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Evaluation of pulmonary nodules on CT using the Lung-RADS system. Clinical value

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Abstract

Introduction: Inspired by the BI-RADS system (Breast Imaging Reporting and Data System), the American College of Radiology (ACR) developed the Lung-RADS system, for the purpose of making standardized reports on lung nodules detected in lung cancer screening (LCS). In Argentina and in many other parts of the world the LCS is not performed due to high costs; however, in chest CT scans pulmonary nodules frequently appear as incidental findings. There are multiple systems to evaluate them based on a series of features that allow subsequent follow-up. Some of them are the Fleischner Guidelines, the British Thoracic Society Guidelines and the Lung-RADS system, the latter being the only one with numerical categorization. In this article we study the usefulness of the Lung-RADS, as a diagnostic, follow-up method for the classification of pulmonary nodules. Objective: Evaluation of the pulmonary nodule diagnosed on chest CT scan, using the Lung-RADS system to determine its clinical importance, comparing the correlation between this classification and the malignancy or benignancy in the histopathological examination.

Material and Method: Descriptive, statistical, observational, retrospective and prospective study. A total of 100 adult patients, both men and women, with a diagnosis of pulmonary nodule were studied between January 2017 and December 2019. Patients without follow-up were excluded. Studies were performed with a 128-slice scanner. The variables under evaluation were: patients' sex and age, size and density of the nodule, malignancy of the lesion found in the anatomopathological study, Lung-RADS category and treatment performed and suggested. For the descriptive analysis we used relative frequencies (percentages) and absolute frequencies (number of cases) for qualitative variables; and mean and standard deviation as well as range of minimum-maximum values for the quantitative variables. For hypothesis tests, Chi-Square tests were performed for qualitative variables. For quantitative variables, Shapiro Wilks and Kolmogorov tests were performed.

Results: In 100 patients in whom Lung-RADS was applied to determine follow-up and treatment, different types of scenarios could be identified regarding the approach and follow-up: some needed recategorization and changes in the diagnostic approach and treatment. As for the statistical analysis, we analyzed the association between the Lung-RADS classification obtained and the presence or absence of malignancy in the anatomopathological examination, and obtained statistically significant results (p-value <0.0001) for this association.

Discussion: The Lung-RADS system and the Fleischner Society Guidelines on pulmonary nodules are used at present. Both have similar criteria and are based on the morphological suspicion of malignancy that includes the density of the nodule (solid, partially solid or ground-glass), the size and, when available, growth or evolution, which can be applied in different groups of patients. Determining the Lung-RADS score has proven its usefulness in this study, based on the pathological correlation of the nodule, with a statistically acceptable result and a good correlation with the treatment and follow-up decision.

Conclusion: The application of the Lung-RADS system to this series of patients has shown a good management of patients' follow-up, with surgical resections in some cases and an expectant approach in others, providing certain security and mostly avoiding the use of unnecessary aggressive treatments.

Key words: Nodule, Lung-RADS, CT, Approach

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Introduction

Inspired by the BI-RADS system (Breast Imaging Reporting and Data System), the American College of Radiology (ACR) developed the Lung-RADS system, for the purpose of making standardized reports on lung nodules detected in patients who had undergone lung cancer screening (LCS), thus reducing the risk of overdiagnosis or unnecessary surgeries, taking into account the fact that lung cancer is one of the leading causes of cancer death in men and women at present. [1]That is why we must emphasize the importance of early detection of lung cancer, with timely follow-up of the pulmonary nodules, whether in detection programs (carried out in developed countries) or in cases of incidental findings in countries where LCS is not performed.

As a matter of fact, LCS is not performed in Argentina yet, but patients and health staff can use the chest CT, with frequent incidental findings of pulmonary nodules. For those cases, several guidelines are used, such as the Fleischner Society and the British Thoracic Society Guidelines, which share treatment and follow-up criteria with the Lung-RADS system, the latter being the only one with a numerical classification scale.

Taking into account the available guidelines, this study evaluates the usefulness of the Lung-RADS system (**Figure N° 1**) using it as a follow-up method (considering the fact that it provides the numerical value based on imaging findings) for the classification of pulmonary nodules in order to apply a follow-up scheme for patients with these nodules.

Based on this system and the recommendations of the general literature, this study retrospectively and prospectively evaluates patients with solitary pulmonary nodule (SPN) applying the Lung-RADS system to determine if this nodule classification can establish a specific expectant or surgical approach to consider its real value.

Objective

To determine the clinical value of the Lung-RADS system in the study of the solitary pulmonary nodule for determining the probability of malignancy of such nodule.

Study hypothesis

The use of the Lung-RADS system for the analysis of pulmonary nodules determines the probability of malignancy of the lesion and provides data useful for considering which approach to be used: expectant, active monitoring or therapeutic.

Materials and method

Descriptive, statistical, observational, retrospective and prospective study.

The American College of Radiology (ACR) developed the Lung-RADS using the computed tomography (CT) for lung cancer screening (LCS) with established criteria that depend on different organizations, such as the ACS (American Cancer Society), ACCP (American College of Chest Physicians), ALA (American Lung Association), ASCO (American Society of Clinical Oncology), ATS (American Thoracic Society) and Centers for Medicare and Medicaid Services, with factors in common: age (≥ 55 years) and smoking history (if the patient is a current smoker, ≥ 30 packs/year, or if the patient quit smoking 15 years before or less).

Inclusion criteria: we selected 100 adult patients diagnosed with solitary pulmonary nodule detected by chest CT, taken from the database of the Diagnostic Imaging Service.

Exclusion criteria: pediatric patients, patients with Lung-RADS 0 and 1 and also patients with known neoplasia.

For the chest computed tomography we used a GE® Optima 660 128-slice scanner. The study was performed interchangeably with or without contrast injection using multi-slice volumetric acquisition

