Beyond Lung Cancer

A Strategic Approach to Interpreting Screening Computed Tomography Scans on the Basis of Mortality Data From the National Lung Screening Trial

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Abstract: Low-dose computed tomography screening in older patients with a heavy-smoking history can be viewed as an opportunity to screen for smoking-related illnesses and not just for lung cancer. Within the National Lung Screening Trial, 24.1% of all deaths were attributed to lung cancer, but there were significant competing causes of mortality in this patient population. Cardiovascular illness caused 24.8% of deaths. Other neoplasms were listed as the cause of death in 22.3%, and respiratory illness was the cause of death in 10.4%. All of these illnesses might be attributed to smoking. Low-dose computed tomography of the thorax may provide information about these diseases, which could be used to guide therapeutic intervention and, hopefully, alter the courses of these diseases. Information about coronary artery calcification, chronic obstructive pulmonary disease, and potential extrapulmonary malignancy should be provided in the report of the screening examination. This must be balanced against the risk of the burden of false-positive findings and the costs, both psychological and financial, associated with additional investigative evaluations.

Key Words: lung cancer screening, incidental findings, thoracic computed tomography, coronary artery calcification, chronic obstructive pulmonary disease, extrapulmonary malignancy, National Lung Screening Trial

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Any program aimed at screening for a particular disease faces the dilemma of encountering unexpected, incidental findings. These may be clinically significant findings or may be benign findings that require no further workup. The decision to further investigate incidental findings of potential clinical significance is then determined by the relevance to the individual patient, with consideration for risks of workup, patient comorbidities and life expectancy, and financial costs. Screening for lung cancer with low-dose computed tomography (LDCT) is similar to other screening programs in that the CT of the chest can reveal findings other than lung cancer. The situation is somewhat unique, however, in that the population undergoing screening may have other diseases directly related to their smoking history. LDCT screening in older patients with a heavy-smoking history can be viewed as an opportunity to screen for smoking-related illnesses and not just for lung cancer.[1]

In a systematic review of selected CT screening studies of the chest [screening for coronary artery disease (CAD) and lung cancer screening], Jacobs et al[2] found that 14.2% of patients undergoing lung cancer screening had at least 1 clinically significant incidental finding requiring further investigation, compared with 7.7% of patients undergoing screening for CAD. This may be attributed to the heavy-smoking history in all participants in lung cancer screening programs and to the larger field of view and length of coverage for lung cancer screening. Another reason for the difference in the prevalence of incidental findings is that pulmonary nodules, which are quite common in the general population, are considered incidental findings in CAD screening, but are the primary objective in lung cancer screening. Hall et al[3] reported a 24% prevalence of significant incidental findings in patients undergoing CT angiography for diagnosis of pulmonary embolism, predominantly pulmonary nodules (13%) and lymphadenopathy (9%).

FINANCIAL IMPLICATIONS OF INCIDENTAL FINDINGS

Lung cancer screening trials are designed to test the ability of LDCT to reduce lung cancer–specific mortality. Although the presence of incidental findings is recorded, and all-cause mortality is included in the analysis, the risks and benefits of pursuing findings unrelated to lung cancer is not the primary objective. There is concern that the expenses involved in evaluating pulmonary nodules that prove to be benign, as well as incidental findings that are often of no clinical significance, could undermine the comparative effectiveness of LDCT screening for lung cancer. Several investigators have evaluated the financial implications of the diagnostic workup of incidental findings.[4–6] Within a lung cancer screening program in Toronto, ON, Canada, the estimated cost of the initial diagnostic workup alone of 486 incidental findings was CAN$45,500 to CAN$51,000 (US$45,590 to US$49,980).[4] Abdominal ultrasound was the most frequently recommended diagnostic examination. Investigators conducting a lung cancer screening program in Torino, Italy found that the most common recommendations were for ultrasound imaging of the thyroid and kidneys.[5] The total cost of the diagnostic workup of 62 incidental findings discovered at baseline screening was US$6575. Remarkably, these 2 programs in 2 different continents suggest an average cost of approximately US$103 to US$106 per incidental finding.

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When distributed over the total number of screening participants, this amounted to US$12.63 to US$12.67 per participant. The differences in health care systems from country to country are such that these numbers are not necessarily applicable worldwide.

