



## Combined Coronary Artery Disease and Lung Cancer Screening with Low Dose Computed Tomography

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### Abstract

Cardiac computed tomography (CT) scans are widely used as a non-invasive diagnostic tool for identifying coronary artery disease (CAD) in patients with low or intermediate risk. However, recent advancements in technology have enabled cardiac CT to be performed in patients who are at high risk for CAD or lung cancer (LC). The updated edition of the National Institute for Health and Care Excellence guidelines recommends cardiac CT as the first-line diagnostic tool for patients with new-onset chest pain due to suspected CAD. In 2014, the United States Preventive Services Task Force recommended annual lung cancer screening with ultra-low dose CT for current and former heavy smokers aged 55 to 80 years. As a result, there is growing interest in performing LC screening in patients with suspected or known CAD undergoing cardiac CT. However, the challenge in performing both cardiac and lung evaluations is the double dose of contrast and radiation typically required for two separate examinations. This review aims to evaluate the current knowledge regarding the opportunity to combine lung and coronary assessment using CT in order to find a protocol that can simultaneously assess the coronary arteries and screen for lung cancer with no increase in contrast or radiation dose. Accordingly, we suggest that a combined use of LDCT screening for both CAD and LC could be beneficial for individuals considered at high-risk for these conditions and would not significantly increase the harms associated to radiation exposure.

**Keywords:** Computed tomography; Coronary artery disease; Low dose radiation lung cancer; Screening

### Introduction

Coronary artery disease (CAD) and cancer are the most common causes of death in developed countries [1]. Statistically, patients that are eligible for cancer screening are usually at high risk of development of CAD, as they frequently share many risk factors [2]. Some studies even suggest an increase in the incidence of CAD in cancer patients compared to individuals who do not have cancer [3,4]. Cardiac computed tomography (CT) scans are widely used as a non-invasive diagnostic tool for identifying CAD in patients with low or intermediate risk [5]. However, recent advancements in technology have enabled cardiac CT to be performed in patients who are at high risk for CAD or lung cancer (LC) [6]. The updated edition of the National Institute for Health and Care Excellence (NICE) guidelines recommends cardiac CT as the first-line diagnostic tool for patients with new-onset chest pain due to suspected CAD [6]. Additionally, symptomatic patients with known CAD and previous percutaneous coronary intervention may benefit from cardiac CT when an unclear stress test suggests a high likelihood of in-stent restenosis or a 'de novo' stenosis [7]. In 2014, the U.S. Preventive Services Task Force recommended annual lung cancer screening with ultra-low dose CT for current and former heavy smokers aged 55 to 80 years [8]. As a result, there is growing interest in performing LC screening in patients with suspected or known CAD undergoing cardiac CT [9]. However, the challenge in performing both cardiac and lung

evaluations are the double dose of contrast and radiation typically required for two separate examinations.

This review aims to evaluate the current knowledge regarding the opportunity to combine lung and coronary assessment using CT in order to find a protocol that can simultaneously assess the coronary arteries and screen for lung cancer with no increase in contrast or radiation dose.

### Background

#### Tobacco as a risk factor

Cigarette smoking is the leading preventable cause of death [10]. The synergistic action of its numerous components affects all organ systems, and it is responsible for tens of millions of deaths globally every year. Cigarettes are associated with about a quarter of all cancers, and smokers are more likely to develop cancer in their lifetime [8]. Tobacco has been demonstrated to be an active player in the development of cancers of the upper and lower respiratory tracts, including LC, as well as other cancers such as esophageal and bladder. Indeed, smoking induces a chronic tumor-promoting state of inflammation as well as a higher risk of genetic mutations [2], two of the fourteen hallmarks of cancer [11]. The likelihood of development of LC in a smoker is proportional to both the absolute number of cigarettes and the time span spent smoking [12]. Moreover, almost 90% of LC deaths are attributable to cigarette smoking [12], making

tobacco the most important modifiable risk factor targeted by sensibilization campaigns in the recent years [13]. Tobacco is also a major cause of endothelial vascular dysfunction through multiple mechanisms [2]. Indeed, cigarettes are responsible for 20-25 % of cardiovascular deaths: [14,15] both active and passive smoking have been shown to predispose individuals to the development of atherosclerosis, CAD, stable angina, thoracic, aortic and cerebral aneurysms, acute coronary syndromes and strokes, as well as sudden death [14-18]. The use of tobacco is therefore considered a major risk factor for both CAD and LC.