Category	Description	Lung-RADS	Findings	Approach	Probability of malignancy
Incomplete	–	0	- Prior CT - Pulmonary regions not evaluated	Additional images and/or comparisons are needed.	n/a
Negative	No nodules or definitely benign nodules.	1	- No nodules. - Nodules with specific calcifications.	Continue annual CT	1%
Benign appearance	Nodules with low likelihood of becoming a clinically active cancer due to their size or lack of growth.	2	- Solid nodules <6 mm or new <4 mm. - Solid part of the nodule <6 mm of the total diameter of the nodule on baseline screening. - Non-solid nodule < 20 mm or > 20 mm unchanged or slowly growing. - Category 3 or 4 nodules unchanged for > than 3 months.		1-2%
Probably benign	Probably benign but with short-term follow-up: includes nodules with low likelihood of becoming a clinically active cancer.	3	- Solid nodules > 6 to < 8 mm or new from 4 to 6 mm. - Solid part of the nodule: > 6 mm (total diameter of the nodule) with solid component < 6 mm. - Subsolid nodule > 20 mm or new nodule	CT at 6 months	5-15%
Suspicious	Findings for which another diagnostic testing or biopsy is recommended.	4 A	- Solid nodule(s) ≥8 mm to <15 mm at baseline - Growing nodule(s) <8 mm - New nodule 6 mm to <8 mm - Subsolid nodule(s): ≥ 6 mm of total diameter with solid component ≥ 6 mm to <8 mm, new solid component or growing solid component <4 mm - Endobronchial nodule	CT at 3 months. PET/CT in case of solid component of more than 8 mm.	> 15%
		4B	- Solid nodule(s): ≥ 15 mm at baseline, or new or growing, and ≥ 8 mm - Subsolid nodule(s): with solid component ≥ 8 mm, or with a new solid component or a growing solid component ≥ 4 mm. - For new large nodules that develop on an annual repeat screening CT, a 1-month LDCT may be recommended to address potentially infectious or inflammatory conditions.	Chest CT with or without contrast as appropriate; PET and biopsy.	> 15%
		4X	- Category 3 or 4 nodules with additional features or imaging findings that increase the suspicion of malignancy, including: spiculations, ground-glass nodules that duplicate their size in 1 year, enlarged regional lymph nodes. - For new large nodules that develop on an annual repeat screening CT, a 1-month LDCT may be recommended to address potentially infectious or inflammatory conditions.		

Figure 1. Lung-RADS classification.

and reconstruction of 0.63 mm of thickness, with 5 mm slice distance in axial, sagittal and coronal planes for the high-resolution system, with inspiratory apnea and completing with discontinuous slices in sustained espiration, and for conventional acquisition, a thickness of 3.75/4 mm every 4 mm. Also, the densitometric MIP (maximum intensity projection) and MinIP (minimum intensity projection) reconstructions were performed and analyzed. The settings of the CT studies were: helical scanning; tube rotation speed, 0.6 seconds; full scan length at 120 Kv; from 100 to 500 mAs automatically set; 1.375:1 of pitch; 40 mm of detector coverage; a percentage of automatic and an average DLP (dose length product) of 900 to 1300 mGy (depending on thickness and height of the patient, due to automatic dosage of the equipment), with a scan time of 9 seconds for the sequence. For the low-dose studies, 120 Kv and 18 to 200 mAs were used (percentage of dose reduction between 40 and 50%), with a scan time of 7 seconds and determining an average DLP of 500 to 700 mGy. (DLP: [mGy * cm] = CTDIvol [mGy] * Scanner length [14 cm]).

For the histopathological examination, staining with hematoxylin and eosin. For patients that needed immunostaining we used specific antibodies for each tumor lineage, depending on the result obtained in the histopathological examination performed in the first instance.

Surgeries recommended for the treatment were mostly lobectomies and the surgical technique used was conventional or video-assisted, depending on the requirements of each particular case.

Diagnostic procedure: data were collected from the records of patients who had undergone chest CT since 2017. Chest CTs were reviewed, and those which showed pulmonary nodules were evaluated, measuring the diameter of the nodules in the lung window (following the current recommendations of the Fleischner Guidelines), obtaining an average diameter between the long and short-axis diameters, including decimals. In cases of multiple nodules, only the most suspicious one was to be measured. A nodule was considered to have grown if it had an increase in size of ≥ 1.5 mm.

Patients with Lung-RADS 1 (including granulomas and hamartomas) were excluded as well as those with known neoplastic processes.

The study variables were: patients' sex and age, size and density of the nodule, malignancy of the lesion found in the anatomopathological study, Lung-RADS category and treatment performed and suggested, expectant or surgical approach and determining the stage of the disease at the moment of the diagnosis. It was considered as advanced stage when local infiltration, infiltration of neighbor structures (pleura, pericardium, central bronchi), heart and great vessels, bone; and extranodal extension (metastasis in extra-pulmonary organs or in the contralateral lung) could be identified.

Patients' data were collected retrospectively in order to allow for a more precise and effective study, apart from the patients who were evaluated prospectively from January 2018. In this regard, we must emphasize the fact that LCS is not performed in Argentina. So, categorized pulmonary nodules were analyzed basing on the findings obtained from imaging in relation to an incidental finding or pulmonary study for clinical symptoms and not through screening, thus smoking wasn't taken into account as a variable, since the objective was to assess mainly the score and no additional data.

Some of the patients evaluated in a prospective manner needed Lung RADS recategorization during follow-up. For the statistical analysis we used the last recategorization. The description of those cases is specified later.

On the other hand, patients who remained stable after periodic follow-ups were recategorized to Lung-RADS 2, and so continued with an annual follow-up without signs of malignancy to date.

Categorized pulmonary nodules were analyzed based on the findings seen in the chest CT in all adult patients, with no age or sex distinction and not differentiating between smokers and non-smokers, but including patients older than 18 years. The Lung-RADS system was used for the analysis, categorization and selection of follow-up approaches for patients with CT-detected pulmonary nodules.

Statistical analysis: for the descriptive analysis, we used relative frequencies (percentages) and absolute frequencies (number of cases) for qualitative variables; and mean and standard deviation as well as range of minimum-maximum values for the quantitative variables. For hypothesis tests, Chi-Square tests were performed for qualitative variables. For quantitative variables, Shapiro Wilks and Kolmogorov tests were performed in the first place in order to analyze variable distribution. Then, Wilcoxon tests were carried out to observe differences between groups. A value of $p < 0.05$ was considered to be statistically significant.

The software used for data analysis was Excel and Infostat professional version 2019.

Results

Data were analyzed from 100 patients, mean age 60 (± 14 years) and an age group between 22 and 90 years. Regarding sex, there were 52 males (52%) and 48 females (48%).

The average size of the nodules was 23.97 ± 16.61 mm, with a minimum diameter of 5 mm and a maximum of 80 mm.

From the total number of cases of the study (n = 100) we found 84 cases (84%) of patients with solid tumors. 57% of the total number of patients (n = 57) had a Lung-RADS classification of 4X and 71% of the population being studied showed malignant tumors (n = 71). With regard to the staging of the tumors, 44% of the total number of patients didn't show an advanced stage (n = 44). 41 patients underwent surgery.

The analysis between the approach suggested by the Lung-RADS system and the final approach used for the diagnosis and treatment of the whole sample (n = 100) has shown that in 66% of the cases (n = 66), the Lung-RADS approach indicated a biopsy, a PET study (positron emission tomography) or surgery, whereas in 16% of the cases (n=16) it suggested annual check-up. The analysis of the selected approach used in all the patients showed that a biopsy was requested in 34% of the cases (n=34) and 28% (n = 28) were requested to undergo surgery.

