REVIEW

Advances in lung cancer screening and early detection

Caichen Li[1,2]*, Huiting Wang[1,2]*, Yu Jiang[2]*, Wenhai Fu[1], Xiwen Liu[2], Ran Zhong[1,2], Bo Cheng[2], Feng Zhu[3], Yang Xiang[1], Jianxing He[2,4], Wenhua Liang[1,2,5]

[1]Department of Thoracic Oncology and Surgery, the First Affiliated Hospital of Guangzhou Medical University, China National Center for Respiratory Medicine, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, Guangzhou 510120, China; [2]Dongguan Affiliated Hospital of Southern Medical University, Dongguan People Hospital, Dongguan 523059, China; [3]Department of Internal Medicine, Detroit Medical Center Sinai-Grace Hospital, Detroit, Michigan 48235, USA; [4]Department of Thoracic Surgery, Nanfang Hospital of Southern Medical University, Guangzhou 510515, China; [5]Department of Oncology, the First People's Hospital of Zhaoqing, Zhaoqing 526020, China

ABSTRACT   Lung cancer is associated with a heavy cancer-related burden in terms of patients' physical and mental health worldwide. Two randomized controlled trials, the US-National Lung Screening Trial (NLST) and Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON), indicated that low-dose CT (LDCT) screening results in a statistically significant decrease in mortality in patients with lung cancer, LDCT has become the standard approach for lung cancer screening. However, many issues in lung cancer screening remain unresolved, such as the screening criteria, high false-positive rate, and radiation exposure. This review first summarizes recent studies on lung cancer screening from the US, Europe, and Asia, and discusses risk-based selection for screening and the related issues. Second, an overview of novel techniques for the differential diagnosis of pulmonary nodules, including artificial intelligence and molecular biomarker-based screening, is presented. Third, current explorations of strategies for suspected malignancy are summarized. Overall, this review aims to help clinicians understand recent progress in lung cancer screening and alleviate the burden of lung cancer.

KEYWORDS   Lung cancer; screening; low-dose CT; early detection; strategies; biomarkers

Introduction

Lung cancer is the second most common cancer and the leading cause of cancer-related mortality worldwide, with an estimated 2.2 million new cases and 1.8 million deaths in 2020, thus imposing severe social and economic burdens[1]. According to histological type, lung cancer can be divided into non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC accounts for approximately 85% of all lung cancers, and adenocarcinoma and squamous cell carcinoma

are the main histopathologic subtypes[2]. Despite advances in surgery, radiotherapy, chemotherapy, molecularly targeted therapy, and immunotherapy, the average 5-year survival rate for lung cancer is only 19%[3].

The 5-year survival rate for early-stage lung cancer is greater than that for advanced-stage lung cancer. Patients with stage IA lung cancer have a high 5-year survival rate exceeding 75%[4]. As cancer progresses, the long-term survival rate dramatically decreases. For instance, the average 5-year survival rate for stage IV lung cancer is less than 10%[4]. Given the frequent absence of symptoms before locally advanced or metastatic deposit, and the aggressive and heterogeneous biological characteristics of the disease, clinical intervention is more effective in earlier stages of lung cancer. Advanced lung cancer is often accompanied by compressing, invading, high metastatic tendency, or paraneoplastic syndromes, thus resulting in poor survival prognosis[5]. Furthermore, advanced lung cancer may correlate with higher tumor mutation burden and genetic instability[6], and transformed cancer cells may use immune evasion approaches to create an immunosuppressive tumor

*These authors contributed equally to this work.
Correspondence to: Jianxing He and Wenhua Liang
E-mail: drjianxing.he@gmail.com and liangwh1987@163.com
ORCID ID: https://orcid.org/0000-0003-1737-8192 and
https://orcid.org/0000-0002-1391-8238

microenvironment and escape anti-tumor immunosurveillance[7]. Consequently, the tumor doubling time is shortened, thus leading to tumor progression and unsatisfactory treatment responses[7].

The 5-year survival rate of early stage lung cancer can be increased by 20%–30% through radical surgery, but approximately 85% of patients with lung cancer are diagnosed in advanced stages[4]. Although the available data on patients with small cell lung cancer are limited, the prognosis appears to be better when the disease is diagnosed at an early stage[8]. Therefore, early screening and diagnosis are the most effective approaches for improving long-term survival and are being actively explored. This review presents an overview of the current evidence and techniques for lung cancer screening, and explores feasible strategies for the early detection and diagnosis of lung cancer. We focus on the evidence for screening with low-dose computed tomography (LDCT) worldwide, the entry criteria for screening, and advances in differential diagnosis and treatment strategies for suspected malignancies.

The evolution of lung cancer screening approaches

Lung cancer screening began in the 1960s, with an aim to diagnose early-stage lung cancer and decrease lung cancer-related mortality. The most common methods used from the 1960s to the 1990s were chest X-ray and sputum cytology. The Mayo clinical trial was the first randomized controlled trial (RCT) focusing on high-risk populations (men 45 years or older who smoked at least 20 cigarettes per day in the prior year). All participants underwent a baseline chest X-ray and sputum cytologic examination, followed by chest X-ray and sputum cytology every 4 months in the screening arm, and yearly chest X-ray and sputum cytology in the control arm. Although more cancer cases were found in the screening groups, no difference in lung cancer deaths was observed between groups[9]. Subsequently, a series of studies examined chest X-ray screening alone or in combination with sputum cytology, but did not find a mortality benefit[10-12]. Given the relatively small sizes of the above trials, a lung study within the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial was performed to compare annual chest radiographic screening with usual care. Importantly, the PLCO trial screened for multiple cancers, and smoking history was not an inclusion criterion. At the 13-year follow-up, annual chest X-ray screening, compared with usual care, was not found to decrease lung cancer mortality[13,14].

Because of the low sensitivity of chest X-rays, the detection of lung cancer by computed tomography was first described and received substantial attention in the 1990s, and has subsequently been shown to be superior to chest X-rays in observational studies[15,16]. LDCT is a computed tomography technique that uses X-rays to create internal body images. The effective radiation dose in chest LDCT is approximately 1.5 mSv, which is 15 times higher than that of traditional chest radiography but less than one-quarter that of conventional chest CT[17]. LDCT has been demonstrated to be the only efficient and promising approach for lung cancer screening, on the basis of 2 independent, sufficiently powered RCTs[18,19].

Screening with LDCT

Evidence from the US and Europe

In 2011, results from the US-based National Lung Screening Trial (NLST) indicated a 20% decrease in lung cancer-related mortality after a median follow-up of 6.5 years in patients undergoing annual LDCT screening compared with scanning by radiography at the same frequency for 3 years[19]. Notably, a relative decrease of 6.7% (95% CI 1.2–13.6, $P = 0.02$) in all-cause mortality was also observed in the LDCT group[19]. In addition, several randomized trials of LDCT screening have been performed in Europe, with different recruitment strategies and numbers of screening rounds (**Table 1**). The only individual trial with a sufficient sample size to demonstrate a lung cancer mortality decrease is the Dutch–Belgian lung-cancer screening trial (NELSON)[18]. In 2020, Koning et al.[18] reported a rate of death due to lung cancer in men that was 24% lower in the screening arm than the control arm after 10 years. A meta-analysis of 7 trials, enrolling more than 84,000 patients with a history of smoking more than 15 pack-years, has indicated a cumulative lower lung cancer mortality in patients scanned with LDCT, with a risk ratio of 0.83 and a nonsignificant decrease in all-cause mortality of 4% with respect to other interventions[31]. This evidence suggests that people with a history of smoking benefit from screening. Hence, chest LDCT has been recommended as the standard screening approach for lung cancer in asymptomatic populations with high risk, in accordance with the National Comprehensive Cancer Network (NCCN), American Cancer Society (ACS), and US Preventive Services Task Force (USPSTF)[32-34].

Table 1 Selected lung cancer screening studies

Study	Interventions	Overall follow-up, years	Participants, n	Inclusion criteria	Primary outcome
NLST[19,20]	LDCT vs. CXR	7.4	53,454	Age 55–75 years, ≥30 pack-years, <10 years ex-smoker	LDCT decreased lung cancer-related mortality (HR = 0.80; P < 0.004)
NELSON[18,21,22]	LDCT vs. no intervention	10	15,789	Age 55–75 years, ≥15 pack-years, <10 years ex-smoker	LDCT decreased lung cancer-related mortality (HR = 0.76; 95% CI 0.62–0.94 in men)
DANTE[23,24]	LDCT vs. no intervention	8.35 (median)	2,811	Age 60–74 years, ≥20 pack-years, <10 years ex-smoker	A non-significant decrease was observed in lung cancer-related mortality (HR = 0.99)
DLCST[22,25,26]	LDCT vs. CXR	10	4,104	Age 50–70 years, ≥20 pack-years, <10 years ex-smoker	A non-significant decrease was observed in lung cancer-related mortality (HR = 1.03)
MILD[27,28]	LDCT vs. no intervention	10	4,099	Age ≥49 years, ≥20 pack-years, <15 years ex-smoker	LDCT decreased cumulative risk of 10-year lung cancer-related mortality (HR = 0.61; P = 0.02)
LUSI[29]	LDCT vs. no intervention	8.8 (median)	4,052	Age 50–69 years, ≥15 pack-years, <10 years ex-smoker	LDCT decreased lung cancer-related mortality only in women (HR = 0.31; P = 0.04)
UKLS[59,169]	LDCT vs. no intervention	10	4,055	Age 50–75 years, LLP_{v2}–defined 5-year lung cancer risk ≥5%	67% of stage I lung cancers were detected in the screening arm; mortality results to be published
ITALUNG[22,165,170,171]	LDCT vs. no intervention	8.5 (median)	3,206	Age 55–69 years, ≥20 pack-years, <10 years ex-smoker	A non-significant decrease was observed in lung cancer-related mortality (HR = 0.7)
DEPISCAN[30]	LDCT vs. CXR	4	765	Age 50–75 years, ≥15 pack-years, <15 years ex-smoker	LDCT enabled the detection of more lung cancers than CXR (8 vs. 1)
Beijing 1-ELCAP cohort[38]	LDCT	5	4,690	Age ≥40 years, without cancer history within 5 years	The diagnosis rate of lung cancer by LDCT was 76.0%, and most of the cancers were detected in an early stage
Shanghai ChestHosp RCT[41]	LDCT vs. usual care	2	6,717	Age 45–70 years, ≥20 pack-years, <15 years ex-smoker	LDCT led to a 74.1% increase in detection of early-stage lung cancer
Shanghai CancerHosp cohort[172]	LDCT	1	11,332	Age 50–80 years, ≥20 pack-years, <5 years ex-smoker	LDCT improved the early diagnosis rate of lung cancer in both smokers and nonsmokers