### **Ischemic heart disease**

Ischemic heart disease is a heterogeneous spectrum of clinical conditions, all characterized by an imbalance between the supply of oxygen from the coronary vessels (myocardial perfusion) and the metabolic demand from cardiac tissue [5]. The main, though not exclusive, cause of ischemic heart disease is the atherosclerosis of epicardial coronary vessels. The leading risk factors supporting the development of atherosclerosis are high values of low-density plasma lipoproteins, low values of high-density lipoproteins, cigarette smoking, high blood pressure and diabetes mellitus.

### **Lung cancer**

LC is the malignancy associated with the highest mortality worldwide [6]. LC is often clinically silent in the early stages of disease development, and approximately two thirds of patients are diagnosed at advanced stages [19]. An advanced stage at diagnosis is associated with a decreased likelihood of full resolution, whereas stage I LC has a significantly more favorable prognosis [19,20]. For this reason, targeted screening of individuals at high risk of development of LC is crucial for early detection and beneficial in terms of mortality [21]. CAD and LC are two disease processes that share common risk factors such as cigarette smoking, hence the importance of combined screening that through a single diagnostic test is able to detect both diseases in the preclinical stages.

### **Screening for CAD in Patients with Risk Factors**

Over time, the definition of cardiovascular ‘high risk’ has changed. Indeed, according to the 2016 ESC prevention guidelines, SCORE estimates between 5% and 10% are considered high risk. Nowadays, the 2021 version of ESC guidelines considers different cut-offs for different categories of atherosclerotic cardiovascular disease risk, taking into account various age groups. This change aimed to prevent the undertreatment of the young and the overtreatment of the elderly.

Coronary computed tomography angiography (CCTA) has an emerging role as a non-invasive tool for evaluating and excluding coronary stenosis in patients with low to medium pre-test probability of CAD. During the last decade, an extensive literature confirmed a very high sensitivity, specificity, and diagnostic accuracy of CCTA in the detection of coronary stenosis as compared to invasive coronary

angiography. Indeed, this imaging modality is associated with the higher diagnostic accuracy mainly in patients with low-to-intermediate CAD risk [22]. Therefore, in the latest ESC guidelines, CT is recommended as an alternative to invasive coronary angiography to rule out the presence of coronary syndrome when the probability of CAD is low to intermediate and when cardiac troponin and/or ECG are normal or inconclusive (Class I, Level A recommendation) [23]. Only limited data are available on the impact of CCTA in asymptomatic individuals with cardiovascular risk factors. The 6 -year follow-up of the CONFIRM study, comprising 1226 asymptomatic subjects, failed to demonstrate an incremental prognostic value of CCTA over the CAC score [24-26].

