REVIEW

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Lung Cancer Screening: Subsequent Evidences of National Lung Screening Trial

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The US National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality and a 6.7% decrease in all-cause mortality. The NLST is the only trial showing positive results in a high-risk population, such as in patients with old age and heavy ever smokers. Lung cancer screening using a low-dose chest computed tomography might be beneficial for the high-risk group. However, there may also be potential adverse outcomes in terms of over diagnosis, bias and cost-effectiveness. Until now, lung cancer screening remains controversial. In this review, we wish to discuss the evolution of lung cancer screening and summarize existing evidences and recommendations.

Keywords: Lung Neoplasms; Early Detection of Cancer; Tomography, X-Ray Computed; Thorax

Introduction

Trials on lung cancer screening had been conducted for more than 40 years. In 1969, the South London Lung Cancer Study suggested that the prognosis of lung cancer improves by earlier radiological detection using chest X-ray (CXR)[1]. In 1970–80, the National Cancer Institute of the United States sponsored three large-scale randomized controlled trials (RCT); the Mayo Lung Project, Johns Hopkins Lung Cancer Screening and the Memorial Sloan-Kettering Lung Cancer Screening Program. Unfortunately, all these trials did not demonstrate the reduction of lung cancer mortality using CXR with or without sputum cytology[2]. Until 2000, it was a common conclusion that lung cancer screening does not reduce the mortality[3].

In 2000, a Lung Screening Study was designed for the feasibility of performing a large scale RCT of lung cancer screening of low-dose chest computed tomography (LDCT) versus CXR[4]. In 2002, the National Cancer Institute of the United States sponsored a National Lung Screening Trial (NLST) in 2002 after the successful feasibility of RCT of LDCT screening was demonstrated[5]. Finally, the NLST demonstrated 20.0% reduction of lung cancer mortality and 6.7% reduction of all-cause mortality in the LDCT group compared to the CXR group[6]. Until now, the NLST is the only trial showing positive results in a high-risk population, such as in patients of old age and heavy ever smokers.

Lung cancer screening using LDCT might be beneficial for the high-risk group. However, it also has the potential adverse outcomes in terms of overdiagnosis bias and cost-effectiveness. Until now, lung cancer screening remains controversial.

Historical Perspective of LDCT Screening before NLST

In three large RCTs of lung cancer screening with CXR, lung cancers were more detected in the CXR group and cases found in the screened arm were diagnosed in earlier stages than those in the control arm. But these trials did not demonstrate a mortality reduction[2]. These paradoxical results suggested the pitfalls of screening as limitation of the study design. Even more, CXR itself was not good enough for the

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detection of resectable tumors (45/206, 22%) in the Mayo Lung Project[2]. In that time, more sensitive and safe screening regimens were needed.

In 1990, LDCT was tested for its feasibility of lung cancer screening because of the high-quality of the diagnostic images and the very low radiation dose[7]. In 1992, the Early Lung Cancer Action Project (ELCAP) was initiated to assess the efficacy of annual computed tomography (CT) screenings for lung cancer[8]. In that period, many prospective cohort studies using LDCT such as the Anti-Lung Cancer Association Project (ALCA)[9], mobile CT[10] and Mayo CT trial were initiated in the United State and Japan[11]. All these trials showed the common finding that LDCT was more sensitive in lung cancer detection than CXR. But in terms of mortality reduction, the results were controversial between the ALCA and Mayo CT trial.

RCTs of LDCT including NLST

Since 2000, many RCTs for lung cancer screening using LDCT had been initiated in the United States and Europe (Figure 1). Most of them did not prove a significant reduction of mortality and even more, the Danish Lung Cancer Screening Trial showed an increased mortality in the screened arm[12].

