Original Article

Coronary computed tomography angiography for assessing the coronary artery and predicting adverse cardiovascular events in patients with thoracic malignancies

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Background: It is unclear whether the parameters derived from coronary computed tomography angiography (CCTA) can identify the impairments of coronary arteries and if they are associated with major adverse cardiovascular events (MACEs) in patients with thoracic malignancies receiving chemotherapy or chemoradiotherapy. This study aimed to investigate the longitudinal changes in coronary arteries using CCTA and to determine their association with MACEs in patients with thoracic malignancies receiving chemotherapy or chemoradiotherapy.

Methods: This cross-sectional study included consecutive patients with thoracic malignancies who received chemotherapy or chemoradiotherapy and who underwent CCTA between June 2013 and May 2019 at Chongqing University Cancer Hospital. The pericoronary fat attenuation index (FAI) of three main coronary arteries before and after chemotherapy or chemoradiotherapy were assessed. The association between CCTA parameters and MACEs was evaluated via the Cox proportional hazards model. Kaplan-Meier survival curves were drawn to compare the MACE-free survival rates.

Results: A total of 1,543 patients were enrolled, 232 of whom developed MACEs. Among the patients, 41.3% were male, and the median age was 67.00 years (interquartile range 56.00–72.00 years). The FAI values were significantly increased after chemotherapy or chemoradiotherapy (all P values <0.05). After treatment, the FAI values were higher in the chemoradiotherapy group than in the chemotherapy group. MACEs were associated with the FAI values before chemotherapy in the left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA) [LAD: hazard ratio (HR) =3.745, 95% confidence interval (CI): 1.193–11.756, P=0.023; LCX: HR =3.460, 95% CI: 1.092–10.832, P=0.031; RCA: HR =4.175, 95% CI: 1.375–12.673, P=0.011] and chemoradiotherapy (LAD: HR =2.856, 95% CI: 1.210–6.742, P=0.016; LCX: HR =2.385, 95% CI: 1.037–5.487; P=0.040; RCA: HR =2.029, 95% CI: 1.074–3.834, P=0.029).

Conclusions: The FAI derived from CCTA, as an imaging biomarker of coronary arterial inflammation, was able to characterize coronary arterial impairment, and the FAI at baseline was associated with MACEs in patients with thoracic malignancies receiving chemotherapy or chemoradiotherapy.

Keywords: Thoracic neoplasms; coronary vessels; computed tomography angiography; major adverse cardiovascular events (MACEs)

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Introduction

Thoracic malignancies, which mainly include lung, esophageal, and breast cancers (1), are primarily treated with chemotherapy and chemoradiotherapy (2-4). However, these treatments exert toxic effects on coronary arteries, leading to hemodynamic alterations, lipid accumulation, and chronic inflammation, which can lead to major adverse cardiovascular events (MACEs), thereby significantly decreasing survival in patients with thoracic malignancies (5-7). Therefore, it is crucial to monitor the damage of coronary arteries and the associated MACEs in patients with thoracic malignancies before and after chemotherapy or chemoradiotherapy.

Coronary computed tomography angiography (CCTA) is a noninvasive imaging modality that is commonly used for diagnosing coronary artery disease (CAD) (8). Recent studies have observed that the coronary artery calcium (CAC) score derived from CCTA is associated with MACEs in patients with breast cancer or lung cancer who undergo radiotherapy (9,10). The Coronary Artery Disease-Reporting and Data System (CAD-RADS) has been demonstrated to predict MACEs in patients with chest pain (11). However, little is known about the value of the CAC score and the CAD-RADS classification in evaluating the risk of MACEs in patients with thoracic malignancies undergoing chemotherapy or chemoradiotherapy (5).

The fat attenuation index (FAI) derived from CCTA has been introduced as a novel imaging biomarker for evaluating coronary arterial inflammation (12). The FAI has been used to track the response to biologic therapy for CAD in psoriasis (13), and a higher FAI is associated with an increased risk of MACEs (14). Nevertheless, it is unclear whether the FAI can be used to identify coronary artery injury and whether the FAI is associated with MACEs in patients with thoracic malignancies treated by chemotherapy or chemoradiotherapy.

Data for the comprehensive evaluation of the longitudinal changes in coronary artery in patients with thoracic malignancies, as well as their association with MACEs, remain lacking. Therefore, we aimed to investigate the longitudinal changes in coronary artery using CCTA and to determine their association with MACEs in patients with thoracic malignancies receiving chemotherapy or chemoradiotherapy. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-944/rc).

Methods

Study population

This retrospective, single-center study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional ethics committee of Chongqing University Cancer Hospital (No. CZLS2023017-A). The requirement for written informed consent was waived due to the retrospective nature of the analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

From June 2013 to May 2019, consecutive patients with thoracic malignancies undergoing CCTA at Chongqing University Cancer Hospital were enrolled. The inclusion criteria were as follows: (I) lung cancer, esophageal cancer, or breast cancer with pathological confirmation and an estimated survival time of at least 1 year; and (II) stable typical/atypical chest pain or angina-like symptoms without confirmed CAD or with confirmed CAD. Meanwhile, the exclusion criteria were as follows: (I) no chemotherapy or chemoradiotherapy; (II) a history of allergy to computed tomography (CT) contrast agents; (III) incomplete baseline, treatment, and/or follow-up information; and (IV) presence of serious imaging artifacts. The flowchart of this study is shown in *Figure 1*, and detailed descriptions of the therapeutic regimens are provided in the Appendix 1. Patients were divided into chemotherapy group and chemoradiotherapy group to facilitate analysis of the differences in CCTA parameters between the two treatment modalities.