European Society of Cardiology recommends against the use of CCTA to rule out CAD in asymptomatic individuals, mainly due to the unknown additional prognostic value of CCTA over CAC scoring. The main clinical applications of CCTA includes the assessment of patients with stable chest pain and low to intermediate pre-test likelihood of CAD. Regarding this clinical subset, the PROMISE trial underlined the potential of CCTA to dramatically reduce the number of unnecessary invasive angiograms (27.9% in the CCTA group, as compared with 52.5% in the functional-testing group), whereas the SCOT-HEART (Scottish Computed Tomography of the Heart) trial showed that the addition of CCTA to the standard clinical care markedly clarifies the diagnosis of angina due to CAD and results in more focused treatment regimes that are associated to a reduction of 38% in fatal and non-fatal myocardial infarction at 1.7 years follow-up [27]. Moreover, an even more impressive reduction (50%) of fatal and non-fatal myocardial infarction rate in patients with undergoing CCTA *vs.* standard of care was recently demonstrated in a sub analysis of SCOT-HEART from the median time for preventive therapy initiation [28]. Indeed, these findings have been explained by the early initiation of a preventive therapy by statin and aspirin after CCTA detection of non-obstructive lesions. In conclusion, the capability of CCTA to combine an early identification and quantification of coronary stenosis and to go outside the lumen looking for atherosclerosis, support the role of CCTA as first-line non-invasive imaging technique in patients with unknown but suspected CAD, underlining the risk continuum of atherosclerosis and its implications for defining CAD by invasive coronary angiography alone.

### **Lung Cancer Screening**

In the last decades, multiple randomized control trials (RCTs) to demonstrate the benefits of LC screening have been conducted globally. Among these, the largest is the National Lung Screening Trial (NLST) [29]. A multicenter RCT conducted in the United States to determine whether high-risk individuals would benefit from a yearly screening for LC with low-dose CT (LDCT) scans compared to a chest X-ray (CXR). Patients considered to be at high risk for LC were enrolled starting in 2002: a total of 53,454 high-risk individuals underwent randomization and were screened either with LDCT or chest radiographies. Eligibility criteria included an age at randomization between 55 and 74 and a

history of cigarette smoking of 30 pack-years or more, including patients who had quit within the previous 15 years. A 20.0% reduction in LC-related mortality in the LDCT group was demonstrated by the NLST compared to CXR [29]. Similar, albeit smaller, RCTs have been conducted in the USA [30], China [31] and Europe, examples of which include the following studies: NELSON (the Netherlands and Belgium) [32], ITALUNG (Italy) [33], UKLS (United Kingdom) [34], DANTE (Italy) [35], DLST (Denmark) [36], MILD (Italy) [37], LUSI (Germany) [38] and DEPISCAN (France) [39]. An ongoing RCT is currently taking place in Brazil [40].

These studies, as well as multiple meta-analyses conducted on them [41,42], conclude that yearly LDCT screening is an effective method for LC screening and leads to a significant decrease in LC-related mortality in high-risk individuals (defined by the NLST as patients aged 55 to 74 with a history of cigarette smoking of 30 pack-years or more) [41,42].

## Technological Development of Cardiac-CT Scanners

Technological developments in the latest generation of CT scanners have made it possible to perform combined cardiopulmonary screening in a single session with a reduction in the dose of radiation administered. The modern CT scanners with 256-320 rows, 16 cm of z-axis coverage, collimation 0.5-0.23 mm, a gantry rotation time of up to 0.28 seconds and last-generation iterative reconstruction algorithms allows, by increasing coverage and temporal resolution, one single axial one-beat acquisition of the entire heart volume, with excellent image quality, significant reduction of the effective dose, higher spatial and temporal resolution compared to low-pitch helical scans. Although the development of new technologies has led to a significant reduction in radiation exposure for CT examinations performed with last-generation systems, the dose-related to the use of ionizing radiation still remains a point of concern, especially because of the increasing and widespread clinical use of CT. A recent study has reported a direct connection between the increase in cancer rates and radiation exposure from CT [36]. Thus, it is crucial to assure that CT scanning has a correct indication for the patient, that the most appropriate protocol is chosen for the specific clinical setting and that all possible precautions are applied to reduce radiation exposure as much as possible. The most relevant factors that need to be optimized, with the goal of minimizing radiation exposure as low as reasonably achievable without significantly compromising image quality are: the scanner type (single- or dual-source; scanner geometry; gantry rotation, available filters), tube voltage, tube current, scan range, scan acquisition time, gating (retrospective gating, prospective triggering, high-pitch helical acquisition), slice thickness, overlap and pitch (for helical scanning) and the reconstruction method (filtered back projection, iterative reconstruction). New-generation CT scanners with wide volume coverage, fast gantry rotation and last-generation IR are an “ideal summation” of multiple factor optimization, including axial ECG-gated scan without overlapping, low

scan time, low tube voltage and current, allowing to achieve good quality exams with an overall effective dose of less than 1 mSv.