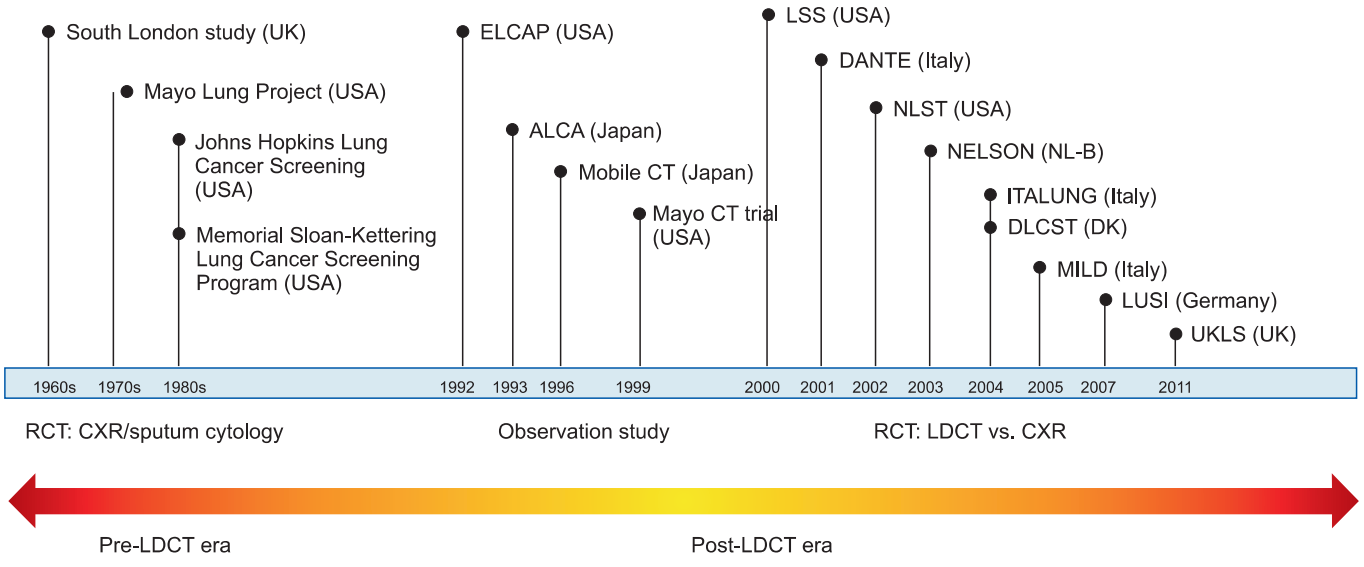

Figure 1. History of lung cancer screening. CT: computed tomography; CXR: chest X-ray; DANTE: Detection and Screening of Early Lung Cancer; LDCT: low-dose chest CT; LSS: Lung Screening Study; NLST: National Lung Screening Trial; RCT: randomized controlled trials; UKLS: UK Lung Screen.

Table 1. Randomized controlled trials on low-dose computed tomography screening for lung cancer

Study	Country	Start	Control	No.	Enroll criteria		
					Age (yr)	Smoking	Others
LSS[13]	USA	2000	CXR	3318	55–74	>30PY, quit<10 yr	-
DANTE[14]	Italy	2001	Obs.	2472	60–74	>20PY, quit<10 yr	Only male subjects?
NLST[6]	USA	2002	CXR	53000	55–74	>30PY, quit<15 yr	-
NELSON[15]	NL-B	2003	Obs.	15822	50–75	>15PY, quit≤10 yr	-
ITALUNG[16]	Italy	2004	Obs.	3206	55–69	>20PY, quit<10 yr	-
DLCST[12]	DK	2004	Obs.	4104	50–70	>20PY, quit<10 yr	-
MILD[17]	Italy	2005	Obs.	4099	≥49	>20PY, quit<10 yr	-
LUSI[18]	Germany	2007	Obs.	4052	50–69	Heavy	-
UKLS[19]	UK	2011	Obs.	32000	50–75	-	Risk>5%/5 yr

LSS: Lung Screening Study; CXR: chest X-ray; DANTE: Detection and Screening of Early Lung Cancer; NLST: National Lung Screening Trial; UKLS: UK Lung Screen; PY: pack years.

NELSON trial and UKLS are under conduction and the results will be published. Of all published results, the NLST was the first and only trial that demonstrated the mortality reduction of lung cancer screening. Table 1 shows the summary of RCTs.

NLST proved the sensitive methods of LDCT for lung cancer screening in terms of stage. The stage distribution from T0 to T2 in the LDCT group resulted in an increase of the number of early-stage lung cancer compared to the CXR group (Figure 2)[20,21]. NLST showed a stage shift toward the early-stage that is potentially curable.

Current Recommendations

The result of NLST was published on 29th June 2011. On 4th July 2011, the International Association for the Study of Lung Cancer (IASLC) published the statement on CT screening for lung cancer in 7 different languages. The National Compre-

