Review Article

Screening and Early Detection Efforts in Lung Cancer

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Lung cancer is the leading cause of cancer-related death in the United States. Since publication of results from the National Lung Screening Trial, several professional organizations, including the US Preventive Services Task Force, have published guidelines recommending low-dose computed tomography for screening in asymptomatic, high-risk individuals. The benefits of screening include detection of cancer at an early stage when a definitive cure is possible, but the risks include overdiagnosis, false-positive results, psychological distress, and radiation exposure. The current review covers the scope of low-dose computed tomography screening, potential risks, costs, and future directions in the efforts for early detection of lung cancer. ***Cancer*** **2015;121:1347-56.** © *2015 American Cancer Society.*

KEYWORDS: cancer screening, lung neoplasms, risk assessment, early detection.

INTRODUCTION

Lung cancer (LC) is the second most common cancer among both men and women in the United States and accounts for more deaths than any other cancer.[1] The 5-year survival rate for LC remains low at 16.8% and is <5% for patients with metastatic disesae.[2] The utility of sputum cytology and chest radiographs alone and in combination has been extensively studied and has not exhibited any benefit as a screening tool.[3,4] Several single-arm trials have suggested that screening with computed tomography (CT) may be of benefit[5]; however, it was not until the publication of the National Lung Screening Trial (NLST) in 2010 that strong evidence was available in support of LC screening.[6]

The results of the NLST lead to several professional societies supporting LC screening for individuals at high risk.[6,7] The US Preventive Services Task Force (USPSTF) guidelines gave a Grade B recommendation for LC screening using annual low-dose CT (LDCT) in high-risk individuals.[8] Since publication of the NLST, additional studies have been completed that further refine an individual's risk, thereby identifying the best candidates for screening.[9,10] This review focuses on current recommendations for LC screening, including risks, benefits, costs, and future directions in the efforts for early detection.

Methods

Articles for this review were chosen based on a Medline search using the following Medical Subject Heading terms: lung neoplasms, early detection of cancer, tomography, x-ray computed, radiation, risk, communication, decision support techniques, biological markers, microRNAs. Reference lists from the relevant articles also were reviewed to assess for missed publications. All authors were in agreement with the final selection of articles.

Screening With LDCT

Over the past 2 decades, several cohort studies and randomized controlled trials (RCTs) have been performed comparing LDCT with usual care or chest x-ray (CXR). A list of select RCTs is provided in Table 1. An important aspect of all trials was the exclusion of individuals with comorbid conditions who were unfit to undergo curative surgery; some trials required participants to have a baseline exercise capacity before undergoing screening.[12] This factor is important in patient selection for LC screening implementation.[8] Table 1 also highlights the differences in inclusion criteria, screening interval, and positive screen algorithms.

The NLST is the largest RCT published to date. It was a multicenter trial conducted in 33 centers across the United States that included 53,454 individuals. Participants who were eligible for screening were between ages 55 and 74 years, had a history of cigarette smoking of at least 30 pack-years, and, if they were former smokers, they must have quit within the last 15 years. Individuals were randomized to screening with either LDCT or CXR. Screening was conducted at yearly

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TABLE 1. Trials Evaluating Low-Dose Computed Tomography Scans for Lung Cancer Screening

	Trial (Reference)						
	DANTE (Infante 2009[11])	NLST (Aberle 2011[6])	DLCST (Saghir 2012[12])	ITALUNG (Lopes Pegna 2013[13])	MILD (Pastorino 2012[14])	NELSON (Horeweg 2013[15])	LUSI (Becker 2012[16])
Location	Italy	United States	Denmark	Italy	Italy	Netherlands and Belgium	Germany
Enrollment period	2001-2006	2002-2004	2004-2006	2004	2005-2011	2003	2007-2011
No. of screening rounds	5	3	5	5	5	4	5
Screening interval, y	1	1	1	1	1 or 2: Randomized	1, 2, 2.5	1
Sample size	2811	53,454	4104	3206	4099	15,822	4052
Sex/age, y	Men/60-74	Men & women/ 55-74	Men & women/ 50-70	Men & women/ 55-69	Men & women/ >49	Men & women/ 50-75	Men & women/ 50-69
Smoking history	>20 Pack-years, current or former smokers	>30 Pack-years, current or former smokers who have quit within the past 15 y	>20 Pack-years, current or former smokers who have quit after age 50 y and for <10 y	>20 Pack-years, current or former smokers	>20 Pack-years, current or former smokers having quit within 10 y of recruitment	Current or former smokers; >15 cig/d × 25 y or >10 cig/d × 30 y; quit <10 y ago	Current or former smokers; >15 cig/d × 25 y or >10 cig/d × 30 y; quit <10 y ago
Positive screen criteria for pulmonary nodule[a] (includes indeterminate screens)	Not specified	Any dimension >4 mm	Greatest dimension >5 mm	Greatest dimension >5 mm	Volume >60 mm^3	Volume >50 mm^3	Greatest dimension >5 mm