## The Lower Radiation, The Lower Side Effects

The use of ionizing radiation for LC screening is a major concern for both physicians and patients. Several studies have shown that the average effective dose of radiation using standard CT scans is around 7 mSv, compared to 1.5 mSv for low-dose CT [43]. Despite this reduction in effective dose, low-dose CT scans have been shown to have a high sensitivity, non-significantly different to standard CT scans [44]. The American College of Radiology has estimated that the average annual dose received by an individual from environmental radiation in the United States is 3 mSv [45]. This value is susceptible to changes depending on several factors, including high altitudes, which make people more vulnerable to cosmic radiation (up to an increase in exposure of 1.5 mSv per year). The ED of radiation emitted by LDCT scans is, therefore, comparable to 6 months of natural environmental radiation [45,46].

Considering that the average effective dose of chest radiographies is lower than 0.15 mSv [47], one low-dose CT scan has an effective dose equivalent to about 10 to 15 standard Chest X-Rays [46]. Recent research even suggests that the radiation exposure of standard two-planes Chest X-Ray can be compared to that of the latest generation of ultra-low dose CT scans [45]. Therefore, taking into consideration the high sensitivity and specificity of LDCT scans as well as the 230 days median tumor doubling time of non-small cell lung cancers [46], the benefit-to-harm ratio of yearly low-dose CT screening of LC is favorable in high-risk individuals [48-50]. Considering all the above, LC screening with low-dose CT scans is currently recommended by the European and USA guidelines in high-risk subjects.

## New CT Protocol for the Simultaneous Screening of CAD and Lung Cancer

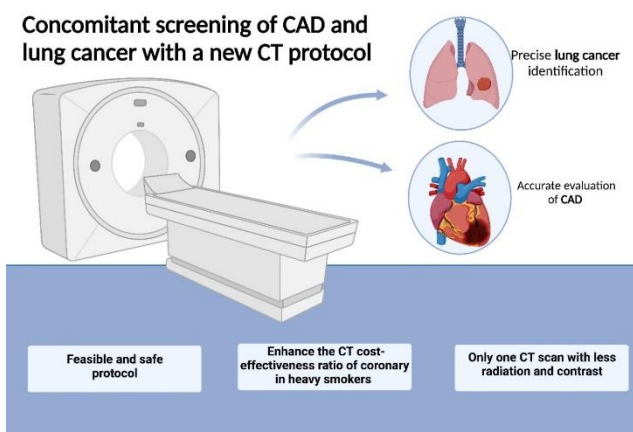
Considering recent research [51,52], a novel imaging protocol known as "Gaudio's Protocol" has emerged as a promising tool for enhancing the effectiveness and cost-effectiveness of CT scans in heavy smokers with suspected or known coronary artery disease. This innovative ultrafast-low-dose CT approach allows for the simultaneous evaluation of both coronary arteries and lung cancer screening, without any increase in contrast or radiation dose (Table 1 and Figure 1).

