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Early detection of lung cancer using ultra-low-dose computed tomography in coronary CT angiography scans among patients with suspected coronary heart disease

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ABSTRACT

Objectives: To assess whether an additional chest ultra-low-dose CT scan to the coronary CT angiography protocol can be used for lung cancer screening among patients with suspected coronary artery disease.
Methods: 175 patients underwent coronary CT angiography for assessment of coronary artery disease, additionally undergoing ultra-low-dose CT screening to early diagnosis of lung cancer in the same scanner (80 kVp and 15 mAs). Patients presenting pulmonary nodules were followed-up for two years, repeating low-dose CTs in intervals of 3, 6, or 12 months based on nodule size and growth rate in accordance with National Comprehensive Cancer Network guidelines.
Results: Ultra-low-dose CT identified 71 patients with solitary pulmonary nodules (41%), with a mean diameter of 5.50 ± 4.00 mm. Twenty-eight were > 6 mm, and in 79% (n = 22) of these cases they were false positive findings, further confirmed by follow-up (n = 20), resection (n = 1), or biopsy (n = 1). Lung cancer was detected in six patients due to CT screening (diagnostic yield: 3%). Among these, four cases could not be detected in the cardiac field of view. Most patients were in early stages of the disease. Two patients diagnosed at advanced stages died due to cancer complications. The addition of the ultra-low-dose CT scan represented a radiation dose increment of 1.22 ± 0.53% (effective dose, 0.11 ± 0.03 mSv).
Conclusions: Lung cancer might be detected using additional ultra-low-dose protocols in coronary CT angiography scans among patients with suspected coronary artery disease.

1. Introduction

Lung cancer remains the most common cancer in men and the third most common in women [1]. According to the World Health Organization 2014 report, there were more than 1.8 million new cases and almost 1.6 million deaths, corresponding to 13% of total cancer incidence and 20% of total cancer mortality [1]. Besides, lung cancer is the most lethal cancer worldwide, and the 5-year survival rate is about 15.6% in the United States [2].

Almost 75% of patients with symptoms due to local or metastatic disease are not eligible to cure, and absence of symptoms at detection is a favourable prognostic factor [3,4]. In this manner, early diagnosis is an important tool to reduce morbidity and mortality, and CT screening demonstrated a 20% decrease in the lung cancer mortality for high-risk

Abbreviations: CAC, coronary artery calcification; CCTA, coronary computed tomography angiography; CAD, coronary artery disease; CT, computed tomography; DLP, dose-length product; ECG, electrocardiogram; ED, Effective radiation dose; FOV, field of view; I-ELCAP, International Early Lung Cancer Action Program; NCCN, National Comprehensive Cancer Network; ULDCT, ultra-low-dose computed tomography

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populations such as heavy-smokers (30 or more pack-years) from 55 to 74 years [5–7]. However, CT screening also has some considerable disadvantages as radiation exposure, patient distress, and over-diagnosis. Aiming to reduce the cumulative radiation dose, many studies have demonstrated that Ultra-Low-Dose CT (ULDCT) could be used to screen high-risk patients for lung cancer, using a radiation dose comparable to standard radiographies and detecting up to 93.3% of all pulmonary nodules [8–11].

Tobacco is also a major risk factor for atherosclerosis, coronary artery disease (CAD), and cerebrovascular disease [12,13], and some studies demonstrated that patients with cancer are more likely to develop atherosclerosis (hazard ratio 1.32, 1.29 for women and men, respectively) [14]. Besides, mainly due to advanced age and long-standing smoking history, most patients who match criteria for lung cancer screening will also be at an intermediate risk for cardiovascular events [15]. For this reason, some studies have sought to identify these patients at risk during CT scans for lung cancer screening, using the coronary artery calcification (CAC) score, a predictive factor for CAD [16]. According to data from the International Early Lung Cancer Action Program (I-ELCAP), approximately 7 million people would be eligible for such screening only in the USA [5]. Likewise, many patients undergoing imaging for cardiovascular conditions could also benefit from lung cancer screening.

