Low-Dose CT Screening for Lung Cancer: Evidence from 2 Decades of Study

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Lung cancer remains the overwhelmingly greatest cause of cancer death in the United States, accounting for more annual deaths than breast, prostate, and colon cancer combined. Accumulated evidence since the mid to late 1990s, however, indicates that low-dose CT screening of high-risk patients enables detection of lung cancer at an early stage and can reduce the risk of dying from lung cancer. CT screening is now a recommended clinical service in the United States, subject to guidelines and reimbursement requirements intended to standardize practice and optimize the balance of benefits and risks. In this review, the evidence on the effectiveness of CT screening will be summarized and the current guidelines and standards will be described in the context of knowledge gained from lung cancer screening studies. In addition, an overview of the potential advances that may improve CT screening will be presented, and the need to better understand the performance in clinical practice outside of the research trial setting will be discussed.

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Despite gradual decreases in smoking rates and advances in treatment, lung cancer remains the most common cause of cancer death. Most lung cancers are still diagnosed at a late stage when they are difficult to cure, and there are millions of smokers and former smokers who are at increased risk and will be for decades. After more than 2 decades of research, evidence has accumulated that early detection by low-dose CT screening has the potential to improve these outcomes. Since the first reports on using low-dose CT to screen for lung cancer, the ability to reduce lung cancer mortality through CT screening has been verified, and evidence from carefully designed and conducted clinical investigations has been translated into everyday practice. Data and observations from screening trials have improved our understanding of the CT manifestations of early lung cancer and have provided information important to the development of guidelines for managing indeterminate lung nodules. Lung cancer CT screening has also provided much of the impetus for reducing radiation dose at chest CT and developing automated and quantitative analysis techniques. In this article, we review the history of lung cancer screening, explain how current screening guidelines are linked to findings from lung cancer screening trials, and describe best practices for optimizing performance. We also highlight technological advances that may improve efficiency and effectiveness. Finally, we note current shortcomings, particularly the need for outcome data from screening outside of the clinical trial setting.

Incidence and Mortality

Lung cancer is the second most frequent cause of cancer (after prostate cancer in men and breast cancer in women) and the most frequent cause of cancer death in the United States for both men and women, with more than 228 000 new cases and nearly 143 000 deaths expected in 2019 (1). The age-adjusted lung cancer mortality rates in the United States have been declining in men since around 1990 and in women since the early to mid-2000s (1), reflecting decreases in smoking rates over time with a lag of approximately 30 years (2). Projections show that if current smoking behaviors continue (ie, prevalence, age of initiation and cessation, and smoking intensity), lung cancer mortality will continue to fall in the coming decades; however, there may still be more than 100 000 U.S. lung cancer deaths in 2035, and more than 50 000 in 2065 (3). This is more than the current number of annual deaths due to breast, prostate, or colon cancer (1).

Worldwide, lung cancer is the most frequently diagnosed cancer (third after breast and colon cancer in women) and the most common cause of cancer death (second to breast cancer in women) overall, although rates and trends vary widely by region in relation to historic tobacco use patterns (4,5). Lung cancer was estimated to account for 388 000 deaths in Europe in 2018 (6) and 610 000 deaths in China in 2015 (7). Rates are highest in North America, Europe, Australia/New Zealand, Micronesia/Polynesia, and Eastern Asia, with the lowest rates in Central America and Eastern, Middle, and Western Africa (4).

Risk Factors

Cigarette smoking transformed lung cancer from a rarely diagnosed disease in the early 20th century (8) to the leading cause of cancer death in U.S. men since the mid-1950s and in U.S. women since the late 1980s (1) and is estimated to be responsible for 87% of lung cancer deaths (9). The risk of lung cancer increases with both the number of cigarettes per day and number of
had distant metastases at diagnosis, only 16% of patients had spread. From 2009 to 2015, however, 57% of patients if the primary tumor could be found and treated before it. The possibility that lung cancer deaths could be greatly reduced, and the lung cancer registry used as the source of data; in approximately 50%–90%, depending on the size of the stage I tumor and the lung cancer registry used as the source of data; in contrast, 5-year survival for stage IV disease, in which distant metastases are present, is 3%–6% (25). This suggests the possibility that lung cancer deaths could be greatly reduced if the primary tumor could be found and treated before it has spread. From 2009 to 2015, however, 57% of patients had distant metastases at diagnosis, only 16% of patients had localized disease, and 5-year survival among all patients with lung cancer was 20.6% (26).

