Original Article

Differences in detection patterns, characteristics, and outcomes of central and peripheral lung cancers in low-dose computed tomography screening

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Background: Although low-dose computed tomography (LDCT) screening is known to be effective for the detection of lung cancers localized in peripheral lung regions at a curable stage, limited data is available regarding the characteristics and outcomes of central lung cancers diagnosed in a screening cohort. This study aimed to determine whether LDCT screening could effectively detect central lung cancers at an early stage and offer survival benefits.

Methods: We analyzed 52,615 adults who underwent lung cancer screening with LDCT between May 2003 and Dec 2019 at a tertiary center in South Korea. Characteristics and outcomes of those diagnosed with lung cancer, stratified by screen-detection status and cancer location, were evaluated.

Results: A total of 352 individuals (281 screen-detected, 71 non-screen-detected) were diagnosed with lung cancer. Compared to screen-detected cancers, non-screen-detected cancers tended to be centrally-located (11.4% vs. 64.8%, P<0.001). Most non-screen-detected central cancers (89.1%) had a negative result on prior LDCT screening. Multivariable regression analyses revealed that for peripheral cancers, screen-detection was associated with a significantly lower probability of diagnosis at an advanced stage [III/IV, odds ratio (OR) =0.15, 95% confidence interval (CI): 0.05–0.45] and mortality [hazard ratio (HR) =0.33, 95% CI: 0.13–0.84]; however, the association was insignificant for central cancers. For screen-detected cancers, central location, compared to peripheral location, was significantly associated with a higher risk of diagnosis at an advanced stage (OR =20.83, 95% CI: 6.67–64.98) and mortality (HR =4.98, 95% CI: 2.26–10.97).

Conclusions: Unlike for peripheral cancers, LDCT screening did not demonstrate an improvement in outcomes of central lung cancers, indicating an important limitation of LDCT screening and the need for developing novel modalities to screen and treat central lung cancer.

Keywords: Lung cancer screening; low-dose computed tomography (LDCT); central lung cancer

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Introduction

Lung cancer is the leading cause of cancer deaths in both men and women worldwide (1). Owing to the latency of symptom presentation, patients are often at an advanced stage of the disease at the time of diagnosis, resulting in poor survival (2). Therefore, widespread efforts have focused on developing safe and effective screening methods to detect and treat lung cancer at an earlier stage. Based on the results of large prospective studies, such as the National Lung Screening Trial (NLST) (3), the Multicentric Italian Lung Detection (MILD) trial (4), and the Dutch-Belgian lung-cancer screening (NELSON) trial (5), which showed significant reduction in lung cancer mortality among smokers who underwent low-dose computed tomography (LDCT) screening, the US Preventive Services Task Force currently recommends LDCT lung cancer screening for individuals aged 50–80 years with a smoking history of ≥20 pack-years, and are either current smokers or have quit smoking within the last 15 years (6). However, many other regions do not yet have criteria for such screening, and emerging data suggest that expending the screening criteria would be beneficial (7,8). In East Asia, where the burden of lung cancer among never-smokers is relatively high and increasing (9-11), LDCT screening has shown promising results of mortality benefits and stage shifts in several real-world cohort studies including never-smokers (12,13), and is widely applied for both never- and ever-smokers as well as for relatively young individuals (14,15).

However, despite the aforementioned benefits of LDCT screening, it is noteworthy that the majority of screen-detected lung cancers were in peripheral lung regions, which are usually early stage adenocarcinomas (16,17). Conversely, central lung cancers have a higher probability of presenting with mediastinal lymph node metastasis, endobronchial lesions, and invasion to large vessels, and are frequently diagnosed as squamous cell carcinomas or small-cell lung cancer (SCLC) with a fast growing and aggressive nature (18-22). Moreover, central lung cancers are known to be more difficult to recognize with LDCT scans because images are unenhanced (23); therefore, even with the application of lung cancer screening, they may have a high risk of being diagnosed at an advanced stage, making it difficult to conduct curative treatment and reduce cancer-related mortality (24). However, limited data is available on the detection stage and clinical outcomes of central lung cancers diagnosed in screening cohorts, and it remains unclear whether LDCT screening can effectively detect central lung cancers at an early stage, leading to survival benefits.

Therefore, we conducted a hospital-based cohort study of asymptomatic participants who underwent lung cancer screening with LDCT in South Korea. The aim of this study was to assess the characteristics and clinical course of diagnosed lung cancers categorized by screen-detection status and central/peripheral location of the primary cancer, and evaluate whether LDCT screening could effectively detect central lung cancers at an early stage and offer survival benefit in a real-world lung cancer screening setting in an Asian population. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-658).

Methods

Study design and participants

This was a single-center, retrospective cohort study of participants aged ≥18 years who voluntarily underwent LDCT screening for lung cancer as part of their health checkups between May 2003 and Dec 2019 at the Health Promotion Center of Seoul National University Bundang Hospital, a tertiary center in South Korea. All participants were asymptomatic at the time of baseline screening. Questionnaires were used to evaluate smoking status and the amount of smoking in pack-years. Never-smokers were defined as individuals who had smoked fewer than 100 cigarettes in their lifetime (25). Participants with a history of lung cancer and participants without data on smoking status were excluded. Thereafter, patients with a diagnosis of histologically confirmed lung cancer were evaluated further. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No: B-2007/625-001), which waived the need for written informed consent from participants.