Suspected CAD is commonly investigated using coronary computed tomography angiography (CCTA), and a CAC scan is often performed as a "filter scan" prior to CCTA to identify possible severe coronary calcification that could compromise the study quality and to reduce the radiation dose by limiting the z-axis length [17]. However, CAC scans have limited field of view (FOV), mostly covering around 40% of lungs, what would be inadequate for lung cancer screening especially due to predominant location in the upper lobes [15,18,19]. Therefore, the aim of this study was to assess whether associating a chest ULDCT scan to the CCTA protocol for patients with suspected CAD would be useful for lung cancer screening.

2. Materials and methods

2.1. Participants

With the approval of our Institutional Review Board and obtained written informed consent, we prospectively included 175 consecutive patients from two centres aged from 40 to 80 years from August 2014 to January 2015. Subjects were symptomatic patients without known heart disease, with either nonacute or acute presentations that underwent CCTA for detection of coronary artery disease. Patients underwent CCTA for suspected heart disease and additionally underwent ULDTC scanning for early lung cancer detection. Differently from the usual lung cancer screening programme, smoking status was not used as an inclusion criterion, and we included smokers, former smokers and non-smokers. Patients were excluded if they had any contraindications to iodinated contrast such as allergies and chronic kidney failure, or if there was any suspicion of pregnancy. Based on the screening findings, patients were followed-up for two years up to January 2017 (See "2.4. Evaluation of screening findings").

2.2. CT protocols

Patients were scanned on a multislice CT system using a 64-row multidetector CT scanner (Ingenuity CT; Philips Healthcare, Best, The Netherlands). Images were acquired using a slice thickness of 0.625 mm and a FOV of 320 mm. Initially, an anteroposterior scanogram (120 kV, 50 mA) was obtained for further planning. Based on the cardiac dimensions on this scanogram, the z-axis length of the subsequent non-contrast calcium scoring CT was defined. The size of this FOV was in the range of 200–220 mm to achieve an in-plane pixel size of approximately $0.4 \times 0.4\,mm^2$ at an image matrix of 512×512. The reconstruction FOV was set to cover the entire heart and the descending aorta and was used for both calcium scoring and CT coronary angiography. CT acquisition for calcium analysis was performed using prospective electrocardiogram (ECG) gating with a gantry rotation time of 400 milliseconds, a tube voltage of 120 kV, and a weight-adapted tube current-time product (80–120 mAs). Images were reconstructed with a section thickness of 2.5 mm and using conventional filtered back projection. The trigger delay for prospective gating in the calcium CT study was adjusted to the heart rate to acquire CT data during diastole of the coronary arteries. CCTA acquisition was performed with the use of 100–120 kVp, 600–800 mA, with a gantry rotation time of 400 ms. Images were reconstructed at 75% of the R–R interval on the ECG, with a section thickness of 0.6 mm and 50% overlap. A bolus of 1 mL/kg of body weight (minimum of 70 mL) of iodixanol (Ultravist 370 [370 mg of iodine per millilitre]; Bayer HealthCare Pharmaceuticals, Berlin, Germany) followed by 80 mL of saline solution was continuously injected into a right antecubital vein through an 18-gauge catheter at a flow rate of 5 mL/s.

All CT lung-screening examinations were performed on the same scanner at 80 kVp and 15 mAs, with iterative reconstruction software. Axial images were obtained at 1.25 mm thickness with 50% overlap and reconstructed with both soft tissue kernels. Axial maximum-intensity projections (16×2.5 mm) and coronal and sagittal multiplanar reformatted images were reconstructed and used for interpretation.

2.3. Radiation

Radiation doses delivered during computed tomography scans were collected from patient CT acquisition protocols. Dose-length product (DLP) was recorded for each patient, analysing separately the doses related to ULDCT, CAC and CCTA scanning. Effective radiation dose (ED) was estimated using the formula "ED (mSv) $\approx DLP \times k$", where k is a conversion coefficient specific for adult chests (0.014 mSv/mGy × cm) [18].

