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Lung cancer screening and the impact of lung parenchyma on pulmonary nodule volumetry

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Dedicated to:

To my newborn Isabella, as she is my present and my future!

To my dear husband for all his love & friendship and for being my Wonderwall!

To my parents that gave me the wings to fly so far!

To my grandparents, that even in heaven, still guard me every day of my life!

To my cousin that never stopped believing in me!

To God for all the blessings in my life.

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Preface:

Triumphal Ode

In the painful light of big electric factory-lamps
I have a fever, and I write.
I write grinding my teeth, a beast for the beauty of this,
For the beauty of this thing wholly unknown to the ancients.

O wheels, O gears, eternal r-r-r-r-r-r!
Strongly restrained spasm of furious mechanism!
In a fury within and without myself,
Through all my nerves dissected, outside,
(…)

In fever, looking at motors as if at tropical Nature
Vast human tropics of iron and fire and force
I sing, and I sing the present, and also the past and the future,
Because the present is all the past and all the future
(…)

Molecules making the mind of Aeschylus feverish in the 100th century,
Moving through these transmission-belts and pistons and fliers,
Howling, grinding, whispering, clattering, clanking,
Becoming an excess of bodily caresses in a single caress in my soul.
(…)

Eia! eia-ho eia!
Eia! I am mechanical heat and electricity!
Eia! the rails, the machine-housings
Eia and hurrah for me-all and everything, machines working, eia!

To leap with everything above everything! Hoopla!

If only I could be everybody everywhere!

London, June 1914
Fernando Pessoa – Álvaro de Campos

I start my dissertation with the poem “Triumphal Ode” by the famous poet Fernando Pessoa and his heteronym Álvaro de Campos.

This heteronym is the dandyish naval engineer who travelled worldwide, aspired to live to the extreme, and signed unbridled poems that vented his exalted sensations.

With Triumphal Ode, the poet celebrates the triumph of the machine, mechanical energy, and modern civilization. This complex and surprising poem was written in 1914, only 13 years after Wilhelm Roentgen received the Nobel Prize in physics due to the discovery of the X-ray. Looking back at the fantastic progress of radiology in the last century, we discover an explosive evolution from X-ray to cross-section modalities and, recently, software and artificial intelligence tools that have extraordinarily changed the modern concepts of radiology and diagnosis.

In just one century, science and technology have taken the medical community to unexpected fields, pushing all imaginable boundaries.

With this motivation and curiosity, bounded by a profound admiration for the past of radiology and great enthusiasm for its present and future, I have undertaken this PhD program focusing my research on lung cancer screening and lung nodule volumetry.

Several large-scale studies have shown the potential for Lung Cancer Screening (LCS) to reduce lung cancer mortality, allowing for the early identification of pulmonary nodules using low-dose computed tomography (LDCT). Appropriate measurement and management of pulmonary nodules are essential in LCS programs. Recent guidelines have recommended using dedicated software tools for nodule volumetry analysis as the preferred method for nodule size measurement.

In this PhD thesis, I will focus on LCS's current state of the art by reviewing the lung nodule volumetry technique and its limiting factors.

My original research investigates the impact of lung parenchyma attenuation on pulmonary nodule volumetry. During this research work and based on my daily clinical activity as a member of the LCS team, I have also published my findings on related topics, such as the most frequent incidental findings in LCS; an alert to the form of lung cancer associated with cystic airspaces; and a letter on pulmonary diseases with abnormal parenchymal density in LCS.

Resumo

O rastreio do cancro do pulmão (RCP) reduz a mortalidade do cancro do pulmão, permitindo a identificação precoce de nódulos pulmonares usando tomografia computorizada de baixa dose (TC-BD).

A medição e orientação adequadas dos nódulos pulmonares são essenciais nos programas de RCP. As diretrizes recomendam a análise da volumetria dos nódulos como o método preferido para a medição do tamanho dos nódulos. Contudo, as ferramentas de inteligência artificial (IA) para análise volumétrica ainda apresentam fatores limitantes, sendo alguns dos mais comuns a localização, tamanho, forma e densidade do nódulo.

O estudo investigou se as alterações na atenuação do parênquima pulmonar adjacente a um nódulo afetam o desempenho da segmentação dos nódulos pulmonares identificados em exames de tomografia computorizada (TC) e ferramentas volumétricas. Dois radiologistas aplicaram retrospetivamente duas ferramentas volumétricas disponíveis comercialmente para avaliar nódulos pulmonares com diâmetros entre 5 e 8 mm detetados por TC-BD de baixa dose durante um programa de rastreio do cancro do pulmão. Os radiologistas registaram os seguintes parâmetros:

- sucesso e adequação da segmentação;
- volume, diâmetros mais longos e mais curtos do nódulo;
- valor médio da atenuação do parênquima pulmonar adjacente;
- presença de alterações intersticiais, enfisema, placas pleurais, ou atelectasia.

Os preditores da segmentação volumétrica adequada do nódulo foram avaliados por análise de regressão. O coeficiente de correlação intra-classe avaliou a concordância inter-observador, e a qualidade da segmentação do nódulo, a qual depende do software.

No total, foram incluídos no estudo dados sobre 1265 nódulos (idade média do doente, 68,3 ± 5,1 anos; 70,2% do sexo masculino). O modelo de regressão revelou que a atenuação do efeito parênquima pulmonar adjacente no tamanho dos nódulos era altamente significativa ('odds ratio' (OR) 0,987, $p < 0,001$). O acordo inter-observador e inter-software sobre a segmentação adequada foram bons. Observou-se também que um pacote de software tinha um melhor desempenho e que as medidas diferiam consistentemente entre pacotes de software.

A conclusão do estudo principal mostrou que a probabilidade de uma boa segmentação dos nódulos pulmonares com diâmetros de 5-8 mm diminui com a atenuação crescente do parênquima adjacente. Estes resultados apoiam a hipótese de que o volume dos nódulos pulmonares não pode ser avaliado sem uma análise crítica do parênquima adjacente.

Numerosos achados incidentais foram detetados durante a revisão dos casos para este estudo. A falta de uniformidade na abordagem dos achados incidentais observados durante o estudo justificou a necessidade de uma publicação separada propondo uma abordagem mais uniforme dos achados incidentais nos estudos de RCP, fornecendo recomendações para a elaboração de relatórios e orientação, incluindo a descrição e análise de alterações que aumentam a atenuação do parênquima pulmonar.

Nos meus estudos durante esta investigação, observei que o cancro do pulmão com características císticas poderia ser mal diagnosticado ou ignorado e que não são sempre detetados nem bem segmentados pelos atuais sistemas de IA. Por conseguinte, considerei apropriado preparar uma publicação adicional para alertar a comunidade médica relativamente aos tipos de cancro do pulmão associados aos espaços aéreos císticos.

Em resumo, foi confirmada a hipótese central de que a volumetria dos nódulos detetados no RCP pode ser afetada pelos valores de atenuação do parênquima pulmonar que rodeia o nódulo. Estes resultados foram publicados para alertar que é necessária uma análise crítica do parênquima que rodeia o nódulo antes de aceitar cegamente os valores numéricos da volumetria dos nódulos para definir a estabilidade ou crescimento. A observação de inconsistências na abordagem aos resultados acidentais e aos tipos de cancro do pulmão cístico levou à decisão de publicar os dois artigos adicionais relacionados com esta investigação.

Palavras-chave

Câncro do pulmão; rastreio; baixa-dose; nódulo; volumetria; densidade do parênquima

Abstract

Lung Cancer Screening (LCS) reduces lung cancer mortality, allowing for the early identification of pulmonary nodules using low-dose computed tomography (LDCT).

Appropriate measurement and management of pulmonary nodules are essential in LCS programs. Guidelines recommend nodule volumetry analysis as the preferred method for nodule size measurement. However, artificial intelligence (AI) tools for volumetric analysis still present limiting factors, some of the most common being the nodule's location, size, shape and density.

The study investigated whether changes in the attenuation of the lung parenchyma adjacent to a nodule affect the performance of nodule segmentation using computed tomography (CT) studies and volumetric tools. Two radiologists retrospectively applied two commercially available volumetric tools to assess lung nodules with diameters of 5–8 mm detected by low-dose chest CT during a lung cancer screening program. The radiologists recorded the following parameters:

- segmentation success and adequacy;
- volume, longest and shortest diameters of the nodule;
- mean attenuation value of the adjacent lung parenchyma;
- presence of interstitial changes, emphysema, pleural plaques, or atelectasis.

Predictors of appropriate volumetric segmentation of the nodule were assessed by regression analysis. Intraclass correlation coefficient assessed the interobserver agreement, and software-dependent appropriateness of nodule segmentation.

In total, data on 1265 nodules (mean patient age, 68.3 ± 5.1 years; 70.2% male) were included in the study. The regression model revealed that the attenuation of the adjacent lung parenchyma effect in the size of the nodules was highly significant (odds ratio 0.987, $p < 0.001$). Interobserver and inter software agreement on appropriate segmentation were good. It was also observed that a software package performed better and that the measurements differed consistently between software packages.

The conclusion from the main study showed that the likelihood of good segmentation of lung nodules with diameters of 5–8 mm declines with increasing attenuation of the adjacent parenchyma. These results support the hypothesis that lung nodule volume may not be assessed without critical analysis of the adjacent parenchyma.

Numerous incidental findings were detected during the review of the cases for this study. Lack of uniformity in the approach to the incidental findings observed during the study justified the need for a separate publication proposing a more uniform approach to incidental findings on LCS studies, providing recommendations for the reporting and management, including the description and analysis of changes that increase the attenuation of the lung parenchyma.

In my studies during this research, I observed that lung cancer with cystic characteristics could be misdiagnosed or overlooked and that they are not well detected or segmented by the current AI systems. I, therefore, felt appropriate to prepare an additional publication to alert the medical community regarding types of lung cancer associated with cystic airspaces.

In summary, the central hypothesis that the volumetry of nodules detected on LCS can be affected by the attenuation values of the lung parenchyma surrounding the nodule was confirmed. These results have been published to alert that critical analysis of the parenchyma surrounding the nodule is needed before blindly accepting the numeric values from nodule volumetry to define stability or growth. Observation of inconsistencies in the approach to incidental findings and cystic lung cancer types led to the decision to publish the two additional papers related to this research.

Keywords

Lung cancer; screening; low-dose; nodule; volumetry; parenchymal density

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List of Acronyms

ACR	American College of Radiology
AI	Artificial Intelligence
AIDR 3D	Adaptive Iterative Dose Reduction using 3D processing
AJCC	According to The American Joint Commission on Cancer
ALARA	As Low as Reasonably Achievable
ANOVA	Analysis of Variance
BTS	British Thoracic Society
CAD	Computer-Assisted Diagnosis
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CT	Computerized Tomography
DANTE	Detection and Screening of Early Lung Cancer with Novel Technology
DIP	Desquamative Interstitial Pneumonia
DLCST	Danish Lung Screening Trial
ELCAP	Early Lung Cancer Action Project
FBP	Filter Back Projection
HR	Hazard Ratio
HU	Hounsfield Units
IARC	International Agency for Research on Cancer
ICC	Intraclass Correlation Coefficient

ICER	Incremental Cost Effectiveness Ratios
I-ELCAP	International Early Lung Cancer Action Project
ILA	Interstitial Lung Abnormalities
ILD	Interstitial Lung Disease
IFs	Incidental Findings
IPF	Idiopathic Pulmonary Fibrosis
IR	Interactive Reconstruction
IRCRB	Institutional Research Committee Review Board
kVp	Peak kiloVoltage
LAM	Lymphangioleiomyomatosis
LCS	Lung Cancer Screening
LDCT	Low-Dose Computed Tomography
LHC	Lung Health Check
LHLP	Liverpool Healthy Lung Programme
LIP	Lymphocytic Interstitial Pneumonia
LLP	Liverpool Lung Project
LUSI	German Lung Cancer Screening Intervention Study
mA	milliAmpere
MILD	Multicentric Italian Lung Detection
MIP	Maximum Intensity Projection
mSv	milliSievert
NELSON	Dutch-Belgian Lung Cancer Screening Trial

NHS	National Health Service
NLST	National Lung Screening Trial
NNS	Number Needed to Screen
NSCLC	Non-Small Cell Lung Cancer
PACS	Picture Archiving and Communication System
PET-CT	Positron emission tomography–computed tomography
QALY	Quality Adjusted Life Years
RB-ILD	Respiratory Bronchiolitis Interstitial Lung Disease
ROI	Region-Of-Interest
SD	Standard Deviation
SDM	Shared Decision Making
SRIF	Smoking-Related Interstitial Fibrosis
STR	Society of Thoracic Radiology
TB	Tuberculosis
UK	United Kingdom
UKLS	UK Lung Cancer Screening
USA	United States of America
VDT	Volume Doubling Time

1. Introduction

1.1 Lung cancer screening: The state-of-the-art

1.1.1 Lung cancer – The size of the problem

Lung cancer is the second most commonly diagnosed malignancy and the leading cause of cancer death worldwide. According to the last global cancer statistics report from 2020, produced by the International Agency for Research on Cancer, every year, 2.2 million new cases are diagnosed (11.4% of all cancer diagnoses), with 1.8 million deaths (18% of all cancer mortality) (1).

Lung cancer is the leading cause of cancer morbidity and mortality in men. In women, it ranks third for incidence, after breast and colorectal cancer, and second for mortality, after breast cancer (1).

Despite advances in the various treatment modalities of this malignancy, most patients are diagnosed at advanced stages of the disease (2,3). Survival in patients diagnosed with non-small cell lung cancer (NSCLC) is strongly related to its stage at diagnosis. According to the American Joint Commission on Cancer (AJCC) staging (8th edition), the 5-year survival ranges from 90% for stage IA1 to 0% for stage IVB (3,4). Unfortunately, seventy per cent of patients are diagnosed with locally advanced or metastatic disease (3). Consequently, despite relatively good outcomes for appropriately treated early-stage patients, the overall 5-year survival rate for all patients with NSCLC is only 18% (3).

The current low survival of this malignancy reflects the absence of a screening test to allow its early diagnosis and specific mortality reduction. Therefore, LCS aims to improve mortality by detecting early-stage disease in high-risk asymptomatic individuals.

1.1.2 Lung cancer screening – From the first trials to the present

For cancer screening to be effective, the benefits to the health of the screened population must outweigh the costs and risks introduced by the screening intervention. Therefore, the malignancy must have high morbidity and mortality, a significant prevalence in the screened population, and evidence that therapy is more effective in its early stage. In addition, a preclinical phase and identifiable risk factors should allow targeted screening of high-risk individuals (3). Several screening trials for lung cancer have been tested based on these criteria.

Two pioneering trials on lung cancer screening using low-dose computed tomography (LDCT) were published more than 20 years ago (5,6). The Mayo Clinic annual computed

tomography (CT) screening included 1,520 individuals older than 50 with a smoking history of more than 20 pack-years and found 68 lung cancers in 66 of the 1520 participants. Most of these cancers were stage I, significantly reducing lung cancer mortality (5). The Early Lung Cancer Action Project (ELCAP) included an annual CT screening of 1,000 high-risk smokers from New York (6). The project was later expanded internationally under the acronym I-ELCAP and enrolled >31,000 high-risk smokers worldwide (7). This project diagnosed lung cancer in 484 participants, 85% in stage I (7). The survival rate of the 302 patients who underwent surgical resection was 92%. Despite concluding that annual CT screening could detect curable lung cancer, the I-ELCAP trial lacked a control arm. As such, the trial's methodology led the research community to question if the increased diagnosis of early tumours resulted from lead-time bias, length bias, or overdiagnosis, which could mean that screening did not impact lung cancer mortality (3).

After several years of research, the National Lung Screening Trial (NLST) was published in 2011 and finally established the recommendation for annual lung cancer screening in the United States of America (USA) using LDCT (8).

NLST was conducted in 33 medical centres in the USA and included 53,454 asymptomatic, high-risk participants (age 55-74 years, smokers or ex-smokers with a history of at least 30 pack-years). The trial showed that annual follow-up of high-risk patients with LDCT (versus plain chest X-ray) reduced lung cancer mortality by 20% and overall mortality by 6.7%. The number needed to screen (NNS) to prevent one death was 320 patients (8).

The lung cancer detection rate did not diminish significantly over the screening years, suggesting an advantage to serial screening. In June 2019, the report on the extended follow-up to 11 years showed a sustained reduction in lung cancer mortality with similar NNS of 303 patients (9).

Some European CT screening trials that started simultaneously with the NLST, such as the Detection and Screening of Early Lung Cancer with Novel Technology (DANTE) and the Danish Lung Screening Trial (DLCST), did not confirm the decreased mortality in their initial reports (10,11). However, in 2018, the Dutch-Belgian Lung Cancer Screening trial (NELSON), the second-largest randomised lung cancer screening trial in Europe, confirmed results similar to NLST. The design of the NELSON trial investigated whether LDCT as a screening tool performed in the first, second, and fourth years could lead to a 25% reduction in lung cancer mortality after ten years of follow-up. The trial involved 15822 smoking or ex-smoking participants and a control group. Contrary to NLTS, the control group participants in the NELSON trial did not perform a chest X-ray (12). Sixty-

nine per cent of the detected lung cancers were stage I tumours. Surgical treatment of lung cancer was threefold more common in the screened arm compared with the control arm and the general population (67.7 vs 24.5%). This trial confirmed that chest LDCT screening in high-risk participants reduced lung cancer mortality by 26% in men and 61% in women at ten years of follow-up (12).

The investigators running the Multicentric Italian Lung Detection (MILD) published their results in April 2019. The trial compared yearly or biennial LDCT screening to no screening in 4,099 current or former smokers with at least a 20 packs-year history who were 49 years or older. Compared to the control arm at ten years, the LDCT arm showed a reduction in mortality from lung cancer by 39% (HR 0.61) and an overall mortality reduction by 20% (HR 0.80). In addition, the benefit from LDCT improved past the fifth screening year, also supporting evidence for the use of long-term screening programs (13).

The German Lung Cancer Screening Intervention Study (LUSI) compared five annual LDCT scans to no intervention in 4,052 patients aged 50 to 69 years with 25-year smoking over 15 cigarettes a day or 30-year history of 10 cigarettes a day. Lung cancer mortality was reduced by 26% at 8.8 years after randomisation. The mortality reduction was more significant in women (HR 0.31) than men (HR 0.94), similarly to the NELSON trial, and may result from differences in tumour subtypes in men and women (14).

Given these results, more and more medical societies and health organisations have recently recognised the role and impact of lung cancer screening programmes on high-risk participants.

In the United Kingdom (UK), the first adaptation of lung cancer screening (UKLS) started in 2010. Instead of covering a countrywide risk population, the trial targeted only high risk patients from areas with a higher lung cancer incidence and historical poorer survival rates. The UKLS was a randomised controlled trial that ran for five years and recruited 4000 high-risk participants. The UKLS confirmed the benefit of LDCT screening, with about 85% of cancers detected at an early stage (stage I and II), of which about 90% benefited from potentially curative therapy (15).

Following the results of the UKLS, a collaborative initiative between the Clinical Commissioning Group, secondary and tertiary care centres, including Liverpool central hospitals (Aintree Hospital NHS Foundation Trust, Liverpool Heart and Chest Hospital NHS Trust, and Royal Liverpool and Broadgreen University Hospitals NHS Foundation Trust) and the University of Liverpool established the Liverpool Healthy Lung Programme (LHLP) in 2016 (16).

The LHLP started with a preliminary duration of three years and is still in place regarding the very positive results. The programme includes patients aged 58–75 with a smoking history or chronic obstructive pulmonary disease (COPD) diagnosis. These patients are invited for a lung health check (LHC) with a respiratory nurse in a community health hub setting (16).

During the LHC, the respiratory nurse performs a detailed risk assessment using information from the subject's medical history and other risk factors, including exposure to asbestos, family history of lung cancer, history of malignancy, and smoking duration. In patients without a pre-existing diagnosis of COPD, lung function is assessed by spirometry. Patients with abnormal lung function, defined by FEV1/FVC ratio less than 70% on spirometry, are referred for further investigation. The five-year risk of lung cancer is estimated using the 'MyLungRisk' calculator, based on the Liverpool Lung Project (LLP) risk model (17). The programme refers to those with a risk of 5% or more to a low-dose CT scan.

According to the last official publication of the programme in 2019, a total of 4 566 subjects attended the appointment for risk assessment, and 3 591 (79%) consented to data sharing. Of those attending, 63% underwent spirometry, and 43% received a recommendation for an LDCT scan. The programme diagnosed 25 cancers, of which 16 (64%) were stage I (16). Comparison with the national stage distribution implied that the programme reduced lung cancer mortality by 22%, in line with the results of the other worldwide trials.

The author of this thesis is part of the radiology team working for the LHLP, and the data from this screening programme is the basis of the current research thesis.

Despite the promising results from the trials above, lung cancer screening programmes using LDCT have been slow to implement and heterogeneous across different countries. So far, there are no nationally organised LCS programmes worldwide, although there is a high level of evidence supporting this strategy (14,18).

In the USA, the US Preventive Service Taskforce and the National Comprehensive Cancer Network have issued guidelines recommending LCS in high-risk groups of smokers and ex-smokers (19–21).

Health authorities have organised screening demonstration projects in various Chinese provinces for highly prevalent cancer types, including lung (19).

Clinicians and policymakers have been discussing LCS implementation throughout Europe. Open questions such as the balance of benefits and harms, cost-efficiency, integration of tobacco cessation, service implementation, and participation rates are still

under discussion. There is no organised nationwide LCS in Europe or the UK to date. In some countries, screening is either a private service covered by regional insurance companies or initial pilot programmes like the LHLP.

1.2 Lung cancer screening: Pros and Cons

Like other screening programmes, LCS's pros and cons must be considered and discussed. These include its cost-effectiveness, radiation exposure risk, false negatives, false positives, patient psychological stress and anxiety, and incidental findings on LDCT.

1.2.1 Cost Effectiveness

The United Nations (UN) aims to reduce by 25% the overall mortality from non-communicable chronic diseases, including cancer (22). Unfortunately, most countries struggle with the budget for health and sustainability, so the most cost-effective health interventions must be prioritized, especially in preventing and detecting disease (22).

