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ADVANCES IN CLINICAL RADIOLOGY

Lung Cancer Screening

Brett W. Carter, MD
Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1478, Houston, TX 77030, USA

KEYWORDS
• Lung cancer • Screening • Computed tomography • Low-dose • Lung-RADS

KEY POINTS

- Multiple clinical trials, including the National Lung Screening Trial (NLST) and the Dutch-Belgian Randomized Lung Cancer Screening (NELSON) trial, have shown the efficacy of lung cancer screening with low-dose computed tomography (LDCT).
- The American College of Radiology has recommended that structured reporting be used for the clinical reporting of LDCT examinations and introduced the Lung CT Screening Reporting and Data System (Lung-RADS) in 2014 to standardize the reporting and management of patients undergoing screening with LDCT.
- Incidental findings are commonly identified on LDCT examinations, some of which, such as extrapulmonary neoplasms, can result in significant patient morbidity and mortality.
- Radiomics and biomarkers have the potential to improve the accuracy of lung cancer screening to decrease overdiagnosis and morbidity.

INTRODUCTION

Lung cancer is the second most common cancer in men and women, and remains the most common cause of cancer-related mortality in the United States. The American Cancer Society estimates that, in 2018, about 234,030 new cases of lung cancer (121,680 in men and 112,350 in women) were diagnosed and that approximately 154,050 deaths (83,550 in men and 70,500 in women) were attributable to lung cancer [1]. Despite recent advances in diagnosis and treatment, the mortality rate in lung and bronchus cancers is 26% and 25%, respectively, and the 5-year survival rate of lung cancer is only 5% [2]. Thus, establishing the diagnosis at an early stage is essential.

Multiple clinical trials have demonstrated the effectiveness of lung cancer screening with low-dose computed tomography (LDCT), including the International Early Lung Cancer Action Project (I-ELCAP), the National Lung Screening Trial (NLST), and the Dutch-Belgian Randomized Lung Cancer Screening (NELSON) trial. The National Cancer Institute's NLST revealed that asymptomatic patients 55 to 74 years old with a 30-pack-year history of smoking who were current or former smokers (those who had quit <15 years earlier) who underwent screening with LDCT had a 20% reduction in lung cancer-specific mortality compared with those screened with chest radiography [3]. More recently, the Dutch-Belgian Randomized Lung Cancer Screening (or NELSON) trial demonstrated that screening of asymptomatic men at high risk for lung cancer with LDCT resulted in a 26% reduction in lung cancer deaths at 10 years of study follow-up [4]. Among women (a smaller subset of the study), the rate-ratio of dying from lung cancer varied between 0.39 and 0.61 in different years of follow-up, suggesting an even larger reduction in lung cancer mortality than in men.

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E-mail address: bcarter2@mdanderson.org

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Because of these results, and others, various professional organizations have recommended annual LDCT for lung cancer in high-risk patients. The US Preventive Services Task Force has given lung cancer screening with LDCT for adults 55 to 80 years old who have a 30-pack-year smoking history and currently smoke or have quit within the past 15 years [5]. Centers for Medicare and Medicaid Services have proposed similar eligibility criteria but with a slightly narrower patient age range of 55 to 77 years [6]. In response to coverage by both Medicare and private insurers, the number of lung cancer screening programs continues to increase. To standardize the reporting of the LDCT examinations performed for screening, the American College of Radiology (ACR) developed the Lung CT Screening Reporting and Data System (Lung-RADS) in 2014, which was modeled after the mammography reporting system (BIRADS). Lung-RADS assessment categories for each LDCT describe the probability of lung cancer and provide associated management recommendations designed to decrease the high 23.3% false-positive rate of the NLST [7,8].

The purpose of this article is to present the current state of lung cancer screening with LDCT with an emphasis placed on optimal communication of results, the reporting of incidental findings, and the evolving role of radiomics and biomarkers in improving the accuracy of screening.

COMMUNICATION OF LOW-DOSE COMPUTED TOMOGRAPHY RESULTS

Communication of LDCT examination results in a timely and effective manner is one of the most important functions of a successful lung cancer screening program. The use of a predefined format, also known as standardized or structured reporting, is recommended by the ACR when relaying results to the health care providers involved in the clinical management of patients undergoing lung cancer screening. Advantages of using structured reporting have been outlined and include the consistent delivery of relevant clinical information, straightforward identification of patients with imaging findings that may require management, and the potential for enhanced data mining and analysis [9]. In general, clinical reports should include information regarding the type of study, scanning technique, comparison examinations, imaging findings, overall impression, Lung-RADS category, and appropriate recommendations for clinical management.

Lung CT Screening Reporting and Data System

Lung-RADS is composed of specific assessment categories and management recommendations for pulmonary nodules and other potentially clinically significant abnormalities detected on LDCT examinations performed for lung cancer screening [10]. The first version of Lung-RADS was published in April 2014. Lung-RADS is designed for the interpretation and reporting of LDCT studies performed for lung cancer screening only; this system should not be used to classify abnormalities identified on other types of CT studies or on other imaging modalities such as fluorodeoxyglucose F18 (FDG)-PET/CT or MRI.