2.4. Evaluation of screening findings

Image interpretation was performed by two radiologists specifically trained in thoracic imaging with five and seven years of experience. Findings were analysed according to the Fleischner Society's *Glossary of Terms* [21]. Nodules were defined as rounded or irregular opacities, well or poorly defined, measuring up to 3 cm in diameter. Those with homogenous soft-tissue attenuation were characterized as solid nodules, and those presenting hazy increased attenuation, within which margins of pulmonary vessels could be indistinct, as ground-glass nodules. Nodules presenting both solid and ground glass attenuation were defined as part solid.

Pulmonary nodules were analysed according to the National Comprehensive Cancer Network (NCCN) guidelines for lung cancer screening [20]. All patients that presented nodules on the initial ULDCT screening were followed-up for two years up to January 2017. Patients repeated low-dose CT in intervals of 3, 6, or 12 months based on nodule size and growth rate in accordance with NCCN guidelines [22].

Positive results required the identification of a noncalcified solid nodule ≥6 mm or a ground-glass nodule > 5 mm, not stable in size for more than two years. Positive findings requiring advanced imaging such as PET/CT or an invasive procedure, such as solid nodules greater than 8 mm, were categorized as "suspicious," and a pulmonary consultation was recommended [22]. All suspicious cases were presented at our weekly multidisciplinary thoracic oncology group meeting. Solid nodules initially categorized as positive results were considered "probably benign" if stable in size during the follow-up period. A lung cancer stage was designated to each patient according to the seventh revision of the TNM classification [23].

Table 1
Baseline Demographic Characteristics of Study Subjects (n = 175).

Variables	Results
Age (y)	64 ± 11 (range, 46–80)
Body mass index (kg/m^2)	26.4 ± 3.2
Sex	
Male	142 (81)
Female	33 (19)
Smoking status	
Never	71 (41)
Current smoker	83 (47)
Former smoker	21 (12)

Note: Data are presented as No (%) or mean ± SD.

Table 2
Ultra-low-dose computed tomography lung cancer screening findings.

Variables	Results
Emphysema	24 (14)
Pulmonary nodules	71 (41)
Mean diameter (mm)	5.50 ± 4.00
Positive results (> 6 mm)	28 (16)
Location	
Right lower lobe	7 (32)
Middle lobe	4 (18)
Left lower lobe	4 (18)
Right upper lobe	9 (41)
Left upper lobe	4 (18)
Lung cancer prevalence	6 (3.43)
Stage IA	1 (16.67)
Stage IIA	3 (50)
Stage IIIB	1 (16.67)
Stage IV	1 (16.67)
ULDCT radiation dose	
DLP (mGy.cm)	8 ± 2
Effective radiation dose (mSv)	0.11 ± 0.03
Increment to CCTA total DLP	1.22 ± 0.53%

Note: CCTA = coronary computed tomography angiography; DLP = dose-length product; ULDCT = ultra-low-dose computed tomography.
Data are presented as No (%) or mean ± SD.

2.5. Statistical analysis

Data analysis included descriptive statistics. All data are reported as mean ± standard deviation (SD), range, or percentage as appropriate. For all statistical analyses, the significance level for differences was set at $p \leq 0.05$. All statistical analyses were performed using commercial software (SPSS ver. 22, SPSS Inc., Chicago, IL, USA; Excel 2010, Microsoft Corporation, Redmond, WA, USA).

3. Results

Baseline characteristics of the study subjects are described in Table 1. Most of patients were male (n = 142; 81%), and mean age was 64 years (SD, ± 11; range, 46–80 years). Mean body mass index was 26.4 ± 3.2 kg/m^2. 59% were smokers or former smokers. Emphysema was present in 24 cases (14%).