CCTA acquisition

All patients underwent CCTA examinations, which were performed on a Brilliance 64 CT scanner (Philips, Amsterdam, the Netherlands). The CCTA protocol schemes included initial nonenhanced calcium-scoring acquisition, which was followed by an arterially enhanced angiography. The scanning parameters were as follows:

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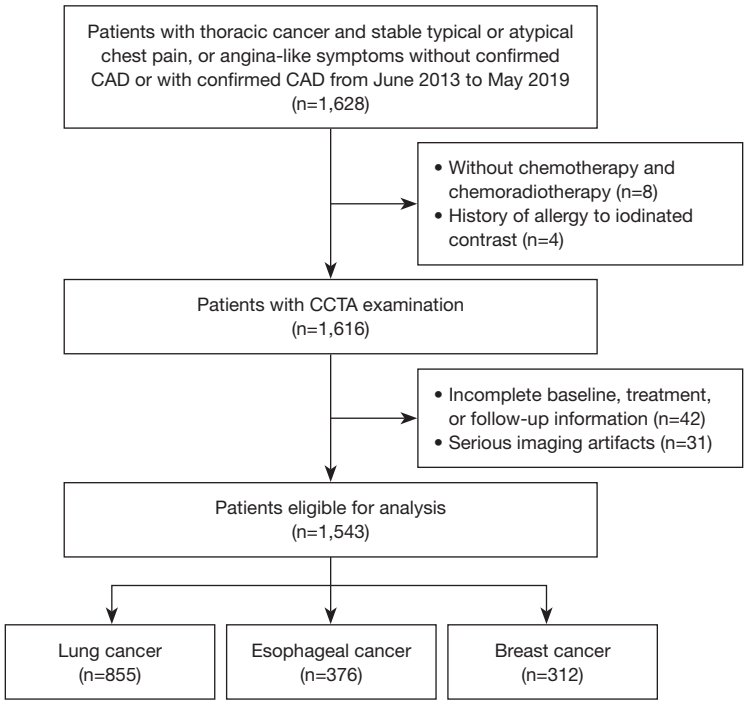

Figure 1 Flowchart of participant enrollment. A total of 1,543 patients with thoracic cancer were retrospectively enrolled. CAD, coronary artery disease; CCTA, coronary computed tomography angiography.

tube voltage, 120 kV; detector collimation, 40 mm; beam pitch, 1.5; slice thickness, 1.0 mm; ad slice gap, 2.0 mm. Electrocardiogram (ECG)-triggered acquisitions were continuously performed for the cardiac scans.

CCTA data analysis

Commercial artificial intelligence software, CoronaryDoc version 5.1.2 (ShuKun Technology, Beijing, China), run on a regular workstation, was used to segment and assess all CCTA images. The CCTA data were calculated with a deep learning algorithm. The CAC score and plaque calculation modules of the software used in this study have obtained the third-class medical device registration certification from the China National Medical Products Administration and the Conformité Européenne certification under the new Medical Device Regulation of the European Union. The CCTA data analyzed by the software were validated in 18 hospitals and comprise more than 10,000 cases and are thus reliable.

The CAC scores were automatically calculated by the software via nonenhanced calcium-scoring scanning (CACScoreDoc, ShuKun Technology), wherein each calcified area was multiplied by a local density factor as determined by the Hounsfield unit (HU) of the calcium (0, 0–129 HU; 1, 130–199 HU; 2, 200–299 HU, 3, 300–399 HU; 4, ≥400 HU) (*Figure 2*). The following plaque types were considered: no plaque, noncalcified plaque, calcified plaque, and mixed plaque. The CAD-RADS was used to classify the severity of stenosis from 0 (absence of CAD) to 5 (total coronary occlusion or subtotal occlusion) by two radiologists with 5 and 10 years of experience in cardiac CT imaging interpretation, respectively. The detailed information of this classification is presented in Table S1. Per-vessel and per-patient CAD-RADS categories were assigned based on the highest-grade stenosis. Analysis of left ventricle function was performed via CoronaryDoc Plus (ShuKun Technology), with ECG-triggered CCTA being used for automatically calculating the left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (ESV), left ventricular stroke volume (LVSV), and left ventricular myocardial mass (LVMM).

Dedicated research analysis software, Coronary FAI Analysis version 1.0.2, ShuKun Technology) was employed for FAI segmentation. For the right coronary artery (RCA), the perivascular FAI was measured according to the proximal 10- to 50-mm segments, while for the left anterior descending artery (LAD) and left circumflex artery (LCX), the proximal 40 mm of each vessel was analyzed (14). The