594

Li et al. Advances in lung cancer screening and early detection

Table 1 Continued

Study	Interventions	Overall follow-up, years	Participants, n	Inclusion criteria	Primary outcome
Shanghai-ChangzhengHosp cohort[43]	LDCT	2	14,506	Age >35 years, asymptomatic participants	The incidental detection rate for stage I lung cancer was 0.97%
Anti-Lung Cancer Association Project[173]	LDCT *vs.* CXR *vs.* sputum cytology	7	1,611	Age ≥40 years, asymptomatic participants	The proportions of positive tests were 9.1%, 2.6%, and 0.7% with low-dose helical CT, chest X-ray, and sputum cytology
Mass screening for lung cancer with mobile spiral computed tomography scanner[15,174]	LDCT	5	5,438	Age 40–74 years	The lung-cancer detection rate with CT was 0.48%, significantly higher than the 0.03%–0.05% for standard mass assessments previously performed in the same geographic area
Hitachi Employee's Health Insurance Group program[175]	LDCT	3	7,956	Age 50–69 years	The prevalence was 0.44% among all participants from baseline, and 0.07% from repeated screening
Hitachi lung cancer screening program[44]	LDCT *vs.* CXR	6	17,935	Aged 50–64 years, <30 pack-years	LDCT decreased lung cancer-related mortality (*HR* = 0.76; *P* < 0.001)
Samsung Medical Center program[176]	LDCT	5	6,406	Age ≥45 years, asymptomatic participants	LDCT helped detect early-stage lung cancer in an asymptomatic Korean population, with a detection rate of 0.36%
K-LUCAS Project[177]	LDCT	1	256	Age 55–75 years, ≥30 pack-years, <10 years ex-smoker	7.4% of participants exhibited positive findings

CI, confidence interval; CXR, chest X-ray; DANTE, Detection and screening of early lung cancer with novel imaging technology; DEPISCAN, french randomized pilot trial of lung cancer screening comparing low-dose CT scan and chest X-ray; DLCST, Danish lung cancer screening trial; HR, hazard ratio; ITALUNG, italian lung cancer screening trial; LDCT, low-dose computed tomography; LUSI, german lung cancer screening intervention; K-LUCAS, korean lung cancer screening; MILD, multi-centric Italian lung detection; NELSON, Dutch–Belgian randomized lung cancer screening trial; NLST, national lung screening trial; UKLS, UK lung cancer screening trial.

In addition, analysis of lung cancer incidence and mortality through the US Surveillance, Epidemiology, and End Results (SEER) and the Global Burden of Disease (GBD) database in recent years has indicated that the proportion of stage I in lung cancer in the US significantly increased after the broad clinical introduction of LDCT screening in 2002, when the NLST trial started[19]. In 2011, after LDCT was approved for lung cancer screening, the lung cancer-related mortality for stages I to III has undergone an average annual decline exceeding 10%, thereby indicating the value of CT screening in increasing overall lung cancer survival at the population level[35].

Evidence from Asia

Lung cancer is more common in women and non-smokers in Asia than in Europe and the US[36], thus indicating that the Asian population may require different lung cancer screening guidelines from those in Western countries. In China, prior studies have mainly included occupational populations for lung cancer screening with chest X-ray and/or sputum cytology[37]. One of the earliest lung cancer screening programs applying LDCT was launched in 2006, involving 4,690 asymptomatic participants in Beijing[38]. The International Early Lung Cancer Action Program (I-ELCAP) algorithm was used to follow up on initial abnormal LDCT scan findings, and 19 of the 25 cases were in stage I. These preliminary results suggested that LDCT can detect lung cancer in early stages[38]. Subsequently, national screening projects for both rural [rural China screening program (RuraCSP)] and urban [cancer Screening program in urban China (CanSPUC)] areas were launched in 2009 and 2012, respectively. However, because LDCT screening trials in China began relatively later than those in other countries, Netherlands-China Big-3 (NELCIN-B3) screening was established[39,40] to investigate the effectiveness of LDCT screening according to a volume-based protocol in the Chinese population. The results will be available in the near future.

Several screening trials funded by the municipal government, such as Shanghai, Guangzhou, in China have reported baseline results. In Shanghai, an LDCT-based lung cancer screening study including 6,717 participants has investigated whether LDCT screening might improve the early-stage lung cancer detection rate in Chinese patients with high-risk profiles[41]. In the 2-year follow-up period, lung cancer was found in 1.5% of patients who received LDCT screening, and LDCT, compared with usual care, resulted in 74.1% greater detection of early stage lung cancer[41]. In addition, according to a modeling study, LDCT-based screening of high-risk

people in Chinese urban areas resulted in 17.2% and 24.2% lower lung cancer-related mortality than did chest radiography-based screening and no screening, respectively[42]. Another LDCT-based screening study including 14,506 participants in Shanghai has reported a lung cancer detection rate of 1.23%, with a 0.97% incidental detection rate of stage I lung cancer[43], thus suggesting the potential benefits of decreased lung cancer morbidity and mortality. Of note, this cohort focused on asymptomatic residents with a minimum age of 35, regardless of risk factors[43].

In Japan, a population-based cohort study was performed in the Hitachi region, including participants 50–64 years of age with a smoking history of less than 30 pack-years[44]. The study demonstrated a lung cancer mortality benefit 24% (0.76, 95% CI 0.67–0.86, $P < 0.001$) above the average for all of Japan[44,45]. A significant decrease in standardized mortality was observed among screened female participants (0.74, 95% CI 0.56–0.97)[45]. Notably, more than 90% of female participants were non-smokers, thus indicating that LDCT-based screening can decrease lung cancer-related mortality in non-smokers and smokers[45]. In Korea, the National Korean Lung Cancer Screening Project (K-LUCAS), a single-arm trial of 256 high-risk patients, used the same inclusion criteria as the NLST[46]. With the lung imaging reporting and data system (Lung-RADS) algorithm, 10 nodules were classified as grade 3; 9 nodules were classified as grade 4; and 1 nodule was finally diagnosed as lung cancer[46].

Although LDCT-based lung cancer screening is increasing in Asia, the entry criteria for trials across countries have not used concordant definitions of high risk. Given the geographic and lifestyle differences across Asia, specific high-risk criteria must be proposed for different areas to improve the benefits of screening in the future. Moreover, implementing individual risk-based screening remains a major challenge that must be addressed.

Risk-based selection for screening

Previous epidemiological studies have indicated that a history of smoking[47,48], second-hand smoke exposure, or environmental oil smoke inhalation[49,50]; history of occupational carcinogen exposure[51]; family history of lung cancer[52,53]; history of cancer[54]; and history of lung diseases (chronic obstructive pulmonary disease, tuberculosis, or pulmonary fibrosis)[55-57] are closely associated with the incidence of lung cancer. However, Bach et al.[58] have indicated that LDCT screening might result in a 3-fold increase in lung cancer diagnosis and a 10-fold increase in lung cancer-related surgery accompanied

596

Li et al. Advances in lung cancer screening and early detection

by potential psychological and physical burden. To balance the benefits and potential harms with screening, the high-risk population must be precisely defined within the general population. Most screening trials in the US and Europe have defined the entry criteria for screening by a combination of age and smoking exposure[32]. The age eligibility has ranged from 40 years of age to no limit in most screening trials. The initial screening age of 55 recommended by NCCN, ACS, and USPSTF has been based primarily on the eligibility criteria for NLST since 2011[19]. The UK Lung Cancer Screening (UKLS) teams have suggested that screening eligibility in people at least 58 years of age would be reasonable, owing to the relatively sharp increase in lung cancer incidence at this age (1%–4.3%)[59]. However, because the appropriate age range for lung cancer screening remains a matter of debate in Asia, the starting screening age in trials conducted in Asia varies among countries (**Table 1**).

Several risk prediction models including multiple risk factors, such as smoking and age, have been developed to identify high-risk groups in recent years. For instance, the Liverpool Lung Project model (LLP)[60], Pan-Canadian Early Detection of Lung Cancer (PanCan)[61], and PLCO$_{2012}$[62] models have shown good diagnostic accuracy on the basis of patients' clinical characteristics, epidemiology, and social risk factors. The LLP model was developed from a case-control study in Liverpool, considering age, male sex, smoking duration, history of COPD, past diagnosis of malignant tumors, and family history of early-onset lung cancer (<60 years) as significant risk factors[60]. The UKLS RCT has applied the LLP model as an entry criterion and identified more lung cancer cases than NLST (1.7% *vs.* 1.03%) at baseline[59]. The PanCan model has used age, smoking duration, pack-years, family history of lung cancer, education level, body-mass index, chest X-ray in the prior 3 years, and history of chronic obstructive pulmonary disease as risk factors[61]. A retrospective study has indicated that the cumulative incidence according to the PanCan model is significantly higher than that in NLST[63]. The PLCO$_{2012}$ model includes age, race, socioeconomic status, BMI, history of COPD, history of cancer, family history of lung cancer, smoking status, and smoking cessation[62]. This model based on individual risk also has shown better diagnostic accuracy than entry criteria based on a combination of age and smoking exposure. Notably, the LLP model used in UKLS has been the only risk model used to select people in RCTs of lung cancer screening. In China, Guo et al.[64] have reported a risk model for selecting high-risk populations that includes age, sex,

smoking, history of tuberculosis, and history of emphysema, on the basis of data from CanSPUC; the C-index of the model has been found to be 0.741 in the validation set for 1-year lung cancer risk. Interestingly, another risk model consisting of 6 variables (age, sex, education level, tuberculosis, hyperlipidemia, and family history of lung cancer) for non-smokers has shown moderate predictive discrimination, with areas under the curve of 0.668, 0.678, and 0.685 for 1-, 3-, and 5-year lung cancer risk, respectively[40]. Risk prediction models may facilitate efficiency and decision-making in key steps in lung cancer screening. Nevertheless, because current evidence is insufficient to determine which models are most clinically beneficial, further clinical studies are needed to validate theoretical prediction.

