Preoperative Assessment of Coronary Arteries by Cardiac Computed Tomography in Patients with Lung Cancer

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Abstract

Background   To retrospectively evaluate characteristics of coronary artery disease (CAD) in patients undergoing lung resection for cancer by using dual-source computed tomography (DSCT), thus increasing our understanding of perioperative evaluation.

Methods   DSCT coronary angiography was performed for perioperative evaluation in 145 patients with non-small cell lung cancer (NSCLC) due to suspected CAD. The imaging characteristics of CAD including extent, distribution and types of plaques, and luminal stenosis and congenial anomalous including origin of coronary arteries and myocardial bridge (MB) were evaluated and compared by sex, smoking behavior, and pathological types.

Results   In total, coronary artery plaques were observed in 130 (89.7%) patients. A total of 205 coronary vessels (1.7 ± 1.3 per patient) and 278 segments (2.4 ± 2.3 per patient) were found to have plaques, respectively. The most frequently involved segment were the left anterior descending (LAD) artery (45.4%) and its proximal segment (24.1%) ($p < 0.05$). Mild narrowing (61.7%) and calcified plaques (52.9%) were most found (all $p < 0.001$). Types of plaques, luminal narrowing and extent were not significantly different by sex, smoking behavior, or pathological type. Anomalous origination of the right coronary ostium from left sinus was observed in 0.7% of patients. MB was observed in 16.6% of patients.

Conclusion   Dual-source CT is a useful preoperative noninvasive test for CAD in patients planning to undergo lung resection for cancer.

Keywords

► coronary artery disease
► lung resection
► non-small cell lung cancer
► computed tomography

Introduction

It is relatively common that lung cancer and coronary artery disease (CAD) occur simultaneously for same risk factors, such as aging and smoking. In addition, some cardiac drugs were proposed to have potential carcinogenic effect.[1] The feasibility and timing of operation for non-small cell lung cancer (NSCLC) are associated with the history of CAD because it may increase perioperative morbidity.[2] In addition, CAD can limit or restrict operations for cancer, and cancer can limit the treatment of CAD. Studies have shown that preoperative noninvasive testing could provide risk stratification for evaluating perioperative risk of cardiovascular events.[3] Commonly used tools for noninvasive assessment of CAD include multislice computed tomography (CT), especially cardiac CT. It can accurately identify plaque

composition and depict the degrees of intracavitary stenosis. It can also easily identify outward remodeling without luminal narrowing that lesions sometimes show, an effect that cannot be seen with invasive coronary angiography.[4,5] Thus, we retrospectively evaluated characteristics of CAD by using cardiac CT for patients planning to undergo lung resection for cancer, thus increasing our understanding of perioperative management.

Materials and Methods

Study Population

According to the Declaration of Helsinki (2000 EDITION), the Institutional Review Board (IRB) in our hospital approved the application for exemption of patients' informed consents because of its retrospective design.

From January 2013 to January 2016, 160 patients with NSCLC who underwent coronary dual-source computed tomography (DSCT) angiography (DSCTA) examination for suspected CAD as preoperative assessment of elective surgery were enrolled in this study. In stages I and II patients who functionally fit with, according to current guideline for therapy of NSCLC[6] and the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC)-TNM classification and stage grouping,[7] surgical resection (lobectomy/pneumonectomy with lymphadenectomy) is recommended. Exclusion criteria for CT scan included patients with a left ventricular ejection fraction of less than 40%, renal dysfunction (glomerular filtration rate <30 mL/min/1.7 m^2), severe heart failure, known allergy to iodine-based contrast medium, and inadequate image quality for imaging analysis. Finally, 145 patients with NSCLC were recruited. Baseline characteristics of patients with NSCLC are listed in ►Table 1.

