EVALUATION OF THE CT ANGIOGRAM SIGN AND ITS RELATIONSHIP WITH THE PATHOLOGICAL FINDING OF RESECTED PRIMARY SOLID LUNG CANCER IN LIGHT OF MODERN ADVANCES IN THE TECHNOLOGY OF CT SCANNERS

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Abstract
Purpose : To evaluate the usefulness of the CT angiogram sign for solid lung masses on dynamic contrast-enhanced, thin-slice CT. Methods : Between January 2010 and March 2014, 300 patients' lung masses were surgically resected at our institution. Of these patients, we excluded 177 patients because the CT was not obtained at our institution ; ground-glass opacity component was present ; or neoadjuvant chemotherapy was administered. The CT images were obtained in both arterial and delayed phases at 1.25-mm and 5-mm sections. We evaluated presence of the CT angiogram sign, CT value, and presence of hypo-enhanced areas. Results : Included 123 patients were 89 men and 34 women, with median age of 72 years (range, 38-86). Neither the presence of the CT angiogram sign nor contrast-enhanced pattern had significant correlation with pathologic findings. Conclusions : In our study, the CT angiogram sign was not useful in evaluating solid lung masses on dynamic contrast-enhanced, thin-slice CT.

Key words : CT angiogram sign, lung cancer, solid pulmonary mass

Introduction

The computed tomography (CT) angiogram sign, which is the presence of contrast-enhancing vessels within tumors, was first reported to be a highly specific sign of lobar bronchioloalveolar carcinoma, which was a subtype in the old classification of lung cancer in 1990[1)] and which is now categorized as a subtype of invasive mucinous adenocarcinoma based on the latest World Health Organization classification[2)]. Until 1999, reports have stated that the sign can likewise be seen in primary pulmonary lymphoma, obstructive pneumonitis, pneumonia, metastatic gastrointestinal adenocarcinoma to the lung, and post-radiation fibrosis[3-10)].

Despite the developments in CT scan machines and techniques of intravenous administration of medium for contrast enhancement, no further reports about the CT angiogram sign have been published in the 21st century.

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In fact, based on our experience, the CT angiogram sign could sometimes be encountered in non-bronchioloalveolar carcinoma cases, such as lung squamous cell carcinoma, other adenocarcinoma subtypes, and small cell lung carcinoma. Additionally, no previous report is available about relationship between pathological type of lung carcinoma and the CT angiogram signs ; therefore, the presence of the CT angiogram sign can sometimes confuse diagnostic radiologists.

The aim of this study was to evaluate the CT angiogram and its relationship with the pathological finding of resected primary lung cancer in light of modern advanced in the technology of CT scanners.

Materials and methods

Patients

At our institution, 300 lung cancer patients who underwent operative resection between January 2010 and March 2014 were enlisted. Of these patients, 177 were excluded because the preoperative CT images were not obtained at our institution ; the lung mass had ground glass opacity component ; and there was neoadjuvant chemotherapy administered. The reason why we excluded the patients underwent neoadjuvant chemotherapy is the therapy might influence on vessel structure inside of tumors. The clinical and pathologic data were obtained from the medical records. Pathological tumor (T) factor and pathologic stage were determined according to the 7th edition of the general rule for clinical and pathological record of lung cancer (The Japan Lung Cancer Society, March 2010) ; The 8th edition of the general rule for clinical and pathological record of lung cancer (The Japan Lung Cancer Society, January 2017) is now available since 2017, however, the patients' clinical and pathological records included in the present retrospective study had been classified according to 7th edition in medical records, therefore, we used the previous edition of the classification. Patients were divided types (squamous cell carcinoma or adenocarcinoma ; adenosquamous carcinoma, small cell lung cancer, or carcinoid were not included because these three types were small number), followed statistical analyses. Informed consent for the use of CT data for analysis was obtained from all patients included in the present study.