TABLE 1. Shows the general characteristics of the population being studied.

Variable	Category	N	Percentages
Sex	Males	48	48
	Females	52	52
Density	Soles	84	84
	Mixed	12	12
	Subsolid	4	4
Lung Rads	2	16	16
	3	9	9
	4 A	9	9
	4 B	9	9
	4 X	57	57
Malignancy	Yes	71	71
	No	29	29
Avanced	No data	28	28
	Yes	28	28
	No	44	44
Surgery	No data	10	10
	Yes	41	41
	No	49	49

Based on the approach that was chosen, we analyzed if it corresponded with the one suggested by the Lung-RADS (**Table 3)**. 87 of the 100 patients underwent the treatment suggested by the Lung-RADS (87%). Results were statistically significant (p-value <0.001).

TABLE 2. Suggested and selected approach

Variable	Categorias	N	Porcentajes
Suggested Lung-Rads approach	Biopsy-PET-Surgery	66	66
	Surgery	1	1
	Check-up-Biopsy-PET	8	8
	Annual check-up	16	16
	Chek-up after 6 months	9	9
	Total	100	100
Selected approach	Biopsy	34	34
	Surgery	28	28
	Check-up	5	5
	Annual control	10	10
	Control in 6 months	11	11
	PET	12	12
	Total	100	100

Then, we analyzed the association between the Lung-RADS classification obtained and the presence or absence of malignancy in the anatomopathological examination (**Graphic 1**). 100% of the cases classified as Lung-RADS 2 were free from malignancies, but this percentage started to decrease as the Lung-RADS classification score got higher: among patients with Lung-RADS 3, only 22.2% showed malignancy; in Lung-RADS 4A the percentage increased to 66.7%; and in patients with Lung-RADS 4B, it increased to 77.8%. 98.2% of patients with Lung-RADS 4X showed malignancy. The results of this association were statistically significant (p-value<0.0001).

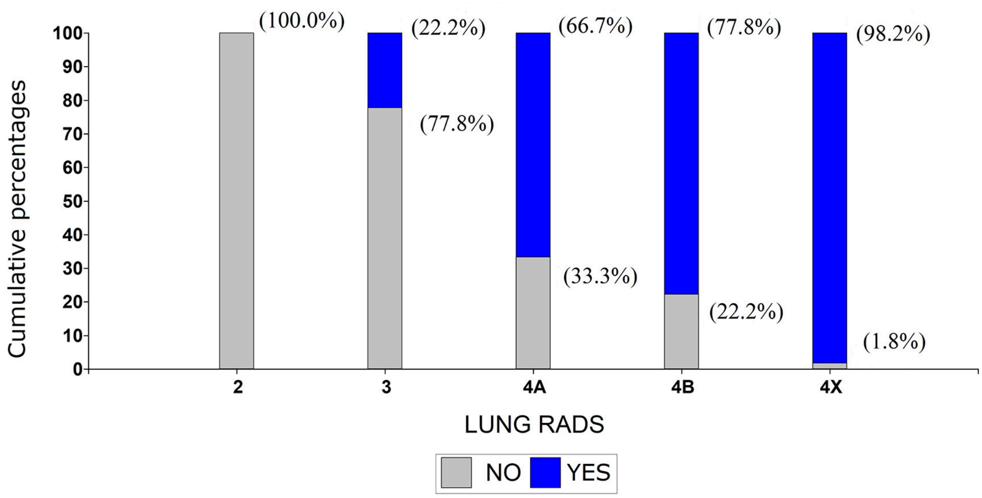
TABLE 3. Correlation between the approach suggested by the Lung-RADS classification and the selected approach

Suggested approach	Selected approach		
	Yes	No	Total
Biopsy-pet-surgery	65	1	66
Surgery	1	0	1
Check-up-biopsy or pet	7	1	8
Annual check-up	8	8	16
Control in 6 months	6	3	9
Total	87	13	100

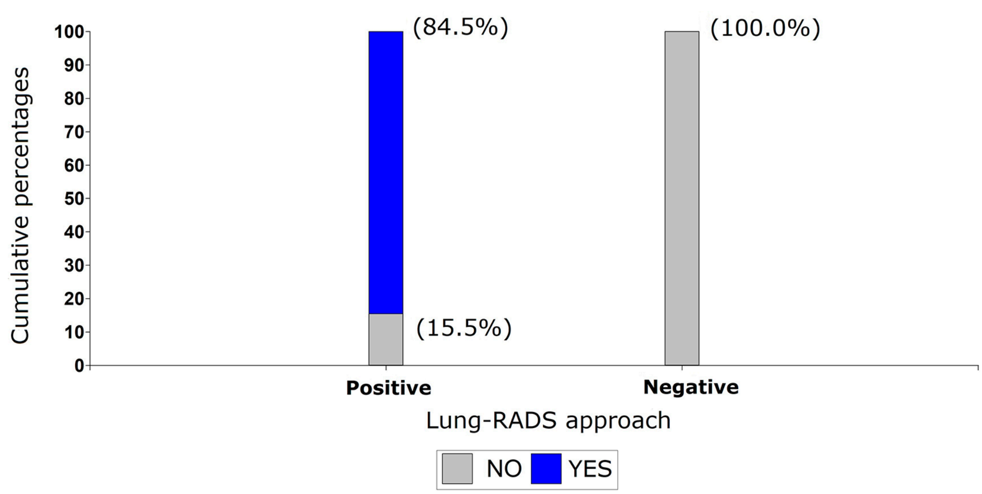
For a better statistical analysis, the Lung-RADS classification was reduced to two groups: positive cases and negative cases. Cases considered as negative were patients with Lung-RADS 2 (n=16); and positive cases were patients with Lung-RADS 3 and 4 (n=84). With such grouping, we analyzed the association with the malignancy of the tumor (**Graphic 2**) and observed that none of the patients with negative Lung-RADS showed malignant tumors in the histopathology. In 15.5% (n=13) of patients with positive Lung-RADS, tumors weren't malignant. This association was statistically significant (p-value <0.0001).

On the basis of this analysis, we calculated the predictive values of the study and its sensitivity/specificity. The positive predictive value (PPV) of the population being evaluated was 100%, that is to say, all the subjects who had a malignant result in the histopathological examination were categorized as Lung-RADS 3 or 4.

The negative predictive value (NPV) of the population being evaluated was 55.2%, meaning that all the patients who had a benign result in the histopathological examination (100%: n=29), the 55.2% (n=16), were categorized as Lung-RADS 2.



