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ARTIGO ORIGINAL

Lung Cancer Screening: Low-Dose Thoracic Computed Tomography Performed in a High-Risk Portuguese Population

Rastreio do Cancro do Pulmão: Tomografia Computadorizada Torácica de Baixa Dose Realizada numa População Portuguesa de Alto Risco

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ABSTRACT

Introduction: The Urgeiriça mines were once the main uranium producer in Portugal. The aim of this study was to estimate the benefit of low-dose chest computed tomography (LDCT) for lung cancer screening in former miners that were considered as being at high-risk.
Methods: A subgroup of former miners of the Uranium National Company exposed to uranium and with a smoking load greater than 20 pack-years, agreed to perform a LDCT. The Fleischner Society Guidelines were used to classify the nodules and establish follow-up.
Results: Initially, 265 former employees of the Uranium National Company were included. The mean time of employment was 15 (0 - 45) years. The non-smokers represented 50.9% and 30.2% were ever smokers; the remaining chose not to respond. One diagnosis of lung cancer was initially made. In the second phase, a subgroup of 66 former miner underwent a LDCT, 37 of whom presented pulmonary nodules. Most computed tomography (CT) scans revealed one single nodule (n = 13) and the mean size was 5 (1 - 16) mm. A suspicious 16 mm spiculated nodule was evaluated with PET/CT, and percutaneous and surgical biopsies, ultimately revealing a benign lesion.
Conclusion: The data highlights the importance of lung cancer screening in high-risk populations. This was, to the best of our knowledge, the first study performed in Portugal and can act as a bridge towards a wider implementation in the country.
Keywords: Early Detection of Cancer; Lung Neoplasms/diagnostic imaging; Tobacco/adverse effects; Tomography, X-Ray Computed; Uranium/adverse effects

RESUMO

Introdução: As minas da Urgeiriça foram, no passado, o principal produtor de urânio em Portugal. O objetivo deste estudo foi estimar o benefício da tomografia computorizada de baixa dose (TCBD) no rastreio do cancro do pulmão em ex-mineiros considerados como grupo de alto risco.
Métodos: Ex-mineiros da Companhia Nacional de Urânio com exposição a urânio e carga tabágica superior a 20 unidades maço ano, concordaram realizar uma TCBD. As recomendações da Sociedade Fleischner foram utilizadas na classificação dos nódulos e no estabelecimento do *follow-up*.
Resultados: Duzentos e sessenta e cinco ex-trabalhadores da Companhia Nacional de Urânio foram incluídos. O tempo médio de trabalho nas minas foi 15 (0 - 45) anos. Os não-fumadores representavam 50,9%, 30,2% referiram fumar ou ter fumado e os restantes não responderam. Foi diagnosticado inicialmente um caso de cancro do pulmão. Numa segunda fase, entre os 66 ex-mineiros rastreados foram identificados 37 com nódulos pulmonares, a maioria com nódulo único (n = 13) e tamanho médio de 5 (1 - 16) mm. Um nódulo espiculado de 16 mm foi avaliado por PET/TC, e por biópsia transtorácica e cirúrgica, revelando uma lesão benigna.
Conclusão: Os dados destacam a importância do rastreio em populações de alto risco. Este foi, tanto quanto é do nosso conhecimento, o primeiro estudo realizado em Portugal, e pode atuar como ponte para uma ampla implementação no país.
Palavras-chave: Deteção Precoce da Neoplasia; Neoplasias do Pulmão/diagnóstico por imagem; Tabaco/efeitos adversos; Tomografia Computorizada; Urânio/efeitos adversos

INTRODUCTION

In 1898, the discovery of radium by Marie Curie started a new chapter in nuclear physics and its application settled the foundation of radiotherapy and brachytherapy.[1] The Mines of Urgeiriça, explored by the British, began operations in 1913, and provided radium to Marie Curie's laboratory. In 1938, the discovery of nuclear fission later transformed Urgeiriça in the main uranium producer in Portugal.[2]

The most important uranium deposits in Portugal were located in the central region of the country, namely in the western part of the Iberian Massif, including the Central Corridor (Serra da Estrela, Lousã, S. Pedro de Açor, Gardunha), and extending further to Serras do Buçaco, Caramulo e Montemuro. There were several mines in these locations, such as Urgeiriça, Bica, Castelejo, Cunha Baixa, Quinta do Bispo and Pinhal de Soto.[3]

During the Second World War, the United States government became involved in Urgeiriça. Their aim was to control all the uranium that was available and therefore prevent the development of the atomic bomb by the Germans. The Portuguese-English agreement for uranium extraction in Urgeiriça ended in 1962, and afterwards uranium was no longer stockpiled in the context of the Cold War stocks and

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started to cater to Portugal's energetic needs.[2]

During the golden period (1962 - 1990), uranium was essential for those who explored it and for the workers who built their lives around this activity. In the following period, contestation regarding uranium mining began as a result of both the environmental impact of radioactivity and public and occupational health issues.[2]

The mining facilities were permanently closed in 2001. Former workers and their families faced an increased risk of lung cancer due to longstanding exposure to radioactive material.