Procedures

Unenhanced LDCT scans were performed at a peak tube voltage of 100 kV and a reference tube current of 20–50 mA using one of the following multi-detector row scanners: Mx-8000 IDT 1, Mx-8000 IDT 2, Mx-8000 IDT 16 (Philips Medical Systems, Cleveland, OH, USA), Brilliance-64, or Brilliance iCT 256 (Philips

Medical Systems, Best, The Netherlands). All LDCT images were reconstructed with 3-mm or thinner slices in the axial plane and a 3-mm slice in the coronal plane and were initially stored in a dedicated electronic Picture Archiving and Communication System (PACS). All images were initially interpreted by experienced board-certified chest radiologists. Participants with a positive nodule, defined as any noncalcified nodule measuring at least 4 mm in the largest diameter, or with abnormalities such as lymphadenopathy or pleural effusion were referred to the pulmonary division, where decisions regarding follow-up and diagnostic evaluations were made by the attending specialist. According to the concurrent consensus guidelines, decisions regarding follow-up and pathologic confirmation of detected nodules, including subsolid nodules, depended mainly on radiologic aspects and were not additionally weighted by demographic factors.

Medical records of participants who were diagnosed with lung cancer were reviewed to obtain data regarding lung cancer detection by LDCT screening, initial radiographic findings, diagnostic evaluation, pathology and staging, treatment, and clinical course. A diagnosis based on a positive nodule or other findings from LDCT screening was defined as screen-detected. A diagnosis based on symptoms or incidental examinations not related to screening was defined as non-screen-detected and further classified as follows: (I) the related lesion could be seen retrospectively on the last LDCT screening but was not mentioned in the report or was noted to be considered benign (missed cancer; false-negative), (II) the related lesion on the last LDCT screening was recommended for further follow-up but was lost due to participant non-compliance, (III) no related lesion could be found retrospectively from last screening LDCT (negative screen). There were no determined criteria with regard to time between the last screening from the diagnosis of lung cancer to define non-screen-detected cancer. A pulmonary physician (YWK) and a radiologist (KWL) reviewed all CT images taken before and after the first report of the relevant cancerous lesion to determine the timeframe of occurrence and location of the cancer and classify non-screen-detected cancer. Cancer location was evaluated using CT scans on which the relevant tumor was first detected. Based on the center of the tumor, cancers were categorized as central or peripheral by location within the inner one-third of the hemithorax (20,26); the three-thirds of the hemithorax were defined based on concentric lines arising from the hilum and following the contour of the lung in both axial and coronal images (27,28). In cases of subsolid tumors, the solid component was utilized for evaluation. In cases with multiple cancerous lesions, the main dominant tumor was determined for further analyses. For inconsistencies regarding radiologic findings and cancer location between reviewers, a consensus was reached by discussion. Initial staging of lung cancer was based on the guidelines of the International Association for the Study of Lung Cancer and the American Joint Committee on Cancer Stage Classification of SCLC and non-small cell lung cancer (NSCLC), eighth edition (29,30). The stage was defined as the pathologic stage if feasible; otherwise, clinical stage was determined. The final status of the screened participants including those diagnosed with lung cancer was tracked using medical records through Dec 31, 2019. Lung cancer related deaths were determined using medical records and data supplemented by the Korea National Statistical Office.

Outcomes

The main outcomes in this study were the characteristics and clinical outcomes of diagnosed lung cancers in our LDCT screening cohort, stratified by screen-detection status and cancer location. Risk of diagnosis at an advanced stage (stage III/IV), and lung cancer-related mortality for central lung cancers were evaluated and compared with those of peripheral lung cancers, further stratified by screen-detection status and histological cancer type.

Statistical analysis

Participant characteristics data are presented as means and standard deviations for continuous variables and frequencies (%) for categorical variables. To compare clinical and radiological characteristics between groups, the (independent) two sample *t*-test was used to analyze continuous variables and Pearson's chi-square or Fisher's exact test to analyze categorical variables. Estimation and comparison of lung cancer-related mortality was initially done with Kaplan-Meier analysis. Univariable and multivariable logistic regression analysis and Cox proportional hazard analysis were used to assess associations between potential factors (cancer location, screen-detection status) and diagnosis at an advanced stage (stage III/IV) and lung cancer-related mortality, respectively. Additional logistic and Cox analyses were performed for subgroups stratified by cancer location and screen-detection status and histological type, respectively. Multivariable modeling was conducted for the evaluated factors with inclusion of age,