Graphic 1



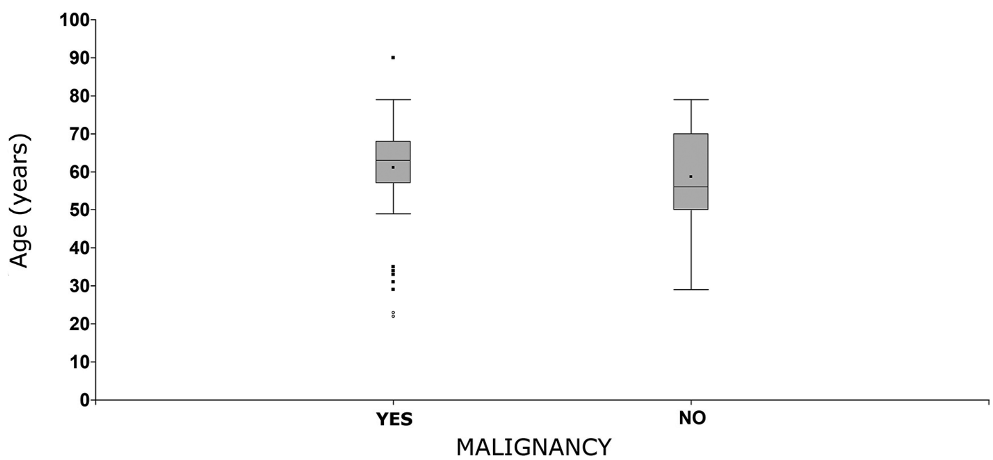
Graphic 2

The sensitivity of the study was 84.6%, and the specificity, 100%. So, by doing these studies, the probability of a Lung-RADS 3 or 4 nodule to have a positive result (malignant tumor) is 84.6%, whereas the possibility of a Lung-RADS 2 nodule to have a negative result (benign tumor) was 100%.

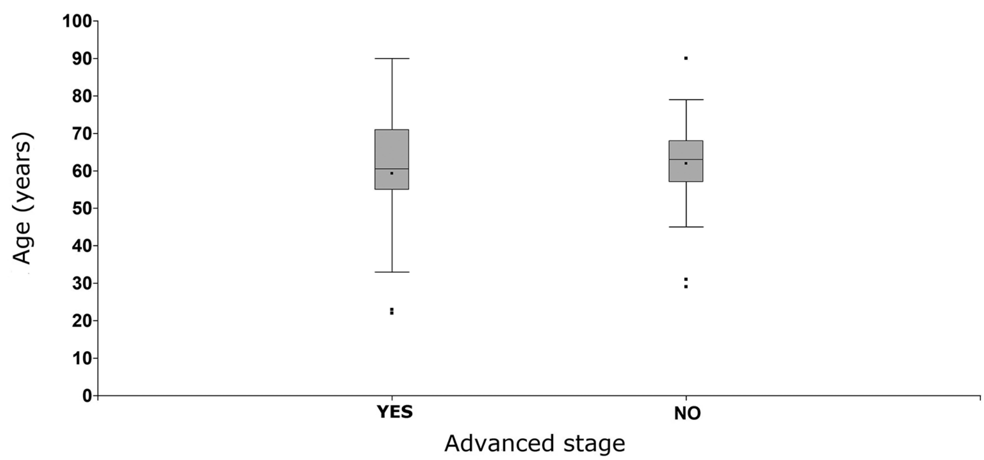
We also analyzed whether the patients' age was related to the malignancy of the tumor (**Graphic 3**). In this case, the mean age observed in each group was similar and the differences weren't statistically significant (p-value: 0.1963). The mean age in the group of patients with malignancy was 61 ± 14 years, whereas the group without malignancy had a mean age of 59 ± 13 years.

The same analysis was carried out to observe if there was any relationship between the stage of the tumor and the age of the patient. Patients with advanced stage had a mean age of 59 ± 17 years, and those without an advanced stage had a mean age of 62 ± 12 years. The differences observed weren't statistically significant (p-value: 0.7374) (**Graphic 4)**.

In patients with malignant tumors, we analyzed if the stage of the tumor, whether it was at an advanced or early stage could be related to the classification obtained with the Lung-RADS (**Graphic 5**). In patients with Lung-RADS 3 classification there weren't any cases of advanced stage tumors. Among patients with Lung-RADS 4A there were two advanced-stage cases (which accounted for 33.3% of the patients of that group). Among Lung-RADS 4B and 4X patients, the percentages of advanced cases were similar: 42.9% and 41.1%, respectively. Results weren't statistically significant (p-value: 0.7090).



Graphic 3



Graphic 4

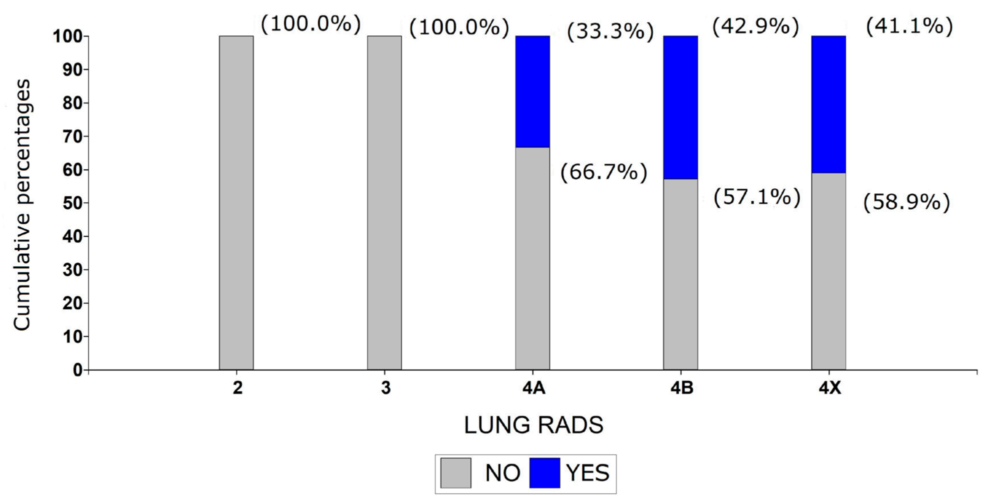
Finally, we evaluated if there was any association between the stage of the tumor and the classification obtained with the Lung-RADS system in patients with malignant tumors, according to the density shown in the studies. In patients with malignant tumors, we only observed cases of solid and mixed density (**Table 4**).

None of the patients with mixed density (n=7) showed advanced stages.

In patients with solid density, the differences observed between advanced and early stage weren't statistically significant (p-value: 0.8116).

Patients with Lung-RADS 4A with advanced-stage tumors represented 50% of that group (n=2), whereas in patients with Lung-RADS 4B and 4X, the percentage was 50% (n=3) and 42.6% (n=23), respectively.