Age and family history are known risk factors for lung cancer, although smoking has been established as the most significant since the 1960s.[4,5] Other carcinogens known to be risk factors include the exposure to asbestos, radon or uranium. The connection between lung disease and mining was recognized in European studies as early as the 16th century and subsequent reports confirmed those early observations and attributed pulmonary malignancies to high radiation levels found in the mines.[5-7]

Considering this, in 2007 the Portuguese Government approved a Health Intervention Programme addressed to the former employees of the Uranium National Company (UNC) and their families. Its coordination was regionally headed by the Department of Public Health and locally by the Public Health Units of Nelas municipallity.

In 2015, eight years after the program implementation, the Portuguese Society of Pulmonology was consulted on that matter. Considering scientific evidence published on the use of low-dose chest computed tomography (LDCT) for lung cancer screening (LCS) in high-risk groups, namely the Nacional Screening Lung Trial (NSLT)[8-11] and the Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON study),[11-13] this test was included as a diagnostic tool in the Health Intervention Program.

This study reports the start of the first lung cancer screening initiative study performed in Portugal and its aim was to estimate the benefit of LDCT in a high-risk group.

METHODS

The first phase of the study included an initial medical assessment to the former employees of the UNC and occurred in Hospital of São Teotónio, in Viseu, between the 8th of November 2007 and the 16th of February 2009.

A questionnaire validated by the department of Public Health was delivered to all participants, allowing data collection. The initial evaluation included chest x-ray, electrocardiogram and abdominal ultrasound. Laboratory tests included complete blood count, prothrombin time and activated partial thromboplastin time, erythrocyte sedimentation rate, urea, creatinine, electrolytes, glucose, cholesterol and triglycerides, uric acid, electrophoretic proteinogram, lactate dehydrogenase, thyroid stimulating hormone, triiodothyronine (T3) and thyroxine (T4), thyroglobulin, alpha fetoprotein, beta 2 microglobulin, CA-125, CA 19-9, CA 15-3, carcinoembryonic antigen (CEA), neuron-specific enolase (NSE) and a urine test.

All participants underwent annual follow-up in primary health care.

In 2015, a selected subgroup of former employees, considered at increased risk of lung cancer, both by the presence of exposure to uranium (worked directly in mining) and a smoking load greater than 20 pack-years, was included in the second phase of the study. These participants agreed to perform a LDCT for LCS after providing informed consent.

A 64 slice Siemens® equipment with the following exposure parameters was used: mAs - 78 efet; Kv 100; Collimation - 0,6 mm; Pitch - 0,7; TR - 0,33 s; CTDI - 3,50 mGy; DLP – 102 mGy/cm - Effective dose: 1.5 mSy). Reconstruction with high resolution algorithm and lung window, as well as low resolution algorithm and mediastinal window was performed.

The software for measuring pulmonary nodules through volumetry was not available in the Radiology Department at the time of the study.

The CT scans performed were reported by the two radiologists who worked together in this study and were blinded to the patients' health record.

The variables considered for the study were age, gender, smoking load, co-morbidities, working time periods in the mines and the presence of lung nodules in LDCT, as well as their characteristics, namely their number, size, and growing pattern. The Fleischner Society Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images were used to classify the nodules and establish patient follow-up.[4]

The Lung-RADS classification is recommended by the American College of Radiology and is applied in low-dose CT lung cancer screening. It was officially released in 2014 after published data from several studies, namely the NLST and the European NELSON trial.[14] The Lung-RADS criteria increased the size threshold for a positive baseline screening result from a 4 mm greatest transverse diameter to a 6 mm transverse bi-dimensional average, and therefore substantially reduced the false positive rate of the previous NSLT criteria; however, sensitivity also decreased.[15]

The Lung-RADS Version 1.1 points out the estimated prevalence rate of nodules in the general population according to the score.[16] A Lung-RADS score of 1 or 2 corresponds to a negative screening.[14] The Score of 1 refers to the presence of no pulmonary nodules or benign nodules, namely nodules with specific calcifications such as complete, central, popcorn, concentric rings and fat containing nodules. A Lung-RADS score of 2 includes nodules with a benign appearance that have a very low (< 1%) likelihood of becoming a clinically active cancer due to size or lack of growth.