To decrease the rate of missed lung cancer detection, Li et al.[65] have aimed to identify new lung cancer risk factors. A population-level analysis in 110,000 participants from 26 lung cancer screening studies has indicated that the proportion of stage I lung cancer among all lung cancer cases decreases with age, and is higher with screening at ages of 40 or 45 than 50 or 55. The findings suggest that a substantial number of cancer foci already exist in people between 40 and 50 years of age[65]. In addition, Peng et al.[66] have performed a comprehensive study combining meta-analysis with Mendelian randomization to determine risk factors causally related to the incidence of lung cancer. The study has revealed that systemic lupus erythematosus is associated with an elevated risk of lung cancer. Meanwhile, a mass screening targeted high-risk and non-high-risk patients over the age of 40 has been performed in Guangzhou, China (NCT04938804), to investigate lung cancer risk factors. In summary, participants at high risk may be identified with an individual risk prediction model combining epidemiological data and biomarkers (discussed below) to achieve maximum benefits in the future.

Advances in differential diagnosis of pulmonary nodules

The developments in lung cancer screening and LDCT have increased the rate of detection of small pulmonary nodules[67]. However, malignant nodules usually lack specific manifestations in LDCT. Differentiating lung cancer (such as minimally invasive adenocarcinoma or minimally invasive adenocarcinoma) from atypical adenomatous hyperplasia and other benign nodules is challenging. Therefore, the ability to accurately detect and diagnose malignant nodules will decrease

the cost of additional examinations and the risk of missing malignant nodules, thus enabling early lung cancer treatment. Furthermore, because of the potential harms of LDCT (as discussed previously), an urgent clinical need exists to develop non-invasive approaches to improve screening accuracy for high-risk patients.

Artificial intelligence (AI)-based screening

AI has played a crucial role in malignant nodule screening and computer-aided diagnosis with advances in medical imaging and the development of deep neural network learning methods. Ding et al.[68] have developed a modified Faster R-CNN (based on Region-Based Convolutional Neural Network) for the detection of malignant pulmonary nodules with a true positive rate of 94.60%. Nasrullah et al.[69] have designed a Faster R-CNN with customized mixed link network (CMixNet) and U-Net-like encoder-decoder architecture for nodule detection. This system yields an average of 8 false positives per scan and a true positive rate of 94.21%. Khosravan et al.[70] have applied a 3D CNN called S4ND based on the Single-Shot Single-Scale lung Nodule Detection system to detect lung nodules without further processing, with a true positive rate of 95.20%. Another team has designed Deep 3D Dual Path Nets (3D DPN26) with 3D Faster R-CNN and achieved a true positive rate of 95.80% with high sensitivity[71].

Automatically detected lung nodules must be diagnosed to determine whether they are benign or malignant. Ren et al.[72] have developed a manifold regularized classification deep neural network (MRC-DNN) to automatically determine benign malignancy with an accuracy of 90.00%. Hussein et al.[73] have used a standard 3D CNN architecture to evaluate the characteristics of different nodules, including calcification, lobulation, sphericity, speculation, margin, and texture, and then generate the malignant score of the nodules with an accuracy of 91.26%. Kang et al.[74] have designed 3D multi-view CNN (MV-CNN) based on 3D Inception and 3D Inception-ResNet architectures. This system allows nodules to be divided into benign and malignant groups. Experiments performed on an LIDC-IDRI dataset with 10-fold cross-validation have indicated an accuracy of 95.25%[74]. At present, the problems of automatic detection and diagnosis of lung nodules have not been completely solved, and include overfitting, a lack of interpretability, and insufficient annotation data. In addition, because this is an emerging field, these models still lack standardization approaches, and their comparability and replicability are also worthy of consideration. Fortunately, the demand for early detection of lung cancer has promoted the development of AI, which is expected to make lung cancer screening more accurate and commonly used.

Biomarkers for screening

A useful biomarker in lung cancer screening should enable clinical decision-making, aid in early diagnosis, and improve risk stratification. The application of biomarkers to predict the diagnosis of malignant nodules must not increase the number of diagnostic procedures for benign nodules or delay the treatment for malignancy[75]. Blood-derived biomarkers may serve as primary and metastatic lesions to better characterize tumor heterogeneity; therefore, blood has been the preferred source of biomarker candidates. In addition, bronchial lavage, exhaled breath, saliva, and urine are potential sources of biomarkers for lung and other respiratory tract cancers. Of note, most biomarkers are currently in development and clinical validation, and few currently available biomarkers have been demonstrated to decrease lung cancer-related mortality.

ctDNA and ctDNA methylation

To date, technologies such as next-generation sequencing technology (NGS) have markedly decreased the limits of detection and promoted the clinical utility of ctDNA screening[76,77]. Although its levels are low in early-stage lung cancer, ctDNA can be detected before treatment in most patients[78]. Newman et al.[79] have developed a method based on CAPP-Seq for NSCLC, with a sensitivity of 100% for patients with stage II–IV cancer and 50% for patients with stage I cancer. Through targeted error correction sequencing (TEC-Seq) using massively parallel sequencing, Phallen et al.[80] have reported a sensitivity of 59% for patients with stage I or II lung cancer. However, these detection methods might decrease the specificity, owing to the presence of mutated genes in noncancerous tissue. Recently, a machine learning approach called DELFI has been used to detect abnormalities in cfDNA through genome-wide analysis of fragmentation patterns for various cancer types[81]. DELFI has detected 94% of patients with cancer across stages and subtypes, with a sensitivity of 91% for stage I or II, and 96% for stage III or IV, and a high specificity of 80%[82].

Cancer is often characterized by hypermethylation of promoters at specific CpG sites associated with tumor suppressor genes[83]. The GRAIL method combines bisulfite sequencing and machine learning to read methylated DNA sequences and has shown high specificity across many cancers[84]. Observational cohort studies and an interventional

598

Li et al. Advances in lung cancer screening and early detection

study have assessed the performance of targeted methylation analysis of cfDNA to detect and localize multiple cancer types[85-87]. The preliminary trials have indicated a specificity of 99.3% (95% CI, 98.3%–99.8%) across all stages[88]. The stage I–III sensitivity has been found to be 67.3% (95% CI, 60.7%–73.3%) in a pre-specified set of 12 cancer types[88]. The recently published results of the Circulating Cell-free Genome Atlas Study (CCGA) have indicated a specificity for cancer signal detection of 99.5% (95% CI, 99.0%–99.8%)[89]. The overall sensitivity for cancer signal detection was 51.5% (49.6%–53.3%), and the stage I–III sensitivity was 67.6% (64.4%–70.6%) in 12 pre-specified cancers[89]. Lung cancer data are expected to be released in the future. In China, Liang et al.[90] have developed a diagnostic model based on targeted DNA methylation sequencing, which has 80% accuracy in the discrimination of benign and malignant lung nodules at different stages of cancer, outperforming the PET-CT, Mayo Clinic, and Veterans Affairs prediction models[91]. Selected clinical trials using liquid biopsy for cancer screening are summarized in **Table 2**.

Autoantibodies

Tumor-associated antigens are usually abnormal proteins expressed as a result of genetic changes in tumor cells or intracellular proteins after necrosis or apoptosis[92,93]. Through an early amplification signal in auto-antibody levels produced during the immune sensing phase, early-stage lung cancer can be detected even in vessel-free tumors[94]. In the Mayo Lung Screening Trial and Kentucky Lung Screening Trial, Trudgen et al.[95] have demonstrated that antibodies can identify 50% of occult cancers as early as 5 years before diagnosis.

The EarlyCDT-Lung trial developed a panel to measure autoantibodies to 7 cancer-associated antigens (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, HuD, and MAGE A4)[94] with a sensitivity of 41% in early stages[96]. The UK NIH has conducted an RCT called Early Diagnosis of Lung Cancer Scotland (ECLS), including 12,208 participants at high risk of developing lung cancer[97]. The intervention arm received the EarlyCDT-Lung test followed by LDCT scanning every 6-months for up to 2 years if positive or received standard clinical care as a control if negative. After 2 years, the hazard ratio for stage III/IV presentation was 0.64 (95% CI 0.41–0.99)[97]. In the German Lung Cancer Screening Intervention Trial (LUSI), EarlyCDT-Lung showed similar effectiveness[98]. Through use of different combinations of biomarkers, autoantibodies may achieve a balance of sensitivity and specificity[99-102]. Because

of significant differences in genetic variation among patients with lung cancer in Europe and Asia, a 7-AAB panel has been developed and approved in China, with a sensitivity of 59%–64% in NSCLC patients[103]. Because the autoantibody test's relatively low sensitivity suggests that it is not useful when performed alone for lung cancer diagnosis, it must be combined with another test. When combined with CT or miRNA, the 7-AAB panel has been found to improve the diagnosis of lung cancer and nodules[104-106], but to be accompanied by a high number of false-positive results[107]. This finding might be due to mutations from normal somatic cells inducing immunity and autoantibody production[108].