Abbreviations: cig/d, cigarettes per day; DANTE, Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays Trial; DLCST, Danish Lung Cancer Screening Trial; ITALUNG, Italian Lung Study; LUSI, Lung Cancer Screening Intervention Trial; MILD, Multicentric Italian Lung Detection Project; NELSON, Nederlands-Leuvens Longkanker Screenings Onderzoek or Dutch-Belgian Lung Cancer Screening Trial; NLST, National Lung Screening Trial.

[a] All trials had a pulmonary nodule management algorithm with specific criteria for follow-up with imaging or invasive testing.

intervals for 3 years. The median duration of follow-up was 6.5 years. Any noncalcified nodule identified on LDCT or CXR that measured at least 4 mm in greatest dimension was considered positive. Thirty-nine percent of participants in the LDCT group and 16% of those in the CXR group had at least 1 positive screen. Across all screening rounds, there was a false-positive rate of 96.4% in the LDCT group and 94.5% in the CXR group, and the vast majority of those individuals were followed with serial imaging (81.1% after the first round of screening[17]). Only 1.8% of screenees underwent percutaneous cytologic examination or biopsy. A 20% decrease in LC-specific mortality and a 6.7% reduction in all-cause mortality were observed in the LDCT group. The number needed to screen with LDCT to prevent 1 death from LC was 320, which was similar to the number needed to screen with mammography among women aged $\geq$50 years.[6]

The ongoing Nederlands-Leuven Longkanker Screenings Network (NELSON) trial is the second largest RCT (n = 15,822) comparing LDCT screening versus no screening. The primary endpoint is a 25% mortality reduction in LC among individuals screened with LDCT at 10 years of follow-up. Data from the trial will be pooled with data from the Danish Lung Cancer Screening Trial (DLCST), with publication anticipated in 2015. The trial uses volumetric measurements to assess growth in screen-detected nodules. A positive screen is defined as a volume >500 mm^3 (approximately 9.8 mm in greatest dimension) or a volume-doubling time <400 days, as indicated in Table 1. This strategy for following screen-detected nodules has resulted in positive rates of 2.6% and 1.8%, respectively, in rounds 1 and 2 of screening[15] compared with the 26.4% positive rate across all rounds of screening in the NLST[6]; and the NELSON trial has demonstrated the potential advantage of volumetric measurements in reducing the number of follow-up examinations needed for individuals with a positive test result. To date, volumetric analysis has not been established as the standard of care here and is not included in the published society guidelines.

Recommendations for LC Screening With LDCT

Given the results of the NLST, several professional societies have published LC screening guidelines (Table 2). Most of those groups have defined high-risk individuals based on inclusion criteria from the NLST and have made recommendations for a similar screening algorithm. A multisociety statement based on a systematic review of the benefits and harms of CT screening, published in 2012,

TABLE 2. Screening Guidelines From Professional Societies for Lung Cancer Screening

Professional Society (Reference)	Recommendation
USPSTF (Moyer 2014[8])	Grade B: Annual low-dose chest CT scan in high-risk individuals (ages 55-80 y, >30 pack-year current or former smokers who have quit within the past 15 y); may discontinue screening if limited life expectancy or >15 y since quitting smoking[a]
ACCP/ASCO (Detterbeck 2013[18])	Grade 2B: Annual low-dose chest CT scan in high-risk individuals (ages 55-74 y, >30 pack-year current or former smokers who have quit within the past 15 y), but only in settings that can deliver the comprehensive care provided to NLST participants
AATS (Jaklitsch 2012[19])	Annual low-dose chest CT scan in high-risk individuals (ages 55-79 y with a >30 pack-year smoking history); individuals ages 50-79 y with a 20 pack-year history and added risk >5% of developing LC within 5 y (grade B); >5-year LC survivors (grade C)[b]
NCCN (National Comprehensive Cancer Network 2014[22])	Grade B: Annual low-dose chest CT scan in high-risk individuals (ages 55-79 y and >30 pack-year current or former smokers who have quit within the past 15 y) or aged >50 y with a >20 pack-year history and 1 additional risk factor[c]
ACS (Wender 2013[20])	Grade B: Annual low-dose chest CT scan in high-risk individuals (ages 55-74 y, >30 pack-year current or former smokers who have quit within the past 15 y) and who are in relative good health
ALA (American Lung Association, 2014[21])	Annual low-dose chest CT scan in high-risk individuals (ages 55-74 y, >30 pack-year current or former smokers who have quit within the past 15 y)