DSCT Technique

DSCT (Somatom Definition, Siemens Medical Solutions, Germany) scanning were applied for all patients with a retrospective electrocardiograph (ECG)-gated mode. Scanning was performed in a craniocaudal direction with the following acquisition parameters: collimation was 64 × 0. 6 mm, pitch 0.2 to 0.5 (selected according to heart rate), gantry rotation time 3.30 s, tube current (body mass index [BMI] < 25 kg/m^2, 220 mA per rotation; BMI ≥ 25 kg/m^2, 330 mA per rotation), and weight-dependent tube potential (weight ≥ 85 kg, 120 kV for each tube; weight < 85 kg, 100 kV for each tube). The nonionic contrast agent (iopamidol, 370 mg/mL; Bracco Sine Pharmaceutical Corp. Ltd., Shanghai, China) with only 60 to 80 mL was injected into an antecubital vein at a flow rate of 5.0 mL/s, followed by 20 mL of a saline solution at the same flow rate. Once the interest region on the left atrium reached the contrast concentration threshold of 100-Hounsfield units, it was automatically initiated for the image acquisition along after a delay of 5 seconds.

Imaging Analysis

Two experienced radiologists independently reviewed each CT scan on a dedicated workstation (Leonardo, Siemens

Table 1 Baseline characteristics of patients

Characteristic	Value
Age, y	70.4 ± 6.4
Male gender (male:female)	1.5:1
Weight (kg)	60.8 ± 10.5
BMI	23.1 ± 3.8
Current Smoking	43.4%
Hypertension	38.6%
Diabetes mellitus	12.4%
LVEF	58.3% ± 10.2%
Lung cancer	
Adenocarcinoma	115
Squamous cell carcinoma	30
Lung surgery	
Lobectomy	144
Right upper lobe	47
Right middle lobe	9
Right lower lobe	30
Left upper lobe	28
Left lower lobe	20
Two lobes	10
Pneumonectomy	1
Wedge resections	16
Sleeve lobectomy	4
Concomitant pathology	
Heart valvular diseases	12
Carotid stenosis	2
Aortal atherosclerosis	46

Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction, measured by echocardiography.

Medical Systems), blinding to the final diagnosis. Any disagreement of anatomical variants and measurements was negotiated until a consensus decision was reached. Maximum intensity projection, curvature plane reconstruction, multiplanar reconstruction, and volume reconstruction were used for observing coronary artery plaques.

Coronary vessels were classified into four branches: right coronary artery (RCA), left main (LM), left circumflex (LCX), and left anterior descending (LAD). In accordance with the classification standard of the American Heart Association, coronary arteries were assessed by dividing them into 15 segments.[8] Anomalous origins of coronary arteries, myocardial bridges (MB), number of involved coronary branches and segments, number and types of plaques, and degree of luminal narrowing by plaques were assessed. The segment plaque chosen for the analysis was the one at a site within the most severely stenotic vessel. Plaques were divided into three types: noncalcified plaque (lesions with lower CT

attenuation than the contrast-enhanced lumen without any calcification), calcified plaque (lesions with a higher CT density than the contrast-enhanced lumen), and mixed plaques (calcified and noncalcified components in a single plaque).[9] Coronary artery stenoses were classified into significant stenoses and nonsignificant stenoses by a 50% threshold of luminal narrowing. Moreover, the stenoses were further divided to normal appearing (degree of stenosis, <25%), mild (degree of stenosis, 25–49%), moderate (degree of stenosis, 50–74%), and severe (degree of stenosis, ≥75%) narrowing on the basis of two orthogonal views.[10] It was defined MB was a tunnel formed by superficial fibers of the myocardium passing through the outer aspect of a coronary artery.

Statistical Analysis

Dedicated SPSS software (Version 16; Chicago, Illinois, United States) were applied for all statistical analyses. Continuous data were expressed as mean values and corresponding standard deviations, and dichotomous data were recorded as numbers and percentages. Comparisons of the prevalence of involved vessels between multi and single-vessel diseases, different types of plaques, degree of stenosis and plaque distributions among different vessels, and segments were performed using a chi-square test or Fisher's exact test. Interobserver variation was evaluated by kappa statistic. Comparisons of the manifestations of CAD between patients of different sexes, smoking behavior, and pathological types were performed using independent sample t-tests. Differences with $p < 0.05$ were considered to be statistically significant.