ULDCT identified 71 (41%) patients with pulmonary nodules (mean diameter, 5.50 ± 4.00 mm) (Table 2). Most cases presented with solid nodules smaller than 6 mm, which were also stable in size (n = 43; 60.56%), and these were considered negative according to NCCN guidelines. The remaining 28 subjects (39.44%) presented nodules bigger than 6 mm, and were identified as positive results. In 79% of these cases (n = 22), these were false positive findings, further confirmed by follow-up (n = 20; diameter range, 6–8 mm), resection (benign nodule; n = 1; diameter, 8.2 mm), or biopsy (granuloma; n = 1; diameter, 14 mm). Lung cancer diagnosis was confirmed by histological study in six patients (8.45%), which initially presented nodules considered "suspicious" (> 8 mm) (Table 3). Most were diagnosed as adenocarcinoma (n = 4). In four cases, neoplasia detection was not possible in the cardiac FOV of calcium score (Fig. 1), and in three cases, patients were never smokers. Lung cancer was identified in early stages in 66% of these patients (stage IA, n = 1; stage IIA, n = 3). The two remaining subjects were diagnosed at stage IIIB and IV and died due to cancer complications.

Average total DLP was 785 ± 66 mGy cm (effective radiation dose, 10.99 ± 0.924 mSv), whereas the addition of the ULDCT scan represented a radiation dose increment of 1.22 ± 0.53% (Table 2). Average calcium score dose-length product was 64 ± 5 mGy cm (effective radiation dose, 0.90 ± 0.07 mSv), and average ULDCT dose-length product was 8 ± 2 mGy cm (effective radiation dose, 0.11 ± 0.03 mSv).

4. Discussion

In our study, both the rate of positive screening tests and the prevalence of lung cancer were within the ones reported in literature. We found 41% of patients presenting pulmonary nodules, of which 8.5% were diagnosed as lung cancer, with an overall prevalence of 3.4%. Some studies had positive screening tests rates varying from 24.2% to 69%, with lung cancer prevalences ranging from 1.3% to 3.6% [5,24–26]. In addition, 66.7% of cancer cases were at stage I or II, similarly to literature (range, 55–63%) [5,24–26]. In the United States, patients with localized disease at diagnosis have a more optimistic 5-year survival rate (52%), compared to those with advanced stage at

Table 3
Clinical and imaging characteristics of patients with lung cancer.

Cases (n = 6)	Parameters							
	Age (y)	Sex	Smoking status	CAC detection	ULDCT detection	Size (mm)	Histologic finding	Tumor stage[e]
1	68	M	Never smoker	yes	yes	8	SCC[b]	IA
2[a]	75	M	Smoker	yes	yes	37	SCC[d]	IIIB
3[a]	72	M	Never smoker	no	yes	34	ACA[d]	IV
4	58	M	Smoker	no	yes	21	ACA[c]	IIA
5	55	M	Never smoker	no	yes	22	ACA[b]	IIA
6	54	F	Smoker	no	yes	25	ACA[c]	IIA

Note: ACA = adenocarcinoma; CAC = coronary artery calcium scanning; F = female; M = male; SCC = squamous cell carcinoma; ULDCT = ultra-low-dose computed tomography
[a] Fatal cancer cases.
[b] Diagnosis confirmed by computed tomography guided biopsy.
[c] Diagnosis confirmed by intraoperative frozen-section biopsy.
[d] Diagnosis confirmed by histological study after tumor resection.
[e] Stage is given according to the 7th edition of the classification by the International Association for the Study of Lung Cancer (21).