Key features of lung lesions

Any pulmonary lesions identified on LDCT should be described in terms of location (pulmonary lobe or segment or bronchus), size, and composition (solid, nonsolid, or part-solid). Specific imaging features concerning for malignancy (spiculation, ground-glass lesion that doubles in size over 1 year, or associated enlarged lymph nodes) should be noted. Other features such as internal fat or specific patterns of calcification should also be included. Any change in lesion size or composition should be reported on follow-up LDCTs.

Pulmonary nodules and other measurable lung lesions should be assessed on lung windows with the size reported as the average diameter rounded to the nearest whole number. The exception is for rounded pulmonary nodules, for which a single diameter measurement can be reported. Specific size thresholds are used to characterize lung lesions at initial screening and each follow-up. Lung lesion growth is defined as an increase in size of more than 1.5 mm on subsequent examinations.

Lung CT screening reporting and data system assessment categories and management

An overall Lung-RADS assessment category is provided as a 2-part alphanumeric score including category (part 1) and modifier (part 2) for each LDCT. The category classifies pulmonary nodules and other lesions as 0 to 4 as based on size, composition, and any significant changes compared with previous studies. The modifiers X, C, and S consider other types of information that are potentially clinically significant.

The overall Lung-RADS category assigned to each case is coded between 0 and 4 based on the pulmonary

lesion with the highest degree of clinical suspicion. Overall, Lung-RADS categories 1 and 2 indicate negative screens and Lung-RADS categories 3 and 4 are considered positive screens. Incomplete assessments resulting from suboptimal imaging technique or the existence of comparison studies are assigned Lung-RADS category 0. Lung-RADS category 1 describes LDCT studies without pulmonary nodules or with lesions that are definitely benign; these scans denote a low probability of malignancy (<1%). Lung-RADS categories 2, 3, 4A, 4B, or 4X describe LDCT scans with pulmonary nodules and other lesions that are not definitely benign (Table 1).

Lung-RADS category 2 includes nodules with a benign appearance or behavior (likelihood of malignancy <1%) and Lung-RADS category 3 denotes lesions that are probably benign (1%–2% probability of malignancy). Lung-RADS category 4 describes pulmonary nodules and other lesions that are suspicious for malignancy. This category includes A and B components, with a probability of malignancy of 5% to 15% for the former (Fig. 1) and greater than 15% for the latter (Fig. 2). Several modifiers (X, C, and S) can augment the Lung-RADS categories. For instance, the X modifier denotes features that increase the suspicion for malignancy of Lung-RADS category 3 or 4 pulmonary lesions including spiculation, rapid growth, or associated lymph node enlargement (Figs. 3 and 4). The X modifier indicates a probability of malignancy of greater than 15%. The other modifiers, C and S, reflect a history of lung cancer and other potentially clinically significant findings, respectively.

Specific recommendations regarding clinical management of abnormal findings are included in each assignment. For example, annual screening with LDCT is recommended for Lung-RADS categories 1 and 2. Six-month follow-up LDCT is recommended for Lung-RADS category 3. Three-month follow-up LDCT or evaluation with FDG-PET/CT (when an 8-mm solid component is present) is recommended for Lung-RADS category 4A. Diagnostic chest CT with or without intravenous contrast, FDG-PET/CT, or tissue sampling may be performed to assess lesions included in the Lung-RADS categories 4B and 4X. Follow-up examinations are particularly helpful in evaluating lesions that are equivocal (Figs. 5 and 6). Additional examinations may be performed to evaluate, stage, and restage lung cancer once a diagnosis has been confirmed; however, these investigations and procedures are not considered lung cancer screening. In addition, specific management may be suggested for other potentially clinically significant abnormalities denoted by modifier S.

TABLE 1
Lung-RADS categories for pulmonary nodules

Type and Size of Pulmonary Nodule on Baseline LDCT	Lung-RADS Category	Size of Pulmonary Nodule on Follow-up CT
Solid pulmonary nodule		
<6 mm	2	New nodule <4 mm
≥6 to <8 mm	3	New nodule 4 to <6 mm
≥8 to <15 mm	4A	Growing nodule <8 mm or new nodule 6 to <8 mm
≥15 mm	4B	New or growing nodule ≥8 mm
Nonsolid pulmonary nodule		
<20 mm	2	Nodule ≥20 mm and unchanged or slowly growing
≥20 mm	3	New nodule ≥20 mm
Part-solid pulmonary nodule		
<6 mm total diameter	2	N/A
≥6 mm total diameter with a solid component <6 mm	3	New nodule <6 mm total diameter
≥6 mm total diameter with a solid component ≥6 to 8 mm	4A	Nodule ≥6 mm with a new or growing <4 mm solid component
Solid component ≥8 mm	4B	Nodule with new or growing ≥4 mm solid component

Limitations

Many limitations of Lung-RADS have been described and can be challenging for the radiologist interpreting LDCT examinations. One of these scenarios is the management of lung nodules identified on LDCTs performed for lung cancer screening in patients who are "aging out" of screening [11]. The Centers for Medicare and Medicaid Services and the US Preventive Services Task Force propose 77 years and 80 years, respectively, as the upper age limit for lung cancer screening [6,12].