This study was approved by the Portuguese Government and coordinated by the Department of Public Health. All selected former miners of the UNC had a considerable high-risk of lung cancer, both due to direct exposure to uranium (from working directly in mining) and a smoking load greater than 20 pack-years, which agreed with the scientific evidence published on the use of LDCT for LCS in high-risk groups, and therefore this study respected ethical criteria. The participants were told about the benefits and potential harms of the LDCT and gave consent to the treatment of their data/clinical information and were aware that their name would not be attached to it, thus ensuring anonymity; they also understood that their consent would not remove their rights to privacy.

RESULTS

The first phase of the study included 265 former employees of the UNC, with a mean age of 58 (32 – 92) years. Eighty-seven percent (n = 230) were male and the remaining 13% (n = 35) female.

Eighty-five-point seven percent (n = 227) answered they were non-smokers, 10.9% (n = 29) responded that were current smokers and 3.4% (n = 9) chose not to answer. In those with current smoking habits, the average smoking load was 17 pack-years. Thirty-point two percent (n = 80) were ever smokers and 50.9% (n = 135) never smoked. Fifty participants did not answer (Table 1).

The number of years of employment in the UNC was known in 95.5% (n = 253) of the participants, with a mean of 15 (0 - 45) years (Fig. 1). The professional categories described were mining, chemical treatment of uranium, motor-vehicle drivers, and administrative services.

Table 1 – Smoking status and medical conditions of the former employees of the Uranium National Company included in the first phase of the study

	n = 265	%
Smoking status		
Non-smokers	227	85.7
Current smokers	29	10.9
No answer	9	3.4
Ever smokers	80	30.2
Never smokers	135	50.9
No answer	50	18.9
Medical conditions		
Already known	**191**	**72**
Most common:		
- Hypertension	70	35
- Diabetes type 2	13	6.5
- Arthritis	10	5
Previous malignancies:	**9**	**4.5**
- Lung adenocarcinoma	1	0.5
- Squamous cell lung cancer	1	0.5
- Prostate carcinoma	2	1.0
- Colorectal cancer	2	1.0
- Squamous cell carcinoma of the skin	1	0.5
- Eyelid basal cell carcinoma	1	0.5
- Chronic lymphocytic leukemia	1	0.5
Diagnosed in the medical evaluation	**9**	**3.4**
- Type 2 diabetes	4	44.5
- Arterial hypertension	2	22.2
- Prostate cancer	1	11.1
- Lung cancer	1	11.1
- Intestinal polyps	1	11.1
No relevant conditions	**65**	**24.6**

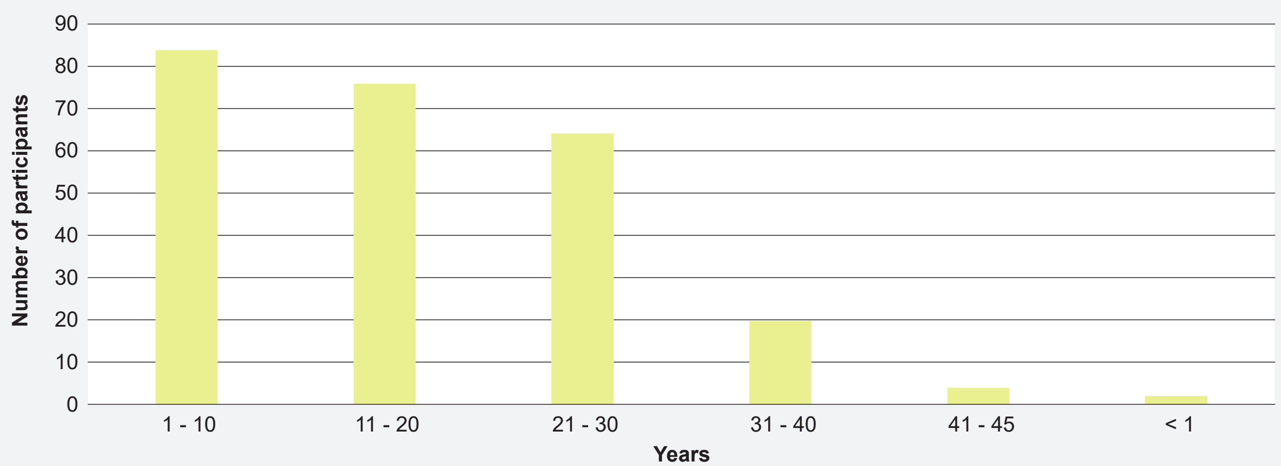

Figure 1 – Distribution for intervals of 10 years of labour of the former employees of the UNC – adapted from 2007 Health Intervention Programme addressed to former miners of Urgeiriça and their families

