștere semnificativă a numărului de pacienți cu expunere profesională ($p=0,040$), rezecții atipice ($p\leq 0,001$) și tumori care nu au putut fi rezecate complet ($p=0,001$) și o tendință ascendentă a diagnosticului de carcinom pulmonar la femeile fumătoare, chiar dacă nu a fost semnificativă statistic ($p=0,098$). Proportia femeilor nou diagnosticate din mediul rural a scăzut semnificativ, de la 36,45% la 17,65% ($p=0,023$).

Debutul pandemiei SARS-COV-2 a determinat subdiagnosticarea semnificativă a cancerului pulmonar, cu o creștere a numărului de tumori avansate la momentul diagnosticării. Este important să analizăm în continuare situația din țara noastră, dat fiind faptul că analiza literaturii de specialitate a raportat rezultate diferite, în funcție de zona geografică.

Cuvinte cheie: *pandemie SARS-COV2, impact, diagnostic, cancer pulmonar, histopatologie.*

Introduction

According to Global Cancer Observatory (GLOBOCAN) 2020, lung cancer is the second most common malignancy (11.4%), right after breast tumors (11.7%). Regarding cancer mortality, lung malignancy is the most common (18%), being almost double than the second, represented by colorectal cancer (9.4%)⁽¹⁻²⁾.

Non-small cell carcinoma is the most common type of lung malignancy (80-85%)⁽³⁾. The SARS-COV-2 pandemic had an important impact on the diagnosis of all pathologies, including lung cancer, with an important economical influence on the medical system⁽⁴⁾.

This study took place at "Marius Nasta" Pneumophtisiology Institute (IPMN), as it is a reference center for thoracic pathology in Romania. We proposed to assess the pandemic impact on lung cancer diagnosis (number of cases, histopathological types, and tumor extension) as this global phenomenon is still affecting us. We investigated if the addressability to medical care was unbalanced in this infectious context, analyzing potential gender, age, residence, and professional exposure variations. We compared our results with specialty literature reviews.

Materials and Methods

This retrospective study included all patients over 18 years old, newly diagnosed with bronchopulmonary carcinoma on typical and atypical resection specimens, in the Pathology Department of IPMN, between March 01, 2019, and February 29, 2021.

In the study were included only the patients that signed the informed consent at admission. They have been grouped into two

cohorts, according to pre-pandemic (March 01, 2019 - February 29, 2020, N=370) and SARS-COV-2 pandemic (March 01, 2020 - February 28, 2021, N=177) periods.

Exclusion criteria were: individuals under 18 years old; primary nonepithelial lung cancer (sarcoma, lymphoma, etc.) or lung metastasis; typical and atypical carcinoids; in situ lesions or dysplasia, without invasive areas; benign tumors; patients with tumor recurrence; patients diagnosed exclusively by bronchoscopy; patients diagnosed in other medical center or in another period; patients with impaired mental health, that don't allow them to sign an informed consent and patients that didn't sign the informed consent or signed it, but later changed their minds.

The study design was observational, descriptive, retrospective, and case-control. Demographic, clinical, and paraclinical information have been collected from the internal database of IPMN. The monitored parameters were: time of diagnosis, gender, age, residence, smoking status, professional exposure, type of surgical resection, the integrality of resection, the histopathological subtype of carcinoma, localization, number and dimension of tumors, pleural, lymphovascular and perineural invasion, pTNM and oncologic history.

All information has been recorded into an Excel file (Microsoft Office Professional Plus 2019). Statistical analysis has been made using IBM SPSS Statistics 21. Statistical tests used were: the qi-square test (coefficient Phi and V correlation of Cramer) and the Mann-Whitney U test; statistical indicators were: median, minimum, maximum, and standard deviation.

The aim of the study is a comparative evaluation of lung cancer diagnosis of patients admitted to the hospital in the pre-pandemic period and during the first year of



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the SARS-COV-2 pandemic (number of cases, histopathological type, and tumoral extension).

We investigated if addressability to medical care was unbalanced in this infectious context, analyzing potential gender, age, residence, and professional exposure variations. We then compared our results with specialty literature reviews.

Results

During the first year of the SARS-COV-2 pandemic, the number of newly diagnosed bronchopulmonary carcinoma significantly decreased: the pandemic cohort included 177 cases (32.36%) and pre-pandemic 370 cases (67.64%) (figure 1).

Numeric distribution of cases throughout one year was different in the pre-pandemic period compared with the pandemic one. In the pre-pandemic period minimum numbers of cases were reported in March 2019 (N=19) and maximum in October 2019 and February 2020 (N=41 patients per month). The study of the numeric evolution of newly diagnosed bronchopulmonary carcinoma in the pandemic period revealed a maximum number of cases in March 2020 (N=29). In April the number of cases was reduced to a minimum (N=5), followed by an ascendent trend with a peak in July (N=21) and a subsequent gradual decrease until

December 2020 (N=8). January 2021 (N=22) is marked by an accelerated increase in the number cases (figure 2).

Gender distribution was almost the same in both cohorts, with a male predominance of $\approx 71\%$ ($p=0.980$).

In the pre-pandemic cohort, the majority of cases were diagnosed during the seventh decade of life, followed by the eighth and the sixth. This trend remained unchanged after the pandemic debut, so statistical tests didn't reveal any significant difference ($p=0.709$) (figure 3). The mean age of patients was similar: 63.9 years old in the pre-pandemic cohort (standard deviation 8.45, confidence interval (CI): (63.04, 64.77)) and 63.36 years old in the pandemic cohort (standard deviation 8.75, CI: (62.06, 64.66)).

The residence of the patients was predominantly urban (67.30% in pre-pandemic and 70.06% in pandemic cohort), without significant variation between cohorts ($p=0.512$).

However, in the pandemic cohort, the proportion of women from rural medium decreased (from 36.5% to 17.65%). This difference was statistically significant $\chi^2=5.164$, $p=0.023$. Men's proportion from each social provenience medium was similar between cohorts (table 1).