Hepatic and renal lesions were also the major cause of potentially clinically relevant incidental findings in the Dutch-Belgian lung cancer screening trial [Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON)].[6] Abdominal ultrasound was the primary diagnostic study recommended, and, in all but 1 case, the lesions were shown to represent benign cysts. The remaining case represented metastatic disease from pancreatic cancer. They concluded that the majority (73%) of incidental findings during screening for lung cancer are not clinically relevant. Incidental findings are clinically relevant in only 7% of the participants and are mostly benign, therefore there was "neglectable benefit" of searching for incidental findings. It should be noted that the authors did not consider emphysema or coronary artery calcification (CAC) clinically relevant, as they did not require further diagnostic investigation.

MORTALITY DATA FROM THE NATIONAL LUNG SCREENING TRIAL (NLST)

The NLST was designed to evaluate the ability of screening with LDCT to reduce lung cancer–specific and all-cause mortality in patients aged 55 to 74 years with at least a 30 pack-year smoking history, relative to screening with chest x-ray (CXR).[7] The trial therefore defined diagnostic algorithms for pulmonary nodules found in either the experimental (LDCT) arm or the control (single-view CXR) arm. The NLST was able to show a 20% reduction in lung cancer mortality with LDCT screening relative to screening with CXR. Lung cancers diagnosed during the trial were treated according to local standards of care. Although data were collected about additional findings such as emphysema, CAC, aortic aneurysm, and mediastinal masses, there was no defined intervention for diseases other than lung cancer.

In the NLST, there were 3875 deaths during the course of the trial, which included 3 years of annual screening and a median of 6.5 years of follow-up. Of the 3856 deaths for which death certificates indicated the cause of death, lung cancer was the cause of death in 930 (including 427 in the LDCT arm and 503 in the CXR arm). A total percentage of 24.1% of all deaths were attributed to lung cancer. This could be calculated as 247 deaths from lung cancer per 100,000 person-years in the LDCT arm and 309 deaths per 100,000 person-years in the CXR arm, which represented a relative reduction in mortality from lung cancer with LDCT screening of 20.0% [95% confidence interval (CI), 6.8-26.7; $P = 0.004$].

There were significant competing causes of mortality in this patient population (Table 1). Cardiovascular illness caused 24.8% of deaths (486 LDCT, 470 CXR). Other neoplasms were listed as the cause of death in 22.3% (416 LDCT, 442 CXR), and respiratory illness was the cause of death in 10.4% (175 LDCT, 226 CXR). All of these illnesses might be attributed to smoking. Although there was very little difference in mortality from diseases other than lung cancer between the LDCT and CXR arms in the NLST, the trial was not designed to intervene for illnesses other than lung cancer.

TABLE 1. Mortality Data From the NLST

Cause of Death	LDCT, n (%)	CXR, n (%)	Total, n (%)
Lung cancer	427 (22.9)	503 (25.3)	930 (24.1)
Other cancers	416 (22.3)	442 (22.2)	858 (24.8)
Cardiovascular disease	486 (26.1)	470 (23.6)	956 (22.3)
Respiratory illness	175 (9.4)	226 (11.4)	401 (10.4)
Other	349 (18.7)	343 (17.2)	692 (17.9)

Cause of death on the death certificate, according to the screening arm.[7]

There are findings on LDCT screening for lung cancer that might be relevant to these competing causes of mortality, specifically CAC, chronic obstructive pulmonary disease (COPD), and extrapulmonary malignancy. It is possible that all-cause mortality might be further reduced in this population of older, heavy smokers by developing guidelines for management of these clinically relevant findings.

CAC

Every individual eligible for LDCT lung cancer screening has at least 2 major risk factors for CAD: age and cigarette smoking. CAD is the leading cause of death worldwide and is the cause of death in 1 of every 6 deaths in the United States. It is estimated that 16.7% of those deaths are attributable to smoking (adjusted for deaths due to ischemic heart disease attributed to smoking).[8] Major risk factors for cardiovascular events include cigarette smoking, hypertension (blood pressure $\geq$ 140/90 mm Hg or on antihypertensive medication), low levels of high-density lipoprotein (HDL) cholesterol (< 40 mg/dL), family history of premature coronary heart disease (CHD) (in a male first-degree relative below 55 y of age; in a female first-degree relative below 65 y of age), and age (men above 45 y; women above 55 y).