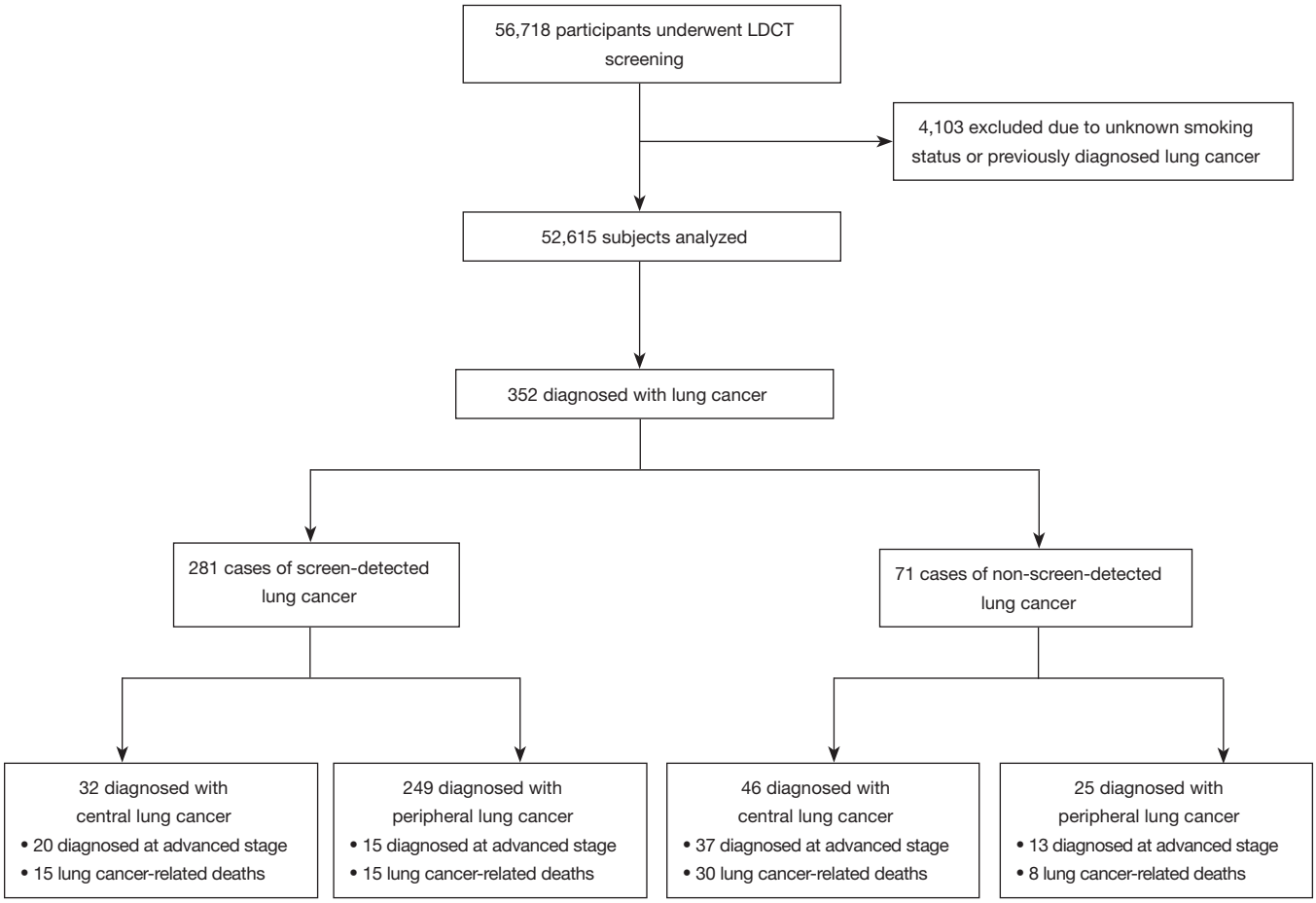

Figure 1 Flow diagram of the study population.

sex, smoking pack-years, and nodule type (solid or subsolid). For mortality, additional Cox analyses were performed with separate models including histological type as a covariate. No covariates included in the regression models had missing values or showed multicollinearity. The 95% confidence intervals (CIs) were calculated; P values <0.05 were considered statistically significant. All analyses were performed using R version 3.5.3 (http://www.R-projecct.org) and STATA, version 16.0 (StataCorp., College Station, TX, US).

Results

Participant characteristics

The flowchart of participants included this study is presented in *Figure 1*. During the study period, 56,718 participants underwent lung cancer screening with LDCT, of which 52,615 were analyzed after excluding those with unknown smoking status or previous history of lung cancer. Among them, 352 (0.7%) were eventually diagnosed with lung cancer. The baseline characteristics of all participants are described in *Table 1*. Over one-third of the screened participants were under 45 years of age at the time of baseline LDCT screening, 67.7% were male, 45.6% were never-smokers, and 6,951 (13.2%) had a positive nodule at baseline LDCT screening. Participants were followed-up for 44.8±50.5 months from baseline LDCT screening, and underwent 2.1±1.9 CT scans (including the first screening).

Characteristics and clinical course of participants diagnosed with lung cancer

Table 2 presents the characteristics of 352 participants diagnosed with lung cancer—281 (79.8%) cases were screen-detected, 71 (20.2%) were non-screen-detected,

Table 1 Characteristics of participants who underwent LDCT screening

Characteristic	Total (n=52,615)
Age at baseline screening, n (%)	
<45 years	18,483 (35.1)
45–49 years	8,809 (16.7)
50–54 years	8,514 (16.2)
55–59 years	6,730 (12.8)
60–64 years	4,494 (8.5)
65–69 years	3,008 (5.7)
70–74 years	1,724 (3.3)
≥75 years	853 (1.6)
Mean ± SD	49.5±11.3
Sex, n (%)	
Male	35,638 (67.7)
Female	16,977 (23.2)
Smoking status at baseline screening, n (%)	
Never-smoker	23,969 (45.6)
Ever-smoker	28,646 (54.4)
Total follow-up months, mean ± SD	44.8±50.5
Number of CT scans including first LDCT, mean ± SD	2.1±1.9
Subjects with positive nodule at first screening, n (%)	6,951 (13.2)
Subjects finally diagnosed with lung cancer, n (%)	352 (0.7)

LDCT, low-dose chest computed tomography; SD, standard deviation.

111 (39.5%) of the screen-detected patients were never-smokers, 177 (63.0%) were initially detected with subsolid lesions, whereas 98.6% of non-screen-detected lung cancer cases presented with solid lesions. Compared to screen-detected cancers, non-screen-detected cancers tended to be centrally-located (11.4% *vs.* 64.8%, P<0.001), have a larger tumor size at first detection (17.5±11.9 *vs.* 46.7±24.4 mm, P<0.001), and have endobronchial lesions confirmed by bronchoscopic evaluation (5.3% *vs.* 57.7%, P<0.001). Data regarding pathologic characteristics, initial staging, and clinical course are presented in *Table 3*. Of the screen-detected cancer cases, 248 (88.3%) were diagnosed as (pre-) invasive adenocarcinoma. Analyses stratified by central location and histologic type revealed that the difference in smoking status between screen-detected and non-screen-detected cases was attributed to the large difference shown in peripheral (pre-) invasive adenocarcinoma cases (current smokers accounted for 26.7% (62/232) screen-detected cases and 80% (8/10) for non-screen-detected cases, respectively (P<0.001)). Compared to screen-detected cancers, non-screen-detected cancers were more likely to be diagnosed at an advanced stage (12.5% *vs.* 70.4%, P<0.001) and less likely to receive curative surgery for initial treatment (92.9% *vs.* 36.6%, P<0.001). *Table 4* presents the characteristics of the 71 non-screen-detected lung cancers; compared to peripheral lung cancers, central cancers had a significantly lower rate of having false-negative results (missed cancer) at last screening (32.0% *vs.* 6.5%, P=0.013) and a higher rate of being detected after a negative screen (64.0% *vs.* 89.1%, P=0.026), being diagnosed at an advanced stage (52.0% *vs.* 80.4%, P=0.012), and resulted in higher mortality (32.0% *vs.* 65.2%, P=0.007).