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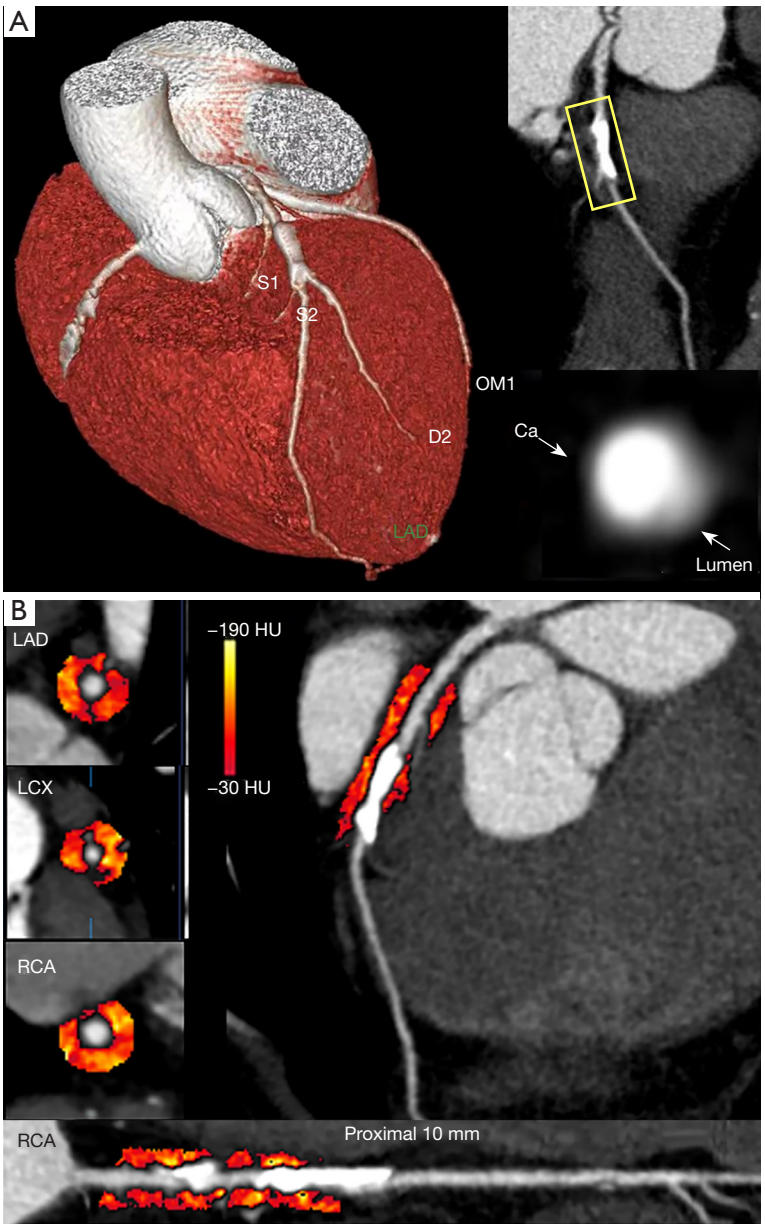

Figure 2 Perivascular FAI analysis and plaque assessment with CCTA. (A) A representative example of plaque assessment in the LAD. CCTA showed calcified plaques in the proximal segment of the LAD (yellow rectangle) with severe luminal stenosis. (B) Perivascular FAI analysis of three major epicardial coronary vessels. FAI, fat attenuation index; CCTA, coronary computed tomography angiography; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; Ca, calcium; HU, Hounsfield unit.

detailed process was as follows. First, a well-trained deep learning model was used to segment the coronary arteries. Second, a skeleton erosion shrinkage algorithm was used to calculate the centerline of each branch. Third, the normal sections of the local blood vessels were cut at equal intervals and were stacked in sequence to reconstruct a three-dimensional straightened blood vessel image, with a sliding window being used to select the starting and ending positions of the FAI along the vessel. Briefly, pericoronary adipose tissue was sampled radially outward from the outer vessel wall of the plaques and measured as voxels with attenuation between –190 and –30 HU (12) (*Figure 2*).

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Definition of MACEs

Twenty-four months of follow-up were conducted after completion of chemotherapy or chemoradiotherapy. Follow-up was performed through a review of medical records and telephone interviews by two radiologists at 3-month intervals until February 2022. MACEs were defined as cardiovascular death, myocardial infarction, stroke, complete heart block, and rehospitalization due to heart failure or aggravated angina symptoms (15).

Statistical analysis

Statistical analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA) and Stata Version 16 (StataCorp, College station, TX, USA). The one-sample Kolmogorov-Smirnov test was used to check the assumption of normal distribution. Normally distributed continuous variables were expressed as the mean ± standard deviation, while nonnormally distributed continuous variables were expressed as medians and quartiles. Categorical variables were reported as counts and percentages. The independent *t*-test and the Wilcoxon signed-rank test were used to compare normally and nonnormally distributed continuous variables, respectively. The Chi-squared test was used to compare categorical variables. The intraobserver and interobserver consistency of CCTA parameters were assessed by two certified radiologists (with 15 and 10 years of experience, respectively). The intraclass correlation coefficient (ICC) was used to assess continuous variables, while the kappa coefficient was used to evaluate categorical variables. Test-retest reliability was determined according to the following scheme: ICC 0.75 or greater, excellent; between 0.6 and 0.74, good; between 0.41 and 0.59, fair; and less than 0.4, poor (16).

Univariable and multivariable Cox proportional hazards models were used to determine the CCTA parameters associated with MACEs. Baseline variables that considered traditional cardiovascular risk factors, including age, sex, obesity (BMI ≥25 kg/m^2), hypertension, diabetes, dyslipidemia, smoking, previous myocardial infarction, known CAD, previous heart failure, or those with a univariate relationship with MACEs (P value <0.1) were entered into multivariate Cox proportional-hazards regression analysis. Kaplan-Meier curves were drawn, and the log-rank test was used to compare the MACE-free survival between different subgroups. Statistical significance was defined as a two-tailed P value <0.05.