CAC is an established independent predictor of cardiovascular events and is strongly associated with advancing age and cigarette smoking history. Quantitative analysis of CAC may be useful in the lung cancer screening population in that patients might be reclassified to a higher risk status on the basis of a high CAC score, and subsequent patient management may be modified.

In 2010, the American College of Cardiology and American Heart Association published a clinical expert consensus document on coronary artery calcium scoring by CT.[9] The statement reported that measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-y risk for a CHD event) and may be reasonable for cardiovascular risk assessment in asymptomatic persons at low to intermediate risk (6% to 10% 10-y risk). Quantitative risk assessment based on the multivariable scoring system of the Framingham Heart Study is available online at http://cvdrisk.nhlbi.nih.gov/calculator.asp. Using this risk assessment tool, a 55-year-old male smoker with normal systolic blood pressure and borderline cholesterol levels (total cholesterol of 200, HDL of 40) would have a 14% 10-year risk for a CHD event and would fall into the intermediate-risk category. A 60-year-old male smoker with a systolic blood pressure of 150 and elevated cholesterol levels (total cholesterol of 300, HDL of 30) would have a > 30% chance of having a heart attack in the next 10 years.

The Agatston scoring method is commonly used for CAC scoring and is calculated by multiplying the area (mm^2) of lesions >130 HU by a density factor ranging from 1 to 4.[10] Although CAC scoring is typically performed on electrocardiogram (ECG)-gated multidetector computed tomography (MDCT) or electron-beam computed tomography, Wu et al[11] demonstrated that CAC scoring using the Agatston method could also be performed on low-dose ungated chest CT scans and was a reliable method of risk stratification. In 483 subjects, the concordance between LDCT and ECG-gated MDCT was high ($\kappa = 0.89$ for the 2 observers) for categorization into 4 major score ranks (0, 1 to 100, 101 to 400, > 400). An alternative scoring method for CAC is volume scoring, developed by Callister et al,[12] which may be more reproducible than the Agatston scoring method.

Deprez et al[13] determined that an acquisition protocol with a kVp other than 120 affects Agatston scoring of CAC. The lower kVp actually increases the calcium density, so that Agatston scores are overestimated. Huang et al[14] compared ECG-gated CT obtained at 120 kVp with LDCT obtained at 100 kVp and found that a visual scoring method was able to categorize CAC on LDCT as none, mild, moderate, and severe and that these 4 categories correlated well with Agatston score risk ranking of 0, 1 to 100, 101 to 400, and >400 HU. Interscan agreement of CAC measurements on LDCT is also good. In 584 participants in the NELSON trial, CAC scores measured on 2 LDCT scans obtained within 4 months of each other were in the same Agatston risk category in 75% of cases.[15]

Visual scoring methods may be a more practical scoring method for risk stratification on LDCT screening examinations compared with the Agatston system.[16,17] Shemesh and colleagues used a 0 to 3 scale (absent, mild, moderate, and severe) for evaluating calcium in the left main, left anterior descending, circumflex, and right coronary arteries. The vessel-specific scores were summed for a total score of 0 to 12. A CAC score of at least 4 was a significant predictor of cardiovascular death (odds ratio, 4.7; 95% CI, 3.3-6.8; $P = 0.0001$), when compared with the reference group of CAC = 0.[16]

A visual scoring method was also evaluated in a retrospective case-control study, which analyzed the relationship between baseline LDCT CAC, CHD, and all-cause mortality, in a subset of the NLST population.[18] Five cardiothoracic radiologists evaluated a total of 1570 LDCTs from 3 groups: group 1 included 210 CHD deaths; group 2 included 314 all-cause deaths (excluding CHD); the control group included 1046 participants alive at conclusion of the trial. Readers performed quantitative analysis of CAC (Agatston scoring), as well as qualitative analysis, based on both an overall and a per-vessel visual assessment (none/0, mild/1, moderate/2, heavy/3), using a set of standard reference CT images (Fig. 1). In predicting time to CHD death, total Agatston scores of 1 to 100, 101 to 1000, and >1000 (reference 0) were associated with hazard ratios (HRs) of 1.3 ($P = 0.40$), 3.5 ($P < 0.001$), and 6.0 ($P < 0.001$), respectively. The visual assessments of 1 to 9, 10 to 19, and 20 to 30 (summing the ordinal scores of 10 vessel segments, reference 0) were associated with HRs of 2.4 ($P = 0.001$), 4.5 ($P < 0.001$), and 6.6 ($P < 0.001$), respectively; the overall visual assessments (none/mild/moderate/heavy) were associated with HRs of 2.1 ($P = 0.008$), 3.7 ($P < 0.001$), 5.9 ($P < 0.001$), respectively.