Computed tomography scanning procedure

During the study period, we used two types of CT scanners (Discovery CT750HD or Discovery CT750HD-A ; GE Healthcare Japan, Tokyo, Japan). All patients were scanned according to our protocol for preoperative evaluation of lung tumors. Scanning images were obtained with the helical technique with the patients in a supine position, using slice thickness of 1.25 mm (thin slice) and 5 mm, before and after intravenous injection of 100 ml of non-ionic, iodinated contrast medium at 350-370 mg/mL in the arterial and delayed phases, followed by flushing with 40 ml of normal saline. For contrast administration, we used an automatic injector that was set to deliver the contrast medium for 20 seconds ; thereafter, scanning was performed at 28 seconds (early phase) and at 90 seconds (delayed phase).

Evaluation of computed tomography images

We evaluated the presence of the CT angiogram sign within the lesion both in the 1.25-mm thin-slice and in the 5-mm-slice axial images. The presence of an intratumoral vessel enhancement was considered as positive (Figs. 1-4) ; whereas the presence of vessels that could be seen only on the edge of the tumor was considered as negative. The pattern of contrast enhancement was evaluated on the CT slice that contained the maximum tumor diameter. First, a region of interest (ROI) was manually defined from a widest area that contained consolidation shadows. Then, using the working station's system, the area within the ROI that had a CT value lower than 0 was excluded ; this area was considered to not include the tumor.

We measured three variables : 1) maximum CT value of the tumor, 2) mean CT value of the tumor, and 3) the presence of an area with relatively less enhancement (>10 HU difference from the CT value) within the tumor.

Statistical analysis

The characteristics of the 2 groups of patients were compared by univariate analysis using the Welch's t test for continuous variables and the Mann-Whitney U-test or χ^2 test for categorical data. The relationship between

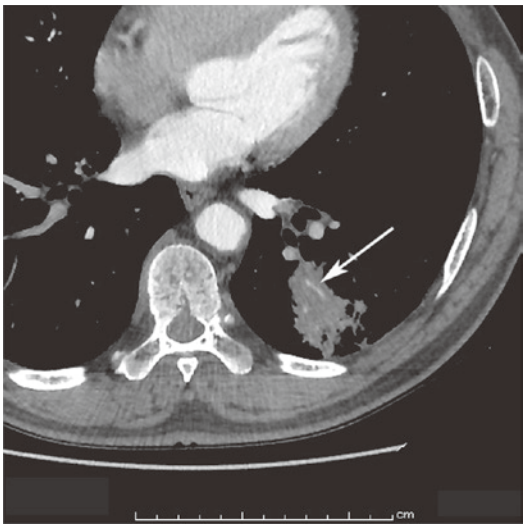

Fig. 1. A 75-year-old woman with lung adenocarcinoma, acinar type
Serial CT scans for follow-up of interstitial pneumonia reveals a lung tumor. A contrast-enhanced chest CT image shows a 45-mm solid mass in the left lower lobe with CT angiogram sign (arrow).

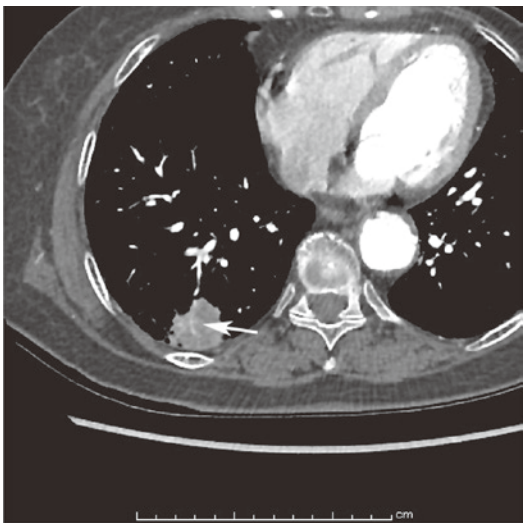

Fig. 2. A 64-year-old man with lung adenocarcinoma, mixed acinar and papillary type
He was noted to have an abnormal density on chest radiograph and was referred to our institution. A chest contrast-enhanced CT image shows a 40-mm solid mass in the right lower lobe with CT angiogram sign (arrow).