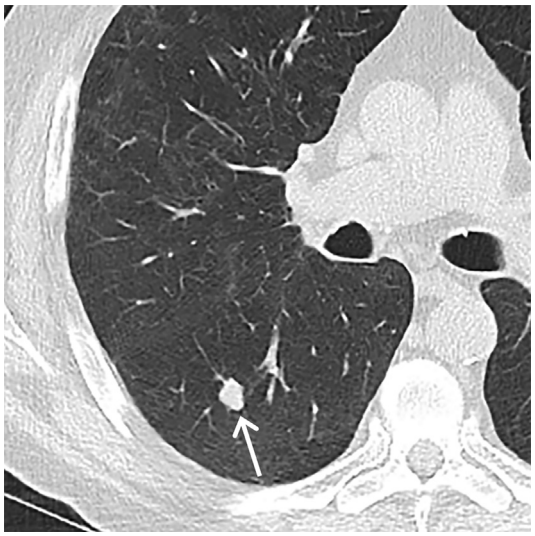

FIG. 1 Baseline axial LDCT of a 64-year-old man demonstrates a 13-mm solid nodule (*arrow*) in the right lower lobe. Based on v1 of Lung-RADS, the examination was assigned an overall category of 4A, and 3-month LDCT and FDG-PET/CT were suggested as possible methods of further management. FDG-PET/CT (not shown) was subsequently performed and demonstrated increased FDG uptake within the nodule. CT-guided biopsy was then performed and revealed squamous cell carcinoma of the lung.

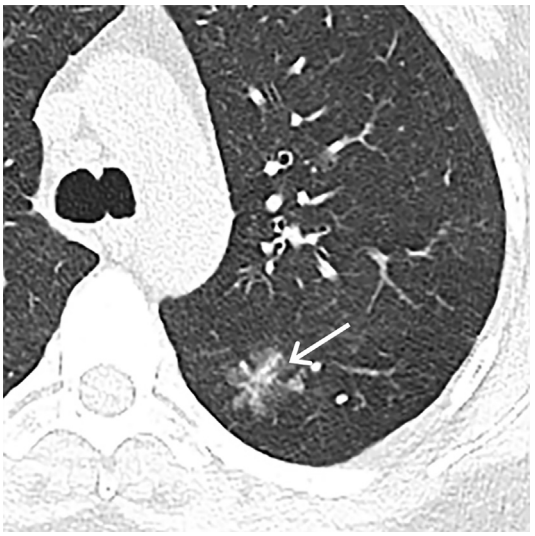

FIG. 2 Baseline axial LDCT of a 55-year-old woman demonstrates a part-solid nodule (*arrow*) in the left lower lobe measuring 20 mm with a 10-mm solid component. Based on v1 of Lung-RADS, the examination was assigned an overall category of 4B, and diagnostic chest CT, FDG-PET/CT and/or tissue sampling were suggested as possible methods of further management. CT-guided biopsy was then performed and revealed adenocarcinoma of the lung.

For patients undergoing screening with LDCT, a Lung-RADS category should be assigned; however, if follow-up assessments will ultimately be performed when patients are outside the age range for screening, then such studies can be performed, if appropriate, outside the lung cancer screening program. Although such examinations would not be assigned a Lung-RADS category, some experts recommend that the time frames suggested in Lung-RADS could still be applied [11].

Another dilemma that may be faced by radiologists interpreting LDCT examinations is when nonsolid (or ground-glass) lesions increase in density but do not change in size. To assess for nodule growth, experts suggest that radiologists should assess overall change in mass, which combines the nodule density and volume, and has been reported to be a more accurate assessment of nodule growth in comparison with diameter or volume measurements [11,13]. Although an increase in attenuation is consistent with growth, and is suggestive of a developing invasive component and a change in mass, such lesions are not discussed in Lung-RADS v1. Thus, it has been suggested that such lesions should be classified as Lung-RADS 4X, as this category gives radiologists discretion to use their experience and judgment when a particular situation is not clearly described but the imaging findings are highly suspicious for lung cancer [11] (Fig. 7).

The identification and measurement of complex subsolid nodules on LDCTs performed for lung cancer screening can pose multiple problems for radiologists. Studies have demonstrated that the interobserver and intraobserver agreement in the classification of pulmonary nodules as solid or subsolid is highly variable [14]. Assessment of the solid component of part-solid nodules should be performed on lung window settings with a sharp filter, as recommended by the Fleischner Society [15]. However, determination of the solid component when it is less than discrete can yield variable measurements and associated Lung-RADS categories on LDCTs, although such lesions are nearly always identifiable as lung adenocarcinoma by thoracic imaging experts [15]. In the setting of a complex subsolid nodule in which the exact measurement of the solid component is difficult to ascertain, the radiologist can use their clinical judgment and assign the X modifier to indicate the strong concern for lung cancer.

