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Outcome of incidentally detected airway nodules

Hyung-Jun Kim[1,2], Deog Kyeom Kim[1,3], Young Whan Kim[1,4], Yeon Joo Lee[1,2], Jong Sun Park[1,2], Young-Jae Cho[1,2], Se Joong Kim[1,2], Ho Il Yoon[1,2], Jae Ho Lee[1,2] and Choon-Taek Lee[1,2]

Affiliations: [1]Dept of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea. [2]Division of Pulmonary and Critical Care Medicine, Dept of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-Si, Republic of Korea. [3]Division of Pulmonary and Critical Care Medicine, Dept of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Republic of Korea. [4]Division of Pulmonary and Critical Care Medicine, Dept of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea.

Correspondence: Choon-Taek Lee, 82 Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-Si, Gyeonggi-do 13620, Republic of Korea. E-mail: ctlee@snu.ac.kr

ABSTRACT Low-dose chest computed tomography (LDCT) screening increased detection of airway nodules. Most nodules appear to be secretions, but pathological lesions may show similar findings. The National Comprehensive Cancer Network (NCCN) recommends repeating LDCT after 1 month and proceeding to bronchoscopy if the nodules persist. However, no reports exist about incidentally detected airway nodules. We investigated the significance of airway nodules detected by LDCT screening.

We screened patients with incidental airway nodules detected by LDCT in the Seoul National University Hospital group. The characteristics of computed tomography, bronchoscopy, pathology and clinical findings were analysed.

Among 53 036 individuals who underwent LDCT screening, 313 (0.6%) had airway nodules. Of these, 186 (59.4%) were followed-up with chest computed tomography and/or bronchoscopy. Seven (3.8%) cases had significant lesions, including leiomyoma (n=2), endobronchial tuberculosis (n=2), chronic inflammation (n=1), hamartoma (n=1) and benign granuloma (n=1). The remaining 179 lesions were transient, suggesting that they were secretions.

The use of LDCT for lung cancer screening demonstrated the low incidence of airway lesions. Most lesions were transient secretions. True pathological lesions were rare, and no malignant lesion was found. The current recommendation of the NCCN guideline is a reasonable approach that can avoid unnecessary bronchoscopy.

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The current NCCN guidelines for incidentally found airway nodules seem to be a reasonable approach http://ow.ly/Ywn6A

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Introduction

Nodules of the tracheobronchial tree are produced by various diseases, including malignancy, benign tumour, infection, trauma, other idiopathic aetiologies such as sarcoidosis, and transient insignificant lesions such as secretions [1–4]. Tracheobronchial tumours are rare, representing 0.4% of all body tumours [5], and 10% are reported to be benign [6]. Primary tumours of the trachea represent 0.1% of body tumours [7]. Early recognition of the airway lesion is crucial for timely intervention to minimise complications related to airway compromise [1]. Furthermore, airway metastasis from extrapulmonary tumours may be the first manifestation of the neoplasm in ∼5% of cases, as shown in a recent study [8]. Diverse types of malignancies may present as airway invasion or metastasis [9, 10].

Early detection of an airway lesion is difficult because these lesions are usually invisible on simple chest radiographs, and symptoms are not evident in the early stage of the disease. Therefore, computed tomography (CT) is recommended to facilitate early intervention when airway lesions are suspected [1]. Several CT findings have been suggested to indicate the nature of airway nodules. Mucus materials present as nodules of low attenuation and have a bubbly appearance, usually in the dependent portion of the airway, while malignant tumours present as polypoid nodules with eccentric wall thickening and benign tumours present as popcorn calcifications with internal fat material [5, 6].

Despite the recent clinical implementation of low-dose chest CT (LDCT) for lung cancer screening in high-risk patients [11, 12], guidelines for cancer screening of airway lesions are not clearly established. The current National Comprehensive Cancer Network (NCCN) guidelines suggest that if endobronchial nodules are suspected on LDCT, follow-up LDCT should be performed after 1 month following vigorous coughing, and bronchoscopic examination is recommended if the lesions persist [13]. However, no evidence has been presented to support the recommendation of a follow-up CT. Previous studies have shown that a CT scan can help to distinguish endobronchial lung cancer in 79–83% of cases [14, 15]. However, these reports were retrospective reviews of diagnosed cancer patients using contrast-enhanced CT. No previous studies are available on the clinical impact of LDCT on airway tumours.