Sadly, the reports on lung cancer cost-effectiveness are heterogeneous, ranging from very favourable to unfavourable, related to the variability in screening protocols, cost of LDCT, and uncertainty regarding the impact on mortality (23–27).

A retrospective cost analysis of the NSLT estimated that annual LDCT costs an additional $1,631 per person and provided an additional 0.0316 life years and 0.0201 quality-adjusted life years (QALY) per person (27). The incremental cost-effectiveness ratios (ICER) were $52,000/ life-year gained and $81,000/QALY gained, which falls below the recommended threshold of $100,000 for efficacy in the USA and compares favourably with screening for breast, colon, and cervical cancer (28).

A more recent cost-effective study based on the regional Manchester Lung Health Check pilot programme confirmed its cost-effectiveness at an ICER of £10,069/ QALY (29). This result is lower than the conventional cost-effectiveness threshold used by the National Institute for Health and Care Excellence (NICE) and comparable to the UKLS trial published in 2016, which estimated an ICER of £8,466/QALY (15).

1.2.2 Radiation exposure risk

Radiation exposure increases the risk of cancer development (3). However, the mean LDCT radiation dose is much less than a standard chest CT dose, with values reported in the NLST as low as 1.4 millisieverts (mSv) (30). This low radiation dose is comparable

with the 7 to 8mSv of a diagnostic chest CT and the 0.1mSv of a chest radiograph (31). The cancer risk from the very low level of radiation of an LDCT is small. Yearly LDCT scanning from age 50 to 75 years will result in an estimated 0.23% and 0.85% increase in the lifetime risk of lung cancer in men and women, respectively (31).

1.2.3 False positives and false negatives

Another concern when evaluating LCS programmes is related to false-positive scans.

The definition of a positive screening result differed substantially between the NLST and most European trials. The NLST defined any non-calcified nodule with a maximum diameter of at least 4 mm as a positive screening result (32). Consequently, the number of false-positive scans was high: 27% of scans in the first two screening rounds, of which 96% were false-positive. According to the NLST nodule management algorithm, these suspicious nodules needed further work-up, either a follow-up LDCT for nodules of 4–10 mm or a referral to a pulmonologist for nodules >10 mm in maximum diameter (32).

The NELSON and some other European trials used a threshold of approximately 10 mm diameter for a positive screening result but also established an indeterminate group of nodules measuring 5–10 mm in diameter (50–500 mm^3 in volume) that required earlier follow-up than the yearly screening interval (33). The NELSON trial investigators only considered nodules with significant growth (>25% volume change) as positive screening results, reducing the number of scans with positive screening results to 2.7% (from 27% in the NLST) and the false positives to approximately 50% (from 96% in the NLST) (32–34).

The definition of false negatives implies the detection of lung cancer on a follow-up LDCT within one year of the initial negative screening study. The sensitivity of LDCT for detecting lung cancer ranges from 80 to 100%, with a false negative rate of 0 to 20%. Lung cancer screening with LDCT outperforms the false negative rates of screening mammography and sigmoidoscopy (20% and 48%, respectively) (35).

1.2.4 Psychological stress and anxiety associated with LCS

A clear disadvantage of the follow-up of lesions during LCS is the psychological stress and anxiety experienced by the patient. Recent studies suggest that LDCT screening is associated with short-term psychological discomfort but does not negatively impact health-related quality of life (36).

1.2.5 Incidental findings on LDCT for lung cancer screening

Incidental findings (IFs) on LCS are LDCT findings that can potentially affect the patient's health and are unrelated to the primary purpose of identifying lung cancer (18). Most IFs are benign and clinically insignificant—the most common being pulmonary findings (69%), cardiovascular findings (67%), and gastrointestinal findings (25%)—but some require urgent recognition and further management (37). The reported prevalence of IFs on LCS ranges from 19% to 94% in more recent reports (37). The lack of standards regarding the reporting and management of IFs on LCS can partly explain this wide variation.

IFs can be seen as a disadvantage of the LCS programmes because they cause stress and anxiety (38). In addition, the presence of an unexpected finding requires good communication with the patient and a standard approach to reporting and management (18).

On the other hand, IFs are also seen as a potential advantage of LCS programmes since they provide an opportunity to detect and treat other pathologies, in addition to the early detection of lung cancer. These include the diagnosis of cardiovascular and pulmonary pathology and the diagnosis of incidental neoplasms, including thyroid, breast, kidney, liver, oesophageal, pancreatic, and mediastinal tumours (3,39).

1.2.6 Newly recognised radiological presentations of lung cancer

Another advantage of the large patient cohorts in LCS programs is the opportunity to learn more and understand the natural history and newly recognized morphological appearances of some types of lung cancer (40). Lung cancers arising in association with cystic airspaces are such an example. The delayed diagnosis of cystic or pericystic lung cancer represents up to 22% of missed lung cancers in screening programs, probably due to the low awareness of this morphological subtype among radiologists and clinicians (40,41). These cancers are becoming more apparent and providing new insights into the pathogenesis of early lung cancer, in part due to the introduction of LCS programmes. Therefore, the awareness of the radiologists and pulmonologists of this type of lesion is essential for their diagnosis (42).

1.2.7 Controversies regarding reporting in LCS

The effectiveness of LCS depends on the balance between costs to the health system and patient and the expected benefits. False positive screening results imply that healthy individuals without lung cancer should be subject to further excessive investigations, including potentially invasive procedures like a lung biopsy (33). An excessive

investigation could also happen in the case of overreporting of IFs, some of which are both extremely common and harmless (43). For instance, the risk of lung cancer in a patient with a small solid pulmonary nodule measuring less than 5mm is the same as in a patient without any pulmonary nodule. Therefore, reporting on pulmonary nodules below this threshold increases the cost of LCS due to excessive investigation and has no benefit for the patient.

However, some IFs may provide a valuable opportunity for intervention. For example, in a patient with coronary artery disease, interventions aimed at reducing risk factors and other lifestyle changes could benefit the patient's health in the long term, or a patient with early-stage breast cancer may benefit from local treatment.

We do not know if the cost-effectiveness of an LCS programme is affected by the decision to report or ignore IFs, which has led to two schools of thought. On the one hand, some authors argue that LCS studies should only report on pulmonary nodules and their growth. On the other hand, some say that screening should maximise every opportunity for health intervention.

The likelihood of a lung nodule corresponding to lung cancer is not solely associated with its imaging features, smoking and family history. Morphological changes in the adjacent lung parenchyma or pleura and non-regional changes such as signs of airways disease and emphysema also increase the likelihood of malignancy of SPN. It follows that we must be aware of the lung as a whole to interpret the malignancy potential of a small pulmonary nodule. Incidental findings may seem unrelated to lung cancer, but they may shed light on diagnosing common risk factors, such as asbestos exposure, pulmonary fibrosis or others.

The nodule segmentation is based on the recognition of its boundaries by the software or human eye. The boundaries are identified by the significant change between the attenuation of the nodule (soft tissue density) and the attenuation of the adjacent lung parenchyma (close to the attenuation values of air). Collapsed or poorly expanded alveoli surrounding a nodule may be erroneously included in the volume or diameter of the nodule, falsely increasing its volume. Furthermore, the minimal size measurable on CT is given by the size of the pixel. Any measurement smaller than the size of the pixel in a given CT scan is unreliable. For reference, in routine LDCT, a pixel would measure 0.7mm or more. Therefore, fractions of a millimetre are not reliable values. The presence of interstitial changes surrounding a nodule may also impact the precision of the nodule measurement. Interstitial changes increase the attenuation of the lung parenchyma and restrict the expansion of the alveoli. Therefore, interstitial changes surrounding a nodule can lead to an overestimation of the size of a nodule.

The inclusion of incidental findings on LCS reports is another controversial point. Some centers opted only to report findings that may require active action, while other centers recommend including any incidental finding in the report. That decision may result in an unnecessary additional investigation of irrelevant findings or lack of action on an incidental finding that may have clinical relevance.

Lung cysts and clusters of emphysematous foci are commonly observed in LCS patients is another point of controversy. Careful analysis of the cystic spaces is needed to recognise those which may correspond to adenocarcinomas of a cystic type.

1.3 Technical requirements for lung cancer screening studies

1.3.1 International recommendations for LCS

The American College of Radiology (ACR) and the Society of Thoracic Radiology (STR) have created guidelines for the technical requirements of LCS studies, which should meet the following criteria (44):

• All CTs must be performed on multidetector CT scanners with at least 16 slices and in full inspiration.

• Intravenous contrast medium should not be administered.

• The CT acquisition should be performed from the pulmonary apices to the costophrenic angles, with contiguous images and an image section thickness less than or equal to 2.5 mm (preferably 1 mm).

• The minimum gantry tube rotation speed should be 0.5 seconds per revolution or higher.

• The principle of ALARA (as low as reasonably achievable) for the lowest level of radiation should be respected without compromising image quality. The maximum recommended dose for a low-dose CT is 3mGy for a participant with mean weight and height (170 cm and 70kg). The radiation dose should be adjusted for participants with lower weight and height and following the protocols of each CT manufacturer.

• The ACR advises that only radiologists performing at least 300 chest CT scans in the last 36 months should report LCS scans.

• All acquired images must be archived in a digital Picture Archiving and Communication System (PACS).

• Studies should be read in workstations with dedicated hardware and software.

• For detection of early signs of lung cancer, the ACR recommends using reconstructions with maximum intensity projection (MIP) to maximize the detection of small solid and subsolid pulmonary nodules.

• All detected nodules should be characterized in continuous thin axial images and classified as solid nodules, part-solid nodules, ground-glass opacities, or calcified nodules.

• If there are previous examinations of the participant, identified nodules should be compared to previous exams.

• The nodules should be measured in the axial plane and in the 'lung window' setting using electronic callipers to calculate the average between short and long-axis diameters of the pulmonary nodule.

1.3.2 Low dose CT in LCS

The LDCT technique is relatively simple, and as its name states, the radiation dose is inferior to a standard chest CT acquisition (45). Due to a high contrast resolution between air and lung nodules, LDCT enables a low radiation dose while maintaining good diagnostic quality. However, there is no consensus regarding the definition of a low-dose acquisition since different factors, like tube voltage (kVp), current (mA), and tube speed rotation, affect dose exposure (45,46). The major screening trials used tube voltages between 90 kVp and 140 kVp and tube current in the range of 30–80mAs (46).

The kVp and mA parameters should be combined to obtain an acceptable radiation dose, considering the patient's body habitus and age. For example, the ACR suggests a CT dose index (CTDI) below 3mGy for standard-size patients, while the NLST recommends an effective dose of approximately 2 mSv for acceptable CT quality (30,44).

The ACR recommends a gantry rotation time below 0.5 seconds because the faster the rotation less motion artefacts and a decreased radiation dose to the patient are achieved. In addition, LDCT collimation should allow thin-section reconstruction images (44).

Most LDCT screening studies have used filtered back-projection for image reconstruction but face the challenge of providing diagnostic image quality at the lowest radiation dose. Nowadays, iterative reconstruction techniques are prevalent in LDCT protocols used for LCS, improving image quality while reducing radiation dose. This technique allows for low-dose and ultra-low-dose CT protocols without negatively affecting the detection of pulmonary nodules (47–50).

1.4 Lung nodule volumetry in LCS

AI tools are available to detect and measure pulmonary nodules. These include semi-automatic and automatic volumetric segmentation techniques. Computer-assisted diagnosis (CAD) software detection and segmentation of lung nodules have lower inter-observer variability in detecting and classifying nodule volume (51).

The theoretical foundation for using volumetry for pulmonary nodules relies on the assumption that volume is more sensitive than the diameter to detect growth, as most lung nodules are not homogeneously spherical (51,52). Measuring the volume of the nodule by computed segmentation better detects asymmetric growth than calculating its volume based on a single diameter or the average diameter. Therefore, the calculation of the volume doubling time (VDT), i.e. the time needed for the nodule to double in volume, is more precise than calculating VDT based on changes in the diameter of the nodule (51).

A minimum increase of 25% in volume is needed to confirm that a nodule has grown in size. In addition, this study also defined the risk of malignancy of a nodule according to its growth rate. In practice, VDTs shorter than 400 days, between 400 and 600 days, or longer than 600 days, would correspond to a risk of malignancy of 9.9%, 4.0%, and 0.8%, respectively (53).

LCS programmes and international medical societies, including the Fleischner Society, advise follow-up for incidental pulmonary nodules larger than 100 mm^3 and smaller than 500mm^3, preferably using lung nodule volumetry software. The British Thoracic Society (BTS) guidelines recommend these tools in the assessment and follow-up for nodules larger than 80 mm^3 and smaller than 500mm^3 in volume (54,55). In the reviewed version v1.1 of the Lung CT Screening Reporting and Data System (Lung-RADS) from 2019, the ACR also suggests using volumetry tools to assess lung nodules (56).

Automatic or semiautomatic volumetry measurements of the pulmonary nodule require the virtual extraction of the nodule from the other pulmonary structures surrounding it in a process called segmentation (51,57). One computational technique that allows the segmentation of nodules is the so-called 'region growing' algorithm, after identifying the nodule by manually placing a seeding point (in the semiautomatic method) or automatically, where the nodule is detected and segmented without the need for a manually selected seeding point. From the selected voxel (smallest volume of image data), the segmentation algorithm identifies the voxels with a similar attenuation value, which are contiguous to the seeding point. Then, the algorithm expands the segmentation result by repeating this process until an abrupt attenuation change identifies the node's margin due to air in the adjacent parenchyma (51,57). The range of attenuation values of ventilated airspaces is close to -950 Hounsfield Units (HU). In contrast, the range of attenuation values within the solid pulmonary nodule is above -500HU, thus accounting for the high contrast between a pulmonary nodule and the adjacent pulmonary parenchyma (51,58).

There have been several studies on pulmonary nodule volumetry's reliability, applications, and limitations. The accuracy of in-vivo segmentation processes cannot be assessed, as it would require excision of the nodules and maintenance of factors like pressure from the adjacent tissues and blood flow. In contrast, we can reliably evaluate the precision of the volumetric measurement (i.e., how close or dispersed the measurements are to each other). A high precision would suffice to accept volumetry for measuring the growth of a nodule by comparing the different volumes over time (51). To eliminate any influence from an unknown accuracy, we should test the precision for each pulmonary nodule volumetry software over a period where actual growth would be unlikely in a so-called zero-change dataset (51).

1.5 Limiting factors of lung nodule volumetry

Several authors have published studies investigating the factors influencing volumetric measurements of a pulmonary nodule.

These factors can be related to the nodule, technical parameters, and others.

1.5.1 Factors related to the nodule

- **Nodule's dimensions**

The studies on nodule size as a limiting factor for volumetry started in phantoms and proved that the error in volume calculation increases with a decreasing nodule size (59,60).

The number of voxels multiplied by the size of the voxel gives the volume of a segmented nodule. Dimensions smaller than the size of the voxel cannot be measured. For example, the volume of an isotropic voxel for a pixel size of 0.7mm is 0.7^3 or $0.343mm^3$. Therefore, the minimal measurable difference in volume would be voxel's volume. Given the nature of the generation of the image data on a CT scan with a glooming or aura surrounding a nodule and the partial volume effect, it is not reasonable to assume that we can measure changes the size of a voxel in the surface of a nodule. The voxels at the nodule's margins contain both nodule tissue and air from the surrounding parenchyma, and minimal changes in the proportion of air or soft tissue densities may affect the "size" of the nodule. When comparing two nodules with different sizes, a larger proportion of the voxels representing a small nodule can be affected by partial volume artefact, as compared to larger nodules, impacting the variability of the volumetric analysis of nodules (61). Therefore, nodules smaller than 8 mm in diameter have more variation (18%–26%) than nodules larger than 8mm (13%–17%) (62,63).

- **Nodule's location**

As a pulmonary nodule grows, it tends to contact adjacent structures like bronchi, vascular structures, and pleura. This contact with the adjacent structures will compromise the delineation of the nodule's margins and influence the volumetric nodule segmentation.

Nodules adjacent to vascular structures or the pleura have a relative volume error of 9% to 17% (64). In addition, nodules adjacent to the pleura or vessels increase the variability of the volume measurement by two and four-fold, respectively, compared to intraparenchymal nodules surrounded by air (65).

- **Nodule's morphology**

The segmentation of a pulmonary nodule is also dependent on its margins. A nodule with smooth and regular contours will have less volume measurement variability than a nodule with lobulated, spiculated, or complex borders. This fact is as valid for software packages (semi-automatic and automatic segmentation) as it would be for manual segmentation by experienced radiologists (65–67).

Irregular and spiculated nodule margins may cause a higher inter-reader measurement variability and underestimate the volume measurement by up to 39%, compared to smooth margins (60,65–67).

1.5.2. Factors related to technical parameters

- **Slice thickness**

Slice thickness is another technical parameter that has been extensively studied. The use of thicker slices during acquisition increases the variability of nodule volumetry (66,68,69).

In one such study, the volume measurement of pulmonary nodules using a 5mm slice thickness had a variability of ±40% compared to when using thin slices of 1.25-mm in thickness (66). The reasoning for the influence exerted by slice thickness is similar to the nodule's size since the percentage of voxels suffering from partial volume artefact also increases with increasing slice thickness.

- **Overlap between CT slices**

The spatial resolution in the z-axis improves, and the partial volume effect reduces with increasing overlap. Therefore, the overlap between acquired CT slices is also related to partial volume averaging.

Volumetry measurements are significantly larger on nonoverlapping than 50% overlap reconstructions with 5-mm slices. Conversely, using 1.25 mm slice thickness, this effect was not seen, and overlapping was unnecessary (70)(69). In another study, overlap, even on thin sections, reduced the absolute per cent bias by 16% in the volume estimation of artificial 5-mm nodules. (51,65).

- **Reconstruction Kernel**

The choice of reconstruction algorithm or kernel is also a recognized limiting factor, but with inconsistent results from the literature.

Christe *et al.* found that soft, low-frequency reconstruction algorithms resulted in larger volumetry results than high-frequency algorithms. Another study by Wang et al. found that soft-tissue reconstructions provided more repeatable measurements than a sharp kernel by comparing images reconstructed at 2 mm thickness and using one analysis package (72,73).

- **Radiation exposure and iterative reconstruction techniques**

The reproducibility and repeatability of volumetry measurements are good regardless of radiation exposure (51,64).

Interactive reconstruction (IR) is at least as accurate as filter back-projection (FBP) algorithms in lung nodule volumetry, as shown by multiple studies, mostly phantom-based (74–76).

- **CT equipment/number of detectors**

The CT equipment is also an essential factor, and the equipment and technical parameters should be consistent across follow-up scans. For example, according to a

study by Das *et al.,* the volume measurement of a pulmonary nodule varies significantly when the operator applies the same volumetry software to images obtained by either 4- and 16-slices CT scanners, but not between 16- and 64-slices CT scanners (64).

- **Intravenous contrast**

The recommendations for LCS with LDCT do not include intravenous contrast administration. Studies have shown that enhanced CT studies result in larger volume measurements using the postcontrast acquisition than the pre-contrast images (77,78). We could explain this result by the increasing attenuation of the nodule itself or vessels surrounding the nodule, meaning that the nodule segmentation in a postcontrast acquisition may be larger, incorporating a more significant proportion of the periphery of a nodule and surrounding parenchyma (51).

- **Pitch**

Studies have proved that different pitches, smaller than pitch=1.4, have negligible differences in lung nodule volumetry (78–80).

- **Software package and segmentation algorithms**

Another apparent factor influencing nodule volumetry is using different software packages. Multiple studies show increased variability in the volume calculations, which can be as high as 50% when comparing different software or other versions of the same software (63,81).

Some more advanced volumetry software tools also offer different lung nodule segmentation algorithms. Some may be for solid nodules or subsolid nodules or even different algorithms for different sizes. Furthermore, Ashraf *et al.* showed that even different algorithms within the same software might influence the volume measurement resulting in a variability greater than 25% (82). This result further supports the need for consistently using the same software and segmentation algorithm.

1.5.3 Factors related to the patient

- **Inspiratory/Expiratory**

LDCT for LCS should be acquired in full inspiration to expand the lung with air (44). We can reason that in the expiratory phase, the parenchymal attenuation will increase due to the smaller air volume and cramping of structures like bronchial walls and vessels. In this scenario, the segmentation result is more likely to include adjacent pixel/voxels from these other structures and consequently increase the volume estimation (51). Three studies support this theory, with two showing a minimal change in volume measurement in full inspiration and another indicating that nodule volume measurements are larger

in the expiratory phase (62,63,83). Conversely, another study comparing CT scans acquired at residual volume versus maximum inspiration showed that both diameter and volume varied, sometimes increasing and decreasing, irrespective of the nodule size (84). These studies support the increased variability and reduced reproducibility of volume measurements when comparing different respiratory phases.

- **Underlying pulmonary diseases**

Less attention and research have been dedicated to understanding the effect of the underlying pulmonary diseases in lung nodule volumetry.

Some authors point out that diffuse interstitial lung diseases, pleural effusions, lung consolidation, atelectasis, and emphysema are potential limitations for nodule detection and volumetry. Still, no study has yet demonstrated this (51,85).

The only study published in the literature investigating volumetry and pulmonary emphysema showed no significant statistical association between variation in lung nodule volume measurements and emphysema percentage (83).

- **Haemodynamic factors (e.g., cardiac cycle)**

We know little about the impact of changes in cardiovascular haemodynamics on the volumetric analysis of pulmonary nodules. A single published study by Boll *et al.* investigated the effect of the cardiac cycle phase on nodule volume in contrast-enhanced and ECG-synchronised CT examinations. The authors explained the results with cardiovascular movement and suggested that this effect will be more critical when the nodule size is smaller (86).

1.5.4. Other factors

- **Operator and scan-related variability**

Operator-related limiting factors for lung nodule volumetry also cause volume measurement variability.