The characteristics and outcomes of all lung cancer cases stratified by central or peripheral location are presented in Tables S1,S2.

Association between central location and outcomes

Figure 2 describes the initial Kaplan–Meier analysis for mortality in subgroups stratified by screen-detection status and cancer location. Univariable and multivariable logistic regression analyses of the evaluated factors associated with diagnosis at an advanced stage are presented in Table S3. Multivariable analyses revealed that central-location (*vs.* peripheral-location) was significantly associated with a higher probability (OR =8.73, 95% CI: 4.10–18.60), and screen-detection (*vs.* non-screen-detection) with a lower probability (OR =0.32, 95% CI: 0.15–0.70) of advanced stage lung cancer diagnosis. Results of the analyses after stratification by cancer location and screen-detection status are shown in *Table 5*. Multivariable analysis showed that although screen-detection was associated with a significantly lower probability of peripheral lung cancer diagnosis at an advanced stage (OR =0.15, 95% CI: 0.05–0.45), there was no significant association between screen-detection and central lung cancer diagnosis at an advanced stage (OR =0.77, 95% CI: 0.23–2.51). When stratified by screen-detection status, compared to peripheral location, central location was significantly associated with a higher probability of advanced stage diagnosis for both screen-

Table 2 Characteristics of lung cancer patients stratified by screen-detection status

Characteristic	Total (n=352)	Screen-detected (n=281)	Non-screen-detected (n=71)	P value
Age at first screening, mean ± SD	59.6±9.8	58.9±9.9	62.2±9.0	0.014
Age at diagnosis, mean ± SD	63.8±10.3	62.4±10.0	69.3±9.9	<0.001
Smoking status at first screening, n (%)				<0.001
Never-smoker	115 (32.7)	111 (39.5)	4 (5.6)	
Current smoker	141 (40.1)	90 (32.0)	51 (71.8)	
Former smoker	96 (27.3)	80 (28.5)	16 (22.5)	
Smoking pack-years at first screening, mean ± SD	23.1±23.6	18.7±21.5	40.7±23.3	<0.001
Type of primary tumor at first detection				<0.001
Solid	174 (49.4)	104 (37.0)	70 (98.6)	
Part-solid	126 (35.8)	125 (44.5)	1 (1.4)	
Pure GGN	52 (14.8)	52 (18.5)	0 (0)	
Location of primary tumor, n (%)				<0.001
Central	78 (22.2)	32 (11.4)	46 (64.8)	
Peripheral	274 (77.8)	249 (88.6)	25 (35.2)	
Lobar location of primary tumor, n (%)				0.244
Right upper lobe	118 (33.5)	91 (32.4)	27 (38.0)	
Right middle lobe	23 (6.5)	21 (7.5)	2 (2.8)	
Right lower lobe	68 (19.3)	55 (19.6)	13 (18.3)	
Left upper lobe	94 (26.7)	73 (26.0)	21 (29.6)	
Left lower lobe	48 (13.6)	41 (14.6)	7 (9.9)	
Main trachea or mediastinum	1 (0.3)	0 (0.0)	1 (1.4)	
Tumor size at first detection (mm), mean ± SD	23.4±19.2	17.5±11.9	46.7±24.4	<0.001
Tumor with endobronchial lesion, n (%)*	56 (15.9)	15 (5.3)	41 (57.7)	<0.001
Number of LDCT screening rounds, mean ± SD	1.7±1.4	1.7±1.4	1.7±1.0	0.768
Time from baseline LDCT screening to pathologic diagnosis, months, mean ± SD	47.8±51.5	39.4±48.1	81.2±51.2	<0.001
Time from last LDCT screening to pathologic diagnosis, months, mean ± SD	27.1±39.1	17.4±30.9	65.3±44.8	<0.001

*, endobronchial tumor or obstructive lesion(s) confirmed by bronchoscopic evaluation. LDCT, low-dose chest computed tomography; SD, standard deviation; GGN, ground glass nodule.

detected (OR =20.83, 95% CI: 6.67–64.98) and non-screen-detected (OR =3.74, 95% CI: 1.23–11.39) lung cancers.

Table S4 presents the results of univariable and multivariable cox proportional hazard analyses for the risk of mortality, which revealed a significantly higher mortality risk for centrally-located lung cancers (*vs.* peripheral location, HR =3.63, 95% CI: 2.02–6.53) and a lower mortality risk among screen-detected (*vs.* non-screen-detected, HR =0.53, 95% CI: 0.31–0.93) lung cancers. Results of the analyses after further stratification by cancer location and screen-detection status are shown in *Table 6*. Multivariable analysis revealed that screen-detection

Table 3 Clinical course of lung cancer patients stratified by screen-detection status