Jacobs et al[19] evaluated 958 participants in the NELSON trial using a case cohort design. After exclusion of participants with a history of cardiovascular disease or with a missing baseline CT screening examination, their evaluation included 150 participants who had died at the end of the follow-up period or had a cardiovascular endpoint, including nonfatal cardiovascular and CHD hospital admissions, and 808 who were alive and without a cardiovascular or CHD endpoint. Agatston scores for coronary calcium were evaluated as a continuous measure and on the basis of 4 risk categories: 0/very low risk, reference category; 1 to 100/low risk; >100 but ≤1000/moderate to high risk; and >1000/very high risk. Data were adjusted for age, sex, smoking, hypertension, hypercholesterolemia, and diabetes.

Within the total group, the CAC score was 0 in 24% of participants: CAC scores of 1 to 100, 100 to 1000, and >1000 were measured in 29%, 30%, and 17% of participants, respectively (Table 2). There were 56 deaths during the 21.5-month follow-up period for all-cause mortality. In this group, multivariate-adjusted HRs for all-cause mortality for CAC scores of 1 to 100, 101 to 1000, and >1000, compared with the reference group of CAC = 0, were 3.00 (95% CI, 0.61-14.93), 6.13 (95% CI, 1.35-27.77), and 10.93 (95% CI, 2.36-50.60), respectively. In the group of 61 participants with fatal and nonfatal CHD endpoints, multivariate-adjusted HRs for coronary events were 1.38 (95% CI, 0.39-4.90), 3.04 (95% CI, 0.95-9.73), and 7.77 (95% CI, 2.44-24.75), respectively, compared with the reference group of CAC = 0.

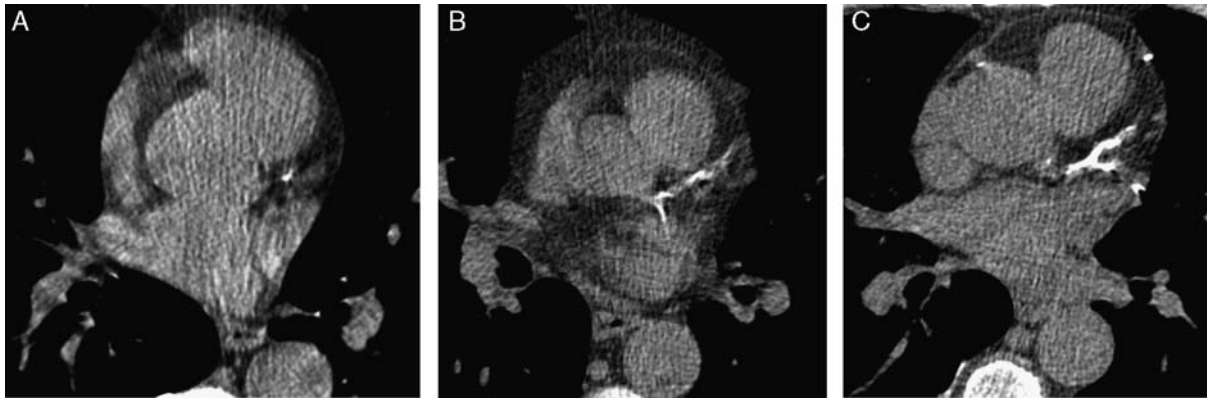

FIGURE 1. A, Mild calcification in the left anterior descending coronary artery. B, Moderate calcification in the left anterior descending coronary artery. C, Heavy calcification in the left anterior descending and first diagonal coronary arteries.

