Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Prevalence of non-calcified pulmonary nodules in screening chest computed tomography

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Keywords
Computed tomography; early detection of cancer; lung neoplasms; pulmonary nodule.

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Received: 23 January 2013;
accepted 14 February 2013.

doi: 10.1111/1759-7714.12038

Abstract

Background: The National Lung Screening Trial revealed that low dose computed tomography (CT) screening reduced lung cancer mortality by 20%. However, nearly all (96.4%) of the positive screening results were false-positive. A higher false-positive rate (FPR) is expected in Korea, where the prevalence of tuberculosis and parasitic diseases are high.

Material and methods: We retrospectively reviewed the records of 1587 cases (906 males, 57.1%; 495 females, 31.2%) in which chest CT was used for health screening from 2006 to 2011 in one institution. The mean ± standard deviation age of the subjects was 62.7 ± 5.7 years and 495 (31.2%) subjects had a smoking history.

Results: Three hundred and thirty six subjects (21.2%) had non-calcified pulmonary nodules (NCPNs) described as solid nodules ($n = 319$), masses ($n = 15$) or pure or mixed ground glass opacities ($n = 36$). The incidence of NCPNs was 23.8% in smokers and 20.0% in non-smokers ($P = 0.08$). During a median follow up duration of 37 months (range, 0–67 months), eight subjects were confirmed to have lung cancer. Positive predictive value (PPV) of positive CT screening was 2.4% and FPR was 97.6%. Among 495 subjects who had a smoking history, 118 subjects displayed NCPNs (23.8%) and four patients were diagnosed with lung cancer, with a PPV and FPR of 3.4% and 96.6%, respectively.

Conclusion: CT screening has low PPV and high FPR, even in subjects with a high risk of lung cancer.

Introduction

Lung cancer is the leading cause of death in western countries[1] and also in Korea.[2] Because of a lack of effective screening methods, the majority of patients are diagnosed in an advanced stage that cannot be treated with curative surgery or radical radiation treatment.

Screening trials performed in the 1960s and 1970s using chest X-ray with or without sputum cytology failed to show a reduction in mortality in patients at a high risk of lung cancer.[3] Low-dose computed tomography (CT) scanning, which acquires images of the entire lungs within a single breath hold, has been utilized as a screening tool since 1990. Some positive results[4,5] have been published. But until the National Lung Screening Trial (NLST),[6] no data had shown the value of the technique in reducing mortality from lung cancer.

NLST reported a 20% reduction of lung cancer mortality with low-dose CT. Blunting the worldwide enthusiasm for the results among the public and national health authorities was the high false-positive rate (FPR) of the approach. The rate of positive screening tests was 24.2%, but nearly all of these (96.4%) were false-positives. Thus, to successfully detect lung cancer in 1% of the affected patients, 23% of people without lung cancer would needlessly undergo further evaluation, with the attendant emotional stress, procedural morbidity, and increased health care costs.

In Korea and other Asian countries, where the prevalence of transient inflammatory nodules is high,[7] even higher FPR is expected. In this survey, we tried to determine the positive rate of non-calcified pulmonary nodules (NCPNs) in routine health screening CT and correlated the findings with follow-up data to calculate the FPR and the positive predictive value (PPV).

Material and methods

This was a retrospective survey that examined the records of 5015 cases who received a chest CT for health screening purposes from 2006 to 2011, in one institution. Demographic data and CT results were downloaded in a spreadsheet format from the health information system of Chonnam National University Hwasun Hospital.

Subjects under 55-years-of-age ($n = 2640$), those who were scanned by cardiac CT only ($n = 705$), and individuals who were diagnosed with malignancy in other organs ($n = 83$), were excluded from this survey. Thus, 1587 subjects were analyzed for the prevalence of NCPNs in screening CT (Fig. 1). The mean ± standard deviation age of subjects was 62.7 ± 5.7 years. Nine hundred and six subjects (57.1%) were male and 495 subjects (31.2%) had a smoking history. From the health-screening interview, subjects who had smoked more than 10 packs in their lifetime were recorded as smokers or ex-smokers.