Characteristic	Total (n=352)	Screen-detected (n=281)	Non-screen-detected (n=71)	P value
Cancer histology, n (%)				<0.001
Adenocarcinoma in situ	21 (6.0)	21 (7.5)	0 (0)	
Minimally invasive adenocarcinoma	42 (11.9)	42 (14.9)	0 (0)	
Invasive adenocarcinoma	208 (59.1)	185 (65.8)	23 (32.4)	
Adenosquamous carcinoma	3 (0.9)	2 (0.7)	1 (1.4)	
Squamous cell carcinoma	46 (13.1)	18 (6.4)	28 (39.4)	
Other non-small cell carcinoma	13 (3.7)	5 (1.8)	8 (11.3)	
Small cell carcinoma	19 (5.4)	8 (2.8)	11 (15.5)	
Lung cancer staging, n (%)				<0.001
0*	21 (6.0)	21 (7.5)	0 (0)	
IA	195 (55.4)	192 (68.3)	3 (4.2)	
IB	30 (8.5)	21 (7.5)	9 (12.7)	
IIA	9 (2.6)	6 (2.1)	3 (4.2)	
IIB	12 (3.4)	6 (2.1)	6 (8.5)	
IIIA	26 (7.4)	14 (5.0)	12 (16.9)	
IIIB	6 (1.7)	2 (0.7)	4 (5.6)	
IIIC	8 (2.3)	3 (1.1)	5 (7.0)	
IV	45 (12.8)	16 (5.7)	29 (40.8)	
Advanced stage at diagnosis (stage III/IV)	85 (24.1)	35 (12.5)	50 (70.4)	<0.001
Initial treatment, n (%)				<0.001
Surgery	287 (81.5)	261 (92.9)	26 (36.6)	
Limited resection, n/N (%)	86/287 (30.0)	85/261 (32.6)	1/26 (3.8)	
Lobectomy, n/N (%)	196/287 (68.3)	176/261 (67.4)	20/26 (76.9)	
Bilobectomy, n/N (%)	3/287 (1.0)	0/261 (0)	3/26 (11.5)	
Pneumonectomy, n/N (%)	2/287 (0.7)	0/261 (0)	2/26 (7.7)	
Chemotherapy with or without radiotherapy	58 (16.5)	18 (6.4)	40 (56.3)	
Supportive care only	7 (2.0)	2 (0.7)	5 (7.0)	
Recurrence after curative treatment, n (%)	31 (8.8)	20 (7.1)	11 (15.5)	0.026
Lung cancer-related death, n (%)	68 (19.3)	30 (10.7)	38 (53.5)	<0.001

*, cases of adenocarcinoma in situ. LDCT, low-dose chest computed tomography.

was significantly associated with a lower risk of mortality among peripheral lung cancers (HR =0.33, 95% CI: 0.13–0.84), but not central lung cancers (HR =0.69, 95% CI: 0.36–1.30). Central location was associated with a higher risk of mortality for both screen-detected (HR =4.98, 95% CI: 2.26–10.97) and non-screen-detected (HR =2.58, 95% CI: 1.15–5.75) lung cancers. When performing additional multivariate analyses including histological type (classified as adenocarcinoma, squamous cell carcinoma, other NSCLC, and SCLC) as a covariate, screen-detection remained significantly associated with a lower risk of mortality among peripheral lung cancers (HR =0.20, 95% CI: 0.07–0.55),

Table 4 Characteristics of non-screen-detected lung cancer patients stratified by cancer location

Characteristic	Total (n=71)	Central lung cancer (n=46)	Peripheral lung cancer (n=25)	P value
Classification of non-screen-detected cancer				
Missed cancer, n (%)	11 (15.5)	3 (6.5)	8 (32.0)	0.013
Non-compliance of participant, n (%)	3 (4.2)	2 (4.3)	1 (4.0)	1.000
Negative screen, n (%)	57 (80.3)	41 (89.1)	16 (64.0)	0.026
Type of primary tumor at first detection				0.352
Solid	70 (98.6)	46 (100)	24 (96.0)	
Part-solid	1 (1.4)	0 (0)	1 (4.0)	
Tumor size at first detection, mm, mean ± SD	46.7±24.4	49.6±24.7	41.3±23.1	0.175
Tumor with endobronchial lesion, n (%)*	41 (57.7)	38 (82.6)	3 (12.0)	<0.001
Time from last LDCT screening to pathologic diagnosis (months), mean ± SD	65.3±44.8	62.1±42.3	71.0±49.4	0.429
Cancer histology, n (%)				0.026
Invasive adenocarcinoma	23 (32.4)	13 (28.3)	10 (40.0)	
Adenosquamous carcinoma	1 (1.4)	1 (2.2)	0 (0)	
Squamous cell carcinoma	28 (39.4)	15 (32.6)	13 (52.0)	
Other non-small cell carcinoma	8 (11.3)	6 (13.0)	2 (8.0)	
Small cell carcinoma	11 (15.5)	11 (23.9)	0 (0)	
Lung cancer staging, n (%)				0.297
IA	3 (4.2)	2 (4.3)	1 (4.0)	
IB	9 (12.7)	4 (8.7)	5 (20.0)	
IIA	3 (4.2)	1 (2.2)	2 (8.0)	
IIB	6 (8.5)	2 (2.2)	4 (16.0)	
IIIA	12 (16.9)	10 (21.7)	2 (8.0)	
IIIB	4 (5.6)	3 (6.5)	1 (4.0)	
IIIC	5 (7.0)	4 (8.7)	1 (4.0)	
IV	29 (40.8)	20 (43.5)	9 (36.0)	
Advanced stage at diagnosis (stage III/IV)	50 (70.4)	37 (80.4)	13 (52.0)	0.012
Initial treatment, n (%)				0.006
Surgery	26 (36.6)	11 (23.9)	15 (60.0)	
Chemotherapy with or without radiotherapy	40 (56.3)	30 (65.2)	10 (40.0)	
Supportive care only	5 (7.0)	5 (10.9)	0 (0)	
Recurrence after curative treatment, n (%)	11 (15.5)	7 (15.2)	4 (16.0)	1.000
Lung cancer-related death, n (%)	38 (53.5)	30 (65.2)	8 (32.0)	0.007

*, endobronchial tumor or obstructive lesion(s) confirmed by bronchoscopic evaluation. LDCT, low-dose chest computed tomography; SD, standard deviation; GGN, ground glass nodule.