The aims of this study were to evaluate the clinical significance of incidentally detected airway nodules from LDCT screening for lung cancer in health promotion centres, to determine the role of follow-up CT, to provide evidence to support the current NCCN guidelines, and to assess whether LDCT is an effective method for detecting early bronchogenic cancer in the airway.

Material and methods

Study design and participants

We reviewed patients who received LDCT for the purpose of lung cancer screening at Seoul National University Bundang Hospital (Seongnam-Si, Republic of Korea), Seoul National University Hospital and Seoul National University Boramae Medical Center (Seoul, Republic of Korea) (the Seoul National University Hospital group) between May 2003 and February 2015; January 1999 and February 2015; and January 2007 and February 2015. This duration was determined by the oldest picture archiving and communicating system data available in each hospital.

This study was conducted in accordance with the amended Declaration of Helsinki and was reviewed by the institutional review board in each hospital (the protocol numbers are B-1501/282-110, H-1505-089-673 and 20150706/16-2015/86-081). Informed consent was not obtained, but patient records and information were anonymised and de-identified prior to analysis. Among LDCT interpretation, keywords implying airway nodules, such as endobronchial, endotracheal, luminal, bronchoscopy, mucus and airway, *etc.*, were initially screened. All screened LDCTs were reviewed to confirm the cases of real airway nodules. Airway nodules were defined as a roughly spherical opacity confined within the lumen of the airway (bronchus and trachea) [16]. Luminal narrowing, atelectasis without airway nodules and nodules within bronchiectatic airways were excluded.

Measurements and definition

Demographic and clinical characteristics were collected, including smoking status, follow-up method and interval, initial and final diagnosis and referral to a pulmonologist. Characteristics of the nodules on CT, such as the longest diameter, Hounsfield unit, shape and margin were recorded. LDCTs were performed according to the standardised protocols of each medical centre (1–5 mm thickness, with radiation dose of 1–2 mSv). Length was measured as the longest diameter using the preset lung window setting of each medical centre (level −500–−700 HU; width 1500–2000 HU). The Hounsfield unit was measured by drawing a round region of interest in the preset mediastinal window setting of each centre (level 25–45 HU; width 250–400 HU) while avoiding grossly visible heterogeneous lesions, such as air, fat and calcification. The location of the nodule was classified as anterior or posterior based on its position relative to an imaginary line crossing the midline of the airway lumen [16]. The initial diagnosis of the nodule was based on the radiologist's interpretation and classified as a secretion, true lesion or both possible.

Final diagnosis was established by CT follow-up and/or bronchoscopy, with or without pathologic confirmation. Secretion was confirmed by the disappearance or alteration of a nodule on a follow-up CT. Finally, the airway nodules were classified as either true lesions or secretions. The clinical and radiological characteristics of each group were compared.

Analysis

All statistical analysis was performed using SPSS 22.0 (IBM, Armonk, NY, USA). The variables were analysed using the Pearson Chi-squared or Fisher's exact tests for categorical variables and the t-test or Mann–Whitney U-test for continuous variables.

Results

Baseline and clinical characteristics

53 036 individuals underwent LDCT in three medical centres. Characteristics such as smoking history, previous cancer history, sex and age were unknown. Initially, 5880 patients were selected by searching keywords of radiologists' interpretations. After excluding false-positive selections by individual CT review, 313 (0.6%) patients were found with airway nodules, and of these patients, 186 (59.4%) were followed-up for proper diagnosis (fig. 1). The reasons for loss of follow-up were high suspicion of secretion (81.9%), failure of the patient to return for follow-up (10.2%), CT study too recent for follow-up to be conducted (3.9%) and referral to other hospitals (3.1%) (table 1).