Abbreviations: AATS, American Association of Thoracic Surgeons; ACCP, American College of Chest Physicians; ACS, American Cancer Society; ALA, American Lung Association; ASCO, American Society of Clinical Oncology; CT, computed tomography; LC, lung cancer; NCCN, National Comprehensive Cancer Network; NLST, National Lung Screening Trial; USPSTF, US Preventive Services Task Force.

[a] The upper age limit was determined by microsimulation modeling (unlike the NLST, in which the cutoff age was 74 years).

[b] Examples of added risk include chronic obstructive pulmonary disease, environmental/occupational exposure, prior cancer/radiation therapy, and genetic/family history.

[c] Examples of additional risk factors include radon or occupational exposure, personal or family history of cancer, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis.

formed the basis for clinical practice guidelines.[18] They recommend screening only for those who meet NLST inclusion criteria and in a setting capable of providing comprehensive cancer care.[7]

The American Association of Thoracic Surgeons and the National Comprehensive Cancer Network have recommended screening for individuals who have risk factors (eg, family history, radon and asbestos exposure) that were not included in the NLST.[19,22] More studies are required to determine the contribution of these factors in the overall development of LC.[23] The American Academy of Family Physicians is the only organization that does not recommend the use of LDCT screening, citing insufficient evidence.[24]

In 2013, the USPSTF recommended annual screening for LC with LDCT for adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. The USPSTF stated that screening should be discontinued once an individual has not smoked for 15 years or develops a health problem that substantially limits their life expectancy or their ability to undergo curative lung surgery.[8]

After the USPSTF recommendation and considering a multisociety policy statement outlining the components of a safe and effective LC screening program,[25] the Centers for Medicare and Medicaid Services released their decision summary in late 2014 stating that LC screening with LDCT, along with a shared decision-making visit, will be covered for eligible participants (based on NLST inclusion criteria) at certified LC screening centers.[26]

Potential Harms of LC Screening With LDCT

Ideal screening maximizes benefits and minimizes harm. A good understanding of the potential harms and communication of the same form an important basis for the effective, widespread implementation of screening. False-positive screens, resulting psychological distress, radiation exposure, incidental findings, overdiagnosis, and financial costs are potential barriers to effective screening.

False-positive results and psychological distress

Unlike colonoscopy, in which an abnormality can be biopsied at the time of the test, LC screening does not result in an immediate pathologic diagnosis. This makes nodule management an integral part of an LC screening program. All of the RCTs listed in Table 1 had a clearly defined nodule management protocol. Although 18,146 of LDCT participants in the NLST had a positive test, only 1.8% underwent biopsy, 3.8 % underwent bronchoscopy, and 4% underwent a surgical procedure.[6] Appropriate adherence to guidelines and the availability of interdisciplinary expertise are important tenets of minimizing the harms of screening. If screen-detected nodules are inappropriately biopsied, this could lead to potential harm. A study by Wiener and colleagues demonstrated a

2-fold variation in the use of CT-guided biopsy based on geographic location. This "minimally invasive" procedure has risk. Pneumothorax occurred in approximately 15% of patients, of which 6% required chest tube insertion, and major bleeding occurred in 1%.[27]

A concern of screening is the distress caused by a false-positive result. This has been extensively studied in breast cancer screening.[28] A mammography screening study compared women who had normal findings, false-positive diagnoses, and those who had breast cancer. The severity of psychological distress in those who had false-positive findings, which persisted for at least 3 years, was between that of healthy women and that of women who had breast cancer.[28] Data on psychological distress are available for incidentally discovered pulmonary nodules. A qualitative analysis studying patients' reactions to pulmonary nodules demonstrated that most participants immediately believed they had cancer.[29] Another study indicated that most experienced at least mild nodule-related distress, which sometimes was mitigated by their clinician.[30]