Results

Preoperative Baseline Characteristics

Cardiac CT scanning was successfully performed in all 145 patients, whose age ranged from 41 to 83 years (mean 70 ± 6 years). Baseline characteristics of subjects in our study are shown in ►Table 1. Of the 145 patients, 7 with severe stenosis underwent invasive coronary angiography, and 3 of whom underwent coronary interventions according to the guidelines of the American College of Cardiology. No patients had angina or postoperative ischemic myocardial infarctions during the 30 days after surgery. These patients had a two-staged operation, first a percutaneous transluminal coronary angioplasty (PTCA) procedure (►Fig. 1A and B), followed by a lung resection 1 to 2 weeks later.

Coronary Anomalies

Anomalous origination for the right coronary ostium from the left sinus (►Fig. 1C) was observed in 0.7% (1/145) of patients. An MB (►Fig. 1D) was observed in 16.6% (24/145) of patients. The most common involved segment for MB was the distal segment of the LAD (18/2175, 0.8%, $p < 0.05$).
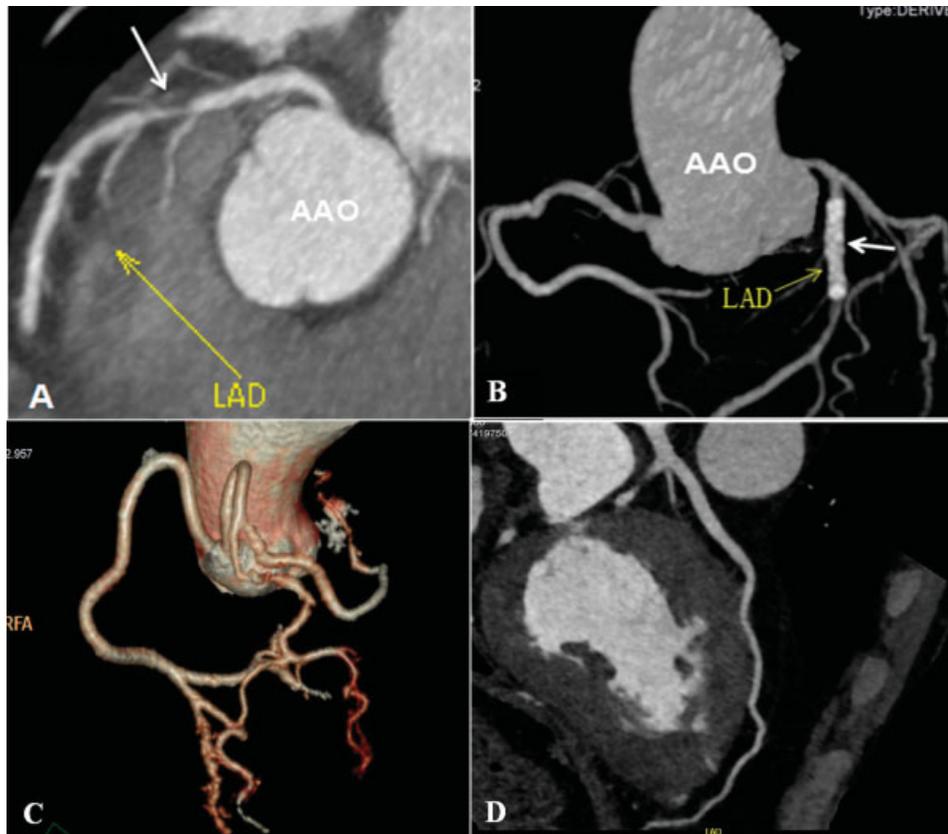
Fig. 1 The curvature plane reconstruction image shows serve stenosis (yellow arrow) caused by a filling defect (**A**). The coronary artery stent (arrow) is implanted in the left anterior descending coronary artery (**B**). The volume rendering image (**C**) shows anomalous origination of the right coronary ostium from the left sinus. The curvature plane reconstruction image (**D**) shows a myocardial bridge (arrow).