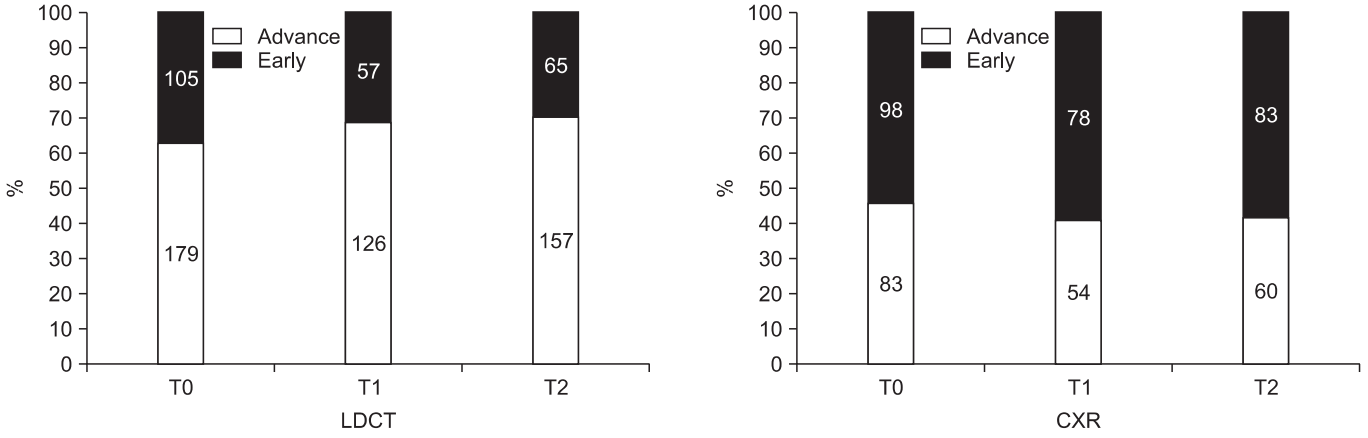

Figure 2. Stage distribution of National Lung Screening Trial. CXR: chest X-ray; LDCT: low dose chest computed tomography.

Table 2. Recommendations for lung cancer computed tomography screening

Organization	Primary population	Other population	Expiration
NCCN	Aged 55–74 yr	Aged≥50 yr	-
	≥30PY smoking, quit<15 yr	≥20PY	
		Additional risk factors*	
ALA	Aged 55–74 yr	-	-
	≥30PY smoking, quit<15 yr		
AATS	Aged 55–79 yr	Aged≥50 yr	-
	≥30PY smoking	≥20PY smoking	
		Additional risk factors†	
		Or lung cancer survivor ≥5 yr	
ACCP & ASCO	Aged 55–74 yr	-	-
	≥30PY smoking, quit<15 yr		
ACS	Aged 55–74 yr	-	-
	≥30PY smoking, quit<15 yr		
USPSTF	Aged 55–80 yr	-	Quit smoking ≥15 yr
	≥30PY smoking, quit<15 yr		

*Additional risk factors: cancer history, lung disease history, family history of lung cancer, radon exposure and occupational exposure.
†Additional risk factors: chronic obstructive lung disease, environmental and occupational exposures, prior cancer or thoracic radiation and genetic or family history.
NCCN: National Comprehensive Cancer Network; ALA: American Lung Association; AATS: American Association for Thoracic Surgery; ACCP & ACOS: American College of Chest Physicians and American Society of Clinical Oncology; ACS: American Cancer Society; USPSTF: US Preventive Services Task Force.

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hensive Cancer Network (NCCN) guideline was published in 2012 and further recommendations followed by the American Lung Association[22] and the American College of Chest Physicians/American Society of Clinical Oncology[23], the American Association for Thoracic Surgery[24] and the American Cancer Society[25] and the US preventive societies task force[26]. Table 2 summarizes the recommendations. The most recommendations are mainly based on the NLST inclusion criteria. Interestingly, the latest guideline, US Preventive Services Task Force (USPSTF) recommended the discontinuation of screening if the patient had not smoked for 15 years.

Selection Criteria for Lung Cancer Screening

There is no clear definition of a high-risk population for lung cancer. But most LDCT screening trials used the inclusion criteria age and smoking history (Table 1). And the most current recommendations apply these criteria (Table 2). Old age and heavy smoking history are generally accepted for LDCT screening. But the UKLS trial used a different approach for participants. It recruited the population according to the Liverpool Lung Project risk model[27]. UKLS selected participants with a 5% risk of developing lung cancer in 5 years[28]. In 2013, Tammemagi et al.[29] suggested selection criteria for lung cancer screening using $PLCO_{M2012}$ criteria. They compared the accuracy of $PLCO_{M2012}$ and NLST criteria to detect lung cancer and concluded that the $PLCO_{M2012}$ model was more sensitive than per NLST defined criteria old age and heavy smoking history.

Until now, there is no concrete evidence for a definition of selection criteria. Only age and smoking history may be not sufficient and some prediction models could not be generalized. As the author mentioned above, of all clinical trials on lung cancer screening, only the UKLS used the prediction model for selection criteria. So the results of UKLS are waiting in the spotlight in terms of selection criteria.

Conclusions

Definitely, NLST made a great advance in lung cancer screening in terms of sensitive screening method and selection criteria. It is said that LDCT screening is prime time, but subsequent positive results are needed. So we are intensively waiting for the results of NELSON and UKLS trials. In the near future, we hope that better biomarkers for selection criteria and more sensitive imaging techniques to predict lung cancer will be applied in mass screening programs.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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