Analyzing exposure to smoking, in the pandemic cohort were 6.05% more smokers, but this difference wasn't significant

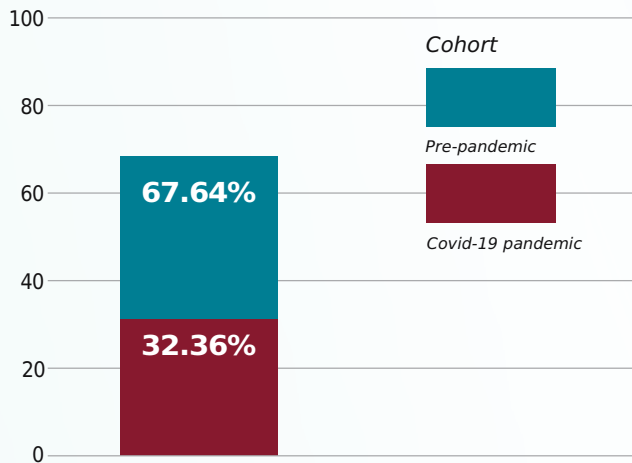


Figure 1. Percentage distribution of cases in pre-pandemic and SARS-COV-2 pandemic cohorts

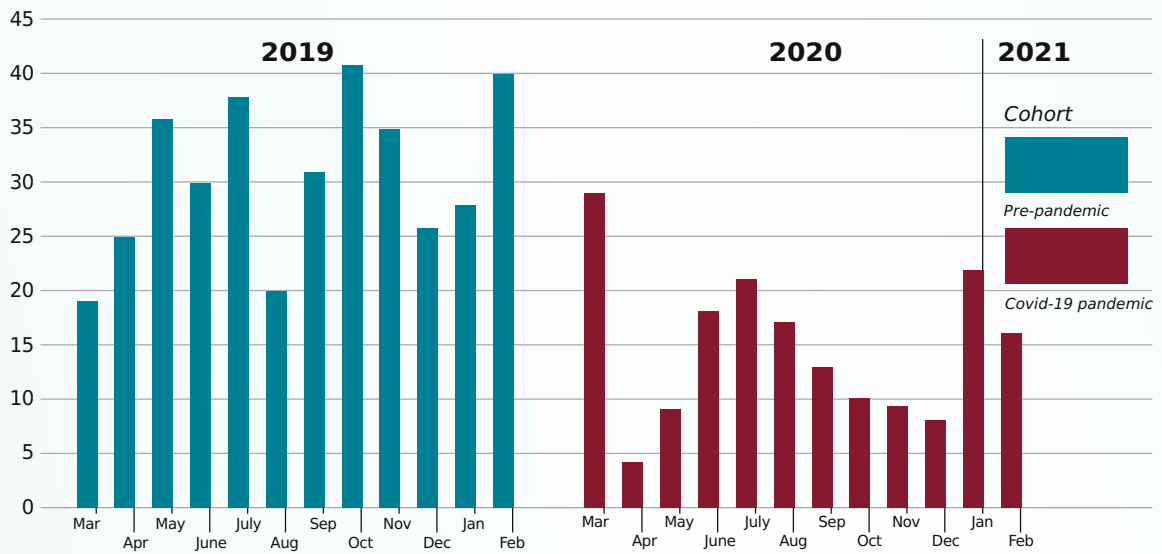


Figure 2. Numeric distribution of cases throughout one year, in the pre-pandemic and SARS-COV-2 pandemic period

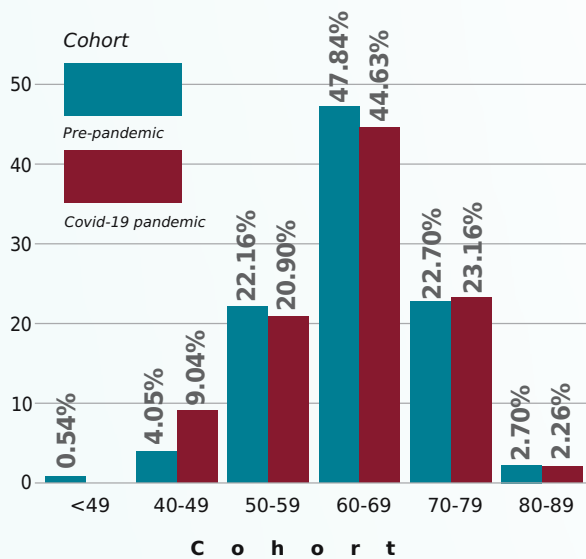


Figure 3. Distribution of cases in pre-pandemic and SARS-COV-2 pandemic cohorts by age



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($p=0.159$). The pre-pandemic cohort included 65.14% of patients exposed to smoking (36.22% active smokers, 28.92% ex-smokers), and 34.86% never-smokers. The pandemic cohort included 71.19% of patients exposed to smoking (38.42% active smokers, 32.77% ex-smokers), and 28.81% never-smokers. Men were more exposed to smoking in both cohorts.

In the pre-pandemic cohort, 72.62% of men were exposed to smoking (39.16% active smokers and 33.46% ex-smokers) and only 46.73% of women admitted to smoking exposure (28.97% active smokers and 17.76% ex-smokers). The difference in smoking exposure between men and women in the pre-pandemic cohort was statistically significant ($\chi^2=22.457$, $p\leq 0.001$).

In the pandemic cohort, the difference in smoking exposure between genders decreased, so it wasn't statistically significant anymore ($p=0,098$). 75.4% of men were exposed to smoking (38.89% active smokers and 36.51% ex-smokers). An elevated level of smoking exposure was also recorded in women, 60.78% admitted that are currently or were smokers (37.25% active smokers and 23.53% ex-smokers). In conclusion, during the pandemic period, we noticed an ascending trend of lung carcinoma diagnosis in smoker women, even though it wasn't significant.

The majority of active smokers patients at the moment of diagnosis declared tobacco

exposure between 40-49 pack-years (PY), without significant differences between cohorts ($p=0.681$).

In the pre-pandemic cohort, patients smoked between 10-160 PY, with a mean of 42.21 PY (standard deviation 20.73, CI: (38.18, 46.24)). During the pandemic, patients smoked between 15-100 PY, with a mean of 42.49 PY (standard deviation 15.86, CI: (38.43, 46.56)).