Chest Radiography

In the 1970s and 1980s, two randomized controlled trials, the Mayo Lung Project (27) and a Czechoslovakian trial (28), investigated whether early detection of lung cancer using chest radiography could reduce lung cancer mortality. Both trials found more cancers at an earlier stage that were more often resectable, and better survival in the screened groups; however, there was no reduction in the number of lung cancer deaths, and the Mayo trial reported no difference in the number of unresectable lung cancers. These findings demonstrate that improved disease detection and increased survival time after diagnosis, expected with screening due to lead time bias, are not equivalent to a reduction in mortality. While these studies had well-recognized limitations, such as low statistical power and intentional or unintentional screenings in the control groups, their conclusions were later supported by the findings of the Prostate, Lung, Colorectal, and Ovarian cancer screening trial (PLCO) conducted by the National Cancer Institute from 1994 to 2009, which found no mortality benefit from chest radiography screening (29).

Low-Dose CT

In the mid and late 1990s, investigators in Japan (30) and the United States (31) demonstrated the potential benefits of low-dose CT screening for lung cancer. Numerous Japanese, U.S., and European studies quickly followed (32–38). Lung cancer was found in 0.9%–2.7% at initial (prevalence) screening (30,31,33–35), three to four times more than with chest radiography (30,31). Importantly, over 50% and up to 93% of the detected lung cancers were stage I. Lung cancer was found in up to 0.6%–1.5% at annual repeat (incidence) screening, with reported stage I proportions of 48%–89% (39–42). While these early single-arm CT studies were highly encouraging, they lacked a control group and could not ascertain whether CT screening actually reduced lung cancer mortality. The randomized controlled U.S. National Lung Screening Trial (NLST), conducted by the National Cancer Institute from 2002 to 2009, thus was specifically designed to determine this (43).

In the NLST, 53439 high-risk volunteer participants at 33 U.S. locations, age 55–74 years, who had smoked a minimum of 30 pack-years and were currently smoking or had quit within the last 15 years, were randomly assigned to undergo three annual screening examinations with either low-dose CT or posteroanterior chest radiography. After median follow-up of 6.5 years, there were 20% fewer deaths from lung cancer among those randomly assigned to the CT arm (P = .004) (44), with one lung cancer death prevented for every 320 screened with CT. The latter rate compares very favorably with the mammography estimate of one death prevented for every 519 women screened for 7 years (45). With a reduction in all-cause mortality in the CT arm of 6.7% (P = .02), the NLST is the only screening trial to find a statistically significant reduction in all-cause mortality, which was largely because a high proportion of deaths (25%) were due

### Abbreviations

ACR = American College of Radiology, CMS = Center for Medicare and Medicaid Services, CTDI _vol _= volumetric CT dose index, I-ELCAP = International Early Lung Cancer Action Project, Lung-RADS = Lung CT Screening Reporting and Data System, NLST = National Lung Screening Trial, PLCO = Prostate, Lung, Colorectal, and Ovarian cancer screening trial, USPSTF = United States Preventive Services Task Force

### Summary

The accumulated evidence and guidelines from 2 decades of clinical investigation have demonstrated that appropriate implementation of CT screening could prevent a substantial number of lung cancer deaths.

### Essentials

- Lung cancer has been the greatest cause of cancer mortality for decades, and this trend is expected to continue.
- Low-dose CT screening can reduce lung cancer mortality.
- Advances in detection and image analysis may improve the efficiency and effectiveness of low-dose CT screening.
- Data on outcomes of CT screening across different clinical practice settings over time will be important for performance assessment and improvement.

### History of Lung Cancer Screening

#### Rationale

The 5-year relative survival for stage I disease, in which the tumor is confined to the primary site, ranges from approximately 50%–90%, depending on the size of the stage I tumor and the lung cancer registry used as the source of data; in contrast, 5-year survival for stage IV disease, in which distant metastases are present, is 3%–6% (25). This suggests the possibility that lung cancer deaths could be greatly reduced if the primary tumor could be found and treated before it has spread. From 2009 to 2015, however, 57% of patients had distant metastases at diagnosis, only 16% of patients had...
to lung cancer. After extending the median follow-up period to 11.3 years, subsequent analyses found that there were 10% fewer lung cancer deaths in the CT arm, with one death prevented for every 303 persons screened (46).