Of the 186 patients followed-up, 165 (88.7%) were male, with an average age of 56.1 years. 63% of the patients were current smokers, 14.5% were former smokers and 19.9% were never-smokers. No subjective symptoms were found in the majority of the patients (86.0%). Sputum was found in 6.5% of patients, followed by cough (2.7%), dyspnoea (2.2%), chest soreness (1.1%), throat pain (0.5%) and palpitation (0.5%) (table 2).

CT findings of airway nodules

The average length of the nodules was 8.48 mm and the median Hounsfield units were −36.5. The trachea was the most common location (49.5%), followed by the left main bronchus (13.4%) and the right lower lobar bronchus (11.8%). 54% of the nodules were found posteriorly within the airways, and the presence of a circumscribed margin (55.9%) was slightly more common than an uncircumscribed margin (44.1%). An obtuse angle (61.3%) and an oval shape (51.1%) were the most common. The initial CT interpretation

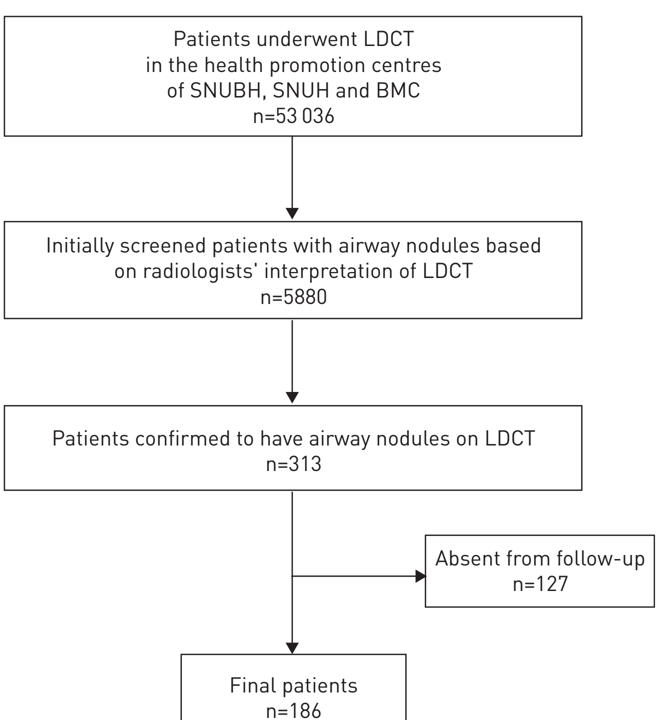

FIGURE 1 Flowchart of the patient selection process. SNUBH: Seoul National University Bundang Hospital; SNUH: Seoul National University Hospital; BMC: Boramae Medical Center; LDCT: low-dose chest computed tomography.

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TABLE 1 Reasons for loss to follow-up	
Subjects n	127
High suspicion of secretion	104 (81.9)
Patient did not return	13 (10.2)
Study too recent for follow-up	5 (3.9)
Referral to other hospital	4 (3.1)
Unclear	1 (0.8)

Data are presented as n (%), unless otherwise stated.

was secretion in 69.9% of cases and indeterminate nodule in 26.9%; true lesions were strongly suggested only in 3.2% of cases (table 3).

Diagnosis

Follow-up of endobronchial or endotracheal nodules was conducted in 186 patients using CT (86.6%), bronchoscopy (9.7%) or both (3.8%) (fig. 2). The median follow-up interval was 9 months, and 31.7% of the patients were referred to a pulmonologist for further evaluation. Finally, 179 (96.3%) of the 186 patients were confirmed to have nodules composed of secretory materials. The remaining seven true airway nodules were found to be leiomyoma (n=2), endobronchial tuberculosis (n=2), chronic inflammation (n=1), hamartoma (n=1) and benign granuloma (n=1) (table 4). No malignant nodules were found.