Professional exposure wasn't similar between cohorts, being 7.61% more frequent during the pandemic than before: 18.38% of pre-pandemic patients (N=68) and 25.99% of pandemic patients (N=46) declared toxic exposure. A Chi-square test indicated that professional exposure was significantly increased in the pandemic cohort: $\chi^2=4.203$, $p=0.040$. Phi coefficient and V coefficient of Cramer (0.088) showed that the relation between the moment of diagnosis and professional exposure is weak ($p=0.040$) (table 2, figure 4).

In the pre-pandemic period there was a clear predominance of typical resection specimens 56.49% (N=209), in contrast with the pandemic period, when atypical resection specimens were more numerous at 60.45% (N=107) (figure 5). A Chi-square test was performed and it revealed a statistically significant difference between cohorts: $\chi^2=13.746$, $p\leq 0.001$. Phi coefficient (-0.159) and V coefficient of Cramer (0.159) showed

Cohort			Residence	Total	
			Urban	Rural	
Pre-pandemic	Gender	Men	68.82% (N=181)	31.18% (N=82)	100.00% (N=263)
		Women	63.55% (N=68)	36.45% (N=39)	100.00% (N=107)
	Total		249	121	370
SARS-COV-2 Pandemic	Gender	Men	65.08% (N=82)	34.92% (N=44)	100.00% (N=126)
		Women	82.35% (N=42)	17.65% (N=9)	100.00% (N=51)
	Total		124	53	177

Table 1. Distribution of cases in pre-pandemic and SARS-COV-2 pandemic cohorts by gender and residence

		Cohort	
		Pre-pandemic	SARS-COV-2 pandemic
Professional exposure	No	81.62% (N=302)	74.01% (N=131)
	Yes	18.38% (N=68)	25.99% (N=46)
Total		100.00% (N=370)	100.00% (N=177)

Table 2. Distribution of cases in pre-pandemic and SARS-COV-2 pandemic cohort by professional exposure

		Cohort	
		Pre-pandemic	SARS-COV-2 Pandemic
Type of surgical resection	Atypical resection	45.51% (N=161)	60.45% (N=107)
	Typical resection	54.49% (N=209)	39.55% (N=70)
Total		100.00% (N=370)	100.00% (N=177)

Table 3. Distribution of cases in pre-pandemic and SARS-COV-2 pandemic cohort by type of surgical resection



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that the relation between the two variables (time of diagnosis and type of surgical intervention) is a weak one ($p \leq 0.001$) (table 3, figure 5).

Regarding the types of typical resection specimens, the study didn't show any significant difference between cohorts ($p = 0.081$). Lobectomy specimens were dominant, representing over 80% of cases in both cohorts. The incidence of lobectomy increased by 8% during the pandemic period, whilst pneumectomy maintained constant ($\approx 11\%$), and no bilobectomy was performed after the pandemic debut.

The squamous cell carcinoma diagnosis was established more frequently on typical resection specimens than on atypical resections. This tendency was observed in both the pre-pandemic (81.11% typical resections vs. 18.89% atypical resections) and the SARS-COV-2 pandemic period (56.67% vs. 43.33%). However, we observed a significant decrease in the frequency of squamous cell carcinoma diagnosis on typical specimens in the pandemic period (Chi-square test, $\chi^2 = 7.170$, $p = 0.007$), most probably because of the increase in the number of advanced cases, without a curative surgical intention.

Comparing the diagnosis of adenocarcinoma in the two cohorts, we didn't notice significant variations regarding the type of specimens (typical or atypical resections) ($p = 0.417$).

We also compared the type of surgical intervention performed, depending on the patient's provenience (urban or rural). In the pre-pandemic period, we didn't notice a statistically significant difference ($p = 0.454$): there were performed 3.61% bilobectomies, 47.79% lobectomies, 7.63% pneumectomies, 40.96% atypical resections for patients from the urban medium and 4.13% bilobectomies, 42.15% lobectomies, 4.96% pneumectomies, 48.76% atypical resections for patients from the rural medium.

During the pandemic period, there was a statistically significant decrease of lobectomies in rural medium patients (by $\approx 20\%$) and at the same time a significant increase of atypical resections in these patients (by $\approx 15\%$), $\chi^2 = 7.517$, $p = 0.023$. There were performed 41.13% lobectomies, 3.23% pneumectomies, 55.65% atypical resections for the patients from the urban medium, and 20.75% lobectomies, 7.55% pneumectomies, 71.70% atypical resections for the patients from the rural medium (table 4).

Histopathological evaluation showed that almost all the tumors were non-small cell carcinoma in both cohorts. This difference is perfectly explained by the limited indications of surgical intervention in small cell carcinoma (in limited-stage disease or advanced disease, only for diagnostic purpose, when other methods failed or aren't indicated)⁽⁵⁾.

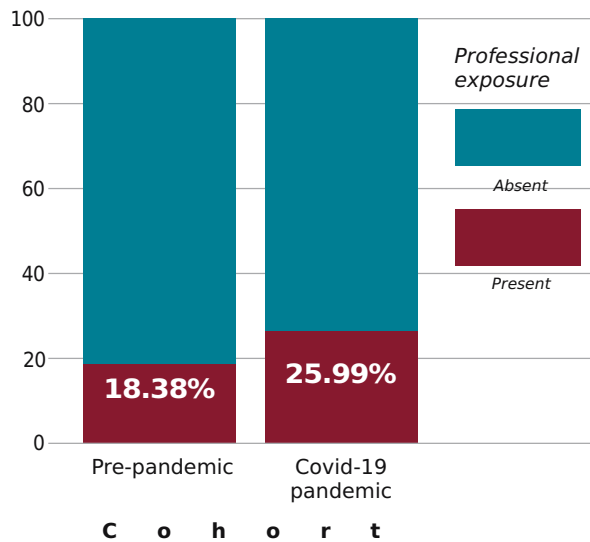


Figure 4. Exposure to respiratory toxics in pre-pandemic and SARS-COV-2 pandemic cohorts