In the descriptive study we observed cases in which after monitoring it was necessary to recategorize the Lung-RADS and thus change the diagnostic/therapeutic approach.



Graphic 5

TABLA 4. Association between the stage of the tumor and the classification obtained with Lung-RADS in patients with malignant tumors

Density	Advance stage	Lung-RADS				Total	p-value
		3	4A	4B	4X		
Solid	No	0	2	3	31	36	0.8116
	Yes	0	2	3	23	28	
	Total	0	4	6	54	64	
Mixed	No	2	2	1	2	7	–
	Yes	0	0	0	0	0	
	Total	2	2	1	2	7	

One of the patients of the Lung-RADS 2 category showed recategorization to 4A for an increase in size and change in the density of the lesion, followed by surgery and diagnosis of pulmonary adenocarcinoma. Then continued with follow-ups with annual tomographic studies.

Another patient with a pulmonary nodule also categorized as Lung RADS 2 in the first instance showed a subsolid nodule that remained stable for 4 years (in this case a review was carried out of previous tomographic studies), identifying certain growth after that time. It was treated with surgery and the definitive diagnosis was lepidic growth adenocarcinoma.

On the other hand, some patients were categorized as Lung-RADS 3 in the first instance and then recategorized as Lung-RADS 4 due to the growth of the lesion, observed in 2 patients, with subsequent surgery and diagnosis of lung cancer in both cases.

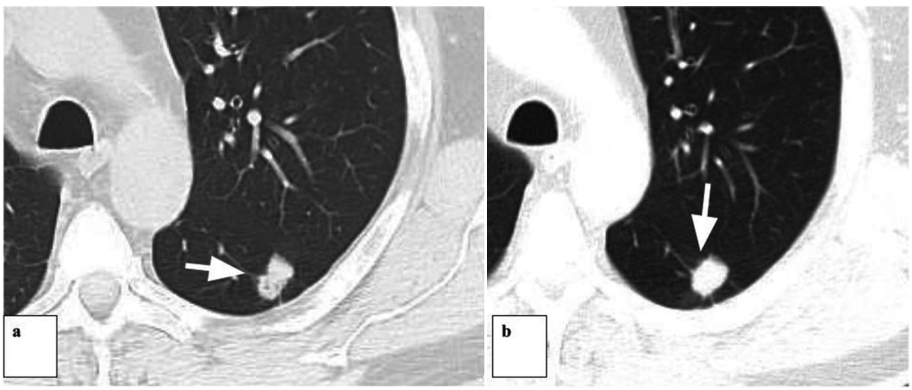


Figure 2. CT with lung window (bone filter, high resolution): control of pulmonary nodule of the apical segment of the left lower lobe. (**a**) shows the hypodense fatty element (arrow). A subsequent study performed one year later (**b**) showed the disappearance of the low-density content and moderate growth, with a mild modification in the morphology and spiculated borders (arrow), thus it was recategorized as Lung-RADS 4A.

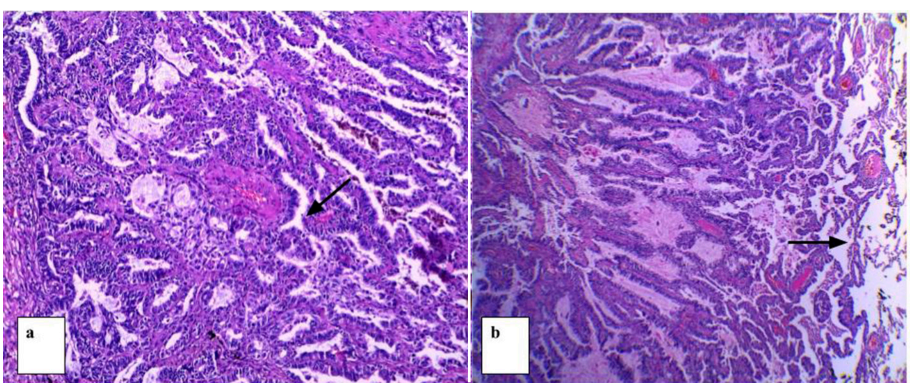


Figure 3. Microscopy of the patient of the case shown in **Figure 1** (staining with hematoxylin and eosin): Atypical cell proliferation at the alveolar level with areas of invasive adenocarcinoma (arrow) (**a**), with initial increase. With a larger increase, presence of regions with normal alveolus with AAH (atypical adenomatous hyperplasia) in some areas (arrow) (**b**).

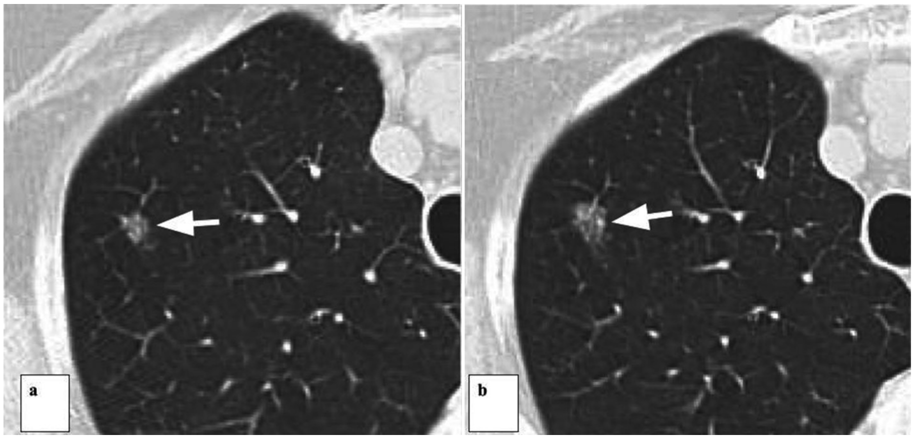


Figure 4. CT with lung window (bone filter, high resolution): patient with subsolid nodule categorized as Lung RADS 2, with annual follow-ups. (**a**) shows the nodule of the tomographic study of 2014 (arrow). (**b**) shows the 2018 study. Certain growth of the lesion could be observed (arrow), so it was decided to perform surgery.

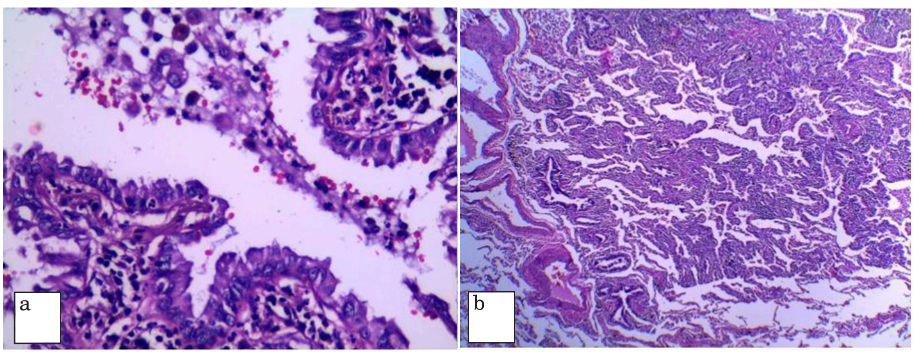


Figure 5. Anatomopathological results of the patient of **Figure 4**. Staining with hematoxylin and eosin (larger increase in **a** and smaller increase in **b**): Atypical cell proliferation of type II pneumocytes at the alveolar level. Lepidic growth adenocarcinoma in situ.