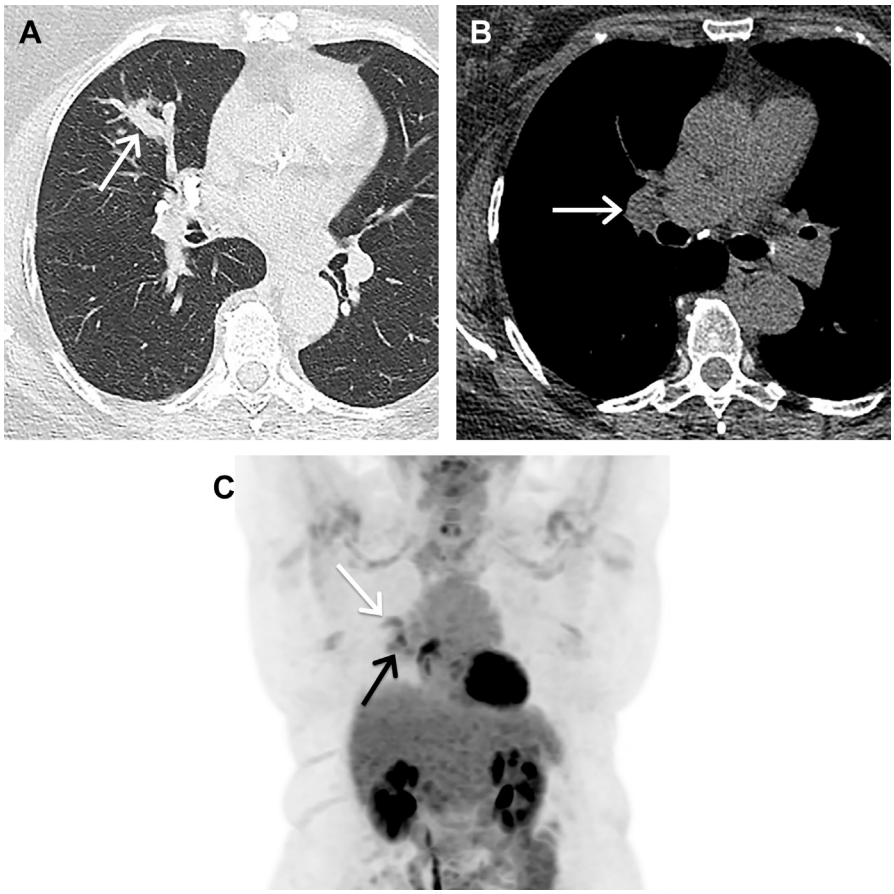

FIG. 3 Baseline axial LDCT of a 74-year-old man on (*A*) lung and (*B*) soft tissue windows demonstrates an endobronchial nodule (*A*, *arrow*) in the middle lobe that expands the bronchus and an enlarged right hilar lymph node (*B*, *arrow*) suspicious for lymph node metastasis. Although an endobronchial nodule is typically given a Lung-RADS category of 4A, the presence of suspicious right hilar lymphadenopathy increased clinical concern for lung cancer; thus, a Lung-RADS category of 4X was assigned. (*C*) Whole body FDG-PET image subsequently obtained shows increased FDG uptake in the endobronchial lesion (*white arrow*) and right hilar lymph node (*black arrow*). Biopsies confirmed lung cancer and ipsilateral hilar lymph node metastasis.

Validation and proposed modifications

Since the publication of Lung-RADS v1, researchers have investigated its accuracy and methods of improving on the guidelines. Pinsky and colleagues [7] applied Lung-RADS to the NLST population and demonstrated that its use may significantly reduce the false-positive result rate with some corresponding decrease in sensitivity. McKee and colleagues [8] assessed the impact of applying Lung-RADS to the frequency of positive and false-negative findings in a clinical lung cancer screening program, and discovered that use of the guidelines increased the positive predictive value by a factor of 2.5, to 17.3%, without increasing the number of false-negative examinations. Chung and colleagues [16] investigated the added value of Lung-RADS category 4X over categories 3, 4A, and 4B for differentiating between benign and malignant subsolid pulmonary nodules, and reported that its inclusion results in high malignancy rates in the hands of experienced radiologists.

Kaminetzky and colleagues [17] published the first prospective validation of more than 1000 patients screened for lung cancer, in which Lung-RADS proved effective in reducing the false-positive rate compared with NLST. Their study showed a 10.4% false-positive rate, which was substantially lower