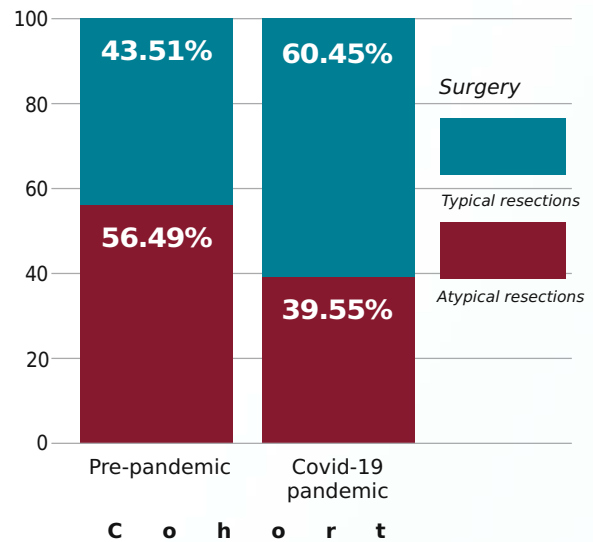


Figure 5. Distribution of cases in pre-pandemic and SARS-COV-2 pandemic cohorts by type of surgical intervention

Cohort		Residence	Urban	Rural
Pre-pandemic	Type of surgical resection	Bilobectomy	3.61% (N=9)	4.13% (N=5)
		Lobectomy	47.79% (N=119)	42.15% (N=51)
		Pneumectomy	7.63% (N=19)	4.96% (N=6)
		Atypical resection	40.96% (N=102)	548.76% (N=9)
	Total		100.00% (N=249)	100.00% (N=121)
SARS-COV-2 Pandemic	Type of surgical resection	Lobectomy	41.13% (N=51)	20.75% (N=11)
		Pneumectomy	3.23% (N=4)	7.55% (N=4)
		Atypical resection	55.65% (N=69)	71.70% (N=38)
	Total		100.00% (N=124)	100.00% (N=53)

Table 4. Distribution of the cases in pre-pandemic and SARS-COV-2 pandemic cohort by type of surgical resection and residence



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In both cohorts, adenocarcinoma represented the dominant (>40%) histopathological type of primitive lung carcinoma, over 85% of these being non-mucinous (figures 6, 7).

Identification of a unique tumor on resection specimens was the rule ($\approx 94\%$ of cases).

Regarding cases with multiple tumors, there were generally two, with only one exception - a case that presented four tumors on a surgical resection specimen.

Evaluation of tumor dimension showed that, in both cohorts, most measured between 40-49 mm. The medium dimension of the tumors was similar between cohorts ($p=0.673$): in the pre-pandemic group was 52.1 mm (standard deviation 24.47, CI: (48.76, 55.43)) and in the pandemic group was 49.32 mm (standard deviation 19.67, CI: (44.59, 54.05)) (figure 8).

For multiple tumor cases, we consider the biggest tumor being the dominant proliferation, which had in medium 59.76 mm (pre-pandemic cohort) and 56 mm (pandemic cohort). The second tumor had 16.69 mm (pre-pandemic cohort) and 33 mm (pandemic cohort). In both cohorts, men were diagnosed with bigger tumors compared with women. The most important, statistically significant difference between genders, was recorded in the pre-pandemic cohort.

In the pre-pandemic cohort men presented tumors between 5-150 mm, with a medium size of 54.95 mm (standard deviation 25.48, CI: (50.89, 59)) and women presented tumors

between 10-100 mm, with a medium size of 44.11 mm (standard deviation 19.47, CI: (38.84, 47.37)).

By analyzing this dataset, it can be observed that in the pre-pandemic period men presented tumors with significantly bigger dimensions compared with women ($U=3164.5, Z=-2.783, p=0.005$).

In the pandemic cohort men presented tumors between 20-100 mm, with a medium size of 50.02 mm (standard deviation 19.14, CI: (44.52, 55.52)) and women presented tumors between 15-110 mm, with a medium size of 47.6 mm (standard deviation 21.33, CI: (37.61, 57.59)). In the pandemic cohort, the medium tumoral dimension increased in women and decreased in men, so it wasn't a significant difference between genders anymore ($p=0.508$).

On typical resection specimens, we evaluated several parameters: pleural, lymphovascular, perineural invasion and pTNM classification.

In the pandemic cohort, an increase in cases of pleural invasion (PL) (60% versus 47.37% in the pre-pandemic cohort) was observed, but it wasn't significant ($p=0.072$). In the pre-pandemic cohort majority of the tumors were PL3 (parietal pleura infiltration) and in the pandemic were PL2 (visceral pleura ulceration) (figure 9).

Lymphovascular invasion was identified in 69.38% of cases in the pre-pandemic cohort

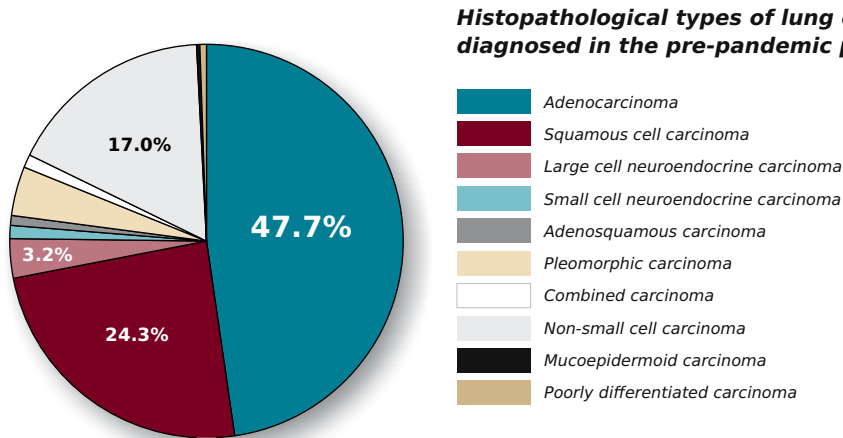


Figure 6. Histopathological types of lung carcinoma diagnosed during the pre-pandemic period