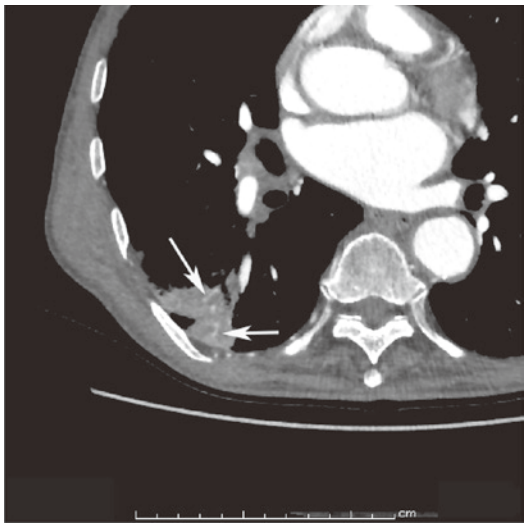

Fig. 3. A 79-year-old man with squamous cell carcinoma of the lung with CT angiogram sign
An abnormal density in the right lower lung field was incidentally detected on chest radiograph and he was referred to our hospital for further investigation. CT scan shows a 65-mm homogeneous, low-attenuating mass in the right lower lobe, with highly enhancing branching vessels or the CT angiogram sign (arrow).

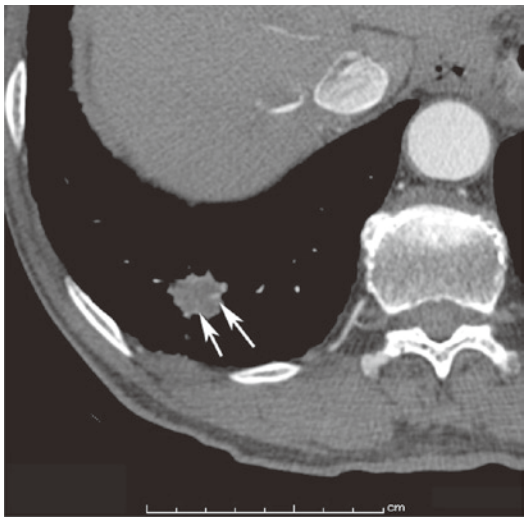

Fig. 4. A 76-year-old man with small cell lung carcinoma with CT angiogram sign
An abnormal lung density was detected on preoperative contrast-enhanced CT work-up for gastric cancer. The chest CT image shows a 20-mm homogeneous, low-attenuating solid mass in the right lower lobe, with contrast-enhancing vessels within the mass (arrow).

the CT findings and the three pathologic types of lung cancer was analyzed by the Kruskal-Wallis test or by the n × m analysis. A P value of <0.05 was considered to indicate statistical significance. Excel 2010 software (Microsoft Corporation, Redmond, WA, USA) with the add-in software Statcel 3 software (The publisher OMS Ltd., Saitama, Japan) was used for statistical analysis.

Results

The present study finally included 123 patients ; 89 were men and 34 were women (Table 1). The median age at the time of diagnosis was 72 years (range, 38-86 years). The pathologic types of the lung masses were squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, small cell lung cancer, and carcinoid. The maximum and mean CT values of all patients are also shown in Table 1. Less-enhanced areas in the tumor mass were seen in 28% in the early phase and in 35% in the delayed phase.

Examination of the relationship of the presence of the CT angiogram sign with CT slice thickness and timing of contrast enhancement demonstrated that compared with the 5-mm slice and delayed-phase scans, the thin-slice CT images in the early phase was the most sensitive setting for detection of the CT angiogram sign (Fig. 5). In 59 (43%) patients with primary solid lung cancer, we could find the CT angiogram sign with the thin-slice CT images in the early phase. Univariate analysis of the variables associated with the presence of a CT angiogram sign on thin-slice early phase images showed that tumor size was significantly larger in patients with CT angiogram sign ; age and sex were similar between the 2 groups (Table 2). Patients without the CT angiogram sign tended to have a lower pathological T factor and pathologic stage than those with the sign. The pathologic type of lung cancer was not significantly different between the 2 groups. Moreover, the CT angiogram sign was seen in patients with squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and small cell carcinoma. Table 3 shows that the pattern of contrast enhancement on CT images and the presence of a less-enhanced area in the tumor were not significantly different between squamous cell carcinoma and adenocarcinoma.