Table 2 – Data regarding the second phase of the study including a subgroup of former miners of the Uranium National Company

	n = 66
Smoking exposure: smoking load > 20 packs-year	66
Worked directly in mining	66
Documented pulmonary nodules in LDCT	**37**
- Solid	29
- Ground-glass	1
- Calcification	7
Location of the nodules (if multiple, it was considered the largest)	**30**
- Upper lobes	16
- Lower lobes	12
- Middle lobe	2
Nodule spiculation	**1**
Emphysema	
- Centrilobular in the upper lobes	4
Follow-up time	
- No indication for follow-up	41
- 12 months	7
- 18 months	5
- 24 months	12
- 5 years	1

Besides tobacco and uranium exposure, there was no history of thoracic radiotherapy or unequivocal known exposure to asbestos. Radon exposure was a confounding factor in this study.

Seventy-two percent (n = 191) of the participants presented to the first medical evaluation with previously known health conditions. The most frequent were hypertension (n = 70), diabetes/impaired glucose tolerance (n = 13), arthritis (n = 10) and previous malignancies (n = 9), namely two cases of lung cancer (Table 1). Regarding underlying benign pulmonary disease, three cases were identified: bronchitis, chronic obstructive pulmonary disease (COPD) and silicosis.

This initial medical evaluation included chest x-ray, electrocardiogram, abdominal ultrasound, and laboratory tests. Although the analytical parameters supported some previously known diagnoses, such as diabetes, they had limited clinical relevance for this study. New diagnoses were made in nine individuals, including one case of lung cancer.

The second phase of this study included a subgroup of 66 former miners at higher risk of developing lung cancer, who underwent LDCT. The mean age of this subgroup was 66 years (SD = ± 7.4). They were all smokers with a smoking load greater than 20 pack-years and worked directly in mining. The period of exposure was between 11 and 40 years. Thirty-seven participants had pulmonary nodules documented on LDCT, which were calcified in seven cases (Table 2).

Most positive CT scans revealed one nodule (n = 13), with a mean of two nodules detected (1 - 7) (Fig. 2). The mean size of the largest nodule had 5 (1 – 16) mm (Fig. 3) and the most suspicious one had 16 mm and presented spiculation (Fig. 2).

Among the 30 LDCT, 29 showed solid nodules and one pure ground glass nodule with no solid component. Regarding those with single solid nodules, eight scans presented a size below 6 mm and four scans within 6 - 8 mm; one single ground glass nodule had 10 mm. As for the remaining 17 low-dose scans that showed multiple nodules, in six scans the dimensions were below 6 mm, in seven scans within 6 - 8 mm and in four scans were greater than 8 mm. A suspicious nodule with spiculation (Fig. 3) was evaluated with PET/CT. The test revealed, in the apical-posterior segment of the upper left lobe, a spiculated nodule causing lung fissure pulling, with 16 x 12 mm of long axial diameter, hypermetabolic (SUV max: 2.3) and features suggestive of malignancy (Fig. 4). Therefore, a percutaneous lung biopsy was performed. The results showed a chronic inflammatory process with a fibrotic area and with no signs of malignancy. The case was discussed in a multidisciplinary team meeting, and a malignant lung tumor was diagnosed, considering the previously known risk factors and the imaging features of the lesion. Therefore, a surgical extemporaneous biopsy was performed. The anatomopathological results showed a cavitated lesion that may have corresponded to bronchiectasis, with a wall made up of inflammatory repair tissue with fibroblast proliferation and collagen deposition.

Patient follow-up was performed according to the 2017 recommendations of the Fleischner Society for incidental pulmonary nodules. In 36 out of 66 of the initial scans there were no relevant changes, and therefore the need for further imaging follow-up was not indicated. As for the remaining 30 scans, some patients underwent follow-up for 12 months, others 18 months, the majority 24 months, and one patient five years. The periods of radiological follow-up also varied, three-six months or six-twelve months and subsequently, if required, 18 to 24 months, depending on the nodules' dimension and growth, and if they were multiple or not.