Several smaller randomized controlled trials were conducted contemporaneously with the NLST. The NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek) trial randomly assigned 15,792 participants in the Netherlands and Belgium to have CT screening (at baseline, 1, 3, and 5 years) or no screening (47). Lung cancer mortality with screening was 24% lower at 10 years overall (95% confidence interval: 6%, 39%), and 33%–59% lower in different years of follow-up in women (48). The Multicentric Italian Lung Detection randomized trial with 4,099 participants reported a 39% reduction in cumulative risk of lung cancer mortality at 10 years with CT screening (95% confidence interval: 5%, 61%, \( P = .02 \)), with one lung cancer death prevented for every 167 participants screened (49). Other randomized controlled trials in Italy (50) and Denmark (51) did not demonstrate a mortality benefit from CT screening, though they were underpowered and considered inconclusive.

Another large study, the International Early Lung Cancer Action Project (I-ELCAP), is a multicenter consortium initiated prior to the NLST and still ongoing. I-ELCAP uses longitudinal observational methods to study the diagnostic and treatment components of CT screening separately. Analyses focus on how frequently screening detects lung cancer at an early stage, and how frequently screen-detected lung cancers are cured, particularly those likely to be life-threatening without treatment, to assess the magnitude of the benefit associated with ongoing CT screening using metrics relevant to persons at risk. In one analysis, 1.5% of 31,567 persons at risk who were screened over a 12-year period were diagnosed with lung cancer, 85% of which were clinical stage I, with 10-year survival rate of 92% in those who underwent surgical resection (52).

Current Screening Guidelines in the United States

The multiple prospective single-arm observational studies demonstrated that CT screening is sensitive for detecting lung cancer at an early stage, while randomized controlled trials confirmed a mortality benefit. In 2013, CT screening for lung cancer was given a grade B recommendation by the United States Preventive Services Task Force (USPSTF), which concluded that there is moderate certainty of moderate net benefit in persons at high risk (53). Because of this, full coverage by private insurers is required under the Affordable Care Act. The 2015 decision memo by the Center for Medicare and Medicaid Services (CMS) also provides coverage for eligible individuals screened at centers that follow CMS requirements (54). CT screening has been endorsed by numerous medical and patient advocacy organizations (55–62), many of which have published lung cancer screening practice guidelines.

The results of screening trials were achieved with infrastructures that facilitated verification of participant eligibility based on age and smoking history, standardization of screening methods, follow-up after screening, and compliance with annual rescreening. Realizing similar benefits and minimizing harms in clinical practice will likely depend on how well these components can be replicated. Many of these important steps in the screening process have been recommended by professional societies or mandated by CMS. This discussion focuses on current guidelines in the United States, where screening has been implemented on a widespread basis as part of routine clinical practice, supplemented by data and approaches from European trials and recommendations.

Considerations prior to Screening

Eligibility.—Current USPSTF eligibility guidelines reflect those used in the NLST, including a minimum age of 55 years, minimum smoking history of 30 pack-years, and quit time of less than 15 years. For reimbursement of CT screening by CMS, health care providers, radiologists, and screening facilities must adhere to specific eligibility guidelines and fulfill multiple additional criteria (Table), many of which are also recommended by the USPSTF. A notable difference is that, based on studies modeling the expected benefit from screening by age (63), the USPSTF recommends annual screening up through 80 years of age, while CMS ends coverage at age 77 years, corresponding to the oldest age at the time of the final annual screen in the NLST.

Some organizations also recommend screening for persons as young as 50 years with a smoking history of 20 or more pack-years if there is another established risk factor for lung cancer (56,60,64), but this has not been recommended by the USPSTF, and thus insurance coverage for such individuals is not required. Persons with symptoms possibly due to lung cancer, such as new cough, hemoptysis, or weight loss, are not considered eligible for screening and should undergo a diagnostic CT scan instead. Screening is not advised for those with a limited life expectancy due to significant comorbidities, or for those unable or unwilling to undergo diagnosis and treatment. Unlike in the NLST, those with a history of lung cancer or treatment for cancer other than nonmelanoma skin cancer in the last 5 years are not specifically excluded.