Table 1. Patient characteristics

	Total (n = 123)
Age in years, median (range)	72 (38-86)
Sex, n (%)	
Men	89 (72%)
Women	34 (28%)
Tumor size in mm, median (range)	32 (12-135)
Pathological T factor, n (%)	
1a	15 (12%)
1b	19 (15%)
2a	64 (52%)
2b	8 (7%)
3	15 (12%)
4	2 (2%)
Pathologic stage, n (%)	
IA	30 (24%)
IB	45 (37%)
IIA	14 (11%)
IIB	11 (9%)
IIIA	22 (18%)
IV	1 (1%)
Pathologic type, n (%)	
Squamous cell carcinoma	35 (28%)
Adenocarcinoma	75 (61%)
Adenosquamous carcinoma	8 (7%)
Small cell lung carcinoma	3 (2%)
Carcinoid	2 (2%)
Early phase, median (range)	
Maximum CT value (HU)	112 (47-312)
Mean CT value (HU)	56 (35-85)
Presence of less-enhanced area, n (%)	35 (28%)
Delayed phase, median (range)	
Maximum CT value (HU)	93 (32.5-105)
Mean CT value (HU)	56.5 (27.5-57)
Presence of less-enhanced area, n (%)	51 (41%)

CT : computed tomography, HU : Hounsfield unit

Discussion

In the present study, there was no significant relationship between the presence of CT angiogram sign and the pathologic type of resected primary solid lung cancer. Furthermore, the patterns of contrast enhancement on

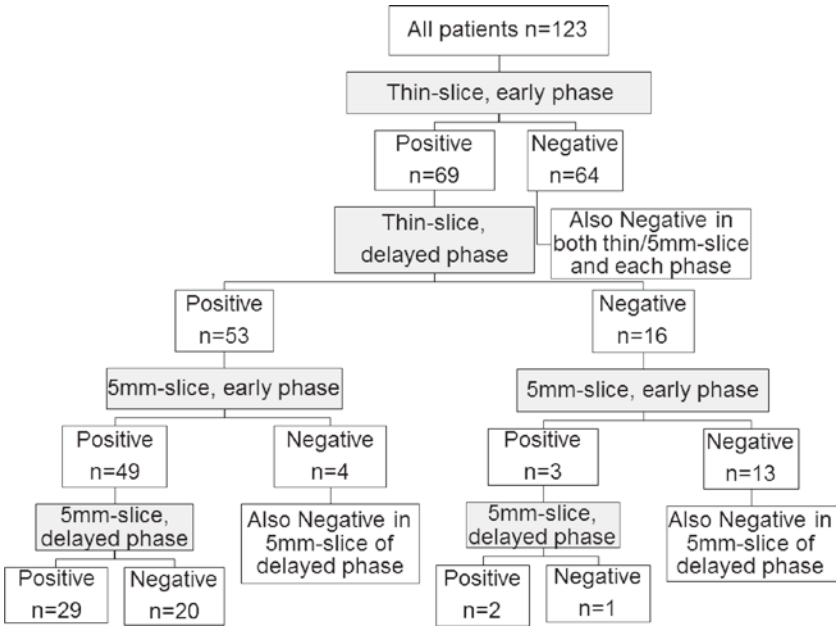

Fig. 5. Relationship between detection of the CT angiogram sign and the CT scan conditions of contrast enhancement phase and scan thickness
The arterial phase thin-slice CT was the most sensitive condition for detecting the CT angiogram sign (n = 69). The remaining 64 patients in whom there was no CT angiogram sign on arterial phase thin-slice CT also did not demonstrate the CT angiogram sign under the other CT conditions.