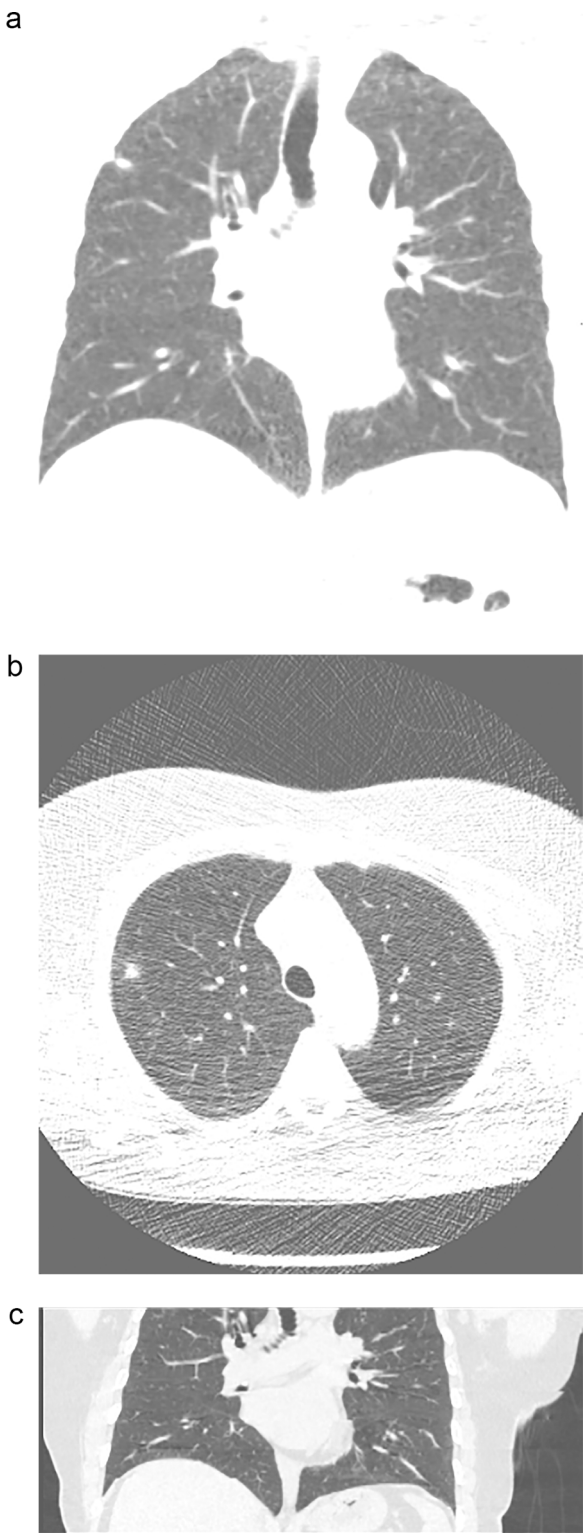

Fig. 1. 55-year-old man with suspected coronary artery disease. Coronal (A) and axial (B) ultra-low-dose CT images revealed a spiculated pulmonary nodule located in the right upper lobe. This lesion could not be visualized in the coronary artery calcium (CAC) scanning, coronal reconstruction (C), due to a shorter field-of-view. Lung cancer diagnosis was confirmed by the histological study, staged as IIA, and lesion was resected.

diagnosis (3.6%) [2]. Both patients that had cancer diagnosed in advanced stages (IIIB and IV) died because of cancer complications. However, due to the associated cardiovascular conditions, mortality rate in our study might be overestimated.

Lung cancer occurs predominantly in the upper lobes [18,19]. Hence, many cases could go undetected using only a cardiac FOV during CCTA. In our series, most nodules detected were in the right upper lobe (41%), what is consistent with the predominance reported in previous studies [18,19]. In addition, 4 of the 6 histologically confirmed cases of lung cancer could not be detected only using a standard CCTA protocol.

Unnecessary exposure to radiation is always a concern to patients. One important parameter of CCTA acquisition that can be directly determined by the CAC score is the scanning z-axis length, which has a direct effect on the radiation dose of the CT study [27,28]. When the z-axis coverage of the CCTA acquisition is planned by determining the limits of the craniocaudal extent of the coronary arteries, the use of the prospectively ECG-triggered CAC images may reduce the total radiation dose of the combined CAC score and CCTA examination by allowing substantial z-axis radiation dose reduction for the portion of the scan [27,28]. Some studies show that adjustment using calcium score can reduce radiation exposure in 16% and be highly effective for CCTA [27,28].