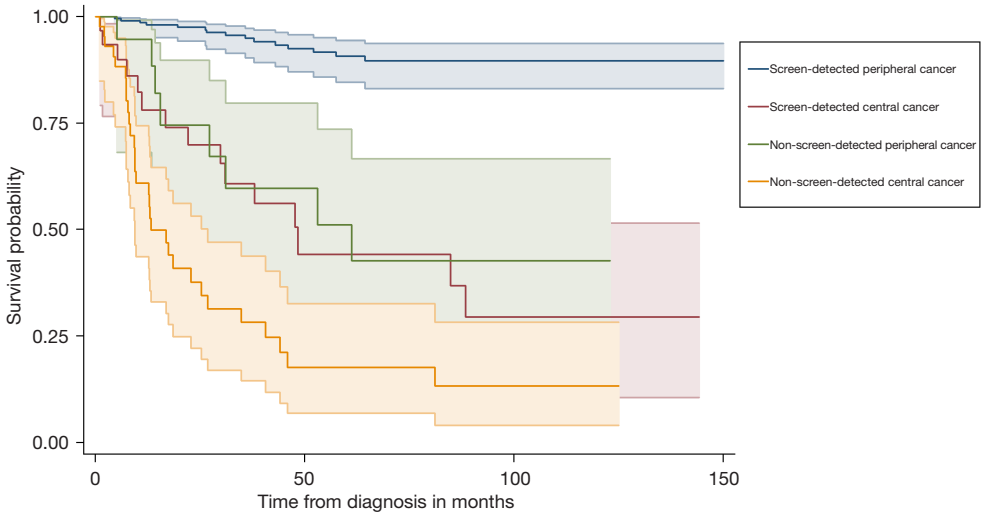

Figure 2 Kaplan-Meier analysis for mortality in subgroups stratified by screen-detection status and cancer location.

and insignificantly for central lung cancers (HR =0.51, 95% CI: 0.25–1.01). For subsets of screen-detected and non-screen detected cancers, after including histology in the multivariate analyses, central location remained significantly associated with a higher risk of mortality for both screen-detected (HR =5.55, 95% CI: 2.40–12.85) and non-screen-detected (HR =3.33, 95% CI: 1.41–7.85) lung cancers.

Results of subgroup analyses evaluating 273 screen-detected NSCLCs are shown in Tables S5,S6. Multivariate analyses revealed that central location was associated with a higher risk of advanced stage diagnosis (OR =14.66, 95% CI: 4.51–47.70) and mortality (HR =3.95, 95% CI: 1.69–9.22). Table S7 shows the sensitivity of LDCT screening for diagnosis of lung cancer, assuming screen-detected cases as true positives and false negative or negative screen cases as false negatives. The sensitivity for peripheral adenocarcinoma was high at 95.9%, compared to 55.2% for central adenocarcinoma. The sensitivity for squamous cell carcinoma was the lowest for both central (28.6%) and peripheral (48.0%) lung cancers.

Discussion

This study, on a large hospital-based cohort of individuals who underwent LDCT for lung cancer screening in South Korea, assessed the characteristics and outcomes of centrally-located lung cancer in comparison with peripherally-located lung cancer with a focus on screen-detection status. The cohort of asymptomatic participants who voluntarily underwent LDCT screening enabled the evaluation of a large number of never-smokers and relatively young individuals, and reflects the real-world state of LDCT screening in East Asia, where it is widely applied to these populations (15,31). In accordance to a prior study evaluating LDCT screening in the Asian population, our data also revealed better outcomes in diagnosed stage and mortality in the screen-detected cancer group (32). Moreover, our study evaluated extended aspects of diagnosed lung cancers in a screening cohort. The important findings from this study are as follows: (I) compared to peripheral lung cancers, central lung cancers were less likely to be screen-detected, and were diagnosed at an advanced stage with unfavorable outcomes. The majority of lung cancers diagnosed after a negative LDCT screening were centrally-located with a positive endobronchial lesion. (II) As expected, compared to non-screen-detection, screen-detection of lung cancer was significantly associated with a lower risk of diagnosis at an advanced stage and mortality. However, although screen-detection led to a significant reduction in the risk of advanced-stage diagnosis and mortality for peripheral lung cancers, it had no significant effect on the outcomes of central lung cancers. (III) Among screen-detected lung cancers, central location remained a significant risk factor for unfavorable staging and poor outcomes. Our findings indicate that central lung cancers, even when detected by LDCT screening, have highly aggressive features. Thus, LDCT screening may be an ineffective tool in the context of detecting and effectively treating central lung cancers at an early stage. To successfully reduce mortality associated

Table 5 Logistic regression for the risk of advanced stage (III or IV) at diagnosis according to location of cancer and detection by screening in lung cancer patients who underwent LDCT screening