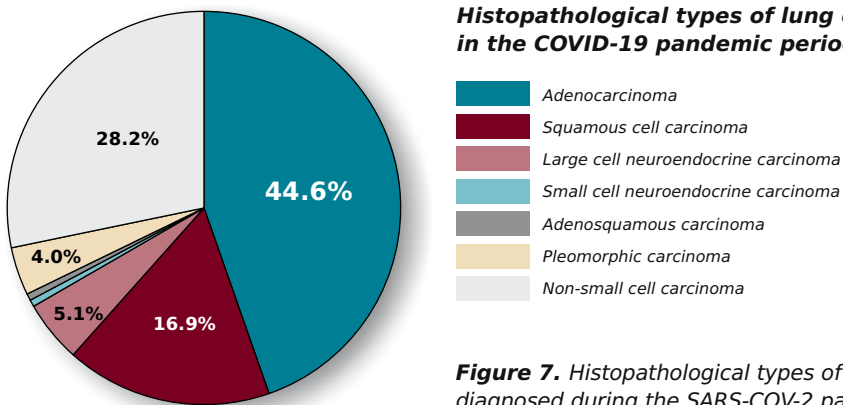


Figure 7. Histopathological types of lung carcinoma diagnosed during the SARS-COV-2 pandemic period

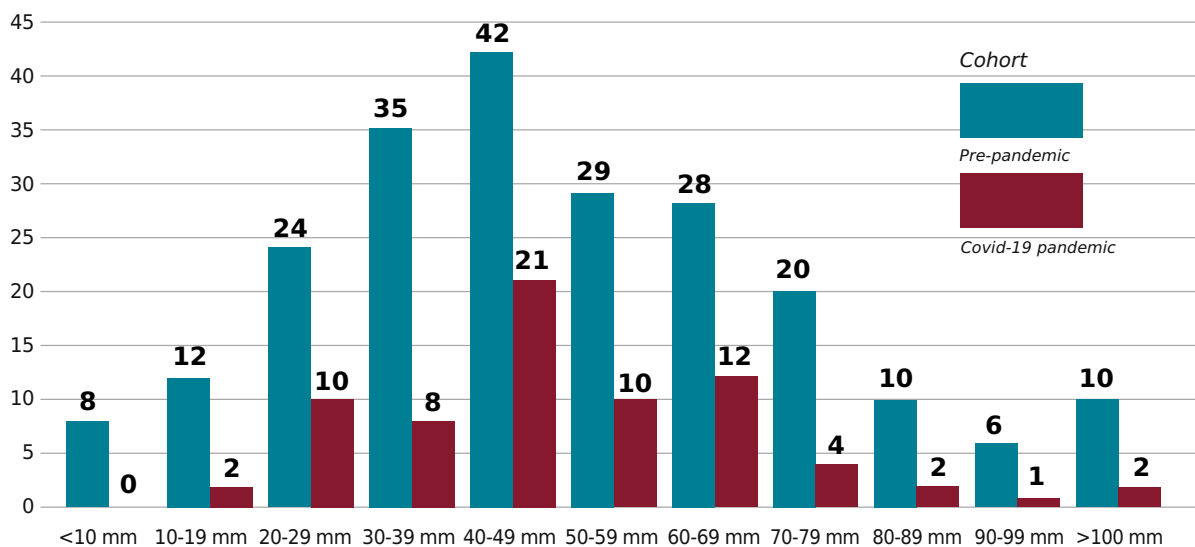


Figure 8. Comparative distribution of primary lung carcinoma according to tumor size in pre-pandemic and COVID-19 pandemic cohorts



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(N=145) and 74.29% of cases in the pandemic cohort (N=52). This 5% increase in lymphovascular invasion incidence in the pandemic wasn't statistically significant ($p=0.435$) (figure 10).

Perineural invasion was identified in 18.66% of cases in the pre-pandemic cohort (N=39) and 10% of cases in the pandemic cohort (N=7). It was a 9% decrease in perineural invasion in the pandemic period, but it wasn't statistically significant ($p=0.091$) (figure 11). Regarding pTNM classification, we were only able to evaluate pT and pN, the differences between cohorts weren't statistically significant ($p=0.213$, respectively $p=0.854$). The information regarding the presence of metastasis (pM) was, unfortunately, inaccessible. Bronchopulmonary carcinomas diagnosed in both cohorts were more frequent pT2 (pre-pandemic: 34.45% of cases, N=72, and pandemic: 41.43% of cases, N=29), followed by pT3 (pre-pandemic: 27.27% of cases, N=57, and pandemic: 28.57% of cases, N=20) (figure 12). Only one case of in situ squamous cell carcinoma was identified, in the pandemic cohort.

Lymph node metastasis was found in 47.85% of cases in the pre-pandemic cohort and 44.29% of cases in the pandemic cohort, both being predominant pN2 (28.23%, N=59 pre-pandemic; 27.14%, N=19 pandemic) (figure 13). Evaluation of surgical specimens showed that complete excision could be performed in

82.78% of pre-pandemic cases (N=173) and 61.43% of pandemic cases (N= 43). In the pre-pandemic cohort, 3.83% of cases (N=8) had macroscopic and 13.4% of cases had microscopic tumoral resection margins (N=28). In the pandemic cohort, 8.57 % of cases (N=6) had macroscopic and 30% of cases had microscopic tumoral resection margins (N=21) (figure 14). A Chi-square test revealed significant statistical differences between cohorts, $\chi^2=13.668$, $p=0.001$; Coefficients Phi and V of Cramer (0.221) showed a weak connection between the two variables ($p=0.001$).

We also evaluated the oncological history of the patients (as a potential factor influencing the addressability to medical care units), but statistical tests didn't reveal significant differences between pre-pandemic (8.92%) and pandemic (10.73%) cohorts ($p=0.498$). In the pre-pandemic cohort, the most frequent localizations of previous neoplasia was the digestive tract (21.21%, N=7), followed by the breast (18.18%, N=6). In the pandemic cohort, the most frequent localization of the previous neoplasia was the breast (26.31%, N=5), followed by the male genital system (21.05%, N=4).