Studies performed by Wormanns *et al.* and Gietema *et al.* used the typical "coffee-break study design" where the patient is imaged twice, at separate points on the same day, and then both volume measurements are compared (51). During this short time, we can assume that no growth has occurred, meaning that any difference in volume measurements between the two CT studies is due to interscan variability. The authors reported an inter-scan variability of around 25% for solid nodules despite an inter and intra-operator variability of just 1% (87,88). These two landmark studies have justified using a 25% increase in volume as the cut-off required for identifying actual growth, as used in some screening studies (13,15), but that is not necessarily true for nodules <8mm.

As can be appreciated from the limited factors enumerated above, it follows that differences in the technical protocol used for the LDCT scan can impact the volumetry of lung nodules, thus justifying the standardisation efforts published by the ACR and STR previously described.

1.6 Lung parenchyma attenuation in CT

Chest CT is one of the most common studies for detecting and quantifying lung abnormalities, measuring the attenuation of the lung parenchyma in HU. Water and air have an attenuation measurement of 0 and -1000HU, respectively (89).

Several authors have researched the cut-off HU values for normal physiological and diseased lung parenchyma in recent decades. The fully expanded lung parenchyma is mainly composed of air, some lung tissue, and blood vessels, with a typical attenuation of about -850 HU in full inspiration. Emphysema replaces normal lung parenchyma with air-containing spaces with CT attenuation closer to air (58). A CT value of −950 HU is generally accepted as a cut-off value between emphysema and normal lung (58,90,91).

Shin *et al.* reported the cut-off of −700 HU between the functional lung and lung parenchyma with diffuse interstitial lung disease (ILD)(92). Several authors have proposed a range of attenuation values between −750 and −200 HU for various interstitial lung diseases with ground-glass opacity (93,94).

The physiological lung parenchyma's attenuation is generally within the threshold band between −950 and −700 HU. Values lower than -950HU are more frequently observed in diseases with loss of the lung parenchyma, such as emphysema and cystic disease. Values higher than -700 HU usually reflect interstitial lung changes (90,93,94). These thresholds are accepted for conventional standard dose chest CT.

Radiation dose is linearly related to the milliampere-seconds value. Lowering the tube current results in a linear reduction of the CT dose if other parameters are held constant (95). However, the resultant LDCT images contain increased noise levels, which interferes with detailed image analyses, specifically with the segmentation of pulmonary nodules. Very few studies compare the normal and abnormal parenchymal attenuation (mainly emphysema and interstitial diseases) in standard dose chest CT and LDCT.

The study from Gierada *et al.* compared standard- and low-dose techniques in the CT quantification of emphysema and found no significant differences in mean attenuation between both protocols (−848 HU and −846 HU, respectively; $p > 0.35$). The study also found that the LDCT technique has minimal effect on CT quantification of emphysema (96). Likewise, another group investigated the impact of a reconstruction algorithm with adaptive iterative dose reduction using 3D (AIDR 3D) processing using an LDCT

protocol when applied to emphysema quantification. Their results showed greater consistency in this low-dose compared to a standard-dose protocol (97). This study suggests that LDCT combined with AIDR 3D processing can replace standard-dose CT for emphysema quantification (97).

In the study by Kubo *et al.,* the authors showed that lesion characterization capability by LDCT images was comparable to standard-dose ones and, therefore, sufficient for evaluating localized lung lesions (98).

The study from Ley *et al.* evaluated ILD patients with image reconstructions with varying combinations of tube current (50mA, 20mA, 15 mA, 10mA) and image-thickness/increment (1/1mm, 2/2mm,3/2.4mm, 5/4mm) simulated from raw data. The authors concluded that all dose settings and slice thickness allow for the correct differentiation between UIP and NSIP (99).

Despite the lack of studies confirming the normal lung parenchyma attenuation range in standard-dose CT and LDCT, previous studies show the feasibility of LDCT in quantifying emphysema and analysing the ILD pattern.

1.7 Conditions with abnormal lung parenchyma density

The attenuation of normal lung parenchyma depends on three main components: the lung tissue, the blood/vessels, and the air. We can categorise lung diseases as either having increased or decreased lung parenchyma attenuation (100). However, the average attenuation of the lung parenchyma may vary significantly even in physiological events such as inspiration and expiration (100).

Commonly, lung attenuation decreases with increasing lung volume, but this is not homogenous because of gravitational effects and elastic recoil, with higher attenuation in the dependent areas (100). The expiratory phase increases lung attenuation in dependent lung regions, especially in the lower lung zones. This asymmetry is probably due to more significant diaphragmatic movement or greater basal lung volume (100). Furthermore, up to 75% of asymptomatic subjects also show air-trapping, especially older patients (101).

A reduction in the blood volume and tissue destruction or loss can decrease lung parenchyma attenuation. Any reduction of the parenchymal attenuation is pathologic but does not necessarily indicate irreversible tissue destruction (100). We can classify diseases with reduced parenchymal attenuation into conditions with (i.e., small airway disease) or without air-trapping and cystic lung disease (102).

The differential diagnosis of small airway diseases primarily associated with air trapping includes constrictive bronchiolitis secondary to smoking, bronchiolitis obliterans, follicular bronchiolitis, and asthma. More unusual differential diagnoses include vasculitis and diffuse idiopathic neuroendocrine cell hyperplasia (102,103).

Diseases with decreased lung density without air-trapping or discernible walls include centrilobular, panlobular, paraseptal and bullous emphysema (102,104). Cystic lung disease is related to true lung cysts with definable walls. Cystic diseases are relatively uncommon and include lymphangioleiomyomatosis (LAM), tuberous sclerosis, Birt-Hogg-Dube´ syndrome, fibrotic (chronic) hypersensitivity pneumonitis, desquamative interstitial pneumonia (DIP), lymphocytic interstitial pneumonia (LIP) or Langerhans cell histiocytosis. LIP often occurs in the setting of Sjogren's syndrome or a form of light chain deposition disease. Pulmonary "cysts" in Langerhans cell histiocytosis most likely represent a combination of cavitated nodules and focal post-inflammatory airway dilatation (102,105).

Conversely, an increase in the density or size of lung tissue, an increase of blood volume in the small vessels or a reduction of the relative amount of air, either from lung volume loss or replacement of air in the airspaces by fluid or cells, increases the lung attenuation (100).

Many diseases can cause a focal or diffuse increase in lung attenuation due to diffuse ground-glass areas, consolidation, or reticulation, often combined. The differential diagnosis of increased lung attenuation is vast, including common pulmonary infections, pulmonary oedema, malignancy, occupational diseases, interstitial lung diseases, and pulmonary haemorrhage, among many more, as seen in table 1.

DISEASES PRESENTING WITH FOCAL OR DIFFUSE INCREASED LUNG ATTENUATION (100,102,106,107)
Pulmonary infection (viral, bacterial, fungus)
Pulmonary oedema
Pulmonary haemorrhage
Malignancy (primary or metastatic)
Hypersensitivity pneumonitis
Organising pneumonia
Vasculitis
Lymphocytic interstitial pneumonia
Interstitial lung diseases
Occupational lung diseases
Eosinophilic pneumonia
Asbestosis
Alveolar proteinosis
Vasculitis
Sarcoidosis
Adult (acute) respiratory distress syndrome
Acute interstitial pneumonia
Alveolar proteinosis

Table 1 - Diseases presenting with focal or diffuse increased lung attenuation

Some diseases do not quite fit into these categories and may appear as "geographic" foci of increased lung attenuation adjacent to foci of diminished density (108). These are diseases associated with a "mosaic" attenuation or perfusion pattern with a heterogeneous lung density (102,108). This heterogeneous attenuation pattern can result from diseases of the small airways, pulmonary vessels, alveoli, or interstitium (102,109).

Small airway disease can be a primary disorder, like respiratory bronchiolitis or constrictive bronchiolitis. However, the small airways may also be present in diseases affecting the parenchyma (e.g., hypersensitivity pneumonitis) or large airways (e.g., bronchiectasis and asthma) (109).

Vascular diseases presenting with the mosaic attenuation pattern may extend from the elastic pulmonary arteries (e.g., chronic thromboembolic pulmonary hypertension) to the distal pulmonary arterioles (e.g., pulmonary arterial hypertension) (109).

One of the best methods to differentiate between causes of mosaic attenuation is to perform expiratory imaging (109).

1.8 The impact of lung parenchyma attenuation in LCS volumetry

Despite the extensive research regarding other limiting factors, we don't fully understand the effect of parenchyma attenuation on pulmonary nodule volumetry.

Pulmonary findings are the most common IFs in patients participating in LCS programs, of which 75% are related to emphysema (37,110).

Emphysema can limit the discriminating power between benign or malignant pulmonary nodules because it increases the overlap of their morphologic characteristics. However, one could reason that emphysema causes the reduction of attenuation of the lung parenchyma surrounding a nodule, increasing the contrast with the pulmonary nodule. This increased contrast could enhance the software's ability to segment the nodule, decreasing the volume measurement variability (51). Rampinelli *et al.* did not find a significant statistical association between variation in volume measurements and the percentage of emphysema (83).

Interstitial lung diseases (ILD) refer to a large group of lung diseases, including smoking-related ILDs, smoking-related interstitial fibrosis (SRIF), idiopathic pulmonary fibrosis (IPF), desquamative interstitial pneumonia (DIP), and respiratory bronchiolitis interstitial lung disease (RB-ILD) (110–112).

On the other hand, Interstitial lung abnormalities (ILA) refer to the incidental finding of mild or even subtle non-dependent parenchymal abnormalities affecting more than 5% of lungs on CT scans in a patient without a previous diagnosis of ILD (107). These abnormalities may include centrilobular nodules, ground-glass or reticular abnormalities, non-emphysematous cysts, traction bronchiectasis, and honeycombing. ILD and ILA are not as common as emphysema or bronchial disease. Still, the prevalence of ILA in LCS could be as high as 16%, and progression from ILA to ILD was seen in 37% of cases over two years in a subgroup of patients enrolled in the National Lung Screening Trial (NLST) (113,114).

So far, no study has investigated the effect of ILA/ILD on volumetry, despite the potential for increased attenuation of the lung parenchyma adjacent to a given pulmonary nodule. Therefore, this is a pertinent, reasonable, tangible, and original research question.

2. Aims and outline of the thesis

The Problem:

The guidelines of most relevant international scientific societies, such as the Fleischner Society and British Thoracic Society (BTS), recommend volumetric analysis using tools integrated into PACS systems to evaluate the size and eventual growth of incidental pulmonary nodules (54,55). However, these tools present intrinsic measurement variability, which might be significant enough to change the therapeutic decision in specific cases.

Lung diseases are known to change the attenuation of the lung parenchyma. Still, no studies have conclusively investigated the influence on volumetry tools when these changes are adjacent to the measured nodule.

Having identified this problem, the following research question was formulated: Will changes in the attenuation of the lung parenchyma adjacent to a nodule affect the nodule segmentation performed by volumetry tools?

Hypothesis:

When the attenuation of the parenchyma adjacent to the nodule is altered (such as in pulmonary interstitial pathology or emphysema), volumetry tools may be less useful due to the lower quality of the nodule's segmentation.

Main objective:

The purpose of this study is:

2. To investigate if volumetry tools are affected by the attenuation of the parenchyma adjacent to a pulmonary nodule.

Secondary objectives:

As secondary objectives, it is intended:

1. To evaluate if the size of the effect investigated (primary objective) varies according to the size of the nodule itself;

2. To determine the inter-observer variability of pulmonary nodule volumetry tools and how it varies according to differences in attenuation of the pulmonary parenchyma adjacent to the nodule.

3. To determine the inter-software variability of pulmonary nodule volumetry tools and how it varies according to differences in attenuation of the pulmonary parenchyma adjacent to the nodule.

3. Methods

Specific methodological issues in this research thesis are highlighted.

3.1 Original research study "Lung cancer screening and the impact of lung parenchyma in pulmonary nodule volumetry" (Appendix 1)

The Institutional Research Committee Review Board approved the research study and waived the requirement for written informed consent due to the use of existing clinical data.

We include the original research study in Appendix 1, as published.

Study sample

The study is a retrospective cross-sectional study (observational, analytical).

All patients participating in an LCS program in the Liverpool Heart and Chest Hospital, a tertiary hospital in Northeastern England, between August 2016 and December 2018, were included in the study. All CT screening examinations were performed with the same equipment (Somatom Definition Flash; Siemens, Erlangen, Germany) using a low-dose CT protocol (Table 2).

Range	Lung apices–bases
Respiratory phase	Inspiration, breath-hold
Enhancement	None
Image reconstruction	2-mm thickness, 1-mm overlap
Kernels	B60f sharp/lung, B30f medium smooth/lung, B20f smooth/mediastinum
Acquisition parameters	kVp and mAs varied according to body habitus
Planned CTDI (vol)	2.03mGy, with 120 kVp and quality reference of 30 mAs

Table 2 – Low-Dose Chest CT Imaging Protocol Parameters

Regarding the inclusion and exclusion criteria: The study included all patients of the National Health System (NHS) included in the lung cancer screening programme of the Merseyside in the north-east of England, between 18 August 2016 and 31 December 2018, who had solid lung nodule(s). The study sample included all low-dose chest CT studies showing solid pulmonary nodules with diameters of 5–8 mm. The study excluded the low-dose chest CT studies with technical (e.g., respiratory motion) artefacts.

The investigators accessed the clinical records of the included patients via the hospital information system, and the following patient data were collected: patient age and sex and previous history of chronic obstructive pulmonary disease (COPD), tuberculosis (TB), and lung surgery.

Readers and measurements

Two cardiothoracic radiologists with 5 (reader 1) and 10 (reader 2) years of experience identified and measured the pulmonary nodules, following the protocol described in Fig. 1.

The investigators used the following volumetric software packages for volume measurement: Carestream Vue PACS v 11.4.01.1011 (Carestream Health, Inc, Rochester, NY; tool 1) and Syngo via VB20 (Siemens Healthineers AG, Erlangen, Germany; tool 2).

Disagreements among readers regarding the inclusion of a pulmonary nodule were resolved by consensus after a discussion between both readers and a third chest radiologist with more than 25 years of experience (consensus decision).

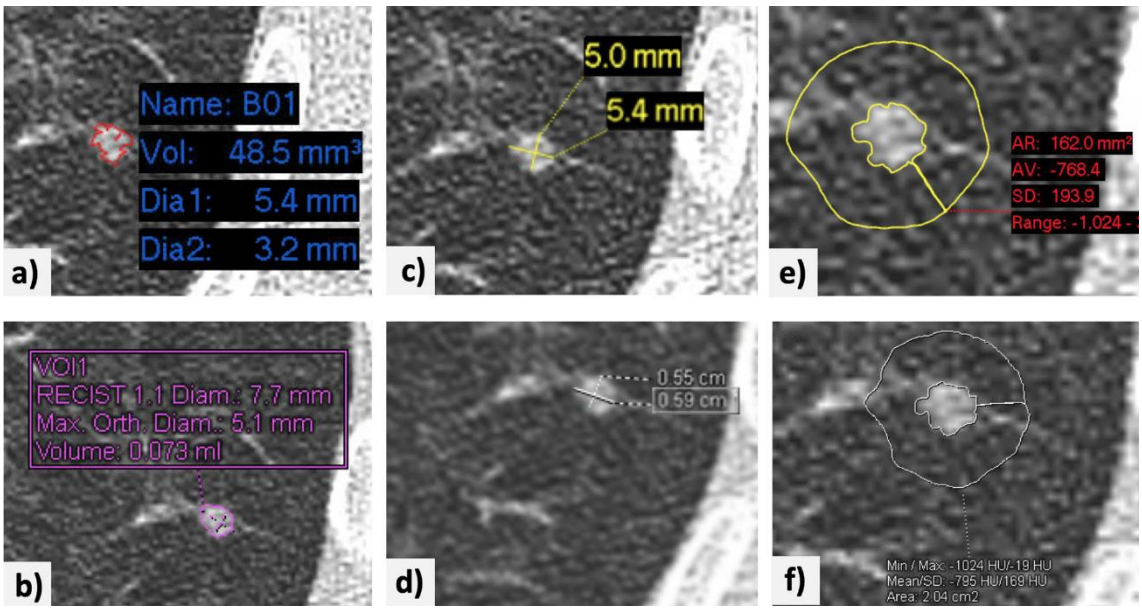

Figure 1 - Example of the implementation of the nodule measurement protocol.

A small nodule is identified in the posterior segment of the left lower lobe of the lung.

a, **b** - The volumetric tools [Vue PACS, ver. 11.4.01.1011; Carestream ″ (tool 1) and Syngo via VB20, Siemens ″ (tool 2)] are used to segment the nodule, yielding volumes of 48.5 and 75 mm3, respectively;

c, **d** - The longest orthogonal diameters are measured manually using electronic callipers tools in both software packages;

e, **f** - A region of interest (5-mm thickness) is drawn manually around the nodule to determine the average attenuation of adjacent lung parenchyma (-768.4 and -795 HU obtained with tools 1 and 2, respectively). The images have been edited to improve the readability of the measurements.

For each nodule identified, the readers used both software packages to record the following:

- Nodule segmentation success or failure (whether the software tool provided a result or notified the user of measurement failure). Failure was defined as three consecutive failed attempts at segmentation;
- Nodule segmentation adequacy or inadequacy (in case of segmentation success, this is a subjective impression by the reader of full nodule inclusion while excluding any vessels and parenchymal consolidation);
- Nodule volume calculated semi-automatically with the software;
- Long - and short-axis nodule diameters (orthogonal and in the axial plane), determined manually with electronic callipers, rounded to one decimal place;
- "Mean attenuation of the adjacent lung parenchyma" in HU, obtained after using the PACS region-of-interest (ROI) tool to delineate an area of about 5 mm thickness surrounding the nodule, rounded to one decimal place (Fig. 2);
- Presence or absence of signs suggestive of interstitial lung abnormalities (ILA) or ILD, emphysema, pleural plaques, and linear atelectasis.

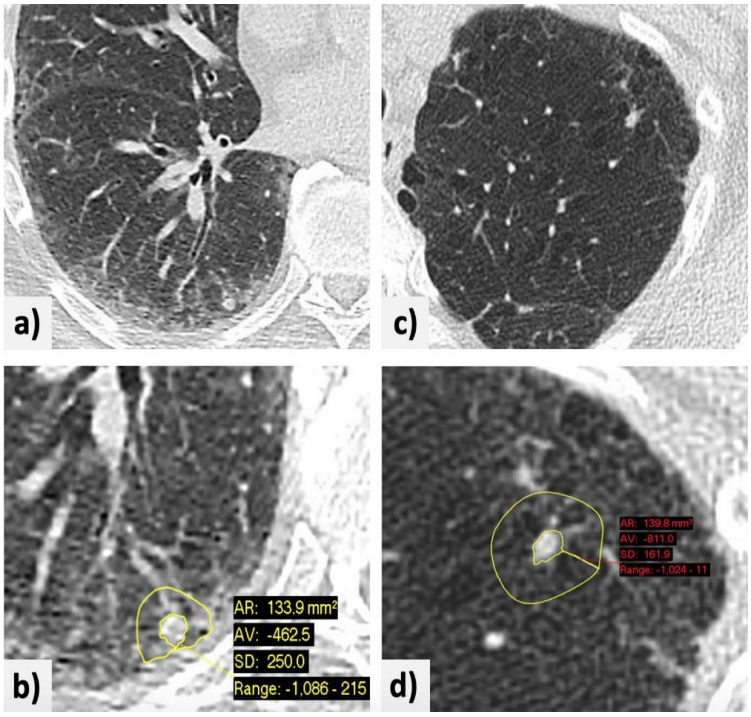

Figure 2 - Examples of the measurement of lung nodules in lung parenchyma with attenuation changes.

a - A small subpleural nodule in the right lower lobe of the lung of a patient with known interstitial lung disease.

b - The nodule is shown with a region of interest drawn manually around it, with a rim of about 5 mm. The average attenuation of the adjacent lung parenchyma on this slice is – 462.5 HU;

c - A nodule in the anterolateral aspect of the left upper lobe of the lung in a patient with known centrilobular and paraseptal emphysema;

d - Manual measurement of the average attenuation of the surrounding lung parenchyma (-811 HU).

Statistical analysis

The clinical and imaging data were analysed using SPSS software (ver. 26.0; IBM Corporation, Armonk, NY, USA). The investigators created the dichotomous variable 'Proper segmentation' for all included cases to reflect the segmentation success and adequacy. They also calculated the continuous variable 'Average of long and short diameters' for all cases, reflecting the average of the nodule's long- and short-axis, manually measured diameters (following the Fleischner Society recommendation) (55).

A descriptive statistical analysis was performed, including sample mean, standard deviation (SD), minimum, maximum and quartiles.

The data were analysed using a binary logistic regression model, with 'Proper segmentation' serving as the dependent variable and 'Average of long and short diameters', 'Mean attenuation of the adjacent lung parenchyma', reader, software package, patient age and sex, and relevant epidemiological factors (previous lung surgery, ILAs/ILD, emphysema, COPD, TB, calcified pleural plaques, and linear atelectasis; reference = absent for all variables) serving as independent variables (predictors).

Automatic selection of the significant independent variables was performed (significance threshold of 0.10). The Nagelkerke R2 value was used to assess how much of the variance of the dependent variable ('Proper segmentation') is explained by the independent variables. The Hosmer– Lemeshow chi-squared goodness-of-fit test and the omnibus

test of model coefficients were used to assess the model's overall fit. Analyses of variance between readers and software packages were performed using the one-way ANOVA test. The intraclass correlation coefficient (ICC) and an absolute agreement–type two-way mixed model, were used to assess interobserver and intersoftware agreement.

3.2 Methods of additional studies conducted

3.2.1 Pulmonary diseases with abnormal parenchymal density: Is this a problem in lung cancer screening?

The general premise of my hypothesis was presented to the medical community in a publication in which I expand on the reasons that led me to investigate this important issue.

3.2.2 Incidental findings in Lung Cancer Screening: Pictorial Essay & Systematic checklist

Numerous incidental findings were detected during the review of the cases for this study. Lack of uniformity in how we report and express management recommendations to the incidental findings observed during the study justified the need for a separate publication proposing a more uniform approach to incidental findings on LCS studies, providing recommendations for the reporting and management, including the description and analysis of changes that increase the attenuation of the lung parenchyma.