A systematic review to evaluate the effect of LDCT screening on patient-centered outcomes demonstrated that screening is associated with short-term psychological discomfort but does not impact distress, worry, or health-related quality of life (HRQoL).[31] Gareen and colleagues studied the impact of LC screening results on participant HRQoL and anxiety in the NLST. Those authors did not observe a significant difference in HRQoL or anxiety at 1 month or 6 months after screening between participants who had false-positive results, significant incidental findings, or negative screening results.[32] In the Danish LC Screening Trial, the use of antidepressants and anxiolytics did not increase among individuals in the screening arm, suggesting that significant adverse mental health outcomes do not result from participating in a screening program.[33]

Incidental findings

The sensitivity of a CT scan is such that other findings unrelated to a lung malignancy are often detected. These include abnormalities in the lung (eg, emphysema, interstitial lung disease, and bronchiectasis), thyroid, and heart. Eight percent of LDCT scans in the NLST identified a clinically significant abnormality that was not suspicious for LC.[6] A Canadian retrospective study demonstrated that coronary calcification was the most common incidental finding.[34] The magnitude and clinical consequence of these downstream incidental findings is not yet defined; however, the potential for these findings should be discussed when screening is offered.

Radiation risk

Undergoing a CT scan incurs radiation exposure. The effective radiation dose from LDCT is about 1.5 milliSieverts (mSv) per examination. By comparison, the approximate radiation dose from a CT pulmonary angiogram is 15 mSv, and that from routine chest CT is 8 mSv.[7,35]

Without accounting for annual repeat or follow-up examinations, the International Commission on Radiologic Protection estimates that, per 100,000 screened, 3 to 6 radiation-induced cancers would occur over a 15-year to 20-year period.[36] One study suggested that a >5% reduction in overall mortality from CT scan screening would outweigh radiation risks.[37]

Overdiagnosis

Overdiagnosis is the detection of a cancer that would not have otherwise become clinically significant. It takes into account the cancer's growth potential and the individual's competing risks for mortality. In LC, the extent to which overdiagnosis occurs is difficult to determine, but that it exists is supported by older screening trials evaluating CXR as the intervention.[38] Extended follow-up for 16 years in the Mayo lung cohort demonstrated an excess of 46 cancers in the screened group compared with the control group, and the estimated rate of overdiagnosis was 51%.[38] Yankelevitz and colleagues analyzed the same Mayo data along with data from the Memorial Sloan-Kettering Cancer Center study using a volume-doubling time cutoff of 400 days, and the overdiagnosis rate using this approach was 5%.[39] The rate of overdiagnosis likely lies somewhere in between. If CXR screen-detected LCs are overdiagnosed in the reported 50% range, then it would appear that the overdiagnosis rate of LDCT would be much higher given the difference in test sensitivity. This is not what has been observed in modeling estimates of overdiagnosis in LDCT-screened groups, although it should be noted that these are limited by the available duration of follow-up. An examination of overdiagnosis in the NLST estimated an overdiagnosis rate of 18.5%, which amounted to 1.38 cases of overdiagnosis per 320 participants needed to screen to prevent 1 death.[40] They also used tumor histology as a factor in the likelihood of overdiagnosis and estimated that 25% of nonminimally invasive adenocarcinomas would have a lead time of at least 5 years.[40] These results are in line with the 25% estimated risk of overdiagnosis in the Italian Continued Observation of Smoking Subjects (COSMOS) study, in which volume-doubling time was used as an indicator of overdiagnosis.[41] Although overdiagnosis may be a potential harm to screening, its true extent is yet to be

