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Lung-RADS used in Lung Cancer Screening: Does granulomatous disease make a difference in a developing country?

Lung-RADS usado no rastreamento do câncer de pulmão: a doença granulomatosa faz diferença em um país em desenvolvimento?

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ABSTRACT

To analyze the outcomes of low-dose computed tomography (LDCT) lung cancer screening using Lung CT Screening Reporting and Data System (Lung-RADS) in a cancer center located at an endemic granulomatous disease region. Retrospectively reviewed the medical records of patients submitted to baseline LDCT lung cancer screening program at a Brazilian cancer center. The eligibility criteria were the same as those for the National Lung Cancer Screening Trial (NLST). The criteria for image findings were those classified according to Lung Imaging Reporting and Data System (Lung-RADS) assessment categories. From May 2017 to April 2018, 552 individuals submitted to baseline LCDT lung cancer screening program, 265 of these were not eligible and 287 were matched. The mean age of 61.7 years (SD, 5.4), the proportion of current smokers was 99.6% (286 participants) with a mean of 45.3 pack-year (SD, 17.8). Negative LDCT scans were reported in 207 (72.1%) patients. Positive LDCT scans were reported in 80 (27.9%) individuals classified Lung-RADS category 3 (19.1%), 4A (5.6%), 4B (2.1%) or 4X (1.0%). In 9 cases had a CT follow-up, 7 of these had stable nodules and 2 had nodules increased. In 4 cases, were indicated percutaneous biopsy and half of these were confirmed as lung cancer. Despite the higher prevalence of lesions on categories 3 and 4A, the use of Lung-RADS allowed to stratify the findings and standardize management decisions in LDCT screening for lung cancer, which corresponds to 0.7% of prevalence in the present study, in areas of endemic granulomatous disease.
Keywords: Lung neoplasms; Early detection of cancer; Tomography scanners.

RESUMO

Analizar o rastreamento de câncer de pulmão por tomografia computadorizada de baixa dose (TCBD) utilizando o sistema Lung Imaging Reporting and Data System (Lung-RADS) em um centro de câncer localizado em uma região endêmica para doença granulomatosa. Foram analisados retrospectivamente os prontuários de pacientes submetidos ao programa de rastreamento de câncer de pulmão por TCBD em um centro de câncer brasileiro. Os critérios de elegibilidade foram iguais aos do *National Lung Cancer Screening Trial* (NLST). Os critérios para achados de imagem foram classificados de acordo com as categorias de avaliação do Lung-RADS. De maio de 2017 a abril de 2018, 552 indivíduos foram submetidos ao programa, sendo 265 deles não elegíveis e 287 elegíveis. A idade média foi de 61,7 anos (DP, 5,4), a

proporção de atuais fumantes foi de 99,6% (286 participantes) com média de 45,3 maços/ano (DP, 17,8). Exames negativos foram relatados em 207 (72,1%) TCBD realizadas. Exames positivos foram relatados em 80 (27,9%) indivíduos, sendo classificados como Lung-RADS categoria 3 (19,1%), 4A (5,6%), 4B (2,1%) ou 4X (1,0%). Foram acompanhados por TC 9 casos, 7 deles apresentaram nódulos estáveis e 2 apresentaram nódulos que cresceram. Em 4 casos, foi indicada biópsia percutânea e em metade destes foi confirmado câncer de pulmão. Apesar da maior prevalência de lesões nas categorias 3 e 4A, o uso do Lung-RADS permitiu estratificar os achados e padronizar as decisões de manejo nos casos de rastreamento de câncer de pulmão por TCBD, possuindo 0,7% de prevalência neste estudo.
Palavras-chave: Neoplasias pulmonares; Detecção precoce de câncer; Tomografia computadorizada.