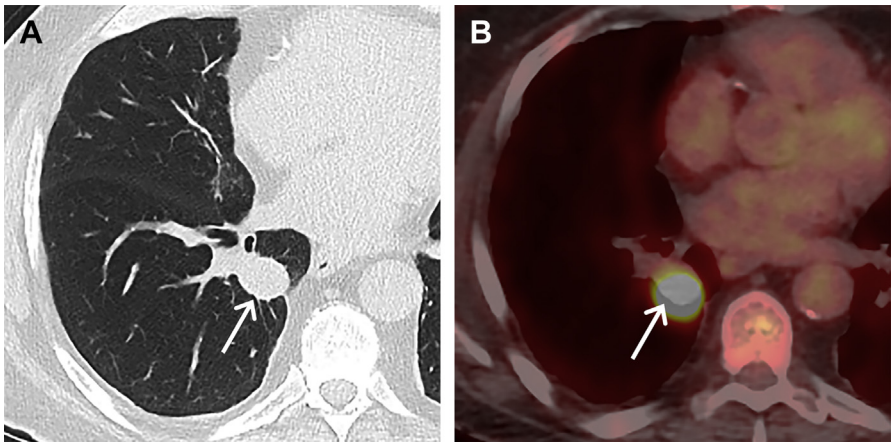

FIG. 4 (*A*) Baseline axial LDCT of a 71-year-old man shows a 14-mm nodule (*arrow*) in the right lower lobe with irregular margins. Based on v1 of Lung-RADS, the examination was assigned an overall category of 4X, and diagnostic chest CT, FDG-PET/CT, and/or tissue sampling were suggested as possible methods of further management. (*B*) Fused axial FDG-PET/CT demonstrates increased FDG uptake in the nodule, which was highly suggestive of malignancy. CT-guided biopsy revealed non-small cell lung cancer.

than the 23.3% rate in the NLST, and attributable by the authors to the higher nodule cutoff size of 6 mm in Lung-RADS compared with the NLST's 4-mm cutoff.

Hsu and colleagues [18] analyzed a retrospective cohort of 1978 consecutive healthy subjects (72.8% nonsmoker) undergoing LDCT to compare the diagnostic accuracy with Lung-RADS and NLST criteria in an Asian population with a high prevalence of adenocarcinoma and proposed a modification of Lung-RADS to clarify the characteristics of subsolid nodules. This group modified Lung-RADS categories 2 and 3 to include subcategories of 2A/2B/2C and 3A/3B/3C, respectively. Modified Lung-RADS, using modified Lung-RADS category 2C as cutoff, had an area under the curve (AUC) of 0.973 in predicting adenocarcinoma spectrum lesions (sensitivity of 100%, specificity of 89.3%), which was significantly higher than that of Lung-RADS (AUC = 0.815, $P<.001$) and NLST (AUC = 0.906, $P<.001$). Furthermore, modified Lung-RADS showed an AUC of 0.992 in predicting invasive adenocarcinoma (sensitivity of 95%, specificity of 97.8%) when category 3B was used as cutoff. Thus, modified Lung-RADS may substantially improve sensitivity while maintaining specificity for detection of adenocarcinoma spectrum lesions in an Asian population, and has the enhanced ability to differentiate invasive from indolent adenocarcinoma by more refined subclassification of subsolid nodules using 2 cutoff values of category 2C and 3B.

Other investigations have proposed modifications to the existing version of Lung-RADS. It is anticipated that updated guidelines will be published by the ACR within the next year.

UNDERSERVED POPULATIONS

A growing focus of lung cancer screening programs is the evaluation of underserved populations. The aforementioned study described by Kaminetzky and colleagues [17] was performed at a screening program that serves an underserved population that is poorly represented in prominent lung cancer screening trials. Greater than 60% of the 1181 patients included in the cohort were ethnic minorities, compared with 10% in the NLST and the ELCAP [3,19]. Hispanics and blacks comprised only 1.8% and 4.5% of the NLST cohort (compared with 31% each in the Kaminetzky study). In addition, this study included other features of a highly urban cohort including high poverty rate, multiple comorbidities, a greater proportion of women (51%), and more current smokers (71%) compared with the NLST (48%) and other trials [3,19–21].

Recently, Li and colleagues [22] assessed the results of the first 2 rounds of screening of a lung cancer screening program targeting a minority, socioeconomically disadvantaged, high-risk population. They concluded that lung cancer screening with LDCT in this population is feasible but may yield a different lung cancer profile than screening in more privileged communities, but noted that adherence to annual follow-up and clinical management recommendations