Discussion

Our study revealed a significant under-diagnosis of lung cancer in IPMN during the

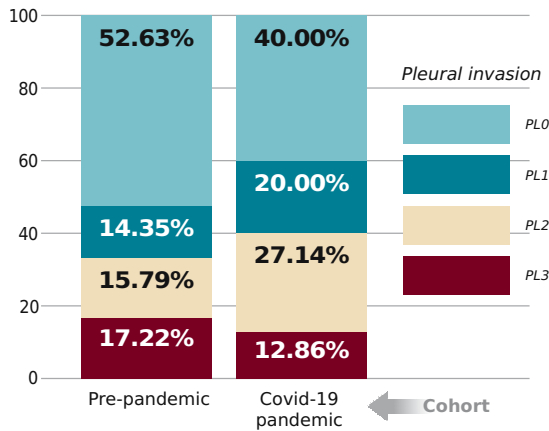


Figure 9. Distribution of the cases in pre-pandemic and COVID-19 pandemic cohorts by pleural invasion

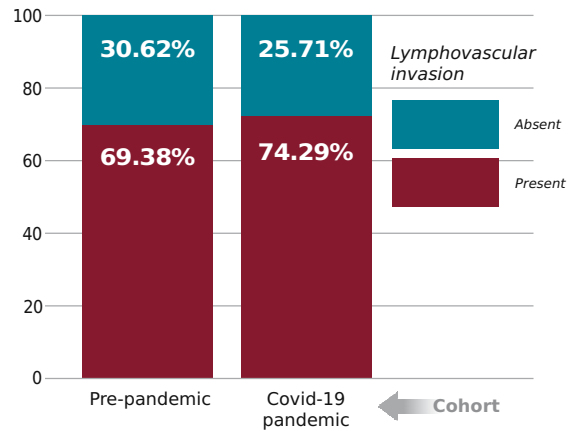


Figure 10. Distribution of cases in pre-pandemic and COVID-19 pandemic cohorts by lymphovascular invasion

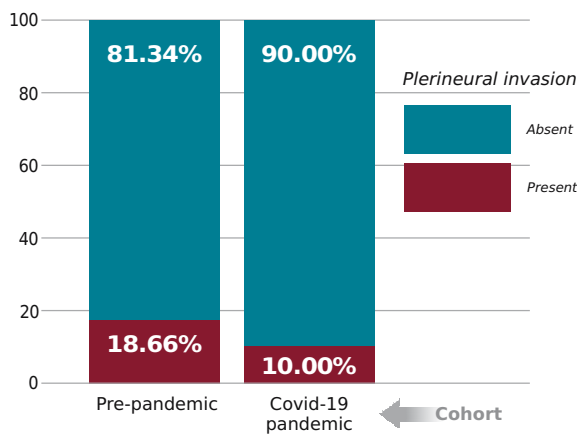


Figure 11. Distribution of cases in pre-pandemic and COVID-19 pandemic cohorts by peri-neural invasion

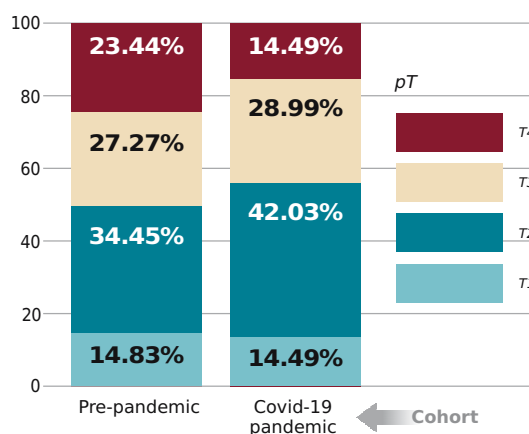


Figure 12. Distribution of cases in pre-pandemic and COVID-19 pandemic cohorts by pT

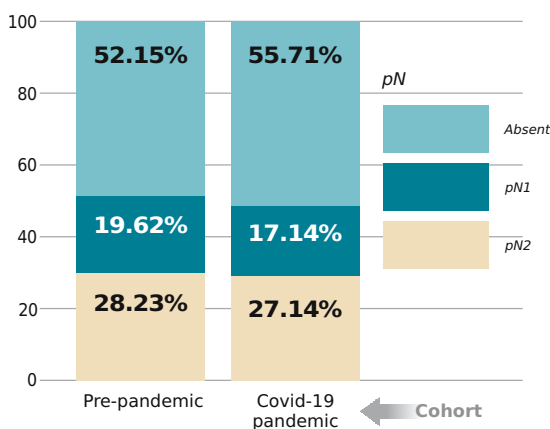


Figure 13. Distribution of cases in pre-pandemic and COVID-19 pandemic cohorts by pN

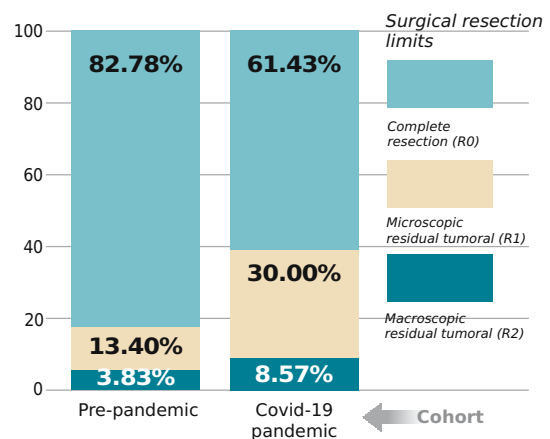


Figure 14. Distribution of the cases in pre-pandemic and COVID-19 pandemic cohorts by surgical resection limits



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first year of the SARS-COV-2 pandemic. This phenomenon is explicable by the difficult access of patients to medical services and by the patients' anxiety of potential intrahospital infection with SARS-CoV-2 virus. Specialty literature review showed different results regarding this aspect.

Some studies showed the same trend as ours (Debra Patt et al, Arnie Purushotham et al, Gurney JK et al, Werner RS et al. Vardhanabhuti V, Serra Mitjà P et al, and Riera R)⁽⁶⁻¹²⁾. Also, Kasymjanova G et al. reported a numeric reduction of lung cancer diagnosis by 34.7% during the pandemic⁽¹³⁾. An Italian study by L. Cantini et al mentioned a slight non-significant numeric decrease (~6.9%) in lung cancers⁽¹⁴⁾. A Korean study by Ji Young Park et al and a Japanese study by Takeshi Terashima et al showed that the numeric trend remained constant during the pandemic period⁽¹⁵⁻¹⁶⁾. We found even a Chinese study by Yu Zhang et al that reported a 48.1% increase of newly diagnosed lung cancer during the pandemic, due to screening methods⁽¹⁷⁾.