Results

Study population and clinical outcomes

Of the 1,628 patients with thoracic malignancy, 85 ineligible patients were excluded (8 patients without chemotherapy or chemoradiotherapy; 4 patients with a history of allergy to CT contrast agents; 42 patients without complete baseline, treatment, and/or follow-up information; and 31 patients with serious imaging artifacts). Finally, 1,543 patients with thoracic malignancy (855 patients with lung cancer, 376 patients with esophageal cancer, and 312 patients with breast cancer) were enrolled, including 808 patients receiving chemotherapy and 735 patients receiving chemoradiotherapy. All patients underwent two CCTA examinations within 1 year, with the median interval between baseline and follow-up CCTA in the chemotherapy group being 362 days [interquartile range (IQR) 352–374 days] and that in the chemoradiotherapy group being 361 days (IQR 350–375 days). Among the patients, 638 (41.3%) were male, and the median age was 67.00 years (IQR 56.00–72.00 years). The clinical characteristics of all patients are summarized by treatment type in *Table 1* and Table S2.

The median follow-up duration was 26 months (IQR 24–33 months). MACEs occurred in 232 patients (15.0%), which included 87 cases of cardiovascular death, 40 cases of complete heart block, 33 strokes, 30 cases of rehospitalization due to heart failure or aggravated angina symptoms, 27 cases of acute myocardial infarction, 15 cardiogenic shocks, and 9 cardiac arrests. Higher FAI values for the LAD, LCX, and RCA were observed in patients with MACEs compared to those without MACEs. There were no significant differences in other baseline characteristics between the two groups. The details are presented in Table S3.

Intraobserver and interobserver consistency

The intra-observer and inter-observer consistency of FAI and left ventricle function data were excellent, with an ICC value of 0.967 [95% confidence interval (CI): 0.933–0.986] and 0.921 (95% CI: 0.880–0.962), respectively. Excellent intra-observer and inter-observer consistency was also observed for the total CAC score, coronary stenosis, and CAD-RADS classification, with the kappa coefficient ranging from 0.852 to 0.931.

CCTA-derived parameters in the chemotherapy group

There were no statistically significant differences in CAC

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Table 1 Clinical characteristics of all patients (n=1,543)

Parameter	Chemotherapy			Chemoradiotherapy		
	Pretreatment (n=445)	Posttreatment (n=363)	P value	Pretreatment (n=428)	Posttreatment (n=307)	P value
Age (years)	67.00 (58.00, 74.00)	67.00 (58.00, 70.00)	0.124	66.00 (56.00, 72.00)	65.50 (55.00, 72.00)	0.882
Sex			0.136			0.227
Female	253 (56.9)	233 (64.2)		236 (55.1)	183 (59.6)	
Male	192 (43.1)	130 (35.8)		192 (44.9)	124 (40.4)	
Body mass index (kg/m^2)	23.45±3.36	23.37±3.38	0.761	23.41±3.45	22.81±5.05	0.056
Obesity	31 (7.0)	23 (6.3)	0.721	31 (7.2)	19 (6.2)	0.259
Hypertension	138 (30.3)	103 (27.6)	0.403	145 (32.4)	98 (30.4)	0.555
Diabetes mellitus	48 (10.5)	51 (13.7)	0.165	63 (14.1)	39 (12.1)	0.424
Smoking	335 (73.5)	253 (67.8)	0.075	333 (74.5)	220 (68.3)	0.06
Dyslipidemia	274 (60.1)	206 (55.2)	0.159	259 (57.9)	199 (61.8)	0.282
Previous MI	12 (2.7)	16 (4.4)	0.186	14 (3.3)	12 (3.9)	0.644
Known CAD	188 (42.2)	154 (42.4)	0.960	177 (41.4)	127 (41.4)	0.997
Previous HF	14 (3.9)	10 (2.2)	0.180	15 (3.5)	11 (3.6)	0.955
TNM			0.990			0.077
I	47 (10.6)	41 (11.3)		36 (8.4)	20 (6.5)	
II	135 (30.3)	109 (30.0)		130 (30.4)	72 (23.5)	
III	213 (47.9)	172 (47.4)		221 (51.6)	175 (57.0)	
IV	50 (11.2)	41 (11.3)		41 (9.6)	40 (13.0)	
Medication use						
Beta-blocker	29 (6.5)	29 (8.0)	0.420	30 (7.0)	22 (7.2)	0.925
Ca2+ channel blocker	34 (7.6)	28 (7.7)	0.969	32 (7.5)	19 (6.2)	0.506
ACEI/ARB	31 (7.0)	26 (7.2)	0.914	34 (7.9)	21 (6.9)	0.583
Statin	84 (18.9)	67 (18.5)	0.879	85 (19.9)	56 (18.3)	0.597
Aspirin	33 (7.4)	25 (6.9)	0.772	34 (7.9)	22 (7.2)	0.704
Mean heart dose (Gy)	–	–		–	14.25±6.65	

Values are expressed as the mean ± standard deviation, median (interquartile range), or n (%). MI, myocardial infarction; CAD, coronary artery disease; HF, heart failure; TNM, tumor-node-metastasis; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker.

score, plaque characteristics, diameter stenosis (DS), or CAD-RADS categories between the three coronary arteries before and after chemotherapy (all P values >0.05; *Table 2*, Table S4). A statistically significant increase in the FAI values of the LAD, LCX, and RCA was observed after treatment (–73.2±6.74, –73.2±8.10, and –73.4±7.40 HU, respectively) compared with those before treatment (–76.6±6.03, –76.3±6.47, and –76.5±5.98 HU, respectively) (all P values <0.001; *Table 2*). Additionally, in each enrolled thoracic malignancy, there was a statistically significant increase in FAI values of the LAD, LCX, and RCA after chemotherapy (all P values <0.05), as shown in Table S5.