Thoracic CT scanning was performed using multi-detector row CT scanners (Light Speed VCT, GE Medical Systems, Milwaukee, WI, USA; SOMATOM Definition Flash, Siemens Medical Systems, Forcheim, Germany) with non-contrast enhanced CT. The scanning parameters for different scanners are summarized in Table 1. Subjects who showed abnormal findings on screening CT were consulted to the pulmonology department. They were evaluated with a follow up CT scan, with or without an antibiotics trial, or biopsy procedures were performed with bronchoscopy or percutaneous needle biopsy.

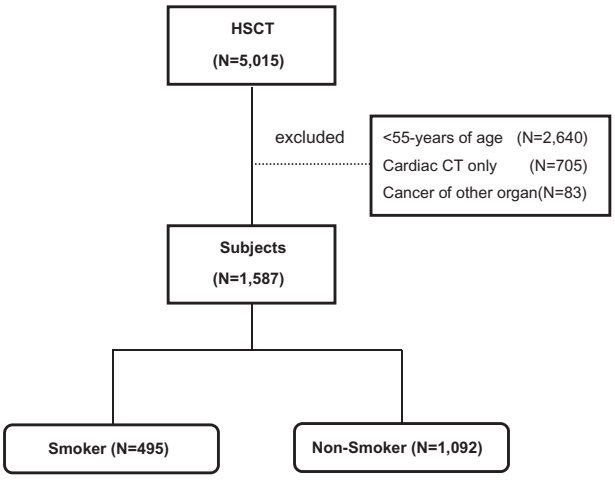

Figure 1 Diagram of subjects who were scanned with health screening chest computed tomography (HSCT) from 2006 to 2011.

Table 1 Computed tomographic scanning parameters of the two different scanners

	Light Speed VCT	SOMATOM Definition Flash
Detector configuration	40 mm coverage	128 * 0.6 mm
Total scan time (sec)	5	5
Pitch	0.98	0.9
Effective mAs	100	80
Peak kilovoltage (kVp)	120	120
Thickness/interval (mm)	3.75/3.75	3/3

Records with descriptions of "nodule," "ground glass opacity," "mass," or "malignancy," within 20 words distance from the word "lung" were searched using SPSS software version 20 (IBM, Somers, NY). The lung nodule was defined as a spot on the lung smaller than 3 cm in diameter. An abnormal spot ≥3 cm in diameter was designated a lung mass. Ground-glass opacity referred to the high resolution CT appearance of a hazy opacity that did not obscure the associated pulmonary vessels. Among the searched data, the authors verified cases with any of the following combinations: lung and nodule; lung and ground glass opacity; lung and mass; and lung and malignancy. As a result, a subject might have a mass and a nodule or ground glass opacity, concurrently.

Cases from the database of health information system of Chonnam National University Hwasun hospital and the Korean central lung cancer registry, with the diagnosis of lung cancer, were searched for a disease code "C34," which is the Korean Standard Statistical Classification (KSSC) code for lung cancer.

Results

Three hundred and thirty six subjects (21.2%) with NCPNs were detected. NCPNs were described as solid nodules ($n = 319$), pure or mixed ground glass opacities ($n = 36$), or masses or malignancy ($n = 15$, Table 2). Among 15 subjects whose CT was interpreted as masses or malignancy, three subjects were diagnosed with lung cancer (patient 3, 4, and 7 of Table 3), four subjects were lost to follow-up, and the remaining eight subjects proved to have benign lesions.

