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Lung Cancer Screening: Adjuncts and Alternatives to Low-Dose CT Scans

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Abstract Lung cancer (LC) is the leading cause of cancer related mortality in US. The National Lung Screening Trial has demonstrated a mortality benefit of using low-dose computed tomography (LDCT) in the screening of LC in high-risk individuals. The US Preventive Service Task Force has given screening for LC with LDCT a grade B recommendation; however, it recognizes gaps in generalizability to the population that would qualify for screening. There are a number of new tests in various stages of evaluation and development that hold promise as adjuncts or alternatives to LDCT. The following is a review of these novel diagnostic tests.

Keywords Lung cancer · Low-dose CT scan · Exhaled breath analysis · Airway epithelial · Gene expression biomarkers · Volatile organic compounds

Introduction

Lung cancer (LC) is the leading cause of cancer-related mortality in the US, causing more deaths than breast, prostate and colon cancer combined [1]. The median 5-year survival for all comers in US is ~16 % [1]. The median 5-year survival for stage I and II LC, however, ranges from 50 to 70 %, making early detection desirable for decreasing LC mortality [1]. Investigations into effective screening with methods including chest radiograph (CXR) and sputum cytology alone and in combination were unable to demonstrate any impact on LC mortality [2••, 3].

In 2011, the results from the National Lung Screening Trial (NLST) were published. This was the first large scale multicenter randomized trial that convincingly demonstrated a mortality benefit by screening high-risk individuals with low-dose computed tomography (LDCT) scans [4••]. The following reviews the evidence and limitations of LC screening with LDCT, and describes the potential use of new techniques in LC screening as adjuncts and alternatives to LDCT.

Low Dose Helical Computed Tomography (LDCT)

Over the last two decades, technical advances have improved the quality of image acquisition and diagnostic yield of computed tomography (CT). The multidetector helical CT, for example, is able to image the entire lung during a single breath hold, using a lower radiation dose than standard CT. The initial studies demonstrated an increased rate of lung nodule detection and higher percentage of detected early-stage LCs with LDCT compared to CXR. Study design, however, precluded conclusions as to the impact of the use of LDCT in LC mortality, because the studies either lacked a control group, were underpowered, or did not have adequate follow-up time [5–11].

The NLST [4••] was designed to detect a 20 % reduction in mortality by LDCT LC screening, with a 90 % power. It included 33 centers across the US, and enrolled 53,454 current or former smokers aged 55–74 years, with a minimum 30-pack-year smoking history. Former smokers had quit within the past 15 years. The participants were

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randomly assigned to screening with LDCT ($n = 26{,}722$) or CXR ($n = 26{,}732$) annually for three screens. The LDCT screenings were consider positive if they revealed a noncalcified nodule measuring at least 4 mm in longest diameter, and CXR screens were positive if they revealed any noncalcified nodule or mass. The median follow-up period was over 6.5 years.

The LDCT-screened group had a higher rate of positive screening tests compared with the CXR group (24.2 vs. 6.9 %). However, the rate of false positive results was high (96.4 % in the LDCT group and 94.5 % in the CXR group). LDCT detected more LC compared to CXR (1,060 vs. 941). Among the patients diagnosed with LC, the LDCT group had significantly more stage I cancers (63 vs. 47.6 %). There were also fewer patients with stage III and IV LCs in the LDCT group compared to the CXR group (29.8 vs. 43.2 %). At the end of the follow-up period, there were 354 LC deaths in the LDCT group and 442 deaths in the CXR group. The LC rate mortality was 247 per 100,000 person-years in the LDCT group, and 309 per 100,000 person-years in the CXR group (a 20 % reduction in mortality in the LDCT group). The overall mortality was reduced by 6.7 %, largely due to the reduction in deaths from LC. The number needed to screen with low-dose CT to prevent one death from LC was 320 [4••], which is comparable to the number of women needed to screen with mammography to save one life from breast cancer [12].

Potential Shortcomings of LDCT Screening

Generalizability of NLST Results

Although randomized controlled studies are considered the most robust method to assess efficacy (performance under ideal conditions), one of their main limitations is their ability to evaluate effectiveness (performance under real conditions). Randomized controlled trials require more standardized and higher levels of medical care than occurs in real practice. In addition, the trial participants are usually not fully representative of the eventual target group [13]. Such is true for the NLST cohort that, when compared to the US population eligible for screening based on trial entry criteria, was younger, healthier, better educated, and more frequently former smokers [4••]. It is therefore unclear if the same mortality benefit will be recognized with large-scale LC screening implementation.