Nodular growth was identified in four cases: 1 mm increase in the six-month follow-up of two patients, and 2 mm in the remaining twelve-month follow-up of two patients. Therefore, shorter intervals of surveillance were performed for 24 months. One patient, with nodular growth, also presented two new nodules with 5 and 7 mm, respectively. Attending to the small dimensions, PET-CT was not the primary option for follow-up. Subsequent control scans,

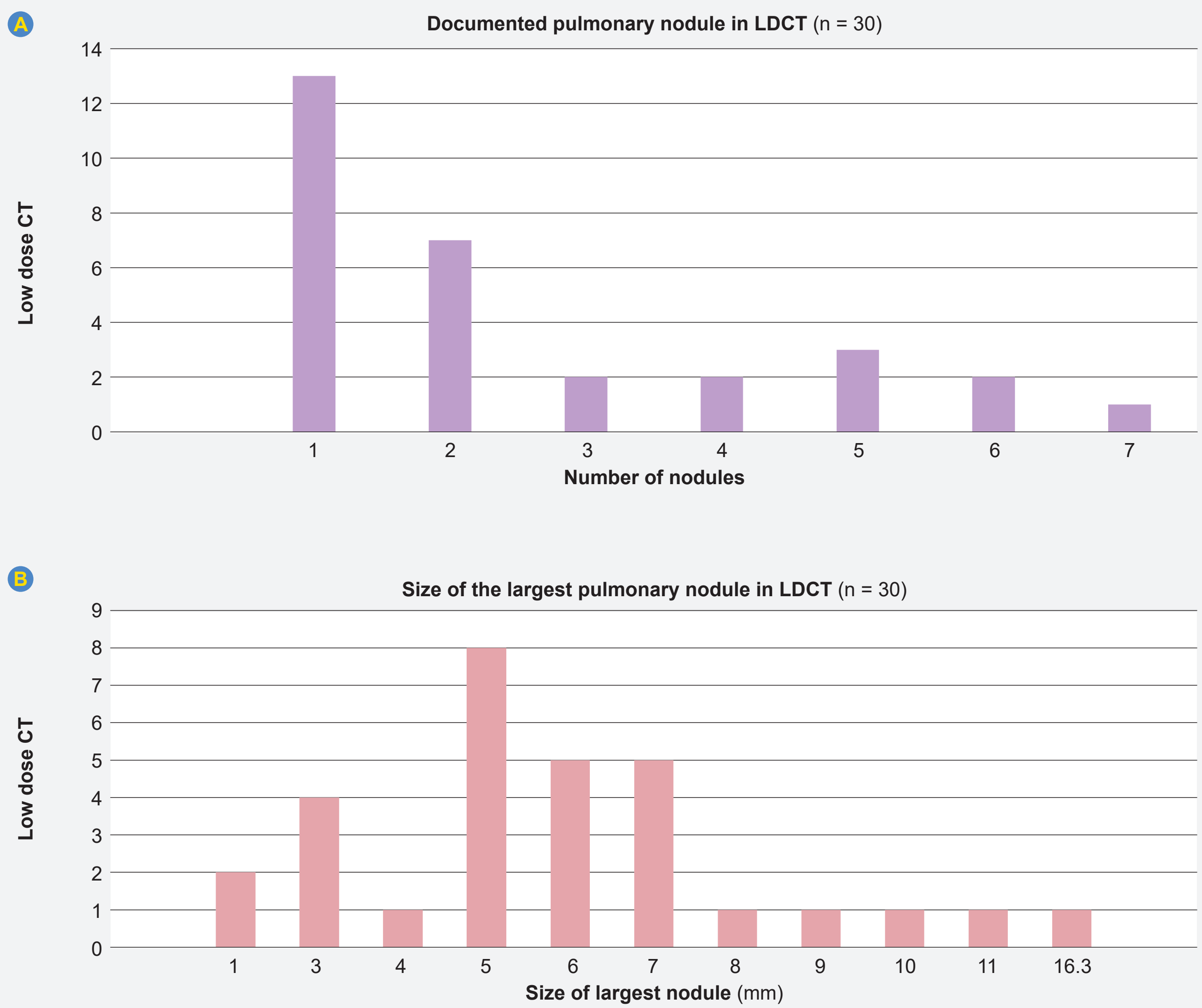

Figure 2 – Number of nodules (A) and size (B) of the largest pulmonary nodule in LDCT performed to a subgroup of 66 former miners of the UNC

in shorter intervals (three-six months), showed stability.