INTRODUCTION

Lung cancer (LC) is the leading cause of cancer death around the world, affecting more than 1.7 million deaths per year.[1] According to the International Agency for Research on Cancer, 1.6 million of new LC cases are diagnosed each year worldwide.[2] In Brazil, 31.270 new LC cases were estimated in 2018, corresponding to an estimated risk of 18.16 per 100,000 men and 11.81 per 100,000 women. LC is the second and fourth cancer most frequent for men or women, respectively.[3,4] The main primary types are denominated like small-cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). NSCLC is the most common, affecting for 80-85% of cases and has three histological subtypes: adenocarcinoma (40%), squamous cell carcinoma (25-30%) and large undifferentiated carcinoma (10-15%). SCLC accounts a small percentage (15-20%) of all LC cases, besides that is an aggressive tumor which justifies the mortality rate in up to 25%.[5,6]

Adenocarcinoma and SCLC have strongest association with cigarette smoking. It is known that tobacco smoking is the major etiological factor, affecting approximately 85% of LC cases.[4] However, a small percentage of smokers develop LC suggesting a multifactorial cause, such as genetic factor, previous respiratory disease, viral infections, occupational exposure to carcinogens, estrogen, diet and obesity, environmental air pollution, age and family history of LC.[5] Therefore, the National Lung Screening Trial (NLST), a randomized trial of screening showed that low-dose computed tomography (LDCT) decreased LC-specific mortality rate by at least 20% compared with chest X-ray screening, using a methodology rigorous conducted by the National Cancer Institute. This trial investigated patients at high-risk of LP, considering individuals between 55 and 74 years of age, current (at least 30 pack-year) or former smokers (quit within 15 years).[7] The United States Preventive Services Task Force has recommended annual screening for LC with LDCT to asymptomatic adults who are at average or high risk for lung cancer (current or former smoker).[8]

The Lung Imaging Reporting and Data System (Lung-RADS) is a structured decision-oriented reporting system designed to reduce the rate of false-positive examination results. Lung-RADS discriminates the variety of nodules regarding size and morphology, classifying nodules into categories 0-4 and findings other than nodules as modifiers X, C and S. It serves as a shorthand language contributing to discuss the nature and implications of imaging findings by the multidisciplinar team. The LC screening studies have proposed the nodule management protocol based on parameters specified by the thoracic oncology groups or strategies recommended by the Fleischner society.[7, 9-12] In Brazil, the LC screening is not well defined by the public health practice, however the First Brazilian Lung Cancer Screening Trial (BRELT1) reported 312 participants (of 790 cases) were positive LDCT scans, with nodules larger than 4 mm.[11] The large number of positive scans in brazilian patients could reflect on the high incidence of tuberculosis. Therefore, LC screening using LDCT and the nodule management protocol could garantee the effectiveness of screening to the brazilian population.

The aim of this article is to analyze the outcomes of low-dose computed tomography (LDCT) lung cancer screening using Lung CT Screening Reporting and Data System (Lung-RADS) in endemic granulomatous disease region.

MATERIALS AND METHODS

Patients

Participants from Lung Cancer Screening Program in a cancer center were enrolled on May 2017. After that, we retrospectively reviewed the medical records of patients submitted to baseline LDCT lung cancer screening program at A.C. Camargo Cancer Center, between May 2017 and April 2018. Inclusion criteria included patients who matched the NLST eligibility criteria,[7] as follows: patients between 55 and 74 years, had a history of cigarette smoking of at least 30 pack

years, and, if former smokers, had quit within the previous 15 years. Patients who had undergone chest CT within 18 months before enrollment, who had previously received a diagnosis of lung cancer, recent hemoptysis, or who had an unexplained weight loss of more than 6.8 kg (15 lb) in the preceding year were excluded. The study was approved by the institutional Research Ethics Committee.

Low-Dose Computed Tomography

All CT examinations were acquired using a multidetector CT scanner with minimum of four channels (Philips, Amsterdam, Netherlands). The average effective dose of 0.30 mSv and mean Dose Length Product (DLP) of 21.3 mGy/cm.[2] The images were obtained at end-inspiration using a 64 x 0.5 mm collimation, FOV of 36 cm, table speed of 39.37 mm/s, rotation time of 0.5 s, 120 kVp, pitch of 0.987:1, noise index of 17.36.