TABLE 3. Risk-Prediction Models for Lung Cancer Screening

Prediction Model (Reference)	Population Used to Derive the Model	Variables/Risk Factors Used in Model Construction	URL
Bach model (Bach 2003[52])	Participants in the CARET study: 18,172 current or former smokers	Age, sex, smoking history (only current or former), exposure to asbestos	http://www.mskcc.org/cancer-care/adult/lung/screening-decision-tool
Spitz model (Spitz 2007[53])	Cases (n = 1851) and controls (n = 2001) in an LC study at the MD Anderson Cancer Center	Age, sex, smoking history (current, former, never), emphysema, asbestos exposure, dust exposure, family history of cancer	http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/epidemiology/clear.html
Liverpool Lung Project model (Cassidy 2008[50])	Cases (579) and controls (1157) in the Liverpool Lung Project Study	Age, sex, smoking history, asbestos exposure, prior pneumonia, family history of cancer, prior malignancy	www.mylungrisk.com
$PLCO_{M2011}$ model (Tammemagi 2011[51])	Control arm (70,962) of the PLCO study	Age, sex, ethnicity, smoking history, socioeconomic status, BMI, family history of LC, COPD, recent CXR	—
Hoggart model (Hoggart 2012[49])	EPIC cohort (82,776 current smokers; 86,259 former smokers; 230,358 never smokers)	Age, sex, smoking history, environmental or occupational exposures, family history of cancer, asthma or hay fever, socioeconomic status, 2 SNPs	—
Modified $PLCO_{M2012}$ model (Tammemagi 2013[9])	73,618 Smokers in the PLCO study and 51,033 participants from the NLST	Similar to $PLCO_{M2011}$	http://www.brocku.ca/lung-cancer-risk-calculator

Abbreviations: BMI, body mass index; CARET, Carotene and Retinol Efficacy Trial; COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; EPIC, European Prospective Investigation into Cancer and Nutrition; LC, lung cancer; NLST, National Lung Screening Trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; $PLCO_{M2011}$, original PLCO model; $PLCO_{M2012}$, modified PLCO model; SNP, single nucleotide polymorphism.

determined, and the current estimates available from LDCT screening trials suggest that, in high-risk patients, the benefits of screening outweigh the risk of overdiagnosis.

Implementation of LC Screening With LDCT

In light of the USPSTF recommendation, several institutions in the United States are now offering screening to high-risk individuals; however, concerns remain about the generalizability of the NLST findings. When participants in the NLST were compared with the US population eligible for LC screening, it was noted that they were younger, had a higher level of education, were less likely to be members of a minority group, and were more likely to be former smokers.[42] In addition, the mortality for surgical resection was lower in the NLST than previously reported in the US population (1% vs 4%).[6] Finally, the NLST was conducted in 33 centers, of which greater than 80% were tertiary-care academic centers, and 76% were designated as National Cancer Institute cancer centers. The multidisciplinary expertise, including thoracic radiology, pulmonary/thoracic surgery, and oncology, resulted in the majority of positive screens being followed with serial imaging. This expertise may not be available at all community sites and has the potential to lead to increased use of invasive procedures. The multisociety statement emphasizes the importance of multidisciplinary care similar in caliber to that of the NLST and recognizes the potential harms from LC screening if it is not conducted properly.[7]

Pinsky and colleagues reanalyzed NLST data to compare screening outcomes between NLST participants aged >65 years and aged <65 years. Although the false-positive rate was higher in the group aged ≥65 years, the positive predictive value was 4.9% in the cohort aged ≥65 years compared with 3% in the cohort aged <65 years. This translates into a number needed to screen of 245 and 364, respectively.[43]

The American College of Chest Physicians and American Thoracic Society published a policy statement

outlining the various components necessary for high-quality LC screening to guide the implementation of screening in the community.[25] These components include identification of the population to screen, screening frequency and duration, technical specifications for the CT scan, nodule identification, structured reporting, nodule management algorithms, smoking cessation, data collection, and shared decision making.

Importance of Smoking Cessation

Despite enrollment in LC screening trials, some individuals continue to smoke. Younger age, lower socioeconomic status, being spouseless, lower body mass index, smoking intensity and duration, and second-hand smoke exposure are associated with continued smoking.[44] Evidence suggests that LDCT screening itself does not influence smoking behavior.[45] Data from the ongoing Dutch-Belgian Lung Cancer Screening Trial (NELSON) indicated that there was no difference in cessation rates between those undergoing LDCT screening and controls.[45] However, those who had abnormal screening results suspicious for LC reported a 6% lower rate of smoking compared with those who had normal results.[46] Because 85% of LCs are related to tobacco use, it is imperative to incorporate smoking cessation into a screening program. In addition, smoking cessation is an extremely cost-effective preventive measure. A study to determine the cost effectiveness of clinical recommendations in the Agency for Health Care Policy and Research guidelines demonstrated that the costs per quality-adjusted life-year (QALY) saved ranged from $1108 to $4542.[47]

Risk Assessment

Before recommendations were made for LC screening with LDCT, several models were developed to aid in determining which individuals had the highest risk of developing LC (Table 3).[48-53] The modified Prostate, Lung, Colorectal, and Ovarian (PLCO) model ($PLCO_{M2012}$) predicted the 6-year risk of LC with high accuracy and was more efficient at identifying individuals for screening compared with NLST entry criteria (sensitivity, 83% vs 71.1%, respectively).[9] Those results support using the $PLCO_{M2012}$ and similar models to better target who best to screen within a high-risk population.