In the NSLT, screening with LDCT had a high rate of false positive results (96 %) and low positive predicted value (< 4 %). Despite this, few medical complications occurred during diagnostic evaluation for positive screens (~1.4 %). This may be due in some part to the location of care in the NLST. Participants were enrolled in urban, tertiary care hospitals with expertise in all aspects of cancer care, including dedicated thoracic radiologists. The majority of positive screens were followed with serial imaging without need for invasive testing. In contrast, community practice gives rise to the potential for considerable variation in the management of solitary pulmonary nodules identified by screening LDCT. One study demonstrated a two-fold variation among geographic regions in the use of CT-guided biopsy, ranging from 14.7 to 36.2 per 100,000 adults [14•, 15]. This variation in management of solitary pulmonary nodules may lead to an increased number of invasive procedures with risk of harm. In addition, the psychological harms of a positive test result should not be underestimated. Studies of breast and prostate cancer screening showed that false-positive screening results were associated with depression and change in self-perception of health status [16, 17].

There are, however, ways to decrease the high false-positive rate from screening with LDCT. Investigators from the NELSON study [18] improved the sensitivity, specificity, positive and negative predictive value of the LDCT for LC screening through the use of semi-automated volumetric software to measure diameter and volume doubling time (VDT). Growth was defined as a change in volume between the first and the second scan of 25 % or greater. Nodules meeting growth criteria were then classified into three categories based on VDT (< 400, 400–600, and > 600 days). This approach to nodule management resulted in a decrease in the rate of test-positive results at baseline from 30 to 2 %. The final results regarding the reduction in mortality from LC from this trial are pending.

Another difference between the NSLT results and community practice is the mortality rate from LC surgery (1 vs. 3–5 % national average) [19, 20]. While the study allowed participants to choose where they had their evaluation and management for screen detected nodules, it is likely that many were managed at an NLST site with high volume and dedicated thoracic surgery support, both of which are associated with better outcomes [15, 19, 20].

Finally, the NSLT did not assess the impact of LDCT screening in other high-risk populations, including those with chronic obstructive pulmonary disease (COPD), first-degree relative with LC, occupational exposure to asbestos and other carcinogens, and prior history of LC or other smoking-related cancers. Therefore, it is unknown the degree to which these populations would benefit from LDCT screening.

Overdiagnosis

Another concern with all screening tests is the possibility of overdiagnosis, defined as the detection of indolent cancers that may have never became symptomatic or

caused death [21–23]. Overdiagnosis causes an increase in screening costs, overtreatment, and morbidity. It also has the potential to increase mortality from unnecessary diagnostic and therapeutic procedures. This phenomenon is a possibility in LC screening, due to the degree of biologic heterogeneity. For instance, it has been described that ground glass nodules can remain stable for years before becoming aggressive [24, 25]. There is data suggesting that the use of volumetric measurements of pulmonary nodules like volume double time [26•, 27•]; and pulmonary function tests [28•] might help to better distinguish between aggressive LC and the slow-growing and indolent ones, which could decrease the rate of overdiagnosis and overtreatment. The period of follow-up in the NLST was not long enough to assess the magnitude of this issue, and further follow-up should be revealing.

Barriers to Implementation

The higher rate of active smokers in the eligible US population represent a potential barrier to LC screening. In a national telephone survey to assess beliefs toward LC screening, it was found that current smokers are less likely to believe that early cancer detection would result in a good chance of survival, and are less likely to consider CT screening for LC [29]. Only half of the current smokers surveyed would opt for surgical resection of a screen-detected LC. When these findings are coupled with the fact that smokers make up 31 % of population below the poverty line [30], smokers are likely to be a more difficult-to-reach target population for large-scale screening efforts.

Radiation Exposure

The risk of carcinogenesis related to the radiation from CT imaging is based on organ-specific doses, and individual susceptibility. The mean effective dose per scan in the NLST was 1.6 miliSevers (mSv) for men and 2.1 mSv for women [31•]. These values are almost half the annual radiation exposure in the US (3 mSv), and one-fifth of the dose from a conventional chest CT [32]. According to one study, the radiation exposure from LDCT would confer a risk of LC of 0.85 % in female smokers, and of 0.23 % in male smokers, increasing their baseline risk by 5 % in women and by 1.5 % in men [33]. Finally, the investigators from the NLST, estimated that the radiation risk from CT screening of 55-year-old smokers would result in one to three LC deaths per 10,000 people screened, and 0.3 new breast cancers per 10,000 females [4]. This radiation-related risk is outweighed by the 20 % reduction in mortality by LDCT screening in a high-risk population. It is uncertain if this risk benefit ratio would be less favorable in populations with a lower risk of developing LC.