Limitations of our study could be that evaluation was made only on surgical resection specimens and on the most frequent form of lung malignancy - carcinoma (excluding the carcinoids).

Numeric distribution of newly diagnosed bronchopulmonary carcinoma throughout one year was different in the pre-pandemic

period compared to the pandemic one. Variations in several cases are explicable by the dynamic of lockdown and other sanitary restrictions imposed in our country.

There weren't any statistically significant differences between cohorts regarding gender, age, and residence of the patients, in concordance with other scientific publications (Ji Young Park et al and L. Cantini et al)⁽¹⁴⁻¹⁵⁾. However, our study showed a significant decrease in rural provenience women (from 36.45% to 17.65%) in the pandemic cohort ($\chi^2=5.164$, $p=0.023$).

Statistical analyses didn't show any difference in the patient's smoking status ($p=0.159$), as Ji Young Park et al noticed⁽¹⁵⁾. Men were more exposed in both cohorts. In contrast, L. Cantini et al showed an increase in current smokers during the pandemic period⁽¹⁴⁾. However, our study revealed that, after the pandemic debut, there were more female smokers getting diagnosed with lung carcinoma.

Statistic tests indicated that professional exposure was significantly increased in the pandemic cohort. Patients with tobacco or professional exposure were more likely to have preexistent pulmonary lesions: chronic obstructive pulmonary disease (COPD), pneumoconiosis etc. When carcinoma is developed on these types of lesions or on others, such as tuberculosis (which is an important health problem in our country), the

symptoms can be more prominent and mimic SARS-CoV-2 infection. That is why the medical addressability of these patients could be increased in the pandemic cohort.

In contrast, we didn't notice a statistically significant difference between cohorts regarding the oncological history of the patients. These antecedents seem to produce anxiety in accessing medical care, due to possible hospital infection with SARS-CoV2.

During the pandemic period, there was a statistically significant increase of atypical resections, from 43.51% to 60.45% ($p \leq 0.001$), these variations being particularly noticed in rural medium patients (atypical resections increased by approximately 15%), $\chi^2=7.517$, $p=0.023$.

We also noticed a significant difference regarding tumor resectability. Complete surgical resection decreased from 82.78% in the pre-pandemic cohort to 61.43% in the pandemic cohort. A Chi-square test revealed significant statistical differences, $\chi^2=13.668$, $p=0.001$; Coefficients Phi and V of Cramer (0.221) showed a weak connection between the two variables ($p=0.001$).

These significant variations (a numeric increase of atypical resection specimens and tumors with incomplete resection) could be the result of numerous advanced cancers, in which surgery was performed for diagnostic purposes, not therapeutic, probably due to delayed presentation.

The follow-up of the pandemic cohort is in progress, hence the difficulties in analyzing the data regarding mortality, metastasis, tumor recurrence, or evolution. All these data will be the subject of another statistical study and will be corroborated with the present one. Literature review supports our result: Cezary Piwkowski et al also reported, in a Polish study, a 20% numeric reduction in curative

surgery; Fu R et al. noticed the same trend⁽¹⁸⁻¹⁹⁾. Ji Young Park et al, Takeshi Terashima et al, L. Cantini et al, Debra Patt et al, Fraser J H Brims et al are only some of the specialists that noticed a numeric increase in more advanced non-small lung carcinoma after SARS-COV-2 pandemic debut^(6,14-23). In contrast, a study by Gurney JK et al didn't show differences in tumor stage after the SARS-COV-2 pandemic debut⁽⁸⁾.

Adenocarcinoma represented the dominant histopathological type of primitive lung carcinoma in both cohorts (over 40%), as L Cantini et al mentioned, the main subtype being non-mucinous (over 85%)⁽¹⁴⁾.

In both cohorts, men were diagnosed with bigger tumors compared to women. This difference is significant in the pre-pandemic cohort ($p=0.005$) and insignificant in the pandemic cohort ($p=0.508$).

Our study didn't show a significant difference in pleural, lymphovascular, and perineural invasion.

In conclusion, our study reported that the SARS-COV-2 pandemic debut determined a significant under-diagnosis of primitive lung cancer in IPMN, with an increase in advanced tumors at the time of diagnosis, probably due to delayed presentation to the hospital.

Patients with a history of smoking, probably having associated COPD, who presented to the doctor due to an acute exacerbation of COPD (possibly induced by SARS-CoV-2 virus), during which pulmonary cancer was incidentally diagnosed. This could be the reason for the higher number of pulmonary cancer cases diagnosed in our cohort in tobacco using females during the pandemic.

Furthermore, due to the delay in presenting to the doctor, the cancer was diagnosed at a more advanced stage and thus some resections were performed for diagnostic and not curative intention.



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Conclusions

The first year of the SARS-COV-2 pandemic determined a significant numeric decrease (almost by half) of newly diagnosed bronchopulmonary carcinoma in the „Marius Nasta” Institute of Pneumophtisiology, Bucharest, Romania.

We observed an increase in the number of patients with professional exposure ($p=0.040$). The number of atypical resections ($p\leq 0.001$), and tumors that couldn't be completely resected ($p=0.001$) was higher in the pandemic period, as a reflection of the more advanced tumors at the time of diagnosis. We noticed a significant decrease in the frequency of squamous cell carcinoma diagnosis on typical specimens in the pandemic period (Chi-square test, $\chi^2=7.170$, $p=0.007$), most probably because the number of advanced cases, without a curative surgical intention, was higher.

It is important to further analyze the situation in our country, given the fact that the literature review reported different results, depending on the geographic area. We also reported other factors that modified the diagnosis of lung carcinoma in this pandemic period.