Variable	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Central lung cancer (n=78)				
Age at diagnosis	1.04 (0.99–1.08)	0.116	1.00 (0.94–1.06)	0.971
Sex (male)	1.68 (0.44–6.46)	0.450	0.70 (0.10–4.86)	0.717
Smoking pack-years	1.01 (0.99–1.03)	0.189	1.00 (0.98–1.03)	0.780
Solid type (*vs.* subsolid)	22.40 (2.50–200.62)	0.005	19.64 (1.56–246.61)	0.021
Screen-detected (*vs.* non-screen-detected)	0.41 (0.15–1.13)	0.083	0.77 (0.23–2.51)	0.663
Peripheral lung cancer (n=274)				
Age at diagnosis	1.04 (1.00–1.09)	0.055	1.02 (0.97–1.07)	0.532
Sex (male)	6.04 (1.40–26.07)	0.016	2.85 (0.48–17.13)	0.251
Smoking pack-years	1.02 (1.00–1.04)	0.013	0.98 (0.95–1.01)	0.170
Solid type (*vs.* subsolid)	28.53 (6.60–123.26)	<0.001	18.28 (3.83–87.09)	<0.001
Screen-detected (*vs.* non-screen-detected)	0.06 (0.02–0.15)	<0.001	0.15 (0.05–0.45)	0.001
Screen-detected lung cancer (n=281)				
Age at diagnosis	1.04 (1.00 -1.08)	0.058	1.01 (0.97–1.06)	0.553
Sex (male)	3.87 (1.32–11.35)	0.013	3.72 (0.67–20.58)	0.132
Smoking pack-years	1.02 (1.01–1.04)	0.003	0.98 (0.96–1.01)	0.164
Solid type (*vs.* subsolid)	40.76 (9.50–174.02)	<0.001	28.56 (5.93–137.60)	<0.001
Central location (*vs.* peripheral location)	26.00 (10.72–63.05)	<0.001	20.83 (6.67–64.98)	<0.001
Non-screen-detected lung cancer (n=71)				
Age at diagnosis	1.00 (0.95–1.05)	0.911	0.99 (0.93–1.05)	0.659
Sex (male)	NA (0–Inf)*	0.992	NA (0–Inf)*	0.992
Smoking pack-years	1.00 (0.98–1.03)	0.803	1.01 (0.98–1.05)	0.384
Solid type (*vs.* subsolid)	NA (0–Inf)†	0.992	NA (0–Inf)†	0.996
Central location (*vs.* peripheral location)	3.79 (1.30–11.07)	0.015	3.74 (1.23–11.39)	0.020

*, calculation was not feasible due to the low number of female patients and related data (n=5, all diagnosed at an advanced stage) in this group; †, calculation was not feasible due to the low number of subsolid tumors and related data (n=1, with no mortality events) in this group. LDCT, low-dose chest computed tomography; OR, odds ratio; CI, confidence interval; NA, not applicable; Inf, infinity.

with central lung cancers, it will be necessary to develop novel clinical/radiological/biological signatures that can be used synergistically with current LDCT screening strategies. Investigations on potential modalities including autofluorescence bronchoscopy and blood biomarkers showed mixed results, and many are still in progress (33,34). Advances in CT imaging techniques and radiomics also have the potential to play an important role (35).

Several screening studies have reported data regarding the localization, histologic subtype, and stage of lung cancers in various regions and populations (3,17,36). However, to our knowledge, our study is the first to report the differences in cancer staging and clinical outcomes between central and peripheral lung cancers diagnosed in a LDCT screening setting and further stratified by whether the cancer was detected by screening. Large-scale screening study data have shown that the benefits of LDCT screening regarding survival for peripheral lung cancer cases is

Table 6 Cox-proportional hazard modelling for the risk of mortality from diagnosis according to location of cancer and detection by screening in lung cancer patients who underwent LDCT screening

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Central lung cancer (n=78)				
Age at diagnosis	1.05 (1.02–1.08)	0.003	1.03 (1.00–1.07)	0.074
Sex (male)	1.98 (0.61–6.40)	0.256	1.07 (0.30–3.79)	0.918
Smoking pack-years	1.01 (1.00–1.02)	0.064	1.00 (0.99–1.02)	0.599
Solid type (*vs.* subsolid)	NA (0–Inf)*	0.996	NA (0–Inf)*	0.996
Screen-detected (*vs.* non-screen-detected)	0.47 (0.25–0.87)	0.017	0.69 (0.36–1.30)	0.246
Peripheral lung cancer (n=274)				
Age at diagnosis	1.07 (1.02–1.13)	0.006	1.06 (1.01–1.12)	0.030
Sex (male)	7.87 (1.06–58.46)	0.044	3.31 (0.38–28.97)	0.280
Smoking pack-years	1.03 (1.01–1.04)	0.001	1.01 (0.98–1.03)	0.567
Solid type (*vs.* subsolid)	6.78 (2.52–18.26)	<0.001	3.27 (1.08–9.91)	0.037
Screen-detected (*vs.* non-screen-detected)	0.12 (0.05–0.29)	<0.001	0.33 (0.13–0.84)	0.021
Screen-detected lung cancer (n=281)				
Age at diagnosis	1.07 (1.03–1.12)	0.002	1.05 (1.00–1.10)	0.035
Sex (male)	3.37 (1.02–11.14)	0.046	1.39 (0.36–5.29)	0.634
Smoking pack-years	1.03 (1.01–1.04)	<0.001	1.00 (0.99–1.02)	0.582
Solid type (*vs.* subsolid)	9.55 (3.66–24.96)	<0.001	4.43 (1.53–12.81)	0.006
Central location (*vs.* peripheral location)	10.12 (4.94–20.74)	<0.001	4.98 (2.26–10.97)	<0.001
Non-screen-detected lung cancer (n=71)				
Age at diagnosis	1.04 (1.00–1.08)	0.047	1.03 (1.00 -1.07)	0.078
Sex (male)	1.30 (0.18–9.63)	0.797	2.24 (0.28–18.05)	0.453
Smoking pack-years	1.01 (0.99–1.02)	0.357	1.00 (0.99–1.02)	0.832
Solid type (*vs.* subsolid)	NA (0–Inf)†	0.998	NA (0–Inf)†	0.998
Central location (*vs.* peripheral location)	2.74 (1.25–6.01)	0.012	2.58 (1.15–5.75)	0.021

*, calculation was not feasible due to the low number of subsolid tumors and related data (n=6, with no mortality events) in this group; †, calculation was not feasible due to the low number of subsolid tumors and related data (n=1, with no mortality events) in this group. LDCT, low-dose chest computed tomography; HR, hazard ratio; CI, confidence interval; NA, not applicable; Inf, infinity.