The characteristics of the seven patients with true airway nodules are summarised in table 5. Four patients had a history of smoking, and two had clinical symptoms including sputum and cough. Six cases were initially suspected to have true airway lesion by the responding radiologist. For example, case 2 had an airway nodule located between the carina and the left main bronchus, and the follow-up CT showed a persistent lesion, leading to a bronchoscopic evaluation. It also showed a polypoid mass and biopsy results confirmed that the lesion was leiomyoma (online supplementary fig. S1a). In contrast, the CT findings in case 6 were initially suspected to be caused by secretion; however, follow-up CT showed a persistent lesion and bronchoscopic evaluation led to the diagnosis of a hamartoma (online supplementary fig. S1b). A case of endobronchial tuberculosis (case 4) was confirmed by sputum smear and culture for *Mycobacterium tuberculosis*, while the other (case 5) was diagnosed by coexisting parenchymal tuberculosis and size reduction of the nodule after anti-tuberculosis medication.

Comparison between secretion and a true airway lesion

We compared the clinical and radiological characteristics between secretions and true airway lesions. True lesions tended to have a higher density (HU) than secreted material ($p=0.004$), and the initial radiologists opinion was significantly correlated with the final diagnosis ($p=0.001$). A history of smoking, an obtuse angle and an ovoid shape suggested secretion rather than a true lesion, but these findings were not statistically significant due to an insufficient number of cases (table 6).

TABLE 2 Baseline and clinical characteristics	
Male	165 (88.7)
Age years	56.10±10.63
Smoking	
Current smoker	118 (63.4)
Former smoker	27 (14.5)
Never-smoker	37 (19.9)
Unknown	4 (2.2)
Duration of smoking pack-years	32.60±17.45
Symptoms#	
None	160 (86.0)
Sputum	12 (6.5)
Cough	5 (2.7)
Dyspnoea	4 (2.2)
Chest soreness	2 (1.1)
Throat pain	1 (0.5)
Palpitation	1 (0.5)

Data are presented as n (%) or mean±SD. #: multiple symptoms possible.

TABLE 3 Characteristics of airway nodules on computed tomography

Size mm	8.48±3.73
Density HU	−36.5 (−106.25–5.25)
Location	
Central airway#	134 (72.0)
Peripheral airway	52 (28.0)
Position	
Posterior	101 (54.3)
Anterior	65 (34.9)
Unclear	20 (10.8)
Shape	
Oval	95 (51.1)
Lobulated	35 (18.8)
Round	34 (18.3)
Complex	22 (11.8)
Initial diagnosis	
Secretion	130 (69.9)
Secretion or true lesion	50 (26.9)
True lesion	6 (3.2)

Data are presented as mean±SD, median (interquartile range) or n (%). #: includes the trachea, right main bronchus and left main bronchus.

Discussion

Lung cancer screening using LDCT has been proven to be effective for detecting early-stage lung cancer in high-risk individuals, although some uncertainty exists regarding the potential harms of screening and the generalisability of the results [11, 17, 18]. LDCT was an effective screening method for detecting early lung cancer presenting as peripheral nodules (solitary pulmonary nodules, including ground-glass opacity nodules). However, most clinicians and researchers doubt that LDCT will be useful for detecting early lung cancer arising in the airways (trachea and bronchus).

Several studies have investigated lesions of the tracheobronchial tree. Lesions with a round or lobulating shape, an uncircumscribed margin, or a CT value of ⩾21.7 HU may indicate true lesions [16]. In other studies, CT findings of bronchial carcinoid tumours have been described [19], and differentiation of anthracofibrosis from endobronchial tuberculosis using CT has proven to be viable [20]. Furthermore, increased fluorodeoxyglucose positron emission tomography/CT uptake at the obstruction site indicates a high probability of malignancy, with certain types of cancer showing a significantly higher standard uptake value than others [21, 22]. However, these studies were based on contrast-enhanced CT with standard-dose radiation, or nuclear imaging with radioactive materials.

Our study is the first to analyse the incidence of incidentally detected airway nodules using LDCT. 53 036 patients underwent LDCT for purpose of lung cancer screening at three medical centres over a ∼10-year period. 313 (0.6%) of these cases were found to have endobronchial or endotracheal nodules. This result is similar to previous reports regarding the general incidence of endobronchial tumours [5, 7].