During a median follow-up of 37 months (range, 0–67 months), eight subjects were confirmed to have lung cancer. Among the eight lung cancer patients, four had a smoking history and four had never smoked. Five patients were diagnosed to have stage I disease. Four patients were surgically

Table 2 Characteristics of 1587 subjects who were screened with chest computed tomography

Characteristic	Number (%)
Age (years, Mean ± SD) (range)	62.7 ± 5.7 (55.0–88.5)
Sex (Male/Female)	906 (57.1%)/681 (42.9%)
Smoking (Current/Ex-smoker/Never smoked)	224(14.1%)/271(17.1%)/1092 (68.8%)
Number of patient with non-calcified nodules	336 (21.2%)
Nodule	319
Ground glass opacity	36
Mass, malignancy	15

SD, standard deviation.

Table 4 Comparison of the 1587 subjects by smoking history

Subgroups	Non-smokers	Smokers	*P*-value
Number (%)	1092 (62.8%)	495 (31.2%)	
Age (mean ± SD)	62.9 ± 5.9	62.1 ± 5.2	0.010
Sex (Male/Female)	417/675	489/6	<0.001
Non calcified nodules	218 (20.0%)	118 (23.8%)	0.080
Lung cancer	4 (0.37%)	4 (0.81%)	0.266

treated and one patient received stereotactic radiation therapy. Detailed records of two patients were not available as they were diagnosed and treated in other institutions (Table 3).

The incidence of NCPNs was 23.8% in smokers and 20.2% in non-smokers ($P = 0.080$, Table 4). In 1587 subjects, the PPV of CT screening was 2.4% and the PFR was 97.6%. Among 495 subjects who had a smoking history, 118 subjects showed NCPN (23.8%). Among them, four patients were diagnosed with lung cancer, giving a PPV of 3.4% and FPR of 96.6% (Table 5).

Discussion

Many lung cancer patients present with advanced disease at the time of diagnosis. Screening that detected lung cancer at earlier stages could enable treatment with a curative intent.[2] Randomized controlled trials conducted in the 1960s through to the 1980s did not demonstrate any correlation between screening chest radiographs and improved lung cancer-specific mortality rate with or without sputum cytology in patients that were deemed to be high-risk (>50-years-of-age or history of smoking).[3] Despite concerns of the design, statistical analysis protocols, and the out-dated imaging modalities of these studies, their data formed the basis of the recommendation against the use of chest radiographs as a screen for lung cancer which remains in force today.[8]

A recent phase III randomized trial (The Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial) reported that lung cancer mortality was not reduced by annual screening with chest radiographs, compared with usual care.[8]

Low-dose, non-contrast, thin-slice helical or spiral chest CT is a candidate for a lung cancer screening tool. The international Early Lung Cancer Action Project screened 31 567 asymptomatic patients at high risk for lung cancer (≥60-years-of-age with at least a 10-pack-year smoking history), using low-dose baseline CT and annual screening in 27 456 study participants.[5] Five hundred and thirty five subjects had suspicious lesions that required biopsies. Lung cancer was diagnosed in 484 participants. Of these, 412 (85%) were clinical stage I with an estimated 10-year survival rate of 88%, regardless of treatment.

The NLST began in 2002 as an initiative by the United States National Cancer Institute to address the concerns of bias and over-diagnosis from single-arm screening studies.[6] The trial was a prospective comparison of spiral CT and standard chest X-ray in 53 000 current or ex-smokers (55–74-years-of-age, 30 pack years). Reductions of 20% in lung cancer-specific mortality and 7% in mortality of any cause in the CT arm were reported.