Circulating tumor cells (CTCs)

CTCs are active tumor cells in the peripheral blood originating from the primary tumor or metastatic deposits. Even early-stage primary tumors can shed CTCs throughout their development, thus providing a sensitive method for tumor screening[109]. Li et al.[110] have found that CTC frequencies vary between patients with lung cancer and healthy control volunteers or patients with benign lung disease, and have reported an area under the receiver operating characteristic curve in the control group of 0.846 (95% CI 0.796–0.887, $P < 0.001$). The positivity rate of CTC in patients with lung cancer was 68.29% when the CTC cutoff value was 2[110]. Wei et al.[111] have found that the numbers of CTCs in patients with NSCLC vary according to the cancer stages and genetic mutations. A prospective study called the AIR Project was conducted in 21 French university centers to determine the value of CTCs in the early detection of lung cancer. Approximately 600 participants underwent yearly LDCT screening and peripheral blood sampling for CTC detection for 3 years plus a 1-year follow-up[112]. The preliminary results indicated that when both CNHC-malignant and CNHC-uncertain were considered positive results, the sensitivity and specificity of CTCs as a biomarker for lung cancer detection were 26.3% (95% CI 11.8–48.8) and 96.2% (95% CI 94.4–97.5) at baseline[113]. Furthermore, a meta-analysis of 21 studies with 3,997 participants has assessed the overall diagnostic accuracy and reported a pooled sensitivity and specificity of 0.72 (95% CI 0.65–0.79) and 0.96 (95% CI 0.91–0.98), thus indicating that CTCs also perform well in the diagnosis of lung cancer[114].

Several studies have analyzed the feasibility of combining LDCT screening with CTC, aiming to compensate for the technical shortcomings of LDCT alone. One study has applied CTC testing in 32 patients with ground-glass nodules selected

Table 2 Clinical trials evaluating the potential applications of ctDNA in lung cancer screening

Identifier	Methods	Initiator	Study type	Estimated enrollment, n	Observational model	Time perspective	Status/results
NCT04814407	ctDNA methylation EMS-ddPCR scLSM-FACS	Taiwan University Hospital	Observational	900	Cohort	Prospective	Recruiting; estimated study completion date is December 31, 2027
NCT04712877	Genetic mutations NGS	Lung Cancer Research Foundation	Observational	1,000	Cohort	Prospective	Not yet recruiting; estimated study completion date is November 1, 2023
NCT03651986	ctDNA methylation NGS	AnchorDx Medical Co., Ltd.	Observational	10,560	Cohort	Prospective	Recruiting; estimated study completion date is June 2023
NCT04253509	ctDNA methylation sequencing	Samsung Medical Center	Observational	280	Cohort	Prospective	Recruiting; estimated study completion date is February 2022
NCT03685569	ctDNA methylation biomarkers	Shanghai Chest Hospital	Observational	300	Cohort	Cross-Sectional	Recruiting; estimated study completion date is December 2019
NCT04698681	Genetic mutations NGS	Calithera Biosciences. Inc	Interventional Clinical Trial	200	Single group assignment	Prospective	Active, not recruiting; estimated study completion date is May 2022
NCT03181490	ctDNA methylation, high-throughput bisulfite DNA sequencing, NGS	The First Affiliated Hospital of Guangzhou Medical University	Observational	1,490	Cohort	Cross-Sectional	Completed; detected early-stage lung cancer and differentiated lung cancers from benign pulmonary nodules
NCT02612350	ctDNA genetic mutations	Pathway Genomics	Observational	1,106	Cohort	Prospective	Completed; provided a new way to investigate screening utility

ctDNA, circulating tumor DNA; EMS-ddPCR, enriched methylation-specific droplet digital PCR; scLSM-FACS, single-cell, locus-specific methylation detection.

600

Li et al. Advances in lung cancer screening and early detection

on the basis of LDCT screening and has identified cancer-related gene mutations in positive patients[99]. Another study has indicated that CTC numbers differ among high-risk LDCT screened patients, patients with NSCLC, and healthy people[115]. However, validation of CTCs in a large-scale prospective trial has been hindered by the lack of a standardized test, thus making the results difficult to compare[116]. Although CTC testing has become more widely used in early lung cancer screening, owing to technological innovations, this method is mainly used to predict metastasis and prognosis, and perform drug modeling[117-120].

microRNAs (miRNAs)

miRNAs are short, non-coding, stable RNA sequences that regulate gene expression post-transcriptionally. Tumor-secreted miRNAs are detectable in the circulating blood[121]. Wang et al.[122] have reported a pooled sensitivity and specificity of 0.75 and 0.7 for of miRNAs as biomarkers for NSCLC detection. The miR-test is a serum-based miRNA test that measures a signature of 13 miRNAs[123]. A large-scale validation study in more than 1,000 high-risk patients has reported an overall accuracy, sensitivity, specificity, and area under the curve of the miR-test of 74.9% (95% CI 72.2%–77.6%), 77.8% (95% CI 64.2%–91.4%), 74.8% (95% CI 72.1%–77.5%), and 0.85 (95% CI 0.78–0.92), respectively[123]. Another test, micro-RNA signature classifier (MSC), is a plasma-based miRNA test that categorizes patients into low, intermediate, or high risk of disease on the basis of pre-defined positivity for 24 miRNA expression ratios[124], with a sensitivity of 87% and specificity of 81% across both arms, and a sensitivity of 88% and specificity of 80% in the LDCT arm[124]. Furthermore, Fehlmann et al.[125], in Germany, have used genome-wide microRNA profiles from blood samples to identify patients with lung cancer. This multicenter cohort study in 3,102 patients from case-control and cohort studies has reported 91.4% accuracy, 82.8% sensitivity, and 93.5% specificity[125]. Nevertheless, application of this method in clinical practice faces many barriers posed by the technical issues remaining to be solved. For instance, detailed validation of the pre-analytical steps affecting miRNA detection and quantification is critical. A valid method for the normalization results is greatly needed[126]. Moreover, circulating miRNAs do not show specificity for a type of cancer—a matter of particular concern.

Circulating protein profiling

Previous studies have shown that antigen 125 (CA125), cytokeratin-19 fragment (CYFRA 21-1), and carcinoembryonic antigen (CEA) are useful for the diagnosis of lung cancer[127-129]. However, data on these markers are limited, and their diagnostic efficacy is not high. Li et al. have proposed a 13-protein blood-based classifier with a negative predictive value of 90%[130]. A panel including 3 serum proteins (CEA, CA125, and CYFRA 21-1) and an AAb has shown 71% sensitivity and 88% specificity for lung cancer in a high-risk population[131]. Lower sensitivity (49%) but higher specificity (96%) has been reported in an independent validation cohort[132]. A four-marker protein panel (4MP) containing the precursor form of surfactant protein B, CA125, CEA, and CYFRA 21-1 has resulted in an area under the receiver operating characteristic curve of 0.79 (95% CI, 0.77–0.82). In combination with a risk prediction model (PLCOm2012), the sensitivity of 4MP can be substantially improved, by 11.9%[133].

Volatile organic compounds

Volatile organic compounds are organic compounds with a high vapor pressure at room temperature, which show distinct patterns according to pathological state and are affected by the modification of proteins in various cellular processes. After production, volatile organic compounds are excreted into the blood, enter the lungs, and are exhaled[134], at which point they can be tested and analyzed. Breath condensate analysis can be used to evaluate the presence of aldehydes, peroxide, leukotriene, cytokines, and adenosine, which are essential biomarkers of several different diseases, including lung cancer[135]. A previous study has reported a sensitivity of 94.2% and a specificity of 49.0% in lung cancer diagnosis based on exhaled-breath data combined with clinical parameters[136]. Although the diagnostic accuracy of exhaled-breath analysis for lung cancer has shown potential, a consensus is lacking regarding the normal reference range.

Other potential sources of biomarkers

DNA polymorphisms[137], chromosomal abnormalities[138], tumor-educated platelets[139,140], extracellular vesicles[141], bacterial biomarkers[142], complement fragments[143], urine metabolites[144], and cytological analytes[145] have also been proposed as potential biomarkers for lung cancer screening. However, the diagnostic potential of these biomarkers for lung cancer must be further evaluated, because the prospective evidence is limited. Combining these potential clinical biomarkers with radiological features, machine learning, and predictive models may improve the detection in screening of asymptomatic high-risk patients and help discriminate between benign and malignant nodules in the future.

Exploration of treatment strategies for suspected malignancy

Guidelines and consensus statements have been released for the diagnosis and management of pulmonary nodules as the positivity rate of lung cancer screening increases rapidly. To date, surgery remains the best strategy for patients with strong clinical suspicion for stage I or II lung cancer[146]. The non-intubated approach is a promising thoracic procedure for GGNs and early-stage lung cancer, providing a safe, beneficial, less invasive alternative to intubated VATS, and enabling significantly shorter hospital stays[147]. During the spontaneous ventilation video-assisted thoracic surgery (SV-VATS) procedure, intraoperative intubation, post-operative chest tube placement, and urinary catheterization are avoided, thereby simplifying the surgical steps, decreasing patients' post-operative discomfort, and enabling faster recovery[148].

However, patients may be ineligible for surgery because of comorbidities, poor physical conditions, or poor pulmonary function[149]. Hence, identifying alternative strategies is crucial. In contrast to conventional radiotherapy, stereotactic body radiation therapy (SBRT) has become the predominant local therapeutic alternative to surgical resection. A pooled analysis of 2 early-terminated prospective trials comparing SBRT with surgery has reported promising results, including 15% greater OS with SBRT[150]. In addition, SBRT has been found to perform well in multiple primary lung cancers (MPLCs)[151,152]. Moreover, combing SBRT and PD-1/PD-L1 inhibitors has shown promise in early-stage NSCLC[153]. Thermal ablation (TA) was introduced to manage pulmonary nodules around the year of 2000. As a stand-alone technique, TA uses single or multiple percutaneous needles to deliver energy that heats or freezes the target area, thus causing necrosis of the target tissue[154]. Yamauchi et al.[155] have conducted the first analysis focusing on cryoablation in patients with medically inoperable stage I NSCLC with tumor sizes mostly less than 2 cm, and reported OS rates of 88% at 2 years and 88% at 3 years. Although TA shows promise, some limitations exist. Contraindications include severe underlying interstitial lung diseases, such as pulmonary fibrosis, severe emphysema, and tumors less than 1 cm from the hilum[156].