CCTA-derived parameters in the chemoradiotherapy group

In the chemoradiotherapy group, no statistically significant differences were observed in CAC score, plaque characteristics, DS, or CAD-RADS categories of the three coronary arteries

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Table 2 Comparison of CCTA parameters before and after chemotherapy and chemoradiotherapy in patients with thoracic cancer

Parameters	Chemotherapy			Chemoradiotherapy		
	Pretreatment (n=445)	Posttreatment (n=363)	P value	Pretreatment (n=428)	Posttreatment (n=307)	P value
Total coronary artery calcium score			0.171			0.324
0 (0)	124 (27.9)	103 (28.4)		158 (36.9)	108 (35.2)	
1 (1 to 10)	55 (12.4)	42 (11.6)		43 (10.0)	20 (6.5)	
2 (11 to 100)	64 (14.3)	75 (20.7)		74 (17.3)	55 (17.9)	
3 (101 to 400)	88 (19.8)	63 (17.3)		73 (17.1)	66 (21.5)	
4 (>400)	114 (25.6)	80 (22.0)		80 (18.7)	58 (18.9)	
Total coronary diameter stenosis			0.656			0.772
None (0%)	107 (24.0)	75 (20.7)		103 (24.1)	82 (26.7)	
Slight (1% to 24%)	43 (9.7)	33 (9.0)		33 (7.7)	19 (6.2)	
Mild (25% to 49%)	84 (18.9)	82 (22.6)		78 (18.2)	52 (16.9)	
Moderate (50% to 69%)	107 (24.0)	87 (24.0)		100 (23.4)	78 (25.4)	
Severe (70% to 99%)	104 (23.4)	86 (23.7)		114 (26.6)	76 (24.8)	
CAD-RADS classification			0.932			0.907
0	106 (23.8)	79 (21.8)		106 (24.8)	84 (27.4)	
1	43 (9.7)	34 (9.4)		30 (7.0)	19 (6.2)	
2	86 (19.3)	78 (21.5)		78 (18.2)	52 (16.8)	
3	104 (23.4)	85 (23.3)		102 (23.8)	76 (24.8)	
4	106 (23.8)	87 (24.0)		112 (26.2)	76 (24.8)	
5	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
LVEF (%)	54.7±6.1	53.9±7.5	0.095	55.0±5.4	54.2±5.6	0.057
LVEDV (mL)	118.1±14.8	117.0±13.4	0.273	120.0±15.8	118.4±15.4	0.172
LVESV (mL)	52.7±9.8	53.3±8.3	0.354	52.5±8.4	53.0±9.3	0.447
LVSV (mL)	63.9±11.3	63.7±12.9	0.814	67.4±12.1	65.8±13.9	0.098
LVMM (g)	99.2±15.9	98.2±10.4	0.303	95.3±12.5	95.9±15.7	0.565
FAI (HU)						
LAD	−76.6±6.03	−73.2±6.74	<0.001	−76.6±6.31	−70.3±6.48	<0.001
LCX	−76.3±6.47	−73.2±8.10	<0.001	−76.7±7.25	−70.4±4.66	<0.001
RCA	−76.5±5.98	−73.4±7.40	<0.001	−76.3±6.52	−70.6±6.19	<0.001

Values are expressed as mean ± standard deviation or as n (%). CCTA, coronary computed tomography angiography; CAD-RADS, Coronary Artery Disease-Reporting and Data System; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVMM, left ventricular myocardial mass; FAI, fat attenuation index; HU, Hounsfield unit; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

before and after chemoradiotherapy (all P values >0.05; *Table 2*, Table S4).

There were higher FAI values in the three coronary arteries observed after chemotherapy treatment than before treatment (all P values <0.001; *Table 2*). The FAI values of the LAD, LCX, and RCA after chemoradiotherapy were significantly increased in each enrolled thoracic malignancy (all P values <0.05), as presented in Table S6.

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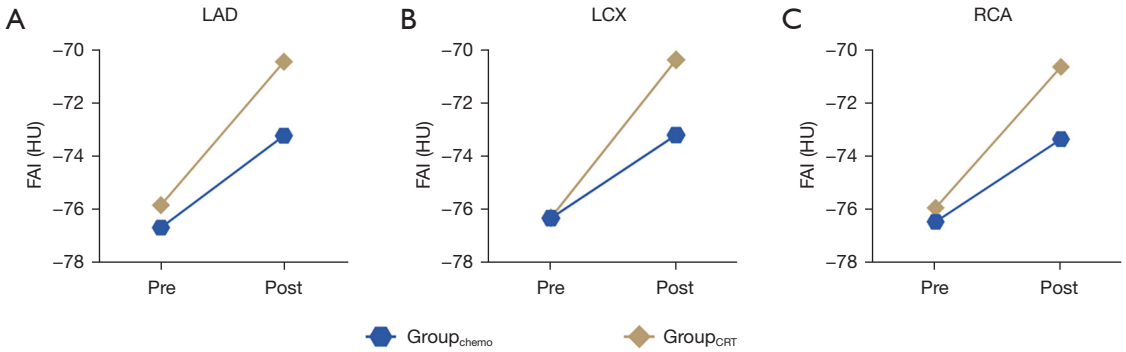

Figure 3 FAI alternations in patients with thoracic cancer before and after chemotherapy and chemoradiotherapy. (A) The FAI values in the LAD were increased after chemotherapy and chemoradiotherapy. (B) The FAI values in the LCX were increased after chemotherapy and chemoradiotherapy. (C) The FAI values in the RCA were increased after chemotherapy and chemoradiotherapy. FAI, fat attenuation index; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; chemo, chemotherapy; CRT, chemoradiotherapy; Pre, pretreatment; Post, posttreatment; HU, Hounsfield unit.