Plaque Distribution and Extent

DSCT scanning revealed 130 (89.7%) subjects with coronary artery plaques and 15 (10.3%) patients without plaques. Coronary artery plaques were detected in 205 coronary vessels (1.7 ± 1.3 per patient; range, 0–4) and 278 segments (2.4 ± 2.3 per patient; range, 0–10). There was no significant difference in the number of patients with vessels between multi-vessel (≥2) and single-vessel disease (72/130 [55.4%] versus 58/130 [44.6%], $p > 0.05$). Regarding plaque distribution, the most frequent major involved vessel with plaques was the LAD artery (93/205, 45.4%, all $p < 0.001$), followed by the RCA (54/205, 26.3%), the LCX (41/205, 20%), and the LM artery (17/205, 8.3%). The most commonly involved coronary segment was the proximal segment of the LAD (67/278, 24.1%, $p < 0.05$). The kappa value for interobserver variation with coronary measurements was 0.79.

Plaque Composition and Luminal Narrowing

Composition of plaques and degree of stenosis are measured and summarized in ►Table 2. In general, 295 plaques (2.3 ± 2.0 per patient; range, 1–12) were found, of which 156 (52.9%) were calcified (►Fig. 2A), 83 (28.1%) were mixed (►Fig. 2B), and 56 (19.0%) were non-calcified (►Fig. 2C) ($p < 0.001$). Of the grading of stenosis, mild stenosis (61.7%) was the most common compared with the others (11.2%, 20.7%, and 6.4% for normal appearing, moderate stenosis, and severe stenosis, respectively, all $p < 0.001$). A total of 215 (72.9%) patients showed nonobstructive stenosis, and 80 (27.1%) showed obstructive stenosis ($p < 0.001$). The kappa value for interobserver variation with coronary measurements was 0.79.

Comparison of CT Findings of CAD among Genders, Smoking Behaviors, and Pathological Types

Comparisons of the extent of involved coronary arteries, types of plaques, and grading of luminal stenosis on CT images between genders, smoking behaviors, and pathological types are analyzed and shown in ►Table 3. Men had more involved coronary vessels and segments compared with women ($p < 0.05$). In addition, more plaques were found in men, especially calcified plaques ($p < 0.05$). The plaques in men commonly resulted in mild narrowing and non-obstructive stenosis of the coronary lumen. Smoking patients had more involved coronary vessels compared with nonsmoking patients, commonly leading to mild narrowing and nonobstructive stenosis of the coronary lumen. There was no significant difference for CT findings of CAD among pathological types of NSCLC in all aspects, except that patients with adenocarcinoma had more mixed plaques ($p < 0.05$) (►Fig. 3).

Discussion

In the case of NSCLC, patients concomitant with CAD during preoperative evaluation for lung resection show increased operative morbidity.[2,11] Meanwhile, the surgeon faces the issue of choosing the timing of a surgical approach for both lung and heart, whether it be concomitantly or in a staged way. These issues indicate that the presence of CAD needs to be screened before elective lung resection. As a non-invasive assessment tool for CAD and pulmonary vessel anatomy, DSCTA exhibits superiority in predicting risk stratification and postoperative cardiovascular events for noncardiac surgeries.[12] Therefore, careful preoperative evaluation of the coronary artery with DSCT in patients undergoing lung resection is imperative, and it can help the clinician to establish a better treatment strategy.

Our results showed MB commonly occurred in the distal segment of the LAD, which is consistent with the study.[13] MB is generally seen to a benign condition. However, anatomical characters of MB, especially its thickness and length, are associated with coronary atherosclerosis development and may induce myocardial infarction.[14] Therefore, knowledge of anatomic properties may contribute to identify low- and high-risk patients before surgery for better intervention measures. DSCT can accomplish this.