Beyond the treatments described above, the possibility of using agents to cure early-stage lung cancer is under investigation. With the adoption of lung cancer screening programs, patients with MPLCs are becoming a growing population in clinical practice worldwide[157]. Post-operative EGFR-TKIs have been found to have efficacy in unresected persistent GGO lesions in patients with MPLC who underwent resection of at least one EGFR-mutated lesion[158]. This observation has also been validated in KRAS-mutated lesions. Targeted therapy has therefore been suggested to serve as an alternative approach to treat MPLCs[159]. Moreover, a phase II trial has confirmed that sintilimab, an antibody to PD-1, has immune-related antitumor activity in GGO-featured lung cancer and is well tolerated among patients with early stage lung cancer[160].

Challenges in lung cancer screening and future directions

Although lung cancer screening through LDCT has meaningful clinical utility, broad concerns regarding its harm to patients have been raised, including false-positive screens, overdiagnosis, and radiation exposure. More than half of all pulmonary nodules are small, benign, and noncalcified[161]. Identifying cancers from false-positive results and preventing overdiagnosis in screening are challenging. NLST has set a positive cut-off threshold of at least 4 mm for any noncalcified nodule, thus leading to a 28.7% false-positive screening rate[162]. Patients may undergo unnecessary invasive examination and treatment because of overdiagnosis. According to an observational study, the LDCT overdiagnosis rate is 13%–27%[163,164]. Given the low specificity of LDCT, this method is currently considered to distinguish benign from malignant lesions through regular follow-up or in combination with other examination methods. Paci et al. have reported a low rate of overdiagnosis after an adequate follow-up period, thus indicating that overdiagnosis can be decreased through adherence to nodule management protocols[165]. The radiation exposure associated with screening is a matter of concern. The cumulative radiation from repeated CT scanning may independently increase the risk of radiation-related cancer[166]. However, some studies have indicated that the radiation of <100 mSv is negligible to the human body. In a secondary analysis based on an LDCT screening program for asymptomatic high-risk smokers 50 years of age or older who were scanned at least once per year[167], the estimated median cumulative effective radiation dose after 10 years of screening was 13.0 mSv for women and 9.3 mSv for men[168]. In addition, other critical clinical questions presented in this review, such as risk-based selection of high-risk patients, nodule management, screening intervals, screening duration, and the standard for diagnosis and

identification of malignant lesions, remain to be answered in the future.

Conclusions

Screening with LDCT provides an opportunity to decrease mortality from lung cancer. With the identification of risk factors and optimization of entry criteria, the application of methods with high diagnostic accuracy, and the development of therapeutic strategies, the clinical benefits of early screening and diagnosis in people with lung cancer will further improve. Simultaneously, liquid biopsies are receiving substantial attention in cancer diagnosis as non-invasive, accurate, and predictive tools. These developments together promote the exploration and development of treatment strategies for detected and suspected malignancies, with the aim of optimizing clinical management and improving the prognosis of cancer patients.

Grant support

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Group leaders: Jianxing He and Wenhua Liang; writers of the consensus: Caichen Li, Huiting Wang, and Yu Jiang; secretaries: Wenhai Fu, Xiwen Liu, Ran Zhong, Bo Cheng, Feng Zhu, and Yang Xiang

References

1. Sung H, Ferlay J, Siegel RL, Soerjomataram I, Torre LA, Jemal A. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71: 209-49.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015; 65: 5-29.

3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020; 70: 7-30.

4. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016; 11: 39-51.

5. Molina JR, Adjei AA, Jett JR. Advances in chemotherapy of non-small cell lung cancer. Chest. 2006; 130: 1211-9.

6. Dudley JC, Lin MT, Le DT, Eshleman JR. Microsatellite instability as a biomarker for PD-1 blockade. Clin Cancer Res. 2016; 22: 813-20.

7. Beatty GL, Gladney WL. Immune escape mechanisms as a guide for cancer immunotherapy. Clin Cancer Res. 2015; 21: 687-92.

8. Chute JP, Chen T, Feigal E, Simon R, Johnson BE. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. J Clin Oncol. 1999; 17: 1794-801.

9. Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR. Lung cancer screening: the Mayo program. J Occup Med. 1986; 28: 746-50.

10. Kubik A, Polak J. Lung cancer detection. Results of a randomized prospective study in Czechoslovakia. Cancer. 1986; 57: 2427-37.

11. Frost JK, Ball WC, Jr., Levin ML, Tockman MS, Baker RR, Carter D, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. Am Rev Respir Dis. 1984; 130: 549-54.

12. Melamed MR, Flehinger BJ, Zaman MB, Heelan RT, Perchick WA, Martini N. Screening for early lung cancer. Results of the Memorial Sloan-Kettering study in New York. Chest. 1984; 86: 44-53.

13. Oken MM, Hocking WG, Kvale PA, Andriole GL, Buys SS, Church TR, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA. 2011; 306: 1865-73.

14. Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, et al. European position statement on lung cancer screening. Lancet Oncol. 2017; 18: e754-66.

15. Sone S, Takashima S, Li F, Yang Z, Honda T, Maruyama Y, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet. 1998; 351: 1242-5.

16. Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology. 1996; 201: 798-802.

17. Safety PJACRRSNAA. Radiation Dose in X-Ray and CT Exams. 2012; 2013: 2.

18. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl Med. 2020; 382: 503-13.

19. The National Lung Screening Trial Research Team. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. The National Lung Screening Trial Research Team. N Engl J Med. 2011; 365: 395-409.

20. National Lung Screening Trial Research Team. Aberle DR, Adams AM, Berg CD, Clapp JD, Clingan KL, Gareen IF, et al. Baseline

characteristics of participants in the randomized national lung screening trial. J Natl Cancer Inst. 2010; 102: 1771-9.

21. Yousaf-Khan U, van der Aalst C, de Jong PA, Heuvelmans M, Scholten E, Lammers JW, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. Thorax. 2017; 72: 48-56.

22. Huang KL, Wang SY, Lu WC, Chang YH, Su J, Lu YT. Effects of low-dose computed tomography on lung cancer screening: a systematic review, meta-analysis, and trial sequential analysis. BMC Pulm Med. 2019; 19: 126.

23. Infante M, Cavuto S, Lutman FR, Passera E, Chiarenza M, Chiesa G, et al. Long-term follow-up results of the DANTE trial, a randomized study of lung cancer screening with spiral computed tomography. Am J Respir Crit Care Med. 2015; 191: 1166-75.

24. Infante M, Lutman FR, Cavuto S, Brambilla G, Chiesa G, Passera E, et al. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. Lung Cancer. 2008; 59: 355-63.

25. Pedersen JH, Ashraf H, Dirksen A, Bach K, Hansen H, Toennesen P, et al. The Danish randomized lung cancer CT screening trial-- overall design and results of the prevalence round. J Thorac Oncol. 2009; 4: 608-14.

26. Wille MM, Dirksen A, Ashraf H, Saghir Z, Bach KS, Brodersen J, et al. Results of the randomized Danish lung cancer screening trial with focus on high-risk profiling. Am J Respir Crit Care Med. 2016; 193: 542-51.

27. Pastorino U, Silva M, Sestini S, Sabia F, Boeri M, Cantarutti A, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial: new confirmation of lung cancer screening efficacy. Ann Oncol. 2019; 30: 1672.

28. Pastorino U, Rossi M, Rosato V, Marchianò A, Sverzellati N, Morosi C, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev. 2012; 21: 308-15.

29. Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA, et al. Lung cancer mortality reduction by LDCT screening-Results from the randomized German LUSI trial. Int J Cancer. 2020; 146: 1503-13.

30. Blanchon T, Brechot JM, Grenier PA, Ferretti GR, Lemarie E, Milleron B, et al. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). Lung Cancer. 2007; 58: 50-58.

31. Sadate A, Occean BV, Beregi J-P, Hamard A, Addala T, de Forges H, et al. Systematic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography. Eur J Cancer. 2020; 134: 107-14.

32. Wood DE, Kazerooni EA, Baum SL, Eapen GA, Ettinger DS, Hou L, et al. Lung cancer screening, version 3.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018; 16: 412-41.

33. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. Cancer screening in the United States, 2019: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2019; 69: 184-210.

34. Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 160: 330-38.

35. Liang W, Liu J, He J. Driving the improvement of lung cancer prognosis. Cancer Cell. 2020; 38: 449-51.

36. Cheng Y, Davies M, Liu D, Li W, Field J. Implementation planning for lung cancer screening in China. Precis Clin Med. 2019; 2: 13-44.

37. Gao G, Yao S, Sun X, Chang R, Jiang Y, Luo X et al. [Establishment of cohort to study lung cancer in Yunnan tin miners]. Zhongguo Fei Ai Za Zhi. 2002; 5: 87-91.

38. Tang W, Wu N, Huang Y, Wang J, Zhao S, Xu Z, et al. [Results of low-dose computed tomography (LDCT) screening for early lung cancer: prevalence in 4 690 asymptomatic participants]. Zhonghua Zhong Liu Za Zhi. 2014; 36: 549-54.

39. Du Y, Zhao Y, Sidorenkov G, de Bock GH, Cui X, Huang Y, et al. Methods of computed tomography screening and management of lung cancer in Tianjin: design of a population-based cohort study. Cancer Biol Med. 2019; 16: 181-8.

40. Guo LW, Lyu ZY, Meng QC, Zheng LY, Chen Q, Liu Y, et al. Construction and validation of a lung cancer risk prediction model for non-smokers in China. Front Oncol. 2021; 11: 766939.

41. Yang W, Qian F, Teng J, Wang H, Manegold C, Pilz LR, et al. Community-based lung cancer screening with low-dose CT in China: results of the baseline screening. Lung Cancer. 2018; 117: 20-6.

42. Wang Z, Han W, Zhang W, Xue F, Wang Y, Hu Y, et al. Mortality outcomes of low-dose computed tomography screening for lung cancer in urban China: a decision analysis and implications for practice. Chin J Cancer. 2017; 36: 57.