We also calculated the Lung-RADS Score[16] for our population and the prevalence of Scores 1 and 2 was 36/66 and 14/66, respectively, representing altogether 75.8% of the screening tests (50/66). As for the Score of 3 and 4, the prevalence in our study was of 13.6% (9/66) and 10.6% (7/66), respectively.

DISCUSSION

This study found a higher prevalence rate of pulmonary nodules among uranium former miners with a history of smoking compared with the one described in the literature for general population.[16]

Radon exposure was assumed as a confounding factor in this study, since radon results from the gaseous decomposition of uranium and radium, and therefore in uranium mining there is also simultaneous exposure to radon. Protracted exposure to radon decay products is the greatest radiation-related health risk from uranium-related mining, and is causally linked to lung cancer. A large proportion of the epidemiological studies performed, exploring adverse health effects from potential radionuclide releases from uranium mining and processing facilities, have lacked the capacity to evaluate causal inferences because of the ecological study design. Thus, assessing the potential risks of multiple combined exposures from uranium mining and processing activities is considered not feasible in practical terms.[17]

The Fleischner Guidelines were selected for lung nodule classification and to establish follow-up, even though they are formally meant to inform management of incidental pulmonary nodules.[4] The Lung-RADS classification could have been used instead, as it is similar to Fleischner's and is specifically designed for the subset of patients intended for low-dose screening studies.[14,16]

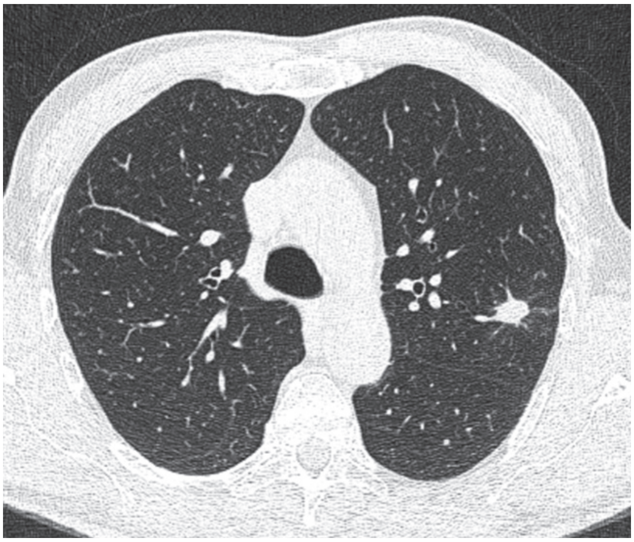

Figure 3 – LDCT reveals in the apical-posterior segment of the upper left lobe a suspect nodule with spiculation

Nonetheless, the minimum threshold size for routine follow-up in the Fleischner classification (nodules ≥ 6 mm), is also the same for a positive screening in Lung-RADS, even though the Fleischner Guidelines recommends follow-up in some nodules below 6 mm (such as with suspicious morphology or upper lobe location).[4]

Apart from that, the classifications are quite distinct, and while Lung-RADS is used in screening programs for lung cancer, the Fleischer classification is used to manage incidental nodules, and therefore separates individuals according to their risk, in low and high-risk, concerning a number of relevant factors.[4] Consequently, the time period for radiological follow-up also has considerable variations. The detection of nodular growth and increase in number are also key-points for scoring in Lung-RADS,[16] while the Fleischner recommendations do not directly include these items.

The estimated prevalence rate in the general population of a Lung-RADS Score of 1 and 2 is 90%.[16] In our group, the Lung-RADS Score of 1 and 2 altogether, presented a lower prevalence rate (75.8%), compared with the estimate for the general population (90%). A Lung-RADS Score of 3 or 4 corresponds to a positive screening. The Score of 3 suggests the presence of benign nodules, with a risk of malignancy of 1% - 2% and short-term follow-up suggested.[15,16] The estimated prevalence rate in the general population is 5%, and in this study, the prevalence rate represented a considerable higher value – 13.6% (9/66). A Lung- RADS Score of 4A or 4B incurs in a higher risk of malignancy, namely 5% - 15% and over >15%, respectively, and an estimated prevalence rate of 2% each in the general population.[14] In this study, a Lung-RADS Score of 4A was obtained in six cases: four revealing nodules with dimensions greater than 8 mm, two revealing nodular growth (increase higher than 1.5 mm), and one presenting simultaneously new nodules and growth. All these results corresponded globally to a prevalence rate of 10.6%, which is a higher figure compared with the general population. A suspicious spiculated nodule (> 15 mm) was scored Lung RADS 4B. PET/CT and a percutaneous and an extemporaneous surgical biopsies were performed and revealed a benign lesion.