TABLE 2. Prevalence of Agatston Score Risk Categories in a Case-Control Study of 958 Participants in the NELSON Trial, and HRs for All-cause Mortality and Fatal and Nonfatal Cardiovascular and CHD Events, Relative to CAC Scores of Zero[18]

CAC Score	Prevalence (%)	HR for All-cause Mortality	HR for Fatal and Nonfatal Cardiovascular Event	HR for Fatal and Nonfatal CHD Event
0	24	Reference	Reference	Reference
1-100	29	3.00	1.76	1.38
101-1000	30	6.13	1.93	3.04
> 1000	17	10.93	5.33	7.77

In asymptomatic patients, the absence of CAC is considered a "negative" cardiovascular risk factor and is associated with a 10-year event rate of approximately 1%.[20] Smokers without CAC, however, are at a higher risk level for all-cause mortality than are nonsmokers without CAC. McEvoy et al[21] evaluated CAC and all-cause mortality in 44,042 asymptomatic individuals, 6020 of whom were smokers. They found that, at each level of elevated CAC score, mortality in smokers was consistently higher than mortality in nonsmokers from the next higher risk level. For example, smokers with CAC scores of 1 to 100 had higher mortality than nonsmokers with CAC scores of 101 to 400. Similarly, the mortality of smokers with CAC scores of 0 was higher than mortality in nonsmokers with CAC scores of 1 to 100.

Patients with high CAC scores are more likely to be treated with statins as a lipid-lowering intervention, as well as to initiate aspirin therapy, dietary changes, and increased exercise.[22] One year after CAC evaluation, 91% of patients with the highest levels of CAC (Agatston scores >526) were adherent to statin therapy, compared with 44% of those with the lowest scores (0 to 30).

Although the LDCT technique used for lung cancer screening has limitations in that it is nongated and has more image noise than coronary artery screening CT scans, calcification within the coronary arteries is visible and measurable. What is not yet known is whether providing information about CAC to a patient undergoing lung cancer screening results in better outcomes. Adding information about CAC to the report on LDCT screening for lung cancer may alert both the patient and his/her physician to the risk for CHD, which might promote healthier lifestyle choices and initiation of statin/aspirin therapy. Given the high mortality from cardiovascular disease in this patient population, any reduction in the number of deaths from CHD could add to the all-cause mortality benefit demonstrated in the LDCT arm of the NLST.

COPD

COPD is an underdiagnosed disease and is infrequently self-reported in patients undergoing screening for lung cancer, despite their heavy-smoking histories.[23,24] An earlier diagnosis of COPD can improve patient management and result in fewer exacerbations. COPD is currently the fourth leading cause of death, and the mortality from COPD has increased over the last 3 decades. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a chronic disease, characterized by persistent airflow limitation that is usually progressive.[25] The chronic airflow limitation characteristic of COPD is due to either small airways disease (obstructive bronchiolitis) or parenchymal destruction (emphysema) or due to a combination of the 2. Some patients may have small airways–predominant disease, whereas others have emphysema-predominant disease, and others may have a mixture of the 2 processes.[26,27]

The diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors, such as tobacco smoke or occupational dust. The diagnosis is established when spirometry confirms that the post-bronchodilator measurement of forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) is <0.70.[25] It is known that the fixed ratio of FEV_1/FVC overestimates COPD in older people, as FEV_1 declines more rapidly than does FVC with increasing age. Others propose using a lower limit of normal threshold for the diagnosis of COPD, where the lower limit of normal is defined as the fifth percentile of the normal distribution for the FEV_1/FVC ratio, FEV_1, and FVC.[28]

COPD is an independent risk factor for lung cancer, and some investigators propose using the diagnosis of COPD as part of a risk stratification model in selecting patients for lung cancer screening.[29]

Two distinct imaging-based COPD phenotypes have been described: an emphysema-predominant group and an airway-predominant group (Fig. 2).[30,31] Emphysema can be assessed visually and scored as a percentage of lung involvement by lung zone, or it can be quantitatively assessed using software analysis. An emphysema index quantifies the percentage of all lung voxels having an attenuation of < -950 HU. It should be noted that quantitative measurements may be affected by the image reconstruction algorithm, section thickness, inspiration level, scanner, gravity, and radiation dose. The low-dose technique used in screening and the variability in slice thicknesses will likely require a different approach to quantitative assessment. The airways can be visually assessed in cross-sections to evaluate wall thickness and luminal narrowing. The right upper lobe apical segmental (B1) bronchus is often the most easily identified bronchus seen in cross-section. Software analysis provides quantitative measurements of cross-sectional airway parameters including the average wall thickness, total wall area, inner perimeter length, and the percentage of the total cross-sectional area of the airway composed of airway wall (wall area percentage).[32] Again, the image noise of LDCT and the variations in scanners and scanner techniques will influence quantitative analysis.