43. Fan L, Wang Y, Zhou Y, Li Q, Yang W, Wang S, et al. Lung cancer screening with low-dose CT: baseline screening results in Shanghai. Acad Radiol. 2019; 26: 1283-91.

44. Nawa T, Fukui K, Nakayama T, Sagawa M, Nakagawa T, Ichimura H, et al. A population-based cohort study to evaluate the effectiveness of lung cancer screening using low-dose CT in Hitachi city, Japan. Jpn J Clin Oncol. 2019; 49: 130-6.

45. Sagawa M, Sugawara T, Ishibashi N, Koyanagi A, Kondo T, Tabata T. Efficacy of low-dose computed tomography screening for lung cancer: the current state of evidence of mortality reduction. Surg Today. 2017; 47: 783-8.

46. Lee J, Lim J, Kim Y, Kim HY, Goo JM, Lee CT, et al. Development of protocol for Korean lung cancer screening project (K-LUCAS) to evaluate effectiveness and feasibility to implement national cancer screening program. Cancer Res Treat. 2019; 51: 1285-94.

47. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, et al. Annual report to the nation on the status of cancer, 1975-2014, featuring survival. J Natl Cancer Inst. 2017; 109: djx030.

48. Centers for Disease Control and Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 2000-2004. MMWR Morb Mortal Wkly Rep. 2008; 57: 1226-8.

49. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta (GA), 2006.

50. Asomaning K, Miller DP, Liu G, Wain JC, Lynch TJ, Su L, et al. Second hand smoke, age of exposure and lung cancer risk. Lung Cancer. 2008; 61: 13-20.

604

Li et al. Advances in lung cancer screening and early detection

51. Markowitz SB, Dickens B. Screening for occupational lung cancer: an unprecedented opportunity. Clin Chest Med. 2020; 41: 723-37.

52. Mayne ST, Buenconsejo J, Janerich DT. Familial cancer history and lung cancer risk in United States nonsmoking men and women. Cancer Epidemiol Biomarkers Prev. 1999; 8: 1065-69.

53. Gorlova OY, Zhang Y, Schabath MB, Lei L, Zhang Q, Amos CI, et al. Never smokers and lung cancer risk: a case-control study of epidemiological factors. Int J Cancer. 2006; 118: 1798-804.

54. Wu GX, Nelson RA, Kim JY, Raz DJ. Non-small cell lung cancer as a second primary among patients with previous malignancy: who is at risk? Clin Lung Cancer. 2017; 18: 543-50 e543.

55. Mayne ST, Buenconsejo J, Janerich DT. Previous lung disease and risk of lung cancer among men and women nonsmokers. Am J Epidemiol. 1999; 149: 13-20.

56. Brenner AV, Wang Z, Kleinerman RA, Wang L, Zhang S, Metayer C, et al. Previous pulmonary diseases and risk of lung cancer in Gansu Province, China. Int J Epidemiol. 2001; 30: 118-24.

57. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am J Respir Crit Care Med. 2000; 161: 5-8.

58. Bach PB, Jett JR, Pastorino U, Tockman MS, Swensen SJ, Begg CB. Computed tomography screening and lung cancer outcomes. JAMA. 2007; 297: 953-61.

59. Field JK, Duffy SW, Baldwin DR, Whynes DK, Devaraj A, Brain KE, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. Thorax. 2016; 71: 161-70.

60. Raji OY, Duffy SW, Agbaje OF, Baker SG, Christiani DC, Cassidy A, et al. Predictive accuracy of the Liverpool Lung Project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. Ann Intern Med. 2012; 157: 242-50.

61. Tammemagi MC, Schmidt H, Martel S, McWilliams A, Goffin JR, Johnston MR, et al. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study. Lancet Oncol. 2017; 18: 1523-31.

62. Tammemagi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, et al. Selection criteria for lung-cancer screening. N Engl J Med. 2013; 368: 728-36.

63. Ten Haaf K, Jeon J, Tammemagi MC, Han SS, Kong CY, Plevritis SK, et al. Risk prediction models for selection of lung cancer screening candidates: a retrospective validation study. PLoS Med. 2017; 14: e1002277.

64. Guo L, Lyu Z, Meng Q, Zheng L, Chen Q, Liu Y, et al. A risk prediction model for selecting high-risk population for computed tomography lung cancer screening in China. Lung Cancer (Amsterdam, Netherlands) 2022; 163: 27-34.

65. Li C, Liang H, Zhong N, He J, Liang W. Optimal starting age for lung cancer screening with low-dose computed tomography: a population level analysis. J Thorac Oncol. 2019; 14: e82-4.

66. Peng H, Li C, Wu X, Wen Y, Lin J, Liang H, et al. Association between systemic lupus erythematosus and lung cancer: results from a pool of cohort studies and Mendelian randomization analysis. J Thorac Dis. 2020; 12: 5299-302.

67. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013; 369: 910-19.

68. Ding J, Li A, Hu Z, Wang L. Accurate pulmonary nodule detection in computed tomography images using deep convolutional neural networks. International Conference on Medical Image Computing and Computer-Assisted Intervention: Springer; 2017: 559-67.

69. Nasrullah N, Sang J, Alam MS, Mateen M, Cai B, Hu H. Automated lung nodule detection and classification using deep learning combined with multiple strategies. Sensors (Basel). 2019; 19: 3722.

70. Khosravan N, Bagci U. S4ND: Single-shot single-scale lung nodule detection. International Conference on Medical Image Computing and Computer-Assisted Intervention: Springer; 2018: 794-802.

71. Zhu W, Liu C, Fan W, Xie X. Deeplung: Deep 3D dual path nets for automated pulmonary nodule detection and classification. 2018 IEEE Winter Conference on Applications of Computer Vision (WACV): IEEE; 2018: 673-81.

72. Ren Y, Tsai MY, Chen L, Wang J, Li S, Liu Y, et al. A manifold learning regularization approach to enhance 3D CT image-based lung nodule classification. Int J Comput Assist Radiol Surg. 2020; 15: 287-95.

73. Hussein S, Cao K, Song Q, Bagci U. Risk stratification of lung nodules using 3D CNN-based multi-task learning. International conference on information processing in medical imaging: Springer; 2017: 249-60.

74. Kang G, Liu K, Hou B, Zhang N. 3D multi-view convolutional neural networks for lung nodule classification. PLoS One. 2017; 12: e0188290.

75. Seijo LM, Peled N, Ajona D, Boeri M, Field JK, Sozzi G, et al. Biomarkers in lung cancer screening: achievements, promises, and challenges. J Thorac Oncol. 2019; 14: 343-57.

76. García-Saenz JA, Ayllón P, Laig M, Acosta-Eyzaguirre D, García-Esquinas M, Montes M, et al. Tumor burden monitoring using cell-free tumor DNA could be limited by tumor heterogeneity in advanced breast cancer and should be evaluated together with radiographic imaging. BMC Cancer. 2017; 17: 210.

77. Sausen M, Phallen J, Adleff V, Jones S, Leary RJ, Barrett MT, et al. Clinical implications of genomic alterations in the tumour and circulation of pancreatic cancer patients. Nat Commun. 2015; 6: 7686.

78. Chabon JJ, Hamilton EG, Kurtz DM, Esfahani MS, Moding EJ, Stehr H, et al. Integrating genomic features for non-invasive early lung cancer detection. Nature. 2020; 580: 245-51.

79. Newman AM, Bratman SV, To J, Wynne JF, Eclov NCW, Modlin LA, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. Nat Med. 2014; 20: 548-54.

80. Phallen J, Sausen M, Adleff V, Leal A, Hruban C, White J, et al. Direct detection of early-stage cancers using circulating tumor DNA. Sci Transl Med. 2017; 9: eaan2415.

81. Cristiano S, Leal A, Phallen J, Fiksel J, Adleff V, Bruhm DC, et al. Genome-wide cell-free DNA fragmentation in patients with cancer. Nature. 2019; 570: 385-89.

82. Mathios D, Johansen JS, Cristiano S, Medina JE, Phallen J, Larsen KR, et al. Detection and characterization of lung cancer using cell-free DNA fragmentomes. Nat Commun. 2021; 12: 5060.

83. Soto J, Rodriguez-Antolin C, Vallespín E, de Castro Carpeño J, Ibanez de Caceres I. The impact of next-generation sequencing on the DNA methylation-based translational cancer research. Transl Res. 2016; 169: 1-18.e11.

84. Oxnard GR, Klein EA, Seiden M, et al. Simultaneous multi-cancer detection and tissue of origin (TOO) localization using targeted bisulfite sequencing of plasma cell-free DNA (cfDNA). J Glob Oncol. 2019; 30: v912.

85. Janes S, Dickson J, Devaraj A, et al. P1. 11-19 trial in progress: cancer screening study with or without low dose lung CT to validate a multi-cancer early detection blood test. J Thorac Oncol. 2019; 14: S523.

86. Liu MC, Cummings S, Vachon CM, Kerlikowske K, Couch FJ, Morris E, et al. Abstract OT3-02-01: Development of cell-free nucleic acid-based tests for early detection of breast cancer: The STRIVE study: AACR; 2018.

87. Nadauld LD, McDonnell CH, 3rd, Beer TM, Liu MC, Klein EA, Hudnut A, et al. The PATHFINDER study: assessment of the implementation of an investigational multi-cancer early detection test into clinical practice. Cancers (Basel). 2021; 13: 3501.

88. Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Ann Oncol. 2020; 31: 745-59.

89. Klein EA, Richards D, Cohn A, Tummala M, Lapham R, Cosgrove D, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. Ann Oncol. 2021; 32: 1167-77.

90. Liang W, Chen Z, Li C, Liu J, Tao J, Liu X, et al. Accurate diagnosis of pulmonary nodules using a noninvasive DNA methylation test. J Clin Invest. 2021; 131: e145973.