Cost-Effectiveness

With the increasing cost of health care, an assessment of cost efficacy is needed prior to widespread LC screening implementation. Cost-effectiveness analysis measures the relative value of a screening method as the incremental economic cost to accomplish a better health outcome [34, 35]. The most commonly used metric unit is the incremental cost-effectiveness ratio per quality adjusted life years (QALYs) gained [34, 35]; <$50,000–$100,000 per QALY gained is generally a well-accepted cutoff in the US to suggest an intervention is cost effective [35]. The World Health Organization recommends interventions with a cost effective ratio < 3 times the gross domestic product (GDP) per capita [35] (about $49,965 in the US in 2012, according to the World Bank). Several cost efficacy analyses for LC screening with LDCT have been performed, with broad results ranging from $2,500 to $2 million per QALYs gained [15, 36–38]. The variability in results can be explained in part by the fact that the cost-effective metric unit is a ratio. An increase in the cost, or a decrease in the effectiveness of the intervention, generates a larger ratio (or less cost effective value). Since the cost of the LDCT screening has a finite limit, the main influencing factor of the cost effective ratio would be the effectiveness of LDCT screening, which is strongly influenced by specific eligibility criteria, as well as the rate of smoking cessation among the participants during the screening [39•]. Interestingly, there has been just one randomized study looking at the rate of smoking cessation at time of LC screening, and it showed no significant difference compared to the control group [40].

The cost-effectiveness analysis from the NLST is currently underway, and the results should be available soon. Even if the results are positive, other programs, like smoking cessation ($5,000 per quality-adjusted life-year to implement the AHRQ smoking cessation guidelines), that have been shown to be cost-effective should not be forgotten [41].

Currently, four organizations, including the US Preventive Services Task Force (USPSTF), the American College of Chest Physicians (ACCP), the American Society of Clinical Oncology (ASCO), and the American Cancer Society (ACS), recommend that LDCT should be considered in a population that meets the NLST criteria; the UPSTF extended the upper age limit from 74 to 79 years. They provided a B-level of evidence for this recommendation [22, 42••]. Two other organizations, the National Comprehensive Cancer Network (NCCN) and the American Association for Thoracic Surgery (AATS), expanded their population target, in addition to those who meet the criteria for the NLST, to individuals aged 50 years or older with at least a 20-pack-year history plus

one defined risk factor for LC (prior LC history, occupational exposure to carcinogens, chronic lung disease, or family history of LC) [22, 42••].

Adjuncts and Alternatives to LDCT Screening

While screening with LDCT has demonstrated a clear mortality benefit, the aforementioned limitations make adjuncts and alternative testing for LC screening desirable to improve the efficacy of screening with LDCT, and allow for the conservative management of screen detected nodules. These newer diagnostic modalities include exhaled breath analysis, airway epithelial gene expression biomarkers and serum sampling for antibodies.

Breath Analysis

Volatile Organic Compounds (VOCs)

A promising area of LC biomarker research is the analysis of volatile organic compounds (VOCs) in the breath. VOCs are organic compounds with a high vapor pressure or volatility that can be detected in the headspace of cancer cells, blood samples, saliva, and in the exhaled breath. There is growing evidence for using exhaled breath VOC analysis in the diagnosis and screening of LC. This relies on the principle that the composition of VOCs in the exhaled breath reflects the metabolic activity within the body. Thus, cancer-related changes in the body's metabolic process and blood chemistry are reflected in measurable changes in the breath through exchange via the lungs [43–45].