Comparison of CCTA-derived parameters between the chemotherapy and chemoradiotherapy groups

The CCTA parameters of the chemotherapy group and the chemoradiotherapy group before and after treatment are summarized in Table S7.

Before treatment, none of the parameters showed any differences between the two treatment groups. Moreover, after treatment, no statistically significant differences were observed in total CAC score, plaque characteristics, DS, CAD-RADS categories, or left ventricle function data (all P values >0.05), but the FAI values of the three coronary arteries were significantly higher in the chemoradiotherapy group than in the chemotherapy group (all P values <0.001), as shown in *Figure 3*. The pretreatment and posttreatment CCTA parameters for each enrolled thoracic malignancy in the two treatment groups are presented in Tables S8-S10.

Association between FAI and MACEs

MACEs were associated with FAI values of the LAD, LCX, and RCA before chemotherapy [LAD: hazard ratio (HR) =3.745, 95% CI: 1.193–11.756, P=0.023; LCX: HR =3.460, 95% CI: 1.092–10.832, P=0.031; RCA: HR =4.175, 95% CI: 1.375–12.673, P=0.011] and chemoradiotherapy (LAD: HR =2.856, 95% CI: 1.210–6.742, P=0.016; LCX: HR =2.385, 95% CI: 1.037–5.487, P=0.040; RCA: HR =2.029, 95% CI: 1.074–3.834, P=0.029), as shown in *Tables 3,4*.

According to a previous study (12), FAI values were divided into high- (≥−70.1 HU) or low-value (<−70.1 HU) groups. The MACE-free survival rates in patients with high FAI values were lower than those in patients with low FAI values both before chemotherapy and chemoradiotherapy, as presented in *Figure 4*. The Kaplan-Meier curves of each thoracic malignancy are shown in Figures S1-S9.

Discussion

This study focused on CCTA parameters in thoracic malignancies. The following observations were made. (I) The FAI increased after chemotherapy or chemoradiotherapy. (II) After treatment, the FAI was significantly higher in the chemoradiotherapy group than in the chemotherapy group. (III) The FAI before chemotherapy or chemoradiotherapy was associated with MACEs.

Chemotherapy and chemoradiotherapy, which are associated with damage to coronary arteries, have toxic effects on coronary endothelial cell function and viability, eventually resulting in plaque formation, coronary artery stenosis, hemodynamic changes, and coronary inflammation, thereby increasing the risk of CAD (17,18). In our study, FAI was increased after chemotherapy or chemoradiotherapy in patients with thoracic malignancies. A recent study found that FAI decrease is associated with moderate-to-severe psoriasis in patients receiving biologic therapy (13). In other research, it was found that FAI decreased after statin treatment in patients with noncalcified and mixed plaques (19). These findings suggest that the dynamic alterations of FAI can be observed not only in the treatment of patients with cancer but also in those without cancer. Therefore, CCTA allows for evaluating the

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Table 3 Univariable and multivariable Cox proportional hazard analysis of baseline characteristics in predicting MACEs in the chemotherapy group

Characteristic	Chemotherapy group			
	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	0.980 (0.939–1.022)	0.352	0.989 (0.937–1.045)	0.716
Male sex	1.251 (0.541–2.891)	0.599	1.742 (0.685–4.431)	0.243
Obesity	3.659 (1.357–9.870)	0.010	2.586 (0.708–9.445)	0.150
Hypertension	0.897 (0.369–2.181)	0.810	0.433 (0.139–1.343)	0.147
Diabetes	0.391 (0.053–2.899)	0.358	0.457 (0.059–3.558)	0.454
Dyslipidemia	1.363 (0.960–1.822)	0.115	0.643 (0.234–1.764)	0.391
Smoking	0.489 (0.181–1.317)	0.157	0.474 (0.138–1.629)	0.236
TNM	1.076 (0.623–1.858)	0.792	–	–
Previous MI	2.536 (0.341–18.887)	0.364	1.347 (0.886–3.801)	0.467
Known CAD	2.587 (0.097–6.104)	0.129	0.844 (0.414–1.709)	0.405
Previous HF	3.021 (0.406–22.452)	0.280	1.014 (0.582–1.764)	0.315
Total stenosis	0.903 (0.693–1.179)	0.456	–	–
Total calcium score	1.115 (0.847–1.469)	0.436	–	–
CAD-RADS classification	0.884 (0.677–1.153)	0.362	–	–
Medication use				
Beta-blocker	0.713 (0.096–5.292)	0.741	–	–
Ca2+ channel blocker	0.942 (0.221–4.019)	0.935	–	–
ACEI/ARB	0.871 (0.296–2.560)	0.802	–	–
Statin	0.879 (0.299–2.584)	0.815	–	–
Aspirin	0.742 (0.174–3.169)	0.688	–	–
LVEF (%)	1.003 (0.968–1.040)	0.844	–	–
LVEDV (mL)	1.011 (0.989–1.034)	0.309	–	–
LVESV (mL)	1.012 (0.979–1.046)	0.485	–	–
LVSV (mL)	1.004 (0.985–1.024)	0.678	–	–
LVMM (g)	1.005 (0.992–1.019)	0.462	–	–
FAI of LAD (HU)	10.324 (4.544–23.453)	<0.001	3.745 (1.193–11.756)	0.023
FAI of LCX (HU)	10.177 (4.483–23.100)	<0.001	3.460 (1.092–10.832)	0.031
FAI of RCA (HU)	11.099 (4.856–25.373)	<0.001	4.175 (1.375–12.673)	0.011

MACE, major adverse cardiovascular event; HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis; MI, myocardial infarction; CAD, coronary artery disease; HF, heart failure; CAD-RADS, Coronary Artery Disease-Reporting and Data System; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVMM, left ventricular myocardial mass; FAI, fat attenuation index; LAD, left anterior descending artery; HU, Hounsfield unit; LCX, left circumflex artery; RCA, right coronary artery.