Quantitative CT analysis of emphysema and airway disease may help in predicting the likelihood of COPD exacerbations. Han et al[33] evaluated the relationship between COPD exacerbation frequency and quantitative CT measures of emphysema and airway disease within the COPDGene study. They measured emphysema severity using Slicer Software (http://www.slicer.org/), with the total emphysema percentage defined as all lung voxels with a CT

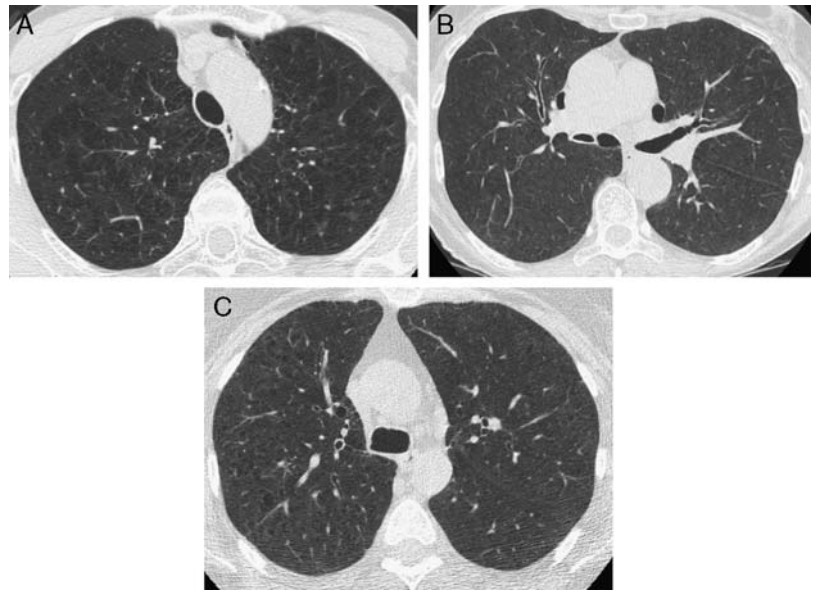

FIGURE 2. A, Emphysema-predominant COPD is characterized by pulmonary parenchymal destruction. B, Airway-predominant COPD is characterized by airway wall thickening, with or without luminal narrowing. C, A mixed pattern of COPD demonstrates both emphysema and airway wall thickening, without either pattern being dominant.

attenuation value of < -950 HU. Automated airway analysis was performed using the Vida Pulmonary workstation (http://www.vidadiagnostics.com/). The emphysema-predominant group had a total percentage of emphysema of at least 35% and a segmental bronchial wall thickness of < 1.75 mm. The airway-predominant group had $< 35\%$ emphysema and a segmental bronchial wall thickness of > 1.75 mm. They found that COPD exacerbations were related to both emphysema severity and airway wall thickness; however, at lower levels of emphysema, airway wall thickness became the predominant factor.

Airway-predominant COPD is likely a precursor of the emphysema-predominant phenotype. Analysis of 78 COPD patients with volumetric MDCT (1 mm slice thickness) and 20 donated lung specimens with micro-CT (16.24 μm isotropic voxel resolution) demonstrated a reduction in the number of airways measuring 2.0 to 2.5 mm in diameter in patients with GOLD stage 1 disease ($P = 0.001$), GOLD stage 2 disease ($P = 0.02$), and GOLD stage 3 or 4 disease ($P < 0.001$).[34] This suggests that narrowing and disappearance of small conducting airways occurs before the onset of emphysematous destruction and may explain the increased peripheral airway resistance in COPD.