Ethical approval

The Institutional Research Committee Review Board approved the research study and waived the requirement for written informed consent due to the use of existing clinical data.

Study sample

The study is a retrospective cross-sectional study.

The study sample is a subset of the study sample of the main study, with scans performed between October and December of 2018 using the same CT scanner equipment and LDCT protocol parameters.

Readers and measurements

A single thoracic radiologist reviewed the images and identified scans with features of IFs defined as LDCT findings that can potentially affect the patient's health and are unrelated to the primary purpose of identifying lung cancer (18).

Statistical analysis

- A simple descriptive statistical analysis was performed, including the incidence of each identified IF.

(Appendix 3)

3.2.3Lung cancer associated with cystic airspaces: a new radiological presentation of lung cancer

In my studies during this research, I observed that lung cancer with cystic characteristics could be misdiagnosed or overlooked and that they are not well detected or segmented by the current AI systems. I, therefore, felt appropriate to prepare an additional publication to alert the medical community regarding types of lung cancer associated with cystic airspaces.

Ethical approval

The Institutional Research Committee Review Board approved the research study and waived the requirement for written informed consent due to the use of existing clinical data.

Study sample

The study is a retrospective cross-sectional study.

The study sample is a subset of the study sample of the main study, with scans performed between January and December of 2018 using the same CT scanner equipment and LDCT protocol parameters.

Readers and measurements

A single thoracic radiologist reviewed the images and identified scans with features suggestive of lung cancer associated with cystic airspaces. For each patient, we identified other archived LDCT scans with the same set of features in the PACS system of the institution.

For each identified patient, we screened the images for all available scans and the respective clinical records to identify patients with a high probability of pericystic lung cancer.

No statistical analysis was performed

(Appendix 4).

4. Results

4.1 Original research study - "Lung cancer screening and the impact of lung parenchyma in pulmonary nodule volumetry."

One thousand four hundred and ninety-seven participants were enrolled in the screening program between August 2016 and December 2018 and had at least one chest LDCT examination during this period. Some participants had additional LDCT scans performed under this LCS program outside of this time frame, which were also included in the study. The earliest scan was dated from 5th April 2016, and the latest was from 2nd August 2020. Data from 971 patients were excluded due to the absence of qualifying lung nodules. Data from three patients were excluded due to respiratory motion artefacts and interpreted as not representing true nodules.

One additional patient was excluded due to a technical issue specific to one software package that failed to access the patient's records. The final sample consisted of 5060 measurements (1265/observer/software package) taken on CT studies of 514 patients (figure 3).

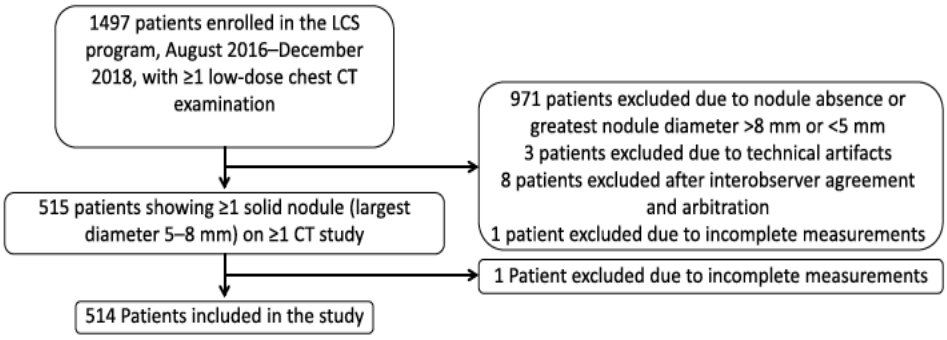

Figure 3 - Flow chart of patient selection and inclusion. LCS, lung cancer screening; CT, computed tomography.

The patients' demographic and clinical characteristics are summarized in Table 3.

Characteristic	*n* (%) or mean ± SD (*n* = 1265)
Age (years)	68.3 ± 5.1
Sex	
Male	888 (70.2)
Female	377 (29.8)
Previous lung surgery	
No	1238 (97.9)
Yes	27 (2.1)
Chronic obstructive pulmonary disease	
No	1198 (94.7)
Yes	67 (5.3)
Tuberculosis	
No	1258 (99.4)
Yes	7 (0.6)

SD, standard deviation

Table 3 - Patients' Demographic and Clinical Characteristics.

Readers 1 and 2 recorded 'Proper segmentation' (defined as success and adequacy of the segmentation) more frequently with tool 2 (88.1% and 88.4%, for reader 1 and reader 2, respectively) than with tool 1 (84.8% and 83.8%, for reader 1 and reader 2, respectively). For readers 1 and 2, the mean nodule volumes (cm3) obtained using tool 1 (102.7 ± 257.7 and 100.3 ± 250.6, for reader 1 and reader 2 respectively) were greater than those obtained using tool 2 (97.1 ± 105.5 and 95.5 ± 98.5, for reader 1 and reader 2 respectively).

For both tools, the volumes recorded by reader 1 were greater than those recorded by reader 2. Both readers also recorded greater 'Average of long and short diameters' (mm) values with tool 2 (5.51 ± 0.94 and 5.51 ±0.95, for reader 1 and reader 2 respectively) than with tool 1 (5.38 ± 0.96 and 5.37 ± 0.96, for reader 1 and reader 2 respectively).

'Average of long and short diameters' values obtained with each software package were similar between readers.

Both readers obtained greater 'Mean attenuation of the adjacent lung parenchyma' values (Hounsfield Units; HU) with tool 1 (– 761.1 ± 85.3 and – 760.3 ± 84.7, for reader 1 and reader 2 respectively) than with tool 2 (– 787.8 ± 82.4 and – 787.5 ± 82.0, for reader 1 and reader 2 respectively). 'Mean attenuation of the adjacent lung parenchyma' values obtained with each software package were similar between readers (Table 4).

Variable	Reader	Tool	*n*	Mean ± SD	Min	Q1	Q2	Q3	Max
Volume (cm^3)	Global		5030	98.9 ± 193.2	0.0	43.5	67.0	100.0	8200.0
	Reader 1	Tool 1	1250	102.7 ± 257.7	3.0	43.9	67.4	100.0	8200.0
		Tool 2	1264	97.1 ± 105.5	0.0	42.0	66.5	110.0	1401.0
	Reader 2	Tool 1	1251	100.3 ± 250.6	1.3	44.0	67.2	100.0	8200.0
		Tool 2	1265	95.5 ± 98.5	0.0	43.0	66.0	110.5	1402.0
Calipers1 (mm)	Global		5060	6.19 ± 1.12	4.0	5.3	6.1	7.0	10.0
	Reader 1	Tool 1	1265	6.13 ± 1.11	4.4	5.2	6.0	7.0	8.4
		Tool 2	1265	6.27 ± 1.11	4.2	5.4	6.2	7.1	9.3
	Reader 2	Tool 1	1265	6.11 ± 1.12	4.0	5.2	6.0	7.0	9.0
		Tool 2	1265	6.26 ± 1.11	4.0	5.3	6.1	7.1	10.0
Calipers2 (mm)	Global		5060	4.68 ± 1.00	1.9	4.0	4.6	5.3	9.1
	Reader 1	Tool 1	1265	4.62 ± 1.00	2.2	3.9	4.5	5.2	8.3
		Tool 2	1265	4.74 ± 1.00	2.3	4.1	4.6	5.3	9.1
	Reader 2	Tool 1	1265	4.63 ± 1.00	1.9	3.9	4.5	5.2	8.5
		Tool 2	1265	4.75 ± 0.99	2.6	4.1	4.6	5.3	8.4
MeanDiameter (mm)	Global		5060	5.44 ± 0.95	3.2	4.7	5.3	6.1	9.2
	Reader 1	Tool 1	1265	5.38 ± 0.96	3.4	4.7	5.2	6.0	8.3

Variable	Reader	Tool	*n*	Mean ± SD	Min	Q1	Q2	Q3	Max
	Reader 2	Tool 2	1265	5.51 ± 0.94	3.6	4.8	5.4	6.2	9.2
		Tool 1	1265	5.37 ± 0.96	3.2	4.7	5.2	6.0	8.8
		Tool 2	1265	5.51 ± 0.95	3.6	4.8	5.4	6.2	8.7
AdjacentLung (HU)	Global		5060	−774.2 ± 84.7	−937.0	−833.0	−790.2	−735.8	−296.0
	Reader 1	Tool 1	1265	−761.1 ± 85.3	−933.4	−821.0	−775.2	−722.5	−306.8
		Tool 2	1265	−787.8 ± 82.4	−932.0	−845.0	−804.0	−752.0	−317.0
	Reader 2	Tool 1	1265	−760.3 ± 84.7	−925.9	−819.9	−775.4	−722.4	−315.1
		Tool 2	1265	−787.5 ± 82.0	−937.0	−845.0	−805.0	−749.5	−296.0

SD, standard deviation; **Min**, minimum; **Q**, quartile; **Max**, maximum; **Volume**, semi-automatic volume measurement by the volumetric tool; **Callipers1**, long-axis diameter of the lung nodule, measured manually using electronic callipers; **Callipers2**, short-axis diameter of the lung nodule, measured manually using electronic callipers; **MeanDiameter**, arithmetic mean of long and short-axis diameters of the lung nodule, measured manually using electronic callipers; **AdjacentLung**, average attenuation in Hounsfield Units of the lung parenchyma surrounding the nodule.

Table 4 - Results for Quantitative Variables.

The binary logistic regression model included data from 5030 valid cases after excluding 30 cases with missing values. The Hosmer–Lemeshow test verified the goodness of model fit ($\chi 2\ 8 = 15.23$, $p = 0.055$), and the omnibus test indicated that the model with predictors differed significantly from the model with only the intercept ($\chi 2\ 5 = 1601.47$, $p < 0.001$). The Nagelkerke R2 value indicated that the model explained 50.3% of the variation in the dependent variable.

The odds of 'Proper segmentation' increased by a factor of 1.558 (95% confidence interval (CI), 1.350–1.797) with each 1-mm increase in 'Average of long and short diameters' ($p < 0.001$) and by a factor of 3.414 (95% CI 1.575–7.401) with a previous history of lung surgery ($p = 0.002$); they decreased by a factor of 0.984 (95% CI 0.982–0.986) with each 1-mm^3 increase in nodule volume ($p < 0.001$), by a factor of 0.987 (95% CI 0.985–0.988) with each 1HU increase in 'Mean attenuation of the adjacent lung parenchyma' ($p < 0.001$), and by a factor of 0.593 (95% CI 0.414–0.849) in the presence of calcified pleural

plaques (p = 0.004). No other variable significantly predicted 'Proper segmentation' (Table 5).

Variable	OR	95% CI	*p*	Effect size
Arithmetic mean of the largest orthogonal diameter	1.558	1.350–1.797	*** <0.001	0.006
Volume	0.984	0.982–0.986	*** <0.001	0.033
Mean attenuation of the adjacent lung parenchyma	0.987	0.985–0.988	*** <0.001	0.195
Previous lung surgery	3.414	1.575–7.401	** 0.002	0.000
Pleural plaques	0.593	0.414–0.849	** 0.004	0.002
Excluded variables			***p***	
Observer			0.584	
Software			0.385	
Age			0.083	
Sex			0.875	
ILA/ILD			0.488	
Emphysema			0.169	
COPD			0.952	
Tuberculosis			0.401	
Linear atelectasis			0.096	

OR, odds ratio; **CI**, confidence interval; *** p < 0.001; ** p < 0.01; **ILA**, interstitial lung abnormality; **ILD**, interstitial lung disease; **COPD**, chronic obstructive pulmonary disease.

Table 5 - Parameter Estimates for the Prediction of Nodule Segmentation Success and Adequacy.

The effect size was greatest for 'Mean attenuation of the adjacent lung parenchyma' (ζ2 = 0.195), followed by nodular volume (ζ2 = 0.033). ICCs for the whole sample and tools 1 and 2 (0.905 (95% CI 0.897–0.912), 0.885 (95% CI 0.872–0.897), and 0.929 (95% CI 0.920–0.936), respectively) indicated very high intersoftware reliability and greater reliability of tool 2 than of tool 1. Analysis of variance (ANOVA) revealed no significant difference between readers for the whole sample ($F_{1,2519} = 0.962$, p = 0.327), tool 1 ($F_{1,1264} = 2.452$, p = 0.118), or tool 2 ($F_{1,1264} = 0.257$, p = 0.621). Similarly, ICCs (0.745

(95% CI 0.722–0.766), 0.741 (95% CI 0.710–0.769), and 0.749 (95% CI 0.717–0.778) for the whole sample, reader 1 and reader 2, respectively) indicated reasonable interobserver reliability, with no significant difference between readers. ANOVA revealed significant differences between software packages for the whole sample ($F_{1,2519} = 41.642$, $p < 0.001$), reader 1 ($F_{1,1264} = 14.615$, $p < 0.001$), and reader 2 ($F_{1,1264} = 28.166$, $p < 0.001$).

4.2 Results of additional studies conducted

From the marginal aspects of my primary research, additional studies provided new insights into the role of volumetry in the case of diseases presenting with abnormal parenchymal attenuation.

It was also highlighted the importance of collecting imaging data as part of a large LCS programme and the opportunities it raises to advance knowledge regarding IFs and the evolution of a new presentation of lung cancer, which is poorly recognised.

4.2.1 Pulmonary diseases with abnormal parenchymal density - Is this a problem in lung cancer screening?

Based on the results and iconography collected during this study and an extensive literature review of lung nodule volumetry in LCS, I have also published a letter to the editor alerting the medical community to the problem of abnormal parenchymal attenuation in LCS.

This was to show that the usefulness of volumetry tools is degraded in areas of abnormal parenchymal attenuation.

This point is illustrated with an example clearly showing the extent of the problem.

With this publication, I aim to increase the medical community's awareness of limiting factors of volumetry tools, focusing mainly on the influence of lung parenchymal density on lung nodule volumetry tools.

4.2.2 Incidental findings in Lung Cancer Screening: Pictorial Essay & Systematic checklist

The results from this study confirm that IFs are common in LCS CT scans. The collected iconography was used to illustrate the wide range of pathologies incidentally identified in LCS.

I present a pictorial essay and systematic checklist on incidental findings in LCS CT to illustrate the most common IFs on LCS, organized by organ.

In the publication, a review was made of the current literature on IFs on LCS, focusing on their prevalence, appropriate communication, and triggering of clinical pathway systems.

Based on my daily clinical practice and experience as an LCS-certified reporting radiologist working in a multidisciplinary team, we present an illustrated checklist and recommendation proposal for the reporting and a standard management approach based on the systematic checklist proposed by the ESR/ERS position paper.

With this publication, I aim to illustrate and review a systematic checklist proposed by the ESR/ERS position paper to alert the importance of a standard approach for evaluating these findings on LCS programs.

4.2.3 Lung cancer associated with cystic airspaces: a new radiological presentation of lung cancer

Lung cancer associated with cystic airspaces is increasingly recognised due to the introduction of LCS programmes. I published a letter to the editor discussing this new presentation of lung cancer and providing new insights into the pathogenesis of early lung cancer

This letter to the editor was based on the argument that LCS programs provide an important prospect for learning and understanding the natural history of lung cancer and new morphological appearances. The support for this letter was the experience during daily clinical work and the marginal findings (not part of the established variables of the original research study) found during the database collection.

An easy-to-understand visual aid to exemplify the classification of this entity was added (Figure 4).

With this publication, I aim to bring the attention of the medical community to this new radiological presentation of lung cancer, once thought to be rare but, in recent years, more commonly recognized regarding screening and follow-up.

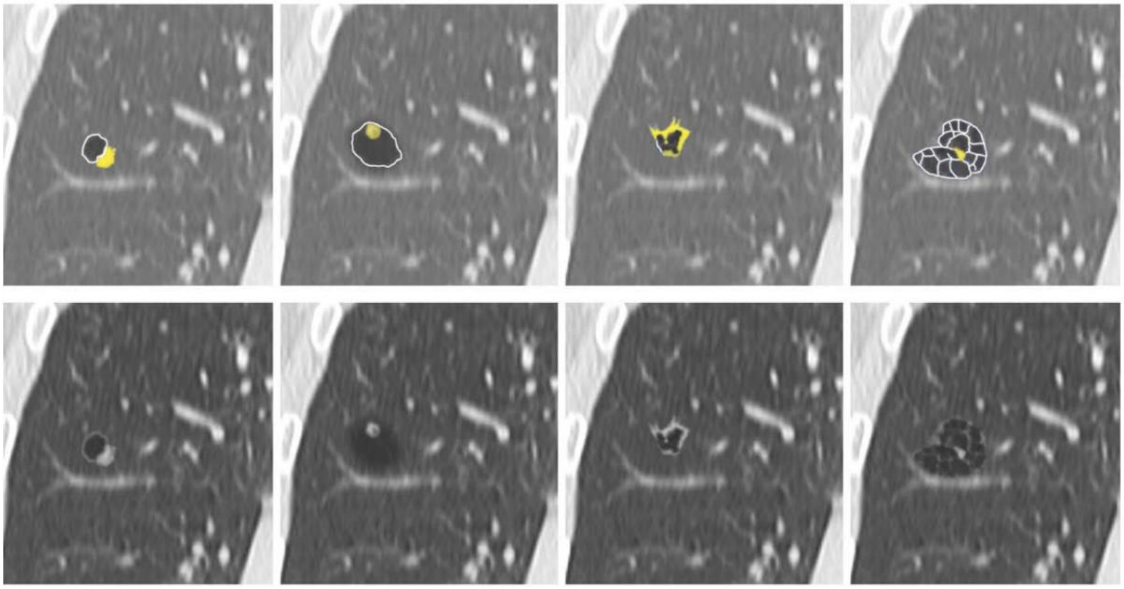

Figure 4. Morphological classification of cystic/pericystic lung lesions. The drawings in the first row of images simulate the different types of cystic/pericystic lung lesions on CT scans: Type I – a nodular lesion outside the cyst wall; type II – a nodular lesion inside the cyst wall; type III – cyst wall thickening without a focal nodule; and type IV – a focal nodule within a complex multicystic lesion.

5. General discussion

5.1 Original research study - "Lung cancer screening and the impact of lung parenchyma in pulmonary nodule volumetry."

This study showed that the probability of proper segmentation of lung nodules with diameters of 5–8 mm is related mainly to the 'Mean attenuation of the adjacent lung parenchyma', followed by nodule volume and the 'Average of long and short diameters'. Given the global variability of 'Mean attenuation of the adjacent lung parenchyma', this finding could have substantial clinical implications.

The results of this study also indicate that the probability of proper segmentation using volumetric software is reduced for smaller nodules (i.e., nodules with smaller diameters). This finding is in line with previous reports that smaller nodules exhibit higher volumetric variability (up to 30% for nodules with diameters < 6 mm) (61,63).

The decreased probability of proper segmentation found in nodules with increasing volume (related to nodule diameter but measured automatically by the volumetry tools) is counterintuitive. This finding may be explained by the fact that the volume calculation relies on the volumetric tool's algorithm. At the same time, the diameter (i.e., the variable 'Average of long and short diameters') is calculated from the manually measured long- and short-axis diameters and, as such, describes the observer's assessment of the nodule (not the tool's measurement). Since an inadequate nodule segmentation is likely to involve over-segmentation and overestimation of volume, this inverse correlation between volume with proper segmentation may reflect an increase in the error of measurement by the volumetric tool. In other words, the over-segmentation is more likely to occur in smaller nodules (in diameter), leading to a higher error and increased volume due to the inclusion of other structures in the adjacent parenchyma.

A previous history of lung surgery and the presence of calcified pleural plaques were also significantly related to proper segmentation in this study, although their effect sizes were negligible. Previous lung surgery increased the probability of adequate segmentation, possibly because partial and total pneumonectomies promote significant changes in vascular and respiratory mechanisms via compensatory overexpansion of the remaining lung. The compensatory, hormonally regulated growth of the remaining lung lobes may also be involved in the attempt to restore normal mass, structure, and function (115–117). However, the literature contains no report on changes in lung parenchyma attenuation

after lung surgery. The negligible effect size and the small number of patients with previous histories of lung surgery in the sample should caution against overinterpretation. The presence of pleural plaques reduced the probability of proper segmentation, possibly due to the architectural distortion of the lung parenchyma that it causes. Also, a systematic review of changes in lung function concerning the presence of pleural plaques in asbestos-exposed population showed a relationship between pleural plaques and changes in respiratory function in the form of a trend towards a restrictive pattern with decreased forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) (118,119). This change in the lung volumes / restrictive pattern may be explained by a subtle increase in the mean lung density due to the decreased lung expansion and therefore lowers the quality of the segmentation of the nodules. Likewise, pleural plaques are associated with an increased lung attenuation due to fibrosis.

The dataset used in this study did not contain information about the proximity of the measured nodules to focal parenchymal changes, such as surgical scars or pleural plaques, which renders interpretation difficult and the model incomplete. This factor could also help to explain the non-significant effect of ILA/ILD-related changes in the model, despite the apparent impact of the average attenuation of the lung parenchyma adjacent to the nodule (117,120–122).

A cut-off of -950 HU is the most widely accepted threshold in quantitative analysis for distinguishing emphysema from normal lung tissue (58,90,91). This threshold is based on the routine full-dose chest CT protocol used in clinical practice. All values in the sample exceeded this threshold, regardless of the presence of emphysema, which could be related to the lower signal-to-noise ratio of the low-dose protocol used in screening. Another interpretation could involve the distortion of the parenchyma by the nodule itself, influencing its surrounding attenuation. As far as the author is aware, no specific threshold has been defined for low-dose protocols. I suspect that it would differ from that used for full-dose protocols, but more evidence is needed.

Analysis of mean values revealed differences in volume measurements between software packages and readers for automatic measurements. Conversely, for manual measurements (long and short-diameter measurements and attenuation of the lung parenchyma adjacent to the nodule), there were only differences between software packages (not readers). I also found good performance in terms of interobserver and intersoftware reliability, although less so for the latter. This finding is in line with the current recommendation that follow-up studies performed in LCS programs be reported by the same reader and performed using the same software package as the baseline study.