References

1. International Agency for Research on Cancer: World Health Organization. *Cancer today*. Accessed March 3 .2022, 3:2022.
2. Dyba T, Randi G, Bray F, et al.: The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. *Eur J Cancer*. 2021, 157:308-347. 10.1016/j.ejca.2021.07.039
3. Suster DI, Mino-Kenudson M: Molecular Pathology of Primary Non-small Cell Lung Cancer. *Arch Med Res*. 2020, 51:784-798. 10.1016/j.arcmed.2020.08.004. Epub 2020 Aug 29
4. Degeling K, Baxter NN, Emery J, et al.: An inverse stage-shift model to estimate the excess mortality and health economic impact of delayed access to cancer services due to the SARS-COV2 pandemic. *Asia Pac J Clin Oncol*. 2021, 17:359-367. 10.1111/ajco.13505. Epub 2021 Feb 10
5. Wang Y, Zou S, Zhao Z, et al.: New insights into small-cell lung cancer development and therapy. *Cell Biol Int*. 2020, 44:1564-1576. 10.1002/cbin.11359. Epub 2020 Apr 18
6. Patt D, Gordan L, Diaz M, et al.: Impact of SARS-COV2 on Cancer Care: How the Pandemic Is Delaying Cancer Diagnosis and Treatment for American Seniors. *JCO Clin Cancer Inform*. 2020, 4:1059-1071.10.1200/CCI.20.00134
7. Purushotham A, Roberts G, Haire K, et al.: The impact of national non-pharmaceutical interventions ('lockdowns') on the presentation of cancer patients. *Ecancermedicalscience*. 2021, 3:1180. 10.3332/ecancer.2021.1180
8. Gurney JK, Dunn A, Liu M, et al.: The impact of COVID-19 on lung cancer detection, diagnosis, and treatment for Māori in Aotearoa New Zealand. *N Z Med J*. 2022 Jun. 10:23-43.
9. Werner RS, Lörtscher A, Kirschner MB, et al.: Surgical management of lung cancer during the SARS-COV2 pandemic - a narrative review and single-centre report. *Swiss Med Wkly*. 2022, 7:30109. 10.4414/smw. 2022.w 30109
10. Vardhanabhuti V, Ng KS: Differential Impact of SARS-COV2 on Cancer Diagnostic Services Based on Body Regions: A Public Facility-Based Study in Hong Kong. *Int J Radiat Oncol Biol Phys*. 2021, 1:331-336.10.1016/j.ijrobp.2021.05.010

11. Serra Mitjà P, Àvila M, García-Olivé I: Impact of the COVID-19 pandemic on lung cancer diagnosis and treatment. *Med Clin (Barc)*. 2022, 11:138-139. 10.1016/j.medcle.2021.07.009
12. Riera R, Bagattini ÂM, Pacheco RL, et al.: Delays and Disruptions in Cancer Health Care Due to SARS-COV2. *Pandemic:2021-7*. 10.1200/GO.20.00639
13. Kasymjanova G, Anwar A, Cohen V: The Impact of SARS-COV2 on the Diagnosis and Treatment of Lung Cancer at a Canadian Academic Center: A Retrospective Chart Review. *Curr Oncol*. 2021;28, 28:4247-4255.10.3390/curroncol28060360
14. Cantini L, Mentrasti G, Russo GL, et al.: Evaluation of COVID-19 impact on DELAYing diagnostic therapeutic pathways of lung cancer patients in Italy (COVID-DELAY study): fewer cases and higher stages from a real-world scenario. *ESMO Open*. 2022, 7:100406-10. 10.1016/j.esmoop.2022.100406
15. Park JY, Lee YJ, Kim T, et al.: Collateral effects of the coronavirus disease 2019 pandemic on lung cancer diagnosis in Korea. *BMC Cancer*. 2020;29, 20:1040. 10.1186/s12885-020-07544-3
16. Terashima T, Tsutsumi A, Iwami E, et al.: Delayed visit and treatment of lung cancer during the coronavirus disease 2019 pandemic in Japan: a retrospective study. *J Int Med Res*. 2022, 50:3000605221097375. 10.1177/03000605221097375
17. Zhang Y, Li J, Li ZK, et al.: Impact of Coronavirus Disease 2019 on Clinical Characteristics in Patients With Lung Cancer: A Large Single-Centre Retrospective Study. *Front Oncol*. 2021, 16:693002. 10.3389/fonc. 2021.693002
18. Piwkowski C, Gabryel P, Orłowski TM, et al.: The impact of the SARS-COV2 pandemic on surgical treatment of lung cancer. *Pol Arch Intern Med*. 2022, 28:16191. 10.20452/pamw.16191. Epub 2022 Jan 13
19. Fu R, Wu L, Zhang C, et al.: Real-World Scenario of Patients With Lung Cancer Amid the Coronavirus Disease 2019 Pandemic in the People's Republic of China. *JTO Clin Res Rep*. 2020, 1:100053. 10.1016/j.jtocrr.2020.100053. Epub 2020 May 20
20. Brims FJH, Kumarasamy C, Nash J, et al.: Hospital-based multidisciplinary lung cancer care in Australia: a survey of the landscape in 2021. *BMJ Open Respir Res*. 2022, 9:001157. 10.1136/bmjresp-2021-001157
21. Vlăsceanu S, Bobocea A, Petreanu CA, Bădărău IA, Moldovan H, Gheorghită D, Antoniac IV, Mirea L, Diaconu CC, Savu C. Pulmonary Crohn's Disease or Crohn's Disease with Lung Sarcoidosis? A Case Report and Literature Review. *Healthcare (Basel)*. 2022 Nov 11;10(11):2267. doi: 10.3390/healthcare10112267. PMID: 36421591; PMCID: PMC9690086.
22. Bolca C, Has A, Bobocea A, Afetelor A, Stoica R, Strambu I, Stoicescu I, Magheran E, Balescu I, Bacalbasa N, Gherghiceanu F, Furtunescu F, Radavoi D, Diaconu C, Paleru C, Cordos I. A Rare Thymic Tumor - Lipofibroadenoma - Always a Postoperative Surprise. *In Vivo*. 2021 Nov-Dec;35(6):3623-3626. doi: 10.21873/invivo.12668. PMID: 34697204; PMCID: PMC8627725..
23. Adjuvant chemotherapy for radically resected non-small cell lung cancer - A retrospective analysis of 311 consecutively treated patients Dediu, M; Horvat, T; (...); Savu, C *Jan 2005 LUNG CANCER 47 (1) , pp.93-101*