CT variables have also been used to help predict mortality in COPD patients. Burgel et al[35] identified 2 phenotypes with increased mortality. CT analysis included a 4-level alveolar destruction scale (no emphysema, mild emphysema affecting $< 20\%$, moderate emphysema affecting between 20% to 50%, and severe emphysema affecting $> 50\%$ of the lung) and a 3-level scale of thickening of the bronchial walls. One category of patients at increased risk for mortality included younger patients with severe respiratory disease, marked emphysema and hyperinflation, low body mass index, and low rates of cardiovascular comorbidities. The second category included older male patients with moderate to severe airflow limitation, a higher prevalence of airway wall thickening. This group was often obese and had higher rates of cardiovascular comorbidities and diabetes.

Smoking cessation, pulmonary rehabilitation, and bronchodilators are likely to be of benefit to all COPD patients, but Burgel and colleagues suggest that identification of phenotypes at higher risk for mortality may allow development of different algorithms for improving outcome. Reporting the presence and severity of emphysema and airway disease at the time of lung cancer screening may alert both the patient and the health care provider to a diagnosis of COPD. Confirmation with spirometry could then allow health care providers to better target these individuals for preventive therapy.

EXTRAPULMONARY MALIGNANCY

The description of extrapulmonary malignancies that are detected incidentally during screening CT scans of the thorax is essentially restricted to lung cancer screening studies (Table 3). This is because of the restricted field of view and limited scan range for studies that perform CT screening for CAD. It is interesting to note that, even within the relatively small number of lung cancer screening studies that have reported on the detection of extrapulmonary malignancies using LDCT, there is considerable heterogeneity in the scan protocols used, and this limits the utility of the information provided. Some of the more important discrepancies between these studies are related to the following parameters: the scan range, duration of CT surveillance, the number of enrolled subjects, and the use of additional imaging modalities.

It is somewhat surprising that, although the lungs are the specific organs of interest in CT lung screening trials, there is a marked discrepancy in detailed information regarding the scan range. It is assumed that image acquisition would extend from the lung apices to the posterior costophrenic recesses, and this is well described by van de Wiel et al[6] and Rampinelli et al.[39] However, several CT lung cancer screening studies, including the landmark NLST and ELCAP trials, provide no specific details

TABLE 3. Description of Study Protocol, the Number of Trial Participants, and the Detection of Extrapulmonary Malignancy in LDCT Lung Cancer Screening Trials[4–7,35–37]

Author	Study Duration	LDCT Scan Range	LDCT Study Cohort	Subjects With Extrapulmonary Malignancy, n (%)	Details of Extrapulmonary Malignancies
MacRedmond et al[37]	Baseline + 2 annual screens	Not specified	449	0	0
Swensen et al[38]	Baseline + 2 annual screens	Sternal notch to iliac crests	1520	17 (1.1)	Renal cell (4), breast (3), lymphoma (2), bronchial carcinoid (2), gastric (2) ovarian (1), spinal metastases (1), pancreatic (1), phaeochromocytoma (1)
van de Wiel et al[6]	Baseline	Lung base to apex	1929	1 (0.05)	Liver metastases
Kucharczyk et al[4]	Baseline + 2 annual screens	Not specified	4073	7 (0.8)	Rib plasmocytoma (2), thyroid (1), breast (4)
Rampinelli et al[39]	Baseline + 4 annual screens	Lung apex to base	5201	27 (0.5)†	Renal cell (5), renal clear cell (2), lymphoma (5), thyroid (3), thymoma (2), pancreas (2), breast (1), urinary tract (1), schwannoma (1), adrenal (1), heptocellular (1), GI stromal (1), prostate (1), ovary (1)
NLST[7]	Baseline + 3 annual screens	Not specified	26,722	416 (1.6)*	No specific details
Priola et al[5]	Baseline + 4 annual screens	Thyroid to iliac crests	519	6 (1.2)	Renal cell (3), thymoma (2), adrenal metastasis (1)

*Number of certified deaths from extrapulmonary malignancy.
†6 malignancies were detected using positron emission tomography/CT: thyroid (3), prostatic (1), GI stromal (1), and pancreatic (1).
GI indicates gastrointestinal.

regarding the scan range.[36,37] Conversely, extended scan ranges have been described by Swensen et al,[38] who imaged from the sternal notch to the iliac crest, and Priola et al,[5] who scanned from the thyroid gland to the iliac crest. It is anticipated that a longer scan range, with inclusion of more anatomic regions, would result in detection of a higher number of extrapulmonary malignancies. Of the studies that provided specific details, the protocols that used an extended scan range had the highest number of extrapulmonary malignancies detected; Swensen et al[38] described 15 extrapulmonary malignancies in 1520 subjects (1.0%), and Priola et al[5] described 6 malignancies in 519 subjects (1.2%).