Different hemodynamics may cause different susceptibilities of each coronary vessel and segment to atherosclerosis.[15] Our results revealed that the proximal segment of the LAD artery was the most frequent major involved vessel with plaques, which is consistent with findings in the general population.[16] Although its plaques may not lead to significant luminal narrowing over a short time due to its large caliber, the cardiovascular event would be serious once the lumen was occluded.

The incidence of adverse future event rate in patients with any coronary plaque was significantly higher than those with a normal MDCT scan.[17] The fact that plaque composition is associated with the clinical consequences of CAD may be an explanation for this. Noncalcified plaques are more likely to cause acute ischemic coronary syndromes due to their unstable characteristics.[18] Patients with calcified plaques may have better long-term clinical outcomes than those with noncalcified and mixed plaques.[19] Therefore, it is imperative to timely evaluate and treat any plaque.

Table 2 Involved manifestation of coronary artery in patients

	Total value
Types of plaque	
Calcified plaque	156 (52.9)
Mixed plaque	83 (28.1)
Noncalcified plaque	56 (19.0)
Grading of stenosis	
Normal appearing	33 (11.2)
Mild narrowing	182 (61.7)
Moderate narrowing	61 (20.7)
Severe narrowing	19 (6.4)
Nonobstructive stenosis	215 (72.9)
Obstructive stenosis	80 (27.1)

Results are given as *n* (percentage). Nonobstructive stenosis includes normal appearing and mild narrowing. Obstructive stenosis includes moderate and severe narrowing.
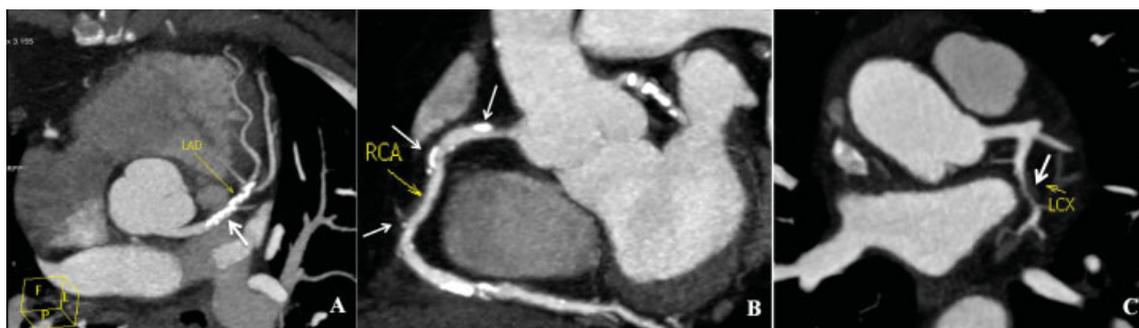
Fig. 2 The curvature plane reconstruction image shows that the density of calcified plaques (arrow) is significantly higher than the contrast-enhanced lumen (**A**). The curvature plane reconstruction image shows many noncalcified plaques and calcified plaques mixed together in the right coronary artery (arrows). Other findings: calcified plaques in the left coronary artery (**B**). The curvature plane reconstruction image shows a filling defect and moderate stenosis in the left circumflex coronary artery (arrow) (**C**). AAO, ascending aorta; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

In our study, men had more involved coronary vessels and segments compared with women. More plaques were found in men, which is consistent with other findings.[20] However, our findings are inconsistent for lumen stenosis. The plaques in men commonly resulted in only mild narrowing and nonobstructive stenosis of the coronary lumen. It is possible that these results are related to other risk factors for CAD in our study, such as older age and diabetes, which were more common for women. Therefore, the coronary artery for women was less likely to develop less severe stenosis.