Individual risk prediction.—Analyses of screening populations show substantial lung cancer risk variation among persons who are eligible under current age and smoking criteria. For example, the risk among NLST participants older than 65 years of age was more than double the risk of those younger than 65 (1.5% vs 0.7%) (65). A risk model developed from PLCO trial control group data (predictor variables included race, socioeconomic status, body mass index, history of chronic obstructive pulmonary disease and cancer, and family history of lung cancer, in addition to age and smoking variables) predicted lung cancer better in the PLCO chest radiography screening group than did NLST age and smoking criteria, missing 41% fewer cancers (66). A model predicting lung cancer mortality developed from the NLST radiography arm participant data found that the three highest risk quintiles in the NLST CT arm accounted for 88% of the deaths prevented by CT screening, while those in the lowest risk quintile accounted for only 1% of the prevented deaths (67). Another model showed that by screening only those above specific model-determined risk thresholds, more lung cancer deaths...
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A comparison of nine models found that lung cancer risk may vary by geographic region or in certain subpopulations, as models based on European data overestimated risk in U.S. populations, and some U.S. models overestimated risk in the heaviest smokers and some underestimated risk in Hispanics and Asian or other groups (68). Prospective studies in the United Kingdom (69) and in Canada (70) have demonstrated the feasibility of using risk models for determining CT screening eligibility, with higher lung cancer incidence and proportion of early stage cancers compared with previous studies observed in the latter. European societies have recommended individual risk assessment (58), and the USPSTF will consider the potential role of individual risk determination in their next guidelines update (71). Practical considerations could be prevented by screening fewer persons than using USPSTF eligibility criteria (11).

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**Shared decision making.**—CMS requires a shared decision-making visit with a qualified health care provider before the first screening examination, a provision unique to lung cancer screening. Shared decision making involves disclosure of the risks and benefits of a course of action by the provider, and expression of personal preferences and values by the patient, to make health care decisions jointly (72,73). This process is also recommended by the USPSTF (53) and other organizations (57,61). Online tools to aid providers and patients have been made available by several sources, including the American College of Radiology (ACR) (74), Agency for Health Care

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### CMS Requirements for Reimbursement of CT Lung Cancer Screening

| Requirement                                      |
|-------------------------------------------------|
| **Patient**                                     |
| Age 55–77 years                                 |
| Minimum 30 pack year smoking history            |
| Currently smoking or quit < 15 years ago         |
| **Health care provider**                        |
| Conduct shared decision-making visit that includes: |
| - Determination of beneficiary eligibility       |
| - Use of one or more decision aids, to include benefits and harms, diagnostic testing, overdiagnosis, false-positive rate, and radiation exposure |
| - Counseling on importance of adhering to annual screening and impact of comorbidities and ability or willingness to undergo diagnosis and treatment |
| - Counseling on importance of smoking cessation and providing information on interventions if appropriate |
| Provide written order that includes:             |
| - Beneficiary date of birth                      |
| - Pack-years smoked                              |
| - Whether current or former smoker and years since quitting |
| - Statement that beneficiary has no signs or symptoms of lung cancer |
| - National Provider Identifier (NPI)             |
| **Radiologist**                                 |
| Board-certified or eligible by American Board of Radiology or equivalent |
| Supervision and interpretation of 300 chest CT scans in past 3 years |
| Meets American College of Radiology continuing education standards |
| Perform screening in eligible facility           |
| **Screening facility**                          |
| Perform low-dose CT with volumetric CT dose index ≤ 3.0 mGy for standard size patients (5’7” and 155 lbs) with appropriate dose reduction and increase for smaller and larger patients, respectively |
| Use standardized lung nodule identification, classification, and reporting system |
| Make smoking cessation interventions available |
| Collect and submit required data to a CMS-approved registry for each screen performed that includes: |
| - Facility identifier                            |
| - Radiologist NPI                                |
| - Patient identifier                             |
| - Ordering practitioner NPI                      |
| - CT scanner manufacturer and model              |
| - Indication (lung cancer screening, absence of signs or symptoms of lung cancer) |
| - Lung nodule identification, classification, and reporting system |
| - Smoking history                                |
| - CTDI<sub>v</sub>                              |
| - Screen date                                    |

Note.— CMS = Center for Medicare and Medicaid Services, CTDI<sub>v</sub> = volumetric CT dose index.
Risks of Screening

The screening process can lead to adverse effects and costs that patients would not have incurred in the absence of screening, for no benefit. Guidelines recommend disclosing the potential harms of screening as part of the shared decision-making process (53,57,61). These risks are relatively small compared with the risk of lung cancer death in the screening-eligible population.