These findings also suggest that the manual measurements of short- and long-axis diameters are more reliable among readers than the volumetric tools' automatic measurements.

The present study was conducted with a large sample of nodule measurements, larger, to my knowledge, than any other published series. However, it has several limitations, including the use of a nonstandard measurement of lung parenchymal attenuation (selected as a reasonable compromise, as no standard exists) and a lack of information on the location of focal parenchymal changes (i.e., pleural plaques and changes resulting from previous lung surgery) relative to lung nodule location. Future research could further investigate the impact of nodule size on the results (i.e., is the impact of the average attenuation of the lung parenchyma adjacent to the nodule in the nodule segmentation more significant in smaller nodules?) and on the estimation of a nodule's VDT (is the VDT a reliable indicator of nodule's growth in nodules with abnormal average attenuation of the lung parenchyma adjacent to the nodule?).

5.2 Discussion of additional studies conducted

5.2.1Pulmonary diseases with abnormal parenchymal density - Is this a problem in lung cancer screening?

Healthcare systems worldwide are implementing LCS programs using LDCT and new software tools for lung nodule detection and segmentation, including automated and semi-automated pulmonary nodule volumetry.

There are recognized limiting factors influencing these volumetry tools. Some of these factors may be related to the CT scanner, acquisition parameters (e.g., slice thickness, section overlap, kernel, reconstruction algorithm), the software, the patient or the nodule itself (e.g., acquisition in inspiration or expiration, size, location, shape, or density) (46).

However, little has been researched on the influence of lung parenchymal attenuation on these tools, even though pulmonary diseases that cause attenuation are common in chest CT studies.

It would be intuitive to consider that diseases that cause decreased lung attenuation, such as cysts and emphysema, would improve the delineation of nodule margins when the decreased lung attenuation is adjacent to the nodule. In turn, this would potentially improve the accuracy of the volumetry tool and reduce its variability. However, few studies have investigated diseases that cause decreased lung attenuation, such as cysts

and emphysema, as factors influencing lung nodule volumetry. So far, no study has shown a consistent effect (46,123).

In the original research study presented in this thesis, it was found that an increased lung attenuation adjacent to a nodule is inversely related to the likelihood of good segmentation of that same nodule by volumetry tools. This letter to the editor discusses the results of the original research to alert the medical community that caution should be exercised in using dedicated lung nodule volumetry tools in patients with diseases accompanied by increased lung density when nodules are located in affected areas.

5.2.2 Incidental findings in Lung Cancer Screening: Pictorial Essay & Systematic checklist

IFs on LCS can be defined as low-dose CT findings that can affect the patient's health and are unrelated to the primary purpose of identifying lung cancer (18,124,125).

The reported prevalence of IFs on LCS ranges from 1% to as high as 94% in recent reports (33,123–125).

Most IFs are benign and clinically insignificant, but some require urgent recognition and further management (33). The most common IFs in LCS are pulmonary (69%), cardiovascular (67%), and gastrointestinal findings (25%).

Different communication strategies have been suggested for reporting IFs on LCS. The ACR has published the Lung CT Screening Reporting and Data System (Lung-RADS) from the ACR, which provides the S modifier for clinically or potentially clinically significant non-lung cancer findings. However, this tool does not help the radiologist to choose IFs to include in the report or to make a management recommendation (126). The ESR and the European Respiratory Society (ERS) recommend the reporting of IFs of clinical significance (i.e., with a significant or adverse impact or for which there is an established intervention that benefits the patient) and general agreement (i.e., minimal interobserver variation), including a recommendation for intervention. This recommendation falls within one of four categories (levels of management): immediate action, the likelihood of non-pulmonary cancer, further investigation, and clinically insignificant (18).

Screening programs should develop a standard approach for the evaluation of these findings. Developing a standard approach to reporting and management of IFs on LCS would promote research into their impact on reducing overall mortality, as well as the development of automatic detection, measurement, and data-mining tools based on AI.

This evidence-based approach could inform public opinion and the political decision-making process while optimizing the cost-effectiveness of LCS programs and the health gains for their participants.

This pictorial illustrates the systematic checklist proposed by the ESR/ERS position paper, intending to improve radiologists' awareness of IFs, especially those with potential clinical relevance.

5.2.3 Lung cancer associated with cystic airspaces: a new radiological presentation of lung cancer

Lung cancers associated with cystic airspaces are usually diagnosed late (36,37). Early diagnosis is difficult given the significant overlap of imaging features between cystic/pericystic malignancies and inflammatory or infectious lesions. The differential diagnoses of cystic/pericystic malignancies include common pathologies like cavitated lesions, as seen in tuberculosis, squamous cell carcinoma, aspergilloma, and rheumatoid nodules. They can even be challenging to distinguish from a severe form of emphysema, distal airway enlargement, or fibrosis. Rare mimickers of these malignancies include amyloid nodules and cystic lung metastasis.

These cancers are becoming more apparent since the introduction of LCS programmes using chest LDCT (37). With this publication, the author aimed to increase the awareness of radiologists and pulmonologists for this type of lesion in LCS, providing a short review of the morphological classification (type I to IV), physiopathology, and pitfalls in CT and PET-CT.

6. Conclusion

The original research study concludes that for lung nodules measuring between 5 and 8 mm in long-axis diameter, an increase in the average attenuation of the adjacent lung parenchyma is related to a decrease in the quality of the nodule's segmentation by volumetric tools, contributing to measurement error. Radiologists and chest physicians should be careful when interpreting the results from volumetry tools in patients with abnormal lung parenchymal attenuation.

I published three other papers focusing on other essential aspects I faced as an LCS reporting radiologist and researcher.

The first paper is titled "Pulmonary diseases that cause abnormal lung parenchymal density: is this a problem in lung cancer screening?" I highlight the importance of improving the awareness of changes in lung parenchymal attenuation as a limiting factor of volumetry. As we move towards early lung cancer detection and the worldwide implementation of LCS programs, I believe that recognizing the potential pitfalls of volumetry tools is essential to deriving the benefits of evidence-based healthcare.

Another paper conveyed a critical insight into lung cancer associated with cystic airspaces, which was once thought to be a rare presentation of lung malignancy but has become more common due to the increased availability of CT scans. This second paper emphasises the morphological signs that must be recognised for a timely and accurate diagnosis.

The other subject was the importance of the incidental findings on LCS. Most IFs on LCS are benign and clinically insignificant but are increasingly recognized. Some require urgent referral for further diagnostic workup. I published a pictorial essay illustrating the systematic checklist proposed by the ESR/ERS position paper on IFs during LCS to familiarize radiologists and pulmonologists with these findings and their management level, especially in those with potential clinical relevance.

Overall, I conclude from my research that (1) radiologists and respiratory physicians should be careful in interpreting volumetry results in LCS for nodules between 5-8mm and in the presence of abnormal lung parenchymal attenuation; (2) LCS radiologists need to be prepared to recognize new morphological appearances of lung cancer and promote early diagnosis and; (3) radiologists need to be aware of the incidental findings that the screening studies identify and how to properly manage these with appropriate communication and triggering of clinical pathway systems.

7. Future perspectives

My study showed that parenchymal changes surrounding a nodule affect its volume measurement. This result is relevant as many pathologies that present parenchymal changes (e.g., ILD) also have an increased incidence of pulmonary nodules. The following step will be to define the clinical implication of these results.

The growth estimation of a pulmonary nodule relies on comparing two volume measurements over a period. The calculation of the VDT (i.e., growth estimation) is a performant indicator of the risk of malignancy of pulmonary nodules between 5 and 8mm. The VDT is highly sensitive to measurement error unless the error at the two time-points (i.e., baseline and follow-up measurement) cancel each other out, or in other words unless the error is constant. A constant measurement error implies lower accuracy but high precision (i.e., low variability between consecutive measurements).

From the original study, it is not clear the extent to which the accuracy and precision of the measurement are affected by the parenchymal changes adjacent to the nodule, and this is a topic for future research.

It is also unclear if parenchymal changes not directly adjacent to the nodule might also be relevant. Other authors have shown that global parenchymal changes do not predict changes to the accuracy of volumetry. However, it is still unclear how localized the changes must be.

My research also revealed opportunities to study the natural history and evolution of peri-cystic lung cancer. Imaging data from LCS may be useful to investigate further the evolution of other lung cancer presentations and other diseases that might share risk factors.

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Appendix

Appendix 1 - Lung cancer screening and the impact of lung parenchyma in pulmonary nodule volumetry

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Insights into Imaging

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The impact of lung parenchyma attenuation on nodule volumetry in lung cancer screening

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Abstract

Background: Recent recommendations for lung nodule management include volumetric analysis using tools that present intrinsic measurement variability, with possible impacts on clinical decisions and patient safety. This study was conducted to evaluate whether changes in the attenuation of the lung parenchyma adjacent to a nodule affect the performance of nodule segmentation using computed tomography (CT) studies and volumetric tools.

Methods: Two radiologists retrospectively applied two commercially available volumetric tools for the assessment of lung nodules with diameters of 5–8 mm detected by low-dose chest CT during a lung cancer screening program. The radiologists recorded the success and adequacy of nodule segmentation, nodule volume, manually and automatically (or semi-automatically) obtained long- and short-axis measurements, mean attenuation of adjacent lung parenchyma, and presence of interstitial lung abnormalities or disease, emphysema, pleural plaques, and linear atelectasis. Regression analysis was performed to identify predictors of good nodule segmentation using the volumetric tools. Interobserver and intersoftware agreement on good nodule segmentation was assessed using the intraclass correlation coefficient.

Results: In total, data on 1265 nodules (mean patient age, 68.3 ± 5.1 years; 70.2% male) were included in the study. In the regression model, attenuation of the adjacent lung parenchyma was highly significant (odds ratio 0.987, $p < 0.001$), with a large effect size. Interobserver and intersoftware agreement on good segmentation was good, although one software package performed better and measurements differed consistently between software packages.

Conclusion: For lung nodules with diameters of 5–8 mm, the likelihood of good segmentation declines with increasing attenuation of the adjacent parenchyma.

Keywords: Lung cancer screening, Volumetry, Segmentation, Interstitial lung disease

Key points

- Lung nodule volumetry is currently recommended for lung nodule management.
- Artificial intelligence tools for volumetric analysis still present with some limiting factors.
- Location, size, shape, density are the most common factors affecting nodule volumetry.
- Attenuation of the lung parenchyma is another limiting factor for nodule volumetry.
- Recognition of these factors has impact on clinical decisions and patient safety.

Background

Although lung nodule management guidelines historically have recommended the measurement of nodules using electronic calipers, artificial intelligence tools are increasingly used for nodule detection and measurement. This shift was introduced mainly in the Dutch–Belgian

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lung cancer screening (*Nederlands–Leuvens Longkanker Screenings Onderzoek* or NELSON) trial, and was subsequently integrated into the guidelines of the Fleischner Society and British Thoracic Society for incidental pulmonary nodules with volumes exceeding 100 and 80 mm^3, respectively. These guidelines clearly identify micronodules (< 5 mm) as benign, and larger nodules (> 8 mm) as having a high risk of malignancy, as supported by data from the NELSON trial. For nodules between 5 and 8 mm, growth rate is a better discriminator between benign and malignant lesions than size or morphological characteristics [1, 2].

The recommendation that pulmonary nodules be measured volumetrically is based on the recognition that nodule diameter does not accurately reflect size or growth, as not all nodules are perfectly spherical or symmetrically growing. Thus, the calculation of nodule volume enables the use of better growth markers, such as the volume doubling time (VDT) [3].

Several recent studies have examined the reliability and limiting factors of pulmonary nodule volumetry, such as location (i.e., adjacency or connection to high-density structures), size, shape, and density [4–6]. Marked volumetric variability among studies for nodules smaller than 6 mm in diameter, and the high probability that the segmentation of ground-glass nodules with currently available software will fail, have been recognized [7, 8]. Technical factors, such as the number of detectors in the computed tomography (CT) scanner, administration of contrast medium, slice thickness, interpolation of reconstructed images, and reconstruction algorithm used, also affect the accuracy of volumetry [9–12].

However, little is known about the impact of changes in the density of adjacent lung parenchyma on the volumetric evaluation of a lung nodule; such changes may alter the degree of contrast between these structures. Empirically, an increase in contrast caused by certain pathological conditions (e.g., emphysema) is assumed to reduce the variability of volume measurement, whereas a decrease in contrast [e.g., due to interstitial lung disease (ILD)] is thought to increase this variability [12]. Data from lung cancer screening programs suggest that the prevalence of ILD is as high as 20% [13]. Effects on nodular volume calculation attributable to changes in the attenuation of the adjacent pulmonary parenchyma would have medical and therapeutic implications for a substantial number of patients and major financial impacts on lung cancer screening programs. This study was conducted to evaluate the effect of the degree of contrast of the parenchyma adjacent to a pulmonary nodule on nodule segmentation using volumetric software.

Materials and methods

The Institutional Research Committee Review Board approved this retrospective cross-sectional study (observational, analytical) and waived the requirement for written informed consent due to the use of existing clinical data.

Study sample

The study sample was derived from all patients participating in a lung cancer screening program in a tertiary hospital in Northeastern England between August 2016 and December 2018. All CT screening examinations were performed with the same equipment (Somatom Definition Flash; Siemens, Erlangen, Germany) using a low-dose CT protocol (Table 1). All CT studies without technical (e.g., respiratory motion) artifacts showing solid pulmonary nodules with diameters of 5–8 mm were included in this study. For the included patients, the clinical records were accessed via the hospital information system, and the following patient data were collected: patient age and sex and previous histories of chronic obstructive pulmonary disease (COPD), tuberculosis (TB), and lung surgery (Table 2).

Readers and measurements

Two cardiothoracic radiologists with 5 (reader 1) and 10 (reader 2) years of experience, respectively, identified and measured the pulmonary nodules, following the protocol

Table 1 Low-dose chest CT imaging protocol parameters

Range	Lung apices–bases
Respiratory phase	Inspiration, breath hold
Enhancement	None
Image reconstruction	2-mm thickness, 1-mm overlap
Kernels	B60f sharp/lung, B30f medium smooth/lung, B20f smooth/mediastinum
Acquisition parameters	kVp and mAs varied according to body habitus
Planned CTDI(vol)	2.03 mGy, with 120 kVp and quality reference of 30 mAs

CT, computed tomography

Table 2 Patients' demographic and clinical characteristics

Characteristic	*n* (%) or mean ± SD (*n* = 1265)
Age (years)	68.3 ± 5.1
Sex	
Male	888 (70.2)
Female	377 (29.8)
Previous lung surgery	
No	1238 (97.9)
Yes	27 (2.1)
Chronic obstructive pulmonary disease	
No	1198 (94.7)
Yes	67 (5.3)
Tuberculosis	
No	1258 (99.4)
Yes	7 (0.6)

SD, standard deviation

described in Fig. 1 and using the Carestream Vue PACS v 11.4.01.1011 (Carestream Health, Inc, Rochester, NY; tool 1) and Syngo via VB20 (Siemens Healthineers AG, Erlangen, Germany; tool 2) volumetric software packages. Disagreements among readers regarding the inclusion of a pulmonary nodule were resolved by consensus after a discussion between both readers and a third chest radiologist with more than 25 years of experience (consensus decision).

For each nodule identified, the readers used both software packages to record the following:

- Nodule segmentation success or failure (whether the software tool provided a result or notified the user of measurement failure). Failure was defined as three consecutive failed attempts at segmentation.
- Nodule segmentation adequacy or inadequacy (in case of segmentation success, this is subjective impression by the reader of full nodule inclusion and with vessel and parenchymal consolidation exclusion).
- Nodule volume, calculated semi-automatically with the software.
- Long- and short-axis nodule diameters (orthogonal and in the axial plane), determined manually with electronic calipers, rounded to one decimal place.

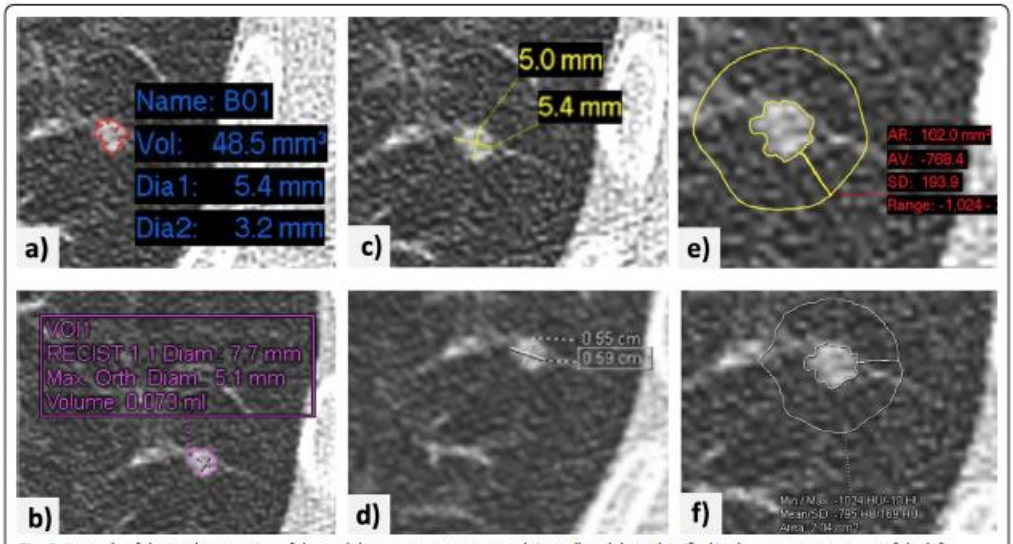

Fig. 1 Example of the implementation of the nodule measurement protocol. A small nodule is identified in the posterior segment of the left lower lobe of the lung. **a**, **b** The volumetric tools [Vue PACS, ver. 11.4.01.1011; Carestream© (tool 1) and Syngo via VB20, Siemens© (tool 2)] are used to segment the nodule, yielding volumes of 48.5 and 75 mm^3, respectively. **c**, **d** The longest orthogonal diameters are measured manually using electronic calipers tools in both software packages. **e**, **f** A region of interest (5-mm thickness) is drawn manually around the nodule for determination of the average attenuation of adjacent lung parenchyma (−768.4 and −795 HU obtained with tools 1 and 2, respectively). The images have been edited to improve the readability of the measurements

- *'Mean attenuation of the adjacent lung parenchyma'*, in Hounsfield units, obtained after using the PACS region-of-interest (ROI) tool to delineate an area of about 5 mm thickness surrounding the nodule, rounded to one decimal place (Fig. 2)
- Presence or absence of signs suggestive of interstitial lung abnormalities (ILA) or ILD, emphysema, pleural plaques, and linear atelectasis.

Statistical analysis

The clinical and imaging data were analyzed using SPSS software (ver. 26.0; IBM Corporation, Armonk, NY, USA). The dichotomous variable *'Proper segmentation'*, reflecting segmentation success and adequacy, and the continuous variable *'Average of long and short diameters'*, reflecting the average of the nodule's long- and short-axis, manually measured, diameters (following the Fleischner Society recommendation [1]), were created and values were calculated for all included cases.

A descriptive statistical analysis is performed including sample mean, standard deviation (SD), minimum, maximum and quartiles (Table 3).