The measurement of VOCs is noninvasive, can be repeated in short intervals, and therefore has potential as a screening test. There are different techniques used to analyze VOC in exhaled breath. Mass spectrometry (MS) is probably the most studied technique. It can be done using gas chromatography (GC-MS) or proton transfer reaction (PTR-MS). This technique allows the detection and measurement of specific VOCs. It is very sensitive, but is also more expensive and requires expert interpretation [15, 45]. Other techniques used to analyze VOCs include laser spectrometry, ion mobility spectrometry, differential mobility spectrometry, and sensor arrays. Gaseous chemical sensors devices (also called electronic noses), use chemical vapor sensor arrays that generate a reading based on their interaction with specific components or the entire composition of the breath. The output depends on the type of sensor being used: color, mass, vibration, conductivity, or a combination. They have a high sensitivity, are easy to use, and are portable; however, they are difficult to calibrate, and they do not identify the specific constituents of the exhaled breath [44–46].

In 1985, Gordon and colleagues were the first to described VOCs in exhaled breath of LC patients. Using a gas chromatography-mass spectrometry (GC-MS) system, [47] the breath of 12 LC patients were analyzed and compared with controls. A significant difference in the detected level of three VOCs allowed for a model that had 93 % accuracy in discriminating those with LC [47]. Since then, there have been multiple studies showing that the pattern of VOCs in the exhaled breath could distinguish patients with and without LC, with sensitivities ranging from 71 to 100 % [48–51•, 52–55]. Interestingly, VOCs can be sensed by dogs, which with adequate training can differentiate patients with lung, colon and breast cancer from normal controls, with a sensitivity and specificity above 90 % [56, 57•, 58].

Despite the promising data, the use of VOCs analysis in the breath for the diagnosis of LC has several limitations. Most of these studies have been done in small populations, with significant variation in the type of control group. Data from multicenter trials assessing their broad applicability is needed. In addition, the varying techniques for VOC analysis in the breath create the need for further standardization, including sample collection, processing and analysis. Also, the impact of air pollution, tobacco use, lung ventilation volumes and tissue blood flow in the obtained results needs to be further studied [59–61]. Finally, given the complexity of the histology and biology of LC, it is very difficult to establish a relationship from a specific pattern of VOCs with LC.

Exhaled Breath Condensate (EBC)

Another noninvasive test being developed for LC detection involves the analysis of nonvolatile compounds in the breath. This is carried out by capturing a breath in a liquid phase, as an exhaled breath condensate (EBC). The breath sample is cooled with ice, dry ice or liquid nitrogen in a condensing chamber. This provides a sample of the fluid layer from the airway epithelium of respiratory tract. Molecules, including like cytokines, DNA, lipid peroxidation products, and nitric oxide metabolites, can then be measured [62, 63].

Chan and colleges [63] found differences in H2O2 levels in EBC samples from LC patients, smokers, former smokers and non-smokers. Carpagnano et al. [64, 65] also found differences in the presence of microsatellite instability in DNA obtained from EBC of LC patients compared to normal controls. Gessner and colleges [66] found similar results with the presence of P53 mutations in patients with NSLC compared to normal controls. Other studies have demonstrated that interleukin2, TNF alpha, leptin, and endothelin-1 are present in higher levels in the EBC from LC patient compared to normal controls. These levels also

appeared to correlate with the stage of the disease [67–69]. Like VOCs, EBC still requires further validation and large scale trials.

Serum Biomarkers

It has been demonstrated that cancer patients develop an autoimmune response with inflammation and possibly tissue damage in response to their tumor. This is believed to be due to circulating serum antibodies known as tumor-associated antigens (TAA) [70]. Current research is focused on developing a selective serologic test that could be used for early detection of occult lung tumors. A panel of six TAAs was validated previously by Boyle et al. [71] This panel included p53, NY_ESO-1, CAGE, SOX 2, and Annexin I, as these have all been implicated in the production of autoantibodies or immune biomarkers in LC. However, the sensitivity and specificity of this panel is 39 and 89 %, respectively. A subsequent study has since been done, comparing this six-TAA panel to a new panel of seven TAAs, consisting of p53, NY-ESO-1, CAGE, GBU4-5, SOX2, HuD, and MAGE A4. This seven-TAA panel showed a sensitivity and specificity of 41 and 91 %, respectively, with a positive predictive value of one in eight and 92 % accuracy [72]. One issue is that some of these proteins alone are not specific to LC. As more research is conducted and more specific markers are discovered, it is hoped that an improvement will be seen in the accuracy and predictive value.