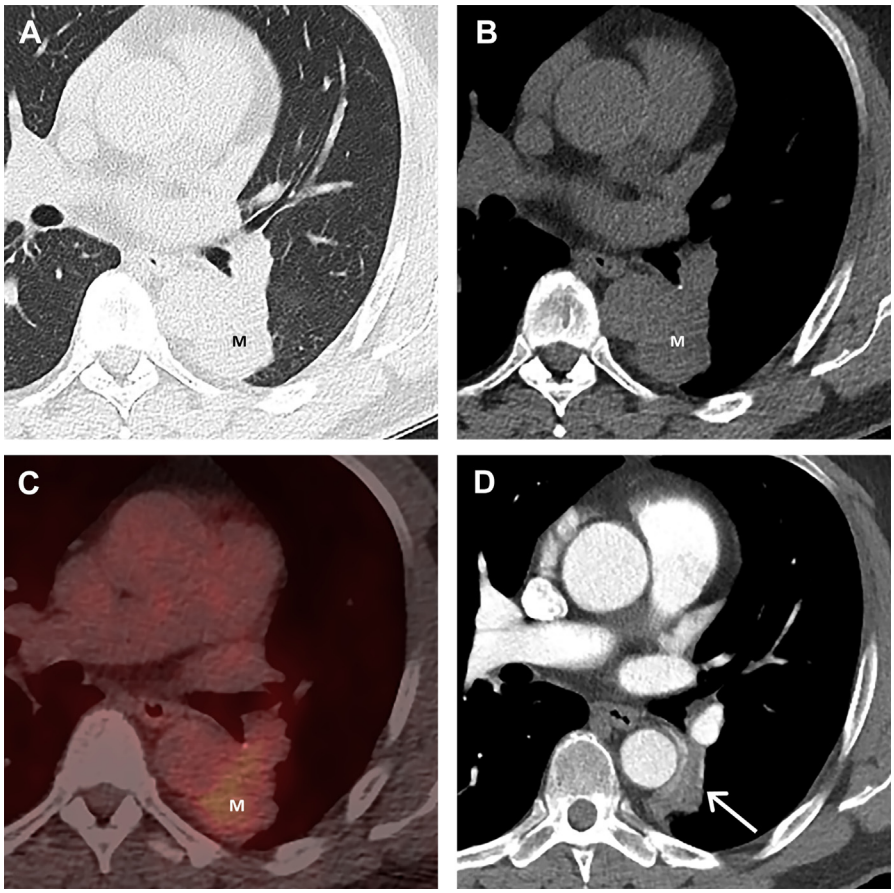

FIG. 5 Baseline axial LDCT of a 60-year-old man on (*A*) lung and (*B*) soft tissue windows demonstrates a 5-cm mass (M) in the medial left lower lobe. Based on v1 of Lung-RADS, the examination was assigned an overall category of 4B, and diagnostic chest CT, FDG-PET/CT and/or tissue sampling were suggested as possible methods of further management. (*C*) Fused axial FDG-PET/CT shows only low-grade FDG uptake within the abnormality (M). CT-guided biopsy and bronchoscopic evaluation were then performed and revealed only inflammatory cells without evidence of malignancy. (*D*) Contrast-enhanced axial CT obtained several weeks after intervention shows marked interval decrease in the opacity (*arrow*) consistent with atelectasis.

are challenging [22]. Kessler and colleagues [23] compared the performance of the Vancouver risk calculator (VRC) with Lung-RADS for a lung cancer screening cohort in an urban, diverse clinical setting. The VRC demonstrated higher sensitivity but lower specificity and accuracy in predicting malignancy compared with Lung-RADS among these patients.

INCIDENTAL FINDINGS

Background

Although the primary goal of lung cancer screening is to identify early lung cancers, LDCT examinations performed for this purpose may demonstrate a wide variety of other pulmonary or extrapulmonary abnormalities from the neck to the upper abdomen that are unexpected and incidental. The clinical significance of these incidental findings is variable, with some leading to further testing, which may be invasive.

Several studies have investigated the frequency of incidental findings detected on LDCT. Morgan and colleagues [24] evaluated 320 patients undergoing lung cancer screening. Of this group, the most commonly reported incidental findings were of pulmonary (69.6%), cardiovascular (67.5%), and gastrointestinal (25.9%)

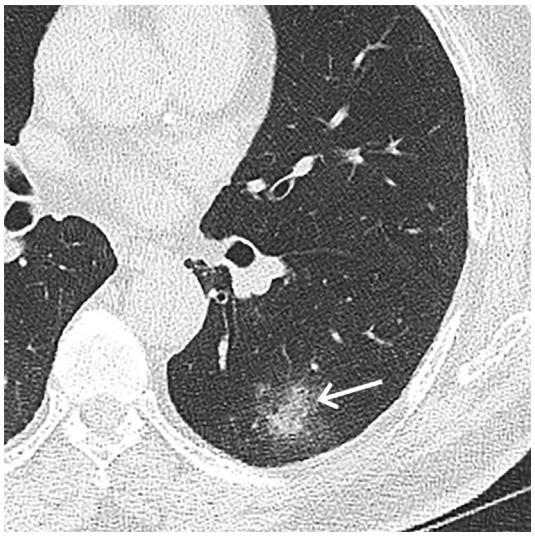

FIG. 6 Axial LDCT of a 73-year-old man shows a part-solid opacity (*arrow*) with ill-defined margins in the left lower lobe. The appearance was suggestive of infection and follow-up LDCT obtained 8 weeks later (not shown) after treatment with antibiotics revealed resolution.

origin, and 15% of LDCT scans had an incidental finding that resulted in further evaluation. In the NELSON trial, the prevalence of incidental findings was 8% [25]. Kucharczyk and colleagues [26] identified incidental findings in 19% of their 4073 screening participants. Most of these incidental findings were considered noncardiovascular (78%) and identified at baseline imaging (80%). A study by Nguyen and colleagues [27], which reviewed prospectively acquired data on 17,309 NLST participants, showed that extrapulmonary findings were noted in 58.7% of the patients undergoing LDCT screening, and 19.6% had findings coded as potentially clinically significant.

Classification

Incidental findings are typically classified based on location within the body. For instance, findings are commonly separated into "pulmonary" and "extrapulmonary" findings. Moreover, extrapulmonary findings may be subdivided into those affecting the cardiovascular system, mediastinum, thyroid gland, pleura, and upper abdomen (Fig. 8). A brief discussion of extrapulmonary neoplasms is included in this article; however, a detailed discussion of other incidental findings detected on LDCT is beyond the scope and has been covered extensively in other publications [28,29].