The data were analyzed using a binary logistic regression model, with *'Proper segmentation'* serving as the dependent variable and *'Average of long and short diameters'*, *'Mean attenuation of the adjacent lung parenchyma'*, reader, software package, patient age and sex, and relevant epidemiological factors (previous lung surgery, ILAs/ILD, emphysema, COPD, TB, calcified pleural plaques, and linear atelectasis; reference = absent for all variables) serving as independent variables (predictors). Automatic selection of the significant independent variables was performed (significance threshold of 0.10). The Nagelkerke R^2 value was used to assess how much of the variance of dependent variable (*'Proper segmentation'*)

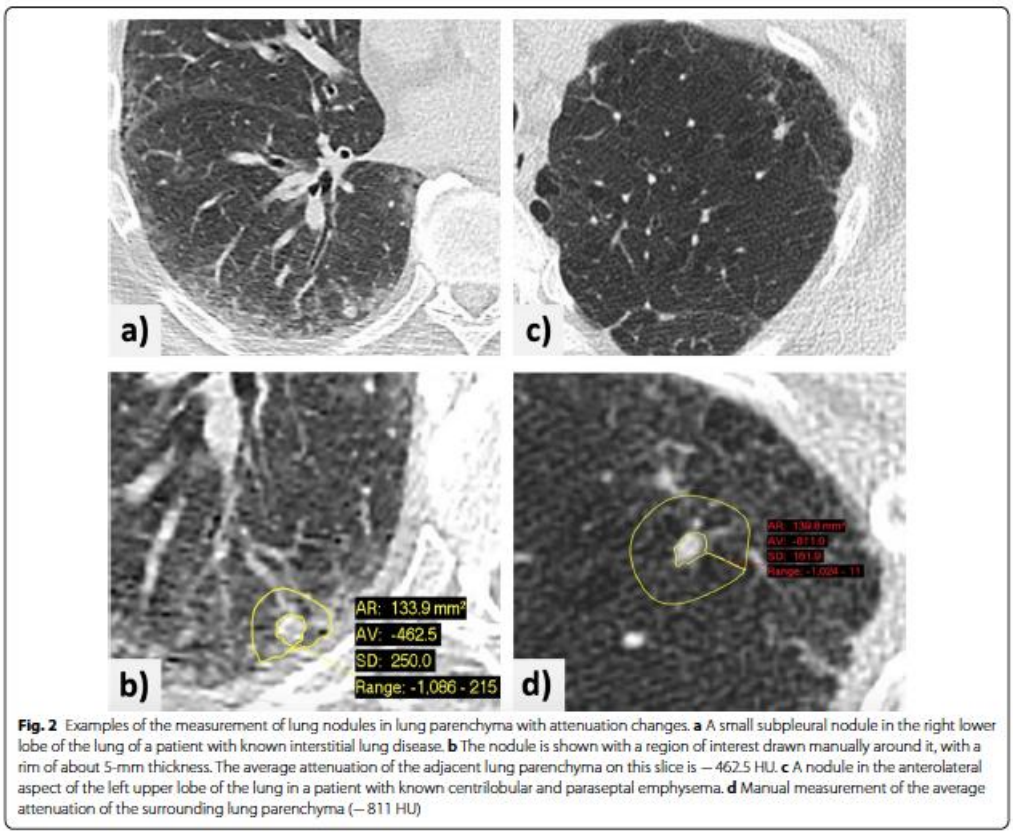

Fig. 2 Examples of the measurement of lung nodules in lung parenchyma with attenuation changes. **a** A small subpleural nodule in the right lower lobe of the lung of a patient with known interstitial lung disease. **b** The nodule is shown with a region of interest drawn manually around it, with a rim of about 5-mm thickness. The average attenuation of the adjacent lung parenchyma on this slice is −462.5 HU. **c** A nodule in the anterolateral aspect of the left upper lobe of the lung in a patient with known centrilobular and paraseptal emphysema. **d** Manual measurement of the average attenuation of the surrounding lung parenchyma (−811 HU)

Table 3 Results for quantitative variables

Variable	Reader	Tool	*n*	Mean ± SD	Min	Q1	Q2	Q3	Max
Volume (cm^3)	Global		5030	98.9 ± 193.2	0.0	43.5	67.0	100.0	8200.0
	Reader 1	Tool 1	1250	102.7 ± 257.7	3.0	43.9	67.4	100.0	8200.0
		Tool 2	1264	97.1 ± 105.5	0.0	42.0	66.5	110.0	1401.0
	Reader 2	Tool 1	1251	100.3 ± 250.6	1.3	44.0	67.2	100.0	8200.0
		Tool 2	1265	95.5 ± 98.5	0.0	43.0	66.0	110.5	1402.0
Manual long-axis diameter (mm)	Global		5060	6.19 ± 1.12	4.0	5.3	6.1	7.0	10.0
	Reader 1	Tool 1	1265	6.13 ± 1.11	4.4	5.2	6.0	7.0	8.4
		Tool 2	1265	6.27 ± 1.11	4.2	5.4	6.2	7.1	9.3
	Reader 2	Tool 1	1265	6.11 ± 1.12	4.0	5.2	6.0	7.0	9.0
		Tool 2	1265	6.26 ± 1.11	4.0	5.3	6.1	7.1	10.0
Manual short-axis diameter (mm)	Global		5060	4.68 ± 1.00	1.9	4.0	4.6	5.3	9.1
	Reader 1	Tool 1	1265	4.62 ± 1.00	2.2	3.9	4.5	5.2	8.3
		Tool 2	1265	4.74 ± 1.00	2.3	4.1	4.6	5.3	9.1
	Reader 2	Tool 1	1265	4.63 ± 1.00	1.9	3.9	4.5	5.2	8.5
		Tool 2	1265	4.75 ± 0.99	2.6	4.1	4.6	5.3	8.4
'Average of long and short diameters' (mm)	Global		5060	5.44 ± 0.95	3.2	4.7	5.3	6.1	9.2
	Reader 1	Tool 1	1265	5.38 ± 0.96	3.4	4.7	5.2	6.0	8.3
		Tool 2	1265	5.51 ± 0.94	3.6	4.8	5.4	6.2	9.2
	Reader 2	Tool 1	1265	5.37 ± 0.96	3.2	4.7	5.2	6.0	8.8
		Tool 2	1265	5.51 ± 0.95	3.6	4.8	5.4	6.2	8.7
'Mean attenuation of the adjacent lung parenchyma' (HU)	Global		5060	−774.2 ± 84.7	−937.0	−833.0	−790.2	−735.8	−296.0
	Reader 1	Tool 1	1265	−761.1 ± 85.3	−933.4	−821.0	−775.2	−722.5	−306.8
		Tool 2	1265	−787.8 ± 82.4	−932.0	−845.0	−804.0	−752.0	−317.0
	Reader 2	Tool 1	1265	−760.3 ± 84.7	−925.9	−819.9	−775.4	−722.4	−315.1
		Tool 2	1265	−787.5 ± 82.0	−937.0	−845.0	−805.0	−749.5	−296.0

SD, standard deviation; Min, minimum; Q, quartile; max, maximum

is explained by the independent variables. The Hosmer–Lemeshow chi-squared goodness-of-fit test and the omnibus test of model coefficients were used to assess the overall fit of the model. Analysis of variance between readers and software packages was performed using the one-way ANOVA test. The intraclass correlation coefficient (ICC) and an absolute agreement–type two-way mixed model were used to assess interobserver and intersoftware agreement.

Results

One thousand four hundred and ninety-seven participants were identified as being enrolled in the screening program between August 2016 and December 2018, and having at least one low-dose chest CT examination during this period of time. Some participants had additional low-dose CT scans performed under this LCS program outside of this time frame, and these were also included in the study. The earliest scan dated from 5th April 2016 and the latest from 2nd August 2020. Data from 971 patients were excluded due to the absence of qualifying lung nodules, data from three patients were excluded due to respiratory motion artifacts, and data from eight patients were excluded after consensus decision. One additional patient was excluded due to technical issue specific to one software package that failed to access the patient's records. The final sample consisted of 5060 measurements (1265/observer/software package) taken on CT studies of 514 patients (Fig. 3). The patients' demographic and clinical characteristics are summarized in Table 2.

Readers 1 and 2 recorded *'Proper segmentation'* (defined as success and adequacy of the segmentation) more frequently with tool 2 (88.1% and 88.4%, for reader 1 and reader 2 respectively) than with tool 1 (84.8% and 83.8%, for reader 1 and reader 2, respectively).

For readers 1 and 2, the mean nodule volumes (cm^3) obtained using tool 1 (102.7 ± 257.7 and 100.3 ± 250.6, for reader 1 and reader 2 respectively) were greater than those obtained using tool 2 (97.1 ± 105.5 and 95.5 ± 98.5, for reader 1 and reader 2 respectively). For both tools, the volumes recorded by reader 1 were greater than those recorded by reader 2. Both readers also recorded greater *'Average of long and short diameters'* (mm) values

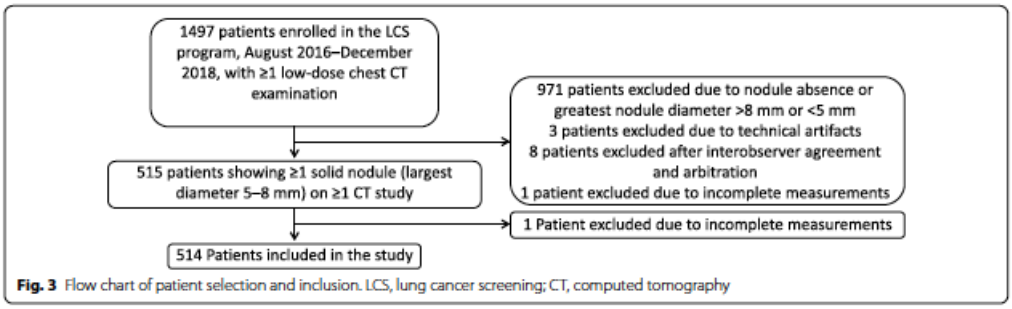

Fig. 3 Flow chart of patient selection and inclusion. LCS, lung cancer screening; CT, computed tomography

with tool 2 (5.51 ± 0.94 and 5.51 ± 0.95, for reader 1 and reader 2 respectively) than with tool 1 (5.38 ± 0.96 and 5.37 ± 0.96, for reader 1 and reader 2 respectively). *'Average of long and short diameters'* values obtained with each software package were similar between readers. Both readers obtained greater *'Mean attenuation of the adjacent lung parenchyma'* values (Hounsfield Units; HU) with tool 1 (−761.1 ± 85.3 and −760.3 ± 84.7, for reader 1 and reader 2 respectively) than with tool 2 (−787.8 ± 82.4 and −787.5 ± 82.0, for reader 1 and reader 2 respectively). *'Mean attenuation of the adjacent lung parenchyma'* values obtained with each software package were similar between readers (Table 3).

The binary logistic regression model included data from 5030 valid cases, after the exclusion of 30 cases with missing values. The Hosmer–Lemeshow test verified the goodness of model fit ($\chi^2_8 = 15.23$, $p = 0.055$) and the omnibus test indicated that the model with predictors differed significantly from the model with only the intercept ($\chi^2_5 = 1601.47$, $p < 0.001$). The Nagelkerke R^2 value indicated that the model explained 50.3% of the variation in the dependent variable.

The odds of *'Proper segmentation'* increased by a factor of 1.558 (95% confidence interval (CI), 1.350–1.797) with each 1-mm increase in *'Average of long and short diameters'* ($p < 0.001$) and by a factor of 3.414 (95% CI 1.575–7.401) with a previous history of lung surgery ($p = 0.002$); they decreased by a factor of 0.984 (95% CI 0.982–0.986) with each 1-mm^3 increase in nodule volume ($p < 0.001$), by a factor of 0.987 (95% CI 0.985–0.988) with each Hounsfield-unit (HU) increase in *'Mean attenuation of the adjacent lung parenchyma'* ($p < 0.001$), and by a factor of 0.593 (95% CI 0.414–0.849) in the presence of calcified pleural plaques ($p = 0.004$). No other variable significantly predicted *'Proper segmentation'* (Table 4). The effect size was greatest for *'Mean attenuation of the adjacent lung parenchyma'* ($\zeta^2 = 0.195$), followed by nodular volume ($\zeta^2 = 0.033$).

ICCs for the whole sample and tools 1 and 2 (0.905 (95% CI 0.897–0.912), 0.885 (95% CI 0.872–0.897), and 0.929 (95% CI 0.920–0.936), respectively) indicated very high intersoftware reliability, and greater reliability of tool 2 than of tool 1. Analysis of variance (ANOVA) revealed no significant difference between readers for the whole sample ($F_{1,2519} = 0.962$, $p = 0.327$), tool 1 ($F_{1,1264} = 2.452$, $p = 0.118$), or tool 2 ($F_{1,1264} = 0.257$, $p = 0.621$). Similarly, ICCs (0.745 (95% CI 0.722–0.766), 0.741 (95% CI 0.710–0.769), and 0.749 (95% CI 0.717–0.778), for the whole sample, reader 1 and reader 2, respectively) indicated reasonable interobserver reliability, with no significant difference between readers. ANOVA revealed significant differences between software packages for the whole sample ($F_{1,2519} = 41.642$, $p < 0.001$), reader 1 ($F_{1,1264} = 14.615$, $p < 0.001$), and reader 2 ($F_{1,1264} = 28.166$, $p < 0.001$).

Discussion

This study showed that the probability of proper segmentation of lung nodules with diameters of 5–8 mm is related mainly to the *'Mean attenuation of the adjacent lung parenchyma'*, followed by nodule volume and the *'Average of long and short diameters'*. Given the global variability of *'Mean attenuation of the adjacent lung parenchyma'*, this finding could have substantial clinical implications.

The results of this study indicate that the probability of proper segmentation using volumetric software is reduced for smaller nodules. This finding is in line with previous reports that smaller nodules exhibit greater volumetric variability (up to 30% for nodules with diameters < 6 mm) [14, 15]. In this context, the decreased probability of proper segmentation with increasing nodule volume (which is related to nodule diameter) is counterintuitive. This finding may be explained by the fact that the automatic calculation of nodule volume is reliant on the volumetric tool's algorithm, while the

Table 4 Parameter estimates for the prediction of nodule segmentation success and adequacy

Variable	OR	95% CI	*p*	Effect size
'Average of long and short diameters'	1.558	1.350–1.797	***< 0.001	0.006
Volume	0.984	0.982–0.986	***< 0.001	0.033
'Mean attenuation of the adjacent lung parenchyma'	0.987	0.985–0.988	***< 0.001	0.195
Previous lung surgery	3.414	1.575–7.401	**0.002	0.000
Pleural plaques	0.593	0.414–0.849	**0.004	0.002
Excluded variables				***p***
Observer				0.584
Software				0.385
Age				0.083
Sex				0.875
ILA/ILD				0.488
Emphysema				0.169
COPD				0.952
Tuberculosis				0.401
Linear atelectasis				0.096

OR, odds ratio; CI, confidence interval; ***$p < 0.001$; **$p < 0.01$

ILA, interstitial lung abnormality; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease

variable *'Average of long and short diameters'* is calculated from the manually measured long- and short-axis diameters of the nodule, and as such, describes the observer's assessment of the nodule. Since an inadequate nodule segmentation is likely to involve over segmentation and overestimation of nodule volume, this inverse correlation between volume with proper segmentation may reflect an increase in the error of measurement by the volumetric tool.

A previous history of lung surgery and the presence of calcified pleural plaques were also related significantly to proper segmentation in this study, although their effect sizes were negligible. Previous lung surgery increased the probability of proper segmentation, possibly because partial and total pneumonectomies promote major changes in vascular and respiratory mechanisms via compensatory overexpansion of the remaining lung, and possibly via hormonally regulated compensatory growth of the remaining lung lobes in the attempt to restore normal mass, structure, and function [16–18]. To our knowledge, however, the literature contains no report on changes lung parenchyma attenuation after lung surgery, and the negligible effect size and small number of patients with previous histories of lung surgery in our sample should caution against over interpretation. The presence of pleural plaques reduced the probability of proper segmentation, possibly due to the architectural distortion of the lung parenchyma that it causes.

The dataset used in this study did not contain information about the proximity of the measured nodules to focal parenchymal changes, such as surgical scars or pleural plaques, which renders interpretation difficult and the model incomplete. This factor could also help to explain the nonsignificant effect of ILA/ILD-related changes in our model, despite the clear effect of the average attenuation of the lung parenchyma adjacent to the nodule and the increased lung parenchymal attenuation caused by ILA/ILD [19–22].

A cutoff of -950 HU is the most widely accepted threshold in quantitative analysis for distinguishing emphysema from normal lung tissue [23–25]. This threshold is based on the routine full-dose chest CT protocol used in clinical practice. All values in our sample exceeded this threshold, regardless of the presence of emphysema, which could be related to the lower signal-to-noise ratio of the low-dose protocol used in screening; and/or the nodule itself may distort the parenchyma and influence its surrounding attenuation. As far as the authors are aware, no specific threshold has been defined for low-dose protocols. We suspect that it would differ from that used for full-dose protocols, but more evidence is needed.

Our analysis of mean values revealed that for automatic measurements there were differences in volume measurements between software packages and readers, but for manual measurements (long and short-diameter measurements and attenuation of the lung parenchyma adjacent to the nodule) there were only differences between software packages (not between readers). We also found good performance in terms of interobserver and intersoftware reliability, although less so for the latter, in line

with the current recommendation that follow-up studies performed in the context of lung cancer screening programs be reported by the same reader and performed using the same software package as the baseline study. These findings also suggest that the manual measurements of short- and long-axis diameters are more reliable among readers than the volumetric tools' automatic measurements.

The present study was conducted with a large sample of nodule measurements; larger, to our knowledge, than any other published series. However, it has several limitations; notably, the use of a nonstandard measurement of lung parenchymal attenuation (selected as a reasonable compromise, as no standard exists) and lack of information on the location of focal parenchymal changes (i.e., pleural plaques and changes resulting from previous lung surgery) relative to lung nodule location. Future research could further examine the effects of nodule size on the results found (is the impact of the average attenuation of the lung parenchyma adjacent to the nodule in the nodule segmentation more significant in smaller nodules?), and how it effects the calculation of a nodule's VDT (is the VDT a reliable indicator of nodule's growth in nodules with abnormal average attenuation of the lung parenchyma adjacent to the nodule?).

Conclusion

For lung nodules measuring between 5 and 8 mm in long-axis diameter, an increase in the average attenuation of the adjacent lung parenchyma is related to a decrease in the quality of the nodule's segmentation by volumetric tools, contributing to measurement error. When following lung nodules in the setting of abnormal lung parenchymal attenuation, care should be taken when interpreting automatic measurements of the nodule to assess growth.

Abbreviations

ANOVA: Analysis of variance; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; HU: Hounsfield unit; ICC: Interclass correlation coefficient; ILA: Interstitial lung abnormality; ILD: Interstitial lung disease; TB: Previous tuberculosis; VDT: Volume doubling time.

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Authors' contributions

Conception—D.P., E.G.P., K.I.; Design of the work D.P., E.G.P., K.I.; Acquisition, analysis and interpretation of data—D.P., E.G.P., K.I.; All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study project was approved at the by the head of Research & Innovation Committee of the Liverpool Heart and Chest Hospital, Dr. Bashir Matata at the Research Committee meeting on 12/07/2019. For this retrospective cross-sectional study (observational, analytical) there was a wave of the requirement for written informed consent due to the use of existing clinical data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Appendix 2 - Pulmonary diseases with abnormal parenchymal density - Is this a problem in lung cancer screening?

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https://dx.doi.org/10.36416/1806-3756/e20220002

LETTER TO THE EDITOR

Pulmonary diseases that cause abnormal lung parenchymal density: is this a problem in lung cancer screening?

Diana Penha[1], Erique Pinto[1], Edson Marchiori[2], Luís Taborda-Barata[1], Klaus Irion[3]

TO THE EDITOR:

This letter addresses recent research regarding how lung parenchymal attenuation influences pulmonary nodule volumetry. This topic is relevant to healthcare stakeholders and patients undergoing lung cancer screening (LCS) programs.

Low-dose chest CT in LCS has been proven to reduce lung cancer deaths by 20% compared with chest radiography.[1] The Hounsfield unit (HU) threshold between normal aerated lung and emphysema varies among authors, but a threshold of −950 HU has been commonly accepted.[2]

Healthcare systems worldwide are implementing LCS programs using low-dose CT and new software tools for lung nodule detection and segmentation, including software tools for automated and semi-automated pulmonary nodule volumetry. International societies recommend the use of such volumetry tools in the assessment of incidental pulmonary nodules and their follow-up if they are larger than 100 mm^3 (Fleischner Society) or 80 mm^3 (British Thoracic Society).[3,4]

From a technical point of view, these tools work by performing virtual extraction of the nodule from the adjacent lung parenchyma and other structures such as bronchial walls and vessels. The so-called "region-growing" segmentation algorithm can perform this extraction either in a semi-automated (i.e., the operator locates the nodule manually) or automated (i.e., the computer system automatically identifies and segments the pulmonary nodules) manner as in computer-aided detection.

Starting from the initial voxel selected, the algorithm tries to identify all the voxels that are contiguous to this point and that have a density value similar to that of the selected point. The process continues until the nodule margin is determined by the abrupt change in density values due to the presence of air in the lung adjacent to the nodule. There is high contrast between ventilated lung parenchymal airspaces close to −950 HU in attenuation and a solid pulmonary nodule (above −500 HU).[5]

A vast body of research has been dedicated to identifying the technical factors influencing volumetry tools. These factors may be related to the CT scanner, acquisition parameters (e.g., slice thickness, section overlap, kernel, reconstruction algorithm), and software used. Other factors are related to the patient or the nodule itself (e.g., acquisition in inspiration or expiration, size, location, shape, or density).[5]

Little has been researched on the influence of lung parenchymal density or lung parenchymal attenuation on these artificial intelligence tools, even though pulmonary diseases that cause abnormal lung parenchymal density are common in chest CT studies. Conditions that cause abnormal lung density can be grouped into two groups: diseases that cause increased parenchymal attenuation (e.g., infection, neoplasms, or interstitial lung disease); and diseases that cause decreased parenchymal attenuation (e.g., emphysema, cysts, bronchiectasis, or honeycombing).

It would be intuitive to consider that diseases that cause decreased lung attenuation, such as cysts and emphysema, would improve delineation of nodule margins when the decreased lung attenuation is adjacent to the nodule and would potentially improve the accuracy of the volumetry tool and reduce its variability (Figure 1A). However, several studies have investigated diseases that cause decreased lung attenuation, such as cysts and emphysema, as factors influencing lung nodule volumetry, and, so far, no consistent effect has been shown.[5,6]

A recent research paper based on a large LCS program showed that increased lung attenuation adjacent to a nodule is inversely related to the likelihood of good segmentation of that same nodule by volumetry tools (Figures 1B and 1C).[7] Therefore, we should exercise caution in using dedicated lung nodule volumetry tools in patients with diseases accompanied by increased lung density when nodules are located in affected areas.

Interstitial lung diseases (ILD) feature increased parenchymal density and are common in LCS patients. Studies concerning LCS programs report ILD in approximately 5% to 25% of the patients. The most common types of ILD found in LCS patients are smoking-related ILD, including smoking-related interstitial fibrosis, idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, and respiratory bronchiolitis ILD.[8]

With this short letter, the authors aim to increase the awareness of radiologists and chest physicians regarding this recently identified limiting factor of volumetry tools. As we move towards early lung cancer detection and the worldwide implementation of LCS programs, we believe that recognizing the potential pitfalls of volumetry tools is essential to deriving the benefits of evidence-based healthcare.

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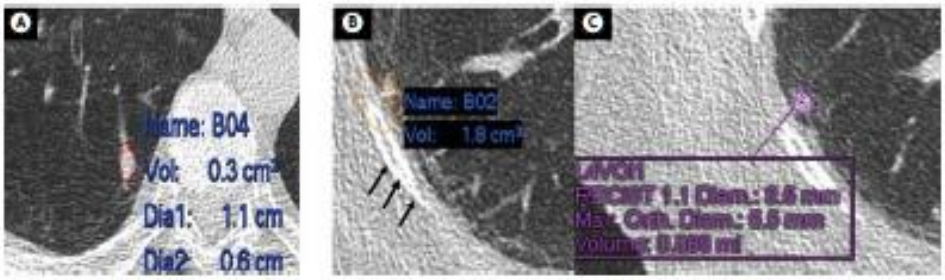

Figure 1. In A, application of a nodule volumetry tool to assess a lung nodule surrounded by pulmonary emphysema (red, "oval-shaped" circle). The segmentation and volume calculation are technically correct. In B, the application of the same nodule volumetry tool to assess a lung nodule surrounded by subpleural reticulation and fibrosis (arrows) in a patient with smoking-related interstitial lung disease under follow-up in a lung cancer screening program showed a significant nodule segmentation error. The incorrect segmentation included the subpleural fibrosis and also the chest wall. This error was influenced by the increased lung parenchymal density surrounding the nodule (reticulation and fibrosis), overestimating the volume of the nodule to be 1.8 cm³, while, in C, the application of a different software tool to assess the same nodule correctly estimated its volume to be 0.089 cm³. This corresponds to a 20-fold error in the volume calculation.