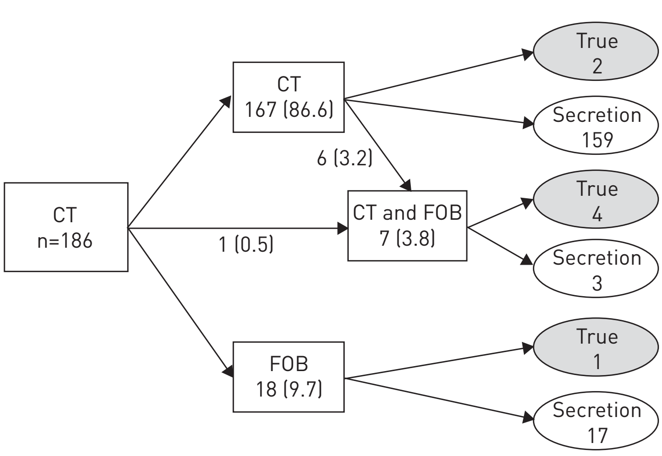

FIGURE 2 Follow-up method of incidentally found airway nodules. Data are presented as n (%). CT: computed tomography; FOB: fibre optic bronchoscopy.

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TABLE 4 Findings of follow-up

Follow-up method	
CT	161 (86.6)
Bronchoscopy	18 (9.7)
Both	7 (3.8)
Follow-up interval months	9 (3–14)
Bronchoscopic evaluation	25 (13.4)
Referral to pulmonologist	59 (31.7)
Final diagnosis	
Secretion	179 (96.3)
Leiomyoma	2 (1.1)
Endobronchial tuberculosis	2 (1.1)
Chronic inflammation	1 (0.5)
Hamartoma	1 (0.5)
Benign granuloma	1 (0.5)

Data are presented as n (%) or median (interquartile range). CT: computed tomography.

Bronchoscopy is the procedure of choice for the evaluation of airway tumours [23]. Flexible fibre optic bronchoscopy is a relatively safe procedure, but it is still invasive and expensive. It may induce procedure- or anaesthesia-related complications such as hypoxaemia (0.2–21%), arrhythmia (1–10%), post-biopsy bleeding (0.12–7.5%), pneumothorax or pneumomediastinum (1–6%), fever (0.9–2.5%) and death (0.1–0.2%) [24].

CT has a role in defining and treating lung cancer with endoluminal invasion [25], and it may be used instead in selected cases when the patient has a contraindication to bronchoscopy or has refused the procedure [26]. A previous study attempting to determine whether CT scans could be substituted for bronchoscopy failed to detect endobronchial tumours in 17% of patients [14]. CT has the disadvantage of a lower sensitivity for detecting endobronchial nodules, but substituting CT for bronchoscopy can have benefits in terms of reducing the related complications.

Our study has shown that incidentally detected airway nodules were mostly secretions (96.3%), and true lesions were not found to be malignant. Considering this incidence and the potential adverse effects of the bronchoscopic procedure, CT follow-up would be sufficient in most cases and bronchoscopy should be undertaken selectively. Of the 186 patients, 161 (86.6%) underwent follow-up CT initially, and 18 (9.7%) of them underwent bronchoscopy primarily as a follow-up method. The other seven (3.8%) patients underwent bronchoscopy after CT follow-up due to persistent nodules. Of the total 25 bronchoscopic exams, only five (2.9%) cases were diagnosed with significant airway lesions, and 20 (11.7%) were found to be secretions. The more prudent application of bronchoscopy did not cause a significant delay in diagnosis. These data could provide a rationale for the current NCCN guideline: repeat LDCT after 1 month with vigorous coughing when endobronchial nodules are suspected on screening CT and further bronchoscopy should be considered if the nodule is not resolved [13].

TABLE 5 Characteristics of true lesion cases

Case	Sex	Age years	Smoking	Symptoms	Initial interpretation	Follow-up	FOB findings	Pathology	Final diagnosis
1	M	75	Former	None	Both#	Both¶	Elevation of normal mucosa	Chronic active inflammation	Chronic inflammation
2	M	41	Current	None	True lesion	Both¶	Polypoid mass	Leiomyoma	Leiomyoma
3	M	40	Current	None	Both#	FOB	Polypoid mass	Leiomyoma	Leiomyoma
4	F	37	Never	Sputum	True lesion	CT	Not done	Not done	EBTB
5	M	46	Never	Cough	True lesion	CT	Not done	Not done	EBTB
6	M	52	Former	None	Secretion	Both¶	Polypoid mass	Mature cartilaginous tissue	Hamartoma
7	F	64	Never	None	Both#	Both	Nodular lesion	Negative for malignant cells	Benign granuloma

Data are presented as n, unless otherwise stated. FOB: fibre optic bronchoscopy; M: male; F: female; CT: computed tomography; EBTB: endobronchial tuberculosis. #: both secretion and true lesions possible; ¶: follow-up CT followed by FOB.