Extrapulmonary neoplasms are one of the most clinically significant incidental findings that can be detected on LDCT. In the CT arm of the NLST, 22.3% of certified deaths (416 of 1865) were attributable to extrapulmonary malignancies, compared with 22.9% of deaths from lung cancer (427 of 1865) [3]. The prevalence of extrapulmonary malignancies reported in LDCT lung cancer screening participants varies from 0% to 1.6% [4,26,30,31]. In a cohort of

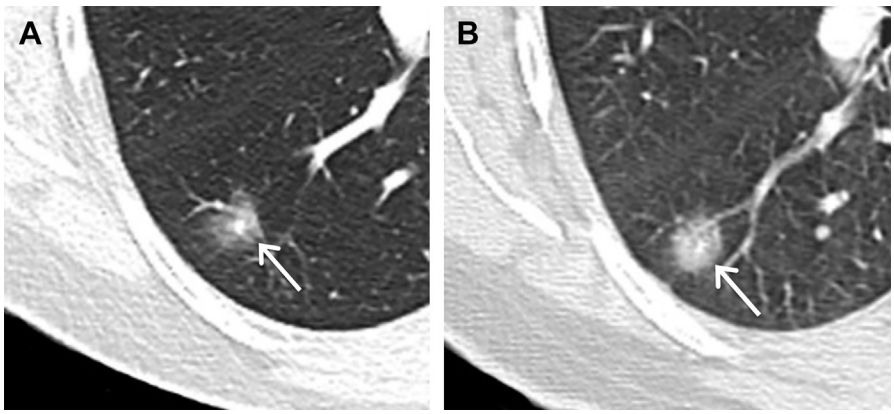

FIG. 7 (*A*) Baseline axial LDCT of a 62-year-old man shows a 22-mm nonsolid nodule (*arrow*) in the right lower lobe. A central vessel is present. Based on v1 of Lung-RADS, the examination was assigned an overall category of 3, and a 6-month follow-up LDCT was recommended. (*B*) Follow-up LDCT obtained 6 months later demonstrates stable size of the nodule (*arrow*), which would normally warrant a Lung-RADS category of 2. However, there has been interval diffuse increase in attenuation, suggesting growth. Therefore, Lung-RADS 4X was assigned, and surgical resection revealed adenocarcinoma.

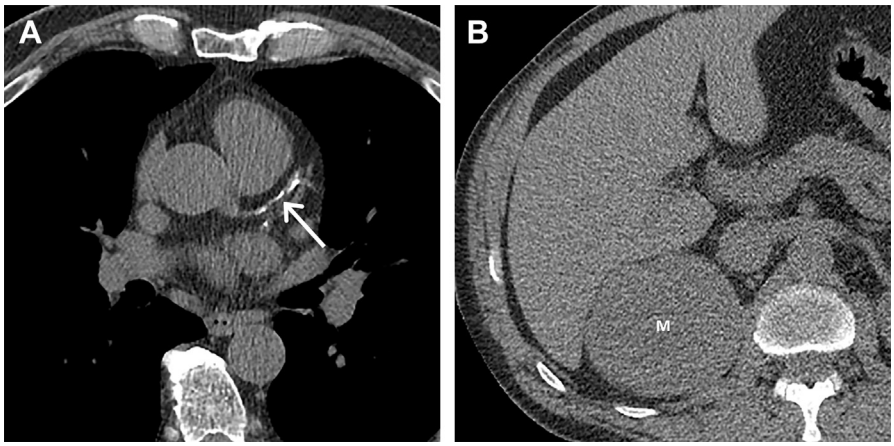

FIG. 8 (*A*) Axial LDCT of a 66-year-old man shows severe coronary artery calcification involving the left anterior descending coronary artery (*arrow*). (*B*) Axial LDCT of a 57-year-old man demonstrates a homogeneous soft tissue mass (M) in the right kidney. Ultrasound-guided biopsy was subsequently performed and revealed renal cell carcinoma.

5201 patients undergoing LDCT for lung cancer screening, 27 extrapulmonary neoplasms were identified by Rampinelli and colleagues [32], of which renal cell carcinoma [7] and lymphoma [5] were the most commonly diagnosed malignancies. Other types of malignancies identified included thyroid cancer [3], thymoma [2], pancreatic neoplasm [2], schwannoma [1], hepatocellular carcinoma [1], gastrointestinal stromal tumor [1], prostate cancer [1], breast cancer [1], adrenal gland neoplasm [1], and ovarian cancer [1].

Reporting and Management

Incidental findings should be documented in the clinical report generated for each LDCT examination using the S modifier. Management of thoracic findings should be determined by approved guidelines published by professional societies, such as the ACR Incidental Findings Committee [33] or the American Thoracic Society/American College of Chest Physicians [34]. In addition, the ACR has published updated recommendations for the management of incidental findings detected in the thyroid gland and the abdomen that can be adapted to manage incidentally detected findings on lung cancer screening [35–37]. Alternatively, institutions and practices may wish to develop their own protocols for their screening programs in a multidisciplinary fashion. Incidental findings should also be tracked by the screening program so that clinically significant abnormalities unrelated to lung lesions are reported and evaluated appropriately.