Diagnostic testing.—The most frequent subsequent test after CT screening is a surveillance CT scan to monitor indeterminate pulmonary nodules, resulting in additional radiation exposure. In the NLST (44), which classified CT studies with at least one noncalcified nodule larger than 4 mm in greatest transverse dimension as positive, 27% of initial CT screens were classified as positive, and 73% of these led to a follow-up CT scan before the next annual screen. However, under current guidelines (discussed below under Lung Nodule Management), in which the solid nodule size threshold for diagnostic follow-up is 6-mm average of length times width, the screen positivity rate would have been reduced by more than half in the NLST with a relatively much smaller decrease in sensitivity (91); the same effect was also found in an analysis of I-ELCAP data (92). More recent reports confirm these projections (93,94). The NELSON trial used a computer software program to measure nodule volume and classified screens as negative (largest nodule < 50 mm³ volume, or 4.6-mm diameter if spherical), positive (largest nodule > 500 mm³, or 9.8-mm diameter if spherical) with referral to clinician for workup, or indeterminate (largest nodule 50–500 mm³, or 4.8–9.8-mm diameter) with recommendation for a 3-month follow-up CT. With this algorithm, at the baseline screen of 7557 Dutch participants, 79.2% were negative, 1.6% were positive, and 19.2% were recommended for the 3-month scan, 5.3% of which were subsequently referred for additional workup due to a potentially malignant volume doubling time (1.0% of the whole cohort) (95).

Over all three screening years in the NLST (44), transthoracic biopsy was performed after a positive CT screen in 1.4% of participants, bronchoscopy in 3.8%, and thoracotomy or thoracoscopic surgery in 4.2%, while lung cancer was diagnosed after a positive CT screen in 3.6%. Among those who underwent an invasive procedure, a major complication of any type occurred in 12% of those with lung cancer, and in 0.1% of those in whom lung cancer was not confirmed. Death from any cause within 60 days of a procedure for a positive CT screen was rare, occurring in 1.5% of those with cancer and 0.1% of those without cancer. Diagnostic evaluation of NLST participants after screening, including both imaging and invasive procedures, was conducted at the discretion of the participants’ personal physicians who were not associated with the trial. Invasive testing rates for the entire NELSON trial have not been reported, but after two screening rounds in 7557 Dutch participants were 3.2% for bronchoscopy, 0.2% for transthoracic biopsy, and 2.0% for an invasive surgical procedure (95). Rates of invasive testing and adverse events in contemporary clinical screening practice are not yet known.

Radiation exposure.—At the highest recommended volumetric CT dose index (CTDIvol) of 3.0 mGy in a standard-size patient, a 25-cm standard scan length, and a k factor of 0.014 mSv · mGy⁻¹ cm⁻¹, a typical effective dose for screening CT would be 1.0 mSv or less (96). The average annual dose from environmental radiation in the United States is 3.1 mSv (97), about three times greater. Based on a linear–no threshold model of ionizing radiation effects, the lifetime attributable risk of any cancer developing due to an 8-mSv chest CT has been estimated as approximately 0.09% in women and 0.05%
in men at 60 years of age (98), equivalent to 0.011% in women and 0.006% in men when scaled linearly to a 1-mSv chest CT.

A single-center trial estimated a 0.05% additional risk of cancer after 10 years of screening and associated follow-up imaging, and one radiation-induced cancer for every 108 screen-detected lung cancers (99). According to the U.S. Food and Drug Administration, a CT with effective dose of 10 mSv may increase the possibility of developing a fatal cancer by 0.05% (100), which scales linearly to a risk of 0.005% for a 1-mSv lung cancer screening CT.

Based on these estimates, after 20 annual screening CT examinations, the increased risk of cancer would be 0.22% in women and 0.12% in men, and that of a fatal cancer 0.1%, from the screening CT examinations alone. These risks are extremely small relative to the estimated lifetime risk of developing lung cancer among all (smokers and nonsmokers) U.S. men of 6.7% and women of 5.9% (1), or the estimated risk for smokers of 15% or higher (101–103).

**Overdiagnosis.**—Overdiagnosis occurs when lung cancers are found that would have never been discovered in the absence of screening. Typically estimated as the difference in the number of cancers diagnosed in screened and control groups, analysis of the initial NLST data found that 18% of the screen-detected cancers in the CT arm may have been overdiagnosed, primarily adenocarcinomas classified at the time as bronchioloalveolar cell type (104). Statistical modeling studies that simulated longer follow-up estimated that 10% would be overdiagnosed (63). Subsequent analysis of data after the extended follow-up of NLST participants revealed an overdiagnosis rate of 3% overall, although it was 79% for adenocarcinomas previously classified as bronchioloalveolar cell type (46). It should be noted that once a cancer has been detected and treated as a result of screening, it cannot be known if it would have become clinically apparent in the absence of screening, so whether any individual cancer was overdiagnosed cannot be determined.