Two experienced radiologists in thoracic diseases with 10 and 15 years of experience each, who were blinded to the clinical information. Both reviewed the images and evaluated as negative (Lung-RADS 1 or 2) or positive (Lung-RADS 3 or 4) screening CT according to Lung-RADS assessment categories.[12] Discordant findings were resolved by consensus. Nodular findings included characteristic of each nodule considering location (lobe and pulmonary segment), size, atenuation (soft tissue, calcification and fat), morphology (solid, part solid, non-solid) and margins (regular, lobed, spiculated).

The medical team informed patients about the results of the LDCT examinations as well as the suspicion for lung cancer. Patients with diagnostic confirmed lung cancer were referred for oncological treatment via the Brazilian Unified Health Care System or private health care system.

Statistical analysis

Patients were classified according to their imaging findings as negative or positive screening CT and the nodules were classified as solid, part solid or non-solid. All data were compiled in Microsoft Excel and presented as mean ± standard deviation. (SD).

Compliance with Ethical Standards Conflict of interest

No conflicts exist for any of the authors.

RESULTS

From May 2017 to April 2018, 552 individuals submitted to baseline LCDT lung cancer screening program. Of these individuals, 265 patients were not included because they did not match the NLST eligibility criteria due low smoking load, symptomatic patients, cancer diagnosis and age under 50 years. The remaining 287 individuals matched the NLST eligibility criteria, showing a mean age of 61.7 years (SD, 5.1), the proportion of current smokers was 99.6% (286 participants) with a mean of 45.3 pack-year (SD, 17.8). The proportion of former smokers was 0.34% (1 participant) with 16 years of smoking cessation. However, women represented 52.6% (151 participants) of the study population (Table 1).

Table 1: Clinical characteristics of patients

Variables	Overall n (%)
Study population	**287 (100)**
Age (years)	
Mean ± SD	61.7 ± 5.1
Range	55 – 74
Gender	
Male	136 (47.4)
Female	151 (52.6)
Smoking status	
Former smokers	286 (99.6)
Current smokers	1 (0.34)
Cumulative smoking	
Mean ± SD	45.3 ± 17.8
Range	30 – 135

Most patients (n=207; 72.1%) had a negative screening CT (Lung-RADS categories 1 or 2) with nodules measuring 3 to 6 mm in size. The remaining 80 (27.9%) individuals showed positive screening CT, considering 19.1% in Lung-RADS category 3, 5.6% in Lung-RADS category 4A, 2.1% in category 4B and 1.0% in category 4X (Table 2). The CT nodule findings (Table 2) were evaluated in 218 (75.9%) individuals, presenting solid (64.8%), part solid (2.7%) and non-solid nodules (8.3%). The average size of solid nodules was 5.5 mm ± 7.1. However, most patients (59.1%) presented solid nodules smaller than 6 mm. All patients classified into Lung-RADS categories 4A and 4B presented solid nodules bigger than 8 mm and 50 individuals Lung-RADS category 3 presented nodule size between 4 to 8 mm. The part solid nodules were visualized in 75% of individuals

classified into Lug-RADS category 3, varying the nodule size in 5 to 12 mm. The non-solid nodules were seen in 58.3% of individuals classified into Lung-RADS category 2 followed by individuals classified in category 3 (29.1%), considering nodule size smaller or bigger than 20 mm (Table 2).

The pulmonary emphysema followed by aortic or coronary atheromatosis were the additional findings found in most patients (n=97) submitted to LCDT independent of the category. One patient classified as Lung-RADS category 3S had an incidental diagnosis of chest wall lymphoma, confirmed after percutaneous biopsy. Patients in Lung-RADS category 4A (n=9) had a CT follow-up, most of them (n=7) showed stable findings and in two patients the nodules increased in size on follow-up CT. In these cases, the histologic results confirmed the diagnosis of lung cancer (prevalence of 0.7% of all screened patients) classified as adenocarcinoma and carcinoid (Figure 1).