RADIOMICS

Radiomics refers to the extraction and analysis of advanced quantitative imaging features from tumors and other lesions detected on medical images, including CT, MRI, and PET [38–41]. The extraction of quantitative descriptors such as kurtosis, uniformity, homogeneity, entropy, and intensity, together with additional features such as size and contour, can be used to profile lesions, infer phenotypic and genomic information, and provide potentially valuable information such as prediction of treatment response and outcomes [42–44].

The potential role of radiomics in the evaluation of lung cancer screening LDCTs continues to evolve. Liu and colleagues proposed a linear classifier based on 24 image traits visually scored by physicians. Several groups have proposed random forest classifiers using several radiomic features ranging from 23 to 583 [45,46]. Others have described the use of deep neural networks. For instance, Buty and colleagues [47] developed a random forest classifier using 4096 appearance features extracted with a pretrained deep neural network and 400 shape features extracted with spherical harmonics and Kumar and colleagues [48] developed a deep neural network model using 5000 features.

More recently, Choi and colleagues [49] developed a radiomics prediction model, with the goal of improving pulmonary nodule classification on LDCT, and compared this model with Lung-RADS. One hundred and three CT radiomic features were extracted from 72 pulmonary nodules (31 benign and 41 malignant)

from the Lung Image Database Consortium image collection (LIDC-IDRI). Distinctive features were identified using a hierarchical clustering method, and a prediction model was constructed using a support vector machine (SVM) classifier coupled with a least absolute shrinkage and selection operator (LASSO). The best SVM-LASSO model consisted of only 2 features: the bounding box anterior-posterior dimension (BB_AP), which measured the extension of a pulmonary nodule in the anterior-posterior direction, and the SD of inverse difference moment (SD_IDM), which measured the directional variation of the local homogeneity feature IDM. This model using 2 CT radiomic features achieved an accuracy of 84.6%, which was 12.4% higher than Lung-RADS.

Despite the continued improvement in the reliability and predictive value of these radiomics studies, there are inherent limitations to the use of quantitative imaging in lung cancer screening [50]. These include technical issues such as the variability in image acquisition and reconstruction of LDCTs performed for screening, segmentation for tumor definition, and software programs used to analyze features. These processes are very time consuming; thus, it would be logistically difficult to perform radiomics in a large number of participants. In order for radiomics to be widely applicable to LDCT screening, technical parameters such as image acquisition and reconstruction would have to be standardized [51]. As reported by Hawkins and colleagues, the variability of scanners and associated imaging parameters affected the ability of the authors to extract quantitative radiomic data and influenced the accuracy of prediction. Finally, the innumerable number of features that can be extracted for analysis and numerous predictive modeling methods available to analyze the data are additional constraints.

BIOMARKERS FOR LUNG CANCER SCREENING

Blood- and serum-based biomarkers have the potential to improve the accuracy of lung cancer screening to decrease overdiagnosis and morbidity [52]. Molecular biomarkers are potentially useful adjuncts to LDCT for lung cancer screening, either by further delineating patient risk before LDCT, or assessing malignant risk of positive LDCT findings [53–57]. Cancer cells, the tumor microenvironment, and the host response to cancer are all potential sources of biomarkers [54,58].

Molecular factors implicated in lung cancer development have been assessed as biomarkers, such as markers of apoptosis, cellular adhesion, cellular growth, and tumor proliferation [57,59]. Epigenetic markers, including DNA methylation, miRNAs, nucleosome remodeling, and histone modifications, have been evaluated [52–54]. Several bodily sources, including whole blood, serum, plasma, bronchial brushings, and sputum, may be used to generate biomarkers [58,59]. Circulating blood-based and serum-based biomarkers are considered relatively easy and inexpensive to collect [44–56].

The EarlyCDT-Lung test is a commercially available blood test that measures a panel of 7 tumor-associated autoantibodies, including p53, NY-ESO-1, CAGE, GBU4–5, SOX2, HuD, and MAGE A4 [60]. The miR-test is a serum-based miRNA test that measures a signature of 13 miRNAv [61]. The MSC is a plasma-based miRNA test that sorts patients into low-, intermediate-, or high-risk categories of disease based on predefined positivity for 24 miRNA expression ratios [62]. Only EarlyCDT-Lung, serum-based miRNA signature (miR-test), and plasma-based miRNA test (MSC) have entered phase 4 of development [54].

Chu and colleagues [52] performed a systematic review of the literature regarding these biomarkers and determined that all 3 biomarker assays show promise for the detection of lung cancer, and that MSC shows promise when used in conjunction with LDCT. Specifically, it achieves a positive likelihood ratio of 18.6 if both LDCT and MSC are positive, and a negative likelihood ratio of 0.03 if both LDCT and MSC are negative. Additional high-quality studies are necessary for further investigation and to help guide clinical implementation.

SUMMARY

Lung cancer screening programs using LDCT continue to proliferate, and radiologists must be able to communicate effectively with patients and referring health care providers regarding examination results, understand the significance of reporting significant non-lung cancer incidental findings, and develop and refine tools such as radiomics and other biomarkers to improve the accuracy of screening.

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