AUTHOR CONTRIBUTIONS

DP and EP: study conception and writing of the manuscript. EM: manuscript review and editing. LTB and KI: manuscript review. All authors: approval of the final version of the manuscript.

CONFLICT OF INTEREST

None.

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Appendix 3 - Incidental findings in Lung Cancer Screening: Pictorial Essay & Systematic checklist

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PICTORIAL ESSAY

Incidental findings on lung cancer screening: pictorial essay and systematic checklist

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ABSTRACT

Lung cancer screening (LCS) programs are increasing worldwide. Incidental findings (IFs) on LCS are defined as low-dose CT findings unrelated to the primary purpose of identifying lung cancer. Most IFs on LCS are benign and clinically insignificant but are being increasingly recognized, and some require urgent referral for further diagnostic workup. Other findings are expected and are known as smoking-related comorbidities, including COPD, cardiovascular disease, emphysema, and interstitial lung disease, and their diagnosis can have a significant impact on patient prognosis. The purpose of this pictorial essay is to illustrate the most common IFs on LCS, organized by organ. We will discuss the current literature on IFs on LCS, focusing on their prevalence, appropriate communication, and triggering of clinical pathway systems.

Keywords: Diagnostic screening programs; Lung neoplasms; Incidental findings.

INTRODUCTION

With the increasing number of lung cancer screening (LCS) programs worldwide, incidental findings (IFs) have also increased significantly.[1-3] IFs on LCS can be defined as low-dose CT (LDCT) findings that can potentially affect the health of the patient and are unrelated to the primary purpose of identifying lung cancer.[1,4,5] Most IFs are benign and clinically insignificant—the most common being pulmonary findings (69%), cardiovascular findings (67%), and gastrointestinal findings (25%)—but some require urgent recognition and further management.[2]

The reported prevalence of IFs on LCS ranges from 1% to 19%, being as high as 94% in more recent reports.[2-6] This wide variation is explained by the lack of standards regarding the reporting and management of IFs on LCS. IFs are also a cause of stress and anxiety. In an ongoing interdisciplinary population-based long-term cohort study, a report of IFs is expected to be given to 10% of participants. The study participants have stated that they are highly interested in this report and that they would not have participated otherwise, even if admitting to increased levels of stress when receiving mail from the study.[7] It is a reasonable expectation, shared by both patients and referring colleagues, that significant IFs should be communicated effectively or acted upon.

Communication standards for urgent and unexpected findings are clear, as addressed by guidelines from the American College of Radiology (ACR) and the European Society of Radiology (ESR).[8,9] IFs, however, may not be urgent nor necessarily unexpected. The ACR Incidental Findings Committee has developed by consensus a series of white papers addressing IFs in multiple organs and systems, including the chest (mediastinal and cardiovascular findings), upper abdomen, and thyroid, although not specific to LCS. These serve as important guidance on reporting, communication, and management of IFs until specific guidelines are developed.[10-14]

Different communication strategies have been suggested for reporting IFs on LCS. The Lung CT Screening Reporting and Data System provides the S modifier for clinically significant or potentially clinically significant non-lung cancer findings[15] but does not specify which IFs should be reported or acted upon. The ESR and the European Respiratory Society (ERS) recommend that IFs that are clinically

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significant (i.e., with a major or adverse impact, or for which there is an established intervention that benefits the patient) and of general agreement (i.e., minimal interobserver variation) be reported and a recommendation for intervention be given. This recommendation falls within one of four categories (levels of management): immediate action, likelihood of nonpulmonary cancer, further investigation, and clinically insignificant (Table 1).[1]

Screening programs should develop a standard approach for the evaluation of these findings. Developing a standard approach to reporting and management of IFs on LCS would promote research into their impact on reducing overall mortality, as well as the development of automatic detection, measurement, and data-mining tools based on artificial intelligence. This evidence-based approach could inform public opinion and the political decision-making process, while optimizing the cost-effectiveness of LCS programs and the health gains to their participants.

This pictorial essay illustrates the systematic checklist proposed by the ESR/ERS position paper.[1] Our objective is to help radiologists familiarize with (and not to miss any) IFs, especially those with potential clinical relevance. Clinically significant IFs on LCS are summarized in Table 2.

NECK

The thyroid gland and neck lymphadenopathy

Depending on its anatomy or whether there is thyroid enlargement, the thyroid gland does not normally appear in its entirety on LDCT scans of the chest. Thyroid enlargement should be stated in the report if it causes deviation of the airway significant enough to cause respiratory symptoms (Figure 1). The most common IFs within the thyroid gland are calcifications, nodules, and cysts. The ACR white paper on incidental thyroid nodules recommends further ultrasound evaluation only for nodules larger than 1.5 cm with invasive behavior or associated with suspicious lymph nodes, because small incidental nodules are largely benign or represent indolent neoplasms (papillary carcinoma in most cases), with a 10-year survival rate of nearly 100%.[16]

Lower neck lymphadenopathy should be reported including size, morphology, shape, margins, and distribution. The criteria for lymphadenopathy include increased size (i.e., > 1 cm in short-axis diameter and on axial images); morphological changes (i.e., rounded shape; ill-defined, irregular margins; and replacement of normal fatty hila with necrosis, cystic change, suspicious calcification, or abnormal enhancement); and asymmetric distribution (i.e., prominent nodes or more than 3 contiguous and confluent lymph nodes along the drainage chain).[17,18]

THORACIC CAVITY

Trachea, bronchi, and bronchioles

Tracheal disease is usually clinically insignificant and is not commonly reported as an IF on LCS. It can present as changes in the tracheobronchial tree (e.g., diffuse dilation, stenosis, and collapse) or as focal lesions of the tracheal wall that can be benign, malignant, or non-neoplastic.[19]

In LCS, most diffuse tracheal changes are associated with COPD, including saber-sheath trachea (Figure 2), tracheocele, and tracheomegaly (Figure 3). Solid focal lesions of the trachea do require further evaluation.[19]

Bronchial wall thickening is common among smokers and usually reflects the chronic bronchitis form of COPD (Figure 3). Reference values for bronchial wall thickness, up to the segmental bronchi, are 1.2-1.4 mm and < 20% of the internal bronchial luminal diameter. This is found on approximately 39% of LDCT scans (Figure 4A).[2]

Bronchiectasis is also common in LCS because of the high prevalence of smoking and COPD (Figure 3), with cylindrical bronchiectasis being the most common type. Signs of infection (e.g., mucous plugging and tree-in-bud sign) should be mentioned in the report because the patient will benefit from further respiratory evaluation.[20]

Bronchial diverticula are also very common. They are mostly clinically insignificant and are not frequently reported.

Lungs

Pulmonary IFs are reported in 16-70% of LCS studies, with emphysema (Figure 5) being the most

Table 1. Levels of management of incidental findings on lung cancer screening, as recommended by the European Society of Radiology/European Respiratory Society.

	Level of management	Action
1	Immediate action	Emergency referral (e.g., pneumothorax)
2	Likelihood of nonpulmonary cancer	Referral to a specialist (e.g., breast mass)
3	Noncancer findings	Referral to a specialist or a general practitioner (e.g., diffuse lung disease and dilated aorta)
4	Clinically insignificant	Prone to observer variation and, because there is no established beneficial intervention, do not need to be reported (e.g., minor atelectasis and renal, liver, or thyroid cysts)

Table 2. Checklist of clinically significant incidental findings on lung cancer screening (levels 1, 2, and 3). (Continued...)

Neok	Level of management	
Thyroid		
Nodules	Ultrasound if > 1.5 cm and invasive or suspicious lymph nodes	2
Enlargement	If airway deviation or compression	3
Lymphadenopathy	Size, morphology, shape, margins, and distribution	2
Chest		
Airways		
Bronchiectasis	+ Referral for respiratory evaluation	3
Lungs		
Emphysema	Type and severity	3
ILD/ILAs	+ Referral to ILD team/MDT	3
Infection		3
Pleura		
Pneumothorax	+ Emergency referral	1
Pleural plaques		3
Pleural effusion		3
Heart and Pericardium		
Coronary or valvular calcifications	+ Cardiovascular risk assessment	3
Stents, grafts, myocardial changes		3
Large pericardial effusion or cysts	May compress adjacent structures	3
Pericardial thickening (> 3-4 mm)		3
Esophagus		
Focal esophageal lesions	Smoking is a risk factor for esophageal cancer.	2
Diffuse wall thickening		3
Esophageal dilation		3
Mediastinum		
Pneumomediastinum	+ Emergency referral	1
Masses		2
Lymphadenopathy		2
Vessels		
Aortic aneurysm/ectasia	+ Referral to vascular MDT	3
Pulmonary artery dilation		3
Atheromatous disease		3
Diaphragm		
Complicated hernias	+ Emergency referral	1
Uncomplicated hernias		3
Diaphragmatic elevation		3
Breast		
New or previously undiagnosed lesion		2
Previous surgery		3
Abdomen		
Liver		
Focal lesion	Based on the hepatic risk profile	2
Biliary system		
Cholecystitis/thickening		2
Cholelithiasis		3
Biliary obstruction		2
Pneumobilia		3
Pancreas, Stomach, and Spleen		
Cysts		2
Solid masses		2
Splenomegaly		3
Kidneys		

ILD: interstitial lung disease; ILAs: interstitial lung abnormalities; and MDT: multidisciplinary team. Levels of management: (1) immediate action; (2) likelihood of nonpulmonary cancer; and (3) noncancer findings.

Table 2. Continued...

Neok		Level of management
Solid renal masses		2
Complex renal cysts		2
Stones >1 cm or in the upper pole		3
Adrenal glands		
Suspicious masses	if > 1 cm, > 10 HU, or growth	2
Masses	if < 1 cm, < 10 HU, or stable for > 1 year => no follow-up required	4
Peritoneum		
Nodules, infiltrative masses, omental haziness, ascites, and peritoneal thickening		2
Previous surgery		3
Bone/Joints		
Vertebral fractures		3
Low vertebral bone density		3
Suspicious bone masses		2
Skin/subcutaneous and Muscles		
New or previously undiagnosed lesion		2

ILD: interstitial lung disease; ILAs: interstitial lung abnormalities; and MDT: multidisciplinary team. Levels of management: (1) immediate action; (2) likelihood of nonpulmonary cancer; and (3) noncancer findings.

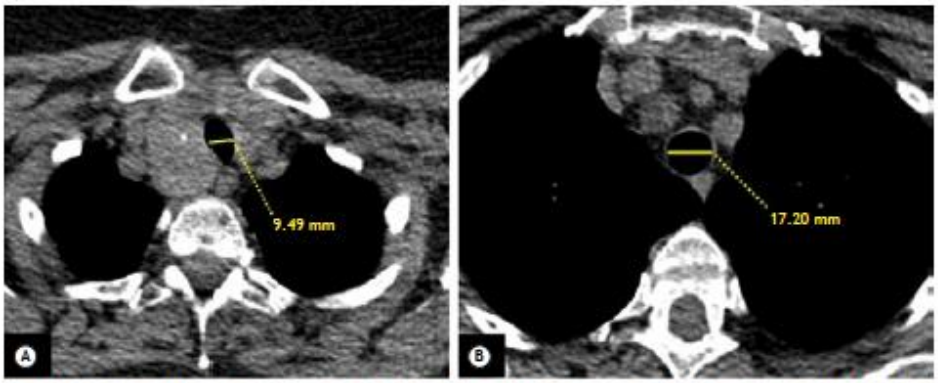

Figure 1. Goiter with tracheal compression. In A, axial image of the upper chest, showing enlargement of the left lobe of the thyroid gland, with coarse calcifications, causing displacement and narrowing of the trachea (tracheal lumen diameter, 9.49 mm). In B, tracheal lumen diameter is 17.20 mm.

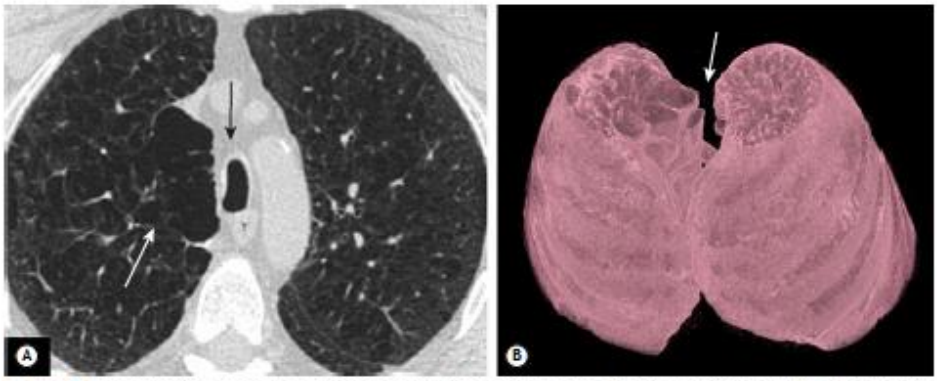

Figure 2. Saber-sheath trachea. In A, axial image of the proximal trachea, showing anatomical findings typical of a saber-sheath trachea (arrow). Note other morphological features of COPD (i.e., emphysema and bronchial wall thickening; white arrow). In B, 3D reconstruction showing decreased coronal diameter and increased sagittal diameter (white arrow).

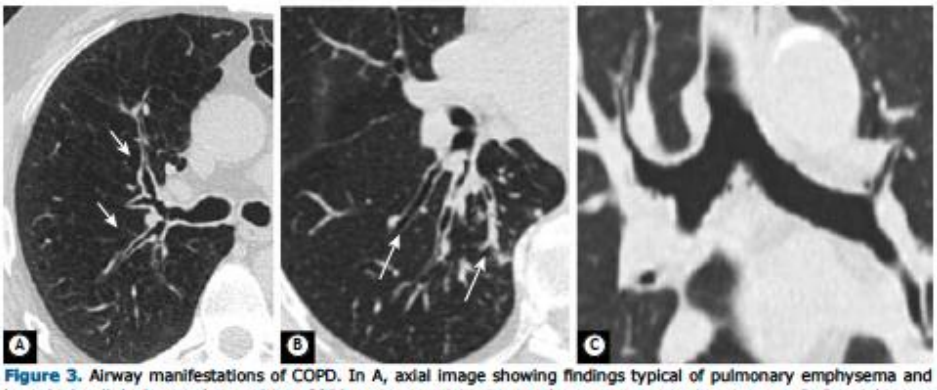

Figure 3. Airway manifestations of COPD. In A, axial image showing findings typical of pulmonary emphysema and bronchial wall thickening (arrows) in a COPD patient participating in a lung cancer screening program. In B, axial image of the right lower lobe, showing cylindrical bronchiectasis (arrows), some of which is filled with mucous plugging. In C, several subcarinal and bronchial diverticula in a heavy smoker.

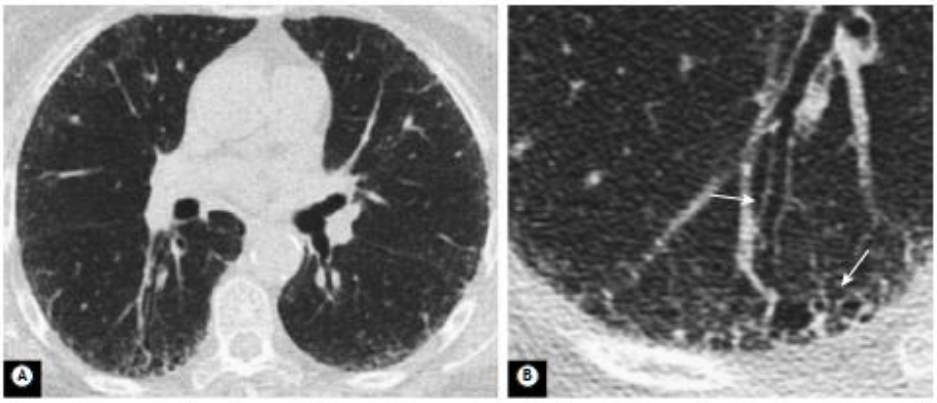

Figure 4. Interstitial lung disease. In A, axial image showing incidental findings of subpleural reticulation with honeycombing affecting the subpleural regions of the lower lobes. In B, a detail of the right lower lobe, showing traction bronchiectasis and mild honeycombing (arrows). The patient was referred for further evaluation, and the multidisciplinary team established a diagnosis of probable usual interstitial pneumonia.

common pulmonary IF.[2,5] According to some authors, emphysema should be interpreted as an expected (i.e., not incidental) comorbidity related to smoking.[2-6]

The LCS radiologist should report the type of emphysema (centrilobular, paraseptal, or panlobular) and grade its severity as trace (0.5% of a lung zone), mild (0.5-5%), moderate (45%), confluent (spanning several secondary pulmonary lobules), or advanced destructive (with hyperexpansion of secondary pulmonary lobules and architectural distortion).[21]

Interstitial lung disease (ILD) is an umbrella term used for a large group of diseases of the lungs (Figure 4) and should be reported, triggering an appointment with the respiratory team/multidisciplinary team. Smoking-related ILDs include smoking-related interstitial fibrosis, idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, and respiratory bronchiolitis ILD.[21]

Osteophyte-induced lung fibrosis is a benign and focal form of fibrosis, seen in older patients as a localized ground-glass opacity, linear atelectasis, or a reticular pattern adjacent to osteoarthritic protrusions or spinal osteophytes, and does not appear to progress. Osteophyte-induced lung fibrosis should not be confused with ILD (Figure 5), especially usual interstitial pneumonia, which has a similar appearance but basilar predominance and is not restricted to a paraspinal location.[22]

Pulmonary infection has also been reported as an IF on LCS in approximately 6% of patients. Ground-glass opacities, consolidations, and tree-in-bud opacities (Figure 6) are nonspecific CT findings of infection and should be reported, prompting further clinical and laboratory evaluation.[21]

Atelectasis is another common IF on LCS. If it is linear and is not associated with a suspicious obstructive lesion, it is usually benign and does not require further evaluation.[21]

Intrapulmonary lymph nodes are common, benign findings within the lung parenchyma, with a prevalence of up to 66%, and do not require further evaluation, as per the recommendations of the British Thoracic Society, Fleischner Society, and ACR.[23,24] The morphological criteria for intrapulmonary lymph nodes are well-defined, noncalcified solid nodules with homogeneous, smooth margins and an oval, lentiform, or triangular shape, < 12 mm in diameter and located in the middle or lower lobes.

Pleura

The most common pleural IFs on LCS are pleural plaques (3.8%) and pleural effusion (1.2%). Pleural effusion may be due to benign conditions such as infection, pulmonary edema, autoimmune disease, and cardiovascular disease, but could also be a manifestation of primary or secondary malignancy and should always be reported and investigated. Pleural plaques are a marker of asbestos exposure (Figure 7). Pleural plaques should always be reported because there are important medical and legal implications to consider, and the patient should be referred to a respiratory specialist.[17]

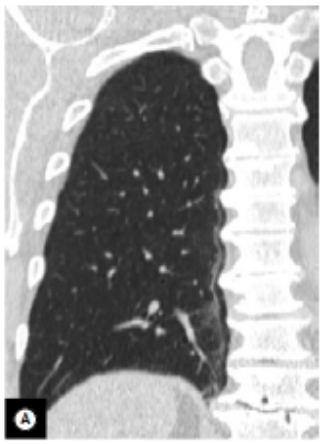

Figure 5. Osteophyte-induced lung fibrosis. Coronal image showing a line of fine fibrosis along the right paraspinal region. Progression of degenerative osteophytosis leads to compression of the adjacent lung parenchyma.