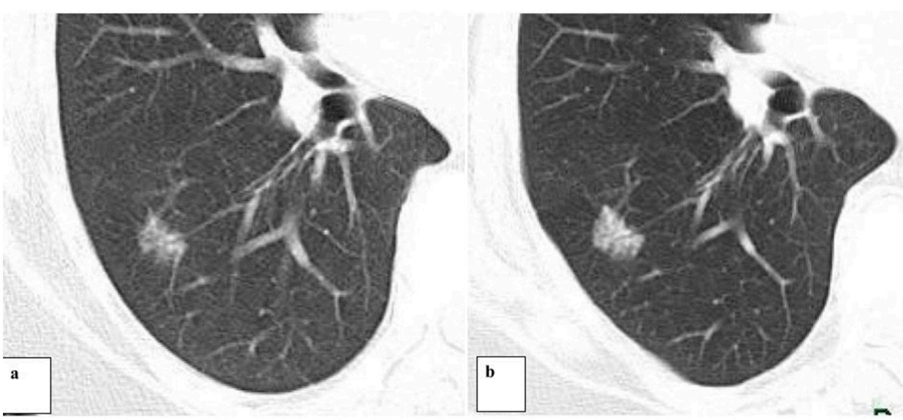


Figure 6. CT with lung window (bone filter, high resolution). Lung-RADS 3 subsequently recategorized as Lung-RADS 4: follow-up of a subsolid nodule, observing growth of the lesion and increase in density (from 2016 in **a** and 2018, in **b**) followed by resection (anatomopathological result, lepidic adenocarcinoma).

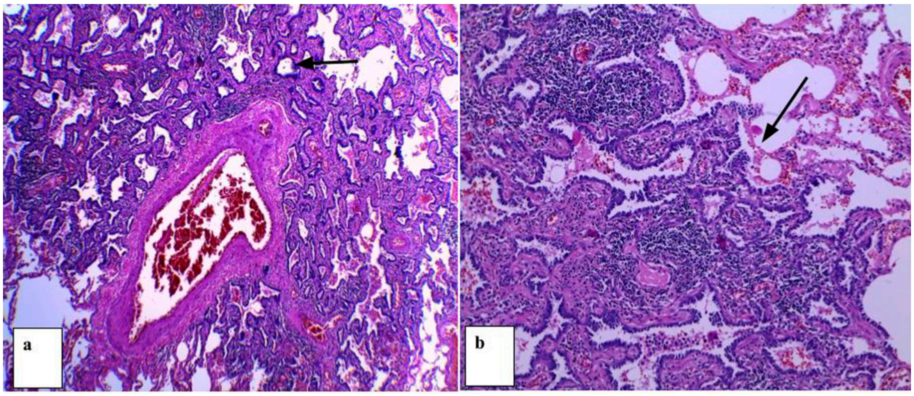


Figure 7. Anatomopathological results of the patient of **Figure 6**. Staining with hematoxylin and eosin (larger increase in a and smaller increase in b): atypical alveolar proliferation: diagnosis of lepidic growth adenocarcinoma.

One of the patients who presented a subsolid nodule with a central solid component of 6 mm in diameter categorized as Lung-RADS 4A underwent a percutaneous biopsy under tomographic guide, with a histopathological diagnosis of AAH (atypical adenomatous hyperplasia). Follow-up done 6 months later showed that the lesion was stable; continued with periodic follow-ups by CT, and recategorized as Lung RADS 3.

Another patient categorized as Lung RADS 4X underwent a percutaneous biopsy under tomographic guide and was diagnosed with hypersensitivity granulomatous alveolitis.

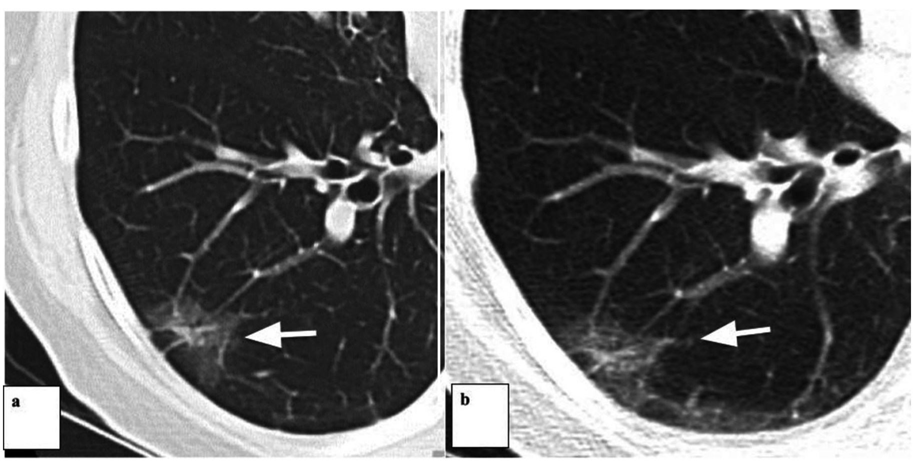


Figure 8. Chest CT in lung window and high resolution: subsolid nodule with central solid component, categorized as Lung-RADS 3 (arrows in **a** and **b**). Percutaneous biopsy under tomographic control, with AAH as a result. Performed after 6 months, determining lesion stability. Continues with periodic follow-ups.