91. Nair VS, Sundaram V, Desai M, Gould MK. Accuracy of models to identify lung nodule cancer risk in the National Lung Screening trial. Am J Respir Crit Care Med. 2018; 197: 1220-3.

92. Solassol J, Maudelonde T, Mange A, Pujol JL. Clinical relevance of autoantibody detection in lung cancer. J Thorac Oncol. 2011; 6: 955-62.

93. Zaenker P, Gray ES, Ziman MR. Autoantibody production in cancer--the humoral immune response toward autologous antigens in cancer patients. Autoimmun Rev. 2016; 15: 477-3.

94. Boyle P, Chapman CJ, Holdenrieder S, Murray A, Robertson C, Wood WC, et al. Clinical validation of an autoantibody test for lung cancer. Ann Oncol. 2011; 22: 383-9.

95. Trudgen K, Khattar NH, Bensadoun E, Arnold S, Stromberg AJ, Hirschowitz EA. Autoantibody profiling for lung cancer screening longitudinal retrospective analysis of CT screening cohorts. PLoS One. 2014; 9: e87947.

96. Jett JR, Peek LJ, Fredericks L, Jewell W, Pingleton WW, Robertson JF. Audit of the autoantibody test, EarlyCDT(R)-lung, in 1600 patients: an evaluation of its performance in routine clinical practice. Lung Cancer. 2014; 83: 51-5.

97. Sullivan FM, Mair FS, Anderson W, Armory P, Briggs A, Chew C, et al. Earlier diagnosis of lung cancer in a randomised trial of an autoantibody blood test followed by imaging. Eur Respir J. 2021; 57: 2000670.

98. Gonzalez Maldonado S, Johnson T, Motsch E, Delorme S, Kaaks R. Can autoantibody tests enhance lung cancer screening? An evaluation of EarlyCDT((R))-Lung in context of the German Lung Cancer Screening Intervention Trial (LUSI). Transl Lung Cancer Res. 2021; 10: 233-42.

99. He Y, Shi J, Shi G, Xu X, Liu Q, Liu C, et al. Using the new cell collector to capture circulating tumor cells from blood in different groups of pulmonary disease: a cohort study. Sci Rep. 2017; 7: 9542.

100. Healey GF, Lam S, Boyle P, Hamilton-Fairley G, Peek LJ, Robertson JF. Signal stratification of autoantibody levels in serum samples and its application to the early detection of lung cancer. J Thorac Dis. 2013; 5: 618-25.

101. Lam S, Boyle P, Healey GF, Maddison P, Peek L, Murray A, et al. EarlyCDT-Lung: an immunobiomarker test as an aid to early detection of lung cancer. Cancer Prev Res (Phila). 2011; 4: 1126-34.

102. Chapman CJ, Healey GF, Murray A, Boyle P, Robertson C, Peek LJ, et al. EarlyCDT®-Lung test: improved clinical utility through additional autoantibody assays. Tumour Biol. 2012; 33: 1319-26.

103. Ren S, Zhang S, Jiang T, He Y, Ma Z, Cai H, et al. Early detection of lung cancer by using an autoantibody panel in Chinese population. Oncoimmunology. 2018; 7: e1384108.

104. He Y, Ren S, Suda K, et al. Tumor autoantibodies (TAAs) panel can improve the accuracy of early diagnosis in lung cancer presenting with ground-glass nodules (GGNs) in Chinese population. 2018; in press.

105. Wang W, Zhuang R, Ma H, Fang L, Wang Z, Lv W, et al. The diagnostic value of a seven-autoantibody panel and a nomogram with a scoring table for predicting the risk of non-small-cell lung cancer. Cancer Sci. 2020; 111: 1699-710.

106. Du Q, Yu R, Wang H, Yan D, Yuan Q, Ma Y, et al. Significance of tumor-associated autoantibodies in the early diagnosis of lung cancer. Clin Respir J. 2018; 12: 2020-8.

107. Tang ZM, Ling ZG, Wang CM, Wu YB, Kong JL. Serum tumor-associated autoantibodies as diagnostic biomarkers for lung cancer: a systematic review and meta-analysis. PLoS One. 2017; 12: e0182117.

108. Hoang ML, Kinde I, Tomasetti C, McMahon KW, Rosenquist TA, Grollman AP, et al. Genome-wide quantification of rare somatic mutations in normal human tissues using massively parallel sequencing. Proc Natl Acad Sci U S A. 2016; 113: 9846-51.

109. Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, et al. EMT and dissemination precede pancreatic tumor formation. Cell. 2012; 148: 349-61.

110. Li Y, Tian X, Gao L, Jiang X, Fu R, Zhang T, et al. Clinical significance of circulating tumor cells and tumor markers in the diagnosis of lung cancer. Cancer Med. 2019; 8: 3782-92.

111. Wei T, Zhu D, Yang Y, Yuan G, Xie H, Shen R. The application of nano-enrichment in CTC detection and the clinical significance of

606

Li et al. Advances in lung cancer screening and early detection

CTCs in non-small cell lung cancer (NSCLC) treatment. PLoS One. 2019; 14: e0219129.

112. Leroy S, Benzaquen J, Mazzetta A, Marchand-Adam s, Padovani B, Israel-Biet D, et al. Circulating tumour cells as a potential screening tool for lung cancer (the AIR study): protocol of a prospective multicentre cohort study in France. BMJ Open. 2017; 7: e018884.

113. Marquette CH, Boutros J, Benzaquen J, Ferreira M, Pastre J, Pison C, et al. Circulating tumour cells as a potential biomarker for lung cancer screening: a prospective cohort study. Lancet Respir Med. 2020; 8: 709-16.

114. Zhao Q, Yuan Z, Wang H, Zhang H, Duan G, Zhang X. Role of circulating tumor cells in diagnosis of lung cancer: a systematic review and meta-analysis. J Int Med Res. 2021; 49: 300060521994926.

115. Manjunath Y, Upparahalli SV, Suvilesh KN, Avella DM, Kimchi ET, Staveley-O'Carroll KF, et al. Circulating tumor cell clusters are a potential biomarker for detection of non-small cell lung cancer. Lung Cancer. 2019; 134: 147-50.

116. Wong MP. Circulating tumor cells as lung cancer biomarkers. J Thorac Dis. 2012; 4: 631-4.

117. Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. Science. 2011; 331: 1559-64.

118. Cristofanilli M, Budd GT, Ellis MJ, Stopeck A, Matera J, Miller MC, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med. 2004; 351: 781-91.

119. Cristofanilli M, Hayes DF, Budd GT, Ellis MJ, Stopeck A, Reuben JM, et al. Circulating tumor cells: a novel prognostic factor for newly diagnosed metastatic breast cancer. J Clin Oncol. 2005; 23: 1420-30.

120. Hayes DF, Cristofanilli M, Budd GT, Ellis MJ, Stopeck A, Miller MC, et al. Circulating tumor cells at each follow-up time point during therapy of metastatic breast cancer patients predict progression-free and overall survival. Clin Cancer Res. 2006; 12: 4218-24.

121. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci U S A. 2008; 105: 10513-8.

122. Wang H, Wu S, Zhao L, Zhao J, Liu J, Wang Z. Clinical use of microRNAs as potential non-invasive biomarkers for detecting non-small cell lung cancer: a meta-analysis. Respirology. 2015; 20: 56-65.

123. Montani F, Marzi MJ, Dezi F, Dama E, Carletti RM, Bonizzi G, et al. miR-Test: a blood test for lung cancer early detection. J Natl Cancer Inst. 2015; 107: djv063.

124. Sozzi G, Boeri M, Rossi M, Verri C, Suatoni P, Bravi F, et al. Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: a correlative MILD trial study. J Clin Oncol. 2014; 32: 768-73.

125. Fehlmann T, Kahraman M, Ludwig N, Backes C, Galata V, Keller V, et al. Evaluating the use of circulating MicroRNA profiles for lung cancer detection in symptomatic patients. JAMA Oncol. 2020; 6: 714-23.

126. McDonald JS, Milosevic D, Reddi HV, Grebe SK, Algeciras-Schimnich A. Analysis of circulating microRNA: preanalytical and analytical challenges. Clin Chem. 2011; 57: 833-40.

127. Patz EF, Jr., Campa MJ, Gottlin EB, Kusmartseva I, Guan XR, Herndon JE, 2nd. Panel of serum biomarkers for the diagnosis of lung cancer. J Clin Oncol. 2007; 25: 5578-83.

128. Rastel D, Ramaioli A, Cornillie F, Thirion B. CYFRA 21-1, a sensitive and specific new tumour marker for squamous cell lung cancer. Report of the first European multicentre evaluation. CYFRA 21-1 Multicentre Study Group. Eur J Cancer. 1994; 30A: 601-6.

129. Bigbee WL, Gopalakrishnan V, Weissfeld JL, Wilson DO, Dacic S, Lokshin AE, et al. A multiplexed serum biomarker immunoassay panel discriminates clinical lung cancer patients from high-risk individuals found to be cancer-free by CT screening. J Thorac Oncol. 2012; 7: 698-708.

130. Li XJ, Hayward C, Fong PY, Dominguez M, Hunsucker SW, Lee LW, et al. A blood-based proteomic classifier for the molecular characterization of pulmonary nodules. Sci Transl Med 2013; 5(207): 207ra142.

131. Doseeva V, Colpitts T, Gao G, Woodcock J, Knezevic V. Performance of a multiplexed dual analyte immunoassay for the early detection of non-small cell lung cancer. J Transl Med. 2015; 13: 55.

132. Mazzone PJ, Wang XF, Han X, Choi H, Seeley M, Scherer R, et al. Evaluation of a serum lung cancer biomarker panel. Biomark Insights. 2018; 13: 1177271917751608.

133. Fahrmann JF, Marsh T, Irajizad E, Patel N, Murage E, Vykoukal J, et al. Blood-based biomarker panel for personalized lung cancer risk assessment. J Clin Oncol. 2022; 40: 876-83.