Pneumothorax is uncommon as an IF on LCS but should be treated as a medical emergency and mentioned in the report, triggering an emergency referral and activation of alert systems in place.[21]

Heart

Cardiovascular IFs on LCS are common, with some studies reporting coronary calcifications on 30-56% of LDCT scans and aortic valve calcifications on 21%.[2,3]

Smoking is a common risk factor for lung cancer and cardiovascular disease, and, as such, cardiovascular IFs on LCS should be considered smoking-related comorbidities. The risk of death from ischemic heart disease is estimated to be 3 times greater in current smokers in the 55- to 74-year age bracket than in nonsmokers.[17]

Coronary artery calcium (CAC) is highly correlated with plaque burden in coronary artery disease, and a CAC score of 1,000 is associated with a 10-fold increased risk of all-cause mortality. Recent studies on CAC and LCS have shown that LDCT can be used for low-cost, noninvasive parallel evaluation of cardiovascular risk in lung screening cohorts.[23-26] Some LCS software programs include identification and quantification of coronary artery calcifications (mild, moderate, or severe; Figure 8), and, in our experience, they should be reported because patients benefit from cardiovascular risk assessment and possible intervention.[17]

Pericardium

According to the ACR,[9] incidental pericardial findings include effusion, thickened pericardial layers, pericardial calcification (Figure 9A), and pericardial cysts. Small pericardial effusions are common and usually require no further workup, but large-volume effusions (Figure 9B) and thickening (> 3-4 mm) of pericardial layers should be reported and trigger further clinical evaluation. Pericardial cysts are the most common benign pericardial

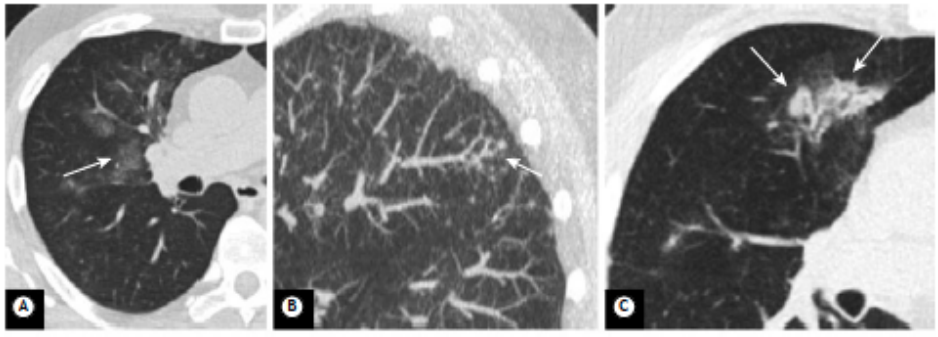

Figure 6. Pulmonary infection. In A, axial image of the right middle lobe, showing focal areas of ground-glass attenuation (arrow) with ill-defined nodularity. In B, a tree-in-bud pattern (arrow). The patient had clinically and microbiologically confirmed pneumonia. In C, axial image of a different patient, showing consolidation with air bronchogram in a predominantly peribronchovascular distribution (arrow). The patient was clinically diagnosed with bronchopneumonia.

masses, presenting with thin walls and located at the cardiophrenic angles. Low-attenuation cysts do not require follow-up, unless they are large enough to risk compression of adjacent structures.[9]

Esophagus

Evaluation of the esophagus on an unenhanced scan is limited, but significant luminal dilation should be reported and could be a sign of achalasia, scleroderma, or other inflammatory conditions. Diffuse esophageal wall thickening is seen in infectious or inflammatory conditions. Although not a common IF on LCS, focal lesions of the esophagus should be reported and trigger further diagnostic workup because smoking is a risk factor for esophageal cancer.[27]

Mediastinum

Mediastinal masses are an uncommon IF on LCS, with a reported prevalence of only 0.77% in high-risk smokers.[17] The most common mediastinal masses are anterior mediastinal masses originating from the thymus or thyroid gland. Masses in the posterior mediastinum are likely neurogenic in origin and should be further evaluated by magnetic resonance imaging.[27] When a mediastinal mass is present, location, texture, and invasive behavior should be reported and the patient should be referred for further evaluation.[9,17,27]

Mediastinal lymph nodes are a common normal finding on chest CT scans. Lymphadenopathy is frequently due to infection, edema, diffuse lung disease

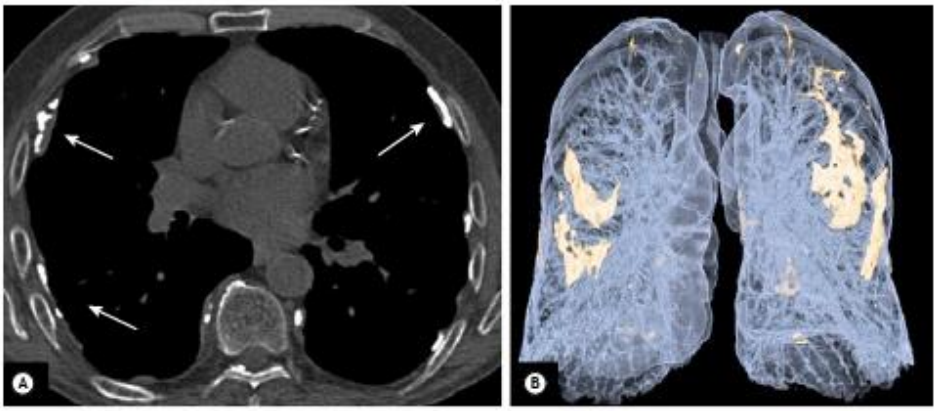

Figure 7. Pleural plaques. In A, axial image with bone window settings, showing several linear calcifications in the costal pleura (arrows). In B, 3D reconstruction of the same patient, showing that the pleural plaques are also affecting the mediastinal pleura and the diaphragmatic pleura.

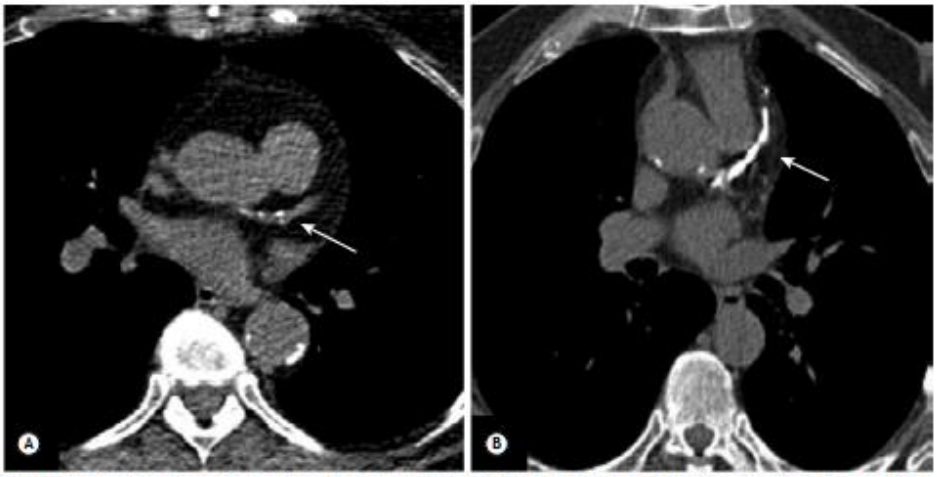

Figure 8. Coronary artery calcifications. In A, axial low-dose CT image showing mild scattered calcified plaques in the proximal left anterior descending coronary artery, findings that should be reported as mild calcifications of the coronary arteries (arrow). In B, severe calcifications of the coronary arteries with heavily calcified plaques distributed along the proximal and mid left anterior descending coronary artery, findings that should be reported as severe calcifications of the coronary arteries (arrow).

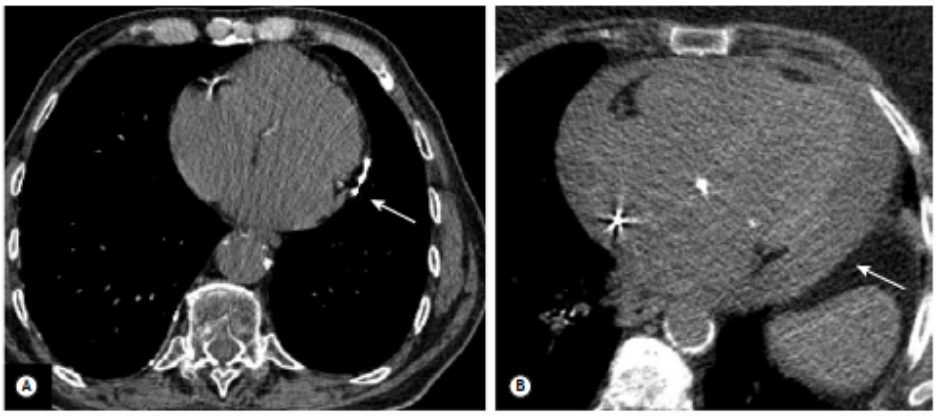

Figure 9. Pericardial effusion and calcifications. In A, axial image showing linear pericardial calcification (arrow), a finding that is likely related to a previous episode of pericarditis. In B, axial image showing a significant pericardial effusion (arrow). A review of the medical records showed that the patient had heart failure, with recent episodes of cardiac decompensation. The pericardial effusion was mentioned and triggered an alert to the cardiac team.

(e.g., sarcoidosis and fibrosis), and, less commonly, lymphoma or metastases. According to the ACR, incidentally detected lymph nodes of < 15 mm in short-axis diameter in patients with no other findings do not require further evaluation.[9]

Pneumomediastinum is not a common IF on LCS but is a medical emergency and requires immediate action from the radiologist, with emergency referral and activation of alert systems in place.

Vessels

Aortic disease is a common IF on LCS, with dilation of the aorta being reported in up to 8.1% of LCS studies.[2,17] Aortic dissection and significant ulcerations are usually undetectable on LDCT given its unenhanced nature.[9]

According to the ACR, the diameter of the aorta is influenced by sex, age, and body surface area.[9] The criteria for aortic aneurysm are more than 5 cm for the ascending aorta and more than 4 cm for the descending aorta. This should be reported, and the patient should be referred to a vascular specialist for further evaluation.

Pulmonary artery dilation has not been studied in the context of LCS but should be reported because an enlargement may reflect primary or secondary pulmonary arterial hypertension or be secondary to chronic pulmonary embolism or other pulmonary disease.[9] The criterion for a dilated main pulmonary artery is 3 cm or more in diameter, or equal in diameter to the ascending aorta.

Diaphragm

Diaphragmatic hernias can be either intrapleural (Bochdalek hernias) or mediastinal, the latter further divided into prevascular (Morgagni-Larrey hernias) or visceral (pericardial or hiatal hernias). Hiatal hernia is the most common transdiaphragmatic IF on LCS, being reported in 9-14% of patients.[2,28]

Most hiatal hernias are not significant but should be reported if they are large enough to cause cardiac compression. Diaphragmatic paralysis from phrenic nerve injury results in an asymmetric position of the diaphragmatic dome and does not need any special mention in the report.

ABDOMINAL CAVITY

A systematic review of the included upper abdomen is mandatory to exclude potentially significant clinical findings (e.g., malignancy) requiring urgent referral (Table 2). The ACR white papers on incidental abdominal findings provide useful guidance for lesions requiring further follow-up.[11-14]

Liver

The most commonly encountered benign hepatic lesions are hepatic cysts, hemangiomas, and focal nodular hyperplasia, usually seen on LDCT scans as a focal hypodense lesion.[12]

In a recent study of IFs on LCS, hepatic cysts were present in 34% of patients (Figure 10A) and are of little or no clinical significance.[28] The need for further characterization of focal liver lesions other than simple cysts is based on patient risk profile and lesion size, with known malignancy (primary liver cancer or other primary malignancy known to metastasize to the liver), hepatic dysfunction, and hepatic risk factors being taken into consideration.[12]

Gallbladder

The gallbladder does not always appear in its entirety on LCS scans depending on the field of view, patient body habitus, and patient height. In our experience,

the most common findings are gallstones, with no further complications.

Pancreas, stomach, and spleen

Pancreatic IFs on LCS are reported in approximately 5% of LCS studies, including pancreatic calcifications (Figure 10B) and cancer.[2] According to the ACR, all incidental pancreatic cysts should be presumed mucinous in nature.[13] Pancreatic cysts and pancreatic solid masses should be reported and further evaluated.[13] Likewise, any gastric or splenic mass, splenic cyst, or splenomegaly should be referred for further evaluation.

Kidneys

Renal cancer has been reported as one of the most common extrapulmonary malignancies in LCS studies.[2,28] Any solid renal lesion should be reported and trigger further specialist evaluation and diagnostic workup (using a renal-mass CT protocol or magnetic resonance imaging study), especially if the lesion is accompanied by suspicious findings such as thick or irregular wall, mural nodule, septa, and calcification. Lesions smaller than 1 cm are likely benign, even if they are solid lesions. Well-defined homogeneous lesions smaller than 3 cm with high density (above 70 HU) can be confidently diagnosed as hyperattenuating cysts (Bosniak category II cysts) according to the ACR.[14] Simple cystic renal lesions are a common IF on routine imaging and are usually easy to recognize because of their water attenuation (0-20 HU).

Renal stones are also common findings on imaging studies. The prevalence of asymptomatic lithiasis in LCS is 10%, and renal stones are considered clinically irrelevant.[17] However, renal stones larger than 10 mm or located in the upper poles tend to be associated with an increased risk of symptoms and benefit from surgical evaluation (and should therefore be reported). If hydronephrosis is identified, it also requires further evaluation.

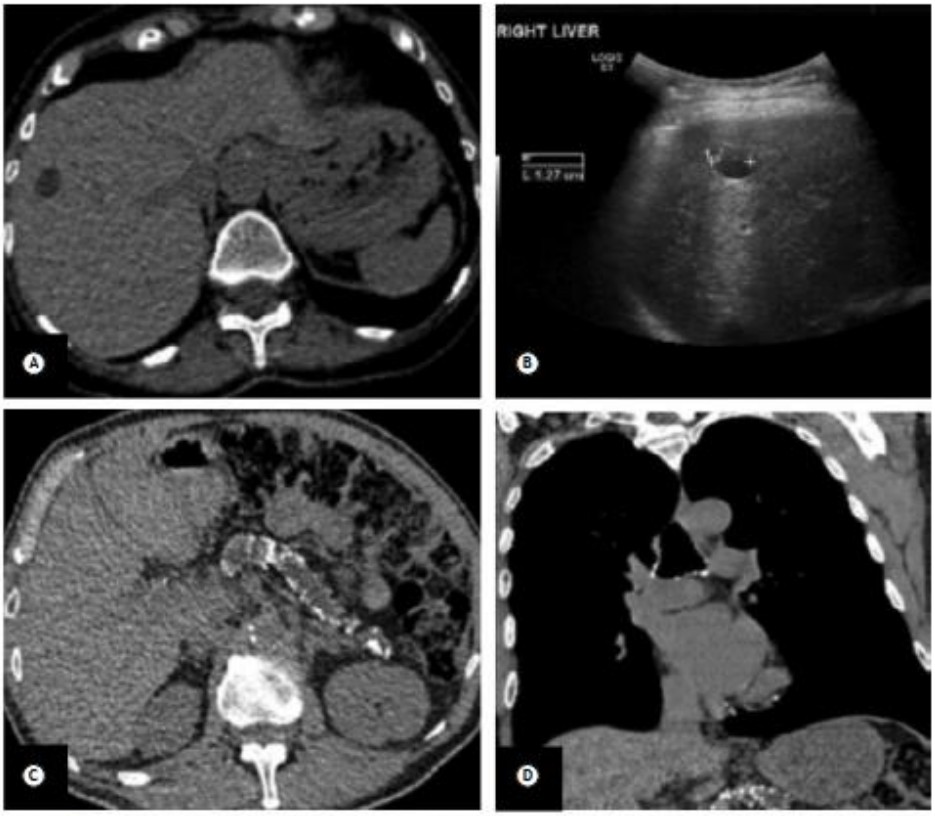

Figure 10. Incidental abdominal findings. In A, axial image showing a focal hypodense liver lesion of 13 mm. Density was found to be inaccurately measured by low-dose CT. This was mentioned in the report, and the medical team decided to request an ultrasound scan. In B, ultrasound scan showing the benign features of a cyst. In C and D, axial and sagittal images of a different patient, showing another incidental finding, i.e., several coarse calcifications in the atrophic pancreatic parenchyma, with dilated pancreatic duct, in keeping with chronic pancreatitis. Pancreatic disease is not commonly depicted on low-dose CT scans for lung cancer screening, because low-dose CT has reduced sensitivity for pancreatic lesions and because the usual field of view does not cover the pancreas.

Adrenal glands

Non-hyperfunctioning adenomas are the most common adrenal lesions in the general population and are seen on as much as 13% of LCS scans.[28] According to the ACR, incidental adrenal lesions smaller than 1 cm in short-axis diameter, containing macroscopic fat, and with average attenuation of less than 10 HU or stable for more than 1 year should be considered benign and do not require follow-up.[11]

Peritoneum

Suspicious signs of peritoneal disease, such as nodules or infiltrative masses in the peritoneal cavity, omental haziness, ascites, and peritoneal thickening, should be reported, and the patient will require referral for specialist and further diagnostic evaluation.[29]

BONE/JOINTS

Incidental osseous findings on LCS include diffuse diseases such as osteoporosis, thoracic kyphosis, osteophytosis, and diffuse idiopathic skeletal hyperostosis, as well as focal lesions, both benign and malignant.[30]

SKIN/SUBCUTANEOUS AND MUSCULAR SYSTEM

In one study of IFs on LCS, the presence of soft-tissue or muscular findings was very low, with incidental sebaceous cysts having only a 1% frequency, despite the fact that sarcopenia is a known smoking-related comorbidity.[28]

The breast is a special soft-tissue compartment, with lesions being seen on up to 7% of LCS scans, with variable clinical significance, despite the fact that LDCT is not a good imaging modality for breast evaluation.[3,28] Breast IFs on LCS include primary and secondary malignancies, as well as benign lesions such as calcifications, fibroadenomas, and lipomas. Breast malignancy is the most worrying finding, and, as such, any new lesion or any lesion not previously documented as benign should be reported and referred for further evaluation.

FINAL CONSIDERATIONS

Clinically significant IFs on LCS are common, and their potential impact should be taken into consideration in the shared decision-making process. LCS programs should develop a standard approach for the evaluation of these findings.

AUTHOR CONTRIBUTIONS

DP and EP made substantial contributions to the conception and design of the work, as well as to the collection of the illustrations used. KI, CM, EM, LTB, BH, SR, and HK made substantial contributions to the review of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

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Appendix 4 -Lung cancer associated with cystic airspaces: a new radiological presentation of lung cancer

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LETTER TO THE EDITOR

Lung cancer associated with cystic airspaces: a new radiological presentation of lung cancer

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TO THE EDITOR:

Lung cancer associated with cystic airspaces, also known as cystic or pericystic lung cancer, was once thought to be a rare presentation of lung malignancy; however, in recent years, these forms have become more commonly recognized.[1] This is likely due to the increased availability of contiguous thin-section CT scans of the chest for the follow-up of patients with general respiratory diseases, as well as to the introduction of lung cancer screening programs.[1]

Cystic/pericystic lung cancer is usually diagnosed late, representing as much as 22% of missed lung cancers in screening programs. This is probably due to the low awareness of this morphological subtype among radiologists and clinicians.[1,2] Current guidelines for lung nodule management consider differences between solid and subsolid nodules but fail to provide a management proposal for cystic and pericystic lung cancers.[2]

Cyst wall thickening or nodularity at the interface between normal and fibrotic/emphysematous lung parenchyma, as well as progressive wall thickening or nodularity abutting a cystic airspace, should raise the suspicion of cystic/pericystic lung cancer.[2]

The morphological classification of cystic/pericystic lung cancer was proposed in 2006 and updated in 2015.[3,4] According to the current classification, a type I lesion is a cystic airspace with an exophytic solid component, whereas a type II lesion is a cystic airspace with an endophytic solid component. A type III lesion presents as asymmetrical or circumferential thickening of the cyst wall. A type IV lesion is a multilocular cystic lesion with interposed solid tissue or a ground-glass component (Figure 1).[3-5] Differences among these types, as well as their growth rate, biological behavior, and prognosis, have yet to be determined.

These lesions were previously thought to arise from congenital cysts; however, recent studies have failed to find histopathological evidence to support that theory.[5] Currently, the two most accepted evidence-based theories are that there is a pre-existing cystic airspace in which malignancy develops or that there is formation of a cyst by a "check-valve mechanism" due to a small malignant lesion that only becomes visible after growth.[2,5]

Whatever the initial pathogenesis, the histology of cystic/pericystic lung cancer differs from that of the more commonly known cavitary lung cancer. Cavitation

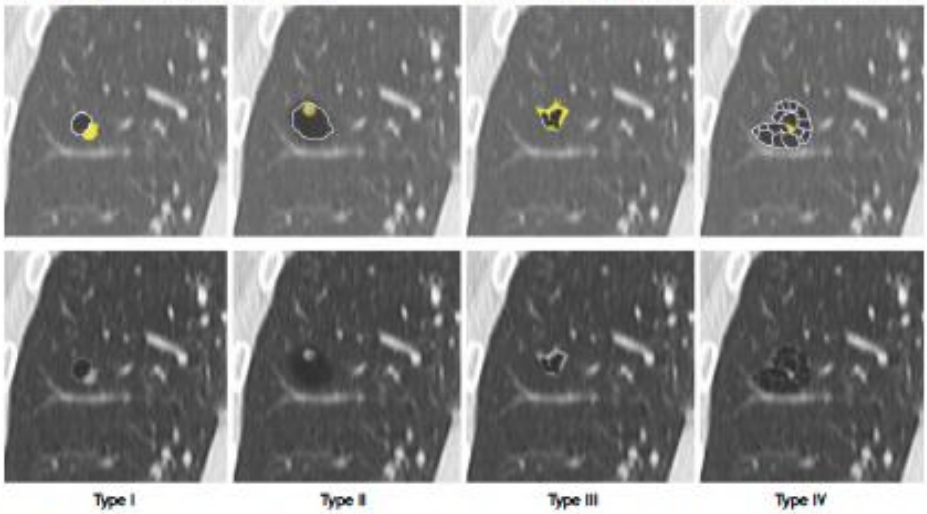

Figure 1. Morphological classification of cystic/pericystic lung lesions. The drawings in the first row of images simulate the different types of cystic/pericystic lung lesions on CT scans: type I—a nodular lesion outside the cyst wall; type II—a nodular lesion inside the cyst wall; type III—cyst wall thickening without a focal nodule; and type IV—a focal nodule within a complex multicystic lesion.

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is usually due to post-treatment necrosis, internal cyst formation, or internal desquamation of tumor cells with subsequent liquefaction.[5] The most common histological type of cavitary lung cancer is non-small cell lung carcinoma, especially squamous cell carcinoma, whereas the most common histological type of cystic/pericystic lung cancer is adenocarcinoma.[2,5]

The delay in diagnosis is due to significant overlap of radiological features between cystic/pericystic malignancies and inflammatory or infectious lesions. Common differential diagnoses include cavitary lesions, such as the ones seen in tuberculosis, squamous cell carcinoma, aspergilloma, and rheumatoid nodules, as well as rare mimickers, such as amyloid nodules and cystic lung metastasis. Cystic/pericystic cancer can be misdiagnosed as a severe form of emphysematous disease, distal airway enlargement, or fibrosis.[5]

When cystic/pericystic malignancy is suspected, histological confirmation and metabolic activity assessment are problematic because of the risk of false-negative results, which represent a potential harm to the patient. 18F-fluorodeoxyglucose positron emission tomography is usually only useful if the solid component of the cystic lesion is larger than 10 mm. Otherwise, the metabolic activity will be wrongly estimated as being mild or even absent. It is difficult to obtain a representative tissue sample from the focal thick wall or small-sized nodular component. In our experience, cystic/pericystic lesions in which positron emission tomography/CT or nondiagnostic biopsy reveals potential pitfalls should be discussed in a multidisciplinary meeting in order to make a decision for follow-up or surgical resection based on the clinical status of the patient and the expertise of the local surgical team.

Here, we sought to increase the awareness of cystic/pericystic lung cancer among radiologists and pulmonologists and highlight the importance of a timely and accurate diagnosis. As we move toward early lung cancer detection and lung cancer screening programs, further studies on these types of lesions are essential to improve knowledge, as well as diagnostic and treatment performance.

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