These data showed a higher prevalence rate of pulmonary nodules among uranium former miners with a history of smoking compared with the one described in the literature for the general population. This fact justifies a higher need of surveillance imaging, supported by the scientific evidence previously mentioned, of the increased risk of lung malignancy in groups with exposure to known risk factors for lung cancer.

As for the suspicious nodule, and despite the benign anatomopathological result, its imaging features were suspicious: the nodule was in the upper lung lobe and had already a considerable size and spiculation. The PET-CT performed showed a hypermetabolic nodule, probably associated with the previously described inflammatory cavitated lesion with a wall made up of inflammatory repair tissue.

We could not establish comparison with the NELSON classification,[12,13] since the measurement of the nodules was volumetric, and this software was not available in the Radiology Department at the time of the study.

Several studies, particularly in the United States and Europe, indicate that LDCT is absolutely recommended in screening for lung tumours in selected individuals at high-risk,[15] as the NLST[8] and the NELSON[12] studies concluded it reduces mortality from lung cancer.

As for NSLT, the results revealed 247 deaths per 100,000 person-years in the LDCT group and the radiography group showed 309 deaths per 100,000 person-years, which represents a relative reduction in mortality from lung cancer with low-dose screening of 20%.[8,11] In consonance, the NELSON study showed that the use of CT screening for nodule volume management reduces lung cancer mortality in 26% among asymptomatic men at high risk.[11,12]

As described in systematic reviews and meta-analysis,[18] within the highest risk subgroups the number of prevented lung-cancer associated deaths are considerably higher than in the lowest risk populations who reported tobacco consumption, and therefore screening should be performed particularly in those, which was in agreement with our selected criteria.

Even though in the end the suspected nodule had been a false-positive result, this fact concurs with several studies[19] with LDCT having high false-positive rates, which results in unnecessary invasive procedures and patient anxiety. Therefore, LDCT leads to an increase in the frequency of