Smoking has also been causally associated with CAD.[21] In our study, smoking patients had more involved coronary

Table 3 Comparison of coronary artery diseases between different sexes, smoking conditions, and pathological types

	Female (n = 57)	Male (n = 88)	p-Value	Smoking (n = 63)	Non-smoking (n = 82)	p-Value	Adenocarcinoma	Squamous cell carcinoma	p-Value
Extent									
Diseased vessels	1.0 ± 1.0	1.7 ± 1.3	**0.001**	1.6 ± 1.3	1.1 ± 1.0	**0.032**	1.3 ± 1.2	1.8 ± 1.2	0.137
Diseased segments	1.4 ± 1.5	2.3 ± 2.2	**0.003**	2.1 ± 2.0	1.4 ± 1.6	0.126	1.8 ± 1.9	2.3 ± 1.8	0.235
Types of plaque									
Total plaques	1.6 ± 1.6	2.5 ± 2.1	**0.013**	1.9 ± 1.3	1.6 ± 0.8	0.135	1.9 ± 1.3	1.8 ± 1.2	0.534
Calcified plaque	1.7 ± 0.9	2.5 ± 1.7	**0.012**	2.2 ± 1.6	1.8 ± 1.0	0.315	2.2 ± 1.6	2.1 ± 1.6	0.805
Mixed plaque	1.4 ± 0.7	1.8 ± 1.2	0.280	1.7 ± 1.1	1.5 ± 0.7	0.669	1.8 ± 1.0	1.5 ± 0.9	**0.012**
Non-calcified plaque	1.3 ± 1.0	1.7 ± 0.8	0.189	1.7 ± 0.7	1.2 ± 0.4	0.245	1.5 ± 0.8	1.5 ± 0.5	0.915
Grading of stenosis									
Normal appearing	1.1 ± 0.3	1.2 ± 0.4	0.472	1.1 ± 0.4	1.2 ± 0.4	0.622	1.1 ± 0.4	1.3 ± 0.5	0.547
Mild narrowing	1.4 ± 0.6	2.1 ± 1.3	**0.000**	2.8 ± 1.6	1.5 ± 0.7	**0.002**	1.8 ± 1.2	2.1 ± 1.1	0.395
Moderate narrowing	1.8 ± 1.3	1.4 ± 0.7	0.516	1.6 ± 1.0	1.8 ± 1.2	0.533	1.5 ± 0.8	1.4 ± 0.8	0.840
Severe narrowing	1.5 ± 0.7	1.1 ± 0.4	0.345	1.2 ± 0.4	1.3 ± 0.5	0.662	1.2 ± 0.5	1.1 ± 0.4	0.635
Nonobstructive stenosis	1.3 ± 0.5	1.8 ± 1.1	**0.001**	2.2 ± 1.5	1.4 ± 0.7	**0.010**	1.6 ± 1.1	1.9 ± 1.0	0.326
Obstructive stenosis	1.7 ± 1.1	1.3 ± 0.6	0.210	1.5 ± 0.9	1.6 ± 0.9	0.800	1.4 ± 0.8	1.3 ± 0.6	0.523