CT scan did not significantly vary among the pathologic types. These results supported our hypothesis that the CT angiogram sign was not specific for bronchioloalveolar carcinoma and was likewise observed in squamous cell carcinoma and small cell lung cancer.

The CT angiogram sign was first reported as a specific sign for bronchioloalveolar carcinoma by Im *et al.*[1], who discussed that the sign represents structures with normal bronchovascular bundle and mucin-producing bronchovascular carcinoma. After this report, several articles have reported that the sign was also seen in primary pulmonary lymphoma, obstructive pneumonitis, pneumonia, lung metastasis from gastrointestinal adenocarcinoma, and post-radiation fibrosis[3-10], therefore, the sign became less specific and not useful for identifying consolidation shadow in chest CT images is tumor or not tumor. R.M. Shah *et al.*[7] evaluated early-phase, contrast-enhanced CT scans and discussed that the appearance of the CT angiogram sign did not necessitate lung consolidation caused by mucin or fluid, but a sufficient difference in the attenuation between vessels and consolidation of cellular materials or retained secretions. According to their report, development of CT scan machines and techniques of contrast enhancement could enable identification of the CT angiogram sign in a wide variety of diseases if the vessel structures in the area of lung consolidation could be preserved.

The vessels (i.e., pulmonary artery, pulmonary vein, bronchial artery, bronchial vein, or angiogenic vessels) that account for the CT angiogram sign in a tumor are not known. As far as we searched PubMed, no previous report has mentioned about this point. As shown in Fig. 5, the arterial phase CT was more sensitive than the delayed phase in finding the CT angiogram sign. This was probably because the vessels that made up the CT angiogram sign enhanced earlier than the mass lesions and that in the delayed arterial phase, contrast enhancement was stronger in the mass than in the vessels. A previous report indicated the transit time of the contrast medium after intravenous injection ; after about 10 seconds,

Table 2. Correlation of the CT angiogram sign with the patient characteristics and pathologic findings

	Patients with CT angiogram sign (n = 59)	Patients without CT angiogram sign (n = 64)	p-value
Age in years, median (range)	71 (38-83)	72 (52-86)	0.6545
Sex, n (%)			0.8866
Men	41 (69%)	48 (75%)	
Women	18 (31%)	16 (25%)	
Tumor size in mm, median (range)	40 (20-135)	28 (12-60)	<0.0001
Pathological T factor, n (%)			0.0023
1a	2 (3%)	13 (20%)	
1b	7 (12%)	12 (19%)	
2a	33 (56%)	31 (48%)	
2b	7 (12%)	1 (2%)	
3	8 (14%)	7 (11%)	
4	2 (3%)	0 (0%)	
Pathologic stage, n (%)			0.0025
IA	7 (12%)	23 (36%)	
IB	21 (36%)	24 (38%)	
IIA	11 (19%)	3 (5%)	
IIB	7 (12%)	4 (6%)	
IIIA	12 (20%)	10 (16%)	
IV	1 (2%)	0 (0%)	
Pathologic type, n (%)			0.5583
Squamous cell carcinoma	18 (31%)	17 (27%)	
Adenocarcinoma	35 (59%)	40 (63%)	
Adenosquamous carcinoma	5 (8%)	3 (5%)	
Small cell lung carcinoma	1 (2%)	2 (3%)	
Carcinoid	0 (0%)	2 (3%)	

CT : computed tomography

it begins to enter the intravascular space in the lungs via the pulmonary arteries ; after 11-19 seconds, it travels via the bronchial arteries ; and at 60 seconds, more than half of the injected dose has reached the extravascular spaces[11]. In the present study, scanning after contrast medium administration was done at 28 seconds for the arterial phase and at 90 seconds for the delayed phase. Our results supported the idea that the vessels that made up the CT angiogram sign might be branches of the pulmonary arteries or bronchial arteries, which are one of the important nutrition vessels for malignant pulmonary tumors[12]. If so, identification of these vessels within a mass, independent of the pathologic type, would be reasonable because nutrition vessels are essential for malignant tumor growth ; however, further study and pathologic evidence are needed.