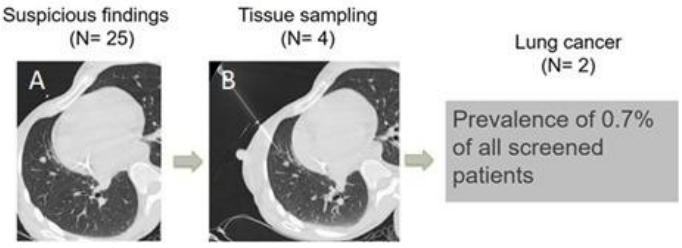

Figure 1. Imaging findings using LDCT. (A) Suspicious findings. (B) Tissue sampling.

Table 2: Lung-RADS category and imaging findings

Lung-RADS category	**Overall n (%)**	**Solid nodules**	**Part solid nodules** *Overall n (%)*	**Non solid nodules**
0	None	None	None	None
1	83 (28.9)	1 (0.5)	None	None
2	124 (43.2)	110 (59.1)	1 (12.5)	14 (58.3)
3	55 (19.1)	50 (26.8)	6 (75)	7 (29.1)
4A	16 (5.6)	16 (8.6)	None	1 (4.1)
4B	6 (2.1)	6 (3.2)	1 (12.5)	2 (8.3)
4X	3 (1.0)	3 (1.6)	None	None
Total	287 (100)	185 (64.5)	8 (2.7)	24 (8.3)

DISCUSSION

Screening for early LC using LDCT in high-risk individuals has the potential to significantly reduce the lung cancer occurrence and the mortality rate. Thus, the use of eligibility criteria and experienced management of detected findings following the baseline LDCT have been explored in LC screening programs to ensure that screening is cost-effective and that potential harms are minimized. However, the high incidence of granulomatous disease should be considered in an endemic region for tuberculosis.[11]

Our data presented lower positive screen rate (72.2) compared to a similar population studied in the BRELT1. Similar results were reported with use of Lung-RADS in comparison with NLST follow-up protocol. The positive screen rate was lower than in the NLST,[12] being associated to higher incidence of granulomatous disease. A total of 18 patients were submitted on follow-up CT to evaluate stable or increased nodules and none participant was submitted to positron Emission Tomography-Computed Tomography (PET/CT) or surgery. In general, only 1.3% of the patients required an invasive biopsy, lower than other studies.[11,12] Percutaneous biopsy was indicated in 4 cases and only 2 patients were diagnosed with lung cancer, showing that our lung cancer histologic distribution was consistent with other screening studies.[11,12]

Developing countries have a lower level of investment in cancer prevention compared with developed countries. Thus, there are many challenges in implementing lung cancer screening programs, such as infrastructure, trained human resources and cost-effectiveness. As in Brazil, pulmonary tuberculosis is endemic in many of these countries, increasing the number of patients with granulomas identified on screening for lung cancer, which may lead to unnecessary additional exams and invasive procedures.[13,14] In this setting, the use of standardized criteria for assessment of LDCT findings is essential to reduce overdiagnosis and costs for the health care systems.

This study has limitations related to its retrospective nature and small sample size. Many patients submitted to LCDT lung cancer screening program was excluded because they did not match the NLST eligibility criteria. The CT nodule findings were not available in all cases. As this is a retrospective study, eventually the images were not available at the PACS. Since it is a cross-sectional study and due to fund limitations, it was not

possible to assess the incidence. Despite that, our results showed that it is possible to use the Lung-RADS criteria to stratify the risk of malignancy at a lung cancer screening program, even in populations with high prevalence of granulomatous disease.

CONCLUSION

Despite the higher prevalence of lesions on categories 3 and 4A at the present study, the use of Lung-RADS allowed to stratify the findings and standardized the management decisions in LDCT screening for lung cancer at an endemic area of granulomatosis diseases.

Studies like this are essential to guide lung cancer screening protocols in particular areas that enable efficient methods of patient care.

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