Results are given as mean ± standard deviation. Non-obstructive stenosis includes normal appearing and mild narrowing. Obstructive stenosis includes moderate and severe narrowing. Bold values represent the significant p values.
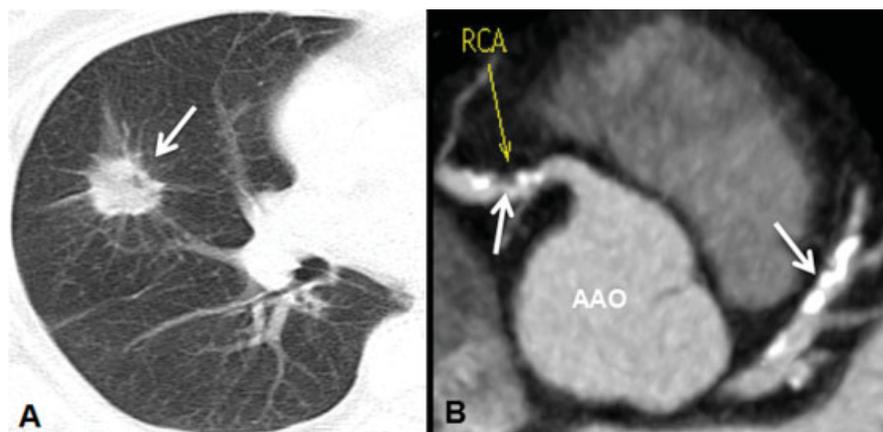
Fig. 3 Coronary plaques in patients with lung cancer. A mass (3.5 × 4.9 cm) (arrow) that proved to be a well-differentiated adenocarcinoma in a 64-year-old smoking man is in the right middle lobe (**A**). Patients with adenocarcinomas had more mixed plaques (**B**) (arrow) compared with those with squamous cell carcinoma. AAO, ascending aorta; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

vessels compared with nonsmoking patients. The mechanisms of atherosclerosis induced by smoking include a decreased availability of nitric oxide (NO) resulting in vasomotor and endothelial dysfunction, an increase in proinflammatory cytokines enhance leukocyte recruitment, leukocyte–endothelial cell interactions, activation of proatherogenic substances, and oxidative modification of lipids.[22] There was no significant difference for CT findings of CAD among pathological types of NSCLC in all aspects, except that patients with adenocarcinoma had more mixed plaques; it is unclear why, and additional study is necessary.

In the study, the percentage of severe luminal narrowing was 5% in patients scheduled for lung resection. It is slightly lower than that in previous study[23] for possibly reason of small number of patients. Severe stenosis was considered as a significant indication for poor prognosis and an indicator of coronary revascularization;[24] hence, these patients identified by DSCTA should deserve increased attention. Seven patients with severe stenosis found by DSCTA adopted invasive coronary angiography, and three met the indications for further coronary intervention. These patients face a difficult choice of undergoing concomitant or staged operations on both the heart and lungs.

There were many studies about the feasibility of concomitant operations, but were controversial.[25,26] Although this approach is attractive because it can quickly treat both diseases with fewer resource expenditures, increased concerns associated with the potential bleeding complications from the heparinization and to possible infections and spread of cancer from the cellular and humoral immunosuppressive effects of cardiopulmonary bypass are used as an argument against this approach. Off-pump coronary artery revascularization may reduce the incidence of complications,[27] but Schoenmakers et al found no significant differences between on- or off-pump techniques in relation to complications.[26] For a staged operation with two surgical incisions (a thoracotomy and a sternotomy), there is also controversy as to which procedure should be performed

first.[28,29] Ambrogi et al considered that a vascular operation had a potential lower perioperative risk and relatively more priority for an early stage NSCLC with slow-growing for elderly patients and therefore it can be performed first.[28] In our series, the three patients underwent the vascular procedure first. A lung resection is then suggested 4 to 6 weeks after open-heart procedure and 1 to 2 weeks after PTCA.[30] No patients had angina or postoperative ischemic myocardial infarctions during the 30 days after surgery. Thus, careful preoperative evaluation of the coronary artery with DSCT in patients undergoing lung resection can help to establish a better treatment strategy.

Limitations

This study does have some limitations. It was a cross-sectional study, and only patients with lung cancer coexisting with CADs were evaluated. Therefore, a selection bias existed. Moreover, a limitation for CT using is its radiation dose. However, radiation exposure from DSCTA is sharply reduced to 60% with attenuation-based online tube current modulation technique as compared with single-source CT (~8 mSv).[30]

Conclusion

In conclusion, DSCTA provided the necessary preoperative information about arteriosclerotic lesions of the coronary arteries in patients with lung cancer before lung resection. It can help the surgeon to plan the management strategy and to stratify the risk of postoperative complications and mortality.

Conflict of Interest
None.

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