Kovalchik and colleagues developed an absolute risk-prediction model for LC mortality in the NLST CXR group. Those authors stratified participants into 5 quintiles for the predicted 5-year risk of death from LC. Their results indicated that the number needed to screen in the 5 quintiles varied from 5276 in the first quintile (lowest risk) to 161 in the fifth quintile (highest risk). The number of false-positives per prevented LC death varied from 1648 (first quintile) to 65 (fifth quintile).[10] The prediction models described above were not used as inclusion criteria for selection in the RCTs listed in Table 1. However, such tools can serve as decision aids to assist patients in understanding their individual risk for developing LC and, thus, can help them make informed decisions. In addition, from a public policy standpoint, such tools have potential to become part of future screening strategies. For example, eliminating the lowest quintile of risk from screening would eliminate a large number of false-positive screens and reduce the number needed to screen.

Communication of Risk

An important aspect of a screening program is informed decision making. Recent research has indicated that the patient's assessment of the benefits and limitations, risks, and costs are important when making medical decisions.[54] However, a national survey demonstrated that only 20% to 30% of discussions about cancer screening include a discussion of reasons for not undergoing testing.[55] The extent to which patient preferences are solicited and providers discuss the benefits, limitations, and costs of LDCT screening is not well understood. There is strong evidence that personalized risk estimates within communication interventions for screening programs enhance informed choices.[56] The risk for a woman aged 56 years with a 32 pack-year smoking history who quit smoking 12 years ago differs from that of a man aged 73 years who is a current smoker with a 75 pack-year history. Also, it has been demonstrated that individuals at risk for LC lack sufficient knowledge about the disease: smokers in particular lack adequate comprehension about what effective screening means and are less willing than nonsmokers to pay the financial costs for LC screening or to undergo surgical therapy for a detected cancer.[57] Effective risk communication and shared decision making will play a crucial role in the widespread implementation of LDCT screening and sustained participation of individuals in the annual screening process.

Cost Efficacy

Black and colleagues examined the cost effectiveness of screening with LDCT in the NLST. According to their analysis, the cost of CT screening per life-year and QALY gained (in US dollars) was $52,000 and $81,000, respectively.[58] Subgroup analyses were conducted and demonstrated that it was more cost efficacious to screen women than men ($46,000 vs $615,000 per QALY gained),

current smokers than former smokers ($43,000 vs $615,000 per QALY gained), both for the 3 oldest age groups and for the 2 quintiles with the highest risk of cancer. Sensitivity analyses also demonstrated that screening became cost ineffective with incremental cost-effectiveness ratios approaching or exceeding $100,000 per QALY gained when costs for the screening examination, follow-up intervals, or surgery were increased, highlighting the importance of proper implementation in the community.[58]

The Future of LC Screening

Successful screening for LC is a critical first step toward cancer control; however, the tools we currently have to determine who best to screen are limited. Although the use of age and smoking history as a means for identifying high-risk individuals was sufficient for the purposes of the NLST, further evaluative measures, including individualized risk assessment, novel testing, and advancements in technology, have the potential to help identify who best to screen and how to interpret a screen-detected nodule. Although most of the research being done is promising, much of the novel testing requires further evaluation and validation before it can be used in a broad-based setting.

Volumetric analysis

The use of multidetector CT for a variety of presenting illnesses has resulted in an increase in the detection of solitary pulmonary nodules, with the potential to increase exponentially as LC screening is implemented. Volumetric nodule measurement can be used in an effort to differentiate benign from malignant nodules. The NELSON trial followed nodules with serial volumetric measurements and accurately predicted which nodules grew and required further evaluation.[59] A recent study demonstrated that the addition of nodule volume to existing nodule malignancy prediction models significantly improved the ability to distinguish benign from malignant disase.[60]

Biomarkers

Several investigations into serologic biomarkers have been conducted to identify who has LC, who is at higher risk for LC, and which nodules are malignant. Although this work holds promise, there is no 1 best available test to replace the clinical factors and current risk-prediction models. Further testing and validation of these biomarkers as individual or adjunct tests for LC screening and early diagnosis are still needed before they are implemented or routinely included in a screening algorithm.