TABLE 6 Comparison between secretions and true airway lesions

	Secretion	True lesion	p-value
Subjects	179	7	
Male	160 (89.4)	5 (71.4)	0.180
Age years	56.31±10.47	50.71±14.07	0.337
Ever smoking	141 (80.6)	4 (57.1)	0.150
Size mm	8.53±3.77	7.09±2.41	0.172
Density (HU)	−39 (−110−−1.70)	30 (−9.33−44)	0.004
Location			0.097
Central airway#	131 (73.2)	3 (42.9)	
Peripheral airway	48 (26.8)	4 (57.1)	
Angle			0.104
Obtuse	112 (64.0)	2 (28.6)	
Not obtuse	63 (36.0)	5 (71.4)	
Shape			0.063
Ovoid	93 (52.0)	1 (14.3)	
Acute or unclear	86 (48.0)	6 (85.7)	
Initial diagnosis			0.001
Secretion	136 (76.0)	1 (14.3)	
Unsure	43 (24.0)	6 (85.7)	
Symptoms	22 (12.3)	2 (28.6)	0.224

Data are presented as n, n (%), mean±SD or median (interquartile range), unless otherwise stated. #: includes the trachea, right main bronchus and left main bronchus.

Although only a small number of cases were confirmed as true airway lesions, a higher HU value may indicate true lesions rather than the presence of secreted materials, and this is in accordance with a previous report [16]. Furthermore, except for one case of a hamartoma that was initially diagnosed as a secretion, six other cases were initially suspected to have true lesions by the attending radiologist. As the data were obtained from three different medical centres, we can assume that the interpretations of qualified radiologists correspond with the final diagnosis of incidentally detected airway nodules.

Interestingly, we did not find any cases of early bronchogenic cancer presenting as airway nodules. We propose several possibilities that may explain the absence of malignancy.

First, the low incidence of airway malignancies may be due to the characteristics of our study population, which are similar to the general population. Despite recent recommendations suggesting LDCT in high-risk populations, the criteria for LDCT are not well established in South Korea. The decision to perform LDCT mostly depends on the patient's personal needs regardless of risk factors for lung cancer such as a history of smoking. However, when high-risk smokers were chosen as a subgroup, only 47 cases of airway nodules were found, and all turned out to be secretory materials [11].

Second, LDCT is not a suitable method for detecting early bronchogenic cancer in contrast to peripheral lung nodules. Among the patients who were screened and diagnosed with lung cancer in the National Lung Screening Trial, only ∼1.8% of them were found to have atelectasis upon LDCT [27]. Neither endobronchial nor endotracheal nodules were mentioned. In the NELSON study of 7155 participants, 34 patients had interval cancers, roughly defined as lung cancers diagnosed after false negative LDCT results. Among the 34, five cancers were not detected initially due to their location in the endobronchial lumen [28]. Endobronchial nodules are still considered as blind spots on screening CTs [29].

This study has some limitations. This is a retrospective study, and the screened population is not a high-risk group for lung cancer. 40% of the patients with airway nodules were not properly followed-up for diagnosis.

In summary, the use of LDCT for lung cancer screening demonstrated the low incidence of airway nodules (0.6%). Secretions were predominant, and true lesions were extremely rare. Furthermore, none of the true lesions were confirmed as malignancies. Most lesions could be diagnosed *via* CT follow-up only, and primary bronchoscopic evaluation was not helpful. Therefore, the current recommendation of LDCT follow-up according to the NCCN guideline for endobronchial nodules appears to be a reasonable approach that can prevent unnecessary bronchoscopy.

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