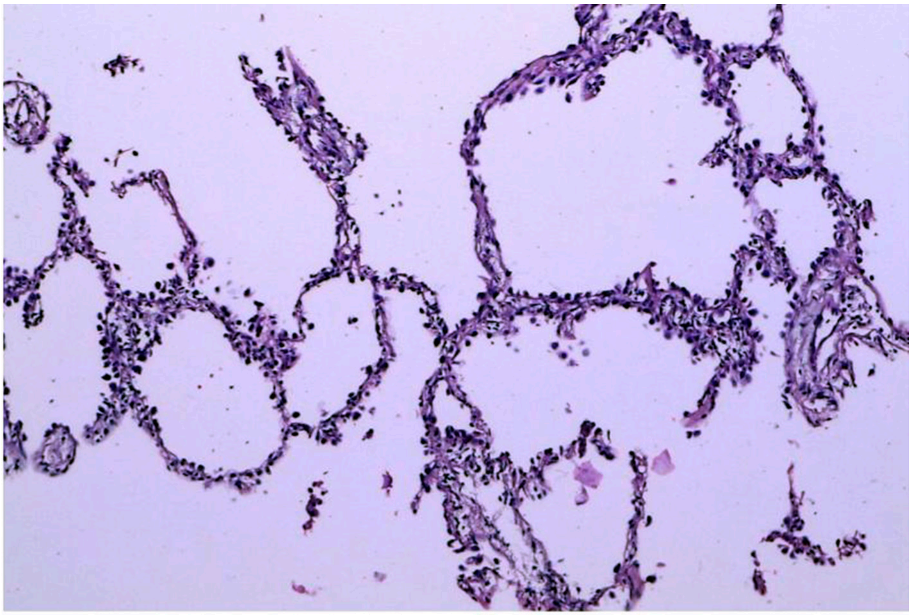


Figure 9. Anatomopathological results of the patient of **Figure 8**. Staining with hematoxylin and eosin: the cells of the alveolar lining are replaced by low, cube-shaped rounded cells with uniform nuclei, variably atypical, scarce cytoplasm and minimum mitotic figures. Atypical proliferation of cube-shaped cells of ≤ 0.5 cm throughout the alveoli. Final diagnosis: AAH.

Figure 10. Chest CT with lung window, bone filter and high resolution: pulmonary nodule with spiculated borders, categorized as Lung-RADS 4X. An increase in the size of the lesion could be observed 3 months after the first control (**a**). A percutaneous biopsy guided by tomography was performed (**b**), with hypersensitivity granulomatous alveolitis as anatomopathological result.

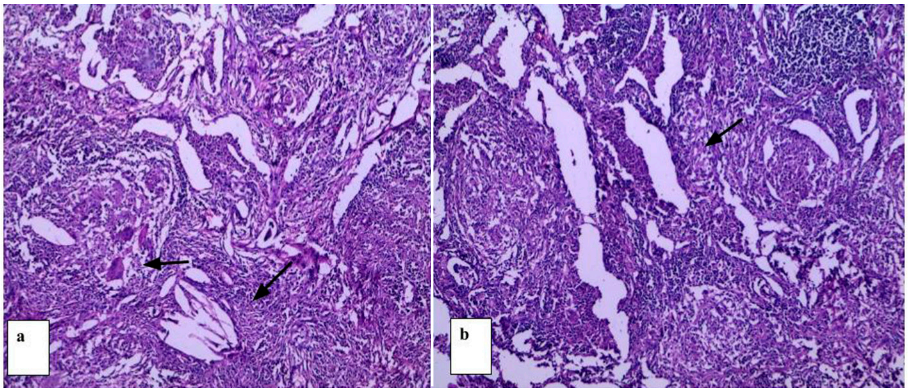


Figure 11. Anatomopathological results of the patient of **Figure 10**. Staining with hematoxylin-eosin, (larger increase in **a** and smaller increase in **b**): granulomas with giant multinucleated giant cells in **a** (arrow head), with cholesterol cleft evidenced in **b** (arrows).

Figura 12. TC de tórax con ventana pulmonar, con filtro óseo y alta resolución (a) y con ventana de mediastino pos inyección de contraste e-v (b): lesión sólida, con bordes espiculados, con aspecto de masa, con algunos cambios retráctiles cicatrizales, localizada en el sector medio del segmento apicoposterior del lóbulo superior izquierdo. Cirugía y Anatomía Patológica: Adenocarcinoma Invasor

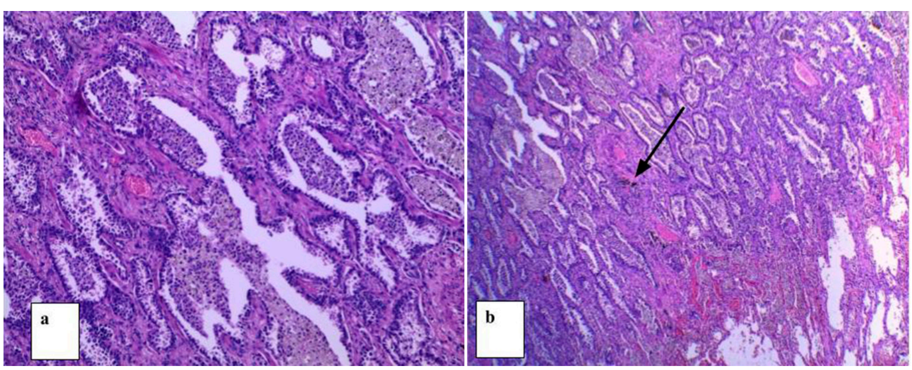


Figura 13. Anatomía patológica correspondiente al paciente de la Figura 12. Tinción con Hematoxilina-eosina, (mayor aumento en a y menor aumento en b): proliferación celular atípica, correspondiente a un Adenocarcinoma Invasor. En b, pueden evidenciarse también algunas células con hemosiderosis (flecha).

Discussion

The evaluation of pulmonary nodules has significantly developed in the last years for the purpose of reducing morbidity and mortality, looking for the timely and early detection of lung cancer and finding the most suitable treatment for each particular case.[3] For some time the characteristics of these nodules have been evaluated in search for answers to achieve the optimum management of the pulmonary nodule,[4] taking into account the size, borders and usefulness of specific methods to that end. The first important breakthrough on this subject was made by the NTLS (National Lung Screening Trial), the first randomized multicenter study to compare lung cancer screening in chest X-ray with low-dose computed tomography, showing the possibility of detecting lung cancer at early stages,[4] with good survival in patients with surgical resection (5-year survival rate of 70%). After this study, several scales were created to classify pulmonary nodules and avoid excess of treatments and invasive procedures and radiation therapy. At present, the most widely used methods for the follow-up of pulmonary nodules are the Lung-RADS system and the recommendations on pulmonary nodules of the Fleischner Society and the British Thoracic Society guidelines[5]. All of them share similar criteria and are based on the morphologic suspicion of malignancy that includes the density of the nodule (solid, partially solid or with ground-glass), the size and, when available, growth or evolution, which can be applied in different groups of patients.

On the other hand, these recommendations clarify the situation helping the specialist provide specific and precise information to the patient, also reducing negative psychosocial factors[6].

In this regard, we must explain that, despite the fact that smoking is an important underlying factor in the detection of lung cancer, it is not included in this study because its objective was to assess the score with no additional data.

Also, the different guidelines share some practical points for a more specific classification. One of them, the fact that the nodule shall be measured in the lung window, with 1.5 mm thick cuts and obtaining an average size if there is irregular morphology[7].