Gaudio et al. conducted an initial study on 30 current or former heavy smoker subjects, followed by a pilot randomized trial on 110 participants to assess the diagnostic ability and radiation exposure of the new protocol. The results showed that the concomitant cardiac and lung CT protocol was non-inferior to the standard cardiac CT protocol in terms of safety, with no increase in contrast or radiation dose required. Additionally, the simultaneous evaluation of both regions demonstrated a non-inferior feasibility, with adequate visualization of coronary artery segments. Notably, the pilot randomized trial also revealed significant findings, including significant coronary stenosis in the group that underwent

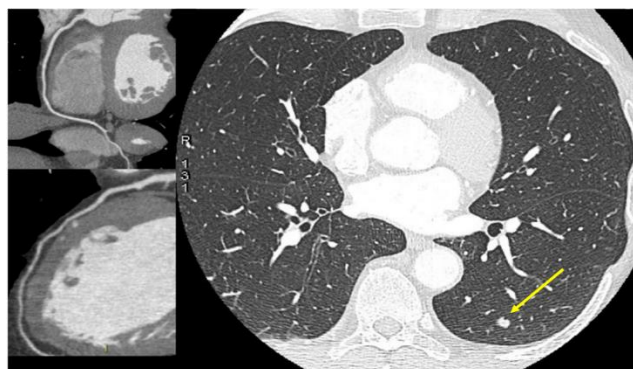
simultaneous cardiac and lung CT, as well as pulmonary nodules >2 mm detected in 7 of the 55 participants in that group.

	Cardiac CT only	Lung CT only	Cardiac CT + Lung CT
Slice thickness	0.625 mm	1.25	0.625
SFOV	Cardiac large	Chest large	Cardiac large
DFOV	16 mm	24-28 cm	16 mm
Tube current (mAs)	Depending on BMI	60 mAs	Depending on BMI
Tube voltage (KVp)	120 KVp	100 to 120 KVp	100 KVp
Contrast-to-noise ratio	12.8	-	13.5
Signal-to-noise ratio	15.5	-	15.5
Effective radiation dose (mSv)	1.4	1.2	1.5
Dose-length product (mGy*cm)	100	86	107

**Table 1:** Technical characteristics and radiation dose of novel computed tomography.



**Figure 1:** Concomitant screening of coronary artery disease and lung cancer with a new ultrafast-low-dose computed tomography protocol.



**Figure 2:** A case of coronary artery disease and lung cancer screening. Ultra-low-dose computed tomography images of the lungs showed a 2-mm pulmonary nodule (yellow arrow) in the left upper lobe (right panel). The cardiac computed tomography revealed a right coronary artery (left upper panel) and left coronary artery (left lower panel) free of significant stenoses.

These results suggest that the novel technique may offer a more comprehensive and effective approach for evaluating cardiac and lung regions, reducing the need for radiation and contrast dye that are required when two separate examinations are conducted (Figure 2). However, the study was limited to a relatively small sample size, and further randomized multi-center trials will be required to confirm these preliminary results and provide more detailed information regarding the optimal CT protocol for simultaneous detection of CAD and lung cancer. Overall, the potential of Gaudio's Protocol in enhancing the cost-effectiveness and diagnostic ability of coronary CT in heavy smokers is promising and warrants further investigation. In conclusion, Gaudio's Protocol shows great promise in revolutionizing the diagnostic approach to coronary artery disease and lung cancer screening, particularly in heavy smokers or those who have been heavy smokers in the past. By allowing for the simultaneous evaluation of both cardiac and lung regions in one CT scan, Gaudio's Protocol could lead to more cost-effective and efficient diagnoses, while minimizing the use of radiation and contrast dye. Although further research is needed to confirm the preliminary findings and determine the optimal CT protocol for simultaneous detection of CAD and lung cancer, the potential of Gaudio's Protocol in improving patient outcomes and reducing healthcare costs is significant. As such, continued investigation and development of this innovative imaging technique should be a priority for researchers and healthcare professionals alike.

## Conclusion

Cigarette smoking is potentially the single most important modifiable risk factor in both CAD and LC. Low-dose CT screening has been shown to effectively detect coronary plaques and pulmonary nodules, reducing mortality in patients at high-risk for CAD and LC respectively.

We suggest that a combined use of LDCT screening for both CAD and LC could be beneficial for individuals considered at high-risk for these conditions and would not significantly increase the harms associated to radiation exposure.

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