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Table 4 Univariable and multivariable Cox proportional hazard analysis of baseline characteristics in predicting MACEs in the chemoradiotherapy group

Characteristic	Chemoradiotherapy group			
	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	0.992 (0.971–1.014)	0.471	0.990 (0.969–1.013)	0.415
Male sex	0.816 (0.503–1.324)	0.410	0.983 (0.570–1.698)	0.953
Obesity	1.593 (0.760–3.336)	0.217	1.752 (0.805–3.816)	0.157
Hypertension	1.547 (0.947–2.528)	0.081	1.276 (0.767–2.125)	0.347
Diabetes	1.280 (0.669–2.447)	0.454	1.059 (0.536–2.092)	0.867
Dyslipidemia	1.727 (0.928–1.901)	0.138	1.896 (0.979–3.674)	0.257
Smoking	1.045 (0.607–1.800)	0.873	0.818 (0.382–1.751)	0.604
TNM	1.014 (0.786–1.308)	0.911	–	–
Previous MI	0.932 (0.228–3.807)	0.921	1.288 (0.304–5.447)	0.730
Known CAD	0.706 (0.423–1.178)	0.183	0.913 (0.698–1.542)	0.541
Previous HF	0.413 (0.057–2.980)	0.380	0.801 (0.670–1.741)	0.499
Total stenosis	1.092 (0.928–1.286)	0.285	–	–
Total calcium score	0.958 (0.818–1.123)	0.600	–	–
CAD-RADS classification	1.132 (0.960–1.335)	0.137	–	–
Medication use				
Beta-blocker	1.074 (0.431–2.674)	0.878	–	–
Ca2+ channel blocker	1.555 (0.770–3.142)	0.218	–	–
ACEI/ARB	0.585 (0.298–1.146)	0.118	–	–
Statin	0.694 (0.354–1.359)	0.287	–	–
Aspirin	0.611 (0.245–1.521)	0.289	–	–
LVEF (%)	1.005 (0.985–1.026)	0.576	–	–
LVEDV (mL)	1.006 (0.993–1.018)	0.327	–	–
LVESV (mL)	1.004 (0.981–1.027)	0.707	–	–
LVSV (mL)	1.003 (0.992–1.014)	0.514	–	–
LVMM (g)	1.010 (0.974–1.023)	0.282	–	–
FAI of LAD (HU)	9.055 (5.548–14.780)	<0.001	2.856 (1.210–6.742)	0.016
FAI of LCX (HU)	6.966 (4.276–11.350)	<0.001	2.385 (1.037–5.487)	0.040
FAI of RCA (HU)	5.693 (3.467–9.348)	<0.001	2.029 (1.074–3.834)	0.029

HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular event; TNM, tumor-node-metastasis; MI, myocardial infarction; CAD, coronary artery disease; HF, heart failure; CAD-RADS, Coronary Artery Disease-Reporting and Data System; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVMM, left ventricular myocardial mass; FAI, fat attenuation index; LAD, left anterior descending artery; HU, Hounsfield unit; LCX, left circumflex artery; RCA, right coronary artery.

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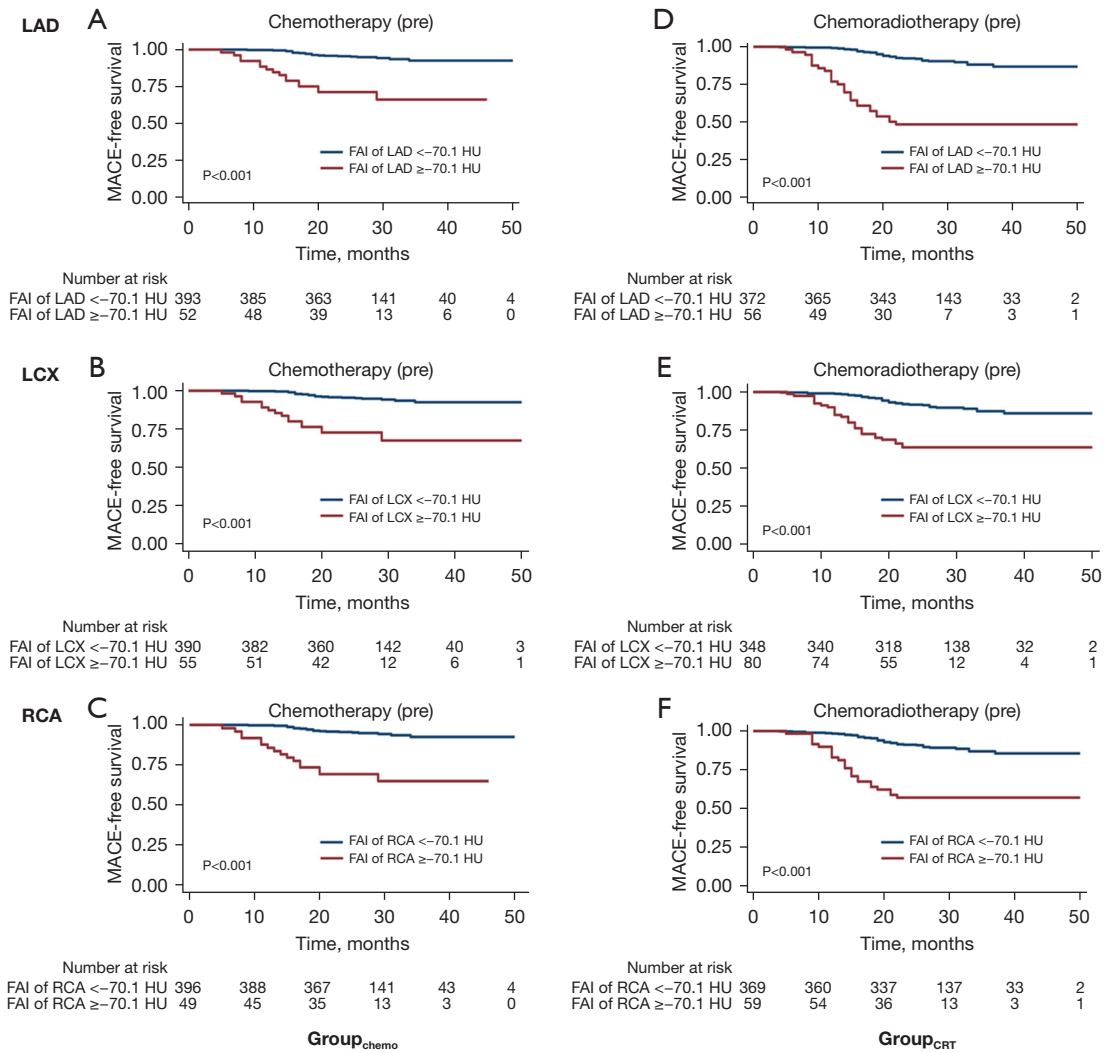