The variable duration of thoracic LDCT surveillance in the lung cancer screening trials also influences the detection of extrapulmonary malignancies. Trials that describe disease prevalence at the time of the baseline screening with LDCT report a smaller number of affected subjects; van de Wiel et al[6] reported extrapulmonary malignancy in 1 of 1929 (0.05%) subjects. In contrast, studies that captured both the prevalence and incidence of disease from baseline and surveillance LDCT scans up to 5 years from trial entry tended to have the highest number of extrapulmonary tumors. Priola et al[5] detected extrapulmonary malignancy in 6 of 519 (1.2%) individuals, whereas the NLST[7] documented that 416 of 26,722 (1.6%) subjects died of extrapulmonary malignancy. Although Rampinelli et al[39] described extrapulmonary malignancy in only 27 of 5201 subjects (0.5%) screened in a 5-year surveillance program, it was noted that the occurrence of disease, although fairly constant, tailed off with longer periods of surveillance; in the first year, 8 of 5201 subjects were diagnosed with extrapulmonary cancer; in the second year, it was 9 of 4825 subjects; in the third year, 4 of 4586; in the fourth year, 2 of 4389; and in the fifth year, 4 of 4127 subjects had extrapulmonary malignancy detected.

The number of enrolled trial subjects varied almost by a factor of 60, from the smallest study, the ProActive Lung Cancer Detection (PALCAD) trial by MacRedmond et al,[40] in which 449 subjects were recruited, to the largest study, by the NLST,[7] in which 26,722 subjects were enrolled into an LDCT screening arm. Despite the considerable variation in subject enrollment, the pattern of extrapulmonary malignancy demonstrates a trend, with renal and thymic malignancies featuring most often. Swensen and colleagues described 4 renal cancers in 15 patients; Rampinelli and colleagues described 7 renal cancers in 27 individuals, and Prioli and colleagues noted 3 renal malignancies in 6 subjects. Prioli and colleagues also noted a relatively high occurrence of thymic cancers affecting 2 of 6 trial participants, and Rampinelli and colleagues described thymic cancer in 2 of 27 subjects diagnosed with extrapulmonary malignancy. Other extrapulmonary malignancies such as thyroid cancer,[4,36] lymphoma,[36,38,39] and breast cancer[4,38,41] were described with less frequency.

There is current interest in further reducing the radiation dose associated with LDCT, with technologies such as iterative reconstruction used to smoothen increased image noise. It is possible that further reduction of the kVp and mAs will increase image noise within soft tissues to the extent that identification of extrapulmonary malignancies is significantly compromised.

Lastly, although LDCT was the principle diagnostic modality, additional imaging technologies were used in

several of the lung cancer screening studies to further characterize abnormalities noted on LDCT. Consequently, additional malignancies were detected that were initially missed on LDCT; 6 of the 27 (22.2%) extrapulmonary malignancies described by Rampinelli et al[39] were detected using positron emission tomography/CT; this included 3 thyroid cancers, 1 prostate cancer, 1 gastrointestinal stromal malignancy, and 1 pancreatic cancer.

It is interesting to observe that, although there is a variation in the detection of extrapulmonary malignancy, in the larger lung cancer screening trials with prolonged surveillance, the number of subjects diagnosed with extrapulmonary malignancy was approximately half that of subjects diagnosed with lung cancer.[5,38] As an emphasis on the importance of this observation, we see that in the LDCT screening arm of the NLST trial 416 of 1865 certified deaths (22.3%) were due to extrapulmonary malignancy, which compared with 427 of 1865 (22.9%) certified deaths from lung cancer.[7]

CONCLUSIONS

CAD, other cancers, and respiratory illness represent significant causes of morbidity and mortality in the lung cancer screening population. LDCT of the thorax may provide information about these diseases, which could be used to guide therapeutic intervention and, hopefully, alter the courses of these diseases. Information about CAC, COPD, and potential extrapulmonary malignancy should be provided in the report of the screening examination. This must be balanced against the risk of the burden of false-positive findings and the costs, both psychological and financial, associated with additional investigative evaluations.

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