A similar study that is ongoing in Europe (Dutch-Belgian NELSON trial) compares CT scanning with standard care in subjects with a history of heavy smoking.[9] The results will

Table 3 Characteristics of eight patients diagnosed with lung cancer

N	Age	Sex	Smoking	Histologic type	Type of attenuation	TNM	Stage	Size (cm)	Initial treatment	Outcome
1	60	M	Never	Adenocarcinoma	GGO	T1aNxMx	IA	2.0	Surgery	21 M alive, NED
2	61	F	Current	Adenocarcinoma	GGO	T1N0M0	IA	0.8	Surgery	43 M alive, NED
3	89	F	Never	Adenocarcinoma	Solid	T1N0M0	IA	2.3	SRS	4 M lost to F/U
4	66	M	Current	Squamous cell cancer	Solid	T3N0Mx	IV	9.8	Chemotherapy	9 M lost to F/U
5	65	M	Ex-smoker	Adenocarcinoma	Solid	T1N0M0	IA	1.5	Surgery	37 M alive, NED
6	73	M	Never	Adenocarcinoma	Solid	T1N0M0	IA	1.5	Surgery	52 M alive, NED
7	68	M	Current	–	Solid	T1N2Mx	IIIA	2.5		
8	59	M	Never	–	Solid	–	–	0.4		

F/U, Follow up; GGO, Ground glass opacity; NED, No evidence of disease; SRS, Stereotactic radiosurgery; TNM, Tumor Lymph nodes Metastasis.

Table 5 Nodule detection rate (NDR), positive predictive value (PPV) and false-positive rate (FPR) of screening computed tomography in 1587 subjects ≥55-years-of-age and in the subgroup with a smoking history ($n = 495$)

	Total ($n = 1,587$)			Smokers ($n = 495$)		
	Normal	Nodule		Normal	Nodule	
Normal	1,251	328	1,579	377	114	491
Cancer	0	8	8	0	4	4
		336	1,587		118	495
NDR		21.2%			23.8%	
PPV		2.4%			3.4%	
FPR		97.6%			96.6%	

FPR, False-positive rate; NDR, Nodule detection rate; PPV, Positive predictive value.

provide important data concerning mortality advantage, cost effectiveness, and clinical management outcomes of lung cancer screening.

Recently, the National Comprehensive Cancer Network released a lung cancer screening guideline recommending screening using low-dose CT for high risk individuals (55–74 years of age with a smoking history).[10] However, unresolved issues need to be addressed before low dose chest CT screening is incorporated in a national screening program.[11,12] Indeed, the present retrospective survey indicates that CT screening has low PPV and high FPR, even in subjects at high risk of lung cancer.

Prospective studies have reported PPV of positive CT findings ranging from 2.8% to 11.6%, and FPR ranging from 10% to 50%, depending on the geographical region.[11] In our study, the PPV was 3.4% and the FPR was 96.6% in subjects >55-years-of-age with a smoking history. The 3.4% PPV of the health screening chest CT corresponded with the rate determined in prospective studies. But, the FPR was markedly higher than the rate found in the prospective studies.

The higher FPR could be attributed to the higher incidence of inflammatory nodules, such as pulmonary tuberculosis or parasite infection, in Korea. However, in the present survey, the incidence of NCPNs (23.8%) was similar to the nodule detection rate of NLST (24.2%).

The FPR of CT screening may be lowered in two ways. Diagnostic accuracy of CT scanning may be improved with novel technologies, such as high-speed multi-detector CT imaging and image processing technology. On the other hand, if we can define the high-risk population with higher specificity, the FPR can be lowered.

However, defining the high-risk population is not easy. Although smoking is the major risk factor of lung cancer and is regarded as a major determinant of high-risk population in current clinical trials, the proportion of lung cancer patients who have never smoked is increasing.[13,14] Especially, the proportion of smokers in female patients with lung cancer is relatively low. As screening for smokers will miss this growing population, sensitive and specific diagnostic biomarkers to identify candidates for CT screening for lung cancer are desperately needed.

Conclusion

With review of data from 1587 subjects who were screened with chest CT scans, we found CT screening has a high false-positive rate, even in subjects with a high risk of lung cancer. Efforts to lower the high false-positive rate of CT screening should be undertaken before health-screening programs adopt lung cancer CT screening.

Disclosure

No authors report any conflict of interest.

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