indubitable. According to the NELSON trial, 84.2% of the 209 screen-detected lung cancers were located in the lung periphery (outer two-thirds of the costal-hilar diameter) and tended to be adenocarcinomas diagnosed at an early stage (17). Although the NLST and MILD trials did not provide information regarding the location of diagnosed lung cancers, a similar distribution of cancer locations is expected, since the majority of screen-detected cancers were early stage (pre-) invasive adenocarcinomas (3,4). Put together with the results of the International Early Lung Cancer Action Project (I-ELCAP) (16), which provided specific data on survival rates for lung cancers detected at an early stage, these data indicate that early-stage detection of peripheral lung cancers using LDCT can lead to favorable outcomes. However, limited data are available regarding stage distribution and clinical outcomes of centrally-located

lung cancers diagnosed in a screening setting. Central lung cancer, is known to be difficult to recognize with unenhanced LDCT scans (23,37), and mostly involves fast-progressing cancers such as SCLC (22). Moreover, even when the detected tumor size is small, central lung cancers have a higher risk of presenting with mediastinal metastasis, resulting in unfavorable staging (20,28,38). In accordance with prior data, the results from our study revealed a high percentage of peripherally-located early-stage cancers in screen-detected lung cancers (16,17). Among 281 screen-detected lung cancers, 88.6% were peripheral cancers, predominantly (pre-) invasive adenocarcinomas and stage I disease. In contrast, only 41.0% of the central lung cancers diagnosed in this screening cohort were screen-detected. Moreover, the majority (89.1%) of non-screen-detected central lung cancers had a negative finding on the previous LDCT screening. False-negative screening results constituted only 6.5% of non-screen-detected central cancers, compared to 32.0% among non-screen-detected peripheral cancers in our study, and 34.9% of all non-screen-detected cancers reported from the NELSON trial (23). Even when screen-detected, central lung cancers tended to be at an advanced stage, with unfavorable survival outcomes compared to those of screen-detected peripheral cancers. Therefore, unlike peripheral cancers, central lung cancers are less likely to benefit from LDCT screening. Our results add important insights to the unsolved problems of lung cancer screening with LDCT lying at the opposite end of the spectrum from overdiagnosis (39).

Although previous screening studies offered limited data on the characteristics and outcomes of central lung cancers, descriptions regarding SCLC, which mainly presents as central cancer, have been reported by a number of studies (40-42). A recent report on NLST data revealed that most SCLC cases (65.2%) diagnosed in participants who underwent LDCT screening were non-screen-detected. Even when screen-detected, 80% of SCLC cases were at an advanced stage (stage III/IV) and lacked survival benefits (40). Results from the Toronto, Mayo Clinic, and MILD screening studies also revealed that LDCT screening is ineffective in improving outcomes in SCLC (41,42). The results of our study extend this knowledge on the lack of benefits from LDCT screening to centrally-located NSCLC, and highlight another limitation of LDCT lung cancer screening. In our study, most (78.2%) of the diagnosed central cancers were NSCLCs. Compared to previous screening studies, the relatively higher proportion of NSCLC among all lung cancer as well as central cancer cases in our study could be due to difference between screening populations, including a substantial proportion of never-smokers (3,5). Our results show that, among screen-detected NSCLC cases, central location was significantly associated with an advanced-stage diagnosis (OR =14.66, 95% CI: 4.51–47.70) and poor survival (HR =3.95, 95% CI: 1.69–9.22). Thus, detection by LDCT screening did not improve the outcomes of central lung NSCLC.

Our study has certain limitations. First, this was a retrospective cohort study from a single center, and the protocols for LDCT screening rounds and intervals and follow-ups for positive findings were not strictly controlled. Since the number and interval of screening rounds were not controlled, we were not able to define and further evaluate 'interval cancers' that manifest between scheduled screening episodes following a negative screen (36,43). The possibility exists that some non-screen-detected cancers would have been screen-detected if a controlled screening protocol was applied. The retrospective design also made it impossible to apply pre-determined management guidelines for positive screening results. Moreover, the number of lung cancer cases not detected by screening may have been underestimated, as participants were not controlled for post-screen follow-ups, and a substantial proportion of lung cancer patients are known to be symptomless. Second, this study was based on a hospital-based design, and therefore the study population may not exactly represent the general population. To minimize selection bias, we included only asymptomatic individuals who underwent LDCT screening as part of their health check-ups and did not set specific conditions such as smoking status or age under which lung cancer screening would be recommended. The concordance of the overall incidence and distribution of pathologic subtypes of lung cancer in our study with the characteristics of previous Asian lung cancer screening cohorts supports the validity of our design (15). Third, the generalizability of our results to screening populations from different races and regions also remains undetermined since all participants were Korean, and the population is different from those of typical large trials from non-Asian regions.

The main strength of our study is the large sample size from a hospital cohort. The incidence of lung cancer and related deaths among never-smokers in East Asia is higher than that in Europe and United States and is increasing further (10,44). Our study represents an asymptomatic Asian population that would undergo LDCT screening in the real-world setting. Moreover, comprehensive data on mortality and clinical and radiological characteristics

associated with diagnosed lung cancer were collected. Above all, our data provide unique results which can aid further discussions on the effectiveness of LDCT screening and the need for novel signatures to aid early detection and treatment of specific lung cancer phenotypes. This will be an important issue related to lung cancer screening to be addressed in the future.

In conclusion, our study on an Asian lung cancer screening cohort that included a substantial proportion of never-smokers indicates that LDCT screening did not demonstrate an improvement in clinical outcomes of central lung cancer. The results were prominent for centrally-located NSCLC. This study highlights a limitation of lung cancer screening with LDCT and indicates the need of further research to develop synergistic clinical/radiological/biological modalities and signatures to successfully screen and treat central lung cancer.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No: B-2007/625–001), which waived the need for written informed consent from participants.

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