**Missed lung cancer.**—Diagnosis of lung cancer after a negative CT screening examination is infrequent but can occur. Of the 7155 Dutch CT arm participants in the NELSON trial, lung cancer was diagnosed within 2 years after a screen that had been interpreted as negative in 34 participants (0.5%); the cancer was visible in retrospect in 20, misinterpreted in two, and no abnormality was identified retrospectively in 12 participants (105). In the NLST, lung cancer was diagnosed in 44 of the 26,722 CT arm participants (0.16%) within a year after a negative CT screen (44). Retrospective review revealed abnormal findings of a positive screen in 40 of these, 22 of which were likely missed, 14 misinterpreted as clinically significant but not suspicious for lung cancer, and four with nodules originally considered to be less than 4 mm or stable for more than 2 years, and four patients with no or minor abnormalities not suspicious for lung cancer (105). It should be noted that the interval between screens in NELSON was 2 years after the first screen and 2.5 years after the second screen, while the interval in NLST was 1 year. In addition to missed peripheral pulmonary nodules, several types of abnormalities were identified retrospectively in these studies, including nodules or enlarged hilar lymph nodes abutting central pulmonary vessels or the mediastinum, endobronchial nodules, and enlarged mediastinal lymph nodes (106,107). Familiarity with these and other presentations of lung cancer, such as cystic or bubbly luencies with thickened walls or nodules as initially recognized in the ELCAP cohort (108), and consolidation simulating pneumonia, is important in screening CT interpretation.

**Incidental findings.**—The reported frequency of clinically significant, actionable findings unrelated to lung cancer in most CT screening studies varies from about 1% to 20%, although there is no standard definition (109). The most common incidental findings at screening CT are the pulmonary abnormalities of emphysema, bronchitis, and interstitial lung disease (110) and cardiovascular disease including coronary artery calcification and thoracic aortic aneurysm (109,111). Being associated with heavy smoking, these findings are common in the screening population and the need for further evaluation is usually based on symptoms and clinical factors. However, neck, chest, or upper abdominal abnormalities may be identified that warrant additional imaging, other diagnostic evaluation, or treatment. The most commonly reported potentially significant abnormality categories in the NLST were cardiovascular (8.5%), renal (2.4%), hepatobiliary (2.1%), adrenal (1.2%), and thyroid (0.6%); the extrathoracic malignancy rate was 0.4% (111). As with screening for lung cancer, detection of incidental findings may reduce morbidity and mortality in some persons, but false-positive findings and overdiagnosis with unnecessary testing and treatment also may occur. Further study is needed to understand the net impact in clinical practice.

**Low-Dose CT Scanning and Interpretation**

**CT Technical Specifications**

The technical guidelines for CT lung screening are intended to provide image quality sufficient for detection and measurement of small pulmonary nodules while limiting radiation exposure as much as possible. Current guidelines of the ACR and American Association of Physicists in Medicine (96) recommend use of CT scanners with 16 or more detector rows and slice thickness of 2.5 mm or less, with 1-mm thickness preferred. These guidelines and CMS requirements limit the CTDI_{vol} to 3.0 mGy for a standard size patient of 5’7” (170 cm) and 155 lbs (70 kg), with appropriate reductions expected for smaller patients and increases for larger patients.

Newer radiation reduction technologies such as tin filtration may allow even greater dose reductions to less than 0.3 mGy (112,113). Automatic exposure control systems, which vary tube output at different anatomic locations during scanning depending on tissue attenuation, can be used to adjust dose for patient size. Care must be taken that appropriate manufacturer-specific settings are used, as some may inadvertently increase dose in some patients.

In addition to standard axial images, generating coronal and sagittal reconstructions and maximum intensity projection
images are recommended (96). Multiplanar reconstructions can be helpful in determining whether certain solid or ground-glass opacities are truly nodules or have the linear or flat configuration of atelectasis and scars. Overlapping maximum intensity projections can improve nodule detection sensitivity by facilitating discrimination of small nodules from vessels (114–116).

Lung Nodule Management

Standardized methods for lung nodule management in CT screening, required by CMS, include the ACR Lung CT Screening Reporting and Data System (Lung-RADS) version 1.1 (117) and the similar guidelines of the National Comprehensive Cancer Network version 2.2019 (64). Lung-RADS 1.1 guidelines now require recording nodule measurements to one decimal point, rather than rounding up to the next highest integer. At the initial screen, no further evaluation before the next annual screen is recommended if there are no solid lung nodules with average diameter of 6.0 mm or larger, part-solid nodules with solid component of 6.0 mm or larger, nonsolid nodules of 30 mm or larger (20 mm in National Comprehensive Cancer Network version 2.2019 and previous Lung-RADS version 1.0), or other findings suspicious for lung cancer such as lobar collapse or mediastinal lymphadenopathy.