Figure 4 MACE-free survival curves stratified by FAI. (A) The MACE-free survival rates in the high-FAI group (≥−70.1 HU) were lower than those in the low-FAI group (<−70.1 HU) in the LAD before chemotherapy. (B) The MACE-free survival rates in the high-FAI group (≥−70.1 HU) were lower than those in the low-FAI group (<−70.1 HU) in the LCX before chemotherapy. (C) The MACE-free survival rates in the high-FAI group (≥−70.1 HU) were lower than those in the low-FAI group (<−70.1 HU) in the RCA before chemotherapy. (D) The MACE-free survival rates in the high-FAI group (≥−70.1 HU) were lower than those in the low-FAI group (<−70.1 HU) in the LAD before chemoradiotherapy. (E) The MACE-free survival rates in the high-FAI group (≥−70.1 HU) were lower than those in the low-FAI group (<−70.1 HU) in the LCX before chemoradiotherapy. (F) The MACE-free survival rates in the high-FAI group (≥−70.1 HU) were lower than those in the low-FAI group (<−70.1 HU) in the RCA before chemoradiotherapy. MACE, main adverse cardiovascular event; FAI, fat attenuation index; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; chemo, chemotherapy; CRT, chemoradiotherapy; Pre, pretreatment; Post, posttreatment; HU, Hounsfield unit.

longitudinal changes of coronary arteries in patients with thoracic malignancies and is beneficial to clinical treatment decision-making (20).

In this study, the FAI was higher in the chemoradiotherapy group than in the chemotherapy group after treatment. This result indicates that chemoradiotherapy may be considerably more deleterious to the coronary arteries compared to chemotherapy. Radiation can cause endothelial cellular stress, including generation of reactive oxygen species, DNA damage, and subcellular injury, as well as accelerated atherosclerosis, necrosis, and fibrosis of the media and adventitia. This eventually leads to irreversible

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structural and functional injury in the coronary artery (21,22). Chemotherapy, as a systemic treatment, transports drugs through veins into the coronary arteries, which may damage the endothelial cells in these arteries and cause cellular dysfunction. However, chemotherapeutics does not have a significant influence on the coronary arterial wall until the cumulative dose is reached (18,23). Moreover, chemoradiotherapy, the combination of chemotherapy and radiotherapy, may result in cumulative toxicity in the coronary arteries. A recent study reported that the risk of toxicity to the coronary arteries is higher in patients with breast cancer who receive both radiation therapy and chemotherapy (24).

Our results confirmed that the higher FAI values in the LAD, LCX, and RCA were associated with MACEs in patients with thoracic malignancies. Several studies indicate that increased FAI is a strong independent predictor of MACEs in patients without cancer (12,14,25). FAI is considered to be a novel method for assessing coronary inflammation (26). Pericoronary inflammation is regarded as an early indicator of CAD and may aid in predicting MACEs (12,27). Pericoronary inflammation may induce local fat breakdown and prevent lipid accumulation, leading to increased FAI values (28). Consequently, the FAI may be able to predict the occurrence of MACEs.

Certain limitations to this study should be considered. First, we employed a retrospective, single-center design, which might have introduced selection bias and constrained the generalizability of the findings. Second, the comparison of CCTA parameters before and after treatment was not based on the same group of patients, which could have introduced variability and confounding factors. Third, more relevant myocardial parameters were not taken into account for a more comprehensive assessment of cardiovascular health. In the future, a prospective, multicenter study will be conducted to further validate these findings.

Conclusions

We found that FAI derived from CCTA, as an imaging biomarker of coronary arterial inflammation, could identify coronary impairment and was associated with MACEs in patients with thoracic malignancies receiving chemotherapy or chemoradiotherapy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklists. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-944/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-944/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional ethics committee of Chongqing University Cancer Hospital (No. CZLS2023017-A). Individual consent for this analysis was waived due to the retrospective nature of the analysis.

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