134. Schnabel R, Fijten R, Smolinska A, Dallinga J, Boumans M-L, Stobberingh E, et al. Analysis of volatile organic compounds in exhaled breath to diagnose ventilator-associated pneumonia. Sci Rep. 2015; 5: 17179.

135. Bartoli ML, Novelli F, Costa F, Malagrino L, Melosini L, Bacci E, et al. Malondialdehyde in exhaled breath condensate as a marker of oxidative stress in different pulmonary diseases. Mediators Inflamm. 2011; 2011: 891752.

136. Kort S, Brusse-Keizer M, Gerritsen JW, Schouwink H, Citgez E, de Jongh F, et al. Improving lung cancer diagnosis by combining exhaled-breath data and clinical parameters. ERJ Open Res. 2020; 6: 00221-2019.

137. Nichols JA, Grob P, de Lusignan S, Kite W, Williams P. Genetic test to stop smoking (GeTSS) trial protocol: randomised controlled trial of a genetic test (Respiragene) and Auckland formula to assess lung cancer risk. BMC Pulm Med. 2014; 14: 77.

138. Halling KC, Rickman OB, Kipp BR, Harwood AR, Doerr CH, Jett JR. A comparison of cytology and fluorescence in situ hybridization for the detection of lung cancer in bronchoscopic specimens. Chest. 2006; 130: 694-701.

139. In 't Veld S, Wurdinger T. Tumor-educated platelets. Blood. 2019; 133: 2359-64.

140. Sumida S. [Problems of blood transfusion with positive anti-ATLA antibodies]. Nihon Rinsho. 1986; 44: 2279-82.

141. Vykoukal J, Sun N, Aguilar-Bonavides C, Katayama H, Tanaka I, Fahrmann J, et al. Plasma-derived extracellular vesicle proteins as a source of biomarkers for lung adenocarcinoma. Oncotarget. 2017; 8: 95466-80.

142. Yan X, Yang M, Liu J, Gao R, Hu J, Li J, et al. Discovery and validation of potential bacterial biomarkers for lung cancer. Am J Cancer Res. 2015; 5: 3111-22.

143. Ajona D, Okroj M, Pajares MJ, Agorreta J, Lozano MD, Zulueta JJ, et al. Complement C4d-specific antibodies for the diagnosis of lung cancer. Oncotarget. 2018; 9: 6346-55.

144. Mathe EA, Patterson AD, Haznadar M, Manna SK, Krausz KW, Bowman ED, et al. Noninvasive urinary metabolomic profiling identifies diagnostic and prognostic markers in lung cancer. Cancer Res. 2014; 74: 3259-70.

145. Subramanian H, Viswanathan P, Cherkezyan L, Iyengar R, Rozhok S, Verleye M, et al. Procedures for risk-stratification of lung cancer using buccal nanocytology. Biomed Opt Express. 2016; 7: 3795-810.

146. van Rens MT, de la Rivière AB, Elbers HR, van Den Bosch JM. Prognostic assessment of 2,361 patients who underwent pulmonary resection for non-small cell lung cancer, stage I, II, and IIIA. Chest. 2000; 117: 374-9.

147. Nezu K, Kushibe K, Tojo T, Takahama M, Kitamura S. Thoracoscopic wedge resection of blebs under local anesthesia with sedation for treatment of a spontaneous pneumothorax. Chest. 1997; 111: 230-5.

148. He J, Liang H, Wang W, Akopov A, Aiolfi A, Ang K-L, et al. Tubeless video-assisted thoracic surgery for pulmonary ground-glass nodules: expert consensus and protocol (Guangzhou). Transl Lung Cancer Res. 2021; 10: 3503-19.

149. Dalwadi SM, Szeja SS, Bernicker EH, Butler EB, Teh BS, Farach AM. Practice patterns and outcomes in elderly stage I non-small-cell Lung cancer: a 2004 to 2012 SEER analysis. Clin Lung Cancer. 2018; 19: e269-76.

150. Chang JY, Bezjak A, Mornex F, Committee IASLC Advanced Radiation Technology Committee. Stereotactic ablative radiotherapy for centrally located early stage non-small-cell lung cancer: what we have learned. J Thorac Oncol. 2015; 10: 577-85.

151. Creach KM, Bradley JD, Mahasittiwat P, Robinson CG. Stereotactic body radiation therapy in the treatment of multiple primary lung cancers. Radiother Oncol. 2012; 104: 19-22.

152. Shintani T, Masago K, Takayama K, Ueki K, Kimino G, Ueki N, et al. Stereotactic body radiotherapy for synchronous primary lung cancer: clinical outcome of 18 cases. Clin Lung Cancer. 2015; 16: e91-6.

153. Chen Y, Gao M, Huang Z, Yu J, Meng X. SBRT combined with PD-1/PD-L1 inhibitors in NSCLC treatment: a focus on the mechanisms, advances, and future challenges. J Hematol Oncol. 2020; 13: 105.

154. Baisi A, De Simone M, Raveglia F, Cioffi U. Thermal ablation in the treatment of lung cancer: present and future. Eur J Cardio-Thorac Surg. 2012; 43: 683-6.

155. Yamauchi Y, Izumi Y, Hashimoto K, Yashiro H, Inoue M, Nakatsuka S, et al. Percutaneous cryoablation for the treatment of medically inoperable stage I non-small cell lung cancer. PLoS One. 2012; 7: e33223.

156. Dupuy DE, Mayo-Smith WW, Abbott GF, DiPetrillo T. Clinical applications of radio-frequency tumor ablation in the thorax. Radiographics. 2002; 22 Spec No: S259-69.

157. Vazquez M, Carter D, Brambilla E, Gazdar A, Noguchi M, Travis WD, et al. Solitary and multiple resected adenocarcinomas after CT screening for lung cancer: histopathologic features and their prognostic implications. Lung Cancer. 2009; 64: 148-54.

158. Cheng B, Li C, Zhao Y, Li J, Xiong S, Liang H, et al. The impact of postoperative EGFR-TKIs treatment on residual GGO lesions after resection for lung cancer. Signal Transduct Target Ther. 2021; 6: 73.

159. Bao Y, Wu J, Zhang J, Yu Y. Diagnosis and treatment of synchronous multiple primary lung cancer – a case report. Onco Targets Ther. 2019; 12: 4281-5.

160. Cheng B. The efficacy of PD-1 antibody sintilimab on ground glass opacity lesions in patients with early-stage multiple primary lung cancer (CCTC-1901, NCT04026841). In: Bo Cheng BCCLYZJH, Department of Thoracic S, Oncology TFAHoGMUSKLoRD, x, National Clinical Research Center for Respiratory Disease GC, The First Affiliated Hospital of Guangzhou Medical University GC, editors. ASCO Annual Meeting: American Society of Clinical Oncology; 2021.

161. National Lung Screening Trial Research Team, Church TR, Black WC, Aberle DR, Berg CD, Clingan KL, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med. 2013; 368: 1980-91.

162. Pinsky PF, Gierada DS, Nath PH, Kazerooni E, Amorosa J. National lung screening trial: variability in nodule detection rates in chest CT studies. Radiology. 2013; 268: 865-73.

163. Sone S, Nakayama T, Honda T, Tsushima K, Li F, Haniuda M, et al. Long-term follow-up study of a population-based 1996-1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography. Lung Cancer. 2007; 58: 329-41.

164. Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midthun DE, Tazelaar HD, et al. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. Radiology. 2007; 242: 555-62.

165. Paci E, Puliti D, Lopes Pegna A, Carrozzi L, Picozzi G, Falaschi F, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax. 2017; 72: 825-31.

166. McCunney RJ, Li J. Radiation risks in lung cancer screening programs: a comparison with nuclear industry workers and atomic bomb survivors. Chest. 2014; 145: 618-24.

167. Veronesi G, Maisonneuve P, Spaggiari L, Rampinelli C, Pardolesi A, Bertolotti R, et al. Diagnostic performance of low-dose computed tomography screening for lung cancer over five years. J Thorac Oncol. 2014; 9: 935-9.

168. Rampinelli C, De Marco P, Origgi D, Maisonneuve P, Casiraghi M, Veronesi G, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. BMJ. 2017; 356: j347.

169. Field JK, Duffy SW, Baldwin DR, Brain KE, Devaraj A, Eisen T, et al. The UK lung cancer screening trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess. 2016; 20: 1-146.

170. Puliti D, Mascalchi M, Carozzi FM, Carrozzi L, Falaschi F, Paci E, et al. Decreased cardiovascular mortality in the ITALUNG lung cancer screening trial: analysis of underlying factors. Lung Cancer. 2019; 138: 72-8.

608

Li et al. Advances in lung cancer screening and early detection

171. Lopes Pegna A, Picozzi G, Falaschi F, Carrozzi L, Falchini M, Maria Carozzi F, et al. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. J Thorac Oncol. 2013; 8: 866-75.

172. Luo X, Zheng S, Liu Q, Wang S, Li Y, Shen L, et al. Should nonsmokers be excluded from early lung cancer screening with low-dose spiral computed tomography? Community-based practice in Shanghai. Transl Oncol. 2017; 10: 485-90.

173. Sobue T, Moriyama N, Kaneko M, Kusumoto M, Kobayashi T, Tsuchiya R, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol. 2002; 20: 911-20.

174. Sone S, Li F, Yang ZG, Honda T, Maruyama Y, Takashima S, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Cancer. 2001; 84: 25-32.

175. Nawa T, Nakagawa T, Kusano S, Kawasaki Y, Sugawara Y, Nakata H. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. Chest. 2002; 122: 15-20.

176. Chong S, Lee KS, Chung MJ, Kim TS, Kim H, Kwon OJ, et al. Lung cancer screening with low-dose helical CT in Korea: experiences at the Samsung Medical Center. J Korean Med Sci. 2005; 20: 402-8.

177. Lee JW, Kim HY, Goo JM, Kim EY, Lee SJ, Kim TJ, et al. Radiological report of pilot study for the Korean Lung Cancer Screening (K-LUCAS) project: feasibility of implementing lung imaging reporting and data system. Korean J Radiol. 2018; 19: 803-8.