Follow-up is recommended for solid nodules that are greater than or equal to a 6.0-mm average diameter on initial screens. This is greater than the thresholds used in screening trials but is supported by I-ELCAP data, showing that such nodules can be safely followed for 1 year (118) and by the relationship between nodule size and frequency of malignancy in the NLST (119,120). In Lung-RADS 1.1, the size threshold for further evaluation of solid perifissural nodules with smooth borders and oval, lentiform, or triangular shape is larger than for other nodules, specifically an average diameter of 10 mm. This reflects observations that such nodules have a malignancy likelihood near zero (121,122). Interreader agreement on classifying nodules as perifissural may be only moderate at best, however, and the risk of miscategorizing a cancer as a perifissural nodule may be increased if they have atypical features, are not attached to a fissure, or are located in the upper lobes (123).

For solid lung nodules that are greater than or equal to 6 mm on initial screens, management recommendations progress with increasing size of the largest nodule, from follow-up CT at 6 months (6 to < 8 mm), to follow-up CT at 3 months or PET/CT (8 to < 15 mm), to PET/CT or diagnostic CT or tissue sampling (≥15 mm). Nodules of any size can be given a higher classification (and more aggressive workup) if there are features that increase the suspicion of malignancy, a practice affirmed by a study that found an increased rate of malignancy when features such as internal nodule structure and border characteristics were considered (124). Lung-RADS also suggests using an individual prediction model (125) developed from Canadian lung cancer screening trial data to help guide management of suspicious nodules; this tool, which quantifies the likelihood that nodules at initial screening CT are malignant based on six CT (emphysema, larger size, upper lobe location, part-solid type, lower nodule number, and spiculation) and three patient (age, female sex, and family history of lung cancer) predictors, has been shown to have high predictive accuracy in several independent data sets (125–127), and better overall performance than Lung-RADS criteria (128).

A 30-mm threshold for further investigation of nonsolid (ground-glass) nodules is supported by I-ELCAP findings that nonsolid nodules of any size could be safely followed at yearly intervals until development of solid components (129). They also found that screen-detected nodules of nonsolid (ground-glass) or mixed nonsolid and solid (part solid) attenuation were less frequent than solid nodules, but more likely to be malignant (130), and advocated management of part-solid nodules based on the size of the solid component alone (131); in Lung-RADS, part-solid nodule management is more aggressive than for solid nodules, and is based on the size of the solid component with size thresholds lower than for pure solid nodules.

The actionable size threshold for new solid or part-solid nodules on annual repeat screens is smaller (4 mm if solid, any size if part solid) than on initial screens. This approach agrees with findings from the NELSON trial (132) and the NLST showing that new solid nodules had a higher rate of malignancy: 6% compared with an overall lung cancer rate of 3% during the first three screening rounds in NELSON (132), and 5.7% compared with 2.7% of all nodules detected on the baseline screen in the NLST (133). On follow-up scans or annual screens, an increase in average diameter of 1.5 mm or more should trigger further evaluation. Growing nodules should be rescreened in 3 months if solid and less than 8 mm or part solid with less than 4 mm solid component, and evaluated with diagnostic CT, PET/CT, or biopsy if solid and greater than or equal to 8 mm or part solid with greater than or equal to 4 mm solid component (solid component must be ≥ 8 mm for PET/CT).

Automated and Quantitative Techniques

Computer algorithms that analyze CT images have the potential to improve efficiency and increase consistency of interpretation in lung cancer screening. Automated methods for pulmonary nodule detection, size measurement, and tissue characterization have been developed and continue to be refined. With further development and study, these methods may assume an increasing role in future clinical practice.

Computer-aided Detection

Agreement among radiologists in lung nodule detection and measurements in lung cancer screening has been moderate (134–136). Nodule detection software increases detection rates at all experience levels, with sensitivity in the 80%–90% range, and improves interobserver agreement (137). False-positive rates generally range from three to eight per scan, but not all cancerous lesions are detected, so nodule detection software may be best used as a “second reader” to improve sensitivity.

Computer-aided Diagnosis

Automated volumetry.—Computer-aided automated measurement of lung nodule volume is independent of nodule shape and orientation and sensitive to size change in all directions (138) and may be a more reliable indicator of nodule size and growth than diameter (139). The NELSON lung cancer
screening trial, which used a nodule management algorithm based on automated volumetric measurements and volume doubling time calculations performed at a central reading site, demonstrated high sensitivity, specificity, and positive and negative predictive values with this approach (95). The volumetric approach has been used in other European trials (69,140,141) and is advocated by the European Society of Radiology and European Respiratory Society (58). Measurement variability appears to be lower with automated volumetry (142–145). Adoption in the United States has been limited, although the nodule volumes that correspond to specific diameter measurements have been provided for reference in the current version of LungRADS. Given the conceptual advantages of automated volumetry, studies focusing on direct comparisons of diameter and volume measurements, their impact on patient management, and interobserver variability for the same nodules are warranted.