In another study looking for biomarkers in NSCLC, four differentially expressed proteins were identified between normal serum and serum from patients with NSCLC. These proteins were SMOX, NOLC1, MALAT1, and HMMR. When looked at alone, NOLC1 was the most significant, with sensitivity and specificity of 45 and 96.2 %, respectively. When all four markers were combined, positive predictive value was highest, with 66.7 % sensitivity, 60 % specificity, and 63.2 % accuracy. When this data was applied to different stages of disease, the highest sensitivity was among stage III patients at 82.4 %, and lowest among stage IV patients at 50 %. Stage I and II patients had sensitivities of 63.6 and 62.5 %, respectively [73].

There is also new research focusing on microRNAs (miRNA), which are small noncoding RNA segments that are able to regulate gene expression [74]. Deregulation of miRNAs expression levels has been found in several human cancers, including lung [75]. Several studies have identified and evaluated different miRNAs as diagnostic and prognostic biomarkers in LC [76–80]. Bianchi and colleagues tested 34 miRNA obtained from serum samples in asymptomatic high-risk patients that showed 80 % accuracy for detecting NSCLC [81]. While this remains promising, there are numerous miRNAs, with new ones still being identified, and further investigation is needed to validate this and other serum-biomarker testing.

Light Induced Fluorescence Endoscopy (LIFE)

Early detection and localization of endobronchial lesions remains a challenge in LC testing. While sputum cytology is capable of detecting occult LC, flexible bronchoscopy is then required to try and localize the lesion, which tends to be successful in only 29 % of cases [82]. Light-induced fluorescence endoscopy (LIFE) is a system that delivers a pulse of white light and collects the reflected light, which is then spectrally analyzed. The number of oscillations over the wavelength range is related to nuclear size, and when an increased number of enlarged nuclei are detected, the tissue is classified as dysplastic [83]. This difference in fluorescence between normal and neoplastic tissue can improve the ability of conventional bronchoscopy to identify intraepithelial neoplasia [84–86].

In one multicenter trial, adding LIFE bronchoscopy to conventional white light bronchoscopy improved the sensitivity of detecting at least one lesion from 37.3 to 75 %, although there was no improvement in positive predictive value [87].

In another prospective study of high-risk patients, autofluorescence bronchoscopy (AFB) and spiral CT, in addition to sputum cytology, were performed for primary LC surveillance. Sputum cytology showed 33 % sensitivity and 64 % specificity for detecting metaplasia, and was unable to detect any carcinoma or carcinoma in situ. When compared with AFB, it failed to detect 100 % of dysplastic lesions and 68 % of metaplastic lesions that were detected by AFB. Pre-malignant changes were 3.16 times more likely to be present on AFB when spiral CT found peripheral lung nodules [88]. Unfortunately, bronchoscopy is limited by scope size, and is often unhelpful in visualizing distal endobronchial lesions.

Airway Epithelial Markers

Cigarette smoke is known to cause damage in the airway, and there is interest in identifying biomarkers that would help identify smokers and former smokers at high risk for developing LC. Spira and colleagues first identified an 80-gene biomarker that could distinguish smokers with and without LC using a DNA microarray capable of detecting smoking-induced changes in gene expression of airway epithelial cells. When this microarray was independently tested, it had an accuracy, sensitivity, and specificity of 83, 80, and 84 %, respectively. When combined with cytopathology from bronchoscopy, the biomarker had 95 % sensitivity and a 95 % negative predictive value [89].

In small cell LC, there has been a focus on the sonic hedgehog (Shh) signaling for screening. Shh is necessary for normal lung development, and has also been found to be active within airway epithelium during acute airway injury repair. The signal increases during repair immediately prior to neuroendocrine differentiation and this pattern has been seen in a subset of small-cell LC cell lines [90]. Detection of an elevated level of Shh signaling in airway epithelium could suggest the possibility of early SCLC in a high-risk patient, before any tumors are detected.

Conclusions

The NLST showed a mortality reduction of 20 % in those screened for LC with LDCT. There are, however, limitations to the generalizability of the findings of this trial, and future studies should track outcomes after population-based screening is implemented in the community setting. It is quite possible that the incorporation of newer diagnostic modalities—including exhaled breath VOCs, airway epithelial gene expression biomarkers or serum sampling for antibodies—into LC risk models and pulmonary nodule management algorithms could improve the efficacy of LDCT as part of a screening for LC in the future.

Compliance with Ethics Guidelines

Conflict of Interest Rolando Sanchez Sanchez, Nichole T. Tanner, Nasar A. Siddiqi, and Gerard A. Silvestri declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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