The Lung-RADS system[8] is currently applicable to lung cancer screening; it follows the classification method of breast cancer and turns continuous data into categorized information according to the systematic grading of the nodules by 4 basic categories determined by the morphologic suspicion of malignancy, taking into account the most suspicious nodule if there is more than one[9]. Also, the Lung-RADS system has recommendation guidelines for the follow-up of particular cases where patients cannot be categorized specifically for having ambiguous scenarios[10]; however, those scenarios weren't suggested in the cases included in this study because these guidelines have been used outside a screening program.

In Argentina there isn't any real published information about screening for early detection of nodules and it isn't usually used in routine studies. Nevertheless, given the very high incidence and accidental detection of pulmonary nodules in routine exams, the Lung-RADS system was applied to the patients of this series for the study of pulmonary nodules discovered by other causes or as a consequence of individual search of tumor disease, because since it has a numerical scale, it provides a more practical classification compared to other available guidelines with the same objective, allowing for better dialog and understanding between the different specialists involved in the management of pulmonary nodules.

According to what is established in the guidelines, small solid nodules, or nodules associated with a lepidic component, or with central or popcorn calcifications (Lung-RADS 1) are usually hamartomas or granulomas, and remain stable. In this study, patients categorized with Lung RADS 1 were excluded, but we included those with Lung RADS 2, that is to say, small nodules (more than 4 mm). Among the nodules that were evaluated in this series of patients (categorized as Lung-RADS 2), there was one exception due to the need to recategorize and the final malignancy finding; a percutaneous needle biopsy was performed, followed by surgery, considering the growth and morphologic change of the nodule, with adenocarcinoma as final diagnosis. So, despite the initial clinically low-risk staging, it is necessary and very important to do the follow-ups indicated by currently available guidelines within the suggested time period, in the event of a Lung-RADS 2 false negative.

In fact, many patients needed to be recategorized during subsequent check-ups. A study done in the National Lung Cancer Center Hospital in Tokyo, Japan, explains that subsolid nodules of less than 5 mm and with pure ground-glass pattern are mostly lesions of atypical adenomatous hyperplasia (AAH). According to the anatomopathological guidelines, they represent a precursor lesion of adenocarcinoma, because they are atypical proliferations of less than 0.5 mm of cube-shaped cells throughout the alveoli and in a large number of cases they have been observed in association with pieces of adenocarcinoma.[12] Some of those lesions may show an increase in their size or may develop a solid component after 3 to 5 years approximately; that is why some guidelines do not recommend annual follow-up[4].

Another study conducted in Tokyo also associated the development of AAH with a genetic predisposition and has proven its coexistence with malignant lung lesions, both primary and secondary, also stating that, despite the fact that smoking doesn't play a part in its appearance, it does in its transformation and evolution towards a neoplastic lesion[13].

The findings of this study correlate with this data. Follow-up was administered for 4 years in 2 patients, and an increase in the size of the nodule was seen in the last check-up, resulting in the recategorization of the Lung-RADS and the decision to perform surgical resection. As an anatomopathological result, the diagnosis was early-stage lepidic adenocarcinoma.

In our statistical analysis, we studied the association between the Lung-RADS classification obtained and the presence or absence of malignancy in the anatomopathological examination (**Figure 2**). 100% of the cases classified as Lung-RADS 2, currently receiving annual follow-ups, were free from malignancies. But this percentage started to decrease as the Lung-RADS classification score got higher. Among patients with Lung-RADS 3, only 22% showed malignancy; in Lung-RADS 4A this percentage increased to 67%; and in patients with Lung-RADS 4B it increased to 77%. 98% of patients with Lung-RADS 4X showed malignancy. The results of these associations between the tomographic/clinical categorization and histopathology were statistically significant (p-value <0.0001).

Likewise, an article published in 2016 by the journal of the American College of Radiology showed that the ACR application, Lung-RADS, increased the positive predictive value in a cohort of CT lung screening by a factor of 2.5, at 17.3%, without increasing the number of tests with false negative results[15].

It is possible that the insufficient number of patients is a weakness of this work, but we can deduce that the use of a categorization system such as Lung-RADS is crucially important for the follow-up of pulmonary nodules, considering that patients who underwent tomographic check-ups according to the corresponding category and showed visible changes in the tomography were benefited from early diagnosis with good survival; and patients with early stage nodules with ground-glass or mixed component remained stable and showed no signs of progression when data were collected. (n = 12).

Patients diagnosed with early stages underwent surgery. Only 27% of the patients (n=27) were at advanced stages of the disease at the moment of the diagnosis.

On the other hand, patients whose images showed a benign aspect are still receiving annual follow-ups without invasive methods, thus making the patient feel more at ease.

Only one of the patients categorized as Lung-RADS 4 had a diagnosis of benignancy, of infectious origin; he/she received specific treatment and didn't show any alterations in subsequent check-ups up to the end of this research.

Patients with nodules categorized as Lung-RADS 4 had the possibility to undergo early treatment without any subsequent check-ups or delays, and in some cases, they could use more specific methods such as PET or lung biopsy to obtain an accurate anatomopathological diagnosis before determining the approach to be used or before starting their treatment such as chemotherapy or neoadjuvant therapy.

Pulmonary diseases, mostly lung cancer, have become stronger in the last years due to some factors not necessarily related to smoking: there are histological types of cancer that affect not only smokers (for example, adenocarcinoma) but also non-smokers, since environmental pollution, work and lifestyle are important factors with an essential role in the development of the disease, apart from smoking. The contribution of new technologies, for example the volumetric multi-slice computed tomography of thin slices as well as the possibility to use low doses of radiation force current physicians to put all their efforts into helping the patient, with the aim of prolonging his/her survival and improving his/her quality of life, with the obligation to keep their knowledge up-to-date and use such knowledge to provide information, education and the best patient care. Thus, it is possible to have medical advances and include lung cancer in our screening scheme using the suitable guidelines for the purpose of detecting this disease at early stages.

Approximately half of lung cancers are presented as advanced disease as soon as they are diagnosed, with a 5-year average survival of 17%. Timely detection and optimum treatment of lung cancers at their early stage are essential, since patients with localized disease increase their 5-year survival to 55%. To do that, it is necessary to use screening systems for cancer detection that are not yet established in healthcare systems in Argentina, as indicated before. However, by applying the criteria of the guidelines set for the categorization and follow-up of pulmonary nodules incidentally discovered in conventional studies, it is possible to contribute to good patient follow-ups with a higher probability of detecting the malignant disease at early stages.

Conclusion

The application of the Lung-RADS system to this series of patients has shown a good management of patients' follow-up with surgical resections in some cases and an expectant approach in others, providing certain security mostly avoiding the use of unnecessary aggressive treatments.

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