The reliability of volumetric measurements depends on the use of appropriate and consistent CT acquisition and reconstruction parameters and analysis software (146–149), particularly for subcentimeter nodules (150). Volumetry is most reliable for solid nodules with aspect ratios that do not deviate excessively from spherical and are isolated or only in minimal contact with other structures. Both technical and anatomic factors can influence measurement accuracy and precision, which decrease as nodule size decreases; awareness of the potential error (ie, 95% confidence limits) associated with nodule volume measurements is paramount for their use in clinical management. Guidance on this issue is under development by the Radiological Society of North America’s Quantitative Imaging Biomarker Alliance (150). Subsolid nodules are potentially more challenging due to the reduced contrast between lesions and normal lung, though performance has been promising (151–154). A current drawback limiting the adoption of both detection and volumetry software is a lack of integration with the software used for clinical viewing and interpretation, requiring the launch of a separate application or use of a separate workstation.

Computer-aided diagnosis.—Computer-aided approaches also have been applied to lung nodules for tissue characterization. With radiomics, quantitative first-, second-, and higher-order statistical parameters are derived from measurements of nodule features such as size, shape, attenuation and its distribution (texture), and edge characteristics. These parameters are then used as variables in mathematical or machine learning models to predict, for example, whether a nodule is malignant (155–158), or the histopathologic features and prognosis of malignant nodules (159,160). Deep learning (161,162) also has been applied for nodule classification, through the use of convolutional neural networks with algorithms that directly analyze the spatial and attenuation features of images at the pixel level and self-modify the values of certain variables within the algorithm, to optimize the discrimination of different image classes such as benign versus malignant or low-grade versus high-grade malignancy.

Radiomics and deep learning have both achieved promising results, with the area under the receiver operating characteristic curve for predicting malignancy calculated at 0.8–0.9 in most studies (156–158,163–168). One particularly successful deep learning approach used the entire volume of more than 42 000 CT scans from nearly 15 000 participants in the NLST to develop a model that achieved an area under the curve of 0.94 on a separate NLST test set of 6716 cases, performed similarly on an independent clinical set of 1139 cases, and outperformed all six radiologists tested (169). These computer-aided methods could potentially allow even earlier diagnosis, reduce diagnostic evaluations and anxiety for benign nodules, and increase consistency and confidence in lesion management. In the future, studies comparing the use of quantitative methods to the current standard of care in patient management will be important for determining their impact on patient outcomes, and whether any performance benefits are worth the additional time and expense.

Utilization and Outcomes in Clinical Practice

Two decades of clinical investigation have produced solid, evidence-based guidelines for conducting lung cancer screening in an effective and safe manner. Still, a large-scale impact of screening on lung cancer mortality will not be achieved without widespread implementation. Thus far, adoption of the test in routine clinical practice has been limited, with estimated screening of less than 2% of the 7.6 million persons eligible in 2016 (170), and 14% of those eligible across 10 states in 2017 (171). There are likely multiple reasons for this, including fear, stigma, and cost concerns for patients; insufficient time or knowledge to conduct shared decision making and manage screening results for providers; and unfamiliarity with eligibility and insurance coverage criteria for both (172).

The effectiveness of CT screening in clinical practice outside of the controlled setting of a clinical trial has yet to be determined. While it may not be possible to directly evaluate the effect of screening on lung cancer mortality, important measures of performance and quality will include the risk levels of the screened populations; screening results; diagnostic evaluation rates, methods, and compliance; cancer detection rates; stage distribution; treatment; survival; and procedure-related adverse events. The ACR Lung Cancer Screening Registry, currently the only registry approved by CMS and in which screening center participation is required for Medicare reimbursement, should facilitate review of many screening outcomes of interest and their variability on a large scale.

Conclusions

The enormous challenge of reducing morbidity and mortality from lung cancer will continue for many years. The accumulated evidence and guidelines from 2 decades of rigorous study have increased confidence that appropriate implementation of CT screening can prevent a substantial number of lung cancer deaths, at low clinical risk. Now, more information is needed about patient outcomes in routine clinical practice across different settings. Continued refinements in patient selection and image analysis methods may further improve the efficiency and effectiveness of CT screening, but there is much room for other advances in the areas of prevention/risk reduction, early detection, and treatment.
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