With an average ULDCT dose-length product of 8 ± 2 mGy cm, an estimated ED of 0.11 ± 0.03 mSv was added to the CCTA protocol, only representing an increment of 1.22 ± 0.53% of total DLP of the scan. This radiation dose is comparable to the ones delivered in chest radiographies which range between 0.05 and 0.24 mSv [29]. For a standard chest CT examination, average ED is approximately 7 mSv [29], whereas for low-dose CT scans used in lung cancer screening, average ED is around 1.4 mSv [30]. The ULDCT effective dose found would represent 1.57% and 7.86% of these values, respectively.

Another advantage of chest ULDCT is the possibility of detecting other thoracic abnormalities. Emphysema, an independent risk factor for lung cancer [31,32], can accurately be detected by ULDCT [33] and was present in 14% of our cases. Chest ULDCT scans might also detect other unsuspected malignancies or benign lesions with clinical implication within breasts, aorta, chest wall, mediastinum, and thyroid. Although we did not find any extrapulmonary tumours, some studies that used low-dose CT for lung cancer screening reported a prevalence of extrapulmonary malignancies usually inferior than 1% [24,34–36]. On the other hand, one should always evaluate whether the benefits of lung cancer screening outweigh the risks that further investigations due to positive screening tests might cause. In our sample, one patient had an unnecessary biopsy and another had an unnecessary surgical resection. These procedures are invasive, associated with risks of morbidity and mortality.

Some authors have suggested that screening for lung cancer during a CCTA scan should be restricted to specific higher risk groups such as heavy tobacco users [15]. However, 50% of lung cancer cases found in our study occurred in non-smokers. Although it is predominantly associated with tobacco use, in the USA there are around 17,000–26,000 annual deaths in patients who never smoked, what would make lung cancer in never smokers the seventh cause of cancer related mortality if considered separately [37].

Our study has some limitations. Even with important preliminary results, larger studies following up patients for longer periods are needed to confirm the role of ULDCT for lung cancer screening especially for reduction in mortality. Due to the small sample size, another limitation was evaluating lung cancer prevalence without analysing overall survival and disease overall specific survival. Furthermore, some studies have shown a reduced diagnostic performance to detect pulmonary nodules for obese patients undergoing ULDCT, as higher body mass indexes are associated with increased image noise [10,11,38]. Although mean body mass index has been provided, such influence was not addressed in our study. In most studies evaluating CCTA in patients with suspected CAD, a higher percentage of male subjects is reported, ranging from 53% to 74% [28,39–42]. In our study, 81% of subjects were men. This slightly superior prevalence was probably random, as we consecutively included patients referred to our service to avoid selection bias. In addition, with the development and

broader application of 64-detector dual source CT, and 128-, 256-, and 320-detector single source CT, lower mean radiation doses for coronary CT angiography have been reported as little as 0.93 mSv using a second-generation 320–detector row CT scanner [43]. This reduction in mean radiation doses for CCTA protocols would make the addition of a chest ULDCT scan even more feasible. Further studies could aim to compare the cost-effectiveness of the association of ULDCT with CCTA against performing two different exams to investigate lung cancer and CAD in higher risk populations.

In conclusion, our results demonstrated that ULDCT might be a useful tool to detect lung cancer if included with CCTA protocols scans among patients with suspected coronary artery disease.

Conflict of interest

Matheus Zanon: none; Gabriel Sartori Pacini: none; Vinicius Valério Silveiro de Souza: none; Edson Marchiori: none; Gustavo Souza Portes Meirelles: none; Gilberto Szarf: none; Felipe Soares Torres: none; Bruno Hochhegger: none.

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