There was no significant difference between the pattern of contrast enhancement on CT scan and the pathologic types (squamous cell carcinoma and adenocarcinoma) of solid primary lung cancer. Some reports[13-15] on dynamic CT for evaluating solitary pulmonary nodules stated that contrast enhancement tended to be stronger in malignant solid lesions than in benign lesions, such as inflammatory changes, granulomas, hamartomas, and so on. Several reports[16,17] showed that dynamic CT may reflect solid lung tumor angiogenesis. However, to the best of our knowledge, there is no available report on the relationship between pathologic type of malignant lung tumor and pattern of contrast enhancement. Using our CT protocol for preoperative evaluation, we did not find

Table 3. Correlation of each pathologic type with patient characteristics, pathologic findings, and radiographic characteristics

	Squamous cell carcinoma $n = 35$	Adenocarcinoma $n = 75$	p-value
Age in years, median (range)	72 (38-82)	71 (46-86)	0.3953
Sex, *n* (%)			0.0003
Men	33 (94%)	46 (61%)	
Women	2 (6%)	29 (39%)	
Tumor size in mm, median (range)	37 (12-70)	30 (14-120)	0.3614
Pathological T factor, *n* (%)			0.3030
1a	3 (9%)	9 (12%)	
1b	3 (9%)	15 (20%)	
2a	21 (60%)	36 (48%)	
2b	4 (11%)	3 (4%)	
3	3 (9%)	12 (16%)	
4	1 (3%)	0	
Pathologic stage, *n* (%)			0.6649
IA	5 (14%)	22 (29%)	
IB	18 (51%)	24 (32%)	
IIA	5 (14%)	6 (8%)	
IIB	1 (3%)	10 (13%)	
IIIA	6 (17%)	13 (17%)	
IV	0	0	
Early phase, median (range)			
Maximum CT value (HU)	115 (59-312)	111 (51-243)	0.3517
Mean CT value (HU)	57.4 (18.4-98.1)	55.6 (7.8-164)	0.7797
Presence of less-enhanced area, *n* (%)	12 (34%)	20 (27%)	0.4172
Delayed phase, median (range)			
Maximum CT value (HU)	93 (36-130)	91 (30-184)	0.8229
Mean CT value (HU)	54 (4.9-95)	56.7 (11.5-102.9)	0.2603
Presence of less-enhanced area, *n* (%)	17 (39%)	28 (37%)	0.2683

CT : computed tomography, HU : Hounsfield unit

significant relationships between these two factors in the present study. One of the major factors for this result might be related to the timing of scanning after injection of the contrast medium. Compared to our study, previous reports[13-17] on angiogenesis and malignancy adjusted their scan timing individually or scanned more than three times in order to make time-attenuation curves. Considering these, further investigations on the pattern of contrast enhancement of solid lung masses on CT are needed.

We acknowledge that there were several limitations in this study. First, this study was a retrospective analysis and included patients who were pathologically diagnosed as lung cancer. However, a clinical setting would first entail diagnosis of the cause of a lung consolidation (e.g., pneumonia, benign or malignant tumor, etc.). Second, we evaluated only axial CT images ; this may have led to an underestimation of the actual number of cases with the CT angiogram sign, which might have been observed on sagittal and coronal images. Third, the number of patients with small cell lung cancer, carcinoid, and adenosquamous carcinoma were small compared with that of patients with squamous cell carcinoma or adenocarcinoma.

In conclusion, the CT angiogram sign can also be detected in lung squamous cell carcinoma, adenocarcinoma other than the bronchioloalveolar carcinoma subtype, and small cell lung carcinoma. Our findings in the study confirmed that despite the modern advanced in CT technology, the CT angiogram sign is still believed to be nonspecific for primary lung tumors. This finding supported the results of the previous studies and the available literature. However, prospective study is needed to confirm these retrospective results.

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