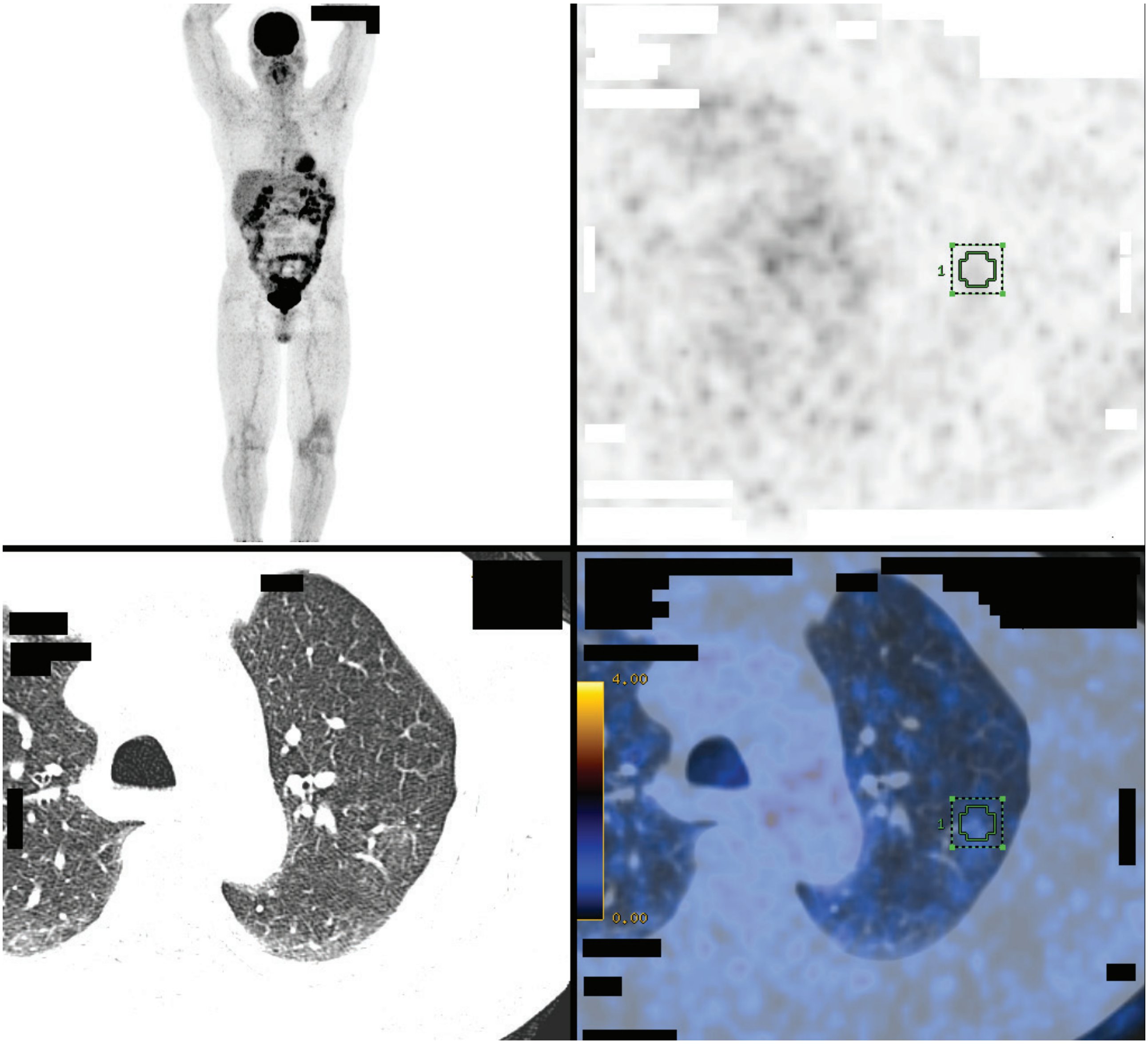

Figure 4 – CT scan and PET-CT: in the apical-posterior segment of the upper left lobe a spiculated nodule causing lung fissure pulling, with 16x12 mm of long axial diameter, hypermetabolic (SUV max: 2.3) and suggestive of malignancy

invasive procedures, such as surgery, biopsy, bronchoscopy or fine needle aspiration cytology but the data from several meta-analyses[19] showed that it does not lead to increased mortality soon after an invasive procedure compared with the control arms. Moreover, LDCT has shown statistically significant mortality benefits, expected to the influenced by the risk of lung cancer in the different target groups.

A risk stratification approach should be used in order to ensure a successful implementation of the LDCT lung cancer screening program in Europe. Therefore, the individuals that enter the screening program should also be provided with the information regarding the benefits and harms of screening and smoking cessation should be offered. Even though COPD and emphysema are the strongest lung cancer risk predictors,[20] they had been less well described in this study: four patients presented with centrilobular emphysema, but we lack data regarding COPD, and therefore we consider that respiratory tests should have been included.

We can also debate the ethical considerations of performing a LDCT in low-risk patients, attending to the harm-to-benefit considerations.[20] Nevertheless, the lower-risk former employees of the UNC were not selected and did not undergo LDCT. Physical harms such as radiation exposure and the potential harms of a biopsy or a resection of a benign lesion, as occurred in our study, should be addressed clearly. This way, these harms can be reduced by ensuring that only patients with a sufficiently high risk of developing lung cancer are screened.[20]

Regarding this study, we can discuss the reasons why no malignant lesion was found until now, considering this was a higher risk population for lung cancer. Primarily, this was a retrospective study and therefore some collected past information could be missing or incomplete. Additionally, another probable reason for the lack of positive results has to do with the long time period that elapsed between uranium exposure in the mines and the low-dose CT being performed. In the past, this imaging test was not considered since there were no studies published on that matter back then. Furthermore, from the 265 former workers and their families, only 66 participated, and so we lack data about many individuals and their health status.

In future studies, it would be important to collect information about all the former workers of the Urgeiriça mines, in order to gauge both the past and present real impact of uranium exposure in this population.

CONCLUSION

Even though no malignant lesions were detected in LDCT, our data highlights the importance of LCS in high-risk populations. To the best of our knowledge, this was the first study performed in Portugal and can act as a bridge towards a wider implementation in the country.

AUTHOR CONTRIBUTIONS

SMC, DM: Study design, data collection and analysis, drafting, writing and critical review of the manuscript.

IA, AE: Data collection and analysis, critical review of the manuscript.

EC, JP, NM: Study design, drafting and critical review of the manuscript.

AJF, CRC: Study design, drafting and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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