MicroRNAs (miRNAs) are small, noncoding RNAs that modulate gene activity, are aberrantly expressed in cancer, and can be measured in biologic fluids. Several miRNAs have been tested in serum, plasma, whole blood, and sputum for the diagnosis and prognosis of nonsmall cell LC (NSCLC) with sensitivity and specificity ranging from 60% to 100%.[61] These can be used as stand-alone tests or in conjunction with another screening test, such as LDCT. The diagnostic performance of a plasma miRNA signature classifier (MSC) was retrospectively evaluated in patients in the randomized Multicenter Italian Lung Detection trial, which indicated that the integration of MSC with LDCT raised screening sensitivity from 87% for MSC and 84% for LDCT alone to 98% with a false-positive rate of 35%. In those with 2 positive tests (MSC and LDCT), integration reduced the false-positive rate of LDCT screening more than 5-fold.[62]

It is also established that patients with cancer produce autoantibodies to tumor proteins that are mutated, misfolded, ectopically presented, over-expressed, aberrantly degraded, or anomalously glycosylated. Studies have been done in the detection of multiplex autoantibodies (eg, anti-p53 antibody) among patients with LC versus healthy controls.[63]

Another series of biomarkers has been developed using a proteomic profiling of serum samples. Pecot and colleagues developed a proteomic signature that was identified as diagnostically additive to already established, standard clinical and chest CT imaging data in the evaluation of smaller nodules (range, 5-20 mm) to help distinguish benignity from malignancy.[64]

The use of bronchial airway epithelial markers for early LC detection is based on the concept of field cancerization (ie, alterations observed in the lung tumor are also present in uninvolved areas of the respiratory tract). By using cytologically normal, large-airway epithelial cells obtained at bronchoscopy in patients with suspected LC, Spira and colleagues developed an 80-gene expression biomarker that distinguished individuals with and without LC. This airway gene-expression biomarker had an accuracy of 83% (80% sensitivity, 84% specificity) in an independent test set, and it had approximately 90% sensitivity for stage I LC across all patients, suggesting its utility as an early diagnostic tool.[65]

Volatile organic compounds

Greater than 3000 different volatile organic compounds (VOCs) have been identified in human breath. According

to the hypothesis of oxidative stress, breath VOCs reflect the biochemical status of the body, with the potential to aid in early LC detection. Experiments have been performed using different technologies, such as gas chromatography, spectrometry, spectroscopy, electronic noses (eg, quartz crystal microbalance, surface acoustic wave sensors, gold nanoparticle sensors, colorimetric sensors), and even canine scent detection, for differentiating VOCs in patients with LC compared with healthy controls.[66] Phillips et al performed VOC analyses using gas chromatography and mass spectrometry and demonstrated a sensitivity of 84.6% and a specificity of 80%.[67] Ehmann et al demonstrated that, when exhaled breath was presented to sniffer dogs, LC was identified with an overall sensitivity of 71% and a specificity of 93% independent of the presence of chronic obstructive pulmonary disease or tobacco smoke.[68] The analysis of breath VOCs is an appealing test, because it is noninvasive and potentially inexpensive.

Conclusion

LC is the deadliest cancer worldwide, and, until recently, there was no proven method for early detection. With the advent of LDCT for screening, there is the potential to save lives in high-risk individuals; however, because of the high false-positive rate, there may be a diminished mortality benefit if screening results in more invasive procedures and surgeries with untoward events. Further refinement of screening eligibility criteria and better management of screen-detected nodules may reduce the number of false-positive results.

LC screening in a comprehensive, multidisciplinary setting with an emphasis on smoking cessation is key. Of equal importance is a balanced presentation of its risks and benefits, such that individuals make informed decisions in line with their beliefs. The use of individualized risk-prediction models may help facilitate these discussions. LC screening should evolve over time, and we can envision biomarkers, VOCs, and airway epithelial markers becoming part of the screening algorithm to further enhance the selection of individuals for screening or to determine